Review Article

What did we learn in 35 years of research on nutrition and supplements for age-related macular degeneration: a systematic review

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ABSTRACT.
The aim of this paper is to summarize all available evidence from systematic reviews, randomized controlled trials (RCTs) and comparative nonrandomized studies (NRS) on the association between nutrition and antioxidant, vitamin, and mineral supplements and the development or progression of age-related macular degeneration (AMD). The Cochrane Database of Systematic Reviews, Cochrane register CENTRAL, MEDLINE and Embase were searched and studies published between January 2015 and May 2021 were included. The certainty of evidence was assessed according to the GRADE methodology. The main outcome measures were development of AMD, progression of AMD, and side effects. We included 7 systematic reviews, 7 RCTs, and 13 NRS. A high consumption of specific nutrients, i.e. β-carotene, lutein and zeaxanthin, copper, folate, magnesium, vitamin A, niacin, vitamin B6, vitamin C, docosahexaenoic acid, and eicosapentaenoic acid, was associated with a lower risk of progression of early to late AMD (high certainty of evidence). Use of antioxidant supplements and adherence to a Mediterranean diet, characterized by a high consumption of vegetables, whole grains, and nuts and a low consumption of red meat, were associated with a decreased risk of progression of early to late AMD (moderate certainty of evidence). A high consumption of alcohol was associated with a higher risk of developing AMD (moderate certainty of evidence). Supplementary vitamin C, vitamin E, or β-carotene were not associated with the development of AMD, and supplementary omega-3 fatty acids were not associated with progression to late AMD (high certainty of evidence). Research in the last 35 years included in our overview supports that a high intake of specific nutrients, the use of antioxidant supplements and adherence to a Mediterranean diet decrease the risk of progression of early to late AMD.

Key words: age-related macular degeneration – AMD – Cochrane – nutrition – supplements – systematic review

†These authors contributed equally to this work.

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Introduction

Age-related macular degeneration (AMD) is the most common cause of blindness and visual impairment in industrialized countries (Wong et al. 2014). As suggested by its name, its prevalence increases strongly after the age of 65 years. The pathogenesis of AMD is multifactorial with many different pathways implicated in its pathophysiology. Other important risk factors are genetic predisposition, race, smoking, and nutrition. The disease affects the macula, which is crucial for central vision. In the early stages of the disease, drusen – deposits underneath the retinal pigment epithelium (RPE) – and areas of hypopigmentation and

hyperpigmentation can be observed. In the later stages of the disease, areas of the RPE become atrophic, and in exudative AMD, abnormal new blood vessels develop from under the RPE and into the subretinal space. This causes damage that is largely irreversible.

Current pharmacological treatment strategies are limited to slowing down the progression of exudative AMD. As AMD still is an incurable eye disease, strategies for primary and secondary prevention are of paramount importance. For example, smoking cessation can have a significant impact on the patients' prognosis and treatment response, even at an older age (Vittorio et al. 2020). In addition, nonpharmacological interventions by way of nutrition and supplements have been investigated. A vast number of studies have investigated the association between dietary components, food groups, antioxidants, and vitamin or mineral supplementation and the development or the progression of AMD.

The aim of this systematic review is to provide a complete overview of the current literature on this clinically relevant topic.

Methods

Information sources, search strategy, and study selection

We conducted a systematic search to identify eligible systematic reviews in the electronic databases Epistemonikos (which contains MEDLINE and Embase) and The Cochrane Database of Systematic Reviews. Systematic reviews published from the 1 January 2015 to 3 May 2021 were eligible. Original studies published in the same period of time were identified by a systematic search in the electronic databases MEDLINE, Embase, and Cochrane register CENTRAL.

The full search strategies are presented in Tables S1 and S2 of the Appendix. The titles and abstracts of all articles were screened by two independent reviewers to identify potentially relevant publications. Relevant reports were examined full text by two

[Correction added on 16 June 2022, after first online publication: Tables A1 to A6 and Figures A1 to A2 were renamed as Tables S1 to S6 and Figures S1 to S2 in this current version.]

independent assessors for eligibility for qualitative and quantitative review. Discrepancies were resolved by involving a third investigator.

Eligibility criteria

Eligible reviews or studies for this systematic review included the general population and patients with early or late AMD; outcomes of interest were the development of AMD (from no AMD to early or late AMD) and progression of AMD (from early to late AMD), respectively. No AMD was defined as no signs of AMD or small ('hard') drusen (less than 63 micrometres), early AMD as medium or larger drusen (more than 63 micrometres) and/or pigmentary abnormalities, and late AMD as choroidal neovascularization and/or geographic atrophy. In addition, reviews or studies that only evaluated the side effects of nutritional interventions were also included. The intervention was standard care in combination with a high intake of specific nutrition and/or use of supplements, compared with standard care without or with a low intake of specific nutrition and/or supplements. Any definition of high or low intake as provided by publications was taken into account. Reviews or studies only reporting on secondary outcome measures, such as macular pigment density or visual acuity, were not included.

Eligible study designs were systematic reviews, randomized controlled trials (RCTs), or comparative nonrandomized studies (NRS) written in English, Dutch, German, Spanish, Italian, and Japanese.

Data extraction and outcome assessment

Data on patient characteristics, interventions, and outcomes were extracted from the included reviews or studies. Results were grouped per dietary pattern, nutrient, vitamin, and supplement. The quality of the retrieved reviews was assessed using AMSTAR-2 (Shea et al. 2017), Cochrane Risk of Bias tool was used for RCTs (Higgins et al. 2022), and ROBINS-I (Sterne et al. 2016) for NRS.

Results were expressed as hazard ratio (HR), odds ratio (OR), or risk ratio (RR) with corresponding 95% confidence interval (CI), if provided. We planned to meta-analyse results

from RCTs evaluating supplements (or update existing meta-analyses from identified systematic reviews) when patients, interventions, and outcomes were comparable. We used a fixed-effect model for the meta-analyses. In case of statistical heterogeneity (judgement based on Chi-square test and I^2), we used a random-effects model. As we expected much heterogeneity regarding observational studies on nutrition, we did not perform a meta-analysis of these results.

The 'Grading of Recommendations, Assessment, Development, and Evaluations' (GRADE) methodology was used to assess the certainty of evidence for the outcomes development and progression of AMD (Guyatt et al. 2011). We adopted the GRADE assessment from the included systematic reviews, if reported. If not or in case of other study designs, two independent investigators graded the certainty of the evidence. For these GRADE assessments, in case of more than one outcome per determinant, we focused on the overarching outcome, i.e. on total AMD rather than early AMD or late AMD (outcome development of AMD) and on late AMD rather than neovascular AMD or geographic atrophy.

Results

Search results

Systematic reviews

Table S1 and Fig. S1 of the Appendix present the search and the selection process for identifying systematic reviews. The electronic databases search yielded 408 references. After excluding duplicates, 379 were screened by title and abstract. Three hundred fifty-one references that were not relevant to the scope of this review were removed. Of the remaining 28 full-text articles, seven articles were included based on the date of search, the research question, and inclusion criteria (Chapman et al. 2019; Dinu et al. 2019; Evans & Lawrenson 2017a, b; Lawrenson & Evans 2015; Waugh et al. 2018; Zhong et al. 2021).

Original studies

Table S2 and Fig. S2 of the Appendix present the search and the selection process for the original studies. The electronic database search

resulted in 3216 references. After excluding duplicates, 2496 were screened by title and abstract of which 2330 references were excluded. Of the remaining 166 references, after reading the full-text article, a total of 20 relevant studies were included (Akuffo et al. 2017; Lin et al. 2017; Merle et al. 2017, 2019; Broadhead et al. 2018; Joachim et al. 2018; Gopinath et al. 2018a,b, 2020; de Koning-Backus et al. 2019; Dighe et al. 2019; Tisdale et al. 2019; Jones et al. 2020; Keenan et al. 2020; Machida et al. 2020; Piatti et al. 2020; Christen et al. 2020a,b; Agrón et al. 2021; García-Layana et al. 2021).

Study characteristics

Systematic reviews
Characteristics of the included systematic reviews can be found in Table 1. Three systematic reviews studied nutrition (Chapman et al. 2019; Dinu et al. 2019; Zhong et al. 2021), two systematic reviews by the same authors included studies on the use of supplements (Evans & Lawrenson 2017a,b), and two systematic reviews included studies on both supplements and nutrition (Lawrenson & Evans 2015; Waugh et al. 2018). The studies included in the systematic reviews were published between 1984 and 2017 and were mostly conducted in Europe, Australia, and the USA.

Original studies
Characteristics of the included original studies can be found in Table 2. The 20 original studies consisted of 7 RCTs on supplements and 13 NRS investigating nutrition. The studies were published between 2017 and 2021. Exposure differed highly between the included studies, with different dosages and different dietary patterns, food components, and supplements. With regard to study population and outcomes, some studies did not clarify the classification used to distinguish between no AMD, early AMD, and late AMD.

Risk of bias assessment

Table 3 shows the results of the critical appraisal of the seven included systematic reviews by the AMSTAR-2 tool. Table 4 shows a summary of the risk of bias assessment of the 13 included NRS by the ROBINS-1 tool. Four studies

scored an overall serious risk of bias, seven studies a moderate risk, one study a low risk, and in one study there was a lack of information to perform the risk of bias assessment. In Table 5, a summary of the risk of bias of the seven included randomized controlled trials can be found. The majority of the studies scored a low risk of bias on most domains. Two studies scored on the majority of the domains an unclear risk of bias (Piatti et al. 2020; Christen et al. 2020a). The complete risk of bias assessments, including support for the judgements provided, are available on request.

The association of nutrition with the development and progression of AMD

A summary of the results can be found in Table 6. Results with a high or moderate certainty of evidence will be discussed here. All results including the OR, HR, or RR and corresponding 95% CI and the graded certainty of evidence can be found in Tables S3 and S4 of the Appendix.

Nutrition associated with a decreased risk of development and progression of AMD
A high dietary intake of β-carotene, lutein and zeaxanthin, copper, folate, magnesium, vitamin A, niacin, vitamin B6, vitamin C, docosahexaenoic acid (DHA) and/or eicosapentaenoic acid (EPA), or alcohol was associated with a lower risk of progression of AMD (high certainty of evidence) (Agrón et al. 2021). A high dietary intake of DHA and/or EPA was also associated with a lower risk of development of early AMD (Zhong et al. 2021).

A Mediterranean diet is characterized by a high intake of vegetables, fruit, legumes, grains, and nuts; a moderate consumption of fish, poultry, dairy, and red wine; use of olive oil instead of butter; and a limited consumption of red meat. Adherence to this diet was associated with a lower risk of developing AMD (moderate certainty of evidence) (Merle et al. 2019). This association was also found for the progression to late AMD (moderate certainty of evidence) (Chapman et al. 2019).

A high intake of the combination of grains, fish, steamed/boiled chicken, vegetables, and nuts was associated with a lower risk of the development of AMD (moderate certainty of

evidence) (Chapman et al. 2019). Additionally, β-cryptoxanthin or fish as solitary food product was associated with a lower risk of developing AMD (moderate certainty of evidence) (Waugh et al. 2018; Dinu et al. 2019). A high intake of calcium or lycopene was associated with a lower risk of progression of AMD (moderate certainty of evidence) (Merle et al. 2017; Tisdale et al. 2019; Agrón et al. 2021).

Nutrition associated with an increased risk of development and progression of AMD
A high dietary intake of linoleic acid, monounsaturated fat, oleic acid, or saturated fat was associated with a higher risk of progression of AMD (high certainty of evidence) (Agrón et al. 2021). A high intake of alcohol was associated with a higher risk of development of AMD (moderate certainty of evidence) (Dinu et al. 2019).

Nutrition not associated with the development and progression of AMD
No association was found between a high dietary intake of total fatty acids, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, or α-linolenic acids and the development of early or late AMD (moderate certainty of evidence) (Zhong et al. 2021). A high dietary intake of DHA and/or EPA was not associated with the development of late AMD (Zhong et al. 2021). Additionally, no association was found between a high dietary intake of α-carotene, β-cryptoxanthin, iron, lactose, thiamine, retinol, riboflavin, vitamin B12, vitamin E, zinc, arachidonic acid, cholesterol, α-linolenic acid, or vegetables and the progression of AMD (moderate certainty of evidence; Keenan et al. 2020; Agrón et al. 2021).

The association of supplements with the development and progression of AMD

Supplements associated with a decreased risk of development and progression of AMD
Daily use of a formula, containing a high dose of vitamin C, vitamin E, β-carotene, zinc as zinc oxide, and copper as cupric oxide (also known as the AREDS formula), was associated with a decreased risk of progression of AMD (moderate certainty of evidence) (Evans & Lawrenson 2017b).

Table 1. Characteristics of eligible systematic reviews included in this review (n = 7).

Reference	Population	Intervention	Comparator	Outcome(s)	Method of detecting the outcome	Search date	Prevention / secondary prevention	Nutrition / supplements	Study type
Chapman et al. (2019)	Adults in the general population, with and/or without AMD	High Mediterranean, Western, and Oriental diet pattern scores High intake of various food groups: olive oil; DHA + EPA; fish consumption; omega 3 and omega 6; glycaemic index; carotenoids; multi-micro-nutrients; meat; alcohol; dairy products	Low intake of the various dietary patterns and food groups	Incidence and progression of AMD	Fundus photographs or self-reported and confirmed by medical record review	Aug-17	Both	Nutrition	All
Dinu et al. (2019)	Clinically healthy adults	High intake of food groups and alcohol. Food groups: vegetables, fruit, nuts, grain, meat, dairy products, fish, butter, margarine, oils, and alcohol	Low intake of the various food groups and alcohol	Occurrence of AMD subgroup analysis for early and late	Fundus photographs or self-reported and confirmed by medical record review	Jan-18	Prevention	Nutrition	Prospective cohort studies
Evans and Lawrenson (2017a)	People in the general population, with or without diseases other than AMD	Antioxidant vitamin or mineral supplementation, alone or in combination: vitamin C, vitamin E, carotenoids (including the macular pigment carotenoids lutein and zeaxanthin), selenium, and zinc	Placebo or no intervention	Development of: any AMD (early or late, or both), late AMD (neovascular AMD or geographic atrophy, or both), neovascular AMD, geographic atrophy; quality of life; resource use and costs	Fundus photographs or self-reported and confirmed by medical record review	Mar-17	Prevention	Supplements	RCTs
Evans and Lawrenson (2017b)	People with AMD	Antioxidant vitamin or mineral supplementation, alone or in combination: vitamin C, vitamin E, carotenoids (including the macular pigment carotenoids lutein and zeaxanthin), selenium, and zinc	Placebo or no intervention	Progression to late AMD; progression to neovascular AMD; progression to geographic atrophy; progression to visual loss; quality of life; resource use and costs	Fundus photographs or self-reported and confirmed by medical record review	Mar-17	Secondary prevention	Supplements	RCTs

Table 1 (Continued)

Reference	Population	Intervention	Comparator	Outcome(s)	Method of detecting the outcome	Search date	Prevention / secondary prevention	Nutrition / supplements	Study type
Lawrenson and Evans (2015)	General population with or without AMD	Omega 3 fatty acids, either as fish oil capsules or dietary manipulation	Placebo or no intervention	Developing incident AMD or new visual loss attributed to AMD; progression of AMD; quality of life; adverse outcomes	Fundus photographs	Feb-15	Both	Both	RCTs
Waugh et al. (2018)	Patient with dry age-related macular degeneration, general population	Any supplement or dietary intake. Focus on AREDS, lutein and zeaxanthin supplementation, fatty acids and antioxidants, homocysteine, folic acid and vitamins; ginkgo biloba extract; HESA-A; saffron; curcumin; zinc	Any comparator	AMD, progression, reverse of complaints	Fundus photographs or self-reported and confirmed by medical record review	Jul-17	Both	Both	All study types
Zhong et al. (2021)	General population with or without AMD	Dietary fatty acid intake	Low intake of dietary fatty acids	Incidence of early or advanced AMD	Fundus photographs or self-reported and confirmed by medical record review	May-20	Secondary prevention	Nutrition	Prospective cohort studies

AMD = age-related macular degeneration; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; RCT = randomized controlled trial.

Supplements associated with an increased risk of development and progression of AMD

Use of multivitamins, containing zinc (15 mg), vitamin E (45 IU), vitamin C (60 mg), β-carotene (5000 IU), vitamin A, folic acid (2.5 mg), vitamin B6 (50 mg), and vitamin B12 (1 mg), was associated with an increased risk of development of AMD (moderate certainty of evidence) (Evans & Lawrenson 2017a).

Supplements not associated with development and progression of AMD

No association was found between supplementary β-carotene and vitamin C and the development of AMD (Evans & Lawrenson 2017a). We updated a meta-analysis regarding supplementary vitamin E and the development of AMD, which can be found in Tables S5 and S6 of the Appendix (Evans & Lawrenson 2017a; Christen et al. 2020a). No association was found between vitamin E and the development of AMD. Additionally, no association was found between supplementary omega-3 fatty acids and the progression of AMD (high certainty of evidence) (Lawrenson & Evans 2015).

Adverse events of nutrition and supplements

The included studies did not report any adverse effects of nutrition. Supplementary β-carotene was associated with an increased risk of lung cancer in smokers (Evans & Lawrenson 2017a). One RCT reported an increased risk of haemorrhagic strokes in persons using vitamin E. However, two other RCTs did not find any difference between the group using vitamin E and the group using placebo (Evans & Lawrenson 2017a). Persons using multivitamin supplements were more likely to have skin rashes compared to persons using placebo (Evans & Lawrenson 2017a).

In the studies comparing zinc and placebo, gastrointestinal symptoms were reported in both groups (Evans & Lawrenson 2017b). One RCT reported a higher prevalence of anaemia in the group using zinc versus the placebo group. Other RCTs did not find a difference (Evans & Lawrenson 2017b).

The included systematic reviews and RCTs related to supplements, i.e.

Table 2. Characteristics of eligible original studies included in this review (n = 20).

Reference	Country	Population	Determinants/interventions	Outcome(s)	Method of detecting the outcome
Nutrition					
Agrón et al. (2021)	USA	Participants aged 50–80 yrs. from AREDS(2) population with no late AMD at baseline	Dietary vitamin A, retinol, vitamin D, vitamin E, vitamin C, thiamine, riboflavin, niacin, vitamin B6, folate, vitamin B12, β-carotene, α-carotene, β-cryptoxanthin, lutein and zeaxanthin, lycopene, calcium, magnesium, iron, zinc, copper, cholesterol, saturated fat, monounsaturated fat, oleic acid, linoleic acid, α-linolenic acid, arachidonic acid, EPA, DHA, lactose, alcohol	Progression of AMD	Fundus photographs
de Koning-Backus et al. (2019)	Netherlands	Participants aged >55 yrs.	Vegetables, fruit, fish, fat products, meat, grains, poultry, eggs, potatoes, legumes, dairy, and various food patterns	Development of AMD	Fundus photographs
Dighe et al. (2019)	USA	Healthy participants aged 45–65 yrs.	Western (unhealthy) dietary pattern and prudent (healthy) dietary pattern	Development of AMD	Fundus photographs
Gopinath et al. (2018a)	Australia	Healthy participants aged ≥49 yrs.	Nitrate (vegetable and nonvegetable)	Development of AMD	Fundus photographs
Gopinath et al. (2018b)	Australia	Healthy participants aged ≥49 yrs.	Flavonoids, flavonols, flavanones, quercetin, and total hesperidin	Development of AMD	Fundus photographs
Gopinath et al. (2020)	Australia	Healthy participants aged ≥49 yrs.	Eggs	Development of AMD	Fundus photographs
Joachim et al. (2018)	The Netherlands and Australia	Participants ≥55 yrs. (The Netherlands) / ≥49 yrs. (Australia) with early AMD lesions in either eye	Fish and lutein-zeaxanthin	Progression of AMD	Fundus photographs
Jones et al. (2020)	Australia and Singapore	Healthy residents aged ≥49 yrs. (Australia) / citizens or long-term residents of age 21 to 75 years (Singapore)	Western diet (red and processed meat, potatoes, fats, fast food, sugar-based items, and alcohol); Asian diet (eggs, fish, poultry, breads, and cereals); and vegetarian diet (fruits, vegetables, dairy products, and nuts)	Development of AMD	Fundus photographs
Keenan et al. (2020)	USA	Men and women aged 50 to 85 yrs. without late AMD at baseline	Mediterranean diet (and its individual components): whole fruits, vegetables, whole grains, nuts, legumes, red meat, fish, monounsaturated fatty acid, saturated fatty acid ratio (MUFA:SFA), and alcohol.	Progression of AMD	Fundus photographs
Lin et al. (2017)	USA	Participants aged 45 to 64 yrs.	Energy-adjusted xanthophyll	Development of AMD	Fundus photographs
Merle et al. (2017)	USA	Participants with at least one eye with nonadvanced AMD at baseline (eligible age not specified)	Vitamin D and calcium	Progression of AMD	Fundus photographs
Merle et al. (2019)	The Netherlands and France	Participants ≥55 yrs. (The Netherlands) / participants ≥73 yrs. (France)	Mediterranean diet	Development of AMD	Fundus photographs

Table 2 (Continued)

Reference	Country	Population	Determinants/interventions	Outcome(s)	Method of detecting the outcome
Tisdale et al. (2019)	USA	Adults (aged 55 to 80 years) who had either no AMD, intermediate AMD (bilateral large drusen), or late AMD in 1 eye	Calcium	Progression of AMD	Fundus photographs
Supplement(s)					
Akuffo et al. (2017)	Ireland	Participants with nonadvanced AMD (eligible age not specified)	AREDS 2 formulation (10 mg/d lutein, 2 mg/d zeaxanthin plus 500 mg/d vitamin C, 400 IU/d of vitamin E, and 2 mg/d copper) with a low dose [25 mg] of zinc and an addition of 10 mg mesozeaxanthin versus AREDS 2 formulation without addition of mesozeaxanthin	Progression of AMD, adverse events	Fundus photographs
Broadhead et al. (2018)	Australia	Participants >50 yrs. with moderate severity AMD	20 mg saffron versus placebo	Progression of AMD, adverse events	Fundus photographs
Christen et al. (2020a)	USA, Canada, and Puerto Rico	Healthy men aged 50 yrs. or older	Selenium (200 lg/d) and/or marine vitamin E (400 IU/d) versus placebo	Development of AMD responsible for a best-corrected visual acuity of 20/30 or worse, total AMD, advanced AMD	Self-report confirmed by medical record review
Christen et al. (2020b)	USA	Healthy men (aged ≥50 yrs.) and women (aged ≥55 yrs.)	Vitamin D or omega-3 fatty acids versus placebo	Development and progression of AMD	Self-report confirmed by medical record review
García-Layana et al. (2021)	Spain and Portugal	Participants ≥50 yrs. with unilateral choroidal neovascularization secondary to AMD with no exudative involvement in the contralateral eye	AREDS original formulation, manganese and selenium, versus AREDS original formulation except for β-carotene, plus DHA, lutein, zeaxanthin, resveratrol, and hydroxytyrosol	Adverse events	NA
Machida et al. (2020)	Japan	Healthy participants aged 20–69 yrs.	60 mg lutein versus placebo	Adverse events	NA
Piatti et al. (2020)	Italy	Participants aged 55 to 80 yrs. with intermediate AMD	Mixture of carotenoids (lutein 10 mg, astaxanthin 4 mg, zeaxanthin 2 mg), antioxidants (vitamin C 90 mg, vitamin E 30 mg, zinc 22.5 mg plus copper 1 mg), and omega-3 fatty acids (fish oil 500 mg, containing EPA 185 mg and DHA 140 mg) versus placebo	Progression of AMD, adverse events	Fundus photographs

AMD = age-related macular degeneration; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; MUFA = monounsaturated fatty acid; SFA = saturated fatty acid ratio; NA: not applicable. yrs = years.

Table 3. Methodological quality of the included systematic reviews (AMSTAR 2) (n = 7).

	1. PICO components	2. A priori study design	3. Study design explanation	4. Comprehensive search strategy	5. Duplicate study selection	6. Duplicate data extraction	7. List of excluded studies	8. Details of included studies	9. Satisfactory technique for risk of bias assessment	10. Funding sources of included studies	11. Appropriate methods to combine findings	12. Potential impact of risk of bias	13. Risk of bias accounted for	14. Heterogeneity explanation and discussion	15. Investigation of publication bias	16. Conflict of interest statement
Chapman et al. (2019)	Y	N	Y	PY	N	N	N	PY	N	N	NA	NA	N	N	NA	Y
Dinu et al. (2019)	Y	N	Y	PY	Y	Y	N	PY	Y	N	Y	N	N	Y	Y	Y
Evans and Lawrenson (2017a)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Evans and Lawrenson (2017b)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Lawrenson and Evans (2015)	Y	N	Y	PY	N	N	Y	Y	Y	Y	NA	NA	N	N	NA	Y
Waugh et al. (2018)	Y	N	Y	PY	N	N	PY	Y	Y	Y	NA	NA	N	N	NA	Y
Zhong et al. (2021)	N	PY	N	PY	Y	Y	N	PY	Y	N	Y	N	N	Y	Y	N

Y = yes; N = no; NA = not applicable; PY = partial yes.

(combinations of) carotenoids, omega-3 fatty acids, vitamin C, ginkgo biloba, and saffron, reported a low and equal distribution of serious adverse events between the groups (Lawrenson & Evans 2015; Evans & Lawrenson 2017b; Broadhead et al. 2018; Waugh et al. 2018; Machida et al. 2020).

Discussion

The present systematic review was designed to provide a complete overview of the current literature on the association between nutrition and supplements and the development or progression of AMD. We included 7 systematic reviews, 7 RCTs, and 13 cohort studies published between 2015 and 2021.

The main findings were that a high consumption of specific nutrients, i.e. β-carotene, lutein and zeaxanthin, copper, folate, magnesium, vitamin A, niacin, vitamin B6, vitamin C, docosahexaenoic acid, and eicosapentaenoic acid, was associated with a lower risk of progression of early to late AMD (Agrón et al. 2021). Moreover, use of antioxidant supplements and adherence to a Mediterranean diet, characterized by a high consumption of vegetables, whole grains, and nuts, and a low consumption of red meat were associated with a decreased risk of progression of early to late AMD (Evans & Lawrenson 2017b; Merle et al. 2019). A high consumption of alcohol was associated with a higher risk of developing AMD (Dinu et al. 2019). Supplementary vitamin C, vitamin E, or β-carotene was not associated with the development of AMD, and supplementary omega-3 fatty acids were not associated with progression to late AMD (Lawrenson & Evans 2015; Evans & Lawrenson 2017a; Christen et al. 2020a).

Strengths and limitations

To the best of our knowledge, this is the first systematic review that addressed the association between nutrition and supplements with both the development and the progression of AMD. The consequence of this comprehensive design is a vast and rather complex amount of data. From this data, we have tried to distil the most reliable results. For this purpose, the GRADE system was used to assess and categorize the certainty of the evidence.

Observational studies on nutrition have different methodological limitations. First, questionnaires on dietary intake are associated with measurement error, for example, due to the tendency of participants to underreport their energy intake (Maki et al. 2014). Also, one-time assessment may not represent the complex, time-dependent exposure to diet. Secondly, the strong correlation between food products and nutritional/food components makes it difficult to untangle the data and to interpret the results. Thirdly, the substitution effect may play a role, which means that the observed association could be due to the displacement of other nutrients. Finally, there is a healthy or unhealthy consumer bias; the intake of a category of food may be associated with other nondietary variables, which is difficult to adjust for in statistical modelling. In addition, recall bias and selection bias may play a role.

Reflection on the results

With the highest certainty of evidence, we found that specific carotenoids, vitamins, and amino acids were associated with a decreased risk of progression of AMD. We also found that a Mediterranean diet was associated with less progression of AMD. One could speculate that these carotenoids, vitamins, and amino acids are in a higher quantity present in the Mediterranean diet. Immunological factors, such as complement and oxidative stress, are important in the pathogenesis of AMD (Guillonneau et al. 2017). Therefore, it is plausible that antioxidants which decrease the risk of AMD modulate the immune and inflammatory responses. The finding that a high consumption of alcohol is associated with a higher risk of development of AMD is probably due to the pro-oxidant effect of alcohol and its ability to modify mechanisms that protect against oxidative stress (Wu & Cederbaum 2003; Jarrett & Boulton 2012). The detrimental effect of alcohol can also be found in many other disease categories, for example cancer and cardiovascular diseases (Rehm et al. 2009). In contrast to this, a high intake of alcohol was associated with a lower risk of progression of AMD (Agrón et al. 2021). This unexpected

Table 4. Risk of bias assessment of the included observational studies (ROBINS-I tool) (*n* = 13).

Reference	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Studies which studied the association of nutrition with the development of AMD								
de Koning-Backus et al. (2019)	Low	Low	Low	Moderate	Serious	Low	Low	Serious
Dighe et al. (2019)	Low	Low	Low	Moderate	Serious	Low	Low	Serious
Gopinath et al. (2018a)	Low	Low	Low	Moderate	Moderate	Low	Low	Moderate
Gopinath et al. (2018b)	Low	Low	Low	Moderate	Serious	Low	Serious	Serious
Gopinath et al. (2020)	Low	Low	Low	Moderate	Serious	Low	Low	Serious
Jones et al. (2020)	Low	Low	Low	Moderate	Moderate	Low	Low	Moderate
Lin et al. (2017)	Low	Low	Low	Moderate	Moderate	Low	Low	Moderate
Merle et al. (2019)	Low	Moderate	Low	Moderate	Moderate	Low	Low	Moderate
Studies which studied the association of nutrition with the progression of AMD								
Agrón et al. (2021)	Low	Low	Low	Low	Low	Low	Low	Low
Joachim et al. (2018)	Moderate	Moderate	Low	Low	No information	Low	Low	Moderate
Keenan et al. (2020)	Low	Low	Low	No information	Moderate	Low	Low	Moderate
Merle et al. (2017)	Low	Low	Low	No information	No information	Low	Low	No information
Tisdale et al. (2019)	Low	Low	Low	Moderate	Low	Low	Low	Moderate

Table 5. Risk of bias assessment of the included RCTs (Cochrane Risk of Bias tool) (*n* = 7).

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment – Outcome: AMD	Blinding of outcome assessment - Outcome: Adverse events	Incomplete outcome data - Outcome: AMD	Incomplete outcome data - Outcome: Adverse events	Selective reporting	Other
Akuffo et al. (2017)	Low	Low	Low	Low	Low	Low	Low	Low	Low
Broadhead et al. (2018)	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Low
Christen et al. (2020a)	Unclear	Unclear	Unclear	Unclear	NA	Unclear	NA	Low	Low
Christen et al. (2020b)	Low	Unclear	Low	Low	NA	Low	NA	Low	Low
García-Layana et al. (2021)	Low	Low	Low	NA	Unclear	NA	Low	Low	Low
Machida et al. (2020)	Low	Low	Low	NA	Unclear	Na	Low	Unclear	Low
Piatti et al. (2020)	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear	Unclear	Low

AMD = age-related macular degeneration; NA = not applicable; RCT = randomized controlled trial.

finding could be due to study design or confounding factors, such as age (Grant et al. 2021). Higher age is strongly associated with AMD progression, while high alcohol consumption may be more prevalent in younger age groups. Important to realize is that this finding was based on observational and not interventional studies. Another striking finding, based on one randomized controlled trial, is the higher risk of developing AMD when using multivitamins (Evans & Lawrenson 2017a). The RCT that found this result was not designed to study AMD as a primary outcome, with medical record review only. This may have affected the reliability of this particular outcome.

The association between dietary and supplementary omega-3 fatty acids and their potential health benefits have been studied extensively. A high intake of two components of omega-3 fatty acids, EPA and DHA, was associated with a lower risk of development and progression of AMD (Chapman et al. 2019). In contrast to this, in two RCTs, including AREDS 2, no association was found between supplementary omega-3 fatty acids and the progression of AMD (Lawrenson & Evans 2015).

Special attention should be addressed to the AREDS and AREDS 2 studies. These RCTs have included the largest number of participants to study the effect of diet and supplements on the risk of AMD. Regarding the use of only the combination of lutein and zeaxanthin, we concluded with a low certainty of evidence that there is no association between the use of these carotenoids and the progression of AMD. However, the authors of the RCT of AREDS 2 suggest that lutein in combination with zeaxanthin could be an appropriate carotenoid substitution instead of β-carotene in the AREDS formula, as β-carotene could increase the incidence of lung cancer in smokers (Chew et al. 2013).

Implications for clinicians and patients

Based on this systematic review, we would recommend persons without AMD a low consumption of alcohol. For patients with early AMD who do not smoke, we recommend taking the AREDS 1 formula, containing vitamin C (500 mg), vitamin E (400 IE), β-carotene (15 mg), zinc as zinc oxide (80 mg), and copper as cupric oxide

Table 6. Summary table.

GRADE	Effect	Protective – decreased risk: Development of AMD	Protective – decreased risk: Progression of AMD	Threatening – increased risk: Development of AMD	Threatening – increased risk: Progression of AMD	No association: Development of AMD	No association: Progression of AMD
High	Convincing	Nutrition: DHA*; EPA*; DHA + EPA* Supplements: -	Nutrition: β-carotene; lutein and zeaxanthin; copper; folate; magnesium; vitamin A; niacin; vitamin B6; vitamin C; DHA; EPA; DHA + EPA; alcohol Supplements: -	Nutrition: - Supplements: -	Nutrition: Linoleic acid; monounsaturated fat; oleic acid; saturated fat Supplements: -	Nutrition: - Supplements: β-carotene; vitamin C; vitamin E	Nutrition: - Supplements: Omega-3 fatty acids
Moderate	Likely	Nutrition: Mediterranean; high intake of grains, fish, steamed/boiled chicken, vegetables, and nuts; β-cryptoxanthin; fish Supplements: -	Nutrition: Mediterranean; calcium; lycopene Supplements: -	Nutrition: Alcohol Supplements: -	Nutrition: - Supplements: -	Nutrition: Total fatty acid; saturated fatty acid, monounsaturated fatty acid, polyunsaturated fatty acid; α-linolenic acid; DHA‡; EPA‡; DHA + EPA‡ Supplements: -	Nutrition: α-carotene; β-cryptoxanthin; iron; lactose; thiamine; retinol; riboflavin; vitamin B12; vitamin E; zinc; arachidonic acid; cholesterol; α-linolenic acid; vegetables Supplements: -
Low	Possibly	Nutrition: Calcium; nuts Supplements: Folic acid, vitamin B6 and vitamin B12	Supplements: AREDS formula† Nutrition: Supplements: Lutein and/or zeaxanthin; zinc	Supplements: Multivitamin Nutrition:	Nutrition: Trans-fat; meat Supplements: -	Nutrition: Lycopene; xanthophyll; nitrate; oils; margarine; butter; vegetables Supplements: Omega-3 fatty acids; selenium; vitamin D	Nutrition: High GI; calcium and vitamin D; trans-fat; fruit; whole grains; legumes; red meat; vegetables Supplements: Vitamin D
Low to very low	Unclear	**Development of AMD:** Nutrition: Western; healthy; Western versus Asian versus vegetarian; high GI; α-carotene; β-carotene; lutein/zeaxanthin; total carotenoids; oranges; flavonoids; dairy products; eggs; recommended versus lower intake of fat products; fruit; grains; legumes; potatoes; poultry Supplements: α-tocopherol and/or β-carotene **Progression of AMD:** Nutrition: lutein/zeaxanthin ≥1 median versus <median; vitamin D; olive oil; fish; nuts Supplements: mesozeaxanthin as addition on AREDS 2; combination of carotenoids, antioxidants, and omega-3 fatty acids§; ginkgo biloba; saffron; vitamin E					

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; GI = glycaemic index.

Convincing effect: GRADE high certainty of evidence for a positive, negative, or the absence of an association. Likely effect: GRADE moderate certainty of evidence for a positive, negative, or the absence of an association. Possibly effect: GRADE low certainty of evidence for a trend of a positive or negative association or the absence of it. Unclear effect: GRADE low certainty of evidence without a trend for a positive or negative association or GRADE very low certainty of evidence.

* Development of early AMD.

† AREDS formula: vitamin C (500 mg), vitamin E (400 IE), β-carotene (15 mg), zinc as zinc oxide (80 mg), and copper as cupric oxide (2 mg).

‡ Development of late AMD.

§ 10 mg lutein, 4 mg astaxanthin, 2 mg zeaxanthin, 90 mg vitamin C, 30 mg vitamin E, 22.5 mg zinc, 1 mg copper, 500 mg fish oil with 185 mg EPA, and 140 mg DHA.

(2 mg). In addition, the preventive effect of lutein (10 mg/day) and zeaxanthin (2 mg/day) as supplements is plausible, making them a good alternative for β-carotene. Secondly, for persons with early AMD, we would recommend a Mediterranean diet, characterized by a high intake of vegetables, fruit, legumes, grains, and nuts; a moderate consumption of fish, poultry, dairy, and red wine; the use of olive oil instead of butter; and a limited consumption of red meat.

Future research

AMD is a multifactorial disorder with multiple genetic and environmental risk factors, of which diet is an important modifiable component (Mitchell et al. 2018). CFH is one of the main genes implicated in AMD and is a key regulator of complement. Different studies have found that a Mediterranean diet in persons with the CFH protective alleles is associated with a decreased risk of late AMD (Keenan et al. 2020). It is plausible that adherence to a Mediterranean diet modulates immune and inflammatory responses. Future research should therefore focus on personalized therapeutic and preventive approaches, for example on the association between nutrition and immunological parameters.

Acknowledgement

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Flow diagram showing the selection for inclusion of systematic reviews.

Figure S2 Flow diagram showing the selection for inclusion of original studies.

Table S1 Search for systematic reviews.

Table S2 Search for original studies.

Table S3 The association of nutrition with the development and progression of AMD.

Table S4 The association of supplements with the development and progression of AMD.

Table S5 Vitamin E versus placebo. Outcome development of any type of AMD.

Table S6 Vitamin E versus placebo. Outcome development of late AMD.