Systematic Review of Lutein and Zeaxanthin and the Maintenance of Vision

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Executive Summary

The objective of this systematic review was to assess whether dietary intake of lutein and zeaxanthin (L/Z) helps maintain vision in adults.

Lutein and zeaxanthin, are xanthophyll carotenoids naturally present in food, especially in dark green leafy vegetables, such as spinach and kale, as well as eggs – in the egg yolk. Eggs have been found to be a particularly bioavailable source of these carotenoids.

With their isomer meso-zeaxanthin, L/Z accumulate in the macula, the central part of the retina responsible for fine detail and central vision. Given their high concentration in this area of the body, research has investigated their potential role in eye health and vision.

A literature review was conducted in the PubMed and CINAHL databases, in May 2018, limited to human cohort and randomised controlled trials. Manual searches were also performed on the reviewed full text papers from the original search. Relevant medical subject heading (MeSH) terms and keywords included: lutein, zeaxanthin, xanthophyll/s, antioxidant/s or carotenoid/s in conjunction with the following: vision, visual performance, visual function, visual acuity, contrast sensitivity, age-related macular degeneration, age-related maculopathy. The main outcomes were measures of vision including visual acuity, contrast sensitivity and age-related macular degeneration (incidence and progression). This review was not concerned with studies in which participants had pre-existing eye disease (other than AMD) including cataracts, retinitis pigmentosa and diabetic retinopathy.

Using the inclusion and exclusion criteria the 762 publications from the original search were reduced to 16 included studies. These 16 studies were 8 cohort studies and 8 randomised controlled trials (RCTs). The cohort studies investigated the relationship between dietary L/Z intake and incidence and/or progression of age-related macular degeneration (AMD) in populations including Blue Mountains Eye Study (BMES) cohort, the Rotterdam cohort, the Nurses Health Study (NHS) cohort, the Health Professionals Follow Up Study (HPFS) cohort and the Atherosclerosis Risk in Community (ARIC) cohort. All cohort studies rated as high quality using the Health Canada Quality Appraisal tool.

The 8 RCTs investigated the effect of supplemental L/Z on AMD progression and/or measures of vision including visual acuity and contrast sensitivity. All RCTs rated as high quality using the Health Canada Quality Appraisal tool.

Cohort studies did not consistently find a statistically significant favourable effect of L/Z intake on early AMD, however when analysis was isolated to individuals at high genetic risk of AMD a 22% reduction in risk was found in the highest levels of intake. High quality cohort studies inconsistently found a favourable effect of L/Z intake on intermediate and advanced AMD – the types of AMD most likely to result in vision loss. In a study investigating genetic risk as an effect modifier, the highest tertile intakes of L/Z were non-significantly associated with an approximately 35% risk reduction in advanced AMD while there was a significant reduced risk of any AMD. Cohort studies may have been subject to residual confounding and/or difficulties in quantifying L/Z intake biasing their findings towards the null.

The AREDS2 RCT found individuals with a background dietary L/Z intake of <1428µg/day benefitted for the 12mg L/Z supplement (HR of 0.74 (95% CI, 0.59-0.94, p=0.01)). Other RCTs included in the systematic review consistently showed L/Z supplementation enhanced contrast sensitivity and visual acuity (although VA results did not always reach statistical significance).

The relationship between L/Z and vision is biologically plausible. Evidence demonstrates the macular pigment has blue light-filtering properties as well as anti-oxidant and possibly anti-inflammatory actions.

Overall, while results from observational cohort studies to date have been inconsistent, the evidence from high quality intervention studies on late AMD and visual performance including contrast sensitivity and visual acuity consistently show favourable effects of L/Z on these health effects suggesting a causal effect. Furthermore, the relationship between L/Z and maintenance of vision has high biological plausibility and levels of intake are possible in the current Australian and New Zealand food environment.

The following systematic review is set out in a way that directly addresses the required elements outlined in Schedule 6 of Standard 1.2.7 of the Food Standards Code.

1. Description of the food-health relationship

S6-2(a) A description of the food or property of food, the health effect and the proposed relationship between the food or property of food and the health effect.

1.1 Description of the food/property of food

The food constituent/s that are the subject of this systematic review are lutein and zeaxanthin. Lutein and zeaxanthin, are xanthophyll carotenoids naturally present in food, especially in dark green leafy vegetables, such as spinach and kale, as well as eggs – in the egg yolk. Eggs contain both lutein and zeaxanthin – in approximately a 1:1 ratio[1]. Following extraction, carotenoids in egg yolks can be separated and quantified using several analytical techniques. The most commonly used technique used is high performance liquid chromatography (HPLC)[2]. Carotenoids cannot be synthesized in vivo, and they therefore must be obtained from dietary consumption.

Table 1 includes a list of commonly consumed foods including their lutein and zeaxanthin content.

Table 1: Lutein and Zeaxanthin Content of Common Foods[3]

Food	Lutein and zeaxanthin (μg/100g)
Kale, cooked	18246
Spinach, raw	12197
Spinach, cooked	11308
Parsley	5562
Peas, green (boiled)	2593
Brussels Sprouts (boiled)	1541
Pistachio nuts, raw	1404
Egg yolk, raw	1094
Broccoli (cooked)	1079
Asparagus, cooked	771
Frozen corn (boiled from frozen)	684
Egg whole, raw	504
Egg whole, cooked (hard-boiled)	353
Avocado (all commercial)	270
Orange (all commercial)	129

Lutein and zeaxanthin are xanthophylls biochemically distinct from other carotenoids due to the presence of hydroxyl groups located at each end of these molecules.

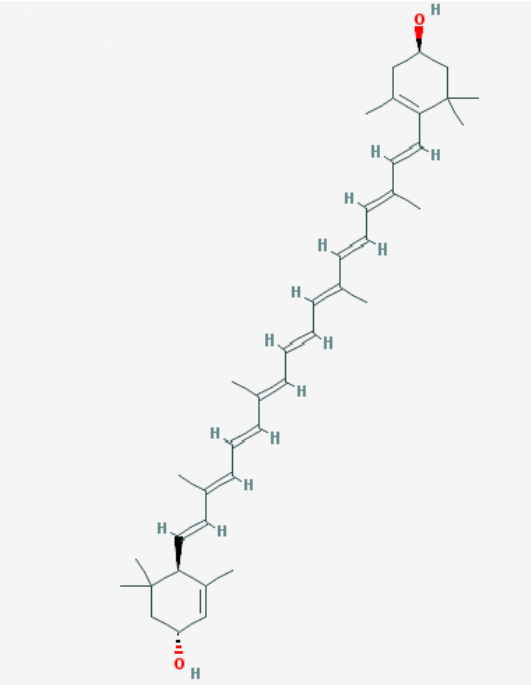


Figure 1a: 2D chemical structure of lutein molecule

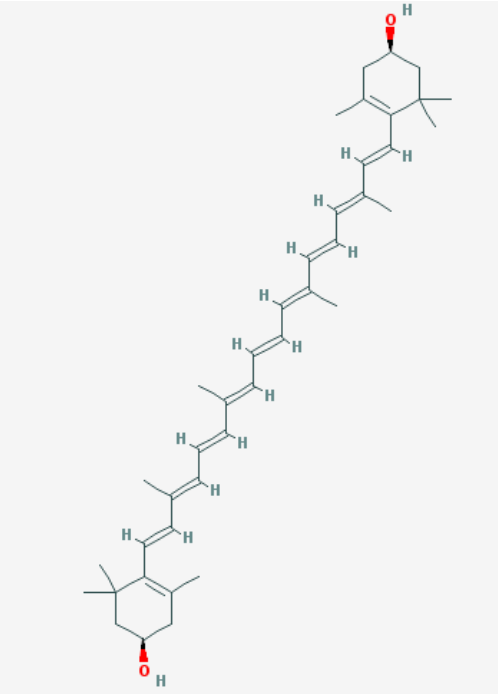


Figure 1b 2D chemical structure of zeaxanthin molecule

Reference: National Center for Biotechnology Information. PubChem Compound Database; CID=5281243, https://pubchem.ncbi.nlm.nih.gov/compound/5281243 (accessed June 8, 2018). National Center for Biotechnology Information. PubChem Compound Database; CID=5280899, https://pubchem.ncbi.nlm.nih.gov/compound/5280899 (accessed June 8, 2018).

There are more than 600 carotenoids found in nature, of which approximately 50 are consumed in the typical diet, and only 14 have been detected in serum[4]. Of these 14, only lutein and zeaxanthin and their metabolites are located in the macula of the eye where they are found at the highest concentrations of anywhere in the human body, suggesting an important functional role for these molecules in the eye[4].

Lutein and Zeaxanthin in the retina of the eye – the macula pigment (MP)

Lutein and zeaxanthin, with their isomer meso-zeaxanthin accumulate in the macula, the central part of the retina responsible for fine detail and central vision. At this location they are referred to as the macular pigment (MP)[5].
Both serum and ocular concentrations of lutein and zeaxanthin have been shown to increase following increased intake of foods rich in these carotenoids[6,7] or ingestion of L/Z supplements[8-10].

MPOD (macular pigment optical density) is a measurement of the attenuation of blue light by macular pigment and is linearly related to the amount (concentration × pathlength × area) of lutein and zeaxanthin in the macula[4].

Dietary intakes of L/Z have been associated with MPOD levels. A review paper by Bernstein and colleagues in 2010 identified more than 24 studies which have demonstrated an increase in macular carotenoids following L/Z supplementation of 2–30 mg per day or a high carotenoid diet[4].

Note: In order to address the research question which is the subject of this systematic review, the dietary intake of L/Z (and not simply measurements of MP or MPOD) is the 'property of the food' in the food-health relationship. Studies that only included a measure of MP and/or MPOD without quantification of L/Z were excluded. See more details provided in section 2.2.

Bioavailability of lutein and zeaxanthin from eggs

Evidence indicates the bioavailability of lutein and zeaxanthin from eggs is higher than from vegetable sources, most likely due to the fat content of eggs[11,12]. Furthermore, it has been suggested that the complex cellular structure of plant sources of L/Z may impede the release of these carotenoids from the chloroplast[13,14] although cooking may enhance bioavailability of carotenoids from plant sources[15].

The consumption of 1 egg per day over 5 weeks has been shown to increase serum lutein levels by 26% and zeaxanthin levels by 38%[16]. A 12-week egg intervention, in which women consumed 6 eggs per week, demonstrated egg intake increased serum zeaxanthin levels as well as macular pigment optical density[7]. Another study found the consumption of 3 eggs per day for 12 weeks increased serum lutein and zeaxanthin by 21% and 48%, respectively[17]. Similar results were also found in a study of healthy young adults, 18-30yrs, whose serum lutein and zeaxanthin levels significantly increased by 20-31% ($p<0.05$) following the consumption of 2-3 eggs per day for 4 weeks[18].

Further evidence of the increased bioavailability of lutein and zeaxanthin from eggs comes from studies assessing eggs enriched with higher amounts of L/Z than standard eggs. Kelly et al, 2014 showed the addition of 1 lutein-enriched egg per day (for 90 days) to the diet of 100 adults significantly increased lutein levels by 76% ($p < 0.001$). Furthermore, the consumption of 1 zeaxanthin-enriched egg per day (for 90 days) to the diet of 100 adults significantly increased zeaxanthin levels by 430% ($p < 0.001$). Researchers suggested the increases in serum L/Z in this trial are comparable with a daily use of 5 mg supplements[19].

More recently, an 8-week intervention study (known as the Egg Xanthophyll Intervention clinical Trial(EXIT)) in adults, 18-65 years, showed serum carotenoid levels increased significantly over time in control (standard egg) and enriched egg groups, but to a significantly greater extent in the enriched egg group ($P<0.001$)[20].

Lutein bioavailability has also been compared between the consumption of 6mg of lutein from lutein-enriched eggs, lutein supplement or spinach in healthy men[21]. After 10 days, serum responses were significantly higher after egg consumption than after a lutein supplement or spinach intake[21].

1.2 Description of the health effect

The health effect that is the subject of this review is *the maintenance of vision*. Vision (often referred to as 'visual function' or 'visual performance' in the literature) can be measured by using standard tests of visual acuity (VA) and contrast sensitivity (CS). No single test reflects all of the parameters of visual function but the most widely used means of testing vision is known as visual acuity, which measures spatial resolving power of the visual system at a 100%[5].

Contrast sensitivity is a measure of the visual system's ability to distinguish objects of different luminance and is measured for different target sites. Contrast sensitivity is a more reflective measure of overall visual performance than visual acuity, in healthy and in diseased eyes[5]. It has been noted that contrast sensitivity is a more sensitive visual indicator compared to visual acuity and can provide additional information at the very beginning of visual dysfunction[22].

How is visual acuity measured?
As part of visual performance examinations, optometrists can determine best corrected visual acuity (BCVA) with decimal charts in an examination room with standardised lighting conditions ([23,24]).

How is contrast sensitivity measured?
Temporal contrast sensitivity can be assessed by the customised, LED-driven tabletop device described by Wooten et al 2010[25]. Contrast sensitivity was measured using the contrast glare tester (CGT-1000; Takagi Seiko, Nagano, Japan). The CGT-1000 is able to determine accurately contrast sensitivity in a rapid and simple automated manner[24].

Furthermore, since the leading cause of blindness in Australians over 55 years of age is age-related macular degeneration (AMD), studies which consider the role of L/Z in preventing or minimising the progression of AMD are also included in this systematic review.

There are three stages of AMD defined in part by the size and number of drusen under the retina[26]:

- **Early AMD.** Early AMD is diagnosed by the presence of medium-sized drusen, which are about the width of an average human hair. People with early AMD typically do not have vision loss.
- **Intermediate AMD.** People with intermediate AMD typically have large drusen, pigment changes in the retina, or both. Again, these changes can only be detected during an eye exam. Intermediate AMD may cause some vision loss, but most people will not experience any symptoms.
- **Late AMD.** In addition to drusen, people with late AMD have vision loss from damage to the macula. There are two types of late AMD:
    - In geographic atrophy (also called dry AMD), there is a gradual breakdown of the light-sensitive cells in the macula that convey visual information to the brain, and of the supporting tissue beneath the macula. These changes cause vision loss.
    - In neovascular AMD (also called wet AMD), abnormal blood vessels grow underneath the retina. ("Neovascular" literally means "new vessels.") These vessels can leak fluid and blood, which may lead to swelling and damage of the macula. The damage may be rapid and severe, unlike the more gradual course of geographic atrophy. It is possible to have both geographic atrophy and neovascular AMD in the same eye, and either condition can appear first.

In the literature, there are a number of definitions, scales and systems used to classify and grade AMD or ARM (age-related maculopathy). These include The Wisconsin Age-Related Maculopathy Grading System[27], an International classification and grading system for age-related maculopathy described by Bird et al, 1995[28] and The Age-Related Eye Disease Study severity scale for age-related macular degeneration[29].

The Wisconsin Age-Related Maculopathy Grading System

Age-related macular degeneration is usually characterized by the presence of drusen and other abnormalities of the retinal pigment epithelium in the macular area. The Wisconsin system is derived from methods used to grade AMD and diabetic retinopathy in some clinical studies and trials. The system was developed for and used in two large population-based studies: the Beaver Dam Eye Study and the Framingham Eye Study[27].

Klein, 1991 details the grading of drusen and other aspects of ARMD including pigmentation and lesions[27].

International classification and grading system for age-related maculopathy

Here age-related maculopathy is defined as a disorder of the macular area of the retina, most often clinically apparent after 50 years of age, characterised by any of the following items, without indication that they are secondary to another disorder:

- Discrete, whitish-yellow spots identified as "drusen" which are external to the neuroretina.
- Areas of increased pigment or hyperpigmentation associated with drusen
- Areas of depigmentation or hypopigmentation of the retinal pigment epithelium most often more sharply demarcated than drusen, without any visibility of choroidal vessels associated with drusen.

Bird, 1995 details grading of drusen, pigmentation of the retina, geographic atrophy and neovascular AMD[28].

The Age-Related Eye Disease Study severity scale for age-related macular degeneration

An important goal of AREDS was the development of a severity scale for AMD, to provide baseline risk categories, to allow tracking of progression along the scale, and to define surrogate outcomes for progression to advanced AMD. This report describes the scale which uses neovascular AMD and geographic atrophy (GA) involving the center of the macula (CGA) as the principal outcome measures. Davis 2005 details grading of drusen, pigment, depigmentation, geographic atrophy and predominance of soft indistinct drusen[29].

Since vision loss is associated with intermediate and advanced AMD our conclusions regarding causal association will focus more heavily on these forms of AMD rather than early AMD, where vision loss is unlikely.

1.3 Description of the proposed food-health relationship

The proposed food-health relationship which is the subject of this review is that increasing dietary intake of lutein and zeaxanthin helps maintain vision in adults. Specifically,

Does eating higher amounts of lutein and zeaxanthin maintain vision in adults compared to eating lower amounts of lutein and zeaxanthin?

The target population is adults. AMD is the leading cause of blindness in Australians over 55 years of age. Since other research studies have investigated the effect of lutein and zeaxanthin intake on vision in adults under the age of 55 years old we did not restrict the population group to a specific age.

2. Retrieval of scientific evidence – systematic review based on the original literature only

S6-2 (b) A description of the search strategy used to capture the scientific evidence relevant to the proposed relationship between the food or property of food and the health effect, including the inclusion and exclusion criteria.

2.1 Search Strategy

Two databases, PubMed and CINAHL were searched in May 2018 for English language studies of dietary lutein and zeaxanthin from either foods, supplements or overall diet that reported on aspects of visual function including visual acuity, contrast sensitivity and/or the development or progression of age-related macular degeneration.

PICOS Statement

P (population): Adults
I or E (intervention or exposure): High dietary or supplemental lutein and/or zeaxanthin
C (comparison): No or low intake of lutein and/or zeaxanthin or placebo
O (outcome): Vision (as measured by visual acuity or contrast sensitivity) or incidence or progression of AMD
S (study design): Cohort or randomised controlled trials

Research Question: Are adults who consume higher amounts of lutein and zeaxanthin, through food or supplements, more likely to maintain vision compared to adults who consume lower amounts of lutein and zeaxanthin?

Search terms included: lutein, zeaxanthin, xanthophyll/s, antioxidant/s or carotenoid/s in conjunction with the following: vision, visual performance, visual function, visual acuity, contrast sensitivity, age-related macular degeneration, age-related maculopathy. Keywords and MeSH term searches were conducted.

Articles were limited to human studies, English language and adults 19+ in PubMed and CINAHL searches.

Studies were limited to higher quality study designs including randomised controlled trials and cohort studies. Case-control and cross-sectional studies were not included in the systematic review.

2.2 Inclusion and Exclusion Criteria

The inclusion criteria were as follows:

- Human studies in adults
- Cohort or randomised controlled studies
- Follow up for at least 1 year or more in cohort studies
- Study outcomes include a measure of vision such as contrast sensitivity, visual acuity or AMD development or progression
- Dietary or supplemental intake of lutein and/or zeaxanthin was quantified
- Measure of effect reported (eg, mean difference or Relative Risks (RR) or Odds Ratio (OR) or Hazard Ratios (HRs) and their CIs were reported)

The exclusion criteria were as follows:

- Animal or in-vitro studies
- Human studies in children
- Non-English language studies
- Studies in which participants had pre-existing eye disease (other than AMD) including cataracts, retinitis pigmentosa and diabetic retinopathy
- If lutein and zeaxanthin were co-administered with omega-3 or other vitamins and minerals (RCTs).
- Outcome was only increase in macular pigment or macular pigment optical density (MPOD) with no other measure of vision reported

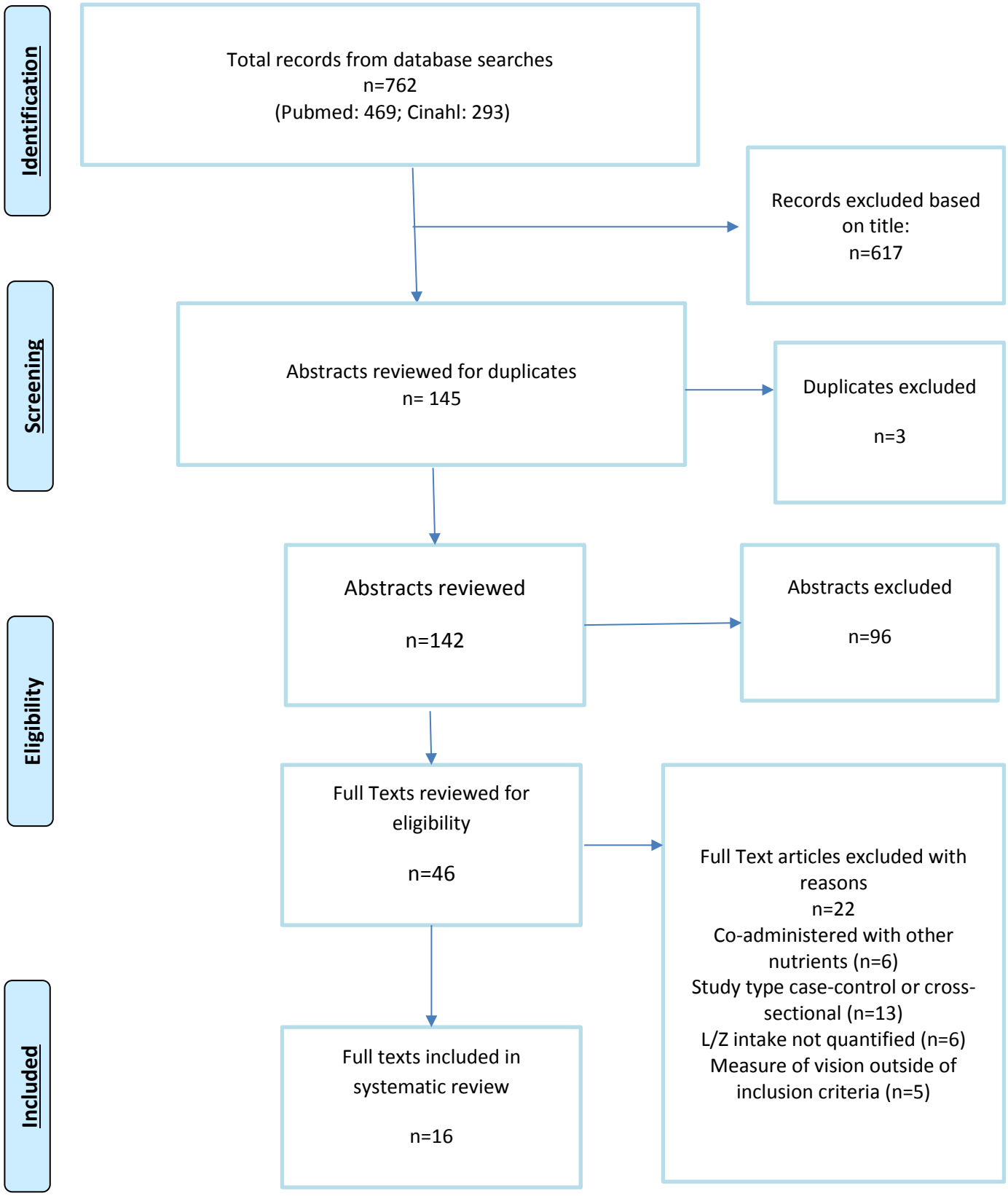


Figure 2: PRISMA Diagram showing the study review and selection process

Search records were reviewed, screened and selected for inclusion by BE and JK. Tabulation of study data was conducted by JK and quality assessment of the included studies was conducted by BE and JK. Any discrepancies in the review or selection of studies or in the quality assessment was discussed and rectified between the authors.

S6-2 (c) A final list of studies based on the inclusion and exclusion criteria. Studies in humans are essential. A relationship between a food or property of food and the health effect cannot be established from animal and *in vitro* studies alone.

2.3 Final list of included studies

Table 2: List of included randomised controlled trials based on the inclusion and exclusion criteria

Study Authors	Study Title	Abstract URL
Ma L, Lin XM, Zou ZY, Xu XR, Li Y, Xu R. 2009	A 12-week lutein supplementation improves visual function in Chinese people with long-term computer display light exposure.	https://www.ncbi.nlm.nih.gov/pubmed/19586568
Weigert G, Kaya S, Pemp B, Sacu S, Lasta M, Werkmeister RM, Dragostinoff N, Simader C, Garhöfer G, Schmidt-Erfurth U, Schmetterer L. 2011[30]	Effects of lutein supplementation on macular pigment optical density and visual acuity in patients with age-related macular degeneration.	https://www.ncbi.nlm.nih.gov/pubmed/21873668
Richer SP, Stiles W, Graham-Hoffman K, Levin M, Ruskin D, Wrobel J, Park DW, Thomas C. 2011[31]	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, 973.	https://www.ncbi.nlm.nih.gov/pubmed/22027699
Sabour-Pickett S, Beatty S, Connolly E, Loughman J, Stack J, Howard A, Klein R, Klein BE, Meuer SM, Myers CE, Akuffo KO, Nolan JM. 2014[32]	Supplementation with three different macular carotenoid formulations in patients with early age-related macular degeneration.	https://www.ncbi.nlm.nih.gov/pubmed/24887490
Huang YM, Dou HL, Huang FF, Xu XR, Zou ZY, Lin XM. 2015[22]	Effect of supplemental lutein and zeaxanthin on serum, macular pigmentation, and visual performance in patients with early age-related macular degeneration.	https://www.ncbi.nlm.nih.gov/pubmed/25815324
Yao Y, Qiu QH, Wu XW, Cai ZY, Xu S, Liang XQ. 2013	Lutein supplementation improves visual performance in Chinese drivers: 1-year randomized, double-blind, placebo-controlled study.	https://www.ncbi.nlm.nih.gov/pubmed/23360692

Age-Related Eye Disease Study 2 (AREDS2) Research Group, Chew EY, Clemons TE, Sangiovanni JP, Danis RP, Ferris FL, Elman MJ, Antoszyk AN, Ruby AJ, Orth D, Bressler SB, Fish GE, Hubbard GB, Klein ML, Chandra SR, Blodi BA, Domalpally A, Friberg T, Wong WT, Rosenfeld PJ, Agrón E, Toth CA, Bernstein PS, Sperduto RD. 2014[33]	Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3.	https://www.ncbi.nlm.nih.gov/pubmed/24310343
Age-Related Eye Disease Study 2 Research Group. Collaborators: Chew EY, Clemons TE, SanGiovanni JP, Danis R, Ferris FL, Elman M, Antoszyk A, Ruby A, Orth D, Bressler S, Fish G, Hubbard B, Klein M, Chandra S, Blodi B, Domalpally A, Friberg T, Wong W, Rosenfeld P, Agron E, Toth C, Bernstein P, Sperduto R. 2013[34]	Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial.	https://www.ncbi.nlm.nih.gov/pubmed/23644932

Table 3: List of included cohort studies based on the inclusion and exclusion criteria

Study Authors	**Study Title**	**Abstract URL**
Flood V, Smith W, Wang JJ, Manzi F, Webb K, Mitchell P. 2002	Dietary antioxidant intake and incidence of early age-related maculopathy: the Blue Mountains Eye Study.	https://www.ncbi.nlm.nih.gov/pubmed/12466170
van Leeuwen R, Boekhoorn S, Vingerling JR, Witteman JC, Klaver CC, Hofman A, de Jong PT. 2005	Dietary intake of antioxidants and risk of age-related macular degeneration.	https://www.ncbi.nlm.nih.gov/pubmed/16380590
Cho E, Hankinson SE, Rosner B, Willett WC, Colditz GA. 2008	Prospective study of lutein/zeaxanthin intake and risk of age-related macular degeneration.	https://www.ncbi.nlm.nih.gov/pubmed/18541575
Tan JS, Wang JJ, Flood V, Rochtchina E, Smith W, Mitchell P. 2008	Dietary antioxidants and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study.	https://www.ncbi.nlm.nih.gov/pubmed/17664009

Ho L, van Leeuwen R, Witteman JC, van Duijn CM, Uitterlinden AG, Hofman A, de Jong PT, Vingerling JR, Klaver CC. 2011[35]	Reducing the genetic risk of age-related macular degeneration with dietary antioxidants, zinc, and ω-3 fatty acids: the Rotterdam study.	https://www.ncbi.nlm.nih.gov/pubmed/21670343
Wang JJ, Buitendijk GH, Rochtchina E, Lee KE, Klein BE, van Duijn CM, Flood VM, Meuer SM, Attia J, Myers C, Holliday EG, Tan AG, Smith WT, Iyengar SK, de Jong PT, Hofman A, Vingerling JR, Mitchell P, Klein R, Klaver CC. 2014	Genetic susceptibility, dietary antioxidants, and long-term incidence of age-related macular degeneration in two populations.	https://www.ncbi.nlm.nih.gov/pubmed/24290803
Wu J, Cho E, Willett WC, Sastry SM, Schaumberg DA. 2015[36]	Intakes of Lutein, Zeaxanthin, and Other Carotenoids and Age-Related Macular Degeneration During 2 Decades of Prospective Follow-up.	https://www.ncbi.nlm.nih.gov/pubmed/26447482
Lin H, Mares JA, LaMonte MJ, Brady WE, Sahli MW, Klein R, Klein BEK, Nie J, Millen AE. 2017[37]	Association between Dietary Xanthophyll (Lutein and Zeaxanthin) Intake and Early Age-Related Macular Degeneration: The Atherosclerosis Risk in Communities Study.	https://www.ncbi.nlm.nih.gov/pubmed/28332910

3. Tabulation of data from the final list of included studies

S6-2 (d) A table with key information from each included study. (i) the study reference (ii) the study design (iii) the objectives (iv) the sample size in the study group and loss to follow-up or non-response (v) the participant characteristics (vi) the method used to measure the food or property of food including amount consumed (vii) confounders measured (viii) the method used to measure the health effect (ix) the study results, including effect size and statistical significance (x) any adverse effects

3.1 Summary of key information from included studies

Tables 4 and 5 below summarise the key information from the included studies.

Table 4: Summary of key information from included intervention studies reporting the effect of L/Z on visual performance and AMD.

Study Reference	Study Design	Study Objectives	Sample Size & loss to follow up	Characteristics of participants	Amount of food/property of food consumed	Method used to measure food/property of food	Confounders Measured	Method used to measure health effect	Study results (including effect size and statistical significance)	Adverse Effects
Visual Acuity and/or Contrast Sensitivity Measures										
Huang YM et al 2015. Quality Rating: 14	RCT Study duration 2 years	To compare the 2-year effect of multiple doses of lutein/ zeaxanthin on serum, macular pigmentation, and visual performance on patients with early age-related macular degeneration (ADM).	n=112 (initial) Loss to follow up= 4 subjects **Proportion loss to follow up = 4%**	Subjects aged over 50 years with clinical diagnosis of early AMD and clear ocular media. No other ocular disorders or unstable systemic or chronic illness. No antioxidant supplement use in previous 6 months. Placebo: Age 69.0±7.5; Male 39.3%; BMI 24.8±3.0kg/m² 10mg lutein: Age 69.7±8.3; Male 34.6%; BMI 24.1±3.4kg/m² 20mg Lutein: Age 69.3±6.9; Male 51.9%; BMI 25.1±3.3kg/m² 10mg Lutein + 10mg Zeaxanthin: Age 68.5±6.9; Male 44.4%; BMI 24.6±3.6kg/m²	All subjects were randomly assigned to take either 10mg lutein, 20mg lutein, lutein 10mg + zeaxanthin 10mg, or a placebo.	All supplements were pre-packed and ready to consume Diet stability was assessed using a validated 120-item FFQ conducted at baseline, 48 weeks, and 2 years.	Information on characteristics and demographics including age, sex, education and BMI was collected using questionnaires and examinations. Serum total cholesterol (TC), triglyceride (TG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), and glucose were measured. No difference in smoking status among groups. Dietary intakes of lutein, zeaxanthin, beta-carotene, and other antioxidants were not significantly different among the groups or during the intervention (for all, P > 0.05).	Best-spectacle corrected visual acuity (BCVA) was measured according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Contrast Sensitivity (CS) was measured with CSV-1000 test system (Vectore-Vision, Dayton, OH) at 4 spatial frequencies (3,6,12 and 18 cycles/degree) with a grade scale from 1 (high contrast) to 8 (low contrast).	Supplementation with 20mg lutein increased MPOD by 34.6%, P< 0.01) and CS at 3 cycles/degree (+1.47±0.39; P<0.01) and 6 cycles/degree (1.62±0.36; P<0.001) for the first 48 weeks. By year 2, the 10mg lutein group reached the same MPOD level (0.442D.U.) as the 20mg lutein group (0.441D.U.). 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). At 2 years, CS at 3cycles/degree in the 10mg lutein group significantly increased (+1.47±0.34 (increased by 16.1%), P < 0.05) to a similar peak value to the 20mg lutein group.	Reported no adverse effects

									No statistical changes of BCVA were observed during the trial.	
Sabour-Pickett S et al 2014. Quality Rating: 9	RCT Study duration 12 months	To investigate the impact of three different macular carotenoid formulations on macular pigment optical density and visual performance in subjects with early age-related macular degeneration.	n=67 (initial) Loss to follow up= 15 subjects **Proportion loss to follow up = 22%**	Subjects with early AMD (the presence of drusen and pigmentary changes) in at least 1 eye; corrected distance visual acuity of ≥6/12 in the study eye. Age: 66±8 years BMI: 26.1±5.5 kg/m² Gender: Male 35%	Subjects were allocated to one of the following groups: Intervention Group 1 (20 mg/day lutein and 2 mg/day zeaxanthin); Intervention Group 2 (10mg/day meso-zeaxanthin, 10mg/day lutein, and2mg/day zeaxanthin); and Group 3 (17 mg/day meso-zeaxanthin, 3 mg/day lutein, and 2 mg/day zeaxanthin). Baseline carotenoid-based diet score: Entire group= 18.7±11.2 Group 1= 17.3±10.9 Group 2= 21.9±12.7 Group 3= 16.0±8.4	All supplements were pre-packed and ready to consume A subject's weekly intake of carotenoid-rich foods was inputted into an L/Z screener to give a carotenoid-based diet score. Values are weighted for frequency of intake of the food and for bioavailability of L and Z within these foods (the range of scores on the L/Z screener is 0–75).	A demographic, medical, ophthalmic, and lifestyle case history was obtained for each subjects at baseline. There was no significant difference between the groups in any baseline data variable (including gender, BMI, diet score, laterality, smoking status, education, BMI, age and AMD severity).	Contrast sensitivity was assessed using the logMAR chart at 5 different spatial frequencies (1.2, 2.4, 6.0, 9.6, and 15.15 cycles per degree).	In group 1 (20mg/day L +2mg/Z) MPOD increased significantly from baseline to 12 months at 1.75 degree only (from 0.16±0.11 to 0.21±0.09; P= 0.018). Statistically significant improvements in letter contrast sensitivity were seen at low spatial frequencies at 1.2 and 2.4 cycles in Group 1 (from 73.0±49.1 to 91.8±48.5; P=0.021 and from 59.7±45.3 to 86.7±54.2; P=0.006, respectively). There was no statistically significant difference between treatment groups including group 1 in term of change in the AMD severity scale (P= 0.455, Pear-son chi-square test).	Not reported in the paper
Richer SP et al 2011. Quality Rating: 15	RCT Study Duration 1 year	To evaluate whether dietary supplementation with the carotenoid zeaxanthin raises macula pigment optical density (MPOD) and has unique visual benefits for patients with early atrophic macular degeneration	n=60 (initial: 57 men, 3 women) Loss to follow up= 8 subjects **Proportion loss to follow up = 13%**	All subjects did not have high-risk retinal characteristics for advanced AMD or with consumption of L (or Zx) beyond the minimal 250 mg/d commonly found in pabulum-type daily multivitamins within 6 months. All subjects had	Subjects were randomly assigned to 1 of 3 groups: 1) 8mg zeaxanthin, 2) 8mg zeaxanthin + 9mg lutein, 3) 9mg lutein (control group)	All supplements were pre-packed and ready to consume Diet was assessed using the FFQ, for the presence of AREDS and AREDS II nutrients, dietary omega n3 fatty acids, and carotenoids (lutein, zeaxanthin, and miscellaneous nutrients within the	Demographic parameters including age, smoking in pack years, alcohol intake, BMI, AMD duration and diabetes were measured and no significant differences were found among the treatment groups. The baseline vision parameters were mostly matched among groups except that the Smith	Conventional high-contrast Early Treatment of Diabetic Retinopathy Study (ETDRS) distance visual acuity was assessed to a fractional line (single letter), displayed randomly on a video projection system at 10 feet (M&S Technologies, Smart Systems II, Park	Randomisation resulted in equal MPOD variance and MPOD increasing in each of the 3 groups from 0.33± 0.17 density units (du) baseline to 0.51±0.18du at 12month (P=0.03),but no between-group differences (Analysis of Variance; P=0.47). In the zeaxanthin group, high-contrast visual acuity improved significantly at 12 month	Reported no adverse effects

		having visual symptoms but lower-risk National Institute of Health/ National Eye Institute/ Aged-Related Eye Disease Study characteristics.		mild-to-moderate age-related macular degeneration (AMD) Age: 74.9±10; Smoking: 0.2±0.5 pack/d/5y; BMI: 29.1±5; Diabetes: 0.2±0.4; AMD duration 41.4±41months; alcohol: 0.8±1 oz		diet at the beginning and end of the study.	Kettlewell Institute Low Luminance low-contrast near test was similarly reduced at 57.7± 17 for the right eyes, 61.6 ±15 for the left eyes, with right eyes in the Zx plus L subgroup having significantly poorer function (1-wayANOVA, P<0.04) consistent with their greater retinopathy.	Ridge, Illinois). Measurements were converted to LogMAR visual acuity. Low-contrast near visual acuity, was assessed with a 10% Weber fraction Colenbrander Mixed Contrast Reading Card (#4031, Precision Vision, LaSalle, Illinois) at 40 cm to a fractional line (single letter) with a LogMAR conversion. Distance photopic contrast sensitivity function (CSF) at 5 spatial frequencies (1.5, 3, 6, 12, and 20 cycles per degree was determined with the Functional Vision Analyzer (Stereo Optical Co., Inc., Chicago, Illinois).	(+1.5lines/8.5 letters; P=0.001), whereas low-contrast visual acuity (+4.3 letters, P>0.05) and CSF (+24%; P=0.09) were insignificantly improved. Lutein group showed significant increase in high-contrast visual acuity (+5.6 letters; P=0.05), low-contrast visual acuity (+7.2 letters; P=0.04) and CSF (+48%; P=0.05). In lutein and zeaxanthin group, significant increase in high-contrast visual acuity (+6.0 letters; P=0.05) and low-contrast visual acuity (+8.8 letters, P=0.02). Insignificant improvement was observed on CSF (+20%, P>0.05).	
Ma L et al 2009. Quality Rating: 13	RCT Study duration 12 weeks	To examine the effect of different doses of lutein supplementation on visual function in subjects with long-term computer display light exposure.	n=37 No attrition **Proportion loss to follow up = 0%**	Subjects aged between 22 and 30 years with average daily computer usage time longer than 10 hr during the previous 2 years and without clinical signs of ocular disease or other abnormalities. Placebo: Female 50%; Age 25.7±2.1 years;	Subjects were assigned to one of the below groups: Placebo, Group L6 (6mg lutein/d) and Group L12 (12mg lutein/d) Baseline measures of dietary lutein: Placebo: 2.2±2.2mg/d Group L6: 2.8±2.2mg/d Group L12: 2.3±1.8mg/d	All supplements were pre-packed and ready to consume Dietary intake was assessed using FFQ and 3 day weighed food record at baseline and final study visit.	No significant baseline difference was found among placebo and two treatment groups, including age, gender, BMI, serum lutein concentration and dietary lutein, retinol equivalents, vitamin C, vitamin E, zinc and beta carotenoid. The three groups also did not differ in visual performance indices, except for higher contrast sensitivity at	Uncorrected visual acuity (UCVA) and best-spectacle corrected visual acuity (BSCVA) were measured with decimal charts in an examination room with standardized lighting conditions. Contrast sensitivity was measured using the contrast glare tester (CGT-1000; Takagi Seiko, Nagano, Japan)	No statistical changes from baseline were observed in uncorrected visual acuity and best-spectacle corrected visual acuity, but there were significant negative correlations between baseline UCVA and UCVA change from baseline (r 0·724, P=0·042) and between baseline BSCVA and BSCVA change from baseline (r 0·798, P=0·016) in Group L12 (12mg lutein/day). No	Not reported in the paper

				BMI 20.7±2.2kg/m² Group L6: Female 50%; Age 24.2±1.6years; BMI 19.6±2.4kg/m² Group L12: Female: 53.8%; Age 24.2±1.2years; BMI 20.4±1.9kg/m²	Measures of dietary lutein at 12 weeks are not reported.		4·08 in Group Placebo (P=0·045). There was no evidence of time-dependent changes or intra-group differences in dietary consumption of the nutrients among groups during the follow-up, except for dietary zinc in Group Placebo, decreasing from 10·5 to 8·7mg over time (P=0·041).		significant correlations were observed in Group L6 and Group Placebo. This suggested a trend toward increase in visual acuity in Group L12 (12mg lutein/day). Contrast sensitivity in Groups L6 (6mg lutein/day) increased with supplementation at visual angles of 6.3° (from 1.82±0.16 to 1.89±0.14; P<0.05) and 2.5° (from 1.78±0.17 to 1.91±0.10; P <0.01). Contrast sensitivity in Groups L12 significantly increased with supplementation at most visual angles including 6.3° (from 1.81±0.15 to 1.91±0.11; P<0.01), 4.0° (from 1.81±0.16 to 1.89±0.13; P<0.01), 2.5° (from 1.76±0.19 to 1.83±0.14; P<0.05), 1.6°° (from 1.62±0.19 to 1.70±0.17; P<0.05)and 1.0° (from 1.33±0.16 to 1.43±0.23; P<0.05).	
Weigert G et al 2011. Quality Rating: 11	RCT Study Duration 6 months	To investigate whether lutein supplementation improves visual acuity (VA) and macular function (mean differential light threshold; MDLT)	n=126 (initial) Loss to follow up= 16 subjects **Proportion loss to follow up = 13%**	Subjects aged between 50 and 90 years, with AMD (stages 2,3 and 4), and clear nonlenticular ocular media and a VA> 0.4. Age 71.6±8.6, Sex: male 56.9% ARED Staging: 2=43%; 3=20%; 4=37%	Subjects were allocated to either placebo or lutein supplementation (the dosage in months 1-3 was 20mg once daily and in months 4-6 was 10mg once daily) All subjects were naive to previous lutein and/or zeaxanthin administration. Dietary intake of	All supplements were pre-packed and ready to consume	Baseline MPOD, MDLT, VA, Blood pressure, pulse rate and intraocular pressure were measured.	Visual acuity (VA) was assessed with ETDRS (Early Treatment Diabetic Retinopathy Study) charts	Lutein significantly increased MPOD by 27.9%± 2.9% (P< 0.001 versus placebo). No significant effect of lutein supplementation on VA was found, although a tendency toward an increase was seen (+2.1±0.4letters; P =0.07 versus placebo). A significant correlation was found between the increase in MPOD after 6 months and the increase in VA after	Not reported in the paper

					lutein was not assessed.				6months (r =0.27, P=0.013).	
Yao Y et al 2013. Quality Rating: 9	RCT Study duration 1 year	to examine the effect of lutein supplementation on visual function in healthy drivers with long-term light exposure.	n=120 Attrition is not reported	Average daily working time as a driver was longer than 10 hours during the previous 2 years. Subjects did not have clinically detectable signs of ocular disease or other abnormalities. Mean age: 36.7years Female: 17.5% BMI:23.65kg/m²	Subjects were allocated to either placebo or intervention group with 20mg lutein daily. Dietary lutein at baseline: Placebo group: 1.96±0.85mg/d Intervention group: 1.66±0.95mg/d	All supplements were pre-packed and ready to consume At the onset and at the end of the intervention, dietary intakes of lutein were quantified using a self-administered, semi-quantitative FFQ.	The baseline characteristics between placebo and intervention groups did not significantly differ in age, gender, BMI, dietary lutein, serum lutein and MPOD.	Refractive error and best corrected visual acuity (BCVA) were determined by a precise spectacle refraction with decimal charts with standardized lighting conditions. BCVA was determined as the average of three measurements. Contrast sensitivity were measured using the contrast glare tester (CGT-2000; Takagi Seiko, Nagano, Japan)	MPOD increased significantly in the intervention group at central measured eccentricities (ie. at 0.25°, 0.5° and 1.0°; P<0.001, P<0.001 and P<0.005, respectively) from 3 month visits and onward.(Percent changes were not provided) There was a trend in intervention group toward an increase in BCVA measured, but there were no significant differences between baseline and 1, 3, 6, and 12months (P=0.9046, P=0.6452, P=0.5589, and P=0.3356, respectively), also there were no significant differences in group Placebo. Significant increases in contrast sensitivity (CS) at most eccentricities at 1.6log, 2.5log, 4.0log and 6.0log for mesophic and 1.0log, 1.6log, 2.5log, 4.0log and 6.0log for photopic conditions at 12 month visit (P<0.05).	No significant side effects or changes in biochemical or hematologic profiles were observed.

Progression of AMD to late AMD										
Age-Related Eye Disease Study 2 (AREDS2) Research Group et al 2014. Quality Rating: 12	RCT (This article is a secondary analysis of the below RCT study) Study Duration 5 years	To examine the effect of lutein/ zeaxanthin supplementation on progression to late AMD.	n=4203 Loss to follow up=841 subjects **Proportion loss to follow up = 20%**	Subjects aged 50 to 85 with bilateral intermediate AMD or advanced AMD in one eye. Race: White 96.6%; Black/ African American 1.3%; Asian 0.8%; American Indian 0.1%; Other (1.2%) Age: <55yrs 2%; ≥55 and <65 yrs 14.3%; ≥65 and <75yrs 36.7%; ≥75 and <80yrs 26.5%; ≥80yrs 20.6% Female 56.7% Absence of other ocular diseases such as high myopia, glaucoma, clinically significant diabetic retinopathy and other diseases that might confound the assessment of the ocular outcome measurements.	In addition to taking the original or a variation of the AREDS supplement, participants were randomly assigned to the following four groups: 1) placebo, 2) lutein/ zeaxanthin (10mg/2mg), 3) omega-3 long-chain polyunsaturated fatty 3 acids (1.0g) and 4) combination of group 2 and 3. Baseline Lutein + zeaxanthin dietary intake (ug/d): Placebo: Q1=121-1403; Q5= 4608-38110 L +Z: Q1=109- 1388; Q5= 4740- 34398 DHA+EPA: Q1=154-1428; Q5= 4554-21513 L+Z+DHA+EPA: Q1=43-1419; Q5= 4492-39790	All supplements were pre-packed and ready to consume Baseline dietary intake of lutein and zeaxanthin was measured based on the Harvard Semi-Quantitative Assessment FFQ.	Baseline characteristics of subjects were measured. The baseline serum levels and dietary intake of the study nutrients, including those in the AREDS supplements, was balanced across treatment groups. Loss to follow up distributions were similar across the 4 treatment groups. No clinically or statistically significant differences in reported serious adverse events, including rates of development of neoplasms were noted across the treatment groups.	Development of advanced AMD was defined as atrophy involving the centre of the macula or neovascular changes of AMD that were detected on central grading of the stereoscopic fundus photographs for 1) definite central geographic atrophy, 2) retinal features of choroidal neovascularisation, or history of treatment for AMD.	In exploratory analysis of lutein/ zeaxanthin vs. no lutein/ zeaxanthin, the adjusted Hazard Ratio of the development of late AMD was 0.90 (95% CI 0.82- 0.99; P=0.04.) No significant changes in visual acuity loss when comparing L/Z vs. no L/Z for ≥10 letters (Adjusted HR 1.01; 95% CI 0.93-1.09; P=0.81); ≥15 letters (Adjusted HR 0.97; 95% CI 0.88-1.06; P=0.47), ≥30 letters (Adjusted HR 0.94; 95%CI 0.84-1.05; P=0.29) and the development of visual acuity worse than 20/100 (Adjusted HR 0.93; 95% CI 0.84-1.04; P=0.20).	Not reported in the paper

Age-Related Eye Disease Study 2 (AREDS2) Research Group et al 2013. Quality Rating: 12	RCT Study duration 5 years	To determine whether adding lutein + zeaxanthin, DHA + EPA or both to the AREDS formulation decreases the risk of developing advanced AMD.	n=4203 Loss to follow up=841 subjects **Proportion loss to follow up = 20%**	Subjects aged 50 to 85 with bilateral intermediate AMD or advanced AMD in one eye. Race: White 96.6%; Black/ African American 1.3%; Asian 0.8%; American Indian 0.1%; Other (1.2%) Age: <55yrs 2%; ≥55 and <65 yrs 14.3%; ≥65 and <75yrs 36.7%; ≥75 and <80yrs 26.5%; ≥80yrs 20.6% Female 56.7% Absence of other ocular diseases such as high myopia, glaucoma, clinically significant diabetic retinopathy and other diseases that might confound the assessment of the ocular outcome measurements.	In addition to taking the original or a variation of the AREDS supplement, participants were randomly assigned to the following four groups: 1) placebo, 2) lutein/ zeaxanthin (10mg/2mg), 3) omega-3 long-chain polyunsaturated fatty 3 acids (1.0g) and 4) combination of group 2 and 3. All subjects agreed to stop current use of supplements containing lutein, zeaxanthin, omega-3, vitamin C, vitamin E, beta-carotene, zinc or copper, other than those supplied by AREDS2 Baseline Lutein + zeaxanthin dietary intake (ug/d): Placebo: Q1=121-1403; Q5= 4608-38110 L +Z: Q1=109- 1388; Q5= 4740- 34398 DHA+EPA: Q1=154-1428; Q5= 4554-21513 L+Z+DHA+EPA: Q1=43-1419; Q5= 4492-39790	All supplements were pre-packed and ready to consume Baseline dietary intake of Lutein and zeaxanthin was measured based on the Harvard Semi-Quantitative Assessment FFQ.	Baseline characteristics of subjects were measured. The baseline serum levels and dietary intake of the study nutrients, including those in the AREDS supplements, was balanced across treatment groups. Loss to follow up distributions were similar across the 4 treatment groups. Participants with ≥ 1 serious adverse events: Placebo (47.3%); L+Z group (46.4%); DHA+EPA (47.3%); L+Z+DHA+EPA (48.1%) No clinically or statistically significant differences in reported serious adverse events, including rates of development of neoplasms, were noted across the treatment groups.	Development of advanced AMD was defined as atrophy involving the centre of the macula or neovascular changes of AMD that were detected on central grading of the stereoscopic fundus photographs for 1) definite central geographic atrophy, 2) retinal features of choroidal neovascularisation, or history of treatment for AMD.	Kaplan-Meier probabilities of progression to advanced AMD by 5 years was 29% for lutein + zeaxanthin. Comparison of L+Z with placebo demonstrated no statistically significant reduction in progression to advanced AMD (adjusted hazard ratio, 0.90; 98.7% CI, 0.76-1.07; P=0.12). The adjusted HR for L+Z VS no L+Z was 0.91 (95%CI, 0.82-1.00; p=0.05) for progression to advanced AMD. A further exploratory analyses stratifying by dietary intake: Participants in lowest quintile, comparison of L+Z vs no L+Z resulted in an adjusted HR of 0.74(95%CI, 0.59-0.94; P=0.01) for progression to advanced AMD. For participants in the highest quintile of L+Z intake the corresponding adjusted HR was 0.90 (95%CI, 0.71-.15; P=0.41), with the results for remaining quintiles similar to that of the highest quintile: Q1: median 696ug/d (Range 552-823); HR 0.74; 95%CI 0.59-0.94; = 0.01 Q2: median 1134ug/d (Range 1030-1244); HR 0.94; 95%CI 0.74-1.21; = 0.65 Q3: median 1585ug/d (Range 1465-1719); HR 0.92; 95%CI 0.72-1.17; =	Not reported in the paper

									0.49 Q4: median 2225ug/d (Range 2036-2452); HR 0.82; 95%CI 0.0.64-1.06; = 0.72 Q5: median 3919ug/d (Range 3201-5249); HR 0.90; 95%CI 0.71-1.15; = 0.41	

Table 5: Summary of key information from included observational (cohort) studies reporting the effect of L/Z on early and late AMD.

Study Reference (Author, Year) Quality Rating	**Study Design**	**Study Aims**	**Sample Characteristics** **• Country** **• Health status** **• Setting (free-living subjects)** **• Age range** **• Gender (M, F)** **• No. in final sample**	**Exposure and Duration** **• Food exposure** **• Duration of follow-up (for measurement of health effects)**	**Diet Assessment Tool**	**Results and Statistics** **Changes in Health Effect**	**Relevant Author's Conclusions**
Flood V et al 2002. Quality Rating: 9	Cohort (BMES) 5 year follow up	To investigate associations between dietary intake, including modest supplement intake, of antioxidant vitamins and zinc at baseline and the 5-year incidence of early age-related maculopathy (ARM).	Mean age: 65.4years Female 59.2% Family history of macular degeneration: 2.55% All Subjects lived in two postcode areas west of Sydney Australia. No. in final sample = 2335 Proportion loss to follow up = 25%	Crude median lutein and zeaxanthin intake: Q1: 288ug (151/1000kcal) Q2: 510ug (259/1000kcal) Q3: 733ug (351/1000kcal) Q4: 967ug (478/1000kcal) Q5: 1466ug (719/1000kcal) Follow up 5 years	Only baseline dietary intake was measured using a 145-item FFQ that was modified for Australian diet. The FFQ included portion size estimates as well as frequency, strength, brand, and type of supplements	Q1: 288ug (151/1000kcal) Adjusted OR= referent Q2: 510ug (259/1000kcal) Adjusted OR=0.9; 95% CI 0.5-1.5 Q3: 733ug (351/1000kcal) Adjusted OR=0.8; 95% CI 0.5-1.4 Q4: 967ug (478/1000kcal) Adjusted OR=0.7; 95% CI0.4-1.3 Q5: 1466ug (719/1000kcal) Adjusted OR=1.0; 95% CI 0.5-1.5.6-1.6 P=0.93	After adjusting for age, gender, family history of ARM, and smoking status at baseline, no associations, or any trends suggesting possible association, were found between baseline intake of lutein and zeaxanthin and the 5 year incidence of early AMD
Tan JS et al 2008. Quality Rating: 9	Cohort (BMES) 10 year follow up	To assess the relationship between baseline dietary and supplement intakes of antioxidants and the long-term risk of incident age-related macular degeneration (AMD).	Mean age : 65years Female: 59.4% History of diabetes: 6.8% History of cardiovascular disease: 17.55% No. in final sample = 2454 Proportion loss to follow up (5 year) = 36% Proportion loss to follow up (10 year) = 16%	Energy-adjusted lutein and zeaxanthin intake: Top tertile: ≥ 942ug/day Median: 743ug/day Missing data for bottom tertile Total follow up 10 years	Only baseline dietary intake was measured by a modified 145-item semiquantitative FFQ. The included questions on dietary supplements including strength and frequency of supplement uses.	Top Tertile (≥ 942ug/day) vs rest of population and neovascular AMD: RR, 0.35; 95% CI,0.13–0.92; P=0.033 Above median (743ug) L/Z and early AMD: RR, 0.66; 95%CI, 0.48–0.92; P=0.013 The associations between late AMD and L/Z: Adjusted RR for late AMD (neovascular and geographic atrophy): T1: adjusted RR= referent T2: adjusted RR=1.11; 95%CI	For dietary lutein and zeaxanthin intake, those in the top tertile had a reduced risk of incident neovascular AMD, and those with above-median intakes had a reduced risk of incident soft or reticular drusen (early AMD). Authors concluded that higher dietary lutein and zeaxanthin intake reduced the risk of long-term incident AMD. These results suggest a possible threshold protective effect of dietary

						0.58-2.13 T3: adjusted RR=0.72; 95%CI 0.34-1.50 P=0.36 Adjusted RR for neovascular AMD only: T1: adjusted RR= referent T2: adjusted RR=1.12; 95%CI 0.52-2.41 T3: adjusted RR=0.37; 95%CI 0.13-1.05 P=0.061	L/Z intake on the risk of incident neovascular AMD or indistinct soft drusen.
van Leeuwen R et al 2005. Quality Rating: 11	Cohort (Rotterdam)	To investigate whether regular dietary intake of antioxidants is associated with a lower risk of incident AMD.	Subjects aged 55 years or older in a middle-class suburb of Rotterdam, the Netherlands, without AMD in either eye (ie. With no drusen or pigment irregularities, hard drusen only, or soft drusen without pigment irregularities. No. in final sample = 4170 Proportion loss to follow up = 10%	Dietary lutein/ zeaxanthin (mean): Q1: 1.4±0.3mg/d (range≤1.8) Q2: 2.0±0.1mg/d (range>1.8-≤2.2) Q3: 2.5±0.2mg/d (range>2.2-≤2.8) Q4: 3.6±1.3mg/d (range>2.8) Range follow up: 0.3 years to 13.9 years Mean follow up: 8 .0years Median follow up: 10.6 years	Dietary intake was measure at baseline by a 170-item semi-quantitative FFQ during interview. The FFQ was validated by comparing the dietary checklist that subjects filled in prior to interview.	The association between dietary lutein/ zeaxanthin (mean intake 2.37±1.08mg/d) and incident AMD was statistically insignificant (Adjusted HR 1.01; 95% CI 0.93-1.09). The HR for incident AMD by Quartile of Energy adjusted dietary intake of L/Z was insignificant (P=0.65). Q1: 1.4±0.3mg/d (range≤1.8) Q2: 2.0±0.1mg/d (range>1.8-≤2.2) Q3: 2.5±0.2mg/d (range>2.2-≤2.8) Q4: 3.6±1.3mg/d (range>2.8)	Results driven mostly by early AMD cases. There was only 42 persons (7.5% of incident AMD) with incident late AMD. "Exclusion of the 42 persons with incident late AMD did not change the results".

Cho E et al 2008. Quality Rating: 11	Cohort (NHS & HPFS)	To evaluate the association between lutein/zeaxanthin intake and AMD risk by smoking status, intake of antioxidant vitamins, and body fatness	Women from the Nurses' Health Study (NHS): Mean age: 59years; BMI ≥25kg/m² (48.3%) Men from the Health Professional Follow-up Study (HPFS): Mean age: 62years; BMI ≥25kg/m² (55%) No diagnosis of AMD or cancer at baseline No. in final sample =71494 women and 41564 men Proportion loss to follow up = 17%	Energy adjusted lutein/ zeaxanthin intake in 1990: Women: Q1: 1097±279 µg/d Q3: 2512±195 µg /d Q5: 5852±2797 µg /d Men: Q1: 1209±317 µg /d Q3: 2865±234 µg /d Q5: 6879±315 µg /d Follow up 18 years	NHS: Diet was assessed with a validated semi-quantitative 60-item FFQ with approximately in 1980 An expanded 130-item FFQ was administered to women in 1984, 1986 and every 4 years thereafter. HPFS: The expanded 130-item FFQ was administered to men in 1986 and every 4 years thereafter.	Quintiles of median L/Z intake: Q1: 1349ug/d for women; 1431ug/d for men Q2: 2052ug/d for women; 2236ug/d for men Q3: 2653ug/d for women; 2953ug/d for men Q4: 3389ug/d for women; 3835ug/d for men Q5: 4930ug/d for women; 5712ug/d for men NHS: The adjusted multivariate RRs for increasing quintiles of median L/Z intake to early AMD were: Q1: RR=referent Q2: RR= 0.84; 95%CI 0.62-1.12 Q3: RR= 0.93; 95%CI 0.69-1.23 Q4: RR= 0.87; 95%CI 0.65-1.17 Q5: RR= 0.89; 95%CI 0.66-1.20 P for trend = 0.62 NHS: The adjusted multivariate RRs for increasing quintiles of median L/Z intake to neovascular AMD were: Q1: RR=referent Q2: RR= 0.89; 95%CI 0.62-1.29 Q3: RR= 0.85; 95%CI 0.58-1.24 Q4: RR= 1.05; 95%CI 0.73-1.52 Q5: RR= 0.79; 95%CI 0.53-1.17 P for trend = 0.42 HPFS: The adjusted multivariate RRs for increasing quintiles of median L/Z intake to early AMD were: Q1: RR=referent Q2: RR= 1.64; 95%CI 1.04-2.57 Q3: RR= 1.38; 95%CI 0.86-2.20 Q4: RR= 0.97; 95%CI 0.58-1.61 Q5: RR= 1.66; 95%CI 1.04-2.64 P for trend = 0.26	Lutein/zeaxanthin intake was not associated with the risk of self-reported early AMD. This association did not vary by smoking status, intakes of vitamins C and E, or body mass index. There was a statistically non-significant and nonlinear inverse association between L/Z intake and neovascular AMD risk. For neovascular AMD, a nonlinear inverse association was found among never smokers. There was no statistically significant difference in the effect of L/Z on the different types of AMD.

						HPFS: The adjusted multivariate RRs for increasing quintiles of median L/Z intake to neovascular AMD were: Q1: RR=referent Q2: RR= 0.67; 95%CI 0.41-1.09 Q3: RR= 0.83; 95%CI 0.51-1.32 Q4: RR= 0.85; 95%CI 0.53-1.36 Q5: RR= 0.62; 95%CI 0.37-1.05 P for trend = 0.19 The pooled adjusted multivariate RRs for increasing quintiles of median L/Z intake to early AMD were: Q1: RR=referent Q2: RR= 1.14; 95%CI 0.59-2.21 Q3: RR= 1.08; 95%CI 0.74-1.57 Q4: RR= 0.90; 95%CI 0.69-1.15 Q5: RR= 1.18; 95%CI 0.64-2.17 P for trend = 0.74 The pooled adjusted multivariate RRs for increasing quintiles of median L/Z intake to neovascular AMD were: Q1: RR=referent Q2: RR= 0.80; 95%CI 0.60-1.08 Q3: RR= 0.84; 95%CI 0.62-1.13 Q4: RR= 0.97; 95%CI 0.73-1.30 Q5: RR= 0.72; 95%CI 0.53-0.99 P for trend = 0.14	

Wu J et al 2015. Quality Rating: 11	Cohort (NHS & NPHS)	To investigate the associations between intakes of carotenoids and AMD.	Nurses' Health study (NHS): Mean age: 62.2 Mean BMI: 26.8kg/m² White: 98% Current Smoker: 11.4% Health Professionals Follow-up study (HPFS): Mean age: 63.2 Mean BMI: 26kg/m² White: 95.8% Current Smoker: 5% All subjects did not have prevalent AMD, cancer (except non-melanoma skin cancer), diabetes mellitus, or cardiovascular disease at baseline. No. in final sample =63443 females from the nurses' health study and n=38603 males from the health professionals follow-up study. Loss to follow up is not reported	Mean daily intake of lutein and zeaxanthin: Nurses' Health study (NHS): Quintile 1: 1657ug/d Quintile 2: 2259ug/d Quintile 3: 2732ug/d Quintile 4: 3338ug/d Quintile 5: 4779ug/d Health Professionals Follow-up study (HPFS): Quintile 1: 1848ug/d Quintile 2: 2563ug/d Quintile 3: 3091ug/d Quintile 4: 3832ug/d Quintile 5: 5468ug/d Follow up 26 years for NHS and 24 years for HPFS	The dietary LZ was assessed by repeated FFQ at baseline and follow-up every 4 years. The FFQs contained at least 15 questions for fruit and juice intake and 30 questions for vegetable intake with common used units or portion sizes were specified for each item.	NHS COHORT: Adjusted relative risks of AMD to calculated median intakes: Advanced AMD: Q1: 1408ug/d: Reference Q2: 2098ug/d: RR 0.84; 95% CI 0.67-1.04 Q3: 2680ug/d: RR 0.78; 95% CI 0.63-0.98 Q4: 3389ug/d: RR 0.72; 95% CI 0.57-0.91 Q5: 4834ug/d: RR 0.68; 95% CI 0.54-0.87 P for trend= 0.003 Intermediate AMD: Q1: 1408ug/d: Reference Q2: 2098ug/d: RR 0.82; 95% CI 0.67-1.00 Q3: 2680ug/d: RR 0.91; 95% CI 0.74-1.11 Q4: 3389ug/d: RR 0.93; 95% CI 0.76-1.14 Q5: 4834ug/d: RR 0.90; 95% CI 0.72-1.11 P for trend= 0.73 HPFS COHORT: Adjusted relative risks of AMD to calculated median intakes: Advanced AMD: Q1: 1511ug/d: Reference Q2: 2313ug/d: RR 1.05; 95% CI 0.75-1.47 Q3: 3012ug/d: RR 1.06; 95% CI 0.75-1.49 Q4: 3864ug/d: RR 1.06; 95% CI 0.75-1.50 Q5: 5629ug/d: RR 1.08; 95% CI 0.75-1.55 P for trend= 0.71 Intermediate AMD: Q1: 1511ug/d: Reference Q2: 2313ug/d: RR 1.27; 95% CI	Calculated intakes of LZ (P for trend = 0.003) was inversely related to advanced AMD in the NHS, whereas the association was insignificant for intermediate AMD. The associations between calculated LZ intake and advanced/ intermediate AMD were insignificant in HPFS

						0.92-1.76 Q3: 3012ug/d: RR 1.13; 95% CI 0.81-1.58 Q4: 3864ug/d: RR 1.06; 95% CI 0.75-1.50 Q5: 5629ug/d: RR 1.20; 95% CI 0.84-1.70 P for trend= 0.65 Pooled adjusted relative risks of advanced AMD to calculated intakes in NHS and HPFS: Q1: Reference Q2: RR 0.90; 95% CI 0.75-1.08 Q3: RR 0.86; 95% CI 0.71-1.03 Q4: RR 0.80; 95% CI 0.67-0.99 Q5: RR 0.79; 95% CI 0.64-0.97 P for trend= 0.04 P for heterogeneity=0.04 Pooled adjusted relative risks of intermediate AMD to calculated intakes in NHS and HPFS: Q1: Reference Q2: RR 0.92; 95% CI 0.78-1.10 Q3: RR 0.96; 95% CI 0.81-1.14 Q4: RR 0.96; 95% CI 0.80-1.14 Q5: RR 0.97; 95% CI 0.81-1.16 P for trend= 0.99 P for heterogeneity=0.17 * The quantity of LZ intake cannot be found for the pooled analysis	

Lin H et al 2017. Quality Rating: 11	Cohort (ARIC)	To examine the association between lutein and zeaxanthin (LZ) intake and prevalent early age-related macular degeneration (AMD) using data from the Atherosclerosis Risk in Communities Study	Age: 53.9±0.1 Sex: Men (45%); Women(55%) Race: African-American (20%); Caucasian (80%) Region: Forsyth County NC (27%); Jackson MS (17%); Minneapolis MN (29%); Washington County MD (27%) BMI: <25kg/m² (34%); ≥25 and <30kg/m² (40%); ≥30kg/m² (26%); 6 Missing data All subjects did not have advanced AMD at baseline No. in final sample = 10295 Proportion loss to follow up = 14%	Overall intake of energy adjusted daily LZ: Q1: 251-456ug/1000kcal Q2: 660-867ug/1000kcal Q3: 1082-1305ug/1000kcal Q4: 1592-2027ug/1000kcal Q5: 2910-4936 µg /1000kcal Follow up 6 years	LZ intake was assessed by the 66-item FFQ at visit 1 and 6 years prior to fundus photography at visit 3.	Q1: 251-456ug/1000kcal: Reference Q2: 660-867ug/1000kcal: Unadjusted OR 1.08; 95% CI 0.82-1.43 Adjusted OR 1.07; 95% CI 0.81-1.42 Q3: 1082-1305ug/1000kcal Unadjusted OR 1.07; 95% CI 0.81-1.42 Adjusted OR 1.07; 95% CI 0.80-1.42 Q4: 1592-2027ug/1000kcal Unadjusted OR 1.07; 95% CI 0.81-1.42 Adjusted OR 1.09; 95% CI 0.81-1.46 Q5: 2910-4936 ug/1000kcal Unadjusted OR 1.03; 95% CI 0.78-1.36 Adjusted OR 1.02; 95% CI 0.76-1.38 P=0.97 (unadjusted) P=0.91 (adjusted) Higher LZ intake was associated with decreased odds of AMD among participants with lower HDL (OR=0.79, 95%CI 0.57-1.09) but not higher HDL (P for interaction= 0.048)	L/Z intake was not associated with early AMD in both the unadjusted and adjusted results.

Association by genetic risk							
Ho L et al 2011. Quality Rating: 9	Cohort (Rotterdam)	To investigate whether dietary nutrients can reduce the genetic risk of early age-related macular degeneration (AMD) conferred by the genetic variants CFHY402H and LOC387715 A69S.	mean age: 67 Gender: female 56.6% BMI: 23.35kg/m² No. in final sample = 2167 No attrition Proportion loss to follow up = 0%	Mean intake of lutein/ zeaxanthin was 2.37±1.08 mg/d Mean intake for 1st Tertile CFHY402H noncarrier: 1.47±0.32 mg/d CFHY402H heterozygous: 1.46±0.34 mg/d CFHY402H homozygous: 1.50±0.25 mg/d LOC387715A69S noncarrier: 1.48±0.31 mg/d LOC387715A69S Carrier: 1.45±0.34 mg/d Mean intake for 3rd Tertile CFHY402H noncarrier: 3.38±1.17 mg/d CFHY402H heterozygous: 3.30±0.6 mg/d CFHY402H homozygous: 3.23±0.46 mg/d LOC387715A69S noncarrier: 3.29±0.71 mg/d LOC387715A69S Carrier: 3.39±1.19 mg/d Median follow up 8.6 years	Dietary intake was measure at baseline by a 170-item semi-quantitative FFQ during interview. The FFQ was validated by comparing the dietary checklist that subjects filled in prior to interview.	CFH Y402H noncarrier: T1: Reference; T2: HR 1.30 (95% CI 0.89-1.88); T3: HR 1.39 (95% CI 0.96-2.03); P=0.13 CFH Y402H heterozygous: T1: HR 1.54 (95% CI 1.07-2.21); T2: HR 1.63 (95% CI 1.13-2.34); T3: HR 1.33 (95% CI 0.92-1.93); P=0.37 CFH Y402H homozygous: T1: HR 2.63 (95% CI 1.60-4.32); T2: HR 2.15 (95% CI 1.38-3.42); T3: HR 1.72(95% CI 0.97-3.03); P=0.05	For L/Z intake, the risk reduction of early AMD was from 2.63 (lowest tertile) to 1.72 (highest tertile) on Homozygous CFH Y402H (P=0.05). Heterozygotes and noncarriers showed insignificant trends with higher intake. Significant synergy index supported the possibility of biological interaction between L/Z intake and CFHY402H, but no significant synergy index was observed between L/Z intake and LOC387715A69S. The study showed that higher dietary intake of L/Z can attenuate the incidence of early AMD in those carrying important genetic risk variants.

Wang JJ et al 2014. Quality Rating: 10	Cohort (BMES & Rotterdam)	To examine effect modification between genetic susceptibility to age-related macular degeneration (AMD) and dietary antioxidant or fish consumption on AMD risk	BMES: Mean age 65.7years; Male 38.6% RS: Mean age 66.6years; Male 40.6% No. in final sample =1833 in BMES and n=3550 in RS Proportion loss to follow up BMES = 25% Proportion loss to follow up Rotterdam = 0.8%	Baseline Dietary LZ intake: BMES: Population Mean: 912±490ug/d T1: mean 442ug/d (range 0-642) T2: mean 810ug/d (range 642-1005) T3: mean 1425ug/d (range 1005-4870) RS: Population Mean: 2365±1070ug/d T1: mean 1478ug/d (range 101-1918) T2: mean 2252ug/d (range 1919-2610) T3: mean 3362ug/d (range 2610-32645) Follow up 15 years	In BMES, Dietary lutein/zeaxanthin (LZ) was estimated using 145-item FFQ. In RS, baseline dietary information was collected using a checklist at home, following by a face-to-face interview using a 170-item semi-quantitative FFQ.	The adjusted ORs for the highest vs other 2 (middle and lowest) tertiles for LZ intake are: Pooled: Genetic Risk Group = 0 risk alleles from CFH or ARMS2: Early AMD: adjusted OR 1.47 95% CI 1.09-1.97 Late AMD: adjusted OR 0.65 95% CI 0.17-2.43 Any AMD: adjusted OR: 1.40 95% CI 1.05-1.87 Genetic Risk Group= 1 risk alleles from CFH or ARMS2: early AMD: adjusted OR 0.91; 95% CI 0.73-1.13 late AMD: adjusted OR 1.06; 95% CI 0.63-1.79 any AMD: adjusted OR 0.92; 95% CI 0.75-1.13 Genetic Risk Group= 2 risk alleles from CFH or ARMS2: early AMD: adjusted OR 0.78; 95% CI 0.62-0.99 late AMD: adjusted OR 0.64; 95% CI 0.40-1.03 any AMD: adjusted OR 0.75; 95% CI 0.60-0.93 RS: Genetic Risk Group= 0 risk alleles from CFH or ARMS2: early AMD: adjusted OR 1.74; 95% CI 1.21-2.50 late AMD: adjusted OR 1.18; 95% CI 0.20-6.82 any AMD adjusted OR 1.69; 95% CI 1.18-2.41	Significant interaction between AMD genetic risk status and LZ intake with respect to risk of early or any AMD was observed in RS but not the BMES. In pooled data analyses of two study populations, a significant interaction was found between AMD genetic risk status and LZ intake with respect to risk of early (P=0.002) and any AMD (P=0.0009). Among participants with high genetic risk status, the highest intake of LZ was associated with a >20% reduced risk of early AMD. By using data from 2 population-based cohorts, we showed consistent evidence that participants with 2 risk alleles of either or both the CFH-rs1061170 or ARMS2-rs10490924 had a significantly reduced risk of early or any AMD if they frequently consumed food items rich in LZ. The effect modification of LZ on participants with high AMD genetic risk suggests the possibility that susceptibility to activation and amplification of the complement pathways can be compensated for by these antioxidants. In conclusion, we showed that dietary intake of LZ is

						Genetic Risk Group= 1 risk alleles from CFH or ARMS2: early AMD: adjusted OR 0.94; 95% CI 0.71-1.24 late AMD: adjusted OR 0.90; 95% CI 0.47-1.73 any AMD: adjusted OR 0.94; 95% CI 0.72-1.22 Genetic Risk Group= 2 risk alleles from CFH or ARMS2: early AMD: adjusted OR 0.78; 95% CI 0.59-1.05 late AMD: adjusted OR 0.70; 95% CI 0.38-1.29 any AMD: adjusted OR 0.77; 95% CI 0.59-1.01 BMES: Genetic Risk Group= 0 risk alleles from CFH or ARMS2: early AMD: adjusted OR 0.99; 95% CI 0.60-1.65 late AMD: adjusted OR 0.30; 95% CI 0.03-2.64 any AMD adjusted OR 0.93; 95% CI 0.57-1.53 Genetic Risk Group= 1 risk alleles from CFH or ARMS2: early AMD: adjusted OR 0.85; 95% CI 0.60-1.21 late AMD: adjusted OR 1.34; 95% CI 0.*55-3.23* *any AMD: adjusted OR 0.90; 95% CI 0.64-1.27* Genetic Risk Group= 2 risk alleles from CFH or ARMS2: early AMD: adjusted OR 0.76; 95% CI 0.51-1.13 late AMD: adjusted OR 0.58; 95% CI 0.28-1.20 any AMD: adjusted OR 0.72; 95% CI 0.50-1.04	associated with an approximate 20% reduction in risk of developing early AMD among persons with a high genetic risk of AMD.

4. Assessment of study quality

S6-2 (e) An assessment of the quality of each included study based on consideration of, as a minimum: (i) a clearly stated hypothesis; (ii) minimisation of bias; (iii) adequate control for confounding; (iv) the study participants' background diets and other relevant lifestyle factors; (v) study duration and follow-up adequate to demonstrate the health effect; (vi) the statistical power to test the hypothesis.

4.1 Quality Appraisal of Individual Studies

The Health Canada 2009 quality appraisal tool was used to assess the quality of included studies (www.hc-sc.gc.ca/fn-an/legislation/guide-ld/health-claims_guidance-orientation_allegations-sante-eng.php (accessed). Individual study score sheets are included in Appendix A. A summary of the scores for each study are provided in tables 6 and 7 below.

Table 6: Summary of individual study quality based on the Health Canada quality appraisal tool for intervention studies

Study Reference	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Total Score (max of 15)	Quality Rating
Randomised Controlled Trials										
Huang et al 2015	1	3	2	2	2	1	2	1	14	Higher
Bovier & Hammond 2015	0	1	2	2	2	1	2	0	10	Higher
Sabour-Pickett et al 2014	1	1	1	2	2	1	0	1	9	Higher
AREDS2 Research Group 2014	1	1	2	2	2	1	2	1	12	Higher
AREDS2 Research Group 2013	1	1	2	2	2	1	2	1	12	Higher
Richer et al 2011	1	4	2	2	2	1	2	1	15	Higher
Weigert et al 2011	1	1	2	2	2	1	1	1	11	Higher
Ma et al 2009	1	2	2	2	2	1	2	1	13	Higher
Yao et al 2013	1	1	2	0	2	1	1	1	9	Higher

*Note item numbers refer to the following: 1. Inclusion/exclusion criteria; 2. Group allocation; 3. Blinding; 4. Attrition; 5. Exposure/intervention; 6. Health effect; 7. Statistical analysis; 8. Potential confounders

Table 7: Summary of individual study quality based on the Health Canada quality appraisal tool for prospective observational studies

Study Reference	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Total Score (max of 12)	Quality Rating
Prospective Cohort Studies										
Flood et al 2002	1	2	1	2	0	0	1	2	9	Higher
Van Leeuwen et al 2005	1	2	2	1	1	0	1	2	11	Higher
Cho et al 2008	1	2	2	2	0	1	1	2	11	Higher
Tan et al 2008	1	2	1	2	0	0	1	2	9	Higher
Ho et al 2011	1	2	2	1	0	0	1	2	9	Higher
Wang et al 2014	1	2	2	2	0	0	1	2	10	Higher
Wu et al 2015	1	2	2	2	0	1	1	2	11	Higher
Lin et al 2017	1	2	2	1	1	1	1	2	11	Higher

*Note item numbers refer to the following: 1. Inclusion/exclusion criteria; 2. Attrition; 3. Exposure; 4. Health outcome; 5. Blinding; 6. Baseline comparability of groups; 7. Statistical analysis; 8. Potential confounders

According to the Health Canada quality appraisal tools, all studies rated as higher quality studies. In RCTs results ranged from 8-15 (out of a possible 15 points). The main reasons for loss of points related to lack of reporting randomisation method and/or lack of allocation concealment (randomised controlled trials). In cohort studies results ranged from 8-11 (out of a possible 12 points). The main reason for loss of points related to a lack of reporting as to whether the outcome assessors were blinded to the exposure status of the individuals. While not reported, it is likely that in most of the studies the assessors were blinded. Some studies also lost a point due to the exposure only being assessed once during the study.

The individual checklist for each included study can be found in Appendix A.

4.1.1 Clearly stated hypothesis

All studies had clearly stated objectives which were related to the relationship between lutein and/or zeaxanthin intake and a measure of vision.

4.1.2 Minimisation of bias

As part of the exclusion criteria, case-control and cross-sectional studies were eliminated due to their higher risk of recall and selection bias compared to cohort and randomised controlled trials.

Selection bias was low to moderate in most studies with the majority of studies reporting good compliance and follow up. Eight of the cohorts included in the studies had loss to follow up rates of ≤10% and a further 7 had rates of 10-20%. Only 2 of the included studies[23,36] did not report details on loss to follow up.

Tan 2008 had a moderate rate of loss to follow up but researchers reported that these moderate losses were unlikely to effect the findings related to L/Z [38].

4.1.3 Adequate control of confounding

Observational (cohort) studies

All cohort studies included in this systematic review were ranked as higher quality and all studies controlled for some confounders during the assessment of the relationship between L/Z and AMD. Smoking is known to be the strongest modifiable risk factor for advanced AMD[39] and all studies measured this confounder and accounted for it at the data analysis stage.

It is noted that not all studies measured or accounted for all possible confounders. For example, while all studies adjusted for energy intake, only Wu et al 2015 considered the effect of a 'healthy eating index' to take into account the possibility that an individual with higher L/Z intakes may generally have a healthier diet which could account for some of the relationship in the study.

As with all observational studies, the possibility of residual confounding can not be ruled out.

The confounders accounted for in each individual study is listed in the footer to the quality appraisal table in appendix A.

Intervention studies were randomised controlled trials and smoking status was equally distributed between intervention and control groups.

4.1.4 Study participants' background diets and other relevant lifestyle factors

In the RCTs subjects were generally instructed to avoid consumption of food sources high in L/Z throughout the study and to keep to their habitual diet throughout the study period[25].

It is noted that in some studies a high background dietary intake of L/Z may have reduced the likelihood of finding an association between L/Z supplement and risk of AMD. For example in the AREDS2 RCT[34], a beneficial effect of taking the L/Z supplement (10mg L/2mg Z) was only found in individuals with the lowest quintile of dietary intake of L/Z (109-1388µg per day). In this group, comparison to no L/Z resulted in a HR of 0.74 (95% CI, 0.59-0.94; p=0.01) for progression to advanced AMD. For participants in the highest quintile of L/Z the corresponding HR was 0.90 (95% CI, 0.71-1.15; p=0.41. The background L/Z dietary intake levels in this study were much higher than intake levels reported to date and suggest adequate L/Z intake from diet may offer sufficient protection without a need for supplements. Intake levels in quintile 5 in the AREDS2 RCT were 4740-34 398 µg (4.7-34.4mg) per day[34].

Other relevant lifestyle factors such as smoking was taken into account in the observational studies as discussed in confounding.

4.1.5 Study duration and follow-up adequate to demonstrate the health effect

Cohort studies included in this review ranged in study duration from 2 years to 26 years of follow up. The shorter cohort studies (up to 7 years) were only long enough to report on the incidence/development of early AMD, whereas the longer cohort studies (10 years to 26 years) were more likely to report on intermediate and/or advanced AMD – the forms of AMD associated with more severe vision loss.

RCT studies ranged in study duration from 12 weeks to 5 years. These timeframes are likely adequate to demonstrate changes in contrast sensitivity, however longer study durations may have been required to adequately demonstrate L/Z supplementation effects on measures of visual acuity. When commenting on the non-significant increase in visual acuity observed in their study, Ma et al 2009 commented that the results might be due to delayed effect of lutein on visual acuity in a short time period (12 weeks)[24]. Similarly, in Yao et al 2013, while L/Z supplementation significantly impacted serum concentrations at 30 days, observed increases in MPOD and contrast sensitivity were not evident until 6 months of supplementation, suggesting slow uptake of L/Z by the retina[23]. As discussed in sections 5 and 6 of this report, the effects on vision are likely dependent on the increase in MPOD which is related to not only the timeframe of the study but the baseline MPOD levels of the participants. It may also take longer to show effects on measures of vision in general population compared to studies in patients with AMD.

4.1.6 The statistical power to test the hypothesis

Not all studies reported on the statistical power to test the hypothesis.

5. Assessment of the body of evidence and conclusion

S6-2 (f) An assessment of the results of the studies as a group by considering whether:
(i) there is a consistent association between the food or property of food and the health effect across all high quality studies;
(ii) there is a causal association between the consumption of the food or property of food and the health effect that is independent of other factors (with most weight given to well-designed experimental studies in humans);
(iii) the proposed relationship between the food or property of food and the health effect is biologically plausible;

5.1 Consistency of association

Assessment of the consistency of the body of evidence was conducted using the Health Canada rating of consistency tool (https://www.canada.ca/en/health-canada/services/food-nutrition/legislation-guidelines/guidance-documents/forms-guidance-document-preparing-submission-food-health-claims.html (accessed 13.06.18). Results of this assessment can be found in tables 8-12.

Table 8: Rating of consistency in direction of effect for early age-related macular degeneration (AMD)

<table>
<tr><td colspan="6">HEALTH OUTCOME 1 EARLY AMD - Total Population</td></tr>
<tr><td colspan="6">A. Total Number of Studies Considered: 6
(Lin, 2017, Cho, 2008 (3 cohorts), Flood 2002, van Leeuwen 2005)</td></tr>
<tr><td colspan="6">Direction of Effect</td></tr>
<tr><td colspan="2">B1. # studies from A showing trend for risk reduction ($p < 0.05$)[1]: 0</td><td colspan="2">B2. # studies from A showing a trend for increase in risk ($p < 0.05$): 0</td><td colspan="2">B3. # studies from A showing no effect ($p > 0.05$): 6</td></tr>
<tr><td colspan="6">Study Quality</td></tr>
<tr><td>C1. # higher quality studies from B1: 0</td><td>C2. # lower quality studies from B1: 0</td><td>C3. # higher quality studies from B2: 0</td><td>C4. # lower quality studies from B2: 0</td><td>C5. # higher quality studies from B3: 6</td><td>C6. # lower quality studies from B3: 0</td></tr>
<tr><td colspan="2">Consistency Rating on Direction of Favourable Effect (Risk Reduction)</td><td colspan="2">Consistency Rating on Direction of Unfavourable Effect</td><td colspan="2">Consistency Rating on No Effect</td></tr>
<tr><td>B1 x 100% = 0%
A</td><td>High (≥ 75%) ☐
Moderate (60-74%) ☐
Low (< 60%) X</td><td>B2 x 100% = 0%
A</td><td>High (≥ 75%) ☐
Moderate (60-74%) ☐
Low (< 60%) X</td><td>B3 x 100% = 100%
A</td><td>High (≥ 75%) X
Moderate (60-74%) ☐
Low (< 60%) ☐</td></tr>
<tr><td colspan="6">Consistency Rating on Direction of Favourable Effect in Higher Quality Studies</td></tr>
<tr><td colspan="3">C1 / (C1 + C3 + C5) x 100% = 0%</td><td colspan="3">High (≥ 75%) ☐
Moderate (60-74%) ☐
Low (< 60%) X</td></tr>
</table>

The 6 observational studies included in this rating of consistency did not show a statistically significant association between L/Z intake and early AMD incidence.

Genetic Susceptibility:

This consistency of association does not include results from the two studies which considered how genetic susceptibility may act as an effect modifier of the relationship between L/Z intake and early AMD development[35,40]. Carriers of the high risk alleles for the genes CFH and LOC387715/HTRA1 have a significantly higher risk of AMD. The CFH Y402H variant increases the risk of AMD up to 11 times and the LOC387715 A69S variant up to 15 times.

Ho et al 2011 found heterozygous and non-carriers of the CFH Y402H allele showed non-significant trends with higher L/Z intake (P trend =0.37 and 0.13, respectively. Homozygous carriers of the CFH Y402H allele showed statistically significant trend with higher L/Z (P trend – 0.05). Authors concluded that L/Z can attenuate the incidence of early AMD in those carrying important genetic risk variants[35].

Wang et al, 2014 used pooled longitudinal data from the BMES and the Rotterdam cohorts and assessed the effect modification between AMD genetic susceptibility and dietary intake of antioxidants including L/Z[40]. In pooled data analyses, a significant interaction between AMD genetic risk status and LZ intake with respect early AMD (P=0.002). Risk alleles of the CFH and ARMS2 genes were included in this study. Authors concluded that by using data from 2 population-based cohorts, they showed consistent evidence that participants with ≥ 2 risk alleles of either or both the CFH-rs1061170 or AMRS2-rs10490924 had a significantly reduced risk of early AMD if they frequently consumed food items rich in L/Z[40]. In the pooled analysis, they found a 22% risk reduction in early AMD in participants with high genetic risk.

Table 9: Rating of consistency in direction of effect for intermediate and late age-related macular degeneration (AMD)

<table>
<tr><td colspan="6">HEALTH OUTCOME: Intermediate and Advanced AMD</td></tr>
<tr><td colspan="6">A. Total Number of Studies Considered: 12 studies (from 3 papers) (Wu, 2015; Cho 2018; Tan 2008)</td></tr>
<tr><td colspan="6">Direction of Effect</td></tr>
<tr><td colspan="2">B1. # studies from A showing trend for risk reduction ($p < 0.05$)[1]: 3</td><td colspan="2">B2. # studies from A showing a trend for increase in risk ($p < 0.05$): 0</td><td colspan="2">B3. # studies from A showing no effect ($p > 0.05$): 9</td></tr>
<tr><td colspan="6">Study Quality</td></tr>
<tr><td>C1. # higher quality studies from B1: 3</td><td>C2. # lower quality studies from B1: 0</td><td>C3. # higher quality studies from B2: 0</td><td>C4. # lower quality studies from B2: 0</td><td>C5. # higher quality studies from B3: 9</td><td>C6. # lower quality studies from B3: 0</td></tr>
<tr><td colspan="2">Consistency Rating on Direction of Favourable Effect (Risk Reduction)</td><td colspan="2">Consistency Rating on Direction of Unfavourable Effect</td><td colspan="2">Consistency Rating on No Effect</td></tr>
<tr><td>B1 x 100% = 25
A</td><td>High (≥ 75%) ☐
Moderate (60-74%) ☐
Low (< 60%) X</td><td>B2 x 100% = 0
A</td><td>High (≥ 75%)
Moderate (60-74%)
Low (< 60%) X</td><td>B3 x 100% = 75
A</td><td>High (≥ 75% X
Moderate (60-74%) ☐
Low (< 60%) ☐</td></tr>
<tr><td colspan="6">Consistency Rating on Direction of Favourable Effect in Higher Quality Studies</td></tr>
<tr><td colspan="3">C1 / (C1 + C3 + C5) x 100% = 25%</td><td colspan="3">High (≥ 75%) ☐
Moderate (60-74%) ☐
Low (< 60%) X</td></tr>
</table>

Overall, observational studies do not consistently show a statistically significant association between L/Z intake and intermediate or late AMD incidence. Although when statistically significant trends for risk reduction of AMD with higher L/Z intakes were found they were for advanced AMD.

Genetic Susceptibility:

As with the early AMD evidence, the consistency of association for L/Z intake and the development of intermediate or late AMD did not include results from studies looking at the relationship by genetic susceptibility. Wang 2014 found the highest tertile intakes of LZ were non-significantly associated with an approximately 35% risk reduction in late AMD while there was a significant reduced risk of any AMD[40].

Table 10: Rating of consistency in direction of effect for intervention studies for late age-related macular degeneration (AMD)

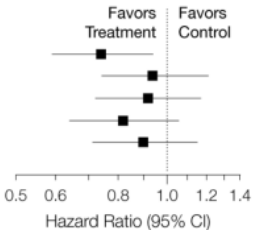
<table>
<tr><td colspan="8">HEALTH OUTCOME: Late AMD</td></tr>
<tr><td colspan="8">A. Total number RCTs included: 4</td></tr>
<tr><td colspan="8">Statistical Significance (SS)</td></tr>
<tr><td colspan="4">B1. # studies with a SS effect of exposure (p<0.05): 2</td><td colspan="4">B2. # studies with a non-SS effect of exposure (p>0.05): 2</td></tr>
<tr><td colspan="8">Direction of Effect[1]</td></tr>
<tr><td colspan="2">C1. # studies from B1 with a SS favourable effect of the exposure: 2</td><td colspan="2">C2. # studies from B1 with a SS unfavourable effect of the exposure: 0</td><td colspan="2">C3. # studies from B2 with a non-SS favourable effect of the exposure: 2</td><td colspan="2">C4. # studies from B2 showing either a non-SS unfavourable effect or no distinguishable effect of the exposure: 0</td></tr>
<tr><td colspan="8">Study Quality</td></tr>
<tr><td>D1. # higher quality studies from C1: 2</td><td>D2. # lower quality studies from C1: 0</td><td>D3. # higher quality studies from C2: 0</td><td>D4. # lower quality studies from C2: 0</td><td>D5. # higher quality studies from C3: 2</td><td>D6. # lower quality studies from C3: 0</td><td>D7. # higher quality studies from C4: 0</td><td>D8. # lower quality studies from C4: 0</td></tr>
<tr><td colspan="8">Consistency Rating on Direction of Favourable Effect</td></tr>
<tr><td colspan="4">(C1 + C3) / A1 x 100 % = 100%</td><td colspan="4">High (≥ 75%) X
Moderate (60-74%) ☐
Low (< 60%) ☐</td></tr>
<tr><td colspan="8">Consistency Rating on Direction of Favourable Effect in Higher Quality Studies</td></tr>
<tr><td colspan="4">(D1 + D5) / (D1 + D3 + D5 + D7) x 100% = 100%</td><td colspan="4">High (≥ 75%) X
Moderate (60-74%) ☐
Low (< 60%) ☐</td></tr>
</table>

Results from intervention studies were highly consistent in showing a statistically significant favourable effect of LZ on development of late AMD. Evidence here is from the AREDS2 RCT[33,34]. In the primary analysis, compared with the placebo group (who still had a median L/Z background dietary intake level of 2725µg/day) L/Z supplementation (additional 12mg/day) demonstrated no statistically significant reduction in progression to advanced AMD (HR: 0.90 (98.7% CI 0.76-1.07) p=0.12)[34]. It was noted, however, that AREDS2 participants had a significantly higher background dietary intake and average serum levels of L/Z compared to the general population (p<0.001) [33]. In subgroup analysis a statistically

significant favourable effect was found in those with the lowest intake of dietary L/Z (<1428µg/day). For persons in this first quintile, comparison of L/Z supplement vs no L/Z supplement resulted in an HR of 0.74 (95% CI, 0.59-0.94, p=0.01)[34]. Figure 3 shows the main effects stratified by quintiles of dietary intake of L/Z.

Figure 3: Comparison of the Main Effects of Lutein + Zeaxanthin vs No Lutein + Zeaxanthin, Stratified by Quintiles of Dietary Intake of Lutein + Zeaxanthin, on Progression to Advanced Age-Related Macular Degeneration (AMD)[34]

Lutein + Zeathanxin Dietary Intake, µg			Treatment		Control			
Quintile	Median[a]	Interquartile Range	Eyes	Advanced AMD Events	Eyes	Advanced AMD Events	Hazard Ratio (95% CI)	*P* Value
1	696	552-823	525	143	530	186	0.74 (0.59-0.94)	.01
2	1134	1030-1244	514	141	544	154	0.94 (0.74-1.21)	.65
3	1585	1465-1719	538	144	558	157	0.92 (0.72-1.17)	.49
4	2225	2036-2452	547	136	548	153	0.82 (0.64-1.06)	.72
5	3919	3201-5249	554	152	556	167	0.90 (0.71-1.15)	.41



[a]Median intake of dietary lutein + zeaxanthin (µg/1000 kcal per day).

It has been suggested that this subgroup result is consistent with the hypothesis that supplements may be more effective when the background dietary intake is below a biologically sufficient threshold[36].

Table 11: Rating of consistency in direction of effect of LZ on visual acuity

HEALTH OUTCOME: VISUAL ACUITY							
A. Total number studies included: 6 (Huang, Richer; Yao; Weigert; Ma, AREDS 2014)							
Statistical Significance (SS)							
B1. # studies with a SS effect of exposure (p<0.05): 1				**B2.** # studies with a non-SS effect of exposure (p>0.05): 5			
Direction of Effect[1]							
C1. # studies from B1 with a SS favourable effect of the exposure: 1		**C2.** # studies from B1 with a SS unfavourable effect of the exposure: 0		**C3.** # studies from B2 with a non-SS favourable effect of the exposure: 4		**C4.** # studies from B2 showing either a non-SS unfavourable effect or no distinguishable effect of the exposure: 1	
Study Quality							
D1. # higher quality studies from C1: 1	**D2.** # lower quality studies from C1: 0	**D3.** # higher quality studies from C2: 0	**D4.** # lower quality studies from C2: 0	**D5.** # higher quality studies from C3: 4	**D6.** # lower quality studies from C3: 0	**D7.** # higher quality studies from C4: 1	**D8.** # lower quality studies from C4: 0
Consistency Rating on Direction of Favourable Effect							
(C1 + C3) / A1 x 100 % = 83%				High (≥ 75%) X Moderate (60-74%) ☐ Low (< 60%) ☐			
Consistency Rating on Direction of Favourable Effect in Higher Quality Studies							
(D1 + D5) / (D1 + D3 + D5 + D7) x 100% = 83%				High (≥ 75%) X Moderate (60-74%) ☐ Low (< 60%) ☐			

While only 1 of the 6 included studies measuring visual acuity demonstrated a statistically significant favourable effect of L/Z, the other 5 showed non-favourable effects. As discussed in the quality section of this systematic review, the lack of statistically significant effects may be due to inadequate length of the studies.

Furthermore evidence from Weigert et al 2011 found that there was a significant correlation between the percentage of change in MPOD after 6 months and the change in visual acuity after 6 months ($p=0.013$)[30]. This indicates that patients with a pronounced increase in MPOD also improved their visual function. Patients who had baseline MPODS of 0.5 or higher showed almost no increase in MPOD during lutein supplementation, indicating that lutein incorporation in the retina is saturable. This is supported by results from Huang et al 2015 which showed the MPOD and visual functions (visual acuity and contrast sensitivity) were similar between the 10mg lutein and the 20mg lutein groups at 2 years. This indicates that the incorporation of L/Z into the retinal tissue is not driven simply by diffusion but is influenced by unique transport proteins in serum and in human retina[22]. While higher doses of L/Z can rapidly increase serum and macular concentrations, lower doses can reach and maintain an efficient macular pigment level in the long term[22].

Table 12: Rating of consistency in direction of effect of LZ on visual acuity

<table>
<tr><td colspan="8">HEALTH OUTCOME: CONTRAST SENSITIVITY</td></tr>
<tr><td colspan="8">A. Total number studies included: 5 (Huang, Richer; Sabour-Pickett; Ma; Yao)</td></tr>
<tr><td colspan="8">Statistical Significance (SS)</td></tr>
<tr><td colspan="4">B1. # studies with a SS effect of exposure (p<0.05): 4</td><td colspan="4">B2. # studies with a non-SS effect of exposure (p>0.05): 1</td></tr>
<tr><td colspan="8">Direction of Effect[1]</td></tr>
<tr><td colspan="2">C1. # studies from B1 with a SS favourable effect of the exposure: 4</td><td colspan="2">C2. # studies from B1 with a SS unfavourable effect of the exposure: 0</td><td colspan="2">C3. # studies from B2 with a non-SS favourable effect of the exposure: 1</td><td colspan="2">C4. # studies from B2 showing either a non-SS unfavourable effect or no distinguishable effect of the exposure: 0</td></tr>
<tr><td colspan="8">Study Quality</td></tr>
<tr><td>D1. # higher quality studies from C1: 4</td><td>D2. # lower quality studies from C1: 0</td><td>D3. # higher quality studies from C2: 0</td><td>D4. # lower quality studies from C2: 0</td><td>D5. # higher quality studies from C3: 1</td><td>D6. # lower quality studies from C3: 0</td><td>D7. # higher quality studies from C4: 0</td><td>D8. # lower quality studies from C4: 0</td></tr>
<tr><td colspan="8">Consistency Rating on Direction of Favourable Effect</td></tr>
<tr><td colspan="4">(C1 + C3) / A1 x 100 % = 100%</td><td colspan="4">High (≥ 75%) X
Moderate (60-74%) ☐
Low (< 60%) ☐</td></tr>
<tr><td colspan="8">Consistency Rating on Direction of Favourable Effect in Higher Quality Studies</td></tr>
<tr><td colspan="4">(D1 + D5) / (D1 + D3 + D5 + D7) x 100% = 100%</td><td colspan="4">High (≥ 75%) X
Moderate (60-74%) ☐
Low (< 60%) ☐</td></tr>
</table>

Demonstrating health effects of L/Z intake on measures of contrast sensitivity and visual acuity appear to be dependent on changes in MPOD. Results from Huang et al 2015 showed that contrast sensitivity

could only improve after MPOD had reached and maintained a relatively high level. This is supported by other studies linking changes in MPOD to visual performance[41,42].

Overall, observational studies inconsistently suggest a possible association between LZ and AMD. The inconsistent nature of these findings may be due to residual confounding, or the reliability of dietary data collected in some studies. For example measurement error including the use of incomplete food composition data may have underestimated L/Z intakes which could have biased the findings towards the null (no effect)[43]. Furthermore, as stated by Wu et al 2015, the observational evidence precludes the level of cause inference that could be derived from randomised controlled trials[36].

Intervention studies consistently suggest favourable effects of higher intakes of L/Z on progression to late AMD (although not always statistically significant) as well as measures of vision including visual acuity and contrast sensitivity (statistically significant).

5.2 Causal association

Tables 13 includes a summary of the findings from the studies assessing early age-related macular degeneration (AMD).

Table 13: Summary of study findings from observational studies on early AMD

Reference and Quality Score	Design •Prospective cohort •Nested case-control	Study Population and Final Sample Size	Centile	Exposure (Dietary Intake/ Circulating Levels)	Incidence of Health Outcome	Multi-variate Adjusted Risk Ratios Between Different Centiles			
						Hazards Ratio	Relative Risk	95% CI	P_{trend}
HEALTH OUTCOME – Early AMD									
Lin et al 2017 (total score 11)	Exploratory analysis of a prospective cohort	Men and women Mean age: 54 years Final sample: 8821	1st Quintile of L/Z intake	251-456ug/1000 kcal	NR	N/A	1.00	N/A	0.91
			2nd Quintile of L/Z intake	660-867ug/1000 kcal	NR	N/A	1.07	0.81-1.42	
			3rd Quintile of L/Z intake	1082-1305ug/1000kcal	NR	N/A	1.07	0.80-1.42	
			4th Quintile of L/Z intake	1592-2027ug/1000kcal	NR	N/A	1.09	0.81-1.46	
			5th Quintile of L/Z intake	2910-4936 ug/1000kcal	NR	N/A	1.02	0.76-1.38	

Cho et al 2008 (total score 11)	Prospective cohort – Nurses Health Study	Women Mean age: 59 years Final sample: 71494	1st Quintile of L/Z intake (median	1349ug/d for women;	NR	N/A	1.00	N/A	0.62
			2nd Quintile of L/Z intake (median)	2052ug/d for women;	NR	N/A	0.84	0.62-1.12	
			3rd Quintile of L/Z intake (median)	2653ug/d for women;	NR	N/A	0.93	0.69-1.23	
			4th Quintile of L/Z intake (median)	3389ug/d for women;	NR	N/A	0.87	0.65-1.17	
			5th Quintile of L/Z intake (median)	4930ug/d for women;	NR	N/A	0.89	0.66-1.20	
Cho et al 2008 (total score 11)	Prospective cohort HPFS	Men Mean age: 62 years Final sample: 41564	1st Quintile of L/Z intake (median	1431ug/d for men;	NR	N/A	1.00	N/A	0.26
			2nd Quintile of L/Z intake (median)	2236ug/d for men	NR	N/A	1.64	1.04-2.57	
			3rd Quintile of L/Z intake (median)	2953ug/d for men;	NR	N/A	1.38	0.86-2.20	
			4th Quintile of L/Z intake (median)	3835ug/d for men	NR	N/A	0.97	0.58-1.61	
			5th Quintile of L/Z intake (median)	5712ug/d for men	NR	N/A	1.66	1.04-2.64	

Cho et al 2008 (total score 11)	Prospective cohort Pooled (NHS + HPHS)	NHS + HPFS Cohorts pooled Final sample: 113058	1st Quintile of L/Z intake (median	1349ug/d for women; 1431ug/d for men;	NR	N/A	1.00	N/A	0.74
			2nd Quintile of L/Z intake (median)	2052ug/d for women; 2236ug/d for men	NR	N/A	1.14	0.59-2.21	
			3rd Quintile of L/Z intake (median)	2653ug/d for women; 2953ug/d for men;	NR	N/A	1.08	0.74-1.57	
			4th Quintile of L/Z intake (median)	3389ug/d for women; 3835ug/d for men	NR	N/A	0.90	0.691.15	
			5th Quintile of L/Z intake (median)	4930ug/d for women; 5712ug/d for men	NR	N/A	1.18	0.64-2.17	
Flood et al 2002 (total score 9)	Prospective cohort	BMES cohort Final sample size at 5 years: 2335	1st Quintile of L/Z intake	288ug (151/1000kcal)	NR	N/A	OR 1.0	NA	0.93
			2nd Quintile of L/Z intake	510ug (259/1000kcal)660-867ug/1000 kcal	NR	N/A	OR 0.9	0.5-1.5	
			3rd Quintile of L/Z intake	733ug (351/1000kcal)	NR	N/A	OR 0.8	0.5-1.4	
			4th Quintile of L/Z intake	967ug (478/1000kcal)	NR	N/A	OR 0.7	0.4-1.3	
			5th Quintile of L/Z intake	1466ug (719/1000kcal)	NR	N/A	OR 1.0	0.6-1.6	

Van Leeuwen et al 2005 (total score 11)	Prospective cohort	Rotterdam cohort Men and women: 55 years or older Final sample size: 4170	Q1	1.4±0.3mg/d (range≤1.8)	NR	1.0	NA	NA	0.65
			Q2	2.0±0.1mg/d (range>1.8-≤2.2)	NR	<1.0			
			Q3	2.5±0.2mg/d (range>2.2-≤2.8)	NR	>1.0			
			Q4	3.6±1.3mg/d (range>2.8)	NR	1.0			
Genetic Risk Studies									
Wang et al 2014 (total score 10)	BMES Cohort	Genetic Risk group =0 Risk Alleles CFH or ARMS2	Highest Tertile vs other 2 tertiles	BMES: T1: mean 442ug/d (range 0-642) T2: mean 810ug/d (range 642-1005) T3: mean 1425ug/d (range 1005-4870)	18.9%	N/A	OR 0.99 Early AMD	0.60-1.65	NR
		Genetic Risk group =1 Risk Alleles CFH or ARMS2			42.9%	N/A	OR 0.85 Early AMD	0.60-1.21	
		Genetic Risk group =2 Risk Alleles CFH or ARMS2			38.2%	N/A	OR 0.76 Early AMD	0.51-1.13	
Wang et al 2014 (total score 10)	Rotterdam Cohort	Genetic Risk group =0 Risk Alleles CFH or ARMS2	Highest Tertile vs other 2 tertiles	RS: T1: mean 1478ug/d (range 101-1918) T2: mean 2252ug/d (range 1919-2610) T3: mean 3362ug/d (range 2610-32645)	20.8%	N/A	OR 1.74 Early AMD	1.21-2.50	NR
		Genetic Risk group =1 Risk Alleles CFH or ARMS2			38%	N/A	OR 0.94 Early AMD	0.71-1.24	
		Genetic Risk group =2 Risk Alleles CFH or ARMS2			41.2%	N/A	OR 0.78 Early AMD	0.59-1.05	

Wang et al 2014 (total score 10)	Pooled (BMES + Rotterdam)	Genetic Risk group =0 Risk Alleles CFH or ARMS2	Highest Tertile vs other 2 tertiles	RS: T1: mean 1478ug/d (range 101-1918) T2: mean 2252ug/d (range 1919-2610) T3: mean 3362ug/d (range 2610-32645)	NR	N/A	OR 1.47 Early AMD	1.09-1.97	P= 0.002
		Genetic Risk group =1 Risk Alleles CFH or ARMS2			NR	N/A	OR 0.91 Early AMD	0.73-1.13	
		Genetic Risk group =2 Risk Alleles CFH or ARMS2			NR	N/A	OR 0.78 Early AMD	0.62-0.99	
Ho et al 2011 (total score 9)	Prospective cohort	Overall Sample population n=2167 Non-carrier CFHY402H n=820	Tertile 1 L/Z Intake	0.08-1.90mg/d (mean 1.47mg/d)	50/269	1.0	N/A	N/A	0.13
			Tertile 2 L/Z Intake	1.91-2.61mg/d (mean 2.26mg/d)	63/290	1.3	N/A	0.89-1.88	
			Tertile 3 L/Z Intake	2.62-17.69mg/d (mean 3.38mg/d)	60/261	1.39	N/A	0.96-2.03	
Ho et al 2011 (total score 9)	Prospective cohort	Overall Sample population n=2167 CFHY402H heterozygous n=858	Tertile 1 L/Z Intake	0.08-1.90mg/d (mean 1.47mg/d)	69/284	1.54	N/A	1.07-2.21	0.37
			Tertile 2 L/Z Intake	1.91-2.61mg/d (mean 2.26mg/d)	71/272	1.63	N/A	1.13-2.34	
			Tertile 3 L/Z Intake	2.62-17.69mg/d (mean 3.38mg/d)	67/302	1.33	N/A	0.92-1.93	
Ho et al 2011 (total score 9)	Prospective cohort	Overall Sample population n: 2167 Homozygous CFHY402H n =213	Tertile 1 L/Z Intake	0.08-1.90mg/d (mean 1.47mg/d)	23/65	2.63	N/A	1.60-4.32	0.05
			Tertile 2 L/Z Intake	1.91-2.61mg/d (mean 2.26mg/d)	31/85	2.15	N/A	1.38-3.42	
			Tertile 3 L/Z Intake	2.62-17.69mg/d (mean 3.38mg/d)	16/63	1.72	N/A	0.97-3.03	

Table 14: Summary of study findings from observational studies on intermediate and advanced AMD

Reference and Quality Score	Design •Prospective cohort •Nested case-control	Study Population and Final Sample Size	Centile	Exposure (Dietary Intake/ Circulating Levels)	Incidence of Health Outcome	Multi-variate Adjusted Risk Ratios Between Different Centiles			
						Hazards Ratio	Relative Risk	95% CI	P_{trend}
HEALTH OUTCOME – Intermediate and Advanced AMD									
Wu et al 2015 (total score 11)	Prospective cohort	Nurses Health Study Sample size: 63 443	1st Quintile of L/Z intake (median)	1408µg/d	NR	N/A	1.0	N/A	0.003 Advanced AMD
			2nd Quintile of L/Z intake (median)	2098µg/d	NR	N/A	0.84	0.67-1.04	
			3rd Quintile of L/Z intake (median)	2680µg/d	NR	N/A	0.78	0.63-0.98	
			4th Quintile of L/Z intake (median)	3389µg/d	NR	N/A	0.72	0.57-0.91	
			5th Quintile of L/Z intake (median)	4834µg/d	NR	N/A	0.68	0.54-0.87	
Wu et al 2015 (total score 11)	Prospective cohort	Nurses Health Study Sample size: 63 443	1st Quintile of L/Z intake (median)	1408µg/d	NR	N/A	1.0	N/A	0.73 Intermediate AMD
			2nd Quintile of L/Z intake (median)	2098µg/d	NR	N/A	0.82	0.67-1.00	
			3rd Quintile of L/Z intake (median)	2680µg/d	NR	N/A	0.91	0.74-1.11	
			4th Quintile of L/Z intake (median)	3389µg/d	NR	N/A	0.93	0.76-1.14	
			5th Quintile of L/Z intake (median)	4834µg/d	NR	N/A	0.90	0.72-1.11	

Wu et al 2015 (total score 11)	Prospective cohort	Health Professional Follow Up Study Sample size: 68 603	1st Quintile of L/Z intake (median)	1511µg/d	NR	N/A	1.0	N/A	0.71 Advanced AMD
			2nd Quintile of L/Z intake (median)	2313µg/d	NR	N/A	1.05	0.75-1.47	
			3rd Quintile of L/Z intake (median)	3012µg/d	NR	N/A	1.06	0.75-1.49	
			4th Quintile of L/Z intake (median)	3864µg/d	NR	N/A	1.06	0.75-1.50	
			5th Quintile of L/Z intake (median)	5629µg/d	NR	N/A	1.08	0.75-1.55	
Wu et al 2015 (total score 11)	Prospective cohort	Health Professional Follow Up Study Sample size: 68 603	1st Quintile of L/Z intake (median)	1511µg/d	NR	N/A	1.0	N/A	0.65 Intermediate AMD
			2nd Quintile of L/Z intake (median)	2313µg/d	NR	N/A	1.27	0.92-1.76	
			3rd Quintile of L/Z intake (median)	3012µg/d	NR	N/A	1.13	0.81-1.58	
			4th Quintile of L/Z intake (median)	3864µg/d	NR	N/A	1.20	0.84-1.70	
			5th Quintile of L/Z intake (median)	5629µg/d	NR	N/A	1.08	0.75-1.55	

Wu et al 2015 (total score 11)	Prospective cohort	Pooled NHS + HPFS Sample size: 132046	1st Quintile of L/Z intake (median)	NR	NR	N/A	1.0	N/A	0.04 Advanced AMD
			2nd Quintile of L/Z intake (median)	NR	NR	N/A	0.90	0.75-1.08	
			3rd Quintile of L/Z intake (median)	NR	NR	N/A	0.86	0.71-1.03	
			4th Quintile of L/Z intake (median)	NR	NR	N/A	0.81	0.67-0.99	
			5th Quintile of L/Z intake (median)	NR	NR	N/A	0.79	0.64-0.97	
Wu et al 2015 (total score 11)	Prospective cohort	Pooled NHS + HPFS Sample size: 132046	1st Quintile of L/Z intake (median)	NR	NR	N/A	1.0	N/A	0.99 Intermediate AMD
			2nd Quintile of L/Z intake (median)	NR	NR	N/A	0.92	0.78-1.10	
			3rd Quintile of L/Z intake (median)	NR	NR	N/A	0.96	0.81-1.14	
			4th Quintile of L/Z intake (median)	NR	NR	N/A	0.96	0.80-1.14	
			5th Quintile of L/Z intake (median)	NR	NR	N/A	0.97	0.81-1.16	

Cho et al 2008 (total score 11)	Prospective cohort Nurses Health Study	Sample size: 71494	1st Quintile of L/Z intake (median)	1349µg/d Women 1431 µg/d men	NR	N/A	1.0	N/A	0.42 Neovascular AMD
			2nd Quintile of L/Z intake (median)	2052µg/d women 2236µg/d men	NR	N/A	0.89	0.62-1.29	
			3rd Quintile of L/Z intake (median)	2653µg/d Women 2953µg/d men	NR	N/A	0.85	0.58-1.24	
			4th Quintile of L/Z intake (median)	3389µg/d women 3835µg/d men	NR	N/A	1.05	0.73-1.52	
			5th Quintile of L/Z intake (median)	4930µg/d women 5712µg/d men	NR	N/A	0.79	0.53-1.17	
Cho et al 2008 (total score 11)	Prospective cohort Health Professionals Follow Up	Sample size: 41564	1st Quintile of L/Z intake (median)	1349µg/d Women 1431 µg/d men	NR	N/A	1.0	N/A	0.19 Neovascular AMD
			2nd Quintile of L/Z intake (median)	2052µg/d women 2236µg/d men	NR	N/A	0.67	0.41-1.09	
			3rd Quintile of L/Z intake (median)	2653µg/d Women 2953µg/d men	NR	N/A	0.83	0.51-1.32	
			4th Quintile of L/Z intake (median)	3389µg/d women 3835µg/d men	NR	N/A	0.85	0.53-1.36	
			5th Quintile of L/Z intake (median)	4930µg/d women 5712µg/d men	NR	N/A	0.62	0.37-1.05	

Cho et al 2008 (total score 11)	Prospective cohort Pooled Data (NHS and HPFS)	Sample size: 113058	1st Quintile of L/Z intake (median)	1349µg/d Women 1431 µg/d men	NR	N/A	1.0	N/A	0.14 Advanced AMD
			2nd Quintile of L/Z intake (median)	2052µg/d women 2236µg/d men	NR	N/A	0.80	0.60-1.08	
			3rd Quintile of L/Z intake (median)	2653µg/d Women 2953µg/d men	NR	N/A	0.84	0.62-1.13	
			4th Quintile of L/Z intake (median)	3389µg/d women 3835µg/d men	NR	N/A	0.97	0.73-1.30	
			5th Quintile of L/Z intake (median)	4930µg/d women 5712µg/d men	NR	N/A	0.72	0.53-0.99	
Tan et al 2008 (total score 9)	Prospective cohort BMES	Sample size: 2454	Tertile 1 L/Z Intake	NR	19/673	N/A	1.00	N/A	0.36 Advanced AMD (Total)
			Tertile 2 L/Z Intake	NR	23/682	N/A	1.11	0.58-2.13	
			Tertile 3 L/Z Intake	≥942 µg/d	17/680	N/A	0.72	0.34-1.50	
Tan et al 2008 (total score 9)	Prospective cohort BMES	Sample size: 2454	Tertile 1 L/Z Intake	NR	13/675	N/A	1.0	N/A	0.061 Neovascular AMD only
			Tertile 2 L/Z Intake	NR	16/684	N/A	1.12	0.52-2.41	
			Tertile 3 L/Z Intake	≥942 µg/d	9/681	N/A	0.37	0.13-1.05	

GENETIC RISK STUDY									
Wang et al 2014 (total score 10)	BMES Cohort	Genetic Risk group =0 Risk Alleles CFH or ARMS2	Highest Tertile vs other 2 tertiles	BMES: T1: mean 442ug/d (range 0-642) T2: mean 810ug/d (range 642-1005) T3: mean 1425ug/d (range 1005-4870)	9.3%	N/A	OR 0.30 Late AMD	0.03-2.64	NR
		Genetic Risk group =1 Risk Alleles CFH or ARMS2			36.1%	N/A	OR 1.34 Late AMD	0.55-3.23	
		Genetic Risk group =2 Risk Alleles CFH or ARMS2			54.7%	N/A	OR 0.58 Late AMD	0.28-1.20	
Wang et al 2014 (total score 10)	Rotterdam Cohort	Total =5383 Genetic Risk group =0 Risk Alleles CFH or ARMS2	Highest Tertile vs other 2 tertiles	RS: T1: mean 1478ug/d (range 101-1918) T2: mean 2252ug/d (range 1919-2610) T3: mean 3362ug/d (range 2610-32645)	5.2%	N/A	OR 1.18 Late AMD	0.20-6.82	NR
		Genetic Risk group =1 Risk Alleles CFH or ARMS2			37.4%	N/A	OR 0.90 Late AMD	0.47-1.73	
		Genetic Risk group =2 Risk Alleles CFH or ARMS2			57.4%	N/A	OR 0.70 Late AMD	0.38-1.29	
Wang et al 2014 (total score 10)	Pooled (BMES + Rotterdam)	Genetic Risk group =0 Risk Alleles CFH or ARMS2	Highest Tertile vs other 2 tertiles	RS: T1: mean 1478ug/d (range 101-1918) T2: mean 2252ug/d (range 1919-2610) T3: mean 3362ug/d (range 2610-32645)	NR	N/A	OR 0.65 Early AMD	0.17-2.43	NS Advanced AMD
		Genetic Risk group =1 Risk Alleles CFH or ARMS2			NR	N/A	OR 1.06 Early AMD	0.63-1.79	
		Genetic Risk group =2 Risk Alleles CFH or ARMS2			NR	N/A	OR 0.64 Early AMD	0.40-1.03	

Although the results from observational studies for an association between L/Z and advanced AMD are mixed, Wu et al 2015 concluded that higher intakes of bioavailable carotenoids are associated with a 40% lower risk of advanced AMD. In this study, unlike the others include in this review, researchers included an analysis using the predicted plasma scores (which takes into account the bioavailability of L/Z and not just the quantity). When predicted plasma scores were used in the analysis, this strengthened the association between L/Z and AMD. This study, in particular, which showed a linear relationship between LZ and advanced AMD lends further support to a temporal association between L/Z and protection against the development of advanced AMD and is suggestive of a causal role[36].

Table 15: Summary of study findings from randomised controlled trials on late/advanced AMD

Reference and Quality Score	Design	Sample Size	Outcome for which study was powered[1]	Study Duration	Food Matrix	Exposure (Food/Bioactive substance Intake Per Day)	Magnitude of Effect[2]		P-value[6]
							Number[3,4]	Percent[3,5]	
HEALTH OUTCOME – LATE/ADVANCED AMD									
Age-Related Eye Disease Study 2 Research Group et al 2014 (total score 12)	RCT	4203	NA	5 years	Supplements	10mg lutein and 2mg zeaxanthin	HR 0.87 (95% CI 0.77-0.95)		L/Z vs. no L/Z P=0.04
Age-Related Eye Disease Study 2 Research Group et al 2013 (total score 12)	RCT	4203	Statistical power of at least 90% was used to detect a 25%reduction in the progression to advanced AMD	5 years	Supplements	10mg lutein and 2mg zeaxanthin	HR 0.90 (98.7% CI 0.76-1.07)	NA	L/Z vs. placebo* P=0.12
Age-Related Eye Disease Study 2 Research Group et al 2013 (total score 12)	RCT	4203		5 years	Supplements + dietary intake	Supplement 10mg L + 2mg Z + dietary intake: Q1: median 696ug/d (Range 552-823)	HR 0.74 (95% CI 0.59-0.94)	NA	P=0.01

Reference and Quality Score	Design	Sample Size	Outcome for which study was powered[1]	Study Duration	Food Matrix	Exposure (Food/Bioactive substance Intake Per Day)	Magnitude of Effect[2]		P-value[6]
							Number[3,4]	Percent[3,5]	
Age-Related Eye Disease Study 2 Research Group et al 2013 (total score 12)	RCT	4203		5 years	Supplements + dietary intake	Supplement 10mg L + 2mg Z + dietary intake Q5: median 3919ug/d (Range 3201-5249	HR 0.90 (95%CI 0.71-1.15)		P=0.41

*Participants in the 'placebo' group were participants in the AREDs trial and therefore still received the AREDS supplement (either within or outside of the secondary randomisation) – there was therefore no true placebo group.

As discussed above, compared with the general population participants sampled in the National Health and Nutrition Survey (NHANES) 2005-2006 of similar ages, AREDS2 participants had a significantly higher serum levels of L/Z ($p<0.001$)[34]. Comparison of dietary intakes with other cohorts, suggested that AREDS2 participants are relatively well nourished[34]. In a report that evaluated the carotenoid intake of 18 cohorts, the median level of dietary intake of L/Z in the AREDS2 participants (~2600µg/day) was exceeded in only 2 of these 18 study cohorts (Nurses Health Study: 3012µg/day and Women's Health Study: 2869µg/day)[44]. The background dietary intake of L/Z in the AREDS2 population may have masked the effect of the L/Z intervention in the higher quintile groups.

For persons in the lowest quintile, comparison of L/Z vs no L/Z resulted in an HR of 0.74 (95% CI, 0.59-0.94; p=0.01) for progression to advanced AMD. Whereas among people with background diets in quintiles 2-5, there was no significant protective effect of L/Z vs no L/Z (HR range 0.82-0.94, $p>0.05$).

Table 16: Summary of study findings from randomised controlled trials on visual acuity

Summary of study findings from intervention studies per health outcome									
Reference and Quality Score	**Design**	**Sample Size**	**Outcome for which study was powered[1]**	**Study Duration**	**Food Matrix**	**Exposure (Food/Bio active substance Intake Per Day)**	**Magnitude of Effect[2]**		**P-value[6]**
							Number[3,4]	**Percent[3,5]**	
HEALTH OUTCOME: VISUAL ACUITY									
Age-Related Eye Disease Study 2 (AREDS2) Research Group et al 2014 (total score 12)	RCT	4203	NA	5 years	Supplement	10mg lutein and 2mg zeaxanthin	NA	NA	NS p>0.05
Richer et al 2011 (total score 15)	RCT	60	NA	1 year	Supplements	8mg zeaxanthin + 9mg lutein	+6.0 letters	NA	high-contrast visual acuity P=0.05 (from baseline)
Richer et al 2011 (total score 15)	RCT	60	NA	1 year	Supplements	8mg zeaxanthin + 9mg lutein	+8.8 letters	NA	low-contrast visual acuity P=0.02 (from baseline)
Weigert G et al 2011 (total score 11)	RCT	110	Statistical power of 80% was used to detect 4% difference	6 months	Supplements	in months 1-3: 20mg lutein in months 4-6 10mg lutein	+2.1±0.4letters	NA	Visual acuity P=0.07
Yao et al 2013 (total score 9)	RCT	120	NA	1 year	Supplements	20mg lutein	From 0.038±0.16 to 0.036±0.24 (-0.002)	Calculated =5.3%	Best corrected visual acuity P=0.3356

Table 17: Summary of study findings from randomised controlled trials on contrast sensitivity

Summary of study findings from intervention studies per health outcome									
Reference and Quality Score	**Design**	**Sample Size**	**Outcome for which study was powered[1]**	**Study Duration**	**Food Matrix**	**Exposure (Food/Bio active substance Intake Per Day)**	**Magnitude of Effect[2]**		**P-value[6]**
							Number[3,4]	**Percent[3,5]**	
HEALTH OUTCOME: CONTRAST SENSITIVITY									
Richer et al 2011 (total score 15)	RCT	60	NA	1 year	Supplements	8mg zeaxanthin + 9mg lutein	NA	+20%	contrast sensitivity function P>0.05
Ma et al 2009 (total score 13)	RCT	37	NA	12 weeks	Supplements	6mg lutein	Range depending on visual angle (+0.07 - +0.13)	Calculated =3.8% - 7.5%	Contrast sensitivity P<0.01 - P<0.05
Yao et al 2013 (total score 9)	RCT	120	NA	1 year	Supplements	20mg lutein	Range depending on visual angle (+0.19 – +0.34)	Calculated =8.2-19.3%	Mesophic and Photopic contrast sensitivity P<0.05
Sabour-Picket et al 2014 (total score 9)	RCT	67	Statistical power 79% was used	12 months	Supplements	20 mg lutein and 2 mg zeaxanthin	Range depending on visual angle (+18.8 letters - +27 letters)	Calculated =25.8%	contrast sensitivity P=0.021
Huang et al 2015 (total score 14)	RCT		80% power to distinguish 30% difference for MPOD change in treatment groups	2 years	Supplements	10mg lutein + 10mg zeaxanthin	Depending on visual angle (+0.14 - +0.21)	Calculated =11.2% - 39.6%	Contrast sensitivity P <0.05
Huang et al 2015 (total score 14)	RCT	108	AS above	2 years	Supplements	10mg lutein	At 3 cycles/degree: from 1.26±0.36 to 1.47±0.34 (+0.21)	Reported =16.1%	Contrast sensitivity P <0.05

[1] If the study did not indicate an outcome for which it was powered, state N/A.
[2] Use Appendix B as a guide and include the Excel spreadsheet used to derive these calculations in an Appendix.
[3] Reporting the magnitude of effect as a number and as a percentage may require computations by the petitioner. Use a system to differentiate the computed values *versus* those taken directly from the study – *e.g.*, italicize all computed values.
[4] For studies with a control/comparison group, report the effect as: (Mean end-of-treatment – Mean baseline)$_{\text{treatment group}}$ – (Mean end-of-treatment – Mean baseline) $_{\text{control group}}$. For studies with a control/comparison group that do not report baseline values, report the effect as: Mean end-of-treatment$_{\text{treatment group}}$ – Mean end-of-treatment $_{\text{control group}}$.
[5] For studies with a control/comparison group, report the effect as: [(Mean end-of-treatment – Mean baseline)/Mean baseline]*100%$_{\text{treatment group}}$ – [(Mean end-of-treatment – Mean baseline)/Mean baseline] *100%$_{\text{control group}}$. For studies with a control/comparison group that do not report baseline values, report the effect as: [(Mean end-of-treatment$_{\text{treatment group}}$ – Mean end-of-treatment $_{\text{control group}}$)/Mean end-of-treatment $_{\text{control group}}$]*100%.
[6] Report between-group p-values. If between-group p-values are not reported in the study, report within-group values and indicate that values apply to within-group analyses.

Overall, evidence from high quality observational cohort studies regarding intake of L/Z from diet and development of early, intermediate and late AMD is inconsistent. Some studies show favourable effects while others do not. This may be due to the nature of the studies, to residual confounding and/or the measurement and quantification of L/Z intake which likely biases findings towards the null (no effect). As noted, Wu et al 2015 took into account the bioavailability of L/Z in foods and found this strengthened the association between L/Z intake and advanced AMD. This is supported by other studies which show correlations between increased serum and/or ocular levels of these carotenoids and visual benefits that were excluded from this review because they did not quantify the level of L/Z intake in the diet[45,46].

Evidence from high quality intervention studies investigating the effect of L/Z supplementation on late AMD consistently demonstrate statistically significant favourable effects.

Evidence from high quality intervention studies investigating the effect of L/Z supplementation on visual performance consistently show statistically significant favourable effects of higher L/Z intake on contrast sensitivity. Evidence from high quality intervention studies investigating the effect of L/Z supplementation on visual performance consistently show favourable effects of higher L/Z intake on visual acuity in the direction of statistical significance. As discussed above, and further in the biological plausibility section, visual performance benefits have been linked to the increase in MPOD which accompanies L/Z dietary intake.

5.3 Biological Plausibility

The proposed food-health relationship between higher intakes of L/Z and the maintenance of vision is highly plausible from a biological perspective. As discussed in section 1.1, ocular concentrations of L/Z (referred to as macular pigment (MP[5])) have been shown to increase following increased intake of foods rich in these carotenoids[6,7,12] or ingestion of L/Z supplements[8-10]. Dietary intakes of L/Z have also been associated with MPOD levels. More than two dozen studies have been published demonstrating an increase in macular carotenoids following L/Z supplementation of 2–30 mg per day or a high carotenoid diet[4].

Importantly, some of the studies included in this review have indicated that MPOD levels need to have increased sufficiently before a benefit to vision will be evident. For example, results from Huang et al 2015 indicate that MPOD might be the foundation for the improvements in visual functions. Contrast sensitivity could only improve after MPOD had reached and maintained a relatively high level[22]. This hypothesis is supported by the positive correlation between changes in MPOD and improvements in

visual functions mentioned in other studies[41],[42] that did not meet the inclusion criteria for this systematic review. Furthermore, the findings from Weigert et al 2011 indicate that patients with a pronounced increase in MPOD (ie, those with low baseline levels) also improved their visual function[30].

Evidence, particularly from animal studies in rhesus monkeys, indicate that macular pigment (MP) provides photoprotection against damaging blue light[47]. As well as their blue light filtration properties, L/Z act as antioxidants in the retina of the eye[48]. There are three major hypotheses for the function of L and Z commonly proposed, i.e., the acuity, visibility, and protective hypotheses[49,50]. These hypotheses are all based on the two fundamental characteristics of the MP, i.e., their light filtration and antioxidant characteristics[48,51]. There is also accumulating evidence that lutein has anti-inflammatory properties[52].

Blue light filtering properties:

Blue wavelengths have been shown to be more dangerous than longer wavelengths of visible light since they are more energetic and seem to be more efficient at generating reactive oxygen species[4].
The filtration of blue light reduces chromatic aberration which can enhance visual acuity and sensitivity[53].

Antioxidant properties:

Lutein and zeaxanthin act as antioxidants in the eye. The retina has a high potential for generation reactive oxygen species (ROS)[51]. In particular, the outer retina, especially membranes of the outer segments of the photoreceptors, has high concentrations of polyunsaturated fatty acids that are susceptible to photo-oxidation[51]. Carotenoids are potent scavengers of free radicals (e.g., superoxide anion and hydroxyl radical) and are particularly efficient at neutralizing singlet oxygen[54].

Anti-inflammatory properties:

Evidence from in vitro and animal models indicates that lutein may protect the retina from ischemic/hypoxic damage. Li et al 2012 suggested that less production of pro-inflammatory factors from Muller cells indicate an anti-inflammatory role of lutein in retinal ischemic/hypoxic injury[52] and that lutein may contribute to preserved retinal function.

Overall, there is a growing and evidence-based consensus that MP is important for optimal visual performance because of its blue light-filtering properties and consequential attenuation of chromatic aberration, veiling luminance, and blue haze[55] as well as anti-oxidant[32] and possibly anti-inflammatory actions[52].

6. Applicability to Australia and New Zealand

S6-2 (f) An assessment of the results of the studies as a group considering whether:
(iv) the amount of the food or property of food to achieve the health effect can be consumed as part of a normal diet of the Australian and New Zealand populations.
S6-2 (g) A conclusion based on the results of the studies that includes:
(i) whether a causal relationship has been established between the food or property of food and the health effect based on the totality and weight of evidence; and
(ii) where there is a causal relationship between the food or property of food and the health effect:
(A) the amount of the food or property of food required to achieve the health effect
(B) whether the amount of the food or property of food to achieve the health effect is likely to be consumed in the diet of the Australian and New Zealand populations or by the target population group, where relevant.

The amount of L/Z suggested to be of benefit for visual benefits ranges from 6mg[56] but for vision maintenance and based on the results from some studies levels lower than this may offer come protection. In well conducted cohort studies, the highest percentile groupings of intake (~2.5-5mg/day), L/Z reduced the risk of early[35], and advanced AMD[36]. Results from AREDS2[34] also suggests that intake levels of approximately 2000µg/day may be high enough to offer some protection given the results showed the bottom 20% of dietary intake of L/Z (<1428µg/day) benefitted from the supplement whereas those with higher dietary intakes (approximately ≥2060µg/day) did not see a statistically significant benefit from the 12mg LZ supplement.

Data on current intake levels of L/Z in the Australian and New Zealand population is limited. The average intake of older Australian adults participating in the Blue Mountains Eye study was 900µg per day, with women reporting slightly higher intakes than men[57]. These numbers suggest the majority of Australians would benefit from increasing L/Z intakes. However the authors of this paper did acknowledge the incomplete food composition data they were using which may have underestimated carotenoid intakes[57]. Average intake levels of L/Z from food up to 4800µg per day have been reported by US women, 45 years and over[58]. In this study the lowest quintile of intake was 1200µg and the highest quintile of intake was 11 700µg suggesting that higher intake levels are achievable.

Furthermore, recent dietary modelling by Eisenhauer et al, 2017 demonstrated that L/Z intakes of >5mg and >10mg were achievable by consuming a carefully selected variety of commonly consumed foods containing L/Z[59].

Overall, while results from observational cohort studies to date have been inconsistent, the evidence from high quality intervention studies on late AMD and visual performance including contrast sensitivity and visual acuity consistently show favourable effects of L/Z on these health effects suggesting a causal effect. Furthermore, the relationship between L/Z and maintenance of vision has high biological plausibility and levels of intake are possible in the current Australian and New Zealand food environment.

In conclusion, this systematic review supports the food-health relationship that increasing dietary intake of lutein and zeaxanthin helps maintain vision (by both protecting from and slowing progression of eye disease) in adults. It is unlikely that further evidence in this area would alter these conclusions.

Appendix A Health Canada Quality Appraisal Checklists for Individual Studies

Intervention Studies

Reference: Huang et al 2015

Item	Question	Score	
		YES (1)	NO /NR(0)
1. Inclusion/exclusion criteria	Were the inclusion and exclusion criteria for study participation reported? (eg. Age greater than 50 years, no history of heart disease)?	1	
2. Group allocation[1]	Was the study described as randomized?	1	
	Was the randomization method reported?	1	
	Was the randomization appropriate?[2]	1	
	Was the allocation concealed?[3]		0
3. Blinding	Were the study subjects blinded to the intervention received?	1	
	Were the researcher personnel blinded to the intervention received by the subjects?	1	
4. Attrition	Were attrition numerically reported?	1	
	Were the reasons for withdrawals and dropouts provided?[4]	1	
5. Exposure/intervention	Was the type of food described (eg. Composition, matrix)?	1	
	Was the amount of food described (i.e. dose)?	1	
6. Health effect	Was the methodology used to measure the health effect reported?	1	
7. Statistical analysis	Was between group statistical analysis of the health effect reported?	1	
	Was an intention-to-treat analysis conducted?[5]	1	
8. Potential confounders	Were potential confounders of the food health relationship considered?[6]	1	
TOTAL SCORE (maximum of 15)		14	
Higher quality	(score 8-15)	Higher	
Lower quality	(score 0-7)		

*Notes:; NR=Not reported [1]Studies without an appropriate control group would be excluded at Step of applying inclusion and exclusion criteria

[2] Examples of appropriate randomization include the use of computer-generated random number table, while date of birth and alternate allocation are examples of inappropriate methods of randomization.

[3] Allocation concealment is not the same as blinding. Allocation concealment refers to the method used to implement the random allocation sequence, e.g. numbered envelopes containing assignment. It protects the assignment sequence before and until allocation. Blinding protects the sequence after subjects have been allocated.

[4] If the study reported no attrition (i.e. no subjects were lost to follow up, withdrew or were excluded) then reasons for withdrawal/dropouts is a "non-applicable" factor. In such circumstances, check 'YES' so as to not unfairly lose a point.

[5] If there was no subject attrition, a per-protocol analysis is appropriate and an intention-to-treat analysis not applicable. In such a case, check 'YES' so as to not unfairly lose a point.[6] Confounding could have occurred during subject selection, study conduct or data analysis. If randomization is successful and between groups differences that may have occurred during study conduct are considered during statistical analysis, then confounders were considered.

Reference: Bovier & Hammond, 2015

Item	Question	Score	
		YES (1)	NO /NR(0)
1. Inclusion/exclusion criteria	Were the inclusion and exclusion criteria for study participation reported? (eg. Age greater than 50 years, no history of heart disease)?		0
2. Group allocation[1]	Was the study described as randomized?	1	
	Was the randomization method reported?		0
	Was the randomization appropriate?[2]		0
	Was the allocation concealed?[3]		0
3. Blinding	Were the study subjects blinded to the intervention received?	1	
	Were the researcher personnel blinded to the intervention received by the subjects?	1	
4. Attrition	Were attrition numerically reported?	1	
	Were the reasons for withdrawals and dropouts provided?[4]	1	
5. Exposure/intervention	Was the type of food described (eg. Composition, matrix)?	1	
	Was the amount of food described (i.e. dose)?	1	
6. Health effect	Was the methodology used to measure the health effect reported?	1	
7. Statistical analysis	Was between group statistical analysis of the health effect reported?	1	
	Was an intention-to-treat analysis conducted?[5]	1	
8. Potential confounders	Were potential confounders of the food health relationship considered?[6]		0
TOTAL SCORE (maximum of 15)		10	
Higher quality	(score 8-15)	Higher	
Lower quality	(score 0-7)		

Reference: Sabour-Pickett, 2014

Item	Question	Score	
		YES (1)	NO /NR(0)
1. Inclusion/exclusion criteria	Were the inclusion and exclusion criteria for study participation reported? (eg. Age greater than 50 years, no history of heart disease)?	1	
2. Group allocation[1]	Was the study described as randomized?	1	
	Was the randomization method reported?		0
	Was the randomization appropriate?[2]		0
	Was the allocation concealed?[3]		0

3. Blinding	Were the study subjects blinded to the intervention received?	1	
	Were the researcher personnel blinded to the intervention received by the subjects?		0
4. Attrition	Were attrition numerically reported?	1	
	Were the reasons for withdrawals and dropouts provided?[4]	1	
5. Exposure/intervention	Was the type of food described (eg. Composition, matrix)?	1	
	Was the amount of food described (i.e. dose)?	1	
6. Health effect	Was the methodology used to measure the health effect reported?	1	
7. Statistical analysis	Was between group statistical analysis of the health effect reported?		0
	Was an intention-to-treat analysis conducted?[5]		0
8. Potential confounders	Were potential confounders of the food health relationship considered?[6]	1	
TOTAL SCORE (maximum of 15)		9	
Higher quality	(score 8-15)	Higher	
Lower quality	(score 0-7)		

Reference: AREDS2 (Chew), 2014

Item	**Question**	**Score**	
		YES (1)	NO /NR(0)
1. Inclusion/exclusion criteria	Were the inclusion and exclusion criteria for study participation reported? (eg. Age greater than 50 years, no history of heart disease)?	1	
2. Group allocation[1]	Was the study described as randomized?	1	
	Was the randomization method reported?		0
	Was the randomization appropriate?[2]		0
	Was the allocation concealed?[3]		0
3. Blinding	Were the study subjects blinded to the intervention received?	1	
	Were the researcher personnel blinded to the intervention received by the subjects?	1	
4. Attrition	Were attrition numerically reported?	1	
	Were the reasons for withdrawals and dropouts provided?[4]	1	
5. Exposure/intervention	Was the type of food described (eg. Composition, matrix)?	1	
	Was the amount of food described (i.e. dose)?	1	

6. Health effect	Was the methodology used to measure the health effect reported?	1	
7. Statistical analysis	Was between group statistical analysis of the health effect reported?	1	
	Was an intention-to-treat analysis conducted?[5]	1	
8. Potential confounders	Were potential confounders of the food health relationship considered?[6]	1	
TOTAL SCORE (maximum of 15)		12	
Higher quality	(score 8-15)	Higher	
Lower quality	(score 0-7)		

Reference: AREDS2, 2013

Item	**Question**	**Score**	
		YES (1)	NO /NR(0)
1. Inclusion/exclusion criteria	Were the inclusion and exclusion criteria for study participation reported? (eg. Age greater than 50 years, no history of heart disease)?	1	
2. Group allocation[1]	Was the study described as randomized?	1	
	Was the randomization method reported?		0
	Was the randomization appropriate?[2]		0
	Was the allocation concealed?[3]		0
3. Blinding	Were the study subjects blinded to the intervention received?	1	
	Were the researcher personnel blinded to the intervention received by the subjects?	1	
4. Attrition	Were attrition numerically reported?	1	
	Were the reasons for withdrawals and dropouts provided?[4]	1	
5. Exposure/intervention	Was the type of food described (eg. Composition, matrix)?	1	
	Was the amount of food described (i.e. dose)?	1	
6. Health effect	Was the methodology used to measure the health effect reported?	1	
7. Statistical analysis	Was between group statistical analysis of the health effect reported?	1	
	Was an intention-to-treat analysis conducted?[5]	1	
8. Potential confounders	Were potential confounders of the food health relationship considered?[6]	1	
TOTAL SCORE (maximum of 15)		12	
Higher quality	(score 8-15)	Higher	

Lower quality	(score 0-7)		

Reference: Richer, 2011

Item	**Question**	**Score**	
		YES (1)	NO /NR(0)
1. Inclusion/exclusion criteria	Were the inclusion and exclusion criteria for study participation reported? (eg. Age greater than 50 years, no history of heart disease)?	1	
2. Group allocation[1]	Was the study described as randomized?	1	
	Was the randomization method reported?	1	
	Was the randomization appropriate?[2]	1	
	Was the allocation concealed?[3]	1	
3. Blinding	Were the study subjects blinded to the intervention received?	1	
	Were the researcher personnel blinded to the intervention received by the subjects?	1	
4. Attrition	Were attrition numerically reported?	1	
	Were the reasons for withdrawals and dropouts provided?[4]	1	
5. Exposure/intervention	Was the type of food described (eg. Composition, matrix)?	1	
	Was the amount of food described (i.e. dose)?	1	
6. Health effect	Was the methodology used to measure the health effect reported?	1	
7. Statistical analysis	Was between group statistical analysis of the health effect reported?	1	
	Was an intention-to-treat analysis conducted?[5]	1	
8. Potential confounders	Were potential confounders of the food health relationship considered?[6]	1	
TOTAL SCORE (maximum of 15)		15	
Higher quality	(score 8-15)	Higher	
Lower quality	(score 0-7)		

Reference: Weigert et al, 2011

Item	Question	Score	
		YES (1)	NO /NR(0)
1. Inclusion/exclusion criteria	Were the inclusion and exclusion criteria for study participation reported? (eg. Age greater than 50 years, no history of heart disease)?	1	
2. Group allocation[1]	Was the study described as randomized?	1	
	Was the randomization method reported?		0
	Was the randomization appropriate?[2]		0
	Was the allocation concealed?[3]		0
3. Blinding	Were the study subjects blinded to the intervention received?	1	
	Were the researcher personnel blinded to the intervention received by the subjects?	1	
4. Attrition	Were attrition numerically reported?	1	
	Were the reasons for withdrawals and dropouts provided?[4]	1	
5. Exposure/intervention	Was the type of food described (eg. Composition, matrix)?	1	
	Was the amount of food described (i.e. dose)?	1	
6. Health effect	Was the methodology used to measure the health effect reported?	1	
7. Statistical analysis	Was between group statistical analysis of the health effect reported?	1	
	Was an intention-to-treat analysis conducted?[5]		0
8. Potential confounders	Were potential confounders of the food health relationship considered?[6]	1	
TOTAL SCORE (maximum of 15)		11	
Higher quality	(score 8-15)	Higher	
Lower quality	(score 0-7)		

Reference: Ma et al, 2009

Item	Question	Score	
		YES (1)	NO /NR(0)
1. Inclusion/exclusion criteria	Were the inclusion and exclusion criteria for study participation reported? (eg. Age greater than 50 years, no history of heart disease)?	1	
2. Group allocation[1]	Was the study described as randomized?	1	
	Was the randomization method reported?	1	
	Was the randomization appropriate?[2]		0
	Was the allocation concealed?[3]		0
3. Blinding	Were the study subjects blinded to the intervention received?	1	

	Were the researcher personnel blinded to the intervention received by the subjects?	1	
4. Attrition	Were attrition numerically reported?	1	
	Were the reasons for withdrawals and dropouts provided?[4]	1	
5. Exposure/intervention	Was the type of food described (eg. Composition, matrix)?	1	
	Was the amount of food described (i.e. dose)?	1	
6. Health effect	Was the methodology used to measure the health effect reported?	1	
7. Statistical analysis	Was between group statistical analysis of the health effect reported?	1	
	Was an intention-to-treat analysis conducted?[5]	1	
8. Potential confounders	Were potential confounders of the food health relationship considered?[6]	1	
TOTAL SCORE (maximum of 15)		13	
Higher quality	(score 8-15)	Higher	
Lower quality	(score 0-7)		

Reference: Yao et al, 2013

Item	**Question**	**Score**	
		YES (1)	NO /NR(0)
1. Inclusion/exclusion criteria	Were the inclusion and exclusion criteria for study participation reported? (eg. Age greater than 50 years, no history of heart disease)?	1	
2. Group allocation[1]	Was the study described as randomized?	1	
	Was the randomization method reported?		0
	Was the randomization appropriate?[2]		0
	Was the allocation concealed?[3]		0
3. Blinding	Were the study subjects blinded to the intervention received?	1	
	Were the researcher personnel blinded to the intervention received by the subjects?	1	
4. Attrition	Were attrition numerically reported?		0
	Were the reasons for withdrawals and dropouts provided?[4]		0
5. Exposure/intervention	Was the type of food described (eg. Composition, matrix)?	1	
	Was the amount of food described (i.e. dose)?	1	
6. Health effect	Was the methodology used to measure the health effect reported?	1	
7. Statistical analysis	Was between group statistical analysis of the health effect reported?	1	
	Was an intention-to-treat analysis conducted?[5]		0

8. Potential confounders	Were potential confounders of the food health relationship considered?[6]	1	
TOTAL SCORE (maximum of 15)		9	
Higher quality	(score 8-15)	Higher	
Lower quality	(score 0-7)		

Cohort Studies

Table 13b. Quality appraisal tool for prospective observational studies			
Assign a score of 1 for each "Yes", and a score of 0 for each "No/NR".			
Reference (Author, year): Flood, 2002			
Item	**Question**	**Score**	
		Yes	No/NR
1. Inclusion/ Exclusion Criteria	Were the inclusion and/or exclusion criteria for study participation reported (*e.g.*, age greater than 50 years, no history of heart disease)?	1	
2. Attrition	Was attrition numerically reported?	1	
	Were the reasons for withdrawals and dropouts provided?[1]	1	
3. Exposure	Was the methodology used to measure the exposure reported?	1	
	Was the exposure assessed more than once?		No
4. Health Outcome	Was the methodology used to measure the health outcome reported?	1	
	Was the health outcome verified (*e.g.*, through assessment of medical records, confirmation by a health professional)?	1	
5. Blinding	Were the outcome assessors blinded to the exposure status?		NR
6. Baseline Comparability of groups	Were the subjects in the different exposure levels compared at baseline?		No
7. Statistical Analysis	Was the statistical significance of the trend reported?	1	
8. Potential Confounders	Were key confounders related to subjects' demographics accounted for in the statistical analysis?[2,3]	1	
	Were key confounders related to other risk factors of the health outcome accounted for in the statistical analysis?[2,4]	1	
TOTAL SCORE (maximum of 12):		9	
Higher quality (Score ≥ 7)		X	
Lower quality (Score ≤ 6)		☐	

Abbreviation: NR, not reported

[1] If the study reported no attrition, (*i.e.*, no subjects were lost to follow-up, withdrew or were excluded) then reasons for withdrawals/dropouts is a "non-applicable" factor. In such a circumstance, please check "yes" so as to not unfairly lose a point.

[2] Confounders considered in this study: Age, gender, family hisotry of ARM, and smoking status.

[3] Confounders related to subjects' demographics accounted for in statistical analysis: age and gender.

[4] Confounders related to other risk factors of the health outcome accounted for in the statistical analysis were smoking and family history of age-related maculopathy.

Table 13b. Quality appraisal tool for prospective observational studies			
Assign a score of 1 for each "Yes", and a score of 0 for each "No/NR".			
Reference (Author, year): Van Leeuwen 2005			
Item	**Question**	**Score**	
		Yes	No/NR
1. Inclusion/ Exclusion Criteria	Were the inclusion and/or exclusion criteria for study participation reported (*e.g.*, age greater than 50 years, no history of heart disease)?	1	
2. Attrition	Was attrition numerically reported?	1	
	Were the reasons for withdrawals and dropouts provided?[1]	1	
3. Exposure	Was the methodology used to measure the exposure reported?	1	
	Was the exposure assessed more than once?	1	
4. Health Outcome	Was the methodology used to measure the health outcome reported?	1	
	Was the health outcome verified (*e.g.*, through assessment of medical records, confirmation by a health professional)?		NR
5. Blinding	Were the outcome assessors blinded to the exposure status?	1	
6. Baseline Comparability of groups	Were the subjects in the different exposure levels compared at baseline?		NR
7. Statistical Analysis	Was the statistical significance of the trend reported?	1	
8. Potential Confounders	Were key confounders related to subjects' demographics accounted for in the statistical analysis?[2,3]	1	
	Were key confounders related to other risk factors of the health outcome accounted for in the statistical analysis?[2,4]	1	
TOTAL SCORE (maximum of 12):		11	
Higher quality (Score ≥ 7)		X	
Lower quality (Score ≤ 6)		☐	

Abbreviation: NR, not reported
[1] If the study reported no attrition, (*i.e.*, no subjects were lost to follow-up, withdrew or were excluded) then reasons for withdrawals/dropouts is a "non-applicable" factor. In such a circumstance, please check "yes" so as to not unfairly lose a point.
[2] Confounders considered in this study: smoking status, number of pack-years, serum total cholesterol, blood pressure, carotid intimamedia thickness and atherosclertic plaques was collected at baseline.
[3] Confounders related to subjects' demographics accounted for in statistical analysis: age and gender.
[4] Confounders related to other risk factors of the health outcome accounted for in the statistical analysis were smoking, alcohol intake, body mass index (BMI), total cholesterol, atherosclerosis score.

Table 13b. Quality appraisal tool for prospective observational studies			
Assign a score of 1 for each "Yes", and a score of 0 for each "No/NR".			
Reference (Author, year): Cho 2008			
Item	**Question**	**Score**	
		Yes	No/NR
1. Inclusion/ Exclusion Criteria	Were the inclusion and/or exclusion criteria for study participation reported (*e.g.*, age greater than 50 years, no history of heart disease)?	1	
2. Attrition	Was attrition numerically reported?	1	
	Were the reasons for withdrawals and dropouts provided?[1]	1	
3. Exposure	Was the methodology used to measure the exposure reported?	1	
	Was the exposure assessed more than once?	1	
4. Health Outcome	Was the methodology used to measure the health outcome reported?	1	
	Was the health outcome verified (*e.g.*, through assessment of medical records, confirmation by a health professional)?	1	
5. Blinding	Were the outcome assessors blinded to the exposure status?		NR
6. Baseline Comparability of groups	Were the subjects in the different exposure levels compared at baseline?	1	
7. Statistical Analysis	Was the statistical significance of the trend reported?	1	
8. Potential Confounders	Were key confounders related to subjects' demographics accounted for in the statistical analysis?[2,3]	1	
	Were key confounders related to other risk factors of the health outcome accounted for in the statistical analysis?[2,4]	1	
TOTAL SCORE (maximum of 12):		11	
Higher quality (Score ≥ 7)		X	
Lower quality (Score ≤ 6)		☐	

Abbreviation: NR, not reported

[1] If the study reported no attrition, (*i.e.*, no subjects were lost to follow-up, withdrew or were excluded) then reasons for withdrawals/dropouts is a "non-applicable" factor. In such a circumstance, please check "yes" so as to not unfairly lose a point.

[2] Confounders considered in this study: age, lutein/zeaxanthin intake, smoking status, BMI, alcohol intake and fish intake.

[3] Confounders related to subjects' demographics accounted for in the statistical analysis were age.

[4] Confounders related to other risk factors of the health outcome accounted for in the statistical analysis were smoking, energy intake, alcohol intake, fish intake, BMI, postmenopausal hormone use in women.

Table 13b. Quality appraisal tool for prospective observational studies			
Assign a score of 1 for each "Yes", and a score of 0 for each "No/NR".			
Reference (Author, year): Tan 2008			
Item	**Question**	**Score**	
		Yes	No/NR
1. Inclusion/ Exclusion Criteria	Were the inclusion and/or exclusion criteria for study participation reported (*e.g.*, age greater than 50 years, no history of heart disease)?	1	
2. Attrition	Was attrition numerically reported?	1	
	Were the reasons for withdrawals and dropouts provided?[1]	1	
3. Exposure	Was the methodology used to measure the exposure reported?	1	
	Was the exposure assessed more than once?		No
4. Health Outcome	Was the methodology used to measure the health outcome reported?	1	
	Was the health outcome verified (*e.g.*, through assessment of medical records, confirmation by a health professional)?	1	
5. Blinding	Were the outcome assessors blinded to the exposure status?		NR
6. Baseline Comparability of groups	Were the subjects in the different exposure levels compared at baseline?		NR
7. Statistical Analysis	Was the statistical significance of the trend reported?	1	
8. Potential Confounders	Were key confounders related to subjects' demographics accounted for in the statistical analysis?[2,3]	1	
	Were key confounders related to other risk factors of the health outcome accounted for in the statistical analysis?[2,4]	1	
TOTAL SCORE (maximum of 12):		9	
Higher quality (Score ≥ 7)		X	
Lower quality (Score ≤ 6)		☐	

Abbreviation: NR, not reported

[1] If the study reported no attrition, (*i.e.*, no subjects were lost to follow-up, withdrew or were excluded) then reasons for withdrawals/dropouts is a "non-applicable" factor. In such a circumstance, please check "yes" so as to not unfairly lose a point.

[2] Confounders considered in this study: demographic information; family history; medications taken; self-reported diagnoses of diabetes, acute myocardial infarction, angina, or stroke; and smoking history, Fasting blood specimens were collected and diabetes was diagnosed either from medical history or fasting blood glucose; energy intake.

[3] Confounders related to subjects' demographics accounted for in the statistical analysis were age.

[4] Confounders related to other risk factors of the health outcome accounted for in the statistical analysis were smoking, family history of age-related macula degeneration, job prestige, white cell count.

Table 13b. Quality appraisal tool for prospective observational studies			
Assign a score of 1 for each "Yes", and a score of 0 for each "No/NR".			
Reference (Author, year): Ho, 2011			
Item	**Question**	**Score**	
		Yes	No/NR
1. Inclusion/ Exclusion Criteria	Were the inclusion and/or exclusion criteria for study participation reported (*e.g.*, age greater than 50 years, no history of heart disease)?	1	
2. Attrition	Was attrition numerically reported?	1	
	Were the reasons for withdrawals and dropouts provided?[1]	1	
3. Exposure	Was the methodology used to measure the exposure reported?	1	
	Was the exposure assessed more than once?	1	
4. Health Outcome	Was the methodology used to measure the health outcome reported?	1	
	Was the health outcome verified (*e.g.*, through assessment of medical records, confirmation by a health professional)?		NR
5. Blinding	Were the outcome assessors blinded to the exposure status?		NR
6. Baseline Comparability of groups	Were the subjects in the different exposure levels compared at baseline?		NR
7. Statistical Analysis	Was the statistical significance of the trend reported?	1	
8. Potential Confounders	Were key confounders related to subjects' demographics accounted for in the statistical analysis?[2,3]	1	
	Were key confounders related to other risk factors of the health outcome accounted for in the statistical analysis?[2,4]	1	
TOTAL SCORE (maximum of 12):		9	
Higher quality (Score ≥ 7)		X	
Lower quality (Score ≤ 6)		☐	

Abbreviation: NR, not reported

[1] If the study reported no attrition, (*i.e.*, no subjects were lost to follow-up, withdrew or were excluded) then reasons for withdrawals/dropouts is a "non-applicable" factor. In such a circumstance, please check "yes" so as to not unfairly lose a point.

[2] Confounders considered in this study: gender, BMI, smoking status, blood pressure, serum lipids, atherosclerosis composite score dietary intake (total energy, alcohol, milk, meat, fish, fruit and vegetable),age, diabetes mellitus, CFHY402H and LOC387715 A69S.

[3] Confounders related to subjects' demographics accounted for in the statistical analysis were age and gender.

[4] Confounders related to other risk factors of the health outcome accounted for in the statistical analysis were smoking and atherosclerosis.

Table 13b. Quality appraisal tool for prospective observational studies			
Assign a score of 1 for each "Yes", and a score of 0 for each "No/NR".			
Reference (Author, year): Wang, 2014			
Item	**Question**	**Score**	
		Yes	No/NR
1. Inclusion/ Exclusion Criteria	Were the inclusion and/or exclusion criteria for study participation reported (*e.g.*, age greater than 50 years, no history of heart disease)?	1	
2. Attrition	Was attrition numerically reported?	1	
	Were the reasons for withdrawals and dropouts provided?[1]	1	
3. Exposure	Was the methodology used to measure the exposure reported?	1	
	Was the exposure assessed more than once?	1	
4. Health Outcome	Was the methodology used to measure the health outcome reported?	1	
	Was the health outcome verified (*e.g.*, through assessment of medical records, confirmation by a health professional)?	1	
5. Blinding	Were the outcome assessors blinded to the exposure status?		NR
6. Baseline Comparability of groups	Were the subjects in the different exposure levels compared at baseline?		NR
7. Statistical Analysis	Was the statistical significance of the trend reported?	1	
8. Potential Confounders	Were key confounders related to subjects' demographics accounted for in the statistical analysis?[2,3]	1	
	Were key confounders related to other risk factors of the health outcome accounted for in the statistical analysis?[2,4]	1	
TOTAL SCORE (maximum of 12):		10	
Higher quality (Score ≥ 7)		X	
Lower quality (Score ≤ 6)		☐	

Abbreviation: NR, not reported

[1] If the study reported no attrition, (*i.e.*, no subjects were lost to follow-up, withdrew or were excluded) then reasons for withdrawals/dropouts is a "non-applicable" factor. In such a circumstance, please check "yes" so as to not unfairly lose a point.

[2] Confounders considered in this study: age, sex, smoking status and study sit, energy and main macronutrient intake of participants.

[3] Confounders related to subjects' demographics accounted for in the statistical analysis were age and gender.

[4] Confounders related to other risk factors of the health outcome accounted for in the statistical analysis were energy intake, smoking, study site.

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Table 13b. Quality appraisal tool for prospective observational studies			
Assign a score of 1 for each "Yes", and a score of 0 for each "No/NR".			
Reference (Author, year): Wu 2015			
Item	**Question**	**Score**	
		Yes	No/NR
1. Inclusion/ Exclusion Criteria	Were the inclusion and/or exclusion criteria for study participation reported (*e.g.*, age greater than 50 years, no history of heart disease)?	1	
2. Attrition	Was attrition numerically reported?	1	
	Were the reasons for withdrawals and dropouts provided?[1]	1	
3. Exposure	Was the methodology used to measure the exposure reported?	1	
	Was the exposure assessed more than once?	1	
4. Health Outcome	Was the methodology used to measure the health outcome reported?	1	
	Was the health outcome verified (*e.g.*, through assessment of medical records, confirmation by a health professional)?	1	
5. Blinding	Were the outcome assessors blinded to the exposure status?		NR
6. Baseline Comparability of groups	Were the subjects in the different exposure levels compared at baseline?	1	
7. Statistical Analysis	Was the statistical significance of the trend reported?	1	
8. Potential Confounders	Were key confounders related to subjects' demographics accounted for in the statistical analysis?[2,3]	1	
	Were key confounders related to other risk factors of the health outcome accounted for in the statistical analysis?[2,4]	1	
TOTAL SCORE (maximum of 12):		11	
Higher quality (Score ≥ 7)		X	
Lower quality (Score ≤ 6)		☐	

Abbreviation: NR, not reported

[1] If the study reported no attrition, (*i.e.*, no subjects were lost to follow-up, withdrew or were excluded) then reasons for withdrawals/dropouts is a "non-applicable" factor. In such a circumstance, please check "yes" so as to not unfairly lose a point.

[2] Confounders considered in this study: Age, BMI, smoking status, pack-years of smoking, physical activity, hypertension, current aspirin use, alcohol intake were measured. Suspected risk factors such as an alternative healthy eating index, an indicator of a healthy dietary pattern.

[3] Confounders related to subjects' demographics accounted for in the statistical analysis were age (in NHS cohort); age and ethnicity (in HPFS cohort).

[4] Confounders related to other risk factors of the health outcome accounted for in the statistical analysis were smoking, body mass index (BMI), smoking, physical activity, healthy eating index, alcohol intake, DHA and ALA intake, hypertension, diabetes mellitus, postmenopausal status, aspirin use.

Table 13b. Quality appraisal tool for prospective observational studies			
Assign a score of 1 for each "Yes", and a score of 0 for each "No/NR".			
Reference (Author, year): Lin 2017			
Item	**Question**	**Score**	
		Yes	No/NR
1. Inclusion/ Exclusion Criteria	Were the inclusion and/or exclusion criteria for study participation reported (*e.g.*, age greater than 50 years, no history of heart disease)?	1	
2. Attrition	Was attrition numerically reported?	1	
	Were the reasons for withdrawals and dropouts provided?[1]	1	
3. Exposure	Was the methodology used to measure the exposure reported?	1	
	Was the exposure assessed more than once?	1	
4. Health Outcome	Was the methodology used to measure the health outcome reported?	1	
	Was the health outcome verified (*e.g.*, through assessment of medical records, confirmation by a health professional)?		No
5. Blinding	Were the outcome assessors blinded to the exposure status?	1	
6. Baseline Comparability of groups	Were the subjects in the different exposure levels compared at baseline?	1	
7. Statistical Analysis	Was the statistical significance of the trend reported?	1	
8. Potential Confounders	Were key confounders related to subjects' demographics accounted for in the statistical analysis?[2,3]	1	
	Were key confounders related to other risk factors of the health outcome accounted for in the statistical analysis?[2,4]	1	
TOTAL SCORE (maximum of 12):		11	
Higher quality (Score ≥ 7)		X	
Lower quality (Score ≤ 6)		☐	

Abbreviation: NR, not reported

[1] If the study reported no attrition, (*i.e.*, no subjects were lost to follow-up, withdrew or were excluded) then reasons for withdrawals/dropouts is a "non-applicable" factor. In such a circumstance, please check "yes" so as to not unfairly lose a point.

[2] Confounders considered in this study Age, sex, race and pack-years of smoking were determined to be included in the multivariable model a priori. A factor was included as a confounder if it were associated with both LZ intake and prevalent AMD at $p<0.20$, and changed the OR 10% after adjustment.

[3] Confounders related to subjects' demographics accounted for in the statistical analysis were age, gender and ethnicity.

[4] Confounders related to other risk factors of the health outcome accounted for in the statistical analysis were smoking, field center, energy intake.

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1. Perry, A., Rasmussen, H. & Johnson, E. Xanthophyll (lutein, zeaxanthin) content in fruits, vegetables and corn and egg products. *Journal of Food Composition and Analysis* **22**, 9-15 (2009).
2. M. Abdel-Aal, E.-S., Akhtar, H., R. Chambers, J. & Zaheer, K. *Lutein and Zeaxanthin Carotenoids in Eggs*, (2017).
3. US Department of Agriculture, A.R.S., Nutrient Data Laboratory. . USDA National Nutrient Database for Standard Reference, Release 27. . (2014).
4. Bernstein, P.S., Delori, F.C., Richer, S., van Kuijk, F.J. & Wenzel, A.J. The value of measurement of macular carotenoid pigment optical densities and distributions in age-related macular degeneration and other retinal disorders. *Vision Res* **50**, 716-728 (2010).
5. Loskutova, E., Nolan, J., Howard, A. & Beatty, S. Macular pigment and its contribution to vision. *Nutrients* **5**, 1962-1969 (2013).
6. Hammond, B.R., Jr.*, et al.* Dietary modification of human macular pigment density. *Invest Ophthalmol Vis Sci* **38**, 1795-1801 (1997).
7. Wenzel, A.J.*, et al.* A 12-wk egg intervention increases serum zeaxanthin and macular pigment optical density in women. *J Nutr* **136**, 2568-2573 (2006).
8. Bone, R.A., Landrum, J.T., Guerra, L.H. & Ruiz, C.A. Lutein and zeaxanthin dietary supplements raise macular pigment density and serum concentrations of these carotenoids in humans. *J Nutr* **133**, 992-998 (2003).
9. Rosenthal, J.M.*, et al.* Dose-ranging study of lutein supplementation in persons aged 60 years or older. *Invest Ophthalmol Vis Sci* **47**, 5227-5233 (2006).
10. Landrum, J.T.*, et al.* A one year study of the macular pigment: the effect of 140 days of a lutein supplement. *Exp Eye Res* **65**, 57-62 (1997).
11. Handelman, G.J., Nightingale, Z.D., Lichtenstein, A.H., Schaefer, E.J. & Blumberg, J.B. Lutein and zeaxanthin concentrations in plasma after dietary supplementation with egg yolk. *Am J Clin Nutr* **70**, 247-251 (1999).
12. Johnson, E.J. The role of carotenoids in human health. *Nutr Clin Care* **5**, 56-65 (2002).
13. Rich, G.T., Faulks, R.M., Wickham, M.S. & Fillery-Travis, A. Solubilization of carotenoids from carrot juice and spinach in lipid phases: II. Modeling the duodenal environment. *Lipids* **38**, 947-956 (2003).
14. Rich, G.T.*, et al.* Solubilization of carotenoids from carrot juice and spinach in lipid phases: I. Modeling the gastric lumen. *Lipids* **38**, 933-945 (2003).
15. Hornero-Mendez, D. & MI., M.-M. Bioaccessibility of carotenes from carrots: Effect of cooking and addition of oil. *Innovative Food Science & Emerging Technologies* **8**, 407-412 (2007).
16. Goodrow, E.F.*, et al.* Consumption of One Egg Per Day Increases Serum Lutein and Zeaxanthin Concentrations in Older Adults without Altering Serum Lipid and Lipoprotein Cholesterol Concentrations. *J Nutr* **136**, 2519-2524 (2006).
17. Blesso, C.N., Andersen, C.J., Bolling, B.W. & Fernandez, M.L. Egg intake improves carotenoid status by increasing plasma HDL cholesterol in adults with metabolic syndrome. *Food Funct* **4**, 213-221 (2013).
18. DiMarco, D.M., Norris, G.H., Millar, C.L., Blesso, C.N. & Fernandez, M.L. Intake of up to 3 Eggs per Day Is Associated with Changes in HDL Function and Increased Plasma Antioxidants in Healthy, Young Adults. *J Nutr* **[Epud ahead of print]**(2017).
19. Kelly, E.R., Plat, J., Haenen, G.R., Kijlstra, A. & Berendschot, T.T. 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* **9**, e92659 (2014).

20. Kelly, D.*, et al.* Serum and macular response to carotenoid-enriched egg supplementation in human subjects: the Egg Xanthophyll Intervention clinical Trial (EXIT). *Br J Nutr* **117**, 108-123 (2017).
21. Chung, H.Y., Rasmussen, H.M. & Johnson, E.J. Lutein bioavailability is higher from lutein-enriched eggs than from supplements and spinach in men. *J Nutr* **134**, 1887-1893 (2004).
22. Huang, Y.M.*, et al.* Effect of supplemental lutein and zeaxanthin on serum, macular pigmentation, and visual performance in patients with early age-related macular degeneration. *Biomed Res Int* **2015**, 564738 (2015).
23. Yao, Y.*, et al.* Lutein supplementation improves visual performance in Chinese drivers: 1-year randomized, double-blind, placebo-controlled study. *Nutrition* **29**, 958-964 (2013).
24. Ma, L.*, et al.* A 12-week lutein supplementation improves visual function in Chinese people with long-term computer display light exposure. *Br J Nutr* **102**, 186-190 (2009).
25. Bovier, E.R. & Hammond, B.R. A randomized placebo-controlled study on the effects of lutein and zeaxanthin on visual processing speed in young healthy subjects. *Arch Biochem Biophys* **572**, 54-57 (2015).
26. NIH. (2018).
27. Klein, R.*, et al.* The Wisconsin age-related maculopathy grading system. *Ophthalmology* **98**, 1128-1134 (1991).
28. Bird, A.C.*, et al.* An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. *Surv Ophthalmol* **39**, 367-374 (1995).
29. Davis, M.D.*, et al.* The Age-Related Eye Disease Study severity scale for age-related macular degeneration: AREDS Report No. 17. *Arch Ophthalmol* **123**, 1484-1498 (2005).
30. Weigert, G.*, et al.* Effects of lutein supplementation on macular pigment optical density and visual acuity in patients with age-related macular degeneration. *Invest Ophthalmol Vis Sci* **52**, 8174-8178 (2011).
31. Richer, S.P.*, 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, 973. *Optometry* **82**, 667-680 e666 (2011).
32. Sabour-Pickett, S.*, et al.* Supplementation with three different macular carotenoid formulations in patients with early age-related macular degeneration. *Retina* **34**, 1757-1766 (2014).
33. Age-Related Eye Disease Study 2 Research, G.*, et al.* Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3. *JAMA Ophthalmol* **132**, 142-149 (2014).
34. Age-Related Eye Disease Study 2 Research, G. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA* **309**, 2005-2015 (2013).
35. Ho, L.*, et al.* Reducing the genetic risk of age-related macular degeneration with dietary antioxidants, zinc, and omega-3 fatty acids: the Rotterdam study. *Arch Ophthalmol* **129**, 758-766 (2011).
36. Wu, J., Cho, E., Willett, W.C., Sastry, S.M. & Schaumberg, D.A. Intakes of Lutein, Zeaxanthin, and Other Carotenoids and Age-Related Macular Degeneration During 2 Decades of Prospective Follow-up. *JAMA Ophthalmol* **133**, 1415-1424 (2015).
37. Lin, H.*, et al.* Association between Dietary Xanthophyll (Lutein and Zeaxanthin) Intake and Early Age-Related Macular Degeneration: The Atherosclerosis Risk in Communities Study. *Ophthalmic Epidemiol* **24**, 311-322 (2017).
38. Tan, J.S.*, et al.* Dietary antioxidants and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Ophthalmology* **115**, 334-341 (2008).

39. Tomany, S.C.*, et al.* Risk factors for incident age-related macular degeneration: pooled findings from 3 continents. *Ophthalmology* **111**, 1280-1287 (2004).
40. Wang, J.J.*, et al.* Genetic susceptibility, dietary antioxidants, and long-term incidence of age-related macular degeneration in two populations. *Ophthalmology* **121**, 667-675 (2014).
41. Nolan, J.M.*, et al.* The impact of macular pigment augmentation on visual performance in normal subjects: COMPASS. *Vision Res* **51**, 459-469 (2011).
42. Loughman, J.*, et al.* The relationship between macular pigment and visual performance. *Vision Res* **50**, 1249-1256 (2010).
43. Flood, V.*, et al.* Dietary antioxidant intake and incidence of early age-related maculopathy: the Blue Mountains Eye Study. *Ophthalmology* **109**, 2272-2278 (2002).
44. Zhang, X.*, et al.* Carotenoid intakes and risk of breast cancer defined by estrogen receptor and progesterone receptor status: a pooled analysis of 18 prospective cohort studies. *Am J Clin Nutr* **95**, 713-725 (2012).
45. Michikawa, T.*, et al.* Serum antioxidants and age-related macular degeneration among older Japanese. *Asia Pac J Clin Nutr* **18**, 1-7 (2009).
46. Fletcher, A.E.*, et al.* Sunlight exposure, antioxidants, and age-related macular degeneration. *Arch Ophthalmol* **126**, 1396-1403 (2008).
47. Barker, F.M., 2nd*, et al.* Nutritional manipulation of primate retinas, V: effects of lutein, zeaxanthin, and n-3 fatty acids on retinal sensitivity to blue-light-induced damage. *Invest Ophthalmol Vis Sci* **52**, 3934-3942 (2011).
48. Jia, Y.P.*, et al.* The Pharmacological Effects of Lutein and Zeaxanthin on Visual Disorders and Cognition Diseases. *Molecules* **22**(2017).
49. Wooten, B.R. & Hammond, B.R. Macular pigment: influences on visual acuity and visibility. *Prog Retin Eye Res* **21**, 225-240 (2002).
50. Reading, V.M. & Weale, R.A. Macular pigment and chromatic aberration. *J Opt Soc Am* **64**, 231-234 (1974).
51. Bernstein, P.S.*, et al.* Lutein, zeaxanthin, and meso-zeaxanthin: The basic and clinical science underlying carotenoid-based nutritional interventions in ocular disease. *Prog Retin Eye Res*, 34-66 (2016).
52. Li, S.Y.*, et al.* Anti-inflammatory effects of lutein in retinal ischemic/hypoxic injury: in vivo and in vitro studies. *Invest Ophthalmol Vis Sci* **53**, 5976-5984 (2012).
53. Scripsema, N.K., Hu, D.N. & Rosen, R.B. Lutein, zeaxanthin and meso-zeaxanthin in the clinical management of eye disease. *J Ophthalmol* **2015**(2015).
54. Stahl, W. & Sies, H. Antioxidant defense: vitamins E and C and carotenoids. *Diabetes* **46 Suppl 2**, S14-18 (1997).
55. Hammond, B.R., Fletcher, L.M., Roos, F., Wittwer, J. & Schalch, W. A double-blind, placebo-controlled study on the effects of lutein and zeaxanthin on photostress recovery, glare disability, and chromatic contrast. *Invest Ophthalmol Vis Sci* **55**, 8583-8589 (2014).
56. Seddon, J.M.*, et al.* Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group. *JAMA* **272**, 1413-1420 (1994).
57. Manzi, F., Flood, V., Webb, K. & Mitchell, P. The intake of carotenoids in an older Australian population: The Blue Mountains Eye Study. *Public Health Nutr* **5**, 347-352 (2002).
58. Chasan-Taber, L.*, et al.* A prospective study of carotenoid and vitamin A intakes and risk of cataract extraction in US women. *Am J Clin Nutr* **70**, 509-516 (1999).
59. Eisenhauer, B., Natoli, S., Liew, G. & Flood, V.M. Lutein and Zeaxanthin-Food Sources, Bioavailability and Dietary Variety in Age-Related Macular Degeneration Protection. *Nutrients* **9**(2017).