Cochrane Netherlands

Voeding en voedingssupplementen bij Leeftijdsgebonden maculadegeneratie

Systematische review

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Lijst met gebruikte afkortingen

ALA	Alfaliponzuur
AMD	Age-related macular degeneration (leeftijdsgebonden maculadegeneratie, LMD)
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
AREDS	Age-related Eye Disease Study
BI	Betrouwbaarheidsinterval
CI	Confidence interval (betrouwbaarheidsinterval)
DHA	Docosahexaeenzuur
EPA	Eicosapentaeenzuur
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazardratio
IE	Internationale eenheden
LMD	Leeftijdsgebonden maculadegeneratie
MD	Mean difference
OR	Oddsratio
PICO	Patient, Intervention, Controle, Outcome
RCT	Randomized Controlled Trial
ROBINS-I	Risk of bias in nonrandomized studies of Interventions
RR	Relatief risico
SR	Systematische review

Inhoudsopgave

1. Inleiding

In het kader van het programma Zinnige Zorg heeft Zorginstituut Nederland een systematische werkwijze ontwikkeld om de zorg die uit het verzekerde basispakket wordt vergoed, door te lichten. Het uiteindelijke doel hiervan is te beoordelen of zorg op een patiëntgerichte, effectieve en doelmatige manier wordt ingezet. Het Zorginstituut gaat daarbij uit van het patiëntenperspectief, de opvattingen van goede zorg zoals weergegeven in richtlijnen of blijkend uit wetenschappelijk onderzoek, en betrokkenheid van relevante partijen gedurende het gehele traject[*].

Eén van de onderwerpen die in het kader van het programma Zinnige Zorg werd doorgelicht is de zorg rondom ziekten van het oog. Naar aanleiding daarvan heeft het Zorginstituut besloten een verdiepingstraject uit te voeren naar het zorgtraject voor mensen met maculadegeneratie[†]. In deze verdiepingsfase beoogt het Zorginstituut samen met de betrokken partijen te komen tot concrete aanbevelingen voor verbetering van de patiëntgerichtheid, effectiviteit en doelmatigheid van deze zorg. Eén van de thema's waar nader onderzoek naar wordt gedaan is voeding bij maculadegeneratie.

In opdracht van het Zorginstituut heeft Cochrane Netherlands een systematische review uitgevoerd naar het effect van voeding(ssupplementen) op het ontstaan of de progressie van leeftijdsgebonden maculadegeneratie (LMD).

2. Vraagstelling

Wat is het effect van voeding(ssupplementen) op het ontstaan of de progressie van LMD?

3. Methoden

3.1 Formuleren PICO's

In overleg met het Zorginstituut en de klinische experts werden de volgende PICO's geformuleerd, waarbij onderscheid wordt gemaakt tussen preventieve interventies en therapeutische interventies.

<u>Effectiviteit van preventieve interventies (PICO 1)</u>

- **Populatie**: Mensen met een verhoogd risico op leeftijdsgebonden maculadegeneratie (LMD) die nog geen klachten hebben. Indien mogelijk wordt onderscheid gemaakt naar risicofactor.
- **Interventies**: Voeding en/of (combinaties van) voedingssupplementen.
- **Vergelijkende interventies (*Comparison*)**: Geen behandeling en geen (aandacht voor) specifieke voedingof voedingssupplementen.
- **Uitkomsten (*Outcomes*)**:
  Primaire eindpunten

[*] https://www.zorginstituutnederland.nl/over-ons/publicaties/publicatie/2019/01/31/werkwijze-systematische-doorlichting-programma-zinnige-zorg
[†] https://www.zorginstituutnederland.nl/publicaties/rapport/2019/08/27/zinnige-zorg---rapport-screeningsfase-ziekten-van-het-oog

- Ontstaan van een vorm van LMD (beginnend of gevorderd, of beide),
- Ontstaan van gevorderd LMD (geografische atrofie of neovasculair, of beide),
- Gerapporteerde bijwerkingen.

Effectiviteit van therapeutische interventies (PICO 2a en 2b)

- **Populatie**: Mensen met LMD. Indien mogelijk wordt onderscheid gemaakt tussen verschillende stadia van LMD, waarbij mensen met eenzijdig eindstadium LMD een sugroep vormen.

2a)

- **Interventies**: Standaardbehandeling volgens richtlijnen met (aandacht voor) specifieke voeding of voedingsadviezen.
- **Vergelijkende interventies (*Comparison*)**: Standaardbehandeling volgens richtlijnen zonder (aandacht voor) specifieke voeding of voedingsadviezen.

2b)

- **Interventies**: Standaardbehandeling volgens richtlijnen met (combinatie van) voedingssupplementen.
- **Vergelijkende interventies (*Comparison*)**: Standaardbehandeling volgens richtlijnen zonder voedingssupplementen of met andere (combinatie van) voedingssupplementen.

- **Uitkomsten (*Outcomes*)**:
  Primaire eindpunten
  - Progressie naar gevorderd LMD (geografische atrofie of neovasculair, of beide),
  - Gerapporteerde bijwerkingen.

  Secundair eindpunt
  - Visus

Voor beide PICO's werden de uitkomsten volgens het GRADE-systeem in overleg met de klinische experts en het Zorginstituut ingedeeld (7-9 'Cruciaal'; 4-6 'Belangrijk; 1-3 'Niet belangrijk') (Guyatt 2011):

- Cruciaal: ontstaan/progressie van LMD (9); bijwerkingen (7).
- Belangrijk: visus (5).

3.2 Identificatie en selectie van relevante onderzoeken

Aan de hand van de aldus geformuleerde vraagstelling werd gezocht naar systematische reviews (SR's) over maculadegeneratie in de volgende elektronische databases: Epistemonikos (bevat MEDLINE en Embase) en The Cochrane Database of Systematic Reviews (inclusief de reviews van de Cochrane Eyes and Vision Group). We beperkten ons hierbij tot systematische reviews verschenen tussen 1 januari 2015 en 10 juni 2020.

In nauw overleg met de klinische experts en afgestemd met het Zorginstituut werden criteria geformuleerd voor de in- en exclusie van SR's die de verschillende PICO-vragen beantwoorden. Relevante SR's onderzochten het effect van bepaalde voeding(ssupplementen) op het ontstaan of de progressie van maculadegeneratie, vergeleken met geen behandeling of geen (aandacht voor) specifieke voeding, voedingsadviezen of voedingssupplementen, en werden gepubliceerd in het Engels, Nederlands, Duits, Spaans, Italiaans of Japans.

Voor de selectie van de meest geschikte review voor een bepaalde onderzoeksvraag werd de volgende procedure gehanteerd (Jadad 1997):

a. De review betreft de PICO van de onderzoeksvraag.
b. Er werd gezocht in MEDLINE en tenminste één andere elektronische database.
c. De risk of bias bepaling is op studieniveau gerapporteerd en betrof tenminste de voor GRADE benodigde belangrijkste kwaliteitsitems.
d. De beschrijvende gegevens en resultaten worden op studieniveau gepresenteerd (effectschattingen met 95% betrouwbaarheidsinterval (95% BI)).

Werd voor een bepaalde onderzoekvraag meer dan één SR geïdentificeerd, dan werd de meest complete of meest recente review geselecteerd voor verdere analyse (in overleg met het Zorginstituut). Werd alleen een SR gevonden die aan criterium a) en b) voldeed, maar niet aan c) of d), dan werd deze SR als uitgangspunt genomen en werden de daarin geïncludeerde onderzoeken verder verwerkt conform de hierna beschreven werkwijze (tenzij het aantal geïncludeerde studies groter is dan 10).

Ter aanvulling op de geïdentificeerde systematische reviews werd in MEDLINE, Embase en het Cochrane register CENTRAL gezocht naar primaire onderzoeken (RCT's of niet-gerandomiseerde vergelijkende studies) die gepubliceerd zijn tussen 1 januari 2015 en 8 juli 2020.

De selectie van systematische reviews en primaire onderzoeken werd uitgevoerd door twee onderzoekers onafhankelijk van elkaar. Verschillen tussen twee beoordelaars werden bediscussieerd. In geval geen overeenstemming bereikt werd, werd een derde onderzoeker ingeschakeld, wiens/wier oordeel leidend was.

3.3 Data-extractie en analyses

Van iedere publicatie werden beschrijvende gegevens verzameld (kenmerken van de patiënten, interventie, controlebehandeling, klinische uitkomsten en de resultaten (effect) welke werden weergegeven in zogenoemde evidencetabellen. Tevens werd van ieder onderzoek de methodologische kwaliteit bepaald. Voor SR's werd daartoe AMSTAR-2 gebruikt (Shea 2017), voor RCT's de Cochrane Risk of Bias tool (Higgins 2011), en voor niet-gerandomiseerde vergelijkende studies ROBINS-I (Sterne 2016). De resultaten van deze beoordelingen werden in tabellen weergegeven.

Extractie van de resultaten en beoordeling van de methodologische kwaliteit werden ook uitgevoerd door twee onderzoekers onafhankelijk van elkaar. Verschillen tussen twee beoordelaars werden bediscussieerd. In geval geen overeenstemming bereikt werd, werd een derde onderzoeker ingeschakeld, wiens/wier oordeel leidend was.

Vervolgens werd gekeken of de meta-analysen van de gevonden reviews geactualiseerd konden worden of dat er nieuwe meta-analyses uitgevoerd konden worden, waarbij de methoden gehanteerd werden zoals beschreven in het Cochrane Handbook (Higgins 2011). Omdat patiënten, interventies en/of uitkomsten in de verschillende studies onvoldoende vergelijkbaar waren (hetgeen werd voorgelegd aan de klinische experts), werden resultaten uit de systematische reviews en primaire onderzoeken op een kwalitatieve wijze gecombineerd en samengevat.

Hiertoe werden de resultaten gegroepeerd per type dieet, voedingsstof, -component of -supplement en kenden twee onderzoekers onafhankelijk van elkaar de mate van *certainty of the evidence* toe aan de hand van de GRADE-methodiek.

Op basis van de GRADE *levels of certainty* en de richting van het gevonden effect werden de dieten, voedingsstoffen, -componenten en -supplementen ingedeeld in vier categorieën (Tabel 1).

Tabel 1 Indeling resultaten o.b.v. GRADE levels of certainty en richting van het gevonden effect

Categorie	Omschrijving
Sterke evidence, aan- of afwezigheid van een effect overtuigend	GRADE high certainty of evidence voor een positief of negatief effect, of voor de afwezigheid van een effect
Sterke evidence, aan- of afwezigheid van een effect waarschijnlijk	GRADE moderate certainty of evidence voor een positief of negatief effect, of voor de afwezigheid van een effect
Beperkte evidence, aan- of afwezigheid van een effect mogelijk	GRADE low certainty of evidence, trend voor een positief of negatief effect, of voor de afwezigheid van een effect
Beperkte evidence, (potentieel) effect onduidelijk	• GRADE low certainty of evidence, geen trend voor een postief of negatief effect, of voor de afwezigheid van een effect • GRADE very low certainty of evidence

De indeling van resultaten in deze vier categorieën werd gecontroleerd door één van de klinische experts en op basis hiervan werden ten slotte voor iedere uitgangsvraag conclusies geformuleerd.

4. Resultaten

4.1 Selectie van onderzoeken

4.1.1 Systematische reviews

Op 10 juni 2020 werd een zoekactie uitgevoerd naar systematische reviews betreffende het effect van voeding(ssupplementen) op (de ontwikkeling van) LMD. Er werd gezocht in Epistemonikos en de Cochrane Library naar systematische reviews over LMD die gepubliceerd waren vanaf 2015. De zoekstrategieën zijn weergegeven in Bijlage 1A.

Er werden 316 potentieel relevante artikelen gevonden (Bijlage 2A). Na ontdubbelen bleven 285 artikelen over, waarvan op basis van de titel en/of het abstract 261 niet relevant bleken. Van de overige 24 onderzoeken werd het volledige artikel bekeken. Er werden 10 relevante systematische reviews geïdentificeerd (Tabel 2). De 14 uitgesloten systematische reviews en de redenen voor exclusie staan samengevat in Bijlage 3A.PVan de potentieel geschikte systematische reviews werd op

basis van de zoekdatum, de PICO-elementen en overlappende ingesloten primaire onderzoeken besloten om zes reviews (Chapman 2019; Dinu 2019; Evans 2017a; Evans 2017b; Lawrenson 2015; Waugh 2018) te includeren.

Tabel 2 Overzicht van systematische reviews betreffende voeding(ssupplementen) bij LMD gepubliceerd in de periode 2015-2020 (n=10)

Reference	Population	Intervention	Comparator	Outcome	Search date	Prevention / intervention	Diet / supplements	Study type
Chapman 2019	Adults in the general population, with and/or without age-related macular degeneration	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	Aug-17	Both	Diet	All
Dinu 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)	Jan-18	Prevention	Diet	Prospective cohort studies
Evans 2017a (prevention)	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	Mar-17	Prevention	Supplements	RCTs
Evans 2017b (intervention)	People with AMD	Antioxidant vitamin or mineral supplementation, alone or in combination: vitamin C, vitamin E, carotenoids (including the macular pigment carotenoids	Placebo or no intervention	Progression to late AMD; Progression to neovascular AMD; Progression to geographic atrophy; Progression to visual	Mar-17	Intervention	Supplements	RCTs

Reference	Population	Intervention	Comparator	Outcome	Search date	Prevention / intervention	Diet / supplements	Study type
		lutein and zeaxanthin), selenium, and zinc		loss; Quality of life; Resource use and costs.				
Feng 2017	Subjects who were diagnosed with AMD	Lutein supplementation (alone or in combination with other antioxidants)	Placebo	Macular pigment optical density	Dec-18	Intervention	Supplements	RCTs
Lawrenson 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	Feb-15	Both	Both	RCTs
Ma 2016	Patients with AMD, healthy subjects	Lutein, zeaxanthin and meso-zeaxanthin supplementation	Placebo	Macular pigment optical density	May-16	Both	Supplements	RCTs
Waugh 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	Jul-17	Both	Both	All study types
Wei 2018	Atrophic AMD patients	Any therapeutic strategy (including lutein; antioxidant complex; zinc-monocysteine)	Placebo or no intervention	Best-corrected visual acuity (BCVA) and GA area change	Dec-17	Intervention	Supplements	RCTs
Zhu 2016	Not described. Included population based and hospital based studies	Fish consumption	Various	AMD	Aug-16	Prevention	Diet	Prospective cohort studies

Tabel 3 Methodologische kwaliteit van de geïncludeerde systematische reviews over voeding(ssupplementen) ter voorkoming van (de progressie van) leeftijdsgebonden maculadegeneratie (AMSTAR 2) (n=6)

	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 2019	Y	N	Y	PY	N	N	N	PY	N	N	NA	NA	N	N	NA	Y
Dinu 2019	Y	N	Y	PY	Y	Y	N	PY	Y	N	Y	N	N	Y	Y	Y
Evans 2017a	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Evans 2017b	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y
Lawrenson 2015	Y	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Waugh 2018	Y	N	Y	PY	N	N	PY	Y	Y	Y	NA	NA	N	N	NA	Y

Y=yes, N=no, PY=partial yes, NA=not applicable

Zie bijlage 5 voor onderbouwing van de in de tabel gepresenteerde scores.

4.1.2 Primaire onderzoeken

Op 8 juli 2020 werd een zoekactie uitgevoerd naar primaire onderzoeken (RCT's of niet-gerandomiseerde vergelijkende onderzoeken) betreffende het effect van voeding(ssupplementen) op het ontstaan of de progressie van LMD. Er werd gezocht in MEDLINE, Embase en het Cochrane register CENTRAL naar onderzoeken gepubliceerd vanaf 2015. De zoekstrategieën zijn weergegeven in Bijlage 1B.

Er werden 2666 potentieel relevante artikelen gevonden (Bijlage 2B). Na ontdubbelen bleven 2051 artikelen over, waarvan op basis van de titel en/of het abstract 1921 niet relevant bleken. Van de overige 130 onderzoeken werd het volledige artikel bekeken en er werden 36 relevante onderzoeken geïdentificeerd. De 95 uitgesloten onderzoeken en de redenen voor exclusie staan samengevat in Bijlage 3B.

Van de 36 relevante artikelen werden in overleg met de opdrachtgever enkel de RCT's (n=5, over voedingssupplementen) en cohortonderzoeken (n=13, over voeding) nader uitgewerkt in dit rapport. De overige 18 onderzoeken werden vanwege een kwalitatief mindere onderzoeksopzet (cross-sectioneel onderzoek of patiëntcontroleonderzoek) terzijde gelegd. Een overzicht van deze onderzoeken, inclusief gegevens over de vraagstelling en resultaten, staat in Bijlage 3C.

4.2 Beschrijving en kwaliteitsbeoordeling van de geïncludeerde onderzoeken

4.2.1 Systematische reviews

Van de zes geïncludeerde SR's onderzochten twee het effect van voeding (Chapman 2019; Dinu 2019) en twee het effect van voedingssupplementen (Evans 2017a; Evans 2017b) op het ontstaan en/of de progressie van LMD. Twee SR's (Lawrenson 2015; Waugh 2018) keken naar zowel voeding als voedingssupplementen. In de evidence tabellen (Bijlage 4) wordt alle beschikbare informatie over deze zes ingesloten reviews samengevat. Een overzicht van de AMSTAR 2-beoordelingen van deze reviews staat in Tabel 3 en de details van deze beoordelingen staan in Bijlage 5.

De review van Chapman (Chapman 2019) zocht in augustus 2017 naar interventie-onderzoeken (alle designs) betreffende de invloed van dieet of voedselinname op het onstaan of de progressie van LMD. Daarbij selecteerden de auteurs onderzoeken van hoge kwaliteit die statistisch significante resultaten rapporteerden. Zij includeerden 18 onderzoeken met in totaal 336916 deelnemers. Onderzochte interventies waren dieetpatroon (bijv. mediterraan, oosters, westers), voedingsstoffen (omega 3-vetzuren, koolhydraten, cartenoïden, multi-micronutriënten) en inname van specifiek voedsel (vlees, zuivel, calcium en alchohol). Daarbij keek de review naar de volgende uitkomsten: ontstaan van enige vorm van LMD; ontstaan van beginnende, matige, gevorderde of neovasculaire LMD; enige progressie van LMD; progressie naar gevorderde LMD; en visus. Deze review behaalde een negatieve score op de AMSTAR 2 items betreffende aanwezigheid van een onderzoeksprotocol (item 2), dubbele selectie en data extractie (items 5 en 6), lijst van geëxcludeerde onderzoeken (item 7), methode van kwaliteitsbeoordeling (item 9), bronnen van financiering van geïncludeerde onderzoeken (item 10), rekening gehouden met potentiële vertekening in en heterogeniteit tussen geïncludeerde onderzoeken in interpratie en discussie (items 13 en 14) (Tabel 2).

Dinu et al. (Dinu 2019) waren geïnteresseerd in de relatie tussen specifieke voedselgroepen of alcohol en het ontstaan van LMD. Ze zochten daartoe in januari 2018 naar prospectieve cohortonderzoeken en includeerden er 26 met in totaal 211676 deelnemers. Ze vergeleken een hoge inname van plantaardige producten, dierlijke producten, vetten of alcohol met een lage inname van dezelfde voedselgroepen en keken daarbij naar het ontstaan van LMD (enige vorm, beginnend of gevorderd). Met uitzondering van de items over de aanwezigheid van een onderzoeksprotocol (item 2), lijst van geëxcludeerde onderzoeken (item 7), bronnen van financiering van geïncludeerde onderzoeken (item 10) en potentiële invloed van vertekening op de resultaten en interpretatie daarvan (items 12 en 13) voldeed de review aan de AMSTAR-2 criteria (Tabel 2).

Eén SR richtte zich specifiek op voedingssupplementen ter preventie van LMD (Evans 2017a). Voor deze review werd in maart 2017 gezocht naar RCT's waarin het effect van antioxidanten (vitaminen en mineralen) op het ontstaan van LMD vergeleken werd met placebo of geen interventie. De vijf geïncludeerde RCT's betroffen in toaal 76756 deelnemers uit een algemene populatie met of zonder andere ziekten dan LMD en onderzochten vitamine C-, vitamine E-, bètacaroteen- en mulitivitaminesupplementen. De review rapporteerde resultaten voor het ontstaan van enige vorm LMD, het ontstaan van gevorderde LMD, neovasculaire LMD of geografische atrofie, en bijwerkingen. De review voldeed aan alle AMSTAR 2-items, alleen ontbrak de uitleg voor het enkel includeren van RCT's (item 3) en kon publicatiebias niet formeel worden onderzocht (item 15) (Tabel 2).

Dezelfde auteurs voerden ook een systematische review uit naar het effect van voedingssupplementen bestaande uit antioxidanten (vitaminen en mineralen) vergeleken met placebo of geen interventie bij mensen met LMD (Evans 2017b). Na een zoekactie in maart 2017 werden 19 RCT's geïncludeerd met in totaal 11162 deelnemers. De meerderheid van de RCT's richtte zich op beginnende LMD en onderzocht het effect van (combinaties van) de volgende antioxidanten: vitamine C, vitamine E, carotenoïden (inclusief luteïne and zeaxanthine), selenium en zink. De uitkomsten waarvoor resultaten werden gerapporteerd, waren progressie tot gevorderde LMD, progressie tot neovasculaire LMD, geografische atrofie of tot visusverlies, en bijwerkingen. Ook deze review scoorde positief voor de meeste AMSTAR-2 items, al werd geen uitleg gegeven voor het enkel includeren van RCT's (item 3), ontbrak een inschatting van de impact van mogelijke bias (item 12) en werd publicatiebias niet formeel onderzocht (item 15) (Tabel 2).

De review van Lawrenson (Lawrenson 2015) onderzocht het effect van omega 3-vetzuren (in voeding of als voedingssupplementen) vergeleken met placebo of geen interventie op het ontstaan of de progressie van LMD. De zoekactie voor deze review werd uitgevoerd in februari 2015 en er werden twee RCT's gevonden met in totaal 2380 deelnemers. Beide RCT's hadden deelnemers met een hoge kans op het ontwikkelen van gevorderde LMD en onderzochten omega 3-vetzuren in de vorm van supplementen. In de review werden resultaten gerapporteerd voor vijfjaars progressie van LMD, incidentie van choroïdale neovascularisatie, visusdaling van drie of meer regels en bijwerkingen. Met uitzondering van onderzoek naar publicatiebias (item 15) voldeed de review aan alle AMSTAR 2-items (Tabel 2).

Waugh et al. (Waugh 2018) zochten in juli 2017 breed naar zowel gerandomiseerde als observationele onderzoeken over voeding of voedingssupplementen bij mensen met de diagnose droge LMD. Van de 45 gevonden onderzoeken, rapporteerden er 32 (met in totaal 170727

deelnemers) relevante uitkomsten voor de onderhavige evidence synthese. Hoewel de review zich richtte op mensen met een diagnose van droge LMD, hadden 10 onderzoeken een populatie zonder LMD. De populatie in de overige onderzoeken varieerde van milde tot gevorderde LMD. Resultaten werden gerapporteerd voor ontwikkeling van LMD (beginnend, matig, gevorderd, totaal), progressie van LMD (enige progressie, progressie naar gevorderde LMD of geografische atrofie), bijwerkingen en gezichtsscherpte (op verschillende manieren en tijdstippen gemeten). Wat betreft AMSTAR 2 kon de review niet voldoen aan de criteria betreffende de aanwezigheid van een protocol (item 2), dubbele selectie en data extractie (items 5 en 6) en het rekening houden met potentiële vertekening in en heterogeniteit tussen geïncludeerde onderzoeken in interpretatie en discussie (items 13 en 14) (Tabel 2).

4.2.2 Primaire onderzoeken

Aanvullend op de SR's werden 18 primaire onderzoeken geïncludeerd (Tabel 4). In de evidence tabellen (Bijlage 4) wordt alle beschikbare informatie over deze onderzoeken samengevat. De kans op vertekening wordt weergegeven in de tabellen 4 t/m 6, details van deze bepalingen zijn te vinden in Bijlage 5.

Tabel 4 Ingesloten primaire onderzoeken (n=18)

Reference	Country	Population	Determinants / interventions	Outcome
Diet / nutrition				
De Koning-Backus 2019	Netherlands	People aged >55 years	Vegetables, fruit, fish, fat products, meat, grains, poultry, eggs, potatoes, legumes, dairy, and various food patterns	Development of AMD
Dighe 2018	USA	Healthy participants aged 45-65 yrs	Western (unhealthy) dietary pattern and prudent (healthy) dietary pattern	Development of AMD
Gopinath 2018a	Australia	Healthy participants aged ≥49 yrs	Nitrate (vegetable and nonvegetable)	Development of AMD
Gopinath 2018b	Australia	Healthy participants aged ≥49 yrs	Flavonoids, flavonols, flavanones, quercetin, and total hesperidin	Development of AMD
Gopinath 2020	Australia	Healthy participants aged ≥49 yrs	Eggs	Development of AMD
Joachim 2018	Netherlands and Australia	Participants ≥55 yrs (Netherlands) / ≥49 yrs (Australia) with early AMD lesions in either eye	Fish and lutein-zeaxanthin	Progression of AMD
Jones 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, sugarbased items and alcohol); Asian diet (eggs, fish, poultry, breads and cereals), and vegetarian diet (fruits, vegetables, dairy products and nuts).	Development of AMD
Keenan 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,	Progression of AMD

			monounsaturated fatty acid : saturated fatty acid ratio (MUFA:SFA), and alcohol.	
Lin 2017	USA	Participants aged 45 to 64 yrs	Energy-adjusted xanthophyll	Development of AMD
Merle 2017	USA	Participants with at least one eye with nonadvanced AMD at baseline (eligible age not specified)	Vitamin D and Calcium	Progression of AMD
Merle 2019	Netherlands and France	Partcipants ≥55 yrs (Netherlands) / participants ≥73 yrs (France)	Mediterranean diet	Development of AMD
Tisdale 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
Wu 2017	USA	Female registered nurses aged 30 to 55 yrs and male health professionals aged 40 to 75 yrs	a-linolenic acid (ALA)	Development of AMD
Supplement(s)				
Akuffo 2017	Ireland	Participants with non-advanced 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 vs. AREDS 2 formulation without addition of mesozeaxanthin	Progression of AMD, Visual acuity, Adverse events
Broadhead 2018	Australia	Participants >50 yrs with moderate severity AMD	20 mg saffron vs. placebo	Progression of AMD, Visual acuity, Adverse events
Forte 2017	Italy	Adults with early-stage AMD (eligible age not specified)	All-E-epilutein plus all-E-lutein vs. all-E-lutein only	Visual acuity
Kim 2020	USA	Participants aged 55 to 90 yrs with geographic atrophy (GA) resulting from AMD	Alpha lipoic acid (ALA) vs. placebo	Visual acuity, Adverse events
Piatti 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,	Progression of AMD, Visual acuity, Adverse events

	containing EPA 185 mg and DHA 140 mg) vs. placebo

Negen onderzoeken keken naar de rol van voeding bij het ontstaan van LMD (PICO 1) (De Koning-Backus 2019; Dighe 2019; Gopinath 2018a; Gopinath 2018b; Gopinath 2020; Jones 2020; Lin 2017; Merle 2019; Wu 2017). Er werden geen primaire onderzoeken geïncludeerd die voedingssupplementen ter preventie van LMD bestudeerden.
Drie onderzoeken van dezelfde auteur werden in Australië uitgevoerd (Gopiniath 2018a; Gopinath 2018b; Gopinath 2020), drie onderzoeken werden in de Verenigde Staten uitgevoerd (Dighe 2018; Lin 2017; Wu 2017), één in Nederland (De Koning-Backus 2019), één in Nederland en Frankrijk (Merle 2019) en één in Australië en Singapore (Jones 2020). De grootte van de onderzoekspopulaties lag tussen de 1278 (Dighe 2018) en 114850 (Wu 2017) deelnemers met een gemiddelde leeftijd tussen de 53 en 79 jaar. Deelnemers werden zes (Lin 2017) tot 28 jaar (Wu 2017) gevolgd en voor één onderzoek werd de exacte follow-upduur niet vermeld (Jones 2020). In drie onderzoeken werd de invloed van een of meerdere voedingspatronen op het ontstaan van LMD onderzocht (Dighe 2018; Jones 2020; Merle 2019), één onderzoek keek naar zowel voedingspatronen als naar afzonderlijke voedselgroepen (De Koning-Backus 2019) en vijf onderzoeken richtten zich op een specifieke voedselgroep of voedingsstof: nitraat (Gopinath 2018a), flavonoïden (Gopinath 2018b), eieren (Gopinath 2020), xanthofyl (Lin 2017) en alfa-linoleenzuur (Wu 2017). Het onstaan van LMD was in alle onderzoeken de uitkomst die bestudeerd werd. Geen van de onderzoeken keek naar bijwerkingen. De kans op vertekening werd als matig ingeschat in vier onderzoeken (Gopinath 2018a; Jones 2020; Lin 2017; Merle 2019) en ernstig in de overige vijf, als gevolg van een mogelijk veranderend voedingspatroon over de tijd en/of door ontbrekende data (Tabel 5).

Tabel 5 Kans op vertekening in de ingesloten observationele onderzoeken naar het effect van voeding op het onstaan van LMD (ROBINS-I tool)

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
De Koning-Backus 2019	Low	Low	Low	Moderate	Serious	Low	Low	Serious
Dighe 2019	Low	Low	Low	Moderate	Serious	Low	Low	Serious
Gopinath 2018a	Low	Low	Low	Moderate	Moderate	Low	Low	Moderate
Gopinath 2018b	Low	Low	Low	Moderate	Serious	Low	Serious	Serious
Gopinath 2020	Low	Low	Low	Moderate	Serious	Low	Low	Serious
Jones 2020	Low	Low	Low	Moderate	Moderate	Low	Low	Moderate
Lin 2017	Low	Low	Low	Moderate	Moderate	Low	Low	Moderate
Merle 2019	Low	Moderate	Low	Moderate	Moderate	Low	Low	Moderate
Wu 2017	Low	Low	Low	Low	Moderate	Serious	Low	Serious

Negen onderzoeken bekeken bij mensen met LMD wat het effect van voeding (PICO 2a, 4 onderzoeken; [Joachim 2018; Keenan 2020; Merle 2017; Tisdale 2019]) of voedingssupplementen

(PICO 2b, 5 RCT's; [Akuffo 2017; Broadhead 2018; Forte 2017; Kim 2020; Piatti 2020]) op de progressie van LMD was (PICO 2). De vier onderzoeken naar voeding en het effect op de progressie van LMD werden uitgevoerd in Nederland en Australië (Joachim 2018) en de Verenigde Staten (Keenan 2020; Merle 2017; Tisdale 2019). Daarbij maakten twee van de onderzoeken gebruik van de Age-related Eye Disease Study (AREDS) cohorten en bestudeerden 7756 deelnemers (Keenan 2020) of 4751 deelnemers (Tisdale 2019). De overige twee onderzoeken vonden plaats in landelijke cohorten of registraties en hadden 835 (Joachim 2018) en 2146 deelnemers (Merle 2017). De gemiddelde leeftijd van de deelnemers lag tussen de 65 en 74 jaar en zij hadden een vroeg stadium LMD (Joachim 2018; Merle 2017) of matige tot gevorderde LMD (Keenan 2020; Tisdale 2019). In twee onderzoeken bevatte de populatie bij aanvang ook deelnemers zonder LMD (Keenan 2020; Tisdale 2019). Deelnemers werden gemiddeld 9,4 jaar (Merle 2017) tot 15 jaar (Joachim 2018) gevolgd. De onderzochte determinanten in de onderzoeken liepen uiteen. Joachim et al. onderzochten visconsumptie en luteïne-zeaxanthine inname (Joachim 2018), Merle et al. waren geïnteresseerd in vitamine D en calcium (Merle 2017), Tisdale et al. bestudeerden ook calcium (Tisdale 2019), en Keenan et al. keken naar een mediteraan dieetpatroon en de componenten daarin (fruit, groente, volkoren graanproducten, noten, peulvruchten, rood vlees, vis, de verhouding tussen enkelvoudig onverzadigd vetzuur en verzadigd vetzuur en alchohol) (Keenan 2020). In de twee onderzoeken die plaatsvonden in de AREDS-populatie gebruikte een groot deel van de deelnemers voedingssupplementen (antioxidanten, zink, luteïne/zeaxanthine, docosahexaeenzuur (DHA) plus eicosapentaeenzuur (EPA), al dan niet in combinatie) (Keenan 2020; Tisdale 2019). In alle vier de onderzoeken was de uitkomst van interesse de progressie van LMD, bijwerkingen of de visus werden niet bestudeerd. De kans op vertekening werd beoordeeld als matig in drie onderzoeken (Joachim 2018; Keenan 2020; Tisdale 2019). Voor het vierde onderzoek waren er geen aanwijzingen voor vertekening, maar kon kans op vertekening door gebrek aan informatie niet volledig worden ingeschat (Tabel 6).

Tabel 6 Kans op vertekening in de ingesloten observationele onderzoeken naar het effect van voeding op progressie van LMD (ROBINS-I tool)

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
Joachim 2018	Moderate	Moderate	Low	Low	No information	Low	Low	Moderate
Keenan 2020	Low	Low	Low	No information	Moderate	Low	Low	Moderate
Merle 2017	Low	Low	Low	No information	No information	Low	Low	No information
Tisdale 2019	Low	Low	Low	Moderate	Low	Low	Low	Moderate

De vijf RCTs die het effect van voedingssupplementen onderzochten, werden uitgevoerd in Italië (Forte 2017; Piatti 2020), Australië (Broadhead 2018), Ierland (Akuffo 2017) en de Verenigde Staten (Kim 2020). De omvang van de onderzoekspopulaties liep uiteen van 40 (Forte 2017) tot 121 (Akuffo 2017) deelnemers met een gemiddelde leeftijd van 64 tot 81 jaar. In alle RCT's werden deelnemers met LMD ingesloten, maar de LMD stadia verschilden tussen de onderzoeken, van beginnende LMD (Forte 2017) tot 'niet-gevorderde' LMD (Akuffo 2017), matige LMD (Broadhead 2018; Piatti 2020) of geografische atrofie (Kim 2020). De deelnemers werden twee maanden (Forte 2017) tot twee jaar (Akuffo 2017; Piatti 2020) gevolgd. In drie RCT's werd een voedingssupplement met een placebo vergeleken: safraan (Broadhead 2018), alfaliponzuur (ALA) (Kim 2020) en een combinatie van carotenoïden, antioxidanten en omega-3 vetzuren (Piatti 2020). De twee andere RCT's onderzochten de toegevoegde waarde van een supplement: mesozeaxanthine in aanvulling op de AREDS-2 formule met zink (Akuffo 2017) en alle-E-epiluteïne in aanvulling op alle-E-luteïne (Forte 2017). Progressie van LMD werd bestudeerd in drie RCT's (Akuffo 2017; Broadhead 2018; Piatti 2020), bijwerkingen in vier RCT's (Akuffo 2017; Broadhead 2018; Kim 2020; Piatti 2020) en visus in alle RCT's. Tabel 7 geeft de kans op vertekening weer in de ingesloten RCT's. In drie RCT's was de randomisatieprocedure niet geheel duidelijk, twee RCT's scoorden een onduidelijke of hoge kans op vertekening bij de uitkomstmeting en in één RCT werd de kans op vertekening als onduidelijk ingeschat als gevolg van onvolledige data en een hoge kans op vertekening door selectieve rapportage.

Tabel 7 Kans op vertekening in de ingesloten RCT's naar het effect van voedingssupplementen op progressie van LMD (Cochrane Risk of Bias tool)

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment - subjective outcomes	Blinding of outcome assessment - objective outcomes	Incomplete outcome data - subjective outcomes	Incomplete outcome data - objective outcomes	Selective reporting	Other
Akuffo 2017	Low	Low	Low	High	Low	Low	Low	Low	Low
Broadhead 2018	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Low
Forte 2017	Unclear	Unclear	Low	NA	Low	NA	Low	Unclear	Low
Kim 2020	Low	Unclear	Low	Low	Low	Low	Low	Low	Low
Piatti 2020	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	High	Low

4.3 Voeding(ssupplementen) ter preventie van LMD (PICO 1)

4.3.1 Voeding

Ontstaan van LMD

Tabel 8 geeft een samenvatting van de resultaten zoals in detail gepresenteerd in Bijlage 6A. De tabel geeft weer welke resultaten betreffende het effect van voeding op het ontstaan van LMD gebaseerd zijn op sterke danwel beperkte evidence. In de tabel staan de resultaten voor het effect van een hoge versus een lage inname van het betreffende eetpatroon, de voedingscomponent of –stof op het ontstaan van LMD. Hierbij wordt geen onderscheid gemaakt tussen verschillende stadia van LMD. Bij de onderzochte eetpatronen werden bepaalde voeding en voedingssstoffen als combinatie onderzocht. Bij een mediterraan eetpatroon werd gekeken naar de gecombineerde

inname van groente, fruit, peulvruchten, volkoren graanproducten, noten, olijfolie, vis, gevogelte, zuivelproducten, rode wijn en rood vlees. Componenten uit de eetpatronen kunnen ook los in de tabel voorkomen, indien deze als aparte determinant werden onderzocht. Resultaten zijn veelal afkomstig uit een enkel onderzoek, maar in het geval van alcohol, vis, vlees, vetzuren noten, groente en fruit, zijn er gecombineerde resultaten uit drie of meer onderzoeken. Details m.b.t. verschillende LMD stadia als uitkomsten en aantallen onderzoeken zijn terug te vinden in Bijlage 6A.

Tabel 8 Samenvatting resultaten voor het effect van voeding (hoge vs. lage inname) op het ontstaan van LMD

Evidence	Effect	Verminderde kans op onstaan LMD	Verhoogde kans op ontstaan LMD	Geen effect
Sterk	**Overtuigend**			
	Waarschijnlijk		Alcohol	
Beperkt	**Mogelijk**	Mediterraan eetpatroon*; eetpatroon met veel granen, vis, gestoomde/gekookte kip, groenten en noten; calcium; vitamine B12; bètacryptoxanthine; omega-3 vetzuren; vis; fruit; granen; noten	Homocysteïne; vlees	Lycopeen; olie; margarine; boter
	Onduidelijk	Westers eetpatroon**; oosters eetpatroon***; vegetarisch eetpatroon; gezond eetpatroon****; koolhydraten; alfacaroteen; bètacaroteen; luteïne/zeaxanthine; flavonoïden; sinaasappels; foliumzuur; vitamine C; vitamine D; vitamine E (α-tocopherol); nitraat; zuivelproducten; eieren; groente; xanthofyl; zink		

***Mediterraan eetpatroon:** hogere inname van groente, fruit, peulvruchten, volkoren producten en noten; gematigde consumptie van vis, gevogelte, zuivelproducten en rode wijn; gebruik van olijfolie i.p.v boter en een beperkte inname van rood vlees. ****Westers eetpatroon:** hogere inname van rood en bewerkt vlees, (gefrituurde) aardappelen, vetrijke (zuivel)producten, eieren, geraffineerde granen, suiker en alcohol. *****Oosters eetpatroon:** hogere inname van fruit, groente, peulvruchten, eieren, volkoren producten, tomaten, vis en gevogelte. ******Gezond eetpatroon:** hogere inname van kruisbloemige -, carotene-, donkergroene blad- en andere groenten, gevogelte, fruit, vis en zeevruchten, volkoren producten, meervoudig onverzadigde vetzuren en noten; beperkte inname van rood en bewerkt vlees, geraffineerde granen en met suiker gezoete dranken.

Er werd voor geen van de bestudeerde eetpatronen, voedingsstoffen of –componenten een overtuigend of waarschijnlijk effect gevonden, uitgezonderd van alcohol. In een meta-analyse van 12 cohortonderzoeken werd een 20% hogere kans op LMD gevonden bij een hoge ten opzichte van een lage consumptie alcohol (RR=1,20; 95% BI 1,04 tot 1,39) (Bijlage 6A). De afkapwaarden voor hoge of lage consumptie verschilden tussen de 12 ingesloten onderzoeken en werden uitgedrukt in aantal keren alcoholgebruik per maand of week, of in aantal gram per dag (uiteenlopend van 20 tot 44 gram gemiddeld per dag). In subgroepanalyses werd een vergelijkbaar effect gevonden voor de kans

op het ontstaan van vroege LMD (10 onderzoeken; RR=1,29; 95% BI 1,16 tot 1,43), terwijl voor de kans op het ontstaan van gevorderde LMD geen verschil werd aangetoond tussen hoge en lage alcoholconsumptie (9 onderzoeken; RR=0,98 (95% BI 0,76 tot 1,27).
Op basis van beperkte evidence werden er aanwijzingen gevonden voor eetpatronen, voedingsstoffen en –componenten die de kans op het ontstaan van LMD al dan niet beïnvloeden (zie Tabel 8 “Mogelijk effect”). Hoewel voor carotenoïden (m.u.v. bètacryptoxanthine en lycopeen) een onduidelijk effect op het ontstaan van LMD gevonden werd, lijkt er een verschil te zijn tussen matige en gevorderde LMD. Op het ontstaan van gevorderde LMD heeft een hoge inname van carotenoïden in de voeding mogelijk een preventieve werking, terwijl er op het onstaan van matige LMD geen effect lijkt te zijn.

Naast de in Tabel 8 beschreven resultaten voor een hoge inname versus een lage inname van bepaalde voeding(sstoffen), vergeleek één onderzoek expliciet de aanbevolen inname van verschillende voedingscategorieën (groente, fruit, vis, vetten, vlees, gevogelte, granen, eieren, aardappelen, peulvruchten en zuivel) met een hogere of lagere inname dan aanbevolen (De Koning-Backus 2019). De inname van de aanbevolen hoeveelheid vis (32 gram/dag) en de combinatie van de aanbevolen hoeveelheden groente (200 gram), fruit (200 gram) en vis (32 gram) per dag resulteerden in een verminderde kans op het ontstaan van LMD (HR’s zijn respectievelijk 0,76 [95% BI 0,60 tot 0,97] en 0,58 [95% BI 0,36 tot 0,93]; very low certainty of evidence). Voor de andere (combinaties van) voedingscategorieën was er een onduidelijk effect op het ontstaan van LMD bij aanbevolen inname vergeleken met een hogere of lagere inname.

Bijwerkingen

Geen van de ingesloten systematische reviews en primaire onderzoeken bestudeerden bijwerkingen van bepaalde voeding(sstoffen).

4.3.1 Voedingssupplementen

Ontstaan van LMD

Tabel 9 geeft een samenvatting van de resultaten zoals in detail gepresenteerd in Bijlage 6B. De tabel toont welke resultaten betreffende het effect van voedingssupplementen op het ontstaan van LMD gebaseerd zijn op sterke danwel beperkte evidence. Hierbij werd uitgegaan van de uitkomst ‘ontstaan van een vorm van LMD’. Alle voedingssupplementen werden vergeleken met placebo. Multivitaminen (in de samenstelling zink 15 mg, vitamine E 45 IE, vitamine C 60 mg, bètacaroteen 5000 IE vitamine A, 20% als bètacaroteen, foliumzuur 2,5 mg, vitamine B6 50 mg en vitamine B12 1 mg) als voedingssupplement hebben waarschijnlijk een negatief effect op het ontstaan van LMD (RR=1,21; 95% BI 1,02 to 1,43). Voor vitamine C (500 mg/dag), vitamine E (50 mg/dag; 500 IE/dag;of 400 IE, 500 IE of 600 IE om de dag) en bètacaroteen (20 mg/dag of 50 mg om de dag) als voedingssupplementen werd overtuigende evidence gevonden dat ze geen invloed hebben op het ontstaan van LMD (respectievelijk RR=0,96 [95% BI 0,79 tot 1,18]; RR=0,97 [95% BI 0,90 tot 1,06]; en RR=1,00 [95% BI 0,88 to 1,14]). Resultaten voor gevorderde LMD waren vergelijkbaar, zij het met een lager GRADE certainty of evidence level, behalve voor vitamine E (RR=1,22; 95% BI 0,89 tot 1,67) (zie Bijlage 6B voor details). Voor vitamine E en bètacaroteen werd tevens het effect op het ontstaan van neovasculaire LMD of geografische atrofie onderzocht, welke onduidelijk bleek (very low certainty of evidence).

Tabel 9 Samenvatting resultaten voor het effect van voedingssupplementen ter preventie van LMD

Evidence	Effect	Verminderde kans op ontstaan LMD	Verhoogde kans op ontstaan LMD	Geen effect
Sterk	**Overtuigend**			Vitamine C; vitamine E; bètacaroteen
	Waarschijnlijk		Multivitaminen*	
Beperkt	**Mogelijk**			
	Onduidelijk	Foliumzuur met vitamine B6 en B12; combinatie van alfatocoferol en bètacaroteen		

* Centrum Silver (zink 15 mg; vitamine E 45 IE; vitamine C 60 mg; bètacaroteen 5000 IE; vitamine A, 20% als bètacaroteen; foliumzuur 2,5 mg; vitamine B6 50 mg; vitamine B12 1 mg)

Bijwerkingen

De ingesloten systematische reviews beschreven bijwerkingen van de gebruikte voedingssupplementen voornamelijk op narratieve wijze. Bètacaroteen werd geassocieerd met een verhoogde kans op longkanker bij mensen die roken (high certainty of evidence). Van vitamine C supplementen werden geen bijwerkingen gerapporteerd. Voor vitamine E werd in één RCT een grotere kans op hersenbloedingen gevonden in de studiegroep die vitamine E kreeg, vergeleken met de placebogroep (HR=1,74; 95% BI 1,04 tot 2,9), terwijl er in twee andere RCT's geen verschil gevonden werd tussen de studiegroepen (low certainty of evidence). Bij het gebruik van multivitaminen werd een verhoogde kans op huiduitslag gerapporteerd (HR=1,08; 95% BI 1,01 tot 1,15; moderate certainty of evidence).

4.4 Effect van voeding(ssupplementen) op de progressie van LMD (PICO 2)

4.4.1 Voeding

Progressie van LMD

Tabel 10 geeft een samenvatting van de resultaten zoals in detail gepresenteerd in Bijlage 6C. In de tabel is te zien voor welke resultaten het effect van voeding (hoge versus lage inname) op de progessie van LMD gebaseerd is op sterke danwel beperkte evidence. De tabel geeft de resultaten weer voor progressie van LMD in het algemeen, zonder onderscheid te maken tussen verschillende stadia van LMD. Alle resultaten werden gevonden in een enkel cohort- of cross-sectioneel onderzoek.

Tabel 10 Samenvatting resultaten voor het effect van voeding (hoge vs. lage inname) op de progressie van LMD

Evidence	Effect	Afname LMD progressie	Toename LMD progressie	Geen effect
Sterk	**Overtuigend**			

	Waarschijnlijk	Mediterraan eetpatroon*		
Beperkt	**Mogelijk**	Oosters eetpatroon**; vitamine D; groente	Westers eetpatroon***; koolhydraten; transvet; rood vlees	Fruit; peulvruchten
	Onduidelijk	Calcium; combinatie van calcium en vitamine D; thiamine; riboflavine; foliumzuur; carotenoïden; enkelvoudig onverzadigde vetzuren; omega-3 vetzuren; olijfolie; granen; noten; vis		

***Mediterraan eetpatroon:** hogere inname van groente, fruit, peulvruchten, volkoren producten en noten; gematigde consumptie van vis, gevogelte, zuivelproducten en rode wijn; gebruik van olijfolie i.p.v boter en een beperkte inname van rood vlees. ** **Oosters eetpatroon:** hogere inname van fruit, groente, peulvruchten, eieren, volkoren producten, tomaten, vis en gevogelte. *** **Westers eetpatroon**: hogere inname van rood en bewerkt vlees, (gefrituurde) aardappelen, vetrijke (zuivel)producten, eieren, geraffineerde granen, suiker en alcohol.

Een mediterraan eetpatroon, bestaande uit een hoge inname van groente, fruit, peulvruchten, volkoren producten, noten en olijfolie en gematigde consumptie van vis, gevogelte, zuivelproducten en rode wijn, heeft waarschijnlijk een gunstig effect op de progressie van (gevorderde) LMD (2 cohortonderzoeken: HR's voor progressie tot gevorderde LMD van 0,74 [95% BI 0,61 tot 0,91] en 0,78 [95% BI 0,71 tot 0,85]; 1 cohortonderzoek: progressie tot neovasculair LMD HR=0,84 [95% BI 0,75 tot 0,95] en progressie tot geografische atrofie HR=0,71 [95% BI 0,63 tot 0,80]). Ook voor een oosters eetpatroon (fruit, groente, peulvruchten, eieren, volkoren producten, tomaten, vis en gevogelte), een hoge inname van groente en vitamine D wijst de gevonden evidence naar een mogelijk gunstig effect. Een westers eetpatroon, gekenmerkt door een hoge inname van rood en bewerkt vlees, gefrituurde producten, aardappelen, vetrijke (zuivel)producten, eieren, geraffineerde granen, suiker en alcohol, heeft mogelijk een negatief effect, evenals een hoge inname van koolhydraten, transvetten en rood vlees. Voor alcohol werden geen onderzoeken met resultaten voor een hoge inname t.o.v. een lage inname gevonden. In één van de onderzoeken werd wel gekeken naar alcoholinname binnen een bepaald interval (5-15 g/dag [vrouwen] of 10-15 g/dag [mannen]) vergeleken met daarbuiten (Keenan 2020). De resultaten suggereren een mogelijk gunstig effect op LMD-progressie voor alcoholinname binnen het interval.

Bijwerkingen

Geen van de ingesloten systematische reviews en primaire onderzoeken bestudeerde bijwerkingen van bepaalde voeding(sstoffen).

Visus

Geen van de ingesloten systematische reviews en primaire onderzoeken bestudeerde het effect van voeding(sstoffen) op de visus.

4.4.2.Voedingssupplementen

Progressie van LMD

Tabel 11 geeft een samenvatting van de resultaten zoals in detail gepresenteerd in Bijlage 6D. Hierin is te zien voor welke resultaten het effect van voedingssupplementen op de progessie van LMD gebaseerd is op sterke danwel beperkte evidence. Daarbij werd uitgegaan van de uitkomst progressie van LMD in het algemeen, zonder onderscheid te maken tussen verschillende stadia van

LMD. De voedingssupplementen werden vergeleken met placebo, met uitzondering van mesozeaxanthine, daarvan werd de toegevoegde waarde bovenop de AREDS-formule onderzocht. Antioxidanten als voedingssupplementen (multivitaminen en mineralen; in de meerderheid van de onderzoeken bestaande uit de AREDS-formule [combinatie van dagelijks 500 mg vitamine C, 400 IE vitamine E, 15 mg bètacaroteen, 80 mg zink als zinkoxide en 2 mg koper als koperoxide]) hebben waarschijnlijk een positief effect op het ontstaan van (gevorderde) LMD (OR=0,72; 95% BI 0,58 tot 0,90). Voor omega-3 vetzuren als voedingssupplementen (650 mg EPA in combinatie met 350 mg DHA of 270 mg EPA in combinatie met 840 mg DHA) werd overtuigende evidence gevonden dat ze geen invloed hebben op de progressie van LMD (HR=0,96 (95% BI 0,84 to 1,10). Resultaten voor afzonderlijke stadia van LMD zijn vergelijkbaar, zij het met een lager GRADE certainty of evidence level (zie Bijlage 6D voor details). Het effect van omega-3 vetzuren in combinatie met carotenoïden en antioxidanten was onduidelijk. Zink als voedingssupplement leidt mogelijk tot een afname van LMD progressie net als luteïne en/of zeaxanthine.

Tabel 11 Samenvatting resultaten voor het effect van voedingssupplementen op de progressie van LMD

Evidence	Effect	Afname LMD progressie	Toename LMD progressie	Geen effect
Sterk	**Overtuigend**			Omega-3 vetzuren
	Waarschijnlijk	Antioxidanten (multivitaminen en mineralen)*		
Beperkt	**Mogelijk**	Zink; luteïne en/of zeaxanthine		
	Onduidelijk	Vitamine E; saffraan; mesozeaxanthine**; combinatie van carotenoïden, antioxidanten en omega-3 vetzuren		

*Supplement bestond (in meerderheid van de onderzoeken) uit de AREDS-formule (combinatie van vitamine C, vitamine E, bètacaroteen, zinkoxide en koperoxide). **als toevoeging op AREDS-formule supplementen.

Bijwerkingen

De ingesloten systematische reviews en RCTs rapporteerden geen ernstige bijwerkingen gerelateerd aan carotenoïden, vitamine E, omega-3 vetzuren, saffraan en combinaties van carotenoïden met vitaminen, mineralen, antioxidanten of vetzuren. In één RCT werd vaker een gele huid gerapporteerd bij gebruik van multivitaminen dan in de placebogroep (very low certainty of evidence). Gebruik van alfaliponzuur gaf vaker aanleiding tot gastrointestinale klachten dan placebo (low certainty of evidence). Ook voor zink als voedingssupplement werden in sommige onderzoeken gastrointestinale symptomen als bijwerking genoteerd, maar dit verschilde niet significant van placebo. In één RCT leidde zinkgebruik vaker tot anemie dan placebo, terwijl in een andere RCT het verschil niet significant was (very low certainty of evidence). Details over de gerapporteerde bijwerkingen zijn te vinden in de evidencetabellen in Bijlage 4.

Visus

De resultaten betreffende visus als uitkomstmaat staan in Bijlage 6E. Vanwege heterogeniteit qua vergelijkingen, wijze waarop de uitkomsten gemeten werden en de follow-upduur zijn de resultaten lastig samen te vatten. In sommige onderzoeken werd een statistisch significant verschil gevonden ten gunste van het gebruik van voedingssupplementen, maar als gevolg van kleine

onderzoekspopulaties en de kans op vertekening zijn de conclusies van deze onderzoeken in beperkte mate extrapoleerbaar en betrouwbaar.

4.4.3 Combinatie van voeding en voedingssupplementen

In één van de onderzoeken werd naar het gecombineerde effect van voeding en voedingssupplementen gekeken op de progressie van LMD (Bijlage 6F). De resultaten suggereren een ongunstig effect op de progressie van LMD voor een hoge versus een lage totale calciuminname. Het is onduidelijk of de gecombineerde inname van vitamine D uit voeding en als supplement een effect heeft op de progressie van LMD. Ook een effect van een hoge totale inname van calcium en vitamine D samen is onduidelijk.

4.5 Conclusies

Mensen zonder LMD

Voeding

Sterke evidence

- Een hoge consumptie van alcohol leidt waarschijnlijk tot een verhoogde kans op het ontstaan van LMD in vergelijking met een lage consumptie van alcohol (GRADE: moderate certainty of evidence).

Beperkte evidence

- Een hoge t.o.v. een lage inname van de volgende voeding(sstoffen) leidt mogelijk tot een verminderde kans op het ontstaan van LMD: calcium, vitamine B12, bètacryptoxanthine, omega-3 vetzuren, vis, fruit, granen of noten (GRADE: low certainty of evidence). Hetzelfde geldt voor een mediterraan eetpatroon of een eetpatroon met veel granen, vis, gestoomde/gekookte kip, groenten en noten (GRADE: low certainty of evidence).
- Een hoge t.o.v. een lage inname van de volgende voeding(sstoffen) leidt mogelijk tot een verhoogde kans op het ontstaan van LMD: homocysteïne en vlees (GRADE: low certainty of evidence)
- Een hoge t.o.v. een lage inname van de volgende voeding(sstoffen) heeft mogelijk geen effect op het ontstaan van LMD: lycopeen, olie, margarine of boter (GRADE: low certainty of evidence).
- Van de volgende voeding(sstoffen) of eetpatronen is een effect op het ontstaan van LMD onduidelijk: koolhydraten, alfacaroteen, bètacaroteen, luteïne/zeaxanthine, flavonoïden, sinaasappels, foliumzuur, vitamine C, vitamine D, vitamine E (α-tocopherol), nitraat, zuivelproducten, eieren, groente, xanthofyl, zink, westers eetpatroon, oosters eetpatroon, vegetarisch eetpatroon of gezond eetpatroon (GRADE: low tot very low certainty of evidence).

Geen evidence

- Er werden geen onderzoeken geïncludeerd waarin bijwerkingen van voeding(sstoffen) bij mensen zonder LMD werden onderzocht.

Voedingssupplementen

Sterke evidence

- Het gebruik van vitamine C, vitamine E of bètacaroteen als voedingssupplement heeft geen effect op het ontstaan van LMD (GRADE: high certainty of evidence).

- Het gebruik van multivitaminen als voedingssupplement leidt waarschijnlijk tot een verhoogde kans op het ontstaan van LMD (GRADE: moderate certainty of evidence).
- De volgende bijwerkingen van voedingssupplementen werden beschreven: een verhoogde kans op longkanker bij mensen die roken bij gebruik van bètacaroteen (GRADE: high certainty of evidence) en huiduitslag bij gebruik van multivitaminen (GRADE: moderate certainty of evidence).

Beperkte evidence

- Van het gebruik van foliumzuur met vitamine B6 en van de combinatie alfatocoferol en bètacaroteen als voedingssupplement is het effect op het ontstaan van LMD onduidelijk.
- Een grotere kans op hersenbloedingen bij gebruik van vitamine E als voedingssupplement werd beschreven (GRADE: low certainty of evidence).

Patiënten met LMD

Voeding

Sterke evidence

- Een mediterraan eetpatroon heeft waarschijnlijk een remmend effect op de progressie van LMD (GRADE: moderate certainty of evidence).

Beperkte evidence

- Een hoge t.o.v. een lage inname van vitamine D of groenten heeft mogelijk een remmend effect op de progressie van LMD: (GRADE: low certainty of evidence). Hetzelfde geldt voor een oosters eetpatroon (GRADE: low certainty of evidence).
- Een hoge t.o.v. een lage inname van koolhydraten, transvetten, rood vlees of een westers eetpatroon leidt mogelijk tot een toename van de progressie van LMD: (GRADE: low certainty of evidence).
- Een hoge t.o.v. een lage inname van fruit en peulvruchten heeft mogelijk geen effect op de progressie van LMD (GRADE: low certainty of evidence).
- Van de volgende voeding(sstoffen) is een effect op de progressie van LMD onduidelijk: calcium, combinatie van calcium en vitamine D, thiamine, riboflavine, foliumzuur, carotenoïden, enkelvoudig onverzadigde vetzuren, omega-3 vetzuren, olijfolie, granen, noten of vis (GRADE: low tot very low certainty of evidence).

Geen evidence

- Er werden geen onderzoeken geïncludeerd waarin bijwerkingen van voeding(sstoffen) bij patiënten met LMD werden onderzocht.
- Er werden geen onderzoeken geïncludeerd waarin het effect van voeding(sstoffen) op de visus van patiënten met LMD werd onderzocht.

Voedingssupplementen

Sterke evidence

- Het gebruik van omega-3 vetzuren als voedingssupplement heeft geen effect op de progressie van LMD (GRADE: high certainty of evidence).

- Het gebruik van antioxidanten (multivitaminen en mineralen) als voedingssupplement heeft waarschijnlijk een remmend effect op de progressie van LMD (GRADE: moderate certainty of evidence).

Beperkte evidence

- Het gebruik van zink of van luteïne en/of zeaxanthine als voedingssupplement heeft mogelijk een remmend effect op de progressie van LMD (GRADE: low certainty of evidence).
- Van de volgende voedingssupplementen is het effect op de progressie van LMD onduidelijk: vitamine E; saffraan; mesozeaxanthine als aanvulling op de AREDS-formule; of de combinatie van carotenoïden, antioxidanten en omega-3 vetzuren (GRADE: low tot very low certainty of evidence).
- De volgende bijwerkingen van voedingssupplementen werden beschreven: gele huid bij gebruik van multivitaminen (GRADE: very low certainty of evidence); anemie bij gebruik van zink (GRADE: very low certainty of evidence); gastrointestinale klachten bij gebruik van alfaliponzuur (GRADE: low certainty of evidence).
- Het effect van voedingssupplementen op de visus van mensen met LMD is onduidelijk.

Combinatie van voeding en voedingssupplementen

Beperkte evidence

- Een hoge totale inname t.o.v. een lage inname van calcium uit voeding en als supplement leidt mogelijk tot een toename van de progressie van LMD (GRADE: low certainty of evidence).
- Het is onduidelijk of de gecombineerde inname van vitamine D uit voeding en als supplement een effect heeft op de progressie van LMD. Ook een effect van een hoge totale inname van calcium en vitamine D samen is onduidelijk. (GRADE: low certainty of evidence).

5. Samenvatting en discussie

Ter beantwoording van de onderzoeksvraag naar het effect van voeding en voedingssupplementen op het ontstaan of de progressie van LMD hebben wij een systematische review uitgevoerd. Er werden zes systematische reviews ingesloten en aanvullend 18 primaire onderzoeken geïdentificeerd, waarvan negen cohortonderzoeken de relatie tussen voeding en het ontstaan van LMD bestudeerden, vier de relatie tussen voeding en de progressie van LMD en vijf RCTs het effect van voedingssupplementen op de progressie van LMD onderzochten.

Voor geen van de bestudeerde voedingscomponenten en voedingssupplementen werd sterke evidence van een preventief effect op het ontstaan van LMD gevonden. Wel geeft een hogere inname van alcohol waarschijnlijk een grotere kans op het ontstaan van LMD en ook van mulitvitaminensupplement bestaande uit een combinatie van 15 mg zink, 45 IE vitamine E, 60 mg vitamine C, 5000 IE bètacaroteen, vitamine A (20% als bètacaroteen), 2,5 mg foliumzuur, 50 mg vitamine B6 en 1 mg vitamine B12 is het effect op het ontstaan van LMD waarschijnlijk ongunstig. Voor vitamine C, vitamine E, of bètacaroteen als voedingssupplement is de evidence overtuigend dat er geen effect is op het ontstaan van LMD.
Om de progressie van LMD te remmen is een mediterraan eetpatroon (hogere inname van groente, fruit, peulvruchten, volkoren producten en noten; gematigde consumptie van vis, gevogelte, zuivelproducten en rode wijn; gebruik van olijfolie i.p.v boter en een beperkte inname van rood

vlees) waarschijnlijk gunstig. Ook suppletie met antioxidanten (in de vorm van een combinatie van 500 mg vitamine C, 400 IE vitamine E, 15 mg bètacaroteen, 80 mg zink als zinkoxide en 2 mg koper als koperoxide, dagelijks) leidt waarschijnlijk tot een afname van de progressie van LMD. Omega-3 vetzuren als voedingssupplement hebben geen effect op de progressie van LMD.
Sterke evidence voor bijwerkingen van voedingssupplementen werd beschreven voor bètacaroteen (geassocieerd met een verhoogde kans op longkanker bij mensen die roken) en het onderzochte multivitaminesupplement (huiduitslag).
Voor een groot deel van de bestudeerde voedingscomponenten en –supplementen was de evidence voor een effect op het onstaan of de progressie van LMD beperkt. In sommige gevallen werd op basis van de grootte en de richting van de resultaten ingeschat dat er een mogelijk effect was (of mogelijk geen effect), zie tabellen 8 t/m 11.

De resultaten voor PICO 1 (preventie) en PICO 2 (therapie) versterken elkaar voor sommige voedingscomponenten en – supplementen. Zo heeft een mediterraan eetpatroon naast een waarschijnlijk gunstig effect op de progressie van LMD mogelijk ook een gunstig effect op het ontstaan van LMD. Voor (rood) vlees wordt een mogelijk ongunstig effect gevonden op zowel het ontstaan als de progressie van LMD.
Daarnaast zien we enkele ogenschijnlijke tegenstellingen in de resultaten. We vonden voor fruit een mogelijk gunstig effect op het ontstaan van LMD, terwijl de evidence voor een effect op de progressie van LMD mogelijk geen effect liet zien. Voor carotenoïden in voeding (bètacryptoxanthine) en als supplementen (luteïne en/of zeaxanthine) werden mogelijk gunstige effecten gevonden op het onstaan en de progressie van LMD, terwijl bètacaroteen als voedingssupplement overtuigend geen effect liet zien op het ontstaan van LMD. Vergelijkbaar zagen we voor omega-3 vetzuren in voeding een mogelijk gunstig effect op het ontstaan van LMD en als voedingssupplement geen effect op de progressie van LMD. Ook suppletie met multivitaminepreparaten leek mogelijk gunstig voor de ene uitkomst (progressie LMD) en ongunstig voor de andere uitkomst (onstaan LMD). Dit weerspiegelt de complexiteit van voedingsonderzoek, waarin vele factoren meespelen, zoals genetische factoren, leefstijl en omgevingsfactoren.
Daarnaast is er aanzienlijke heterogeniteit mogelijk tussen onderzoeken qua inname/dosering, samenstelling en combinaties van voedingscomponenten en – supplementen. Deze complexiteit en heterogeniteit kan leiden tot inconsistente resultaten tussen onderzoeken.

De 18 onderzoeken die vanwege een kwalitatief minder onderzoeksdesign niet in detail zijn uitgewerkt in dit rapport, gaan alle over voeding en hebben vergelijkbare conclusies over een mediterraan eetpatroon, de consumptie van vlees en inname van vetzuren.

In de huidige Nederlandse richtlijn over maculadegeneratie (NOG 2014) was één van de deelvragen: “Welk voedingsadvies kan gegeven worden ter preventie van LMD in het andere oog?” Er werd geen systematisch literatuuronderzoek uitgevoerd, maar in de beantwoording van de vraag wordt wel de systematische review van Evans betrokken, die ook is ingesloten in dit rapport (Evans 2017a). De richtlijn beveelt aan dat patiënten met LMD AREDS categorie 3 of 4 of ernstige LMD aan één oog of 2 ogen, (niet centrale) geografische atrofie aan één of 2 ogen of ernstig LMD of visusverlies door LMD een advies krijgen om een voedingssupplement te gebruiken, bestaande uit: vitamine C (500 mg), vitamine E (400 IU), zeaxanthine (2mg), zink (25-80 mg), koper (2 mg), luteïne (10 mg). Patiënten met LMD die roken of gerookt hebben, dienen het advies te krijgen om geen voedingssupplement met bètacaroteen te gebruiken. Ten aanzien van voeding worden er in de richtlijn geen aanbevelingen gedaan, maar er wordt wel gerefereerd naar het algemene advies van de

Gezondheidsraad inzake gezonde voeding (variatie en ruim groente, fruit, volkoren graanproducten, vette vis en magere zuivel- en vleesproducten; beperkte inname van verzadigde en enkelvoudig trans-onverzadigde vetzuren, voedingsmiddelen en dranken met gemakkelijk vergistbare suikers en dranken met een hoog gehalte aan voedingszuren; matig met alcohol). De bevindingen uit de onderhavige systematische review onderbouwen de aanbevelingen over voedingssupplementen in de richtlijn. Ook de resultaten betreffende de effecten van een mediterraan dieet en alcoholinname op het ontstaan of de progressie van LMD bekrachtigen het algemene advies van de Gezondheidsraad waaraan gerefereerd wordt in de richtlijn.

Onze systematische review laat zien dat het onderwerp voeding(ssupplementen) bij maculadegeneratie in de belangstelling staat bij onderzoekers. Naast 10 relevante systematische reviews vonden we, aanvullend op de systematische reviews, nog 36 primaire onderzoeken die gepubliceerd werden in de laatste vijf jaar. Relevante publicaties verschenen niet alleen in oogheelkundige tijdschriften (23/36; 65%), maar ook in voedingstijdschriften (9/36; 25%) en algemene tijdschriften (4/36; 11%) (Bijlage 7).

De hoeveelheid data en de al eerder genoemde complexiteit en heterogeniteit van voedingsonderzoek, leverden een groot aantal vergelijkingen op en maakten het samenvatten van alle informatie uitdagend. Het was praktisch niet haalbaar om uitgebreide Summary of findings tabellen te maken voor elke vergelijking. In plaats daarvan hebben we de resultaten op een andere, meer kwalitatieve wijze weergegeven om de interpretatie ervan te vergemakkelijken. Hierbij moet worden opgemerkt dat de weergave van de resultaten in de tabellen 8 t/m 11 de richting van een (mogelijk) effect weergeven en niet zozeer de grootte. Voor fruit, bijvoorbeeld, is op basis van de kwantitatieve resultaten slechts een gering effect te wachten (zie Bijlage 6A). In veel van de ingesloten systematische reviews en primaire onderzoeken over voeding werd een hoge met een lage inname vergeleken (hoogste versus laagste kwintiel, kwartiel of tertiel), wat het identificeren van een directe dosis-respons relatie of afkapwaarden voor inname moeilijk maakt.

Bij het beoordelen van de certainty of evidence volgens GRADE start observationeel onderzoek in principe op ‘low certainty of evidence’, tenzij de ROBINS-I tool gebruikt wordt voor het beoordelen van de methodologische kwaliteit (dan start op high certainty of evidence) (Schünemann 2019). Voor de geïncludeerde primaire onderzoeken hebben we de kans op vertekening beoordeeld en voor observationele onderzoeken gebruikten we daarvoor de ROBINS-I tool. Sommige van de resultaten, echter, werden gebaseerd op observationele onderzoeken uit de geïncludeerde SR’s. Voor deze onderzoeken hebben we het oordeel van de reviewauteurs betreffende de methodologische kwaliteit overgenomen en in geen van de ingesloten SRs werd ROBINS-I gebruikt. We hebben de volgende procedure gevolgd voor het GRADE ‘risk of bias’ domein: onderzoek beoordeeld met ROBINS-I startte op ‘high’, overig op low (conform GRADE-richtlijnen). In de gevallen waarin de reviewauteurs de methodologische kwaliteit echter als hoog beoordeelden, startte de beoordeling van de certainty of evidence op moderate.

Samenvattend: we hebben met een systematische zoekactie de evidence t.a.v. effect van voeding en voedingssupplementen op het ontstaan en de progressie van LMD in kaart gebracht hebben. Daarbij hebben we vrijwel niets gevonden over de rol van voeding(ssupplementen) in combinatie met huidige behandeling (injecties). Het identificeren van een directe dosis-respons relatie of afkapwaarden voor inname was lastig, aangezien de meeste onderzoeken ‘hoge’ met een ‘lage’ inname vergeleken (waarvoor verschillende definities werden gehanteerd).Certainty in de gevonden evidence is overwegend beperkt, maar voor aantal voedingscomponenten en –supplementen was er sterke evidence voor de aan- of afwezigheid van een effect, hetgeen de informatie en aanbevelingen

in de huidige richtlijn onderbouwt en algemene voedingsadviezen van de Gezondheidsraad bekrachtigt.

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Bijlagen

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Bijlage 2. Study flows
Bijlage 3. Uitgesloten onderzoeken
Bijlage 4. Evidence Tables
Bijlage 5. Overzicht van de kans op vertekening (risk of bias) in de geïncludeerde onderzoeken
Bijlage 6. Resultaten
Bijlage 7. Overzicht medisch-wetenschappelijke tijdschriften

Bijlage 1. Zoekstrategieën

1A: Systematische reviews

Datum zoekactie: 10 Juni 2020

Epistemonikos (https://www.epistemonikos.org/en/)

(advanced_title_en:(("macular degeneration" OR "retinal neovascularization" OR "choroidal neovascularization" OR "macula lutea" OR "retinal degeneration" OR "choroid degeneration" OR maculopathy)) OR advanced_abstract_en:(("macular degeneration" OR "retinal neovascularization" OR "choroidal neovascularization" OR "macula lutea" OR "retinal degeneration" OR "choroid degeneration" OR maculopathy))) [Filters: protocol=no, classification=systematic-review, min_year=2015, max_year=2020]	286

The Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Macular Degeneration] explode all trees	2391
#2	MeSH descriptor: [Retinal Degeneration] explode all trees	2517
#3	MeSH descriptor: [Retinal Neovascularization] explode all trees	77
#4	MeSH descriptor: [Macula Lutea] explode all trees	432
#5	((macul* or retina* or choroid*) NEAR/4 degener*):ti,ab,kw	3290
#6	((macul* or retina* or choroid*) NEAR/4 neovasc*):ti,ab,kw	2031
#7	Maculopath*:ti,ab,kw	384
#8	(macul* NEAR/2 lutea*):ti,ab,kw	502
#9	(macul* NEAR/3 dystroph*):ti,ab,kw	32
#10	(macul* NEAR/2 syndrome):ti,ab,kw	12
#11	((macul* or geographic) NEAR/2 atroph*):ti,ab,kw	396
#12	((macul* or retina*) NEAR/2 edema*):ti,ab,kw	3137
#13	(AMD or ARMD or CNV):ti,ab,kw	2861
#14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 with Cochrane Library publication date Between Jan 2015 and Jun 2020, in Cochrane Reviews	30

1B: Primaire onderzoeken

Datum zoekactie: 08 Juli 2020

MEDLINE (Ovid)

#	Searches	Results
1	exp "Macular Degeneration"/ or exp "Retinal Degeneration"/ or exp "Retinal Neovascularization"/ or exp "Macula Lutea"/	54537
2	(((macul* or retina* or choroid*) adj4 (degener* or neovasc* or lutea* or dystroph* or syndrome or edema*)) or Maculopath* or (geographic adj2 atroph*) or (AMD or ARMD or CNV)).ti,ab,kf.	63644
3	1 or 2	87940
4	exp "Dietary Supplements"/ or exp vitamins/ or exp antioxidants/ or exp carotenoids/ or exp Zinc/ or exp selenium/ or exp xanthophylls/ or exp Lutein/ or exp Copper/ or exp "diet, food, and nutrition"/ or exp minerals/ or exp Dietary Fats/	2295387
5	(nutrition* or nutrient* or diet* or supplement* or food or fruit* or vegetable* or meat or zinc or lutein* or copper or retinol or caroten* or ascorbic-acid or tocopherol* or cobalamin* or antioxidant* or (anti adj2 oxidant*) or riboflavin* or selenium or xanthophyll* or zeaxanthin* or vitamin* or omega or fatty-acid* or mineral* or fish or nuts or dairy or grain or cereal or legumes or oil or alcohol).ti,ab,kf.	2828474
6	4 or 5	4058284
7	3 and 6	8338
8	limit 7 to yr="2015 -Current"	2789
9	((cohort or (control and study)).af. or (control and group*).tw. or exp "epidemiologic studies"/ or program.tw. or "clinical trial".pt. or comparative stud*.af. or evaluation-studies.af. or exp "statistics as topic"/ or survey*.af. or follow-up*.af. or time-factors.af. or ci.tw.) not ((animals/ not humans/) or comment.pt. or editorial.pt. or review.pt. or meta analysis.pt. or case report.tw. or exp consensus/ or guideline.pt. or history.sh.)	6943923
10	8 and 9	703
11	(Randomized Controlled Trial or Controlled Clinical Trial).pt. or (randomized or randomized).ab,ti. or placebo.ab,ti. or drug therapy.fs. or randomly.ab,ti. or trial.ab,ti. or groups.ab,ti.	4802703
12	8 and 11	745
13	10 or 12	1180
14	(exp animals/ not humans/) or (mouse or mice or rat or rats or rabbit* or pig or pigs or cat or cats or dog or dogs).ti.	4986711
15	13 not 14	1007

Embase (embase.com)

No.	Query	Results	Date
#22	#14 OR #21	1493	08/Jul/20
#21	#10 AND #20	1439	08/Jul/20
#20	#19 NOT 'review'/it	14119355	08/Jul/20
#19	#18 NOT #17	14714629	08/Jul/20
#18	#15 OR #16	18706362	08/Jul/20

#17	(rat:ti OR rats:ti OR mouse:ti OR mice:ti OR swine:ti OR porcine:ti OR murine:ti OR sheep:ti OR lambs:ti OR pigs:ti OR piglets:ti OR rabbit:ti OR rabbits:ti OR cat:ti OR cats:ti OR dog:ti OR dogs:ti OR cattle:ti OR bovine:ti OR monkey:ti OR monkeys:ti OR trout:ti OR marmoset*:ti) AND 'animal experiment'/de OR ('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))	2298567	08/Jul/20
#16	((control:ti,ab,kw,de AND (group*:ti,ab,kw,de OR study:ti,ab,kw,de) OR (time:ti,ab,kw,de AND factors:ti,ab,kw,de) OR program:ti,ab,kw,de OR survey*:ti,ab,kw,de OR ci:ti,ab,kw,de OR cohort:ti,ab,kw,de OR comparative:ti,ab,kw,de) AND stud*:ti,ab,kw,de OR evaluation:ti,ab,kw,de) AND studies:ti,ab,kw,de OR 'follow up*':ti,ab,kw,de	3313904	08/Jul/20
#15	'controlled study'/exp OR 'comparative study'/exp OR 'clinical study'/exp OR 'therapeutic research'/exp OR 'statistics'/exp	15147554	08/Jul/20
#14	#10 AND #13	392	08/Jul/20
#13	#11 NOT #12	4554036	08/Jul/20
#12	((random* NEXT/1 sampl* NEAR/7 ('cross section*' OR questionnaire* OR survey OR surveys OR database OR databases)):ti,ab) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab OR 'randomized controlled':ti,ab OR 'randomly assigned':ti,ab) OR ('cross-sectional study' NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab OR 'randomized controlled':ti,ab OR 'control group':ti,ab OR 'control groups':ti,ab)) OR ('case control*':ti,ab AND random*:ti,ab NOT ('randomised controlled':ti,ab OR 'randomized controlled':ti,ab)) OR ('systematic review':ti NOT (trial:ti OR study:ti)) OR (nonrandom*:ti,ab NOT random*:ti,ab) OR 'random field*':ti,ab OR (('random cluster' NEAR/3 sampl*):ti,ab) OR (review:ab AND review:it NOT trial:ti) OR ('we searched':ab AND (review:ti OR review:it)) OR 'update review':ab OR ((databases NEAR/4 searched):ab) OR ((rat:ti OR rats:ti OR mouse:ti OR mice:ti OR swine:ti OR porcine:ti OR murine:ti OR sheep:ti OR lambs:ti OR pigs:ti OR piglets:ti OR rabbit:ti OR rabbits:ti OR cat:ti OR cats:ti OR dog:ti OR dogs:ti OR cattle:ti OR bovine:ti OR monkey:ti OR monkeys:ti OR trout:ti OR marmoset*:ti) AND 'animal experiment'/de) OR ('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))	3232312	08/Jul/20
#11	'randomized controlled trial'/de OR 'controlled clinical study'/de OR random*:ti,ab OR 'randomization'/de OR 'intermethod comparison'/de OR placebo:ti,ab OR compare:ti OR compared:ti OR comparison:ti OR ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)) OR ((open NEXT/1 label):ti,ab) OR (((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab) OR 'double blind procedure'/de OR ((parallel NEXT/1 group*):ti,ab) OR crossover:ti,ab OR 'cross over':ti,ab OR (((assign* OR match OR matched OR allocation) NEAR/5 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab) OR assigned:ti,ab OR allocated:ti,ab OR ((controlled NEAR/7 (study OR design OR trial)):ti,ab) OR volunteer:ti,ab OR volunteers:ti,ab OR 'human experiment'/de OR trial:ti	5047197	08/Jul/20
#10	#7 AND (2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py) AND [embase]/lim NOT 'conference abstract'/it	3023	08/Jul/20
#9	#7 AND (2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py) AND [embase]/lim	4647	08/Jul/20

#8	#7 AND (2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py)	5106	08/Jul/20
#7	#3 AND #6	14201	08/Jul/20
#6	#4 OR #5	5163260	08/Jul/20
#5	nutrition*:ti,ab,kw OR nutrient*:ti,ab,kw OR diet*:ti,ab,kw OR supplement*:ti,ab,kw OR food:ti,ab,kw OR fruit*:ti,ab,kw OR vegetable*:ti,ab,kw OR meat:ti,ab,kw OR zinc:ti,ab,kw OR lutein*:ti,ab,kw OR copper:ti,ab,kw OR retinol:ti,ab,kw OR caroten*:ti,ab,kw OR 'ascorbic acid':ti,ab,kw OR tocopherol*:ti,ab,kw OR cobalamin*:ti,ab,kw OR antioxidant*:ti,ab,kw OR ((anti NEAR/2 oxidant*):ti,ab,kw) OR riboflavin*:ti,ab,kw OR selenium:ti,ab,kw OR xanthophyll*:ti,ab,kw OR zeaxanthin*:ti,ab,kw OR vitamin*:ti,ab,kw OR omega:ti,ab,kw OR 'fatty acid*':ti,ab,kw OR mineral*:ti,ab,kw OR fish:ti,ab,kw OR nuts:ti,ab,kw OR dairy:ti,ab,kw OR grain:ti,ab,kw OR cereal:ti,ab,kw OR legumes:ti,ab,kw OR oil:ti,ab,kw OR alcohol:ti,ab,kw	3494012	08/Jul/20
#4	'dietary supplement'/exp OR 'vitamin'/exp OR 'antioxidant'/exp OR 'carotenoid'/exp OR 'zinc'/exp OR 'mineral'/exp OR 'selenium'/exp OR 'xanthophyll'/exp OR 'copper'/exp OR 'nutrition'/exp OR 'fatty acid'/exp	3550701	08/Jul/20
#3	#1 OR #2	121956	08/Jul/20
#2	(((macul* OR retina* OR choroid*) NEAR/4 (degener* OR neovasc* OR lutea* OR dystroph* OR syndrome OR edema*)):ti,ab,kw) OR maculopath*:ti,ab,kw OR ((geographic NEAR/2 atroph*):ti,ab,kw) OR amd:ti,ab,kw OR armd:ti,ab,kw OR cnv:ti,ab,kw	88705	08/Jul/20
#1	'macular degeneration'/exp OR 'retina degeneration'/exp OR 'retina neovascularization'/exp OR 'retina macula lutea'/exp	75707	08/Jul/20

Cochrane Central Register of Controlled Trials (http://crso.cochrane.org/)

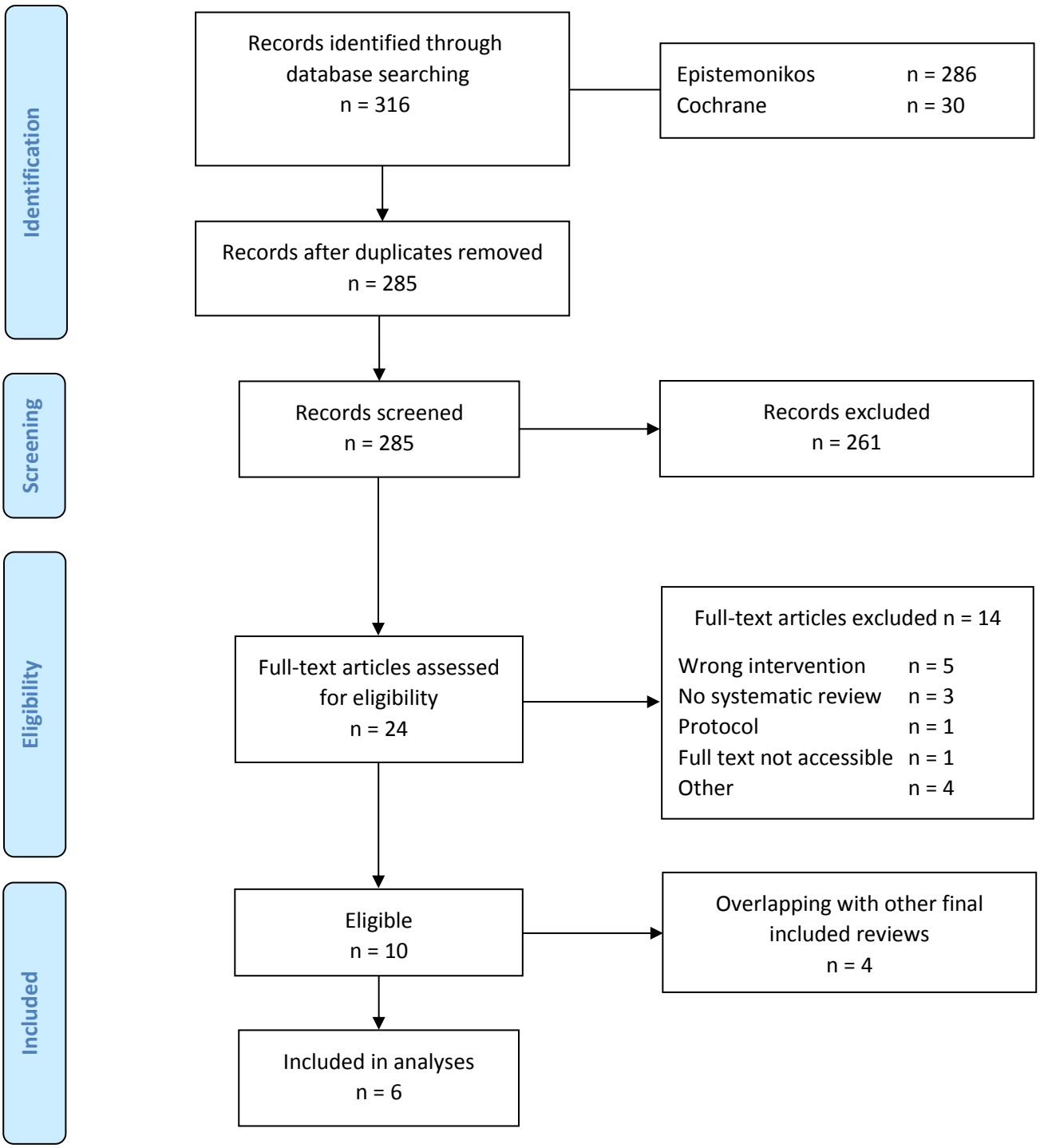
#1	MESH DESCRIPTOR Macular Degeneration EXPLODE ALL TREES	2363
#2	MESH DESCRIPTOR Retinal Degeneration EXPLODE ALL TREES	2487
#3	MESH DESCRIPTOR Retinal Neovascularization EXPLODE ALL TREES	75
#4	MESH DESCRIPTOR Macula Lutea EXPLODE ALL TREES	427
#5	(((macul* or retina* or choroid*) NEAR4 (degener* or neovasc* or lutea* or dystroph* or syndrome or edema*)) or Maculopath* or (geographic NEAR2 atroph*) or (AMD or ARMD or CNV)):ti,ab,kw,EH	7173
#6	#1 OR #2 OR #3 OR #4 OR #5	7650
#7	MESH DESCRIPTOR Dietary Supplements EXPLODE ALL TREES	11966
#8	MESH DESCRIPTOR vitamins EXPLODE ALL TREES	18721
#9	MESH DESCRIPTOR antioxidants EXPLODE ALL TREES	15594
#10	MESH DESCRIPTOR carotenoids EXPLODE ALL TREES	4045
#11	MESH DESCRIPTOR Zinc EXPLODE ALL TREES	1596
#12	MESH DESCRIPTOR selenium EXPLODE ALL TREES	690
#13	MESH DESCRIPTOR xanthophylls EXPLODE ALL TREES	295
#14	MESH DESCRIPTOR Lutein EXPLODE ALL TREES	207
#15	MESH DESCRIPTOR diet, food, and nutrition EXPLODE ALL TREES	65227
#16	MESH DESCRIPTOR minerals EXPLODE ALL TREES	3767
#17	MESH DESCRIPTOR Dietary Fats EXPLODE ALL TREES	7309
#18	(nutrition* or nutrient* or diet* or supplement* or food or fruit* or vegetable* or	214867

	meat or zinc or lutein* or copper or retinol or caroten* or ascorbic-acid or tocopherol* or cobalamin* or antioxidant* or (anti NEAR2 oxidant*) or riboflavin* or selenium or xanthophyll* or zeaxanthin* or vitamin* or omega or fatty-acid* or mineral* or fish or nuts or dairy or grain or cereal or legumes or oil or alcohol):ti,ab,kw,eh	
#19	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	246074
#20	#6 AND #19	819
#21	2015 TO 2020:YR	537532
#22	#20 AND #21	260
#23	(clinicaltrials OR WHO):SO AND 2015 TO 2020:YR	157066
#24	#22 NOT #23	221
#25	conference:pt	161688
#26	#24 NOT #25	166

Bijlage 2. Study flows

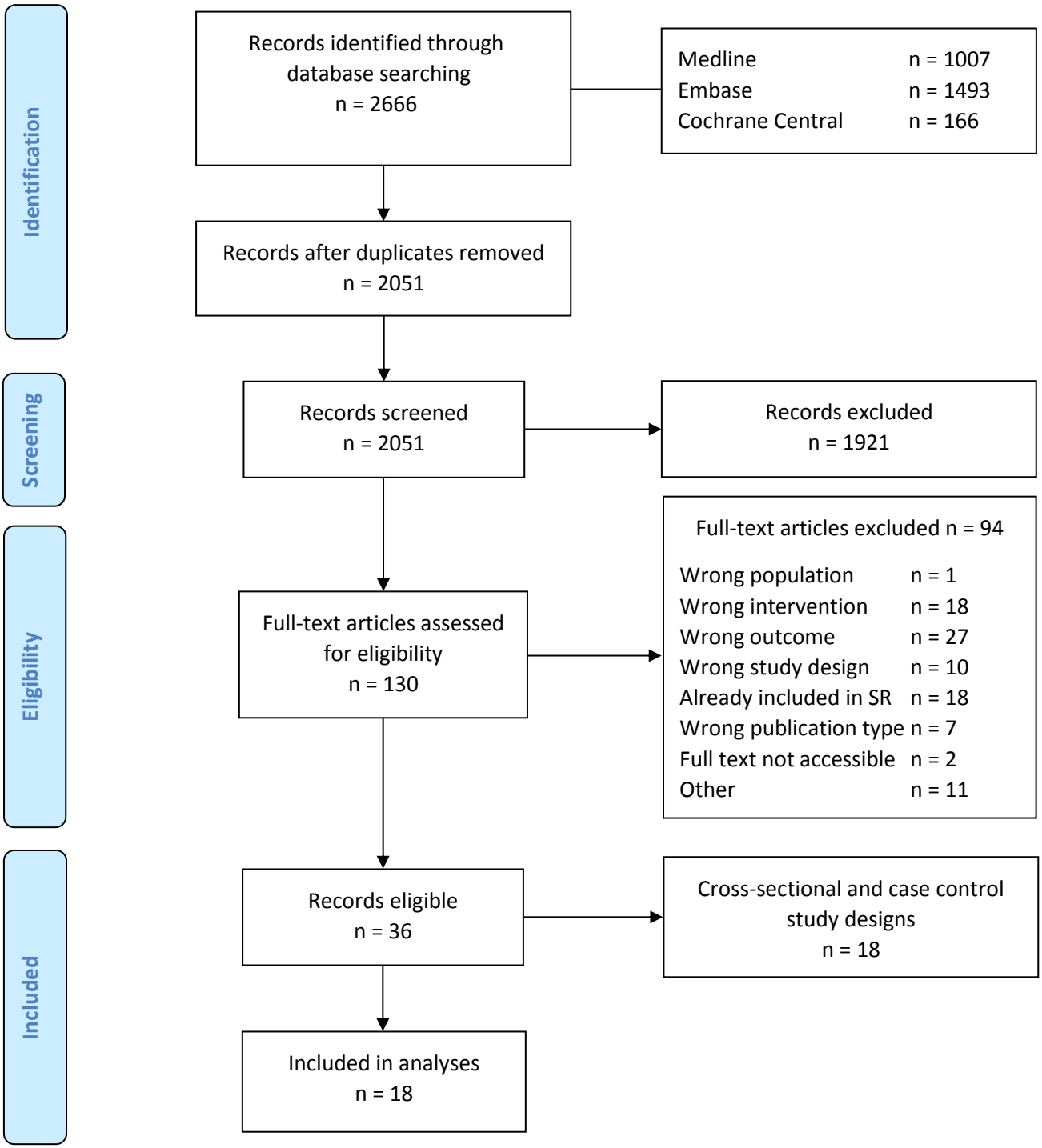
2A: Systematische reviews

Figuur. Study flow van de selectie van systematische reviews van onderzoeken betreffende dieet en voedingssupplementen bij patiënten met leeftijdsgebonden maculadegeneratie.



2B: Primaire onderzoeken

Figuur. Study flow van de selectie van primaire onderzoeken betreffende dieet en voedingssupplementen bij patiënten met leeftijdsgebonden maculadegeneratie.



Bijlage 3. Uitgesloten onderzoeken

In de tabellen staat per onderzoek vermeld wat de reden voor exclusie is.
Onderzoeken werden uitgesloten wanneer de volledige tekst van het artikel niet toegankelijk was via de abonnementen van het UMC Utrecht (“no PDF”); wanneer de bestudeerde interventie (“wrong intervention”) of uitkomst (“wrong outcome”) niet overeenkwam met de geformuleerde PICO’s; of wanneer het onderzoeksdesign (“no systematic review”; “wrong design”; “review of guidelines”; “review of reviews”) of publicatietype (bijvoorbeeld een opiniestuk, ingezonden brief, onderzoeksprotocol of abstract voor een congres) niet voldeed. Voor systematische reviews waren het ontbreken van een risk of bias beoordeling op studieniveau of een zoekactie in een enkele database ook redenen voor exclusie. Primaire onderzoeken die ook al opgenomen waren in één van de ingesloten systematische reviews werden om die reden uitgesloten. Overige redenen voor exclusie werden samengenomen onder het label “other”. De voornaamste zijn taal en focus op (interactie) met genetisch profiel.

3A: Systematische reviews

Tabel – Uitgesloten systematische reviews betreffende dieet en voedingssupplementen bij patiënten met leeftijdsgebonden maculadegeneratie (n=14)

Referentie	Reden
Annweiler 2016	Wrong intervention
García-Montalvo 2015	No systematic review
Gopalasamy 2016	No systematic review
Horani 2019	No systematic review
Huang 2015	Wrong intervention
Lawrenson 2019	Review of guidelines
Lindsley 2016	Review of reviews
Mukhtar 2019	Risk of bias not reported at study level
Nebbioso 2019	Wrong intervention
Rojas-Fernandez 2017	Searched only one database
Sepahi 2020	Full text not accessible
Welte 2017	Wrong intervention
Wu 2016	Wrong intervention
Xu 2020	Protocol of a review

Referenties

Annweiler C, Drouet M, Duval GT, Paré PY, Leruez S, Dinomais M, et al. Circulating vitamin D concentration and age-related macular degeneration: Systematic review and meta-analysis. Maturitas. 2016;88:101-12.

García-Montalvo IA, Matías-Pérez D. [NUTRITIONAL COMPONENTS AND MACULAR DEGENERATION AGE-RELATED]. Nutrición hospitalaria. 2015;32(1):50-4.

Gopalasamy K, Gayathri R, Vishnu P. Age related macular degeneration: A systematic review. Journal of Pharmaceutical Sciences and Research. 2016;8(6):416-20.

Horani M, Mahmood S, Aslam TM. Macular Atrophy of the Retinal Pigment Epithelium in Patients with Neovascular Age-Related Macular Degeneration: What is the Link? Part I: A Review of Disease Characterization and Morphological Associations. Ophthalmology and therapy. 2019;8(2):235-49.

Huang P, Wang F, Sah BK, Jiang J, Ni Z, Wang J, et al. Homocysteine and the risk of age-related macular degeneration: a systematic review and meta-analysis. Scientific reports. 2015;5:10585.

Lawrenson JG, Evans JR, Downie LE. A Critical Appraisal of National and International Clinical Practice Guidelines Reporting Nutritional Recommendations for Age-Related Macular Degeneration: Are Recommendations Evidence-Based? Nutrients. 2019;11(4).

Lindsley K, Li T, Ssemanda E, Virgili G, Dickersin K. Interventions for Age-Related Macular Degeneration: Are Practice Guidelines Based on Systematic Reviews? Ophthalmology. 2016;123(4):884-97.

Mukhtar S, Ambati BK. The value of nutritional supplements in treating Age-Related Macular Degeneration: a review of the literature. International ophthalmology. 2019;39(12):2975-83.

Nebbioso M, Lambiase A, Cerini A, Limoli PG, La C, Greco A. Therapeutic Approaches with Intravitreal Injections in Geographic Atrophy Secondary to Age-Related Macular Degeneration: Current Drugs and Potential Molecules. International journal of molecular sciences. 2019;20(7).

Rojas-Fernandez CH, Tyber K. Benefits, Potential Harms, and Optimal Use of Nutritional Supplementation for Preventing Progression of Age-Related Macular Degeneration. The Annals of pharmacotherapy. 2017;51(3):264-70.

Sepahi S, Ghorani-Azam A, Hossieni SM, Mohajeri SA, Khodavrdi E. Pharmacological effects of saffron and its constituents in ocular disorders from in vitro studies to clinical trials; a systematic review. Current neuropharmacology. 2020.

Welte AK, Hahn U, Büssing A, Krummenauer F. [Systematic Review of the Application of Complementary and Alternative Medicine and their Potential Therapeutic Benefits in the Treatment of Ophthalmology Patients]. Klinische Monatsblatter fur Augenheilkunde. 2017;234(5):686-96.

Wu W, Weng Y, Guo X, Feng L, Xia H, Jiang Z, et al. The Association Between Serum Vitamin D Levels and Age-Related Macular Degeneration: A Systematic Meta-Analytic Review. Investigative ophthalmology & visual science. 2016;57(4):2168-77.

Xu Y, Lu B, Zhou Y, Ren S, Pang G, Deng A. Is dietary fat associated with the risk of age-related macular degeneration? Protocol for a systematic review and meta-analysis. Medicine. 2020;99(17):e19081.

3B: Primaire onderzoeken

Tabel – Uitgesloten primaire onderzoeken betreffende dieet en voedingssupplementen bij patiënten met leeftijdsgebonden maculadegeneratie (n=94)

Referentie	Reden
[No author listed] 2016	Wrong outcome
[No author listed] 2018	Other (language)
[No author listed] 2019	Wrong publication type (erratum)
[No author listed] 2019	Wrong outcome
Abreu-Gonzalez 2018	Wrong population
Age-Related Eye Disease Study Group 2018	Wrong intervention
Akuffo 2015	Already included in SR
Aljohi 2019	Wrong outcome
Amin 2019	Wrong outcome
Aoki 2016	Already included in SR
Assel 2018	Other (focus on genes)
Aufartova 2015	Wrong intervention
Awh 2015	Other (focus on genes)
Azar 2017	Wrong outcome
Berendschot 2015	Wrong publication type (conference abstract)
Berrow 2016	Wrong outcome
Bone 2018	Wrong outcome
Bone 2020	Wrong design
Bott 2018	Wrong intervention
Braakhuis 2017	Wrong outcome
Bro 2017	Wrong publication type (review)
Brooks 2016	Wrong intervention
Buhler 2016	Wrong intervention
Chang 2017	Other (in vitro study)
Chatziralli 2017	Wrong outcome
Cheng 2017	Wrong intervention
Chew 2015	Wrong outcome
Corvi 2017	Wrong design
Cougnard-Grégoire 2015	Wrong intervention
Cougnard-Gregoire 2016	Already included in SR
Crosby-Nwaobi 2016	Wrong design
Domalpally 2018	Wrong intervention
Domalpally 2019	Wrong intervention
Douillard 2018	Wrong outcome
Dow 2016	Wrong intervention
Elbaz-Hayoun 2019	Other (in vitro study)
Huang 2015	Already included in SR
Ferrero 2018	Wrong outcome
Finger 2016	Wrong intervention
Fujimura 2016	Wrong design

Gattoussi 2017	Wrong intervention
Georgiou 2015	Full text not accessible
Glaser 2015	Wrong outcome
Gopinath 2015	Wrong design
Gopinath 2017	Already included in SR
Gurbuz 2018	Wrong design
Hogg 2017	Already included in SR
Huang 2015	Wrong outcome
Jee 2016	Wrong intervention
Jee 2016	Wrong intervention
Joachim 2015	Already included in SR
Jonczyk-Skorka 2015	Full text not accessible
Kakigi 2015	Wrong design
Kelly 2017	Already included in SR
Korobelnik 2017	Wrong outcome
Kovalevskaya 2015	Other (language)
Lashay 2016	Already included in SR
Leung 2019	Wrong design
Li 2017	Other (language)
Li 2018	Wrong outcome
Matsuura 2017	Wrong outcome
Merle 2015	Already included in SR
Merle 2016	Already included in SR
Merle 2019	Other (duplicate)
Meyers 2015	Other (interaction with genes)
Moran 2017	Wrong intervention
Moran 2018	Wrong intervention
Obana 2015	Wrong outcome
Olk 2015	Already included in SR
Park 2015	Wrong intervention
Parodi 2016	Wrong design
Parravano 2019	Wrong outcome
Riazi 2017	Already included in SR
Sawa 2020	Wrong outcome
Song 2019	Wrong intervention
Souied 2015	Wrong publication type (mini review)
Stevens 2015	Wrong outcome
Stringham 2017	Wrong outcome
Stringham 2017	Wrong outcome
Sulich 2015	Wrong outcome
Tang 2019	Wrong publication type (protocol)
Tao 2016	Already included in SR
Tao 2016	Already included in SR

Thurnham 2015	Wrong outcome
Thurnham 2015	Other (duplicate)
Tian 2015	Wrong outcome
Uzun 2017	Wrong publication type (letter)
Valldeperas X Romera 2015	Wrong publication type (conference abstract)
Van Asten 2019	Other (focus on genes)
Van der Made 2017	Wrong outcome
Wolf-Schnurrbusch 2015	Already included in SR
Wu 2015	Already included in SR
Wu 2017	Already included in SR
Yoon 2016	Wrong design

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3C. Niet-ingesloten cross-sectionele onderzoeken en patiëntcontroleonderzoeken

Overzicht van resultaten van niet-geïncludeerde cross-sectionele onderzoeken en patiëntcontroleonderzoeken naar voeding ter voorkoming van leeftijdsgebonden maculadegeneratie (n=15)

Reference	Study design	Population	Determinants	Outcome	Results
Arslan 2019	Case-control study	AMD vs. healthy controls	Dietary antioxidants; all kinds of food groups: beverages; cereals and potato; fruits and olive; vegetables; sugar and chocolate; legume; dairy; meat; oils. see table 3: protein, carbohydrates; fiber; fat; omega 3; omega 6; vitamin A; Lutein+zeaxantin; carotenoids; vitamin C; vitamin E; Vitamin B12; Folid acid; Vitamin B 6; Zinc; Seleniium; fruit intake; vegetable intake; fish intake; red meat intake	AMD	It was found that the individuals who consumed **fruits** every day (OR: 0.56, p<0.05) or 3–5 times in a week (OR: 0.75; p<0.05) and those who consumed **vegetables** every day (OR: 0.80, p>0.05) or 3–5 times in a week (OR: 0.96, p>0.05) had a low risk of developing AMD. Similarly, the likelihood of developing AMD was lower in individuals who consumed **fish** every day (OR: 0.35, p<0.05) or 3–5 times in a week (OR: 0.68, p<0.05) than in those who consumed it only once in a week or less often. By contrast, the participants who consumed **red meat** every day had 1.2 times higher risk of developing AMD than the individuals who consumed it once in a week or less often (p<0.05). No difference was observed in the risk of developing AMD between individuals who consumed red meat 3–5 times in a week and those who consumed less (OR: 1.0, p>0.05).
Chatziralli 2017	Case-control study	AMD vs. healthy controls	Alcohol consumption	AMD	There was no statistically significant differences between patients and controls regarding (…) **alcohol** consumption.
Chiu 2017	Cross-sectional study	Patients of ophthalmic centers	Oriental pattern: whole grains; fruit; poultry; fish and seafood; rice; low-fat dairy; dark-yellow vegetables; cruciferous vegetables; legumes; other vegetables; soup; tomatoes, green-leaf vegetables Western pattern: high-fat dairy; sweets and desserts; eggs; potatoes;	Early AMD, advanced AMD	It was found that, "in general, the eight minor patterns were subsets or extensions of either one of the two major dietary patterns **(Oriental** and **Western patterns**) and consisted of fewer characteristic foods than the two major dietary patterns. Unlike the two major patterns, which were more strongly associated with both early and advanced AMD, none of the eight minors were associated with early AMD and only four minor patterns, including the **Steak pattern** (odds ratio comparing the highest to lowest quintile of the pattern score = 1.73 [95% confidence interval: 1.24 to 2.41; P_{trend} = 0.02]), the **Breakfast pattern** (0.60 [0.44 to 0.82]; P_{trend} = 0.004]), the **Caribbean pattern** (0.64 [0.47 to 0.89; P_{trend} = 0.009]),

			butter or margarine; red meats; gravies; processed meats; refined grains; french fries; high-energy drinks Steak pattern: potatoes; butter or margarine; red meats; gravies Breakfast pattern: cold breakfast cereal; fruit juices; whole grains; fruit Caribbean pattern: organ meats; poultry; fish and seafood; rice; low-fat dairy Peanut pattern: peanuts; snacks; high-fat dairy; sweets and desserts		and the **Peanut pattern** (0.64 [0.46 to 0.89; P_{trend} = 0.03]), were significantly associated with advanced AMD."
Gopinath 2017	Case-control study	Late AMD vs. healthy controls	Micronutrients (vit. E, Retinol, Betacarotene, vit. A, vit C, Zinc, Floate) and major food groups (fruits, vegetables, fish)	Late AMD	Analysis of major food group consumption shows that significantly fewer AMD cases were meeting RDI of **vegetables** compared with control subjects: 52.9% versus 64.5%, p=0.0002. No significant differences in the proportion meeting the RDI of **fruits** or **fish** were observed between AMD cases and controls. Also, no significant differences in adjusted mean intakes of **fruits**, **vegetables** or **fish** between AMD cases and controls were found. After multivariable adjustment, cases with late-stage AMD compared with controls had significantly lower intakes of **vitamin E** (7.4 vs 9.8 mg/day; p<0.0001), **beta-carotene** (6232 vs 7738 µg/day; p<0.0001), **vitamin C** (161 vs 184 mg/day; p=0.0002) and **folate** (498.3 vs 602 µg/day; p<0.0001); but had higher intakes of **zinc** (13.0 vs 11.9 mg/ day; p<0.0001).

Kang 2019	Cross-sectional study	General population	Cereals, legumes, meat, fish, vegetables, seaweeds, fruit, dairy products, drinks, alcohol, snacks	AMD (early, late, any)	Early AMD showed similar results in the model 1 and 2. The **meat** group was associated with a statistically significant difference among each quartile group ($p < 0.05$ in models 1 and 2), but the results reveal no definite odds change when compared with the first quartile. The **fish** group was associated with a 43% decrease in odds for early AMD in model 1 and a 39% decrease in model 2 after adjustment for covariates in the third quartile (OR, 0.57; 95% CI, 0.38–0.84 in model 1, OR, 0.61; 95% CI, 0.40–0.92 in model 2). However, the odds for the **fish** group were not reduced for the second and fourth quartiles. Although ORs showed downward trend across quartiles for early AMD in model 2 in the **fruit** group, analysis of the other food groups did not show any statistically significant association. Late age-related macular degeneration and multiple logistic regression analyses. The **legume** group was associated with statistically significant differences among quartile groups ($p < 0.05$ in model 2), and a 69% decrease in odds for late AMD in model 2 in the third quartile (OR, 0.21; 95% CI, 0.05– 0.93). Although ORs showed upward trend across quartiles for late AMD in the **meat** group, analysis of other food groups did not show any statistically significant association.
Kim 2017	Cross-sectional study	Elderly men	Cereals/potatoes/sugar products, Beans/nuts/seeds, Meats and eggs, Fishes and shellfishes, Milk and dairy products, Fruits and vegetables, Mushrooms, Seaweeds; Nutrients: carbohydrate, protein, fat, calcium, phosphorus, iron, thiamin, riboflavin, niacin, vit. C, vit. A, a-carotene, b-carotene, b-cryptoxanthin, luein-zeaxanthin, lycopene.	AMD	For the current smokers, AMD was inversely associated with **fruits** and **vegatables** [OR (95% CI) = 0.36 (0.14–0.96), p for trend = 0.0576], **vitamin C** [OR (95% CI) = 0.32 (0.12–0.85), p for trend = 0.0561], **α-carotene** [OR (95% CI) = 0.23 (0.08–0.67), p for trend = 0.0038] and **β-carotene** [OR (95% CI) = 0.13 (0.04–0.46), p for trend = 0.0003] intake after adjusted for confounding factors. For nonsmokers and former smokers, however, there was no association between intake of **fruits** and **vegetables** and **antioxidant** nutrients and AMD.

Kim 2018	Cross-sectional study	Elderly women	Cereal and cereal products, Potatoes and starch products, Sugar and sugar products, Beans and bean products, Nuts and seeds products, Mushrooms, Seaweeds, fuit and vegetables, Meat and meat products, Eggs and egg products, Fish and shellfish, Milk and dairy products, Oil and fat, Beverages, Seasoning; Daily nutrients (carbohydrate, protein, fat, calcium, iron, thiamin, riboflavin, niacin, vit. C, vit. A), carotenoids and flavonoids intake.	AMD	The subjects with AMD consumed less **vegetable** (274.1 g/day in subjects without AMD vs 237.0 g/day in subjects with AMD, P-value = 0.006), and **fruit** and **vegetable** (424.3 g/day in subjects without AMD vs 367.0 g/day in subjects with AMD, P-value = 0.009) than those without AMD. **Sugar** and **oil/fat** consumption of subjects without AMD are higher than those with AMD in our subjects. However, the mean percentages of daily calories from **sugar** (5.1 g) and **oil/fat** (3.8 g) were 1.3 and 1.9%, respectively. Subjects with AMD consumed fewer **antioxidant** nutrients including **vitamin A** (P-value = 0.019), **β-carotene** (P-value = 0.006) and **flavonols** (P-value = 0.031) than those without AMD. **Energy intake** and other nutrients were not significantly different between the groups after adjusting for confounding factors. women with higher **fruit** and **vegetable** intakes had ORs<1.0, but there was no statistically significant decreasing risk across intake quartiles. OR for the highest **vegetable** intake quartile category compared with the lowest quartile category was 0.44 (95% CI 0.25, 0.77, P for trend = 0.002). Subjects in the highest quartiles showed significantly decreased prevalence of AMD by 62% for **vitamin A** (OR (95% CI) 0.38 (0.21–0.68), P for trend = 0.001), 64% for **β-carotene** (OR (95% CI) 0.36 (0.19–0.67), P for trend o0.001) and 55% for **flavonols** (OR (95% CI) 0.45 (0.25–0.82), P for trend = 0.008). There was no significant association between **fish** consumption and AMD. A significant negative association between **fruit** and **vegetable** intake and the prevalence of AMD (OR (95% CI) for subjects consuming ⩾500 g = 0.61 (0.38–0.97) compared with those consuming<500 g) was found.
McCarter 2019	Cross-sectional study	Women	Dietary pattern healthy vs. unhealthy based on the various food items. The 'healthy' dietary pattern was characterised (in decreasing order of factor loadings) by lutein/zeaxanthin-rich vegetables, green leafy vegetables, alliums, vegetables, fruit, tomatoes, legumes, nuts, oily fish, low-fat dairy products, pizza, dressings/sauces/condiments, wholegrain breakfast cereal and red	Any AMD	There was no significant difference in AMD risk (i.e. controls versus AMD) across quartiles of either the **'healthy' or 'unhealthy' dietary pattern**.

			meat. The 'unhealthy' dietary pattern was characterised (in decreasing order of factor loadings) by chips, French fries, alcohol, high fat dairy products, soups, desserts, sugars and sweets, wholegrains, dressings/sauces/condiments, processed meat, potatoes, eggs, refined grains, refined breakfast cereal, chocolate, vegetables, red meat, white fish and shellfish.		
Munch 2016	Cross-sectional study	General population	Vitamin A, beta-carotene, vitamin E, vitamin C, zinc and copper	Macular drusen	The odds of having macular drusen >63 lm were increased for participants in the highest quartile of daily **vitamin A** intake with an odds ratio (OR) of 1.82 (95% confidence interval (CI 95) 1.02–3.24, p = 0.042) compared with participants in the lowest quartile of daily vitamin A intake. Participants in the second lowest quartile of **copper** intake had reduced odds for having macular drusen >63 lm with OR = 0.53 (CI95 0.30–0.96, p = 0.035; Table 2) compared with the lowest quartile. Having macular drusen >63 lm was not significantly associated with the daily intake of **beta-carotene, vitamin C, vitamin E** and **zinc**.

Ng 2019	Case-control study	AMD vs. no AMD	Carotenoids, saturated fatty acids, monounsaturated fatty acids, omega-6 polyunsaturated fatty acids, omega-3 polyunsaturated fatty acids, green leafy vegetables (e.g., Chinese kale, broccoli, spinach), tomato, red carrots, other vegetables (e.g., turnip, celery cabbage, cabbage and potato), red meat (pork, beef, lamb), poultry (chicken, duck, pigeon), oily fish (mackerel, eel, woo fish, salmon, sardine), white meat fish (e.g., sea bass, tilapia, cod), other seafood (e.g., prawn, seafood, crab, mussels, scallop), walnuts, peanuts, other nuts (e.g., almond, pistachio, cashew), milk, cheese, preserved vegetables, preserved meat.	Neovascular AMD	Of all tested carotenoids, including **lutein** and **zeaxanthin** combined, **beta-carotene** and **lycopene**, they were significantly lower in AMD subjects compared to controls (p = 0.013, 0.036 and 0.001 respectively) (Figure 1). For **omega-3 polyunsaturated fatty acids** (PUFAs)**, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)** were significantly lower in AMD subjects than the control group (p < 0.0005 and p = 0.002 respectively) (Table 2). In contrary, the **eicosatrienoic acid** was significantly higher in AMD group. Other omega-3 PUFAs including **α-linolenic acid** (ALA**)** and **docosapentaenoic acid** were inconsistently lower in AMD subjects (0.05 < p < 0.1). For **omega-6 PUFAs**, **arachidonic acid** (ARA) level (p < 0.0005) and **eicosadienoic acid** level (p = 0.004) were significantly higher in AMD. significantly higher in AMD subjects, but **dihomo-γ-linolenic acid** was lower (P = 0.002). For the **monounsaturated fatty acids** (MUFAs), the **oleic acid level** and **heptadecenoic acid** level were significantly higher in AMD group. Most **saturated fatty acids** (SFAs) were significantly higher in AMD group. When the subjects had low **carotenoid** levels (when comparing the bottom quartile to top quartile), the odds ratio of having AMD was 2.78 for **beta-carotene**, 6.02 for **lycopene**, and 4.82 for **combined lutein and zeathanxin**. A low level of omega-3 PUFA increased the odds ratio of developing AMD by 6.33 for **DHA**, 7.79 for **EPA** and 3.11 for **ALA**. In contrary, a low level of **ARA** and **eicosatrienoic acid** were protective, with odds ratio being 0.11 and 0.16 respectively. When the subjects had high levels of **eicosadienoic acid** (omega-6 PUFA), oleic acid (MUFA), palmitic acid (SFA) and **pentadecylic acid** (SFA), when comparing the top quartile to bottom quartile, the odds ratio of having AMD were 2.63, 14.10, 11.48 and 33.75 respectively. AMD group had higher intake frequency in Chinese preserved vegetable (p = 0.045) and preserved meats (p = 0.025). For vegetables, the AMD group had a lower serving size of both **green leafy vegetables** (Choi Sum, Pok Choi, Chinese kale, broccoli, spinach) (p < 0.001) and **other vegetables** (turnip, celery cabbage, cabbage and potatoes) (p < 0.001) when compared with control. The AMD group also had higher frequency in eating **red meat** including pork, beef and lamb (p = 0.012) and poultry (p = 0.031) compared with controls, although controls had higher serving size in **poultry** each time (p = 0.030). For seafood, **fish** intake did not show significant difference between both groups, but AMD group had significantly less frequency of intake in **other seafood** (prawn, shrimp, crab, mussels, scallop) than in controls (p = 0.006).

Nunes 2018	Nested Case-control	AMD vs. no AMD	Mediterranean diet and individual components	AMD	Intake of **sandwiches** was significantly more frequent in participants without AMD (P = 0.025). The number of **meals/d**, consumption of traditional meals, light meals, breakfast, fast-food and premade meals were similarly distributed in both groups. Energy intake was significantly higher in participants without AMD (P = 0.003). A high adherence to the **Mediterranean diet** (cutoffmediSCORE≥6) was associated with a decreased risk for AMD for 67.2% of participants without AMD and 32.8% with AMD (P = 0.009) and an OR of 0.73 (95% CI, 0.58–0.93). When analyzing the individual food groups that comprise the mediSCORE (Table 2), **vegetables** and **fruit** and **nuts** were the only groups with a statistically different consumption between participants with and without AMD. Consumption of **vegetables** above the sex-specific median as well as **fruits** and **nuts** were higher in the group without AMD (P < 0.001 and P = 0.005, respectively). A higher consumption of **vegetables** and **fruits** and **nuts** was associated with no AMD with an OR = 0.63 (95% CI, 0.52–0.76; P < 0.001) for **vegetables** consumption and an OR 0.78 (95% CI, 0.65–0.94; P = 0.010) for **fruits** and **nuts** consumption. A significantly higher consumption of **water, total fat, fibers, mono- and polyunsaturated fatty acids, linoleic acid, vitamin A, carotene, alpha-tocopherol, vitamin C, folate, magnesium, iron,** and **zinc** was found in the group without AMD.
Raimundo 2018	Nested Case-control	AMD vs. no AMD	Mediterranean diet	AMD	High **mediSCORE** (cut-off mediSCORE ≥6, Fig. 2) seems to be associated with decreased prevalence of AMD in our sample [38.4% versus 50.5%, p = 0.041, OR: 0.62 (95% CI: 0.38–0.97)]. When looking at the individual food groups that compose the mediSCORE (Table 3), **fruit** consumption above the sex-specific median is higher in the group without AMD (54.5% versus 45.5%, p = 0.029). We have found a significantly higher consumption **of caffeine, fibres, beta-carotene, vitamin C** and **vitamin E** in the group without AMD (Table 4). No significant differences were found regarding the consumption of **monounsaturated fats, omega-3, omega-6, zinc** or **alcohol**.

Roh 2020	Cross-sectional study	Patients visiting Department of Ophthalmology	Fatty acid intake	Any AMD, early AMD, intermediate AMD, advanced AMD	Highest quintile of **trans fat** intake was positively associated with AMD compared with the lowest quintile (OR, 2.36; 95% CI, 1.02–5.45; P for trend = 0.0156). No association was observed between the intake of **saturated fat** (P for trend = 0.11) and presence of AMD. The highest quintile of polyunsaturated fatty acids (**PUFA)** and monounsaturated fatty acids (**MUFA)** intake were inversely associated with AMD presence compared with the lowest quintile (OR, 0.25; 95% CI, 0.10–0.64; P for trend = 0.0063; and OR, 0.24; 95% CI, 0.10–0.55; P for trend < 0.0001, respectively). Among the different types of **PUFA**, the highest quintile of omega-6 fatty was inversely associated with presence of AMD (OR, 0.30; 95% CI, 0.12–0.74; P for trend = 0.0165),whereas there was no association between presence of AMD and omega-3 FA (P for trend = 0.23). For early AMD (vs. control), **trans fat** intake was not significantly associated with the presence of the disease (P for trend = 0.12). Only the highest quintile of **MUFA** intake was inversely associated with the presence of early AMD compared with the lowest quintile (OR, 0.26; 95% CI, 0.09–0.78; P for trend = 0.007). For intermediate AMD (vs. control), the highest quintile of **trans fat** intake was associated with the presence of the disease (OR, 2.26; 95% CI, 0.89–5.77; P for trend = 0.0228) compared with the lowest quintile. There was also an inverse association between **PUFA** and **MUFA** intake and presence of intermediate AMD (vs. control, the highest vs. lowest quintile; OR, 0.20; 95% CI, 0.07–0.54; P for trend = 0.0013 and OR, 0.17; 95% CI, 0.06–0.44; P for trend < 0.0001, respectively). Similar to what was observed for the comparison considering all stages of AMD, there was no association between **omega-3 FA** intake and presence of intermediate AMD (vs. control; P for trend = 0.11). However, the highest quintile of **omega-6 FA** intake presented an inverse association with presence of intermediate AMD (vs. control: OR, 0.22; 95% CI, 0.08–0.59; P for trend = 0.0034). For advanced AMD (vs. controls), no association was found for **trans fat** and **saturated fat** intake (P for trend = 0.12 and P for trend = 0.21, respectively). An increased quintile of **PUFA** and **MUFA** intake were inversely associated with the presence of advanced AMD (vs. control) (OR, 0.13; 95% CI, 0.03–0.55; P for trend = 0.0223 and OR, 0.26; 95% CI, 0.07–0.89; P for trend = 0.0044, respectively).

Sasaki 2010	Cross-sectional study	General population	Saturated fatty acid intake	Early AMD	Subjects in the highest quartile of **saturated fatty acid** (SFA) intake were less likely to have early AMD compared with those in the lowest quartile (OR, 0.71, 95% CI: 0.52-0.96). A significant trend of decreasing OR for AMD with increasing **SFA** intake was noted (P = 0.011). There was no association between other fatty acid types, including **n-3 PUFA**, and presence of early AMD.
Zhang 2018	Cross-sectional study	General population	Drinking alcohol; Diet: meat, egg, fish, vegetables	AMD	Subjects living on a diet of **meat** or **egg** showed a higher prevalence of AMD compared with those on a **diet** of **fish** or **vegetables**. No association was identified between the prevalence of AMD and drinking **tea** or **alcohol**.

Overzicht van resultaten van niet-geïncludeerde cross-sectionele onderzoeken en patiëntcontroleonderzoeken naar voeding ter behandeling van leeftijdsgebonden maculadegeneratie (n=3)

Reference	Study design	Population	Determinants	Outcome	Results
Dharamdasani 2020a	Cross-sectional study	Patients with neovascular AMD undergoing anti-vascular endothelial growth factor therapy	Zinc, vitamin A, vitamin C, vitamine E, beta-carotene, retinol	Visual acuity	Increasing quartiles of **zinc** intake were not significantly associated with visual acuity (VA) by better eye or worse eye. Further, intake of other **antioxidants** (**vitamins A, C and E, beta-carotene** and **retinol**) was not significantly associated with fluid presence, mean central macular thickness and VA (results not shown).
Dharamdasani 2020b	Cross-sectional study	Patients with neovascular AMD undergoing anti-vascular endothelial growth factor therapy	Zinc, beta-carotene	Visual acuity	Dietary intake of **zinc** and **b-carotene** at baseline was not associated with change in visual acuity over 12-months (p=0.3 and p=0.8, respectively).
Qureshi 2018	Before-after study	Patients with AMD	Diet advice in which participants were provided a 1950 kcal diet plan, having vitamins A, C, E, Zinc, Folate, Lutein and Zeaxanthin.	Visual improvement	After four months of intake of **Therapeutic Diet** by 106 patients, only 48 patients had shown visual improvement by 2-3 lines at a 6 meters/20ft distance, and in the rest 58 patients, there was no further deterioration.

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Bijlage 4. Evidencetabellen

4A: Systematische reviews

Evidencetabellen van geïncludeerde systematische reviews betreffende voeding(ssupplementen) voor de preventie of behandeling van LMD

Chapman 2019. Role of diet and food intake in age-related macular degeneration: a systematic review	
Methods	
• **Design**	Systematic review without meta-analysis
• **Source of funding and competing interest**	No source of funding, no competing interest.
• **Search date**	August 2017
• **Searched databases and other sources**	Allied and Complementary Medicine Database, Cochrane Library, Embase, Google Scholar, Medline (Ovid) and Scopus
• **Included study designs**	Randomized Controlled Trials, controlled clinical trials, clinical trials, prospective cohort studies, case-control studies, cross-sectional studies, case reports, guidelines, meta-analyses, and practice guidelines.
• **Number of included studies**	18
• **Statistical analysis**	Descriptive statistics
Study characteristics	
• **Inclusion criteria**	Intervention studies assessing the influence of diet or food intake on the incidence and/ or progression of AMD in adults. Studies required outcomes that reached some level of statistical significance.
• **Exclusion criteria**	Studies with a quality level 4 and 5 based on the Oxford Centre for Evidence-based Medicine 2011 Levels of Evidence, and studies assessing supplement interventions only.
• **Patient & disease characteristics**	Number of participants: 336.916 Countries: Australia (7 studies), France (1 study) Japan (1 study), USA (8 studies), Europe (1 study) Age (yrs): range 50-90 (9 studies), mean age range 53-73.2 (11 studies) Male/Female: male only (1 study), female only (1 study), % female range 32.5-66.1 (13 studies), unclear (3 studies)

• **Intervention(s)**	Dietary pattern, nutrients, and specific food (meat, dairy, calcium, and alcohol). Food intake interventions were delivered as single or multiple combinations and included nutrition deficiency factors. Where a study contained both food intake and supplement interventions, the study was included only if food data were analysed independently from supplement data. No restrictions on the duration of the intervention.
• **Comparator(s)**	Any comparator; see results
Results	
• **Development of AMD**	Dietary Pattern *High Mediterranean diet score (quartile 4) vs. low Mediterranean diet score (quartile 1)* **Neovascular AMD (1 Cross-sectional study, n=4753):** OR=0.53 (95% CI 0.27–1.04) *High oriental pattern score (quintile 5) vs. low oriental pattern score (quintile 1)* **Early AMD (1 Cross-sectional study, n=4088):** OR=0.74 (95% CI 0.59–0.91) *High western pattern score (quintile 5) vs. low western pattern score (quintile 1)* **Early AMD (1 Cross-sectional study, n=4088):** OR=1.56 (95% CI 1.18–2.06) *High intake of grains, fish, steamed/boiled chicken, vegetables, and nuts (quartile 4) vs. low intake (quartile 1)* **Advanced AMD (1 cohort study, n=19,768):** OR=0.49 (95% CI0.28–0.87) Nutrients: Omega-3 fatty acids (DHA and EPA), fish and fats *High intake of omega-3 fatty acids (auintile 5) vs. low intake (auintile 1)* **Neovascular AMD (1 Case-Control study, n=530):** OR=0.2 (95% CI 0.1–0.4) *High intake of omega-3 fatty acids 9 (ALA+DHA +EPA) (quartile 4) vs. low intake (quartile 1)* **Early AMD (1 cohort study, n=5604):** OR=0.85 (95% CI 0.71–1.02) *High intake of EPA + DHA (excluding supplements) (quintile 5) vs. low intake (quintile 1)* **Intermediate AMD (1 cohort study, n=114,850):** HR=0.86 (95% CI 0.72–1.02) *Fish consumption of ≥1 servings per week vs. fish consumption of <1 serving per week*

Late AMD (1 cohort study, n=3654): OR=0.48 (95% CI 0.29–0.79)

Consumption of >2 servings of fish per week vs. consumption of <1 servings of fish per month
Neovascular AMD (1 Case-Control study, n=4519): OR=0.61 (95% CI 0.37–1.00) SanGiovanni et al. 2007

Consumption of ≥2 servings of fish per week vs. <1 serving of fish per week
Intermediate and late AMD (1 Case-Control study, n=681): OR=0.63 (95% CI 0.41–0.97)

Total fatty fish consumption of ≥5/week vs. total fatty fish consumption of almost never
Intermediate AMD (1 cohort study, n=114,850): HR=0.61 (95% CI 0.46–0.82)

Consumption of >1 serving baked/broiled fish per week vs. <1 serving of baked/broiled fish per month
Neovascular AMD (1 Case-Control study, n=4519): OR=0.65 (95% CI 0.45–0.93)

Canned tuna consumption of ≥5 per week vs. canned tuna consumption of almost never
Intermediate AMD (1 cohort study, n=114,850): HR=0.68 (95% CI 0.44–1.05)

Nutrients: carbohydrates
High-GI diet (quartile 4) vs. low (quartile 1)
Early AMD (1 cohort study, n=2641): RR=1.77 (95% CI 1.13–2.78)
Any AMD (1 cohort study, n=3977): RR=1.05 (95% CI 0.91–1.22)

Bread, cereal, and oatmeal (quartile 4) vs. Low (quartile 1)
Early AMD (1 cohort study, n=2641): RR=0.67 (95% CI 0.44–1.02)

Nutrients: carotenoids
High intake of Lutein/zeaxanthin (quintile 5) vs. low intake of Lutein/zeaxanthin (quintile 1)
Late AMD (1 cohort study, n=102,046): RR=0.59 (95% CI 0.48–0.73)

High intake of β-Cryptoxanthin (quintile 5) vs. low intake of β-Cryptoxanthin (quintile 1)
Late AMD (1 cohort study, n=102,046): RR=0.73 (95% CI 0.60–0.89)

High intake of α-Carotene (quintile 5) vs. low intake of α-Carotene (quintile 1)
Late AMD (1 cohort study, n=102,046): RR=0.69 (95% CI 0.56–0.84)

High intake of β-carotene (quintile 5) vs. low intake of β-carotene (quintile 1)
Neovascular AMD (1 Case-Control study, n=530): OR=0.2 (95% CI 0.1–0.4)
Late AMD (1 cohort study, n=102,046): RR=0.82 (95% CI 0.67–1.01)

High intake of food-sourced β-carotene (quintile 5) vs. low intake of food-sourced β-carotene (quintile 1)
Late AMD (1 cohort study, n=102,046): RR=0.64 (95% CI 0.52–0.79)

High intake of food-sourced 'total' carotene (quintile 5) vs. low intake of food-sourced 'total' carotene (quintile 1)
Late AMD (1 cohort study, n=102,046): RR=0.64 (95% CI 0.51–0.79)

High intake of food-sourced 'total' carotenoid index (β-carotene + 'total' carotene) (quintile 5) vs. low intake of food-sourced 'total' carotenoid index (β-carotene + 'total' carotene) (quintile 1)
Late AMD (1 cohort study, n=102,046): RR=0.65 (95% CI 0.53–0.80)

<u>Nutrients: multi-micronutrients</u>
High intake of zinc (quintile 5) vs. low intake (quintile 1)
Neovascular AMD (1 Case-Control study, n=530): OR=0.1 (95% CI 0.1–0.4)

High intake of vitamin D (quintile 5) vs. low intake (quintile 1)
Neovascular AMD (1 Case-Control study, n=530): OR=0.4 (95% CI 0.2–0.8)

High intake of α-tocopherol (quintile 5) vs. low intake (quintile 1)
Neovascular AMD (1 Case-Control study, n=530): OR=0.2 (95% CI 0.1–0.3)

High intake of vitamin C (quintile 5) vs. low intake (quintile 1)
Neovascular AMD (1 Case-Control study, n=530): OR=0.4 (95% CI 0.2–0.8)

Specific food
Red meat intake ≥ median score vs. red meat intake ≤ median score
Advanced AMD (1 cohort study, n=19,768): OR=1.46 (95% CI 1.00–2.17)

Red meat (fresh and processed) consumption ≥ 10 times per week vs. ≤4 times per week
Early AMD (1 cohort study, n=5604): OR=1.47 (95% CI 1.21–1.79)

Red meat (fresh and processed) consumption ≥ 10 times per week vs. ≤4.5 times per week
Intermediate AMD (1 cohort study, n=5604): OR=1.39 (95% CI 1.09–1.78)

Red meat (fresh) consumption ≥ 6.5 times per week vs. ≤2.5 times per week
Early AMD (1 cohort study, n=5604): OR=1.34 (95% CI 1.10–1.65)
Intermediate AMD (1 cohort study, n=5604): OR=1.31 (95% CI 1.10–1.69)

Red meat (processed) consumption ≥ 4 times per week vs. ≤1 times per week
Early AMD (1 cohort study, n=5604): OR=1.13 (95% CI 0.94–1.37)

Salami or continental sausage consumption ≥ 1 time per week vs. <1 time per month
Early AMD (1 cohort study, n=5604): OR=1.45 (95% CI 1.12–1.88)
Intermediate AMD (1 cohort study, n=5604): OR=1.36 (95% CI 1.00–1.86)
Late AMD (1 cohort study, n=5604): OR=2.37 (95% CI 1.05–5.37)

Chicken consumption ≥ 3.5 times per week vs. ≤1 time per week
Late AMD (1 cohort study, n=5604): OR=0.43 (95% CI 0.20–0.91)

Luncheon meat ≥1 time per week vs. <1 time per month

	Intermediate AMD (1 cohort study, n=5604): OR=1.23 (95% CI 0.97–1.57) *Low total dairy intake of <0.78 servings per day vs. high total dairy intake of ≥2.75 servings per day* **Late AMD (1 cohort study, n=2037):** OR=2.80 (95% CI 1.21–3.04) *Low reduced/low-fat dairy intake of ≤0.00 servings per day vs. high reduced/low-fat dairy intake of ≥1.18 servings per day* **Late AMD (1 cohort study, n=2037):** OR=3.10 (95% CI 1.18–8.14) *Low regular fat dairy intake of ≤0.17 servings per day vs. high regular fat dairy intake of ≥1.53 servings per day* **Late AMD (1 cohort study, n=2037):** OR=2.60 (95% CI 1.12–6.03) *Low dietary calcium intake ≤565.1mg per day vs. high dietary calcium intake ≥1247.3 mg per day* **Late AMD (1 cohort study, n=2037):** OR=2.99 (95% CI 1.23–7.25) *Alcohol intake ≥20 g per day vs. intake 1-9 g per day* **Early AMD (1 cohort study, n=20,963):** OR=1.21 (95% CI 1.06–1.38) *Wine intake of ≥20 g per day vs. lifetime abstainers* **Early AMD (1 cohort study, n=20,963):** OR=1.26 (95% CI 1.09–1.46)
• **Progression of AMD**	<u>Dietary Pattern</u> *High adherence to the Mediterranean diet vs. low adherence to the Mediterranean diet* **Progression to advanced AMD (1 cohort study, n=2525):** HR=0.74 (95% CI0.61–0.91) *High oriental pattern score (quintile 5) vs. low score (quintile 1)* **Progression to late AMD (1 Cross-sectional study, n=4088):** OR=0.38 (95% CI 0.27–0.54) *High western pattern score (quintile 5) vs. low score (quintile 1)* **Progression to late AMD (1 Cross-sectional study, n=4088):** OR=3.70 (95% CI 2.31–5.92)

	Regular use of olive oil vs. no use of olive oil **Progression to late AMD (1 cohort study, n=654):** OR=0.44 (95% CI0.21–0.91) <u>Nutrients: omega-3 fatty acids (DHA and EPA), fish and fats</u> *High intake of EPA + DHA vs. low intake* **Progression to advanced AMD (1 cohort study, n=114,850):** HR=0.68 (95% CI 0.46–0.99) <u>Nutrients: carbohydrates</u> *High-GI diet vs. low-GI diet* **Any progression of AMD (1 cohort study, n=3977):** RR=1.10 (95% CI 1.00–1.20) **Progression from early AMD (1 cohort study, n=3977):** RR=1.08 (95% CI 0.91–1.30) **Progression from intermediate AMD (1 cohort study, n=3977):** RR=1.17 (95% CI 1.01–1.36) <u>Nutrients: carotenoids</u> No studies identified. <u>Nutrients: multi-micronutrients</u> No studies identified. <u>Specific food</u> No studies identified.
• **Adverse events**	Not assessed
• **Visual acuity**	<u>Nutrients: Omega-3 fatty acids (DHA and EPA), fish and fats</u> *High ratio of omega-6 fatty acids to omega-3 fatty acids (LA + AA to DHA + EPA) in the diet (tertile 3) vs. low ratio* **Best corrected visual acuity <6/9 attributed to incident AMD (1 cohort study, n=38,022):** RR=1.77 CI: 1.27–2.47) *High ratio of omega-6 fatty acids to all omega-3 fatty acids (LA + AA to DHA + EPA + DPA + ALA) in the diet (tertile 3) vs. low ratio* **Best corrected visual acuity <6/9 attributed to incident AMD (1 cohort study, n=38,022):** RR=1.55 CI: 1.11–2.16)

	High intake of omega-3 fatty acids (tertile 3) vs. low intake (tertile 1) **Best corrected visual acuity <6/9 attributed to incident AMD (1 cohort study, n=38,022):** RR=0.59 (95% CI 0.42–0.83) *High intake of DHA (tertile 3) vs. low intake (tertile 1)* **Best corrected visual acuity <6/9 attributed to incident AMD (1 cohort study, n=38,022):** RR=0.59 (95% CI 0.42–0.81) *High intake of EPA (tertile 3) vs. low intake (tertile 1)* **Best corrected visual acuity <6/9 attributed to incident AMD (1 cohort study, n=38,022):** RR=0.63 (95% CI 0.46–0.88) *Consumption of >2 servings of fish per week vs. consumption of <1 servings of fish per month* **Best corrected visual acuity <6/9 attributed to incident AMD (1 cohort study, n=38,022):** RR=0.58 (95% CI 0.38–0.87) *Consumption of dark-meat fish ≥1 servings per week vs. consumption of <1 servings of dark-meat fish per month* **Best corrected visual acuity <6/9 attributed to incident AMD (1 cohort study, n=38,022):** RR=0.56 (95% CI 0.32–0.99) *Consumption of cane tune fish ≥1 servings per week vs. consumption of <1 servings of cane tune fish per month* **Best corrected visual acuity <6/9 attributed to incident AMD (1 cohort study, n=38,022):** RR=0.56 (95% CI 0.40–0.80)
• **Other**	Nutrients: omega-3 fatty acids (DHA and EPA), fish and fats *High trans-fat consumption (quartile 4) vs. low trans-fat consumption (quartile 1)* **Late AMD* (1 Cohort study, n=5604):** OR=1.76 (95% CI 0.92–3.37) *Consumption of ≥100 mL/week of olive oil vs. consumption of <1 mL/week* **Late AMD* (1 Cohort study, n=5604):** OR=0.48 (95% CI 0.22–1.04) *Unclear whether outcome is development of late AMD or progression to late AMD
Limitations	

• **Limitations**	**AMSTAR 2**: No protocol is available Search strategy limited to database searches and reference lists Study selection and data-extraction not in duplicate No list of excluded studies is provided Study quality was assessed based on study design only. Sources of funding of included studies were not reported The potential impact of risk of bias on the results was not assessed or discussed **Oxford Centre for Evidence-based Medicine 2011 Levels of Evidence**: The review included 13 studies with level 2 study quality and 5 studies with level 3 study quality.
• **Other comments**	The studies were given a study quality level based on the Oxford Centre for Evidence-based Medicine 2011 Levels of Evidence. 3 studies with level 4 or 5 study quality were excluded.

Dinu 2019 - Food groups and risk of age-related macular degeneration: a systematic review with meta-analysis	
Methods	
• **Design**	Systematic review and meta-analysis
• **Source of funding and competing interest**	There was no external funding for this study. Competing interest: none known.
• **Search date**	January 2018
• **Searched databases and other sources**	MEDLINE, Embase, Web of Science, Google Scholar
• **Included study designs**	Prospective cohort studies
• **Number of included studies**	26
• **Statistical analysis**	Random effects model using DerSimonian and Laird method was used to pool multivariable adjusted RRs or ORs. Statistical heterogeneity was estimated using the Chi square Cochran Q test with the I^2 statistic
Study characteristics	
• **Inclusion criteria**	Prospective cohort studies that assessed the consumption of food groups and alcohol as the exposure variable, reported the occurrence of AMD as the outcome, provided risk estimates with confidence intervals or standard errors (or sufficient data to

	calculate them), evaluated subjects aged ≥ 18 years at baseline, reported clear definitions of method used to evaluate the food consumption and reported data on food groups' consumption in relation to early and/or late AMD.
• **Exclusion criteria**	Cross-sectional and case-control studies.
• **Patient & disease characteristics**	Number of participants: 211,676 (range: 22-2590) Countries: Australia (10 studies), Denmark (1 study), Iceland (1 study), Japan (1 study), Netherlands (1 study), South Korea (1 study) USA (10 studies), Australia/Netherlands (1 study) Age (yrs): range 30-90 Male/Female: male only (1 study), female only (1 study), both (24 studies)
• **Intervention(s)**	High consumption of various food sources: 1. Plant products 2. Animal products 3. Dietary fats 4. Alcohol
• **Comparator(s)**	Low consumption of the same food sources
Results	
• **Development of AMD**	*High consumption vs. low consumption of vegetables* **Early AMD** (3 studies, n=131,379): RR=0.92 (95% CI 0.67 to 1.25) **Late AMD** (3 studies, n=132,525): RR=0.80 (95% CI 0.76 to 1.00) **Any AMD*** (4 studies, n=133,904): RR=0.92 (95% CI 0.82 to 1.03) *High consumption vs. low consumption of fruit* **Early AMD** (2 studies, n=130,000): RR=0.92 (95% CI 0.82 to 1.03) **Late AMD** (3 studies, n=132,525): RR=0.83 (95% CI 0.62 to 1.12) **Any AMD*** (3 studies, n=132,525): RR=0.91 (95% CI 0.82 to 1.01) *High consumption vs. low consumption of grain* **Any AMD** (2 studies, n=4335): RR=0.84 (95% CI 0.62 to 1.13) *High consumption vs. low consumption of nuts* **Early AMD** (1 study, n=1925): RR=0.73 (95% CI 0.51 to 1.04)

Late AMD (3 studies, n=4711): RR=0.83 (95% CI 0.62 to 1.10)
Any AMD* (3 studies, n=4711): RR=0.81 (95% CI 0.64 to 1.02)

High consumption vs. low consumption of meat
Early AMD (4 studies, n=28,225): RR=1.17 (95% CI 1.02 to 1.34)
Late AMD (4 studies, n=28,158): RR=0.99 (95% CI 0.70 to 1.39)
Any AMD* (6 studies, n=31,011): RR=1.11 (95% CI 0.96 to 1.27)

High consumption vs. low consumption of dairy products
Early AMD (2 studies, n=3511): RR=1.18 (95% CI 0.93 to 1.50)
Late AMD (2 studies, n=2298): RR=0.97 (95% CI 0.27 to 3.48)
Any AMD* (3 studies, n=3772): RR=1.07 (95% CI 0.68 to 1.70)

High consumption vs. low consumption of fish
Early AMD (5 studies, n=49,828): RR=0.84 (95% CI 0.73 to 0.97)
Late AMD (6 studies, n=127,968): RR=0.79 (95% CI 0.70 to 0.90)
Any AMD* (8 studies, n=167,464): RR=0.82 (95% CI 0.75 to 0.90)

High consumption vs. low consumption of oils
Early AMD (2 studies, n=7078): RR=1.13 (95% CI 0.93 to 1.37)
Late AMD (1 study, n=5604): RR=1.05 (95% CI 0.53 to 2.07)
Any AMD* (2 studies, n=7078): RR=1.10 (95% CI 0.98 to 1.23)

High consumption vs. low consumption of butter
Early AMD (2 studies, n=7862): RR=0.99 (95% CI 0.75 to 1.30)
Late AMD (2 studies, n=7862): RR=0.85 (95% CI 0.49 to 1.47)
Any AMD* (2 studies, n=7862): RR=1.04 (95% CI 0.93 to 1.16)

High consumption vs. low consumption of margarine

	Early AMD (3 studies, n=9336): RR=1.07 (95% CI 0.85 to 1.35) **Late AMD** (2 studies, n=7862): RR=0.98 (95% CI 0.56 to 1.70) **Any AMD*** (3 studies, n=9336): RR=1.05 (95% CI 0.91 to 1.21) *High consumption vs. low consumption of alcohol (sensitivity analysis)* **Early AMD** (10 studies, n=118,259): RR=1.29 (95% CI 1.16 to 1.43) **Late AMD** (9 studies, n=97,653): RR=0.98 (95% CI 0.76 to 1.27) **Any AMD*** (12 studies, n=120,956): RR=1.20 (95% CI 1.04 to 1.39) *The outcome 'Any AMD' is a combination of early and late AMD, which are presented as subgroups; Studies and particpants could be included in both subgroups, and therefore might be counted twice in the overall effect estimate for Any AMD. However, in this evidence table, the total number of unique studies and particpants was summed (i.e. studies and particpants included both for early and late AMD were counted only once).
• **Progression of AMD**	Not assessed
• **Adverse events**	Not assessed
• **Visual acuity**	Not assessed
• **Other**	Not assessed
Limitations	
• **Limitations**	**AMSTAR 2**: No protocol is available Search strategy limited to database searches No list of excluded studies is provided Information about included studies in terms of population, intervention, comparator and outcome is limited Sources of funding of included studies were not reported The potential impact of risk of bias on the results was not assessed or discussed **Newcastle–Ottawa Scale assessment**: 93% of the studies had a high quality. The mean NOS score was 7.96 ± 0.93 (range 6-9). Representativeness of the exposed cohort: 11 studies low quality Selection of the non-exposed cohort: all studies good quality

	Ascertainment of exposure: 2 studies low quality Demonstration that outcome of interest was not present at start of study: 7 studies low quality Comparability of cases and non cases: 1 study low quality, 4 studies intermediate quality Assessment of outcome: 1 study low quality Sufficient duration of follow-up: all studies good quality Adequacy of follow up: all studies good quality
• **Other comments**	In the meta-analyses for the outcome 'any AMD', studies reporting on both early AMD and late AMD were included twice. Statistically it is not appropriate to include one study multiple times in the same analysis, so the results for any AMD need to be interpreted with caution.

Evans 2017a. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration.	
Methods	
• **Design**	Systematic review and meta-analysis
• **Source of funding and competing interest**	Source of funding: National Institute for Health Research (NIHR), UK • Richard Wormald, Co-ordinating Editor for Cochrane Eyes and Vision (CEV) acknowledges financial support for his CEV research sessions from the Department of Health through the award made by the NIHR to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Specialist Biomedical Research Centre for Ophthalmology. • This review was supported by the NIHR, via Cochrane Infrastructure funding to the CEV UK editorial base which funds part of Jennifer Evans's salary. Competing interest: none known
• **Search date**	29 March 2017
• **Searched databases and other sources**	Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Allied and Complementary Medicine Database (AMED), OpenGrey (System for Information on Grey Literature in Europe), ISRCTN registry, US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform. In addition, the Science Citation Index were searched, as well as the reference lists of reports of included trials. Also the investigators of included and excluded trials were contacted to ask if they knew of any other relevant published or unpublished trials.
• **Included study designs**	Randomised controlled trials (RCTs)
• **Number of included studies**	5
• **Statistical analysis**	Pooling of risk ratios (RRs) or mean differences (MD) using a fixed-effect model, after testing for heterogeneity between trials

	using a Chi^2 test
Study characteristics	
• **Inclusion criteria**	RCTs that compared antioxidant vitamin or mineral supplements (alone or in combination) with control (placebo or no treatment) in a general population with or without diseases other than age-related macular degeneration (AMD). Antioxidants were defined as "any vitamin or mineral that was known to have antioxidant properties in vivo or which was known to be an important component of an antioxidant enzyme present in the retina" and included vitamin C, vitamin E, carotenoids (including the macula pigment carotenoids lutein and zeaxanthin), selenium and zinc.
• **Exclusion criteria**	RCTs in which the participants were exclusively people with AMD
• **Patient & disease characteristics**	Number of participants: n= 76,756 Countries: Australia (1 RCT), Finland (1 RCT), USA (3 RCTs) Age (yrs): range 40-84 (3 RCTs), ≥45 (1 RCT), mean age 64 (1 RCT) Male/Female: male only (3 RCTs), female only (1 RCT), 56% female (1 RCT) Smoking: ≥ 5 cigarettes/day (inclusion criterion in 1 RCT)
• **Intervention(s)**	Vitamin C, vitamin E, carotenoids (including the macula pigment carotenoids lutein and zeaxanthin), selenium and zinc supplements, alone or in combination
• **Comparator(s)**	Placebo or no treatment; however all included studies used a placebo as comparator
Results	
• **Development of AMD**	*Vitamin E vs. placebo* *(doses of vitamin E used: 50 mg/day, 400 IU/alternate days, 600 IU/alternate days, and 500 IU/day)* **Any AMD** (4 RCTs, n=55,614): RR=0.97 (95% CI 0.90 to 1.06) (GRADE High) **Late AMD** (either neovascular AMD or geographic atrophy or both) (4 RCTs, n=55,614): RR=1.22 (95% CI 0.89 to 1.67) (GRADE Moderate) **Neovascular AMD** (1 RCT, n=941): RR=3.62 (95% CI 0.77 to 16.95) (GRADE Very low) **Geographic atrophy** (1 RCT, n=941): RR=2.71 (95% CI 0.28 to 26.00) (GRADE Very low) *Beta-carotene vs. placebo* *(dose of beta-carotene used was 20 mg/day in one study and 50 mg/alternate days in the other study)* **Any AMD** (2 RCTs, n=22,083): RR=1.00 (95% CI 0.88 to 1.14) (GRADE High) **Late AMD** (either neovascular AMD or geographic atrophy or both) (2 RCTs, n=22,083): RR=0.90 (95% CI 0.65 to 1.24) (GRADE Moderate)

	Neovascular AMD (1 RCT, n=941): RR=0.61 (95% CI 0.17 to 2.15) (GRADE Very low) **Geographic atrophy** (1 RCT, n=941): RR=0.31 (95% CI 0.03 to 2.93) (GRADE Very low) *Vitamin C vs. placebo* *(dose of vitamin C used was 500 mg/day)* **Any AMD** (1 RCT, n=14,236): RR=0.96 (95% CI 0.79 to 1.18) (GRADE High) **Late AMD** (either neovascular AMD or geographic atrophy or both) (1 RCT, n=14,236): RR=0.94 (95% CI 0.61 to 1.46) (GRADE Moderate) **Neovascular AMD** and **Geographic atrophy**: not reported in any of the included studies *Multivitamin vs. placebo* *(Multivitamin used was Centrum Silver [zinc 15 mg, vitamin E 45 IU, vitamin C 60 mg, beta-carotene 5000 IU vitamin A, 20% as beta carotene, folic acid 2.5 mg, vitamin B6 50 mg, vitamin B12 1 mg])* **Any AMD** (1 RCT, n= 14,233): RR=1.21 (95% CI 1.02 to 1.43) (GRADE Moderate) **Late AMD** (either neovascular AMD or geographic atrophy or both) (1 RCT, n= 14,233): RR=1.22 (95% CI 0.88 to 1.69) (GRADE Moderate)
• **Progression of AMD**	Not applicable
• **Adverse events (AE)**	*Vitamin E vs. placebo* *(doses of vitamin E used: 50 mg/day, 400 IU/alternate days, 600 IU/alternate days, and 500 IU/day)* "Two trials reported similar numbers of AEs in vitamin E and placebo group. Another trial reported excess of haemorrhagic strokes in vitamin E group (39 vs 23 events, hazard ratio 1.74, 95% CI 1.04 to 2.91)." (GRADE Low) *Beta-carotene vs. placebo* *(dose of beta-carotene used was 20 mg/day in one study and 50 mg/alternate days in the other study)* "Beta-carotene associated with increased risk of lung cancer in people who smoke." (GRADE High) *Vitamin C vs. placebo* *(dose of vitamin C used was 500 mg/day)* No adverse effects reported in any of the studies.

	Multivitamin vs. placebo *(Multivitamin used was Centrum Silver [zinc 15 mg, vitamin E 45 IU, vitamin C 60 mg, beta-carotene 5000 IU vitamin A, 20% as beta carotene, folic acid 2.5 mg, vitamin B6 50 mg, vitamin B12 1 mg])* “"Those taking the active versus placebo multivitamin were more likely to have skin rashes (2111 and 1973 men in corresponding active and placebo multivitamin groups; HR 1.08, 95% CI 1.01 to 1.15; P = 0.016)". PHS II” (GRADE moderate)
• **Visual acuity**	Not assessed
• **Other**	*Vitamin E vs. placebo* *(doses of vitamin E used: 50 mg/day, 400 IU/alternate days, 600 IU/alternate days, and 500 IU/day)* **Quality of life** and **Resource use and cost**: not reported in any of the included studies *Beta-carotene vs. placebo* *(dose of beta-carotene used was 20 mg/day in one study and 50 mg/alternate days in the other study)* **Quality of life** and **Resource use and cost**: not reported in any of the included studies *Vitamin C vs. placebo* *(dose of vitamin C used was 500 mg/day)* **Quality of life** and **Resource use and cost**: not reported in any of the included studies *Multivitamin vs. placebo* *(Multivitamin used was Centrum Silver [zinc 15 mg, vitamin E 45 IU, vitamin C 60 mg, beta-carotene 5000 IU vitamin A, 20% as beta carotene, folic acid 2.5 mg, vitamin B6 50 mg, vitamin B12 1 mg])* **Quality of life** and **Resource use and cost**: not reported in any of the included studies
Limitations	
• **Limitations**	**AMSTAR 2:** High confidence in the results of the review **Cochrane Risk of bias tool**: The authors considered all five included trials to be at low risk of bias. In one of the trials the risk of bias due to selective reporting was unclear, all other domains in all five studies were judged to be at low risk of bias.
• **Other comments**	The Age-related Eye Disease Study was not included in this review, because “Age-related maculopathy outcomes for people without age-related maculopathy at baseline were not reported” (AREDS 2001) or participants had AMD (AREDS 2 2008). In the

	discussion section the review authors added: "However, there were 2180 people recruited with no, mild, or borderline AMD (AREDS 2001). The study reported no benefit of the study treatment for these people, however, the number of events was small."

Evans 2017b. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration	
Methods	
• **Design**	Systematic review and meta-analysis
• **Source of funding and competing interest**	Source of funding • Internal sources: Moorfields Eye Hospital NHS Trust, UK • External sources: Guide Dogs for the Blind Association, UK. National Institute for Health Research (NIHR), UK. Competing interest: none known
• **Search date**	29 March 2017
• **Searched databases and other sources**	Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Allied and Complementary Medicine Database (AMED), OpenGrey (System for Information on Grey Literature in Europe, the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/ en).
• **Included study designs**	Randomised controlled trials (RCTs)
• **Number of included studies**	19
• **Statistical analysis**	Pooling of risk ratios (RRs), odds ratios (ORs), or mean differences (MD) mainly using a fixed-effect model, after testing for heterogeneity between trials using a Chi^2 test .
Study characteristics	
• **Inclusion criteria**	RCTs that compared antioxidant vitamin or mineral supplementation (alone or in combination) to placebo or no intervention in people with age-related macular degeneration (AMD) in one or both eyes. Antioxidants were defined as "any vitamin or mineral that was known to have antioxidant properties in vivo, or that was known to be an important component of an antioxidant enzyme present in the retina" and included vitamin C, vitamin E, carotenoids (including the macular pigment carotenoids lutein and zeaxanthin), selenium, and zinc.
• **Exclusion criteria**	No exclusion criteria mentioned
• **Patient & disease characteristics**	Number of participants: n=11,162

	Countries: USA (6 RCTs); UK (3 RCTs); Austria (2 RCTs); China (2 RCTs); Australia, France, Ireland, Italy, Switzerland, and combined Netherlands and UK (each 1 RCT) Mean age: range 65 to 75 years (18 RCTs), unknown in 1 RCT Male/Female: % females ranged from 4% to 80% (16 RCTs), unknown in 3 RCTs Stage of AMD: early AMD in 10 RCTs; both early and late AMD in 4 RCTs; late stage AMD in 1 RCT; 'at high risk of progression to late AMD' in 1 RCT; non-serous AMD in 1 RCT; 'late in one eye and any AMD in the other eye, or AMD of 'sufficient severity' in both eyes' in 1 RCT; neovascular AMD in one eye and drusen in the other eye in 1 RCT
• **Intervention(s)**	Vitamin C, vitamin E, carotenoids (including the macular pigment carotenoids lutein and zeaxanthin), selenium, and zinc, alone or in combination.
• **Comparator(s)**	Placebo or no intervention
Results	
• **Development of AMD**	Not applicable
• **Progression of AMD**	*Multivitamin vs. placebo* *(Most of the evidence is drawn from the AREDS study which studied antioxidants (vitamin C 500 mg, vitamin E 400 IU, beta-carotene 15 mg daily) plus zinc 80mg as zinc oxide, copper 2 mg as cupric oxide (daily))* **Progression to late AMD (neovascular AMD, geographic atrophy or both)** (3 RCTs, n=2445): OR=0.72 (95% CI 0.58 to 0.90) (GRADE Moderate) **Progression to neovascular AMD** (1 RCT, n=1206): OR=0.62 (95% CI 0.47 to 0.82) (GRADE Moderate) **Progression to geographic atrophy** (1 RCT, n=1206): OR=0.75 (95% CI 0.51 to 1.10) (GRADE Moderate) **Progression to visual loss** (1 RCT, n=1791): OR=0.77 (95% CI 0.62 to 0.96) (GRADE Moderate) *Lutein and/or zeaxanthin vs. placebo* *(Most of the evidence s drawn from the AREDS2 study in which participants took a daily dose of lutein 10mg and zeaxanthin 2mg or placebo. All participants in the study took AREDS formula (vitamin C, E, zinc with/without beta-carotene))* **Progression to late AMD** (1 RCT, 6891 eyes): RR=0.94 (95% CI 0.87 to 1.01) (GRADE Low) **Progression to neovascular AMD** (1 RCT, 6891 eyes): RR=0.92 (95% CI 0.84 to 1.02) (GRADE Low) **Progression to geographic atrophy** (1 RCT, 6891 eyes): RR=0.92 (95% CI 0.80 to 1.05) (GRADE Low) **Progression to visual loss** (1 RCT, 6656 eyes): RR=0.98 (95% CI 0.91 to 1.05) (GRADE Low) *Vitamin E vs. placebo*

	(Vitamin E 500 IU per day: natural vitamin E in soybean oil medium) **Progression to late AMD (neovascular AMD, geographic atrophy or both)** (1 RCT, n=998): RR==1.36 (95% CI 0.31 to 6.05) (GRADE Very low) **Progression to visual loss** (1 RCT, n=1179): RR=1.04 (95% CI 0.74 to 1.47) (GRADE Low) *Zinc vs. placebo* *(Most of the evidence is drawn from the AREDS study which studied a daily dose of zinc 80 mg as zinc oxide, copper 2 mg as cupric oxide.)* **Progression to late AMD (neovascular AMD, geographic atrophy or both)** (3 RCTs, n=3790): OR=0.83 (95% CI 0.70 to 0.98) (GRADE Low) **Progression to neovascular AMD** (1 RCT, n=2442): OR=0.76 (95% CI 0.62 to 0.93) (GRADE Moderate) **Progression to geographic atrophy** (1 RCT, n=2442): OR=0.84 (95% CI 0.64 to 1.10) (GRADE Moderate) **Progression to visual loss** (2 RCTs, n=3791): OR=0.87 (95% CI 0.75 to 1.00) (GRADE Moderate)
• **Adverse events**	*Multivitamin vs. placebo* *(Most of the evidence is drawn from the AREDS study which studied antioxidants (vitamin C 500 mg, vitamin E 400 IU, beta-carotene 15 mg daily) plus zinc 80mg as zinc oxide, copper 2 mg as cupric oxide (daily))* "Data from AREDS study suggested no serious adverse effects associated with multivitamin use (hazard ratio for mortality 0.87, 95% CI 0.60 to 1.25) but participants in the antioxidant arms more frequently reported yellow skin (8.3% versus 6.0%, P = 0.008)" (GRADE Very low) *Lutein and/or zeaxanthin vs. placebo* *(Most of the evidence s drawn from the AREDS2 study in which participants took a daily dose of lutein 10mg and zeaxanthin 2mg or placebo. <u>All participants in the study took AREDS formula</u> (vitamin C, E, zinc with/without beta-carotene))* "Data from AREDS2 suggested no serious adverse effects associated with lutein and zeaxanthin use (hazard ratio for mortality was 1.06 (95% CI 0.87 to 1.31)." (GRADE Very low) *Vitamin E vs. placebo* *(Vitamin E 500 IU per day: natural vitamin E in soybean oil medium)* "No serious adverse effects were seen. Similar numbers of people in the vitamin E and placebo groups withdrew due to adverse effects (four versus seven), reported any adverse effect (91 versus 83), or ocular adverse effect (105 versus 90)." (GRADE Very

	low) *Zinc vs. placebo* *(Most of the evidence is drawn from the AREDS study which studied a daily dose of zinc 80 mg as zinc oxide, copper 2 mg as cupric oxide.)* "In some studies, gastrointestinal symptoms was reported as a reason for withdrawal. Of 286 people randomised into trials of zinc sulfate supplementation compared with placebo (not including AREDS), 5/146 zinc-treated people withdrew due to gastrointestinal symptoms compared with 2/140 controls. No-one developed copper-deficiency anaemia (high zinc intakes can inhibit copper absorption). In AREDS participants in the zinc arms reported more anaemia (13.2% versus 10.2%, P = 0.004), however, serum haematocrit levels were the same. In AREDS zinc was associated with higher risk of genitourinary problems in men, but no difference seen between high- and low-dose zinc groups in AREDS2." (GRADE Very low)
• **Visual acuity**	Not assessed
• **Other**	*Multivitamin vs placebo* *(Most of the evidence is drawn from the AREDS study which studied antioxidants (vitamin C 500 mg, vitamin E 400 IU, beta-carotene 15 mg daily) plus zinc 80mg as zinc oxide, copper 2 mg as cupric oxide (daily))* **Quality of life** (1 RCT, n=110) assessed withNational Eye Institute Visual Function Questionnaire (NEI-VFQ) score (higher scores better): "The mean change in NEI-VFQ score in the control group was -8.7; The mean NEI-VFQ quality of life score in the intervention group was 12.3 higher (4.24 higher to 20.36 higher)" (GRADE Low) **Resource use and cost**: not reported in any of the included studies *Lutein and/or zeaxanthin vs. placebo* *(Most of the evidence s drawn from the AREDS2 study in which participants took a daily dose of lutein 10mg and zeaxanthin 2mg or placebo. All participants in the study took AREDS formula (vitamin C, E, zinc with/without beta-carotene))* **Quality of life** (1 RCT, n=108) assessed with Visual Function Questionnaire (VFQ) score (higher scores better): "The mean VFQ quality of life score in the control group was 77.3. The mean VFQ quality of life score in the intervention group was 1.48 higher (5.53 lower to 8.49 higher)" (GRADE Moderate) **Resource use and cost**: not reported in any of the included studies *Vitamin E vs. placebo* *(Vitamin E 500 IU per day: natural vitamin E in soybean oil medium)* **Quality of life** and **Resource use and cost**: not reported in any of the included studies

	Zinc vs. placebo *(Most of the evidence is drawn from the AREDS study which studied a daily dose of zinc 80 mg as zinc oxide, copper 2 mg as cupric oxide.)* **Quality of life** and **Resource use and cost**: not reported in any of the included studies

Limitations	
• **Limitations**	**AMSTAR 2**: High confidence in the results of the review **Cochrane Risk of bias tool**: The authors state that "As the majority of the trials were placebo-controlled, we mostly assessed them as being at low risk of bias. In particular, the two trials that contributed most of the data to this review were judged at low risk of bias (AREDS 2001; AREDS2 2013). There was some variable reporting of the smaller trials; the extent to which attrition bias may have played a role was not always clear. There was some evidence of selective outcome reporting with respect to data on visual acuity."
• **Other comments**	As all participants in AREDS2 2013 took multivitamin supplements, the results may not have represented a true reflection of the effect of lutein supplementation, but rather the added value of lutein to multivitamin supplements.

Lawrenson 2015. Omega 3 fatty acids for preventing or slowing the progression of age-related macular degeneration	
Methods	
• **Design**	Systematic review and meta-analysis
• **Source of funding and competing interest**	Source of Funding: National Institute for Health Research, UK. ○ Richard Wormald, Co-ordinating Editor for the Cochrane Eyes and Vision Group (CEVG) acknowledges financial support for his CEVG research sessions from the Department of Health through the award made by the National Institute for Health Research to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Specialist Biomedical Research Centre for Ophthalmology. ○ The NIHR also funds the CEVG Editorial Base in London. Competing interest: none known

• **Search date**	2 February 2015
• **Searched databases and other sources**	Cochrane Central Register of Controlled Trials CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register), Ovid MEDLINE, EMBASE, Latin American and Caribbean Health Sciences Literature Database (LILACS), the ISRCTN registry, ClinicalTrials.gov and the World Health Organization (WHO) International ClinicalTrials Registry Platform (ICTRP).
• **Included study designs**	Randomised controlled trials (RCTs)
• **Number of included studies**	2
• **Statistical analysis**	In general for binary outcomes the risk ratio (RR) was used. For data on progression of AMD, log hazard ratios and standard errors were obtained from Cox proportional hazards regression models. These results were combined using the generic inverse variance method and since only two trials were available for analysis, a fixed-effect model was used. Heterogeneity was assessed by examining the forest plot, along with the Chi^2 test and the I^2 statistic.
Study characteristics	
• **Inclusion criteria**	RCTs where increased dietary intake of omega 3 fatty acids was compared to placebo or no intervention, including people from the general population with or without AMD. The definition of AMD was taken as defined by study investigators (for example using a standardised grading scheme, or AMD leading to a reduction in visual acuity).
• **Exclusion criteria**	No apparent exclusion criteria are mentioned in the review.
• **Patient & disease characteristics**	Number of participants: 2380 (300 and 2080) Countries: USA and France Mean age: 74 y in both RCTs Gender distribution (% males): 35 and 45
• **Intervention(s)**	Any type and any dose of omega 3 fatty acids, either as fish oil capsules or dietary manipulation (for example increased consumption of oily fish). The intervention could be delivered either as monotherapy or in combination with other measures, where the study design allowed for the effect of the omega 3 treatment to be isolated. We imposed no restriction on the duration of treatment.
• **Comparator(s)**	Placebo or no intervention; however all included studies used a placebo as comparator.
Results	
• **Development of AMD**	Not applicable
• **Progression of AMD**	*Omega-3 vs. placebo* *(Omega-3 supplement in one RCT contained 650 mg EPA and 350 mg DHA once daily for 5 yrs (and additional original AREDS formula of antioxidant vitamins and zinc) and 840 mg DHA and 270 mg EPA daily for 3 years in other RCT.)*

	Progression of AMD over 5 years (2 studies, 2343 participants): HR=0.96 (95% CI: 0.84 to 1.10) (GRADE High) **Incidence of choroidal neovascularisation at 24 months** (1 study, 224 participants): RR=1.06 (95% CI: 0.47 to 2.40) (GRADE moderate) **Incidence of choroidal neovascularisation at 36 months** (1 study, 195 participants): RR=1.12 (95% CI: 0.53 to 2.38) (GRADE moderate) **Loss of 3 or more lines of visual acuity at 24 months** (1 study, 236 participants): RR=1.14 (95% CI 0.53 to 2.45) (GRADE moderate) **Loss of 3 or more lines of visual acuity at 36 months** (1 study, 230 participants): RR=1.25 (95% CI 0.69 to 2.26) (GRADE moderate)
• **Adverse events**	*Omega-3 vs. placebo* *(Omega-3 supplement in one RCT contained 650 mg EPA and 350 mg DHA once daily for 5 yrs (and additional original AREDS formula of antioxidant vitamins and zinc) and 840 mg DHA and 270 mg EPA daily for 3 years in other RCT.)* Adverse events (2 studies, 2343 participants): RR=1.01 (95% CI: 0.94 to 1.09) (GRADE High).
• **Visual acuity**	Not assessed
• **Other**	Not assessed
Limitations	
• **Limitations**	**AMSTAR 2**: • High confidence in the results of the review. • Partial yes on comprehensive search strategy (no content experts included) **Cochrane Risk of bias tool**: • Attrition bias: 1 study unclear risk • Low risk of bias for all other domains and studies
• **Other comments**	None

Waugh 2018. Treatments for dry age-related macular degeneration and Stargardt disease: a systematic review
• **Methods**

• **Design**	Systematic review and meta-analysis (PROSPERO CRD42016038708)
• **Source of funding and competing interest**	Funding: The National Institute for Health Research HTA programme No competing interest
• **Search date**	13 July 2017
• **Searched databases and other sources**	MEDLINE, EMBASE, Web of Science, The Cochrane Library, ARVO website, reference lists of reviews, ClinicalTrials.gov, the WHO search portal and UK Clinical Trials; experts in the field were consulted for any other relevant literature
• **Included study designs**	Randomised controlled trials (RCTs), controlled clinical trials with a concurrent control group, observational studies
• **Number of included studies**	45
• **Statistical analysis**	Descriptive statistics
• **Study characteristics**	
• **Inclusion criteria**	Studies about nutrition and nutritional interventions in people with a confirmed diagnosis of dry AMD
• **Exclusion criteria**	Observational studies with < 10 participants (or eyes)
• **Patient & disease characteristics**	Number of participants: 170727 (in n=32 studies reporting relevant outcomes for the current evidence synthesis) Countries: Australia (3 studies), Austria (1 study), China (3 studies), France (2 studies), Finland (1 study), Germany (1 study), Hungary (1 study), Iran (1 study), Ireland (1 study), Italy (2 studies), Netherlands (1 study), Spain (1 study), Switzerland (1 study), Taiwan (1 study), UK (3 studies), USA (8 studies), UK and Netherlands (1 study) Age (yrs): mean age range 43 to 82 (29 studies), unclear (3 studies) Male/Female: male only (2 studies), female only (2 studies), % female range 4 to 72 (27 studies), unclear (1 study) AMD stage: no AMD (10 studies), early AMD (8 studies), early or moderate AMD (4 studies), early AMD in study eye, late AMD in other eye (3 studies), non-exudative AMD (1 study), dry AMD (2 studies), AMD grade 0-4 (1 study), AMD grade 2-4 (1 study), atrophic AMD (1 study), AMD not further specified (1 study)
• **Intervention(s)**	Nutrition and nutritional interventions
• **Comparator(s)**	Any comparator; see results
• **Results**	
• **Development of AMD**	<u>Homocysteine levels, folic acid and B vitamins</u> *Folic acid (2.5 mg/day), vitamin B6 (50 mg/day), vitamin B12 (1 mg/day) vs. placebo* **Total AMD (includes neovascular) (1 RCT, n=5205):** RR= 0.66 (95% CI 0.47 to 0.93) **Visually significant AMD, BCVA loss to 20/30 or worse (1 RCT, n=5205):** RR= 0.59 (95% CI 0.36 to 0.95)

Serum homocysteine per 1-SD (=5.09 mmol/L) increase
Incident early AMD (1 cohort study; n=1390): OR=1.33 (95% CI 1.09 to 1.63)
Incident late AMD (1 cohort study; n=1390): OR=1.25 (95% CI 0.93 to 1.69)
Incident any AMD (1 cohort study; n=1390): OR=1.33 (95% CI 1.11 to 1.60)

Serum vitamin B-12 per 1-SD (=144.9 pmol/L) increase
Incident early AMD (1 cohort study; n=1390): OR=0.77 (95% CI 0.62 to 0.96)
Incident late AMD (1 cohort study; n=1390): OR=0.66 (95% CI 0.45 to 0.96)
Incident any AMD (1 cohort study; n=1390): OR=0.73 (95% CI 0.60 to 0.89)

Serum folate per 1-SD (=9.1 nmol/L) increase
Incident early AMD (1 cohort study; n=1390): OR=0.93 (95% CI 0.77 to 1.13)
Incident late AMD (1 cohort study; n=1390): OR=0.89 (95% CI 0.66 to 1.20)
Incident any AMD (1 cohort study; n=1390): OR=0.91 (95% CI 0.77 to 1.07)

Carotenoids

High intake of Lutein/zeaxanthin (quintile 5) vs. low intake of Lutein/zeaxanthin (quintile 1)

Intermediate AMD (1 cohort study, n=102,046): RR=0.93 (95% CI 0.78 to 1.12)

Late AMD (1 cohort study, n=102,046): RR=0.59 (95% CI 0.48 to 0.73)

High intake of β-Cryptoxanthin (quintile 5) vs. low intake of β-Cryptoxanthin (quintile 1)

Intermediate AMD (1 cohort study, n=102,046): RR=0.85 (95% CI 0.72 to 1.02)

Late AMD (1 cohort study, n=102,046): RR=0.73 (95% CI 0.60 to 0.89)

High intake of Lycopene (quintile 5) vs. low intake of Lycopene (quintile 1)

Intermediate AMD (1 cohort study, n=102,046): RR=1.04 (95% CI 0.87 to 1.23)

Late AMD (1 cohort study, n=102,046): RR=0.93 (95% CI 0.76 to 1.13)

High intake of α-Carotene (quintile 5) vs. low intake of α-Carotene (quintile 1)

Intermediate AMD (1 cohort study, n=102,046): RR=0.94 (95% CI 0.79 to 1.12)

Late AMD (1 cohort study, n=102,046): RR=0.69 (95% CI 0.56 to 0.84)

High intake of β-carotene (quintile 5) vs. low intake of β-carotene (quintile 1)
Intermediate AMD (1 cohort study, n=102,046): RR=1.03 (95% CI 0.85 to 1.24)
Late AMD (1 cohort study, n=102,046): RR=0.82 (95% CI 0.67 to 1.01)

High intake of food-sourced β-carotene (quintile 5) vs. low intake of food-sourced β-carotene (quintile 1)
Intermediate AMD (1 cohort study, n=102,046): RR=1.02 (95% CI 0.84 to 1.24)
Late AMD (1 cohort study, n=102,046): RR=0.64 (95% CI 0.52 to 0.79)

High intake of food-sourced 'total' carotene (quintile 5) vs. low intake of food-sourced 'total' carotene (quintile 1)
Intermediate AMD (1 cohort study, n=102,046): RR=0.99 (95% CI 0.82 to 1.19)
Late AMD (1 cohort study, n=102,046): RR=0.64 (95% CI 0.51 to 0.79)

High intake of food-sourced 'total' carotenoid index (β-carotene + 'total' carotene) (quintile 5) vs. low intake of food-sourced 'total' carotenoid index (β-carotene + 'total' carotene (quintile 1)
Intermediate AMD (1 cohort study, n=102,046): RR=0.92 (95% CI 0.77 to 1.10)
Late AMD (1 cohort study, n=102,046): RR=0.65 (95% CI 0.53 to 0.80)

Antioxidant effects of vitamins
Vitamin E (natural-source; 600 IU on alternate days) and low dose aspirin vs. placebo
Visually significant AMD (1 RCT, n=39,421): RR=0.93 (95% CI 0.72 to 1.19)
Advanced AMD (1 RCT, n=39,421): RR=1.13 (95% CI 0.67 to 1.92)
All AMD (1 RCT, n=39,421): RR=0.90 (95% CI 0.77 to 1.06)

Vitamin E (500 international units (335 mg dα-tocopherol) in a soybean oil suspension in gelatin capsule, daily) vs. placebo
Early AMD; soft distinct or soft indistinct or pigment changes (1 RCT, n=1193): RR=1.05 (95% CI 0.69 to 1.61)
Early AMD; Large/soft drusen or nongeographical RPE atrophy (1 RCT, n=1193): RR=1.12 (95% CI 0.66 to 1.9)
Late AMD; soft distinct or soft indistinct or pigment changes (1 RCT, n=1193): RR=1.36 (95% CI 0.67 to 2.77)
Late AMD; Large/soft drusen or nongeographical RPE atrophy (1 RCT, n=1193): RR=1.00 (NR)

	Multivitamin (no details provided) vs. placebo **Visually significant AMD (1 RCT, n=14,233):** HR=1.19 (95% CI 0.94 to 1.50) **Advanced AMD (1 RCT, n=14,233):** RR=1.22 (95% CI 0.88 to 1.70) **All AMD (1 RCT, n=14,233):** RR=1.22 (95% CI 1.03 to 1.44) *Alpha-tocopherol (50 mg) vs. beta-carotene (20 mg) vs. alpha-tocopherol (50 mg) + beta-carotene (20 mg) vs. placebo* **All AMD incidence (1 RCT; n=941)**: 31.6% vs. 29.1% vs. 28.4% vs. 24.9%; p=0.468 - **AMD class I (dry maculopathy, with hard drusen and/or pigmentary changes)**: 65% vs. 64% vs. 64% vs. 46% - **AMD class II (soft macular drusen)**: 2% vs. 2% vs. 6% vs. 6% - **AMD class III (disciform degeneration)**: 6% vs. 2% vs. 2% vs. 0% - **AMD class IV (geographic atrophy)**: 2% vs. 0% vs. 1% vs. 1%
• **Progression of AMD**	<u>Homocysteine levels, folic acid and B vitamins</u> *Folate and vitamin B intake* **Progression to geographic atrophy (1 cohort study; n=2525)**: "After adjustment, progressors had a lower intake of thiamine (p=0.01), riboflavin (p=0.03) and folate (p=0.001) than non-progressors. No statistically significant variation was seen for niacin, vitamin B-6 or vitamin B-12. Multivariate analysis showed a significant trend for a lower risk of progression with increasing folate (p=0.007), a borderline association for thiamine (p=0.053), and no association with riboflavin (p=0.20)." <u>Carotenoids</u> *Intake of lutein and zeaxanthin (mg/d) continuous* **Increase in AMD severity one or more levels in the worse affected eye (1 cohort study, n=254):** OR=2.65 (95% CI 1.13 to 6.22) **Increase in AMD severity one or more levels in either eye; or an increase in ≥ 2 steps in the grades of size, total number, area occupied by a lesion, and spread (1 cohort study, n=254):** OR=1.72 (95% CI 0.78 to 3.78) **Qualitative (better, worse, same) from macular photographs (1 cohort study, n=254):** OR=1.84 (95% CI 0.84 to 4.00) *Energy adjusted intake of ω-3 fatty acids(g)* **Increase in AMD severity one or more levels in the worse affected eye (1 cohort study, n=254):** OR=1.82 (95% CI 0.99 to 3.37) **Increase in AMD severity one or more levels in either eye; or an increase in ≥ 2 steps in the grades of size, total number, area occupied by a lesion, and spread (1 cohort study, n=254):** OR=1.58 (95% CI 0.88 to 2.84) **Qualitative (better, worse, same) from macular photographs (1 cohort study, n=254):** OR=1.65 (95% CI 0.92 to 2.96)

	Triple therapy + zeaxanthin vs. triple therapy *(triple therapy: intravitreal bevacizumab, intravitral dexamethason, and reduced-fluence photodynamic therapy with verteporfin (PDT); all patients also were taking multivitamin and an AREDS 1 antioxidant regimen)* **% of fellow eyes that developed CNV (1 cohort study; n=240):** 6.25% vs. 12.50%; p=0.03 <u>Carotenoids and other nutrients</u> *Supplements (12 mg lutein, 0.6 mg zeaxanthin, 15 mg vitamin E, 150 mg vitamin C, 20 mg zinc oxide, 0.4 mg copper) vs. placebo* **% AMD progression at 12 months (1 RCT, n=433, 493 eyes):** 41.7 vs. 47.4; p=NS **% Progression to late AMD (central GA or CNV) (1 RCT, n=433, 493 eyes):** 14.3 vs. 17.1; p=NS <u>Antioxidant effect</u> *Vitamin E (500 IU [335 mg dα tocopherol] daily) vs. placebo* **Progression of AMD; soft distinct or soft indistinct or pigment changes (1 RCT, n=1193):** RR=1.09 (95% CI 0.84 to 1.42) **Progression of AMD; large/soft drusen or nongeographical RPE atrophy (1 RCT, n=1193):** RR=1.31 (95% CI 0.83 to 2.07)
• **Adverse events**	<u>Carotenoids</u> *Lutein (months 1 to 3: 20 mg once daily, months 4 to 6: 10 mg once daily) vs. placebo* **Serious adverse events leading to study withdrawal (1 RCT, n=126):** 2.4% vs. 2.4% *Lutein 10 mg vs. lutein 20 mg vs. lutein 10 mg + Zeaxanthin 10 mg vs. placebo* **Adverse events (2 RCT, n=220):** 0 vs. 0 vs. 0 vs. 0 *Carotenoid-enriched eggs vs. placebo eggs* **Adverse events (1 RCT, n=50):** 0 vs. 0 *Zeaxanthine 8mg vs. Zeaxanthine 8 mg + lutein 9mg vs. lutein 9 mg* **Adverse events (1 RCT, n=60)**: “Two deaths (unrelated to study intervention), 1 case of pneumonia. No other significant adverse events.” <u>Carotenoids and other nutrients</u> *Lutein combined with vitamins and minerals vs. placebo*

Adverse events (1 RCT, n=30): 0 vs. 0

Lutein vs. lutein and carotenoids, antioxidants, vitamins, minerals vs. placebo

(Dose details lutein 10 mg; 2500 IU vitamin A, 15,000 IUnatural beta carotene, 1,500-mg vitamin C, 400 IU vitamin D3, 500 IU natural vitamin E, 50mg vitamin B1, 10mg vitamin B2, 70mg vitamin B3, 50mg vitamins B5 and B6, 500mcg vitamin B12, 800mcg folic acid, 300mcg biotin, 500mg Calcium, 300mg magnesium, 75mcg iodine, 25mg zinc, 1mg copper, 2mg manganese, 200mcg selenium, 200mcg chromium, 75mcg molybdenum, 600mcg lycopene, 60mg bilberry extract, 150mg alpha lipoic acid, 200mg N-acetyl cysteine, 100mg quercetin; 100mg rutin, 250mg citrus bioflavonoids, 50mg plant enzymes, 5mg black pepper extract, 325mg malic acid, 900mg taurine, 100mg L-glycine,10mg L-glutathione, 2mg)

boron

Major cardiovascular event or death (any cause) (1 RCT, n=90): 4 vs. 0 vs. 3

Lutein 10 mg vs. Lutein 10 mg + Omega-3 fatty acid (DHA/EPA) 160 mg (The ingredients of the supplement in both arms also included: vitamin C 10mg, vitamin E 20 mg, niacin / vitamin B3 10mg, copper 0.25 mg, zinc 10 mg, zeaxanthine 1 mg.)

Systemic or ocular disorders (1 RCT, n=79): 0 vs. 0

Nutritional supplementation with carotenoids (lutein, zeaxanthin, astaxanthin), oligoelements and antioxidant vitamins vs. no nutritional supplements

(Dose details: vitamin C (180 mg), vitamin E (30 mg), zinc (22.5 mg), copper (1 mg), lutein (10 mg), zeaxanthin (1 mg), astaxanthin (4 mg). 1 tablet a day)

Adverse reaction leading to study withdrawal or discontinuation (1 RCT, n=145): 0 vs. 0

Fatty acids and antioxidants

Docosahexaenoic acid (280mg DHA, 90mg eicosapentaenoic acid, EPA, 2mg vitamin E; 3 times a day) vs. placebo

% with at least 1 treatment emergent adverse event (1 RCT, n=300): 4.7 vs. 1.6; p=NS

% with ocular adverse event (1 RCT, n=300): 58.7 vs. 50; p=NS

% with worsening of cateract (1 RCT, n=300): 50 vs. 62.5; p=0.032

% with serious non ocular event (1 RCT, n=300): 23.1 vs. 23.6; p=NS

% deaths (1 RCT, n=300): 2.2 vs. 4.7

Antioxidant effects of vitamins

	Vitamin E (500 IU [335 mg dα tocopherol] daily) vs. placebo **% with adverse events potentially related to study capsule (1 RCT, n=1193):** 15 vs 14; p=0.49 **% with ocular adverse events (1 RCT, n=1193):** 18 vs 15; p=0.23 **% with serious adverse events (1 RCT, n=1193):** 0 vs. 0 **% with adverse reaction leading to withdrawal (1 RCT, n=1193):** 0.7 vs. 1.2
• **Visual acuity**	<u>Carotenoids</u> *Lutein based supplement (vitamin C 150 mg, cupric oxide 400 µg, vitamin E 15 mg, lutein 12 mg, zeaxanthin 0.6 mg, zinc 20 mg, omega-3 fatty acids 1,080 mg per day) vs. no supplement* **Visual acuity, logMAR (1 RCT, n=14):** "no significant difference between the groups" *Lutein (10 mg daily in one RCT and 20 mg 3 months once daily followed by 10 mg 3 months once daily in other RCT) vs. placebo* **Mean (SD) visual acuity (1 RCT, n=84)**: 0.09 (0.14) vs. 0.09 (0.13) p<0.05 **Mean (SD) change in visual acuity (ETDRS) (1 RCT, n=126):** 2.1 (0.4) vs. 1 (NR); p=0.07 *Lutein 10 mg vs. lutein 20 mg vs. lutein 10 mg + Zeaxanthin 10 mg vs. placebo* **Mean (95% CI) best-corrected visual acuity, logMAR (1 RCT, n=108):** -0.04 (-0.11 to 0.03) vs. -0.02 (-0.11 to 0.06) vs. -0.04 (-0.10 to 0.01) vs. -0.00 (-0.06 to 0.05) **Mean (SD) best-corrected visual acuity at 2 years, logMAR (1 RCT, n=112):** 0.26 (0.15) vs. 0.28 (0.16) vs. 0.27 (0.24) vs. 0.30 (0.25) *Carotenoid-enriched eggs vs. placebo eggs* **Mean (SD) best-corrected visual acuity final visit (1 RCT, n=50):** 107.7 (4.45) vs. 105.4 (4.78); p=0.035 *Zeaxanthine 8mg vs. Zeaxanthine 8 mg + lutein 9mg vs. lutein 9 mg* **Mean (SE) ETDSR Colenbrander eye near high-contrast visual acuity (1 RCT, n=60)**: 96.8 (8.35) vs. 92.8 (5.9) vs. 98.9 (5.7); p=NS *Lutein 20 mg + zeaxanthin 2 mg vs. Meso-zeaxanthin 10 mg + Lutein 10 mg + zeaxanthin 2 mg vs. Meso-zeaxanthin 17 mg + Lutein 3 mg + zeaxanthin 2 mg* **Best-corrected visual acuity (1 RCT, n=67):** "observed effects over time did not differ between the groups"

Lutein complex: lutein 12g + zeaxanthin 2 mg vs. no intervention

Mean (SD) best-corrected visual acuity, logMAR (1 before-after study, n=56): 0.09 (0.08) vs. 0.14 (0.09)

Carotenoids and other nutrients

Supplements (lutein, zeaxanthin, vitamin E, vitamin C, zinc, copper) vs. placebo

(Dose details: lutein 12mg, zeaxanthin 0.6mg, vitamin E 15mg, vitamin C 150mg, zinc oxide 20 mg, copper 0.4mg (daily dose))

Mean (SD) best-corrected visual acuity at 12 months (1 RCT, n=433, 493 eyes): 79.7 (8.9) vs. 80.4 (9.8)

Lutein vs. lutein and carotenoids, antioxidants, vitamins, minerals vs. placebo

(Dose details: lutein 10 mg; 2500 IU vitamin A, 15,000 IUnatural beta carotene, 1,500-mg vitamin C, 400 IU vitamin D3, 500 IU natural vitamin E, 50mg vitamin B1, 10mg vitamin B2, 70mg vitamin B3, 50mg vitamins B5 and B6, 500mcg vitamin B12, 800mcg folic acid, 300mcg biotin, 500mg Calcium, 300mg magnesium, 75mcg iodine, 25mg zinc, 1mg copper, 2mg manganese, 200mcg selenium, 200mcg chromium, 75mcg molybdenum, 600mcg lycopene, 60mg bilberry extract, 150mg alpha lipoic acid, 200mg N-acetyl cysteine, 100mg quercetin; 100mg rutin, 250mg citrus bioflavonoids, 50mg plant enzymes, 5mg black pepper extract, 325mg malic acid, 900mg taurine, 100mg L-glycine,10mg L-glutathione, 2mg)

Near visual acuity change, letters (95% CI) (1 RCT, n=90): 5.4 (2.5 to 8.2) vs. 3.5 (1.2 to 5.8) vs. -0.2 (-3.0 to 2.7); p=0.013

Distance visual acuity change, logMAR, Right eye / Left eye (95% CI) (1 RCT, n=90): -0.10 (-0.19 to -0.01) / -0.03 (-0.09 to 0.03) vs.-0.03 (-0.12 to 0.07) / -0.06 (-0.14 to 0.03) vs. -0.14 (-0.30 to 0.03) / 0.05 (-0.14 to 0.23); p=0.01 / p=NS

10mg lutein, 1mg zeaxanthin, 225mg fish oil [of which 100mg docosahexaenoic acid, DHA, and 30mg eicosapentaenoic acid, EPA], antioxidants [60mg vitamin C, 20mg vitamin E, 10mg zinc, 0.25mg copper] vs. 20mg lutein, 2mg zeaxanthin, 500mg fish oil [of which 200mg DHA, and 60mg EPA], antioxidants [120mg vitamin C, 40mg vitamin E, 20mg zinc, 0.5mg copper] vs. placebo

Mean (SD) best-corrected visual acuity at 12 months (1 RCT, n=172): 0.104 (0.18) vs. 0.064 (0.16) vs. 0.127 (0.16); p=NS

Mean (SD) best-corrected visual acuity change in reading letters at 12 months (1 RCT, n=172): 1.46 (2.8) vs. 2.02 (3.1) vs. 0.08 (2.8); p=0.038 for placebo vs. doasage 1; p=0.006 for placebo vs. dosage 2; p=0.354 for dosage 1 vs. dosage 2

Lutein (12 mg), zeaxanthin (0.6 mg), docosahexaenoic acid (DHA; 280 mg) vs. placebo

Mean (SEM) visual acuity, ETDRS letters (1 RCT, n=44): 74.3 (9.2) vs. 75.9 (5.8); p=NS

Lutein 10 mg vs. Lutein 10 mg + Omega-3 fatty acid (DHA/EPA) 160 mg (The ingredients of the supplement in both arms also included: vitamin C 10mg, vitamin E 20 mg, niacin / vitamin B3 10mg, copper 0.25 mg, zinc 10 mg, zeaxanthine 1 mg.)

Mean (SD) best-corrected visual acuity letter score, ETDRS letters at 12 months (1 RCT, n=79): 81 (5) vs. 80 (10)

Nutritional supplementation with carotenoids (lutein, zeaxanthin, astaxanthin), oligoelements and antioxidant vitamins vs. no nutritional supplements

(Dose details: vitamin C (180 mg), vitamin E (30 mg), zinc (22.5 mg), copper (1 mg), lutein (10 mg), zeaxanthin (1 mg), astaxanthin (4 mg))

Mean (SD) best-corrected visual acuity at 24 months, ETDRS letter score (1 RCT, n=145): 81.4 (7.2) vs. 76.8 (8.9); p=0.003

Mean (95% CI) change in best-corrected visual acuity at 24 months, ETDRS letter score (1RCT, n=145): –0.02 (–1.42 to 1.36) vs. -4.18 (–7.34 to –1.01); p=0.008

Fatty acids and antioxidants

Phototrop (100 mg acetyl-L-carnitine, 530 mg n-3 fatty acids, 10 mg co-enzyme Q10) vs. placebo (soy oil)

Mean visual acuity at 12 months, Snellen (1 RCT, n=106): 0.6 vs. 0.52

% patients with detarioration in visual acuity at 12 months, Snellen (1 RCT, n=106): 23 vs. 45; p=0.015

Mean (SD) change in visual acuity at 12 months, logMAR (1 RCT, n=106): 0.009 (0.23) vs. -0.14; (0.23); p=NS

% patients with deterioration in visual acuity at 12 months, logMAR (1 RCT, n=106): 25 vs. 45; p=0.027

Docosahexaenoic acid (280mg DHA, 90mg EPA, 2mg vitamin E) vs. placebo

Mean (SD) best-corrected visual acuity change at 3 years, logMAR (1 RCT, n=300): -0.155 (0.297) vs. -0.116 (0.258); p=0.311

% with a decrease of >15 letters on ETDRS at 3 years (1 RCT, n=300): 17.8 vs. 14.3; p=0.469

α-lipoic acid (0.2 g) vs. vitamin C (1.0 g)

Mean (SD) best-corrected visual acuity at 3 months, logMAR (1 RCT, n=100): 0.66 (0.41) vs. 0.63 (0.42); p=NS

Antioxidant effects of vitamins

Vitamin E (500 IU [335 mg dα tocopherol] daily) vs. placebo

Best corrected visual acuity (1 RCT, n=1193): "no differences between groups"

Loss of > 9 letters (two lines) of visual acuity (1 RCT, n=1193): 59/587 vs. 57/592; RR=1.04 (95% CI 0.74 to 1.47)

Saffron

	Saffron (50 mg in one RCT, 20 mg in other) vs. placebo **Mean (SD) best-corrected visual acuity at 12 weeks, logMAR (1 RCT, n=54):** 0.41 (0.41) vs. 0.65 (0.54); p=0.001 **Mean (SD) visual acuity at 90 days, Snellen (1 randomized crossover trial, n=25):** 0.80 (0.20) vs. 0.72 (0.24); p<0.01 **% visual acuity increased by one line, Snellen (1 randomized crossover trial, n=25):** 80 vs. 0
• **Other**	Fatty acids and antioxidants *Olive oil consumption, 'regular users' vs. 'Non users' of olive oil* **Prevalence of early AMD (1 cohort study, n=654, 1269 eyes):** 20.4% vs. 23.1% **Prevalence of late AMD (1 cohort study, n=654, 1269 eyes):** 3.5% vs. 6.9% "After multivariate adjustment, regular consumption of olive oil was significantly associated with late AMD (OR = 0.44, 95% CI: 0.21;0.91, p = 0.03), but not with early AMD (OR = 0.84, 95%CI: 0.59;1.24 (1.21 in the table), p = 0.36) (adjusted for age, gender, educational level, marital status, smoking, BMI, regular consumption of raw fruits, regular consumption of cooked fruits and vegetables, plasma HDL-cholesterol, plasma total n-3 PUFAs, plasma total n-6 PUFAs and total energy intake. Eyes without AMD were the reference)." "No associations were found between regular consumption of n-3 rich oils, n-6 rich oils, mixed oils, butter and margarine and AMD, whatever the stage."
• **Limitations**	
• **Limitations**	**AMSTAR 2**: High confidence in the results of the review. A few remarks: Protocol available, but no search strategy included. Search strategy is very broad and contains no specific search terms regarding supplements Study selection and data-extraction was done by 1 reviewer and checked by another reviewer **Cochrane Risk of bias tool (25 RCTs):** 13 studies had unclear risk of bias for random sequence generation; 1 study had high risk and 23 studies had unclear risk of bias for allocation concealment; 3 studies had high risk and 11 studies had unclear risk of bias for blinding of participants and personnel; 1 study had high risk and 18 studies had unclear risk of bias for blinding of outcome assessment; 8 studies had high risk and 9 studies had unclear risk of bias for incomplete outcome data; 6 studies had high risk and 1 study had unclear risk of bias due to selective reporting. **Newcastle Ottawa Scale (7 studies):**

	The quality of 3 studies was rated as ‘fair’, and the quality of 4 studies was rated as ‘good’.
• **Other comments**	-

NR=not reported; NS=not significant

4B: Primaire onderzoeken

Evidencetabellen van geïncludeerde primaire onderzoeken betreffende voeding voor de preventie van LMD

De Koning-Backus 2019 - Intake of Vegetables, Fruit, and Fish is Beneficial for Age-Related Macular Degeneration	
Methods	
• **Design**	Prospective cohort study.
• **Source of funding and competing interests**	Source of funding: Uitzicht; vereniging Bartiméus Sonneheerdt; Stichting Oogfonds; Landelijke Stichting voor Blinden en Slechtzienden; Algemene Nederlandse Vereniging ter voorkoming van Blindheid; Novartis research foundation; MaculaFonds; Stichting Erasmus Trustfonds; the European Union's Horizon 2020 research and innovation program; Erasmus Medical Center and Erasmus University, Rotterdam, the Netherlands; Netherlands Organization for the Health Research and Development; the Research Institute for Diseases in the Elderly; the Ministry of Education, Culture and Science; the Ministry for Health, Welfare and Sports; the European Commission; the Municipality of Rotterdam. Sponsors and funding organizations had no role in the design or conduct of this research. Competing interests: not reported.
• **Setting**	Population based study in The Netherlands.
• **Sample size**	4202
• **Study dates**	Inclusion between 1990 and 1993, last follow-up examination between 2009 and 2011.
• **Follow-up**	Mean follow-up of 9.1 (SD: 5.8) years.
Patient characteristics	
• **Eligibility criteria**	People aged >55 years with gradable fundus photographs at baseline, at least 1 follow-up eye examination, and valid dietary assessments.
• **Exclusion criteria**	Persons with a diagnosis of dementia; persons living in nursing homes; persons with macular pathology other than AMD hindering appropriate grading of the macula; and persons with prevalent early or late AMD at baseline.
• **AMD definition**	Each eye was graded according to the Wisconsin Age-related Maculopathy Grading and classified using the Rotterdam classification. Classification of the person was based upon the eye with the most severe AMD stage. The outcome was incident AMD (i.e., persons who developed signs of early or late AMD during the study period); no AMD was used as the reference. Early AMD was defined by the presence of soft distinct drusen with pigmentary changes, soft indistinct drusen with or without pigmentary changes, or reticular pseudodrusen with or without

	pigmentary changes. Late AMD was defined by the presence of geographic atrophy or neovascular AMD. No AMD was defined as no signs of early or late AMD.
• **Patient & disease characteristics**	*Reported as no AMD vs. incident AMD* Mean age (SD): 66.5 (7.2) vs 67.0 (6.9) % Male: 40.7 vs. 41.0 % Past smoking: 42.7 vs. 45.5 % Current smoking: 22.9 vs. 22.3 Mean BMI (SD): 26.4 (3.6) vs. 26.2 (3.5) Race: not reported Other ocular pathology: excluded
Interventions	
• **Determinants**	Recommended dietary intake of the following food categories: vegetables, fruit, fish, fat products, meat, grains, poultry, eggs, potatoes, legumes, and dairy. As recommended minimum intake, the following values were taken: vegetables 200 g/day; fruit 200 g/day; fish 32 g/day; fat products 15 g/day; meat 32 to 71 g/day; grains 210 g/day (men) and 175 g/day (women); poultry 16 g/day; eggs 16 g/day; potatoes 143 g/day (men) and 114 g/day (women); legumes 21 g/day; dairy 150 g/day. In addition, the following food patterns were analyzed: 1. Vegetables >200 g/day; fruit >200 g/day; fish >32 g/day; egg, poultry, or meat >80 g/day; dairy 150 g/day; potatoes, legumes, or grains >319 g/day; fat products >15 g/day 2. Vegetables >200 g/day; fruit >200 g/day; fish >32 g/day; egg, poultry, or meat >80 g/day 3. Vegetables >200 g/day; fruit >200 g/day; fish >32 g/day; egg or poultry >48 g/day 4. Vegetables >200 g/day; fruit >200 g/day; fish >32 g/day; poultry >16 g/day 5. Vegetables >200 g/day; fruit >200 g/day; fish >32 g/day; 32 g/day < meat < 71 g/day 6. Vegetables >200 g/day; fruit >200 g/day; poultry >16 g/day 7. Vegetables >200 g/day; fruit >200 g/day; egg >32 g/day 8. Vegetables >200 g/day; fruit >200 g/day; 32 g/day < meat < 71 g/day 9. Vegetables >200 g/day; fruit >200 g/day; fish >32 g/day Dietary intake was assessed using a 2-stage approach: (1) a self-administered checklist at home in which subjects were asked which foods were consumed weekly, or at least twice a month during the preceding year, and (2) a structured interview with a trained dietician at the research center reviewing self- administered checklists for frequencies and amounts.
Results	

• **Development of AMD**	*All comparisons are for people following the recommended intakes of food categories and patterns vs. those with lower intakes* *Vegetables*: HR=1.01 (95% CI 0.86 to 1.18) *Fruit*: HR=1.03 (95% CI 0.89 to 1.20) *Fish*: HR=0.76 (95% CI 0.60 to 0.97) *Fat products*: HR=1.00 (95% CI 0.81 to 1.23) *Meat 32-71 g*: HR=0.91 (95% CI 0.65 to 1.28) *Grains*: HR=1.00 (95% CI 0.83 to 1.20) *Poultry*: HR=0.92 (95% CI 0.78 to 1.09) *Eggs*: HR=1.10 (95% CI 0.67 to 1.78) *Potatoes*: HR=0.91 (95% CI 0.78 to 1.06) *Legumes*: HR=1.11 (95% CI 0.90 to 1.36) *Dairy*: HR=1.13 (95% CI 0.95 to 1.35) *Food pattern 1**: HR=0.90 (95% CI 0.22 to 3.64) *Food pattern 2**: HR=0.96 (95% CI 0.36 to 2.57) *Food pattern 3**: HR=0.95 (95% CI 0.35 to 2.56) *Food pattern 4**: HR=0.65 (95% CI 0.36 to 1.18) *Food pattern 5**: HR=0.74 (95% CI 0.33 to 1.66) *Food pattern 6**: HR=0.81 (95% CI 0.60 to 1.10) *Food pattern 7**: HR=1.62 (95% CI 0.67 to 3.92) *Food pattern 8**: HR=1.01 (95% CI 0.72 to 1.41) *Food pattern 9**: HR=0.58 (95% CI 0.36 to 0.93) Analyses are adjusted for age, sex, smoking, BMI, hypertension, education, total energy intake and net annual income. *See the description of the food patterns at ‘determinants’.
• **Adverse events**	Not assessed.
Limitations and other comments	

• **Limitations**	The study is at moderate risk of bias due to deviations from the intended interventions and at serious risk of bias due to exclusion of participants with missing data. The risk of bias for all other domains is low.

Dighe 2019 - Diet patterns and the incidence of age-related macular degeneration in the Atherosclerosis Risk in Communities (ARIC) study	
Methods	
• **Design**	Prospective cohort study
• **Source of funding and competing interests**	Source of funding**:** National Institutes of Health, National Institute on Aging, National Heart, Lung, and Blood Institute, Department of Health and Human Services. National Human Genome Research Institute, National Institutes of Health. Competing interests: None declared.
• **Setting**	Population based study in the United States.
• **Sample size**	1278
• **Study dates**	1987 to 2017
• **Follow-up**	Mean 18 years of follow-up
Patient characteristics	
• **Eligibility criteria**	Healthy participants.
• **Exclusion criteria**	Participants identified as outliers for energy (total calorie intake <500 or >3500 kcal) or with nongradeable retinal photographs.
• **AMD definition**	Graders, masked to previous outcomes, graded all retinal photographs by the Wisconsin Age-Related Maculopathy Grading System. Participants were categorised as having incident early AMD if they had any of the following: (1) soft drusen (≥63 µm circle) within a grid area >500 µm circle, (2) any soft drusen ≥125 µm circle (either distinct or indistinct) present in the grid along with the presence of any pigmentary abnormality (increased/decreased pigmentation in the grid) or (3) large (≥125 µm circle) soft indistinct drusen present. Presence of either geographic atrophy, retinal pigment epithelial detachments, subretinal haemorrhage, subretinal fibrous scar, subretinal new vessels or history of treatment (laser, intravitreal injections) was categorised as late AMD.
• **Patient & disease characteristics**	*Reported as no AMD vs any AMD* Mean age (SD): 58.4 (5.0) vs. 61.3 (4.7) % Male: 42 vs. 44

	% Current smoking: 11 vs. 13 % Former smoking: 41 vs. 49 % Never smoking: 49 vs. 38 % Normal weight (BMI<25.0): 29 vs. 29 % Overweight (BMI 25.0-30.0): 44 vs. 46 % Obese (BMI ≥30.0): 27 vs. 25 % White race: 83 vs. 97 % African-American: 17 vs. 3 Other ocular pathology: not reported
Interventions	
• **Determinants**	Western (unhealthy) dietary pattern and Prudent (healthy) dietary pattern. "Processed meat, fried food, dessert, eggs, refined grains, high fat dairy and sugar sweetened beverages loaded higher on the Western pattern. Cruciferous, carotene, dark green leafy and other vegetables, poultry, fresh fruits, fish and sea foods loaded higher on the Prudent pattern." Diet was assessed at visits 1 and 3 using a modified Willet's 66-line item Food Frequency Questionnaire (FFQ). Usual dietary intake over the past year was assessed in nine categories ranging from never to ≥6 times a day, assuming standard portion sizes.
Results	
• **Development of AMD**	*Western pattern (tertile 3 vs tertile 1)* **Any AMD:** 49/426 vs. 45/426; model 1 OR=1.43 (95% CI 0.83 to 2.46); model 2 OR=1.69 (95% CI 0.88 to 3.25) **Early AMD:** 44/417 vs. 33/407; model 1 OR=1.10 (95% CI 0.61 to 2.00); model 2 OR=1.41 (95% CI 0.69 to 2.88) *Western pattern (>= median vs. <median)* **Late AMD:** 9/639 vs. 18/639; model 1 OR=3.44 (95% CI 1.33 to 8.87); model 2 OR=3.00 (95% CI 1.06 to 8.47) *Prudent pattern (tertile 3 vs. tertile 1)* **Any AMD:** 48/426 vs. 42/426; model 1 OR=0.90 (95% CI 0.56 to 1.46); model 2 OR=0.84 (95% CI 0.49 to 1.46) **Early AMD:** 37/411 vs. 36/415; model 1 OR=1.00 (95% CI 0.59 to 1.68); model 2 OR=0.97 (95% CI 0.53 to 1.78) **Late AMD:** 17/639 vs. 10/639; model 1 OR=0.51 (95% CI 0.22 to 1.18); model 2 OR=0.43 (95% CI 0.18 to 1.05)

	Model 1: Adjusted for age, race, education, daily energy intake (kcal) and smoking status. *Model 2: Model 1 further adjusted for inverse probability weights.*
• **Adverse events**	Not assessed.
Limitations and other comments	
• **Limitations**	The study has a moderate risk of bias due to deviations from the intended interventions, and a serious risk of bias due to exclusion of almost 80% of the participants because of missing data. No other indications of bias.

Gopinath 2018a – Association of Dietary Nitrate Intake with the 15-Year Incidence of Age-Related Macular Degeneration	
Methods	
• **Design**	Longitudinal population based cohort study
• **Source of funding and competing interests**	Source of funding: Australian National Health and Medical Research Council; Westmead Institute for Medical Research; National Health and Medical Research Council (NHMRC) Senior Research Fellowship; Royal Perth Hospital Medical Research Foundation Fellowship; NHMRC Career Development Fellowship. Competing interests: No potential conflict of interest was reported by the authors.
• **Setting**	Population-based study in a region west of Sydney, Australia.
• **Sample size**	2037
• **Study dates**	Participants included between 1992-1994, last follow-up between 2007-2009.
• **Follow-up**	15 years
Patient characteristics	
• **Eligibility criteria**	Healthy participants aged > 49 years.
• **Exclusion criteria**	Follow-up < 15 years.
• **AMD definition**	Early AMD was defined as the absence of late AMD and presence of either: (1) large (>125-mm diameter) indistinct soft or reticular drusen or (2) both large distinct soft drusen and retinal pigmentary abnormalities (hyperpigmentation or hypopigmentation) in either eye. Late AMD was defined as the presence of neovascular AMD or geographic atrophy in either eye.
• **Patient & disease characteristics**	Mean age (SD): 63.8 (8.3) % Male: 43.3 % Current Smokers: 12.4

	Mean BMI (SD): not reported Race: not reported Other ocular pathology: not reported
Interventions	
• **Determinants**	1. Total nitrate intake in quartiles (≤87.0 mg/day, 87.1-119.5 mg/day, 119.5-162.3 mg/day, ≥162.3 mg/day) 2. Total vegetable nitrate intake in quartiles (≤68.9 mg/day, 69.0-100.0 mg/day, 100.0-141.6 mg/day, ≥141.7 mg/day) 3. Total nonvegetable nitrate intake in quartiles (≤15.5 mg/day, 15.5-18.6 mg/day, 18.6-22.0 mg/day, ≥22.0 mg/day) Dietary data were collected using a validated 145-item self-administered food frequency questionnaire (FFQ). Foods listed in the FFQ were categorized into major food categories and subcategories similar to those used for the 1995 Australian National Nutrition Survey.
Results	
• **Development of AMD**	*Total nitrate 2nd quartile vs. 1st quartile* **Early AMD at 15 years:** OR* (95% CI) =0.79 (0.54-1.15) **Late AMD at 15 years:** OR*(95% CI) = 1.11 (0.54-2.28) *Total nitrate 3rd quartile vs. 1st quartile* **Early AMD at 15 years:** OR* (95% CI) = 0.61 (0.41-0.90) **Late AMD at 15 years:** OR*(95% CI) = 1.38 (0.71-2.71) *Total nitrate 4th quartile vs. 1st quartile* **Early AMD at 15 years:** OR*(95% CI) = 0.74 (0.51-1.08) **Late AMD at 15 years:** OR*(95% CI) = 1.07 (0.53-2.17) *Total vegetable nitrate 2nd quartile vs. 1st quartile* **Early AMD at 15 years:** OR*(95% CI) = 0.78 (0.54-1.13) **Late AMD at 15 years:** OR*(95% CI) = 1.72 (0.82-3.60) *Total vegetable nitrate 3rd quartile vs. 1st quartile* **Early AMD at 15 years:** OR*(95% CI) = 0.65 (0.44-0.96) **Late AMD at 15 years:** OR*(95% CI) = 1.75 (0.84-3.63) *Total vegetable nitrate 4th quartile vs. 1st quartile*

	Early AMD at 15 years: OR*(95% CI) = 0.69 (0.47-1.00) **Late AMD at 15 years:** OR*(95% CI) = 1.38 (0.65-2.94) *Total nonvegetable nitrate 2nd quartile vs. 1st quartile* **Early AMD at 15 years:** OR*(95% CI) = 0.90 (0.61-1.32) **Late AMD at 15 years:** OR*(95% CI) = 1.12 (0.57-2.21) *Total nonvegetable nitrate 3rd quartile vs. 1st quartile* **Early AMD at 15 years:** OR*(95% CI) = 0.79 (0.54-1.17) **Late AMD at 15 years:** OR*(95% CI) = 0.87 (0.44-1.72) *Total nonvegetable nitrate 4th quartile vs. 1st quartile* **Early AMD at 15 years:** OR*(95% CI) = 0.82 (0.56-1.20) **Late AMD at 15 years:** OR*(95% CI) = 0.98 (0.51-1.88) * Adjusted for age, sex, current smoking, fish consumption, and CFH and ARMS2 SNPS (rs1061170 and rs10490924).
• **Adverse events**	Not assessed.
Limitations and other comments	
• **Limitations**	The study had a moderate risk of bias due to deviations of the intended intervention and a moderate risk of bias due to exclusion of individuals with missing data. A low risk of bias was found for all other domains.

Gopinath 2018b - Dietary flavonoids and the prevalence and 15-y incidence of age-related macular degeneration	
Methods	
• **Design**	Prospective cohort study
• **Source of funding and competing interests**	The Blue Mountains Eye Study was funded by the Australian National Health and Medical Research Council (grants 974159, 991407, 211069, and 262120) and the Westmead Institute for Medical Research. The salary of JMH was supported by a National Health and Medical Research Council (NHMRC) Senior Research Fellowship and a Royal Perth Hospital Medical Research Foundation Fellowship. The salary of JRL is supported by an NHMRC Career Development Fellowship (ID: 1107474). The authors declare no conflicts of interests.
• **Setting**	Population-based cohort study of common eye diseases and other health outcomes in a suburban Australian population located west of Sydney.

• **Sample size**	2856 at baseline; 2037 followed up
• **Study dates**	1992 to 1994
• **Follow-up**	15 years
Patient characteristics	
• **Eligibility criteria**	Residents aged ≥49 y
• **Exclusion criteria**	Not reported.
• **AMD definition**	Two 30° stereoscopic color retinal photographs of the macula of both eyes were taken, which were graded for the presence of early and late AMD using the Wisconsin AMD Grading System. Early AMD was defined as the absence of late AMD and the presence of either 1) large (>125-µm diameter) indistinct soft or reticular drusen or 2) both large distinct soft drusen and retinal pigmentary abnormalities (hyperpigmentation or hypopigmentation) in either eye. Similarly, late AMD was defined as the presence of neovascular AMD or geographic atrophy in either eye. Any AMD was defined as having early or late AMD. A retinal specialist adjudicated all uncertain retinal pathology and confirmed all late AMD cases.
• **Patient & disease characteristics**	*Reported as prevalence versus incidence* Mean age (SD): 65.3 (9.3) vs. 63.8 (8.3) % Male: 44.1 vs. 43.3 % Current smoking: 14.2 vs. 12.4 Mean BMI (SD): Not reported Race: Not reported% AMD type early: 4.6 vs. 15.3 % AMD type late: 1.7 vs. 4.1
Interventions	
• **Determinants**	Intake of all flavonoids, total flavonols, total flavanones, total quercetin, and total hesperidin. Dietary data were collected with the use of a 145-item self-administered food-frequency questionnaire (FFQ). The FFQ is modified for the Australian diet and vernacular from an early Willett FFQ . Intakes of flavonoid classes (in milligrams per day) were calculated by multiplying the estimated intake (grams of edible portion per day) from the FFQ, with the flavonoid class content (milligrams of edible portion per day) of each food item on the questionnaire. 2856 patients were included in the prevalence analysis, while 2037 patients were included in the incidence analysis.
Results	
• **Development of AMD**	**15-y incidence of AMD:** *Intake of all flavonoids*

Early AMD: Q1; OR=1.0 (reference)
Q2; OR=1.13 (95% CI 0.75 to 1.71)
Q3; OR=0.94 (95% CI 0.62 to 1.42)
Q4; OR=1.22 (95% CI 0.82 to 1.81)
Late AMD: Q1; OR=1.0 (reference)
Q2; OR=0.72 (95% CI 0.33 to 1.58)
Q3; OR=1.17 (95% CI 0.60 to 2.29)
Q4; OR=1.00 (95% CI 0.50 to 2.00)
Intake of total flavones
Early AMD: Q1; OR=1.0 (reference)
Q2; OR=0.97 (95% CI 0.66 to 1.44)
Q3; OR=0.83 (95% CI 0.56 to 1.23)
Q4; OR=0.75 (95% CI 0.50 to 1.11)
Late AMD: Q1; OR=1.0 (reference)
Q2; OR=2.36 (95% CI 1.13 to 5.01)*
Q3; OR=1.46 (95% CI 0.66 to 3.23)
Q4; OR=1.52 (95% CI 0.66 to 3.49)
Intake of total flavanones
Early AMD: Q1; OR=1.0 (reference)
Q2; OR=0.92 (95% CI 0.62 to 1.38)
Q3; OR=0.97 (95% CI 0.67 to 1.41)
Q4; OR=0.82 (95% CI 0.55 to 1.22)
Late AMD: Q1; OR=1.0 (reference)
Q2; OR=1.15 (95% CI 0.62 to 2.11)
Q3; OR=0.69 (95% CI 0.36 to 1.32)
Q4; OR=0.55 (95% CI 0.27 to 1.09)
Intake of total hesperidin vs. reference group (adjusted OR (95% CI))
Early AMD: Q1; OR=1.0 (reference)
Q2; OR=1.03 (95% CI 0.69 to 1.53)

	Q3; OR=1.11 (95% CI 0.76 to 1.62) Q4; OR=0.85 (95% CI 0.57 to 1.26) **Late AMD:** Q1; OR=1.0 (reference) Q2; OR=1.22 (95% CI 0.65 to 2.27) Q3; OR=0.88 (95% CI 0.46 to 1.68) Q4; OR=0.54 (95% CI 0.26 to 1.13) *Intake of >=1 serving of oranges per day vs. no intake of oranges* **Late AMD**: 0.39 (95% CI 0.18 to 0.85) "No significant associations were observed between the consumption of apples, orange juice, tea, red wine, and beer with the 15-y incidence of AMD (data not shown)." *P<0.05 compared to reference *All ORs are adjusted for age, sex, current smoking, fish consumption, intakes of lutein and zeaxanthin, and CFH and ARMS2 SNPs (rs1061170 and rs10490924).*
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	"We cannot discount the effect of residual confounding from unmeasured or unaccounted factors (e.g., inflammatory markers) on observed associations." "The number of participants who developed incident AMD was small, and this might have reduced the power to detect modest associations with flavonoid intake." The study had a moderate risk of bias for deviations of the intended intervention and a serious risk of bias due to missing data as many participants with missing data were excluded from the study. There is also a serious bias in reporting of results; for the food groups, only statistically significant results were reported.

Q: quartile

Gopinath 2020 - Consumption of eggs and the 15-year incidence of age-related macular degeneration	
Methods	
• **Design**	Prospective cohort study

• **Source of funding and competing interests**	The Blue Mountains Eye Study was funded by the Australian National Health and Medical Research Council (Grant Nos. 974159, 991407, 211069, 262120), and the Westmead Institute for Medical Research. The authors declare no conflicts of interests.
• **Setting**	Population-based cohort study of the most frequent eye diseases as well as other health conditions in a suburban Australian population.
• **Sample size**	2034
• **Study dates**	1992 to 1994
• **Follow-up**	15 years
Patient characteristics	
• **Eligibility criteria**	Residents aged >49 years.
• **Exclusion criteria**	Not reported.
• **AMD definition**	The Wisconsin AMD Grading System was used to determine the presence of early and late AMD from retinal photographs of the macula of both eyes. Early AMD was classified based on the absence of late AMD and presence of either: 1) large (>125-mm diameter) indistinct soft or reticular drusen or 2) both large distinct soft drusen and retinal pigmentary abnormalities (hyperpigmentation or hypopigmentation) in either eye. Late-stage AMD was based on the presence of neovascular AMD or geographic atrophy in either eye. Any AMD was classified as having early or late AMD.
• **Patient & disease characteristics**	*Reported as <1 egg/week and >1 egg/week* Mean age (SD): 64.2 (8.3) vs. 63.5 (8.3) % Male: 38.6 vs. 46.5 % Current smoking: 11.3 vs. 13.2 Mean BMI (SD): not reported Race: not reported Other ocular pathology: not reported
Interventions	
• **Determinants**	Information on dietary intakes were collected using a 145-item self-administered food frequency questionnaire (FFQ). The FFQ is modified for Australian diet from a prior FFQ. Intake of eggs was calculated through summing up consumption in all forms e.g. boiled, poached, fried, scrambled and/or omelette. Egg consumption was defined into the following categories: <1 egg/week (n=845), 2-4 eggs/week (n=728); 5-6 eggs/week (n=390); and >1 egg/day (n=71).
Results	

• **Development of AMD**	Total egg consumption vs. reference (adjusted OR (95% CI)) **15-year incidence of early AMD (n=268)** Age-sex adjusted**:** <1 egg/week; OR=1.0 (reference) 2-4 eggs/week; OR=0.86 (95% CI 0.64 to 1.16) 5-6 eggs/week; OR=0.98 (95% CI 0.68 to 1.40) >1 egg/day; OR=1.32 (95% CI 0.67 to 2.58) Multivariable adjusted****:** <1 egg/week; OR=1.0 (reference) 2-4 eggs/week; OR=0.85 (95% CI 0.61 to 1.18) 5-6 eggs/week; OR=0.94 (95% CI 0.63 to 1.42) >1 egg/day; OR=1.25 (95% CI 0.56 to 2.77) **15-year incidence of late AMD (n=84)** Age-sex adjusted: <1 egg/week; OR=1.0 (reference) 2-4 eggs/week; OR=0.55 (95% CI 0.32 to 0.93)* 5-6 eggs/week; OR=0.61 (95% CI 0.32 to 1.15) >1 egg/day; OR=0.74 (95% CI 0.22 to 2.50) Multivariable adjusted**: <1 egg/week; OR=1.0 (reference) 2-4 eggs/week; OR=0.51 (95% CI 0.28 to 0.92)* 5-6 eggs/week; OR=0.62 (95% CI 0.30 to 1.27) >1 egg/day; OR=0.63 (95% CI 0.14 to 2.78) **15-year incidence of neovascular AMD (n=51)** Age-sex adjusted: <1 egg/week; OR=1.0 (reference) 2-4 eggs/week; OR=0.52 (95% CI 0.26 to 1.03) 5-6 eggs/week; OR=0.70 (95% CI 0.33 to 1.52) >1 egg/day; OR=0.94 (95% CI 0.22 to 4.11) Multivariable adjusted**: <1 egg/week; OR=1.0 (reference) 2-4 eggs/week; OR=0.38 (95% CI 0.17 to 0.86)* 5-6 eggs/week; OR=0.94 (95% CI 0.42 to 2.09)

>1 egg/day; OR=1.21 (95% CI 0.27 to 5.42)

15-year incidence of geographic atrophy (n=28)

Age-sex adjusted: <1 egg/week; OR=1.0 (reference)

2-4 eggs/week; OR=0.67 (95% CI 0.29 to 1.57)

5-6 eggs/week; OR=0.43 (95% CI 0.12 to 1.51)

>1 egg/day; OR=0.61 (95% CI 0.07 to 5.04)

Multivariable adjusted**: <1 egg/week; OR=1.0 (reference)

2-4 eggs/week; OR=0.70 (95% CI 0.29 to 1.70)

5-6 eggs/week; OR=0.23 (95% CI 0.05 to 1.11)

>1 egg/day; Not estimable

AMD onset at 5 or 10 year follow-up (n=55)

Age-sex adjusted: <1 egg/week; OR=1.0 (reference)

2-4 eggs/week; OR=0.43 (95% CI 0.22 to 0.82)*

5-6 eggs/week; OR=0.28 (95% CI 0.11 to 0.73)*

>1 egg/day; OR=0.39 (95% CI 0.05 to 3.12)

Multivariable adjusted**: <1 egg/week; OR=1.0 (reference)

2-4 eggs/week; OR=0.46 (95% CI 0.22 to 0.97)*

5-6 eggs/week; OR=0.35 (95% CI 0.13 to 0.95)*

>1 egg/day; OR=0.37 (95% CI 0.04 to 3.21)

AMD onset at 15 year follow-up (n=29)

Age-sex adjusted: <1 egg/week; OR=1.0 (reference)

2-4 eggs/week; OR=0.86 (95% CI 0.34 to 2.21)

5-6 eggs/week; OR=1.70 (95% CI 0.65 to 4.42)

>1 egg/day; OR=1.91 (95% CI 0.39 to 9.42)

Multivariable adjusted**: <1 egg/week; OR=1.0 (reference)

2-4 eggs/week; OR=0.60 (95% CI 0.20 to 1.80)

	5-6 eggs/week; OR=1.25 (95% CI 0.40 to 3.93) >1 egg/day; OR=0.92 (95% CI 0.10 to 8.21) **P<0.05* ***Adjusted for age, sex, current smoking, white cell count, fish consumption, dietary intakes of lutein and zeaxanthin, and CFH and ARMS2 SNPS (rs1061170 and rs10490924).*
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	”Moderate egg consumption could be marker or proxy of other lifestyle patterns that are associated with optimal macula health. While we adjusted for several confounders including dietary factors in our analysis, residual or unmeasured confounders might have been overlooked.” ”A causal association of baseline egg consumption with incident late AMD cannot be confirmed because of the observational nature of BMES.” The study had a moderate risk of bias due to deviations from the intended intervention and a serious risk of bias due to missing data as many participants with missing data were excluded from the study.

Jones 2020 - Exploring Factors Underlying Ethnic Difference in Age-related Macular Degeneration Prevalence	
Methods	
• **Design**	Analyses of data collected in two population-based studies.
• **Source of funding and competing interests**	Source of funding: National Health & Medical Research Council, Australia: Project grant [ID 590204]. The sponsor or funding organization had no role in the design or conduct of the research. Competing interests: None of the authors has any conflicts of interest to disclose, nor any financial disclosure to make.
• **Setting**	Population-based studies from Australia and Singapore.
• **Sample size**	2862 participants in the European sample (Blue Mountains Eye Study, BMES). 1900 participants in the Asian sample (Singapore Multi-Ethnic Cohort Study, MEC).
• **Study dates**	BMES: data collected from 1992 to 1994 and from 1999 to 2000. MEC: data collected between 2004 to 2007 and between 2007 to 2010.
• **Follow-up**	Not reported.

Patient characteristics	
• **Eligibility criteria**	BMES: permanent residents aged 49+ of two postcode areas of the Blue Mountains region, west of Sydney. MEC: random sample of Singapore citizens or long-term residents of age 21 to 75 years with disproportionate sampling stratified by ethnicity to increase the numbers for ethnic minorities, i.e. Malays and Indians.
• **Exclusion criteria**	Participants aged <50 years; participants who had total daily energy intake of ≤500 kcal or ≥7000 kcal; participants who fell outside the gender specific total energy intake cut-offs (mean ± 3 standard deviations).
• **AMD definition**	"Retinal photographic grading followed the Wisconsin Age-related Maculopathy Grading System in BMES or a modified Wisconsin grading protocol used in the Multi-Ethnic Study of Atherosclerosis3 in MEC. Classification of early and late AMD lesions was identical to the Wisconsin grading protocol in both samples. The same 5-step AMD severity scale developed in the Three Continent AMD Consortium was used to code AMD status in both samples. We defined no AMD (level 10), early AMD (levels 20–40) or late AMD (level 50) and combined early and late AMD as "any AMD".
• **Patient & disease characteristics**	Mean age (SD): 63.5 (9.3) % Male: 46% % Smoking: 10% Mean BMI (SD): not reported. Race: European ancestry 2862/4762 (60%) (BMES); Asian ancestry 1900/4762 (40%) (MEC) Other ocular pathology: not reported.
Interventions	
• **Determinants**	Western diet (red and processed meat, potatoes, fats, fast food, sugarbased items and alcohol); Asian diet (eggs, fish, poultry, breads and cereals), and vegetarian diet (fruits, vegetables, dairy products and nuts). Dietary information was obtained using a validated 145-item food frequency questionnaire (FFQ) (BMES; n=2862) or using a validated 169-item FFQ (MEC; n=1900). Authors computed Alternative Healthy Eating Index (AHEI) scores after slightly modifying the food items included: excluding trans-fat intake (not available in both samples), sodium consumption (available in BMES only) and preserved and canned fruit (containing sugar).
Results	
• **Development of AMD**	*Western diet vs. Asian diet vs. Vegetarian diet* "After adjusting for ethnicity, age, sex and smoking, none of these Factor scores was significantly associated with prevalence of any AMD" *Healthy eating (Alternative Healthy Eating Index [AHEI])* "In a multivariable-adjusted logistic regression model, only ethnicity, age, sex and smoking were significantly associated with any AMD, and AHEI scores and calories intake were not"

	N.B. At the time of data extraction, the online supplementary files with additional details regarding the results were not available.
• **Adverse events**	Not assessed.
Limitations and other comments	
• **Limitations**	Online supplementary files with additional information were not available. Dietary pattern could have changed over time, for which no measurements or adjustments were done. In addition, there was a moderate risk of bias due to missing data. No indications of risk of bias regarding the remaining ROBINS-I-domains. Overall risk of bias was judged to be moderate.

Lin 2017 - Association between Dietary Xanthophyll (Lutein and Zeaxanthin) Intake and Early Age-Related Macular Degeneration: The Atherosclerosis Risk in Communities Study	
Methods	
• **Design**	Population-based prospective cohort study
• **Source of funding and competing interests**	This research is supported by the NIH National Institute on Aging grant number R01 AG041776, NIH National Heart, Lung, and Blood Institute grant number R01 HL103706, and the NIH Office of Dietary Supplements grant number R01 HL103706-S1 and an unrestricted grant from Research to Prevent Blindness. The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research. Kristin Meyers' affiliation was with the University of Wisconsin during her efforts on this manuscript. As of February 2015, she has been an employee of Eli Lilly and Company and her efforts on this manuscript have been limited to critical review. Other co-authors had no conflicts of interest to disclose.
• **Setting**	Population-based study in four geographic regions in the United States.
• **Sample size**	10,295
• **Study dates**	1987 to 1989
• **Follow-up**	6 years

Patient characteristics	
• **Eligibility criteria**	Participants aged 45 to 64.
• **Exclusion criteria**	Participants who were neither Caucasian nor African American (n = 34); had missing or ungradable fundus photographs (n = 1250); declined to provide consent for research unrelated to cardiovascular disease outcomes (n = 796); had advanced AMD (n = 14); or had missing data on visit 1 xanthophyll intake (n = 224), pack-years of smoking (n = 155), HDL (n = 118) or HDL2 data (n = 1). Participants with implausible caloric intake (women: <500 or >3600 kcal; men: <600 or >4200 kcal) or with >10 missing values on the visit 1 FFQ.
• **AMD definition**	Prevalent AMD status was ascertained via fundus photographs taken at visit 3 (1993–1995), using a non-mydriatic automatically focusing camera and without pharmacologic dilation. Patients were asked to sit in a darkened room for 5 minutes, after which the camera was centered on the region between the optic disc and the fovea of a randomly chosen eye. Non stereoscopic 45-degree color film retinal images thus obtained were then evaluated by a masked grader at the University of Wisconsin Fundus Photograph Reading Center. Given the low prevalence of advanced AMD (presence of geographic atrophy or choroidal neovascularization, n = 14), the primary endpoint variable used in the present analyses was prevalent early AMD (presence of soft drusen with diameter ≥63 µm or retinal pigment epithelium depigmentation, in the absence of advanced AMD). The primary endpoint variable used in the present analyses was prevalent early AMD (presence of soft drusen with diameter ≥63 µm or retinal pigment epithelium depigmentation, in the absence of advanced AMD).
• **Patient & disease characteristics**	*Reported as total vs. quintiles of energy-adjusted xanthophyll intake* Mean age (SD): 53.9 (0.1) vs. 53.5 (0.1) vs. 53.7 (0.1) vs. 53.8 (0.1) vs. 53.9 (0.1) vs. 54.4 (0.1) % Male: 45 vs. 57 vs. 49 vs. 45 vs. 38 vs. 38 % Former smoking: 33 vs. 36 vs. 34 vs. 35 vs. 32 vs. 30 % Current smoking: 23 vs. 25 vs. 24 vs. 22 vs. 21 vs. 22 % BMI Not overweight or obese: 34 vs. 33 vs. 36 vs. 35 vs. 34 vs. 30 % BMI Overweight: 40 vs. 42 vs. 41 vs. 39 vs. 39 vs. 40 % BMI Obese: 26 vs. 25 vs. 23 vs. 26 vs. 27 vs. 30 % African-American: 20 vs. 4 vs. 10 vs. 18 vs. 29 vs. 39 % Caucasian: 80 vs. 96 vs. 90 vs. 82 vs. 71 vs. 61 Other ocular pathology: not reported
Interventions	
• **Determinants**	Energy-adjusted xanthophyll intake measured with a 66-item food frequency questionnaire (FFQ). This instrument was modified from a version developed by Willet and colleagues, and its validity and reliability has been previously

	demonstrated. Dietary xanthophyll intake was adjusted for estimated daily caloric intake using the multivariate nutrient density model. The 2nd to 5th quintiles determine the various groups of energy-adjusted xanthophyll and they were compared to the first quintile (n=2059 for each quintile).
Results	
• **Development of AMD**	**Development of early AMD:** Q1; n=102/2059; OR=1.00 (ref) Q2; n=110/2059; OR=1.07 (95% CI 0.81 to 1.42) Q3; n=109/2059; OR=1.07 (95% CI 0.80 to 1.42) Q4; n=109/2059; OR=1.09 (95% CI 0.81 to 1.46) Q5; n=105/2059; OR=1.02 (95% CI 0.76 to 1.38) *Analyses adjusted for age, sex, race, pack-years of smoking, field center, and visit 1 daily caloric intake*
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	"The availability of prevalent rather than incident cases of early AMD as an outcome precludes inference of causality." There was a moderate risk of bias due to deviations from the intended intervention and a moderate risk of bias due to exclusion of participants with missing data.

Q: quintile

Merle 2019 - Mediterranean Diet and Incidence of Advanced Age-Related Macular Degeneration	
Methods	
• **Design**	Prospective cohort study
• **Source of funding and competing interests**	Funding: European Union's Horizon 2020 Research and Innovation Programme; Erasmus Medical Center and Erasmus University, Rotterdam, The Netherlands; the Organization for the Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly (RIDE); the Ministry of Education, Culture and Science; the Ministry for Health, Welfare and Sports; the European Commission (DG XII); the Municipality of Rotterdam, Rotterdam, The Netherlands; Oogfonds; Bartiméus Sonneheerdt Vereniging; Landelijke Stichting voor Blinden en Slechtzienden; Algemene Nederlandse Vereniging Ter Voorkoming Van Blindheid; Novartis Foundation; MaculaFonds. Laboratoires Théa; Fondation Voir et Entendre; Retina France Agence Nationale de la Recherche (ANR 2010-PRSP-011 VISA); Caisse Nationale pour la Solidarité et l'Autonomie. Laboratoires Théa participated in the

	design of the Antioxydants, Lipides Essentiels, Nutrition et Maladies Oculaires Study, but none of the sponsors participated in the collection, management, statistical analysis, or interpretation of the data, or in the preparation, review, or approval of the present manuscript. All other funding organizations had no role in the design or conduct of this research and provided unrestricted grants. Competing interests: Competing financial interest of members of the EYE-RISK consortium not otherwise disclosed: Verena Arndt, Sebastian Bühren, Tanja Endermann, and Markus Zumbansen are employees of AYOXXA.
• **Setting**	Population-based prospective cohorts in the Netherlands (Rotterdam Study (RS)-I) and France (Alienor).
• **Sample size**	4996
• **Study dates**	1990 to 2011 for RS-1 and 2006 to 2012 for Alienor.
• **Follow-up**	Mean follow-up time was 9.9 years (range, 0.6 to 21.7 years) in the RS-I and 4.1 years (range, 2.5 to 5.0 years) in the Alienor Study.
Patient characteristics	
• **Eligibility criteria**	Rotterdam Study I: persons 55 years of age or older. The Antioxydants, Lipides Essentiels, Nutrition et Maladies Oculaires Study (Alienor): participants 73 years of age or older. In this substudy, participants free of advanced AMD at baseline with complete and reliable dietary data and follow-up information were included.
• **Exclusion criteria**	Not reported
• **AMD definition**	Retinal photographs of both eyes were graded by trained graders of each study and were interpreted according to a modification of the Wisconsin Age-Related System for RS-I and according to the International Classification for the Alienor Study. All advanced AMD cases were adjudicated and confirmed by retina specialists of the corresponding study. Phenotype harmonization was performed within the EYE-RISK Consortium. Advanced AMD was defined by the presence of neovascular or atrophic AMD. Neovascular AMD included serous or hemorrhagic detachment of the retinal pigment epithelium or sensory retina, subretinal, or suberetinal pigment epithelium hemorrhages, and fibrous scar tissue. Geographic atrophy was defined as a discrete area of retinal depigmentation 175 mm in diameter or larger characterized by a sharp border and the presence of visible choroidal vessels. Early AMD (in the absence of advanced AMD) was defined by the presence of (1) soft indistinct (>=125 mm, decreasing density from the center outward and fuzzy edges) or reticular drusen only or soft distinct drusen (>=63 mm, with uniform density and sharp edges) and pigmentary abnormalities, or by (2) soft indistinct large drusen (>=125 mm, decreasing density from the center outward and fuzzy edges) or reticular drusen and pigmentary abnormalities (corresponding to grades 2 and 3 of the Rotterdam Classification). No AMD was defined by the absence of early AMD and advanced

	AMD.
• **Patient & disease characteristics**	*Rotterdam Study I vs. Alienor Study* Mean age (SD): 66.9 (7.3) vs. 79.2 (4.2) % Male: 40.8 vs. 38.0 % Never Smoking: 36.3 vs. 65.1 % <20 pack-years: 28.4 vs. 17.4 % >20 pack-years: 35.3 vs. 17.5 Mean BMI (SD): 26.3 (3.6) vs. 26.0 (4.0) Race: not reported Other ocular pathology: not reported
Interventions	
• **Determinants**	Adherence to the Mediterranean diet (MeDi) was assessed using the MeDi score developed by Trichopoulou et al. This score included 9 components - vegetables, fruits, legumes, cereals, fish, meat, dairy products, alcohol, and the MUFAs-to-SFAs ratio. The total MeDi score was computed by adding the scores (0 or 1 point) for each component for each participant. Scores ranged from 0 (nonadherence) to 9 (perfect adherence). Participants were classified according to 3 categories of the MeDi score: low (0-3), medium (4-5), or high (6-9).
Results	
• **Development of AMD**	*Reported as high Mediterranean Diet score vs. low Mediterranean Diet score* **Advanced AMD**: HR=0.53 (95% CI 0.33 to 0.84)* **Advanced AMD:** HR= 0.59 (95% CI 0.37 to 0.95)** **Neovascular AMD:** HR= 0.88 (95% CI 0.49 to 1.57)** **Atrophic AMD**: HR=0.42 (95% CI 0.20 to 0.90)** **Unadjusted* ***Adjusted for gender, total energy intake, age-related macular degeneration grade at baseline, education, body mass index, smoking, supplement use of multivitamins or minerals, and presence of diabetes and hypercholesterolemia.*
• **Adverse events**	Not assessed.
Limitations and other comments	

• **Limitations**	The study has a moderate risk of bias for selection of participants into the study, a moderate risk of bias due to deviations from the intended interventions and a moderate risk of bias due to exclusion of individuals with missing data. For all other domains, the risk of bias was low.

Wu 2017 - Dietary intake of α-linolenic acid and risk of age-related macular degeneration	
Methods	
• **Design**	Prospective study of two cohorts (Nurses' Health Study [NHS] and Health Professionals Follow-up Study [HPFS])
• **Source of funding and competing interests**	Source of funding: grants EY017362, EY013834, EY000365, EY009611, EY021900, UM1 CA186107, UM1 CA167552, and R01 CA49449 from NIH. Competing interests: none of the authors reported a conflict of interest related to the study.
• **Setting**	Population of health professionals, United States
• **Sample size**	114850
• **Study dates**	NHS: from 1984 to 2012; HPFS: 1986 to 2010
• **Follow-up**	24 (HPFS) to 28y (NHS) years
Patient characteristics	
• **Eligibility criteria**	NHS: female registered nurses aged between 30 and 55 y at baseline. HPFS: male health professionals aged between 40 and 75 y at baseline. For this study the study population was restricted to those who were ≥50 y old at baseline and then participants were added to the analysis once they reached age 50 y.
• **Exclusion criteria**	Participants who did not return the initial FFQ; who left >70 food items blank in the FFQ; who reported implausible dietary intake (<600 or >3500 kcal/d for the NHS and <800 or >4200 kcal/d for the HPFS); who had prevalent AMD, cancer (except non-melanoma skin cancer), diabetes, and cardiovascular disease; who never reported an eye exam over the entire follow-up period and skipped the person-time during any 2-y questionnaire interval in which they did not report an eye exam. In addition, cases with only small hard drusen (drusen size <63-µm diameter circle) were excluded.
• **AMD definition**	"We defined intermediate AMD as having ≥1 of the following signs in ≥1 eye: intermediate drusen (≥63 and <125 µm), pigment abnormalities, large drusen (≥125 µm), or any noncentral geographic atrophy (GA). We defined neovascular AMD as having any of the following signs in ≥1 eye: retinal pigment epithelium detachment, subretinal neovascular membrane, disciform scar, or history of treatment with laser, photodynamic, or anti–vascular endothelial growth

	factor therapy for AMD. Central GA was defined as having a central GA lesion involving the center of the macula in ≥1 eye. Advanced AMD included both neovascular AMD and central GA. Additionally, all case definitions, except those recent neovascular AMD cases that had anti–vascular endothelial growth factor therapy, included a visual acuity of 20/30 or worse primarily due to AMD."
• **Patient & disease characteristics**	Mean age (SD) in years, per quintile of α-linolenic acid intake: • NHS: Q1 64 (7); Q2 63 (7); Q3 63 (7); Q4 64 (7); Q5 64 (7) • HPFS: Q1 64 (9); Q2 64 (9); Q3 64 (9); Q4 64 (9); Q5 64 (9) % Male: 32 % Smoking: Current, per quintile of α-linolenic acid intake: • NHS: Q1 10; Q2 9; Q3 10; Q4 10; Q5 12 • HPFS: Q1 5; Q2 5; Q3 4; Q4 5; Q5 6 Mean BMI (SD), kg/m^2, per quintile of α-linolenic acid intake: • NHS: Q1 26.1 (5.0); Q2 26.6 (5.1); Q3 26.8 (5.2); Q4 27.0 (5.4); Q5 27.1 (5.5) • HPFS: Q1 25.5 (3.2); Q2 26.0 (3.5); Q3 26.3 (3.6); Q4 26.4 (3.7); Q5 26.4 (3.7) Race: % Caucasian, per quintile of α-linolenic acid intake: • NHS: Q1 96; Q2 98; Q3 98; Q4 98; Q5 96 • HPFS: Q1 94; Q2 95; Q3 96; Q4 96; Q5 95 Other ocular pathology: not reported.
Interventions	
• **Determinants**	a-linolenic acid (ALA), a plant-derived omega-3 fatty acid. Participants were asked every 4 year to report how often, on average over the past year, they had consumed each food item (9 possible responses ranging from "≤1 time/mo" to "≥6 times/d"). The major sources of ALA intake among 131 FFQ items include mayonnaise or other creamy salad dressing; oil and vinegar dressing; beef, pork, or lamb as a main dish; margarine; american or cheddar cheese; walnut consumption; low-fat mayonnaise consumption; and flax seed oil and flax seed. We adjusted all the nutrient intakes for total energy using the residual method to reflect the composition of the diet.
Results	
• **Development of AMD**	*(Combined cohorts)* **Intermediate AMD** *Per quintile of α-linolenic acid intake, n/N; HR Model 1; HR Model 2; HR Model 3* Q1: 285/423453; Reference category in all models

Q2: 313/424964; HR= 1.15 (95% CI 0.97 to 1.34); HR= 1.16 (95% CI 0.99 to 1.37); HR=1.17 (95% CI 0.99 to 1.38)

Q3: 270/425081; HR= 0.99 (95% CI 0.84 to 1.17); HR= 1.01 (95% CI 0.85 to 1.21); HR= 1.02 (95% CI 0.85 to 1.22)

Q4: 348/425321; HR= 1.26 (95% CI 1.07 to 1.47); HR= 1.28 (95% CI 1.07 to 1.52); HR= 1.28 (95% CI 1.07 to 1.54)

Q5: 373/425171; HR= 1.31 (95% CI 1.12 to 1.53); HR= 1.27 (95% CI 1.05 to 1.54); HR= 1.28 (95% CI 1.05 to 1.56)

Additional analysis according to quintiles of cumulative average intake of α-linolenic acid before and after 2002 (Model 2)

- Up to 2002: Q1: Reference; Q2: HR=1.13 (95%CI 0.91 to 1.41); Q3: HR=0.96 (95%CI 0.76 to 1.22); Q4: HR=1.30 (95%CI 1.03 to 1.64); Q5: HR=1.36 (95% CI 1.06 to 1.75)
- After 2002: Q1: Reference; Q2: HR=0.96 (95%CI 0.75 to 1.23); Q3: HR=1.12 (95%CI 0.87 to 1.43); Q4: HR=0.95 (95%CI 0.73 to 1.24); Q5: HR=0.85 (95% CI 0.64 to 1.13)

Advanced AMD

Per quintile of α-linolenic acid intake, n/N; HR Model 1; HR Model 2; HR Model 3

Q1: 255/423448; Reference category in all models

Q2: 269/425008; HR= 1.09 (95% CI 0.92 to 1.29); HR= 1.07 (95% CI 0.90 to 1.28); HR= 1.06 (95% CI 0.89 to 1.27)

Q3: 279/425066; HR= 1.12 (95% CI 0.94 to 1.32); HR= 1.09 (95% CI 0.91 to 1.31); HR= 1.08 (95% CI 0.89 to 1.30)

Q4: 261/425395; HR= 1.02 (95% CI 0.86 to 1.22); HR= 0.98 (95% CI 0.81 to 1.19); HR= 0.97 (95% CI 0.80 to 1.18)

Q5: 292/425260; HR= 1.11 (95% CI 0.94 to 1.32); HR= 1.06 (95% CI 0.86 to 1.30); HR= 1.05 (95% CI 0.85 to 1.30)

Additional analysis according to quintiles of cumulative average intake of α-linolenic acid before and after 2002 (Model 2)

- Up to 2002: Q1: Reference; Q2: HR=1.11 (95%CI 0.85 to 1.46); Q3: HR=1.28 (95%CI 0.97 to 1.68); Q4: HR=1.05 (95%CI 0.78 to 1.41); Q5: HR=1.09 (95% CI 0.79 to 1.49)
- After 2002: Q1: Reference; Q2: HR=0.76 (95%CI 0.59 to 0.96); Q3: HR=0.98 (95%CI 0.78 to 1.24); Q4: HR=1.01 (95%CI 0.79 to 1.29); Q5: HR=0.84 (95% CI 0.65 to 1.10)

Model 1 included age (continuous), race (Caucasian or not), BMI (in kg/m2: <18.5, 18.5–23, 23–25, 25–30, 30–35, or >35), pack-years of smoking (never, 1–9, 10–24, 25–44, 45–64, or ≥65 y), physical activity (<3, 3–8.9, 9–17.9, 18–26.9, or ≥27 h of metabolic equivalent tasks/wk), current aspirin use (≥1 tablet/wk or none), history of hypertension and hypercholesterolemia, DHA (quintiles), and total energy intake (quintiles). In the NHS, models were additionally

	adjusted for postmenopausal status and menopausal hormone use (never, current, and past). *Model 2 = multivariate model 1 + linoleic acid (quintiles).* *Model 3 = multivariate model 1 + linoleic acid + monounsaturated fat + saturated fat + trans-fat (all in quintiles). P-trend was calculated by modeling the median value of each category as a continuous variable.*
• **Adverse events**	Not assessed.
Limitations and other comments	
• **Limitations**	There is a serious risk of bias due to the risk of outcome misclassification as the diagnosis of intermediate AMD as initial detection was done by the participant's eye physician in a clinical examination, and, in addition, due to missing data.

AMD: age-related macular degeneration; HPFS: Health Professionals Follow-up Study; NHS: Nurses' Health Study; Ref: reference; Q: quintile

Evidencetabellen van geïncludeerde primaire onderzoeken betreffende voeding voor de behandeling van LMD

Joachim 2018 - Joint Contribution of Genetic Susceptibility and Modifiable Factors to the Progression of Age-Related Macular Degeneration over 10 Years	
• **Methods**	
• **Design**	Individual and pooled data analyses of 2 population-based cohorts
• **Source of funding and competing interests**	Source of funding: National Health and Medical Research Council, Canberra, Australia; National Health and Medical Research Council, Canberra, Australia; Wellcome Trust, London, United Kingdom, as part of Wellcome Trust Case Control Consortium 2; National Institutes of Health, Bethesda, Maryland; Research to Prevent Blindness, Inc, New York, New York; Erasmus Medical Center and Erasmus University, Rotterdam, The Netherlands, Organization for the Health Research and Development; the Research Institute for Diseases in the Elderly; the Ministry of Education, Culture and Science; the Ministry for Health, Welfare and Sports; the European Commission (DG XII); the Municipality of Rotterdam, The Netherlands; Topcon Europe; MaculaFonds; Stichting Oogfonds; Landelijke Stichting voor Blinden en Slechtzienden; Stichting Winckel Sweep; Algemene Nederlandse Vereniging ter Voorkoming van Blindheid, Blindenpenning; Novartis; the National Health and Medical Research Council; the National Institutes of Health; Funders had no role in the design or conduct of this research. Competing interest: Authors are funded by Nestle, Metagenics, Bayer, Novartis, and Allergan.

• **Setting**	Population-based cohorts from the Netherlands and Australia.
• **Sample size**	835
• **Study dates**	Blue Mountains Eye Study: baseline: 1992 – 1994, year of follow-up: not reported. Rotterdam Study: baseline: 1990-1993, year of final follow-up: 2002 - 2004
• **Follow-up**	Blue Mountains Eye Study: 15 years Rotterdam Study: 10 years
• **Patient characteristics**	
• **Eligibility criteria**	Blue Mountains Eye Study: participants with early AMD lesions in either eye at baseline, 49 years of age or older. Rotterdam Study: participants with early AMD lesions in either eye at baseline, 55 years of age or older who underwent ophthalmic examinations and retinal photography.
• **Exclusion criteria**	Not reported.
• **AMD definition**	A 5-step severity scale that was developed after phenotype harmonization of AMD in the 3CC18 was used to define AMD severity. The scale defines AMD by levels 10, 20, 30, 40, and 50, corresponding to no AMD, mild early AMD, moderate early AMD, severe early AMD, and late AMD. Early AMD was defined as levels 20 to 40 and late AMD was defined as level 50. Progression of AMD was defined as an increment in the steps along the severity scale from level 20 to 50 in eyes that had level 20 or higher AMD at baseline. The increment from level 10 to 20 (from no AMD to mild early AMD) was not included in this report because it was considered to be the initial development of AMD. Progression was categorized as either any progression (1-step increment) versus no progression or 2-step progression (2-step increment in the 3CC AMD severity scale) versus 1-step increment or less over a period of 10 years.
• **Patient & disease characteristics**	*Reported as no progression vs. ≥ 1-step progression* Mean age (SD): 67.3 (7.8) vs. 70.3 (7.4) % Male: 44.7 vs. 40.8 % Never Smoking: 41.3 vs. 38.9 % Past Smoking: 39.7 vs. 42.3 % Current Smoking: 19.0 vs. 18.8 Mean BMI (SD): not reported Race: not reported. Other ocular pathology: not reported.

	AMD stage: not reported Visual acuity at baseline: not reported.
• **Interventions**	
• **Determinants**	Fish consumption and lutein-zeaxanthin intake. Dietary information was obtained from a validated 145-item semiquantitative food frequency questionnaire in the BMES. The electronic Australian Tables of Food Composition and the United States Department of Agriculture carotenoid food composition database were used to calculate the intake of most nutrients, including luteinezeaxanthin intake, in micrograms. Data on fish consumption were obtained from the food frequency questionnaire and defined as less than 1 serving per week, termed infrequent fish consumption, compared with 1 serving per week or more. In the Rotterdam Study, dietary data were collected by a trained dietician at the research center using a 170-item validated semiquantitative food frequency questionnaire. A computerized Dutch Food Composition Table was used to convert the dietary data into total energy and nutrient intakes per day. Low intake of lutein-zeaxanthin was defined as intake of less than the median and high intake was defined as intake of more than the median.
• **Results**	
• **Progression of AMD**	*Fish consumption. ≥1 servings/week vs. <1 servings/week* **≥1 step progression**: 170/440 vs. 166/395; RR=0.92 (95% CI 0.78 to 1.08) **≥2 step progression**: 83/440 vs. 64/395; RR=1.16 (95% CI 0.87 to 1.57) **≥1 step progression**: 31/411 vs. 40/368; RR=0.69 (95% CI 0.44 to 1.09)* **≥2 step progression**: 16/411 vs. 16/368; RR=0.90 (95% CI 0.45 to 1.76)* **≥1 step progression**: event rate not reported; RR=1.21 (95% CI 0.88 to 1.67)** **≥2 step progression**: event rate not reported; RR=0.94 (95% CI 0.61 to 1.44)** *Lutein-zeaxanthin intake* ≥1 *median vs. <median* **≥1 step progression**: 176/418 vs. 160/417; RR=1.10 (95% CI 0.93 to 1.30) **≥2 step progression**: 79/325 vs. 156/409; RR=0.64 (95% CI 0.51 to 0.80) **≥1 step progression**: 38/362 vs. 37/361; RR=1.02 (95% CI 0.67 to 1.57) **≥2 step progression**: 17/362 vs. 16/361; RR=1.06 (95% CI 0.54 to 2.06) **≥1 step progression**: event rate not reported; RR=0.93 (95% CI 0.68 to 1.28) **≥2 step progression**: event rate not reported; RR=0.88 (95% CI 0.58 to 1.35)

	** Model accounted for competing risks* *** adjusted for age, gender, smoking status, and baseline AMD severity*
• **Visual acuity**	Not reported.
• **Adverse events**	Not assessed.
• **Limitations and other comments**	
• **Limitations**	The study was at moderate risk of bias due to confounding and at moderate risk of bias due to selection of participants. There was unclear risk of bias due to missing data. For all other domains, risk of bias was low.

Keenan 2020 - Adherence to the Mediterranean Diet and Progression to Late Age-Related Macular Degeneration in the Age-Related Eye Disease Studies 1 and 2	
• **Methods**	
• **Design**	Retrospective analysis of two multi-center, phase III, four-arm, double-masked randomized trials (AREDS and AREDS2).
• **Source of funding and competing interests**	Source of funding: supported by intramural program funds and contracts (AREDS (Contract NOI-EY-0-2127) and AREDS2 (Contract HHS-N-260-2005-00007-C; ADB Contract N01-EY-5-0007) from the National Eye Institute/National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland. Funds were contributed to these contracts by the following National Institutes of Health institutes: Office of Dietary Supplements; National Center for Complementary and Alternative Medicine; National Institute on Aging; National Heart, Lung, and Blood Institute; National Institute of Neurological Disorders and Stroke. Competing interests: author(s) have no proprietary or commercial interest in any materials discussed in the article.
• **Setting**	AREDS - Eleven retinal specialty clinics in US. / AREDS2 - Eighty-two retinal specialty clinics in US.
• **Sample size**	7756 participants (AREDS n=4255; AREDS2 n=3611; n=110 who were in both cohorts were counted only once), 13204 eyes.
• **Study dates**	AREDS: 1992 to 1998 / AREDS2: 2006 to 2008
• **Follow-up**	Median of 10.2 years
• **Patient characteristics**	
• **Eligibility criteria**	• AREDS: men and women aged 55 to 80 years, free of any illness or condition that would make long-term follow-

	up or compliance with study medications unlikely or difficult. • AREDS2: men and women aged 50 to 85 years with bilateral intermediate AMD or advanced AMD in 1 eye. • For the analyses, eyes without late AMD at baseline in white participants with at least 2 study visits were eligible.
• **Exclusion criteria**	Participants who had missing data for the outcomes or for any covariate, or if the food frequency questionnaire (FFQ) was absent.
• **AMD definition**	"In AREDS and the initial five-year AREDS2, progression to late AMD was defined by fundus photograph grades, as described previously. However, in AREDS2, for eyes with no late AMD at the five-year study close-out, progression to late AMD in the 10-year follow-on study was defined by a positive event of late AMD from at least one of the following: (i) Fundus Photographic Reading Center (University of Wisconsin) grading of fundus photographs, as described previously, (ii) clinician (AREDS2 investigator) grading from dilated fundus examination, spectral domain optical coherence tomography, color fundus photographs, and treatment history, (iii) structured telephone interview ascertainment of history of anti-VEGF injections specifically for late AMD, and (iv) verified report of late AMD from ophthalmology medical records. Since not all four sources captured data separately for GA and neovascular AMD, late AMD subtype analysis was not performed for progression events that occurred between the AREDS2 close-out and the 10-year follow-on study."
• **Patient & disease characteristics**	*Combined cohorts / AREDS / AREDS2* Mean age (SD) in years: 71 (6.6) / 69 (5.1) / 73 (7.7) % Male: 43 / 44 / 43 % Smoking: • Never: 44 / 45 / 43 • Former: 49 / 48 / 51 • Current: 7 / 7 / 6 % with BMI in kg / m^2: • ≤ 25: not reported / 33 / not reported • >25 - ≤30: not reported / 42 / not reported • >30: not reported / 25 / not reported. Race: not reported. Other ocular pathology: not reported. AMD stage: AMD severity stage 3-4 (AREDS) or ≥7 in worse eye (AREDS2): not reported / 53 / 77 Visual acuity at baseline: not reported.
• **Interventions**	
• **Determinants**	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, expressed in the Alternative Mediterranean Diet Index [aMedi] score. Participants in the two cohorts received the following supplements: AREDS : antioxidants (n=945), zinc (n=904), or combination (n=888) vs. placebo (n=903) AREDS2: lutein/zeaxanthin (n=1044), docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA) (n=1069), or the combination (n=1079) vs. AREDS supplements (n=1012)
• **Results**	
• **Progression of AMD**	*Mediterranean diet (Combined cohorts) (per tertile of the modified aMedi score)* **Progression to late AMD:** T1: 1554/4206; Reference; T2: 1399/4262; HR=0.87 (95%CI 0.80 to 0.94) T3: 1534/4736; HR=0.78 (95%CI 0.71 to 0.85) **Progression to geographic atrophy:** T1: 804/4206; Reference T2: 675/4262; HR=0.80 (95%CI 0.71 to 0.90) T3: 715/4736; HR=0.71 (95%CI 0.63 to 0.80) **Progression to neovascular AMD:** T1: 698/4206; Reference T2: 636/4262; HR=0.90 (95%CI 0.90 to 1.01) T3: 684/4736; HR=0.84 (95%CI 0.75 to 0.95) "Similar analyses that included adjustment for treatment assignment did not demonstrate different results in AREDS or AREDS2.[…] In addition, analyses that included the interaction term between aMedi and treatment assignment showed no significant interactions for any outcome in AREDS or AREDS2, even at the nominal level." *Fish Intake, Q4 vs. Q1– (AREDS/ AREDS2)* **Progression to late AMD:** HR=0.69 (95%CI 0.58 to 0.82) / HR=0.92 (95%CI 0.78 to 1.07) **Progression to geographic atrophy:** HR=0.69 (95%CI 0.57 to 0.85) / HR=0.77 (95%CI 0.61 to 0.98) **Progression to neovascular AMD:** HR=0.71 (95%CI 0.57 to 0.88) / HR=1.00 (95%CI 0.80 to 1.25)

Whole fruit intake, Q4 vs. Q1 (AREDS/ AREDS2)
Progression to late AMD: HR=0.94 (95%CI 0.79 to 1.12) / HR=0.94 (95%CI 0.82 to 1.07)
Progression to geographic atrophy: HR=0.98 (95%CI 0.80 to 1.19) / HR=0.79 (95%CI 0.64 to 0.98)
Progression to neovascular AMD: HR=0.97 (95%CI 0.78 to 1.21) / HR=1.05 (95%CI 0.86 to 1.28)

Vegetable intake, Q4 vs. Q1 (AREDS/ AREDS2)
Progression to late AMD: HR=0.77 (95%CI 0.65 to 0.93) / HR=0.90 (95%CI 0.78 to 1.04)
Progression to geographic atrophy: HR=0.82 (95%CI 0.66 to 1.02) / HR=0.93 (95%CI 0.74 to 1.17)
Progression to neovascular AMD: HR=0.86 (95%CI 0.69 to 1.08) / HR=0.96 (95%CI 0.78 to 1.19)

Whole grain intake, Q4 vs. Q1 (AREDS/ AREDS2)
Progression to late AMD: HR=0.86 (95%CI 0.73 to 1.01) / HR=0.99 (95%CI 0.87 to 1.12)
Progression to geographic atrophy: HR=0.78 (95%CI 0.64 to 0.95) / HR=0.96 (95%CI 0.79 to 1.18)
Progression to neovascular AMD: HR=0.98 (95%CI 0.79 to 1.21) / HR=0.97 (95%CI 0.81 to 1.17)

Nut intake, Q4 vs. Q1 (AREDS/ AREDS2)
Progression to late AMD: HR=0.89 (95%CI 0.76 to 1.04) / HR=1.07 (95%CI 0.94 to 1.22)
Progression to geographic atrophy: HR=0.87 (95%CI 0.73 to 1.05) / HR=1.17 (95%CI 0.95 to 1.44)
Progression to neovascular AMD: HR=0.86 (95%CI 0.70 to 1.05) / HR=0.99 (95%CI 0.81 to 1.19)

Legume intake, Q4 vs. Q1 (AREDS/ AREDS2)
Progression to late AMD: HR=0.99 (95%CI 0.84 to 1.18) / HR=0.98 (95%CI 0.85 to 1.14)
Progression to geographic atrophy: HR=0.95 (95%CI 0.77 to 1.17) / HR=0.97 (95%CI 0.77 to 1.23)
Progression to neovascular AMD: HR=1.17 (95%CI 0.94 to 1.46) / HR=0.97 (95%CI 0.79 to 1.20)

Red meat intake, Q4 vs. Q1 (AREDS/ AREDS2)
Progression to late AMD: HR=1.20 (95%CI 1.00 to 1.45) / HR=1.12 (95%CI 0.98 to 1.28)
Progression to geographic atrophy: HR=1.12 (95%CI 0.90 to 1.39) / HR=1.16 (95%CI 0.94 to 1.44)
Progression to neovascular AMD: HR=1.20 (95%CI 0.96 to 1.51) / HR=1.16 (95%CI 0.95 to 1.41)

	MUFA: SFA intake, Q4 vs. Q1 (AREDS/ AREDS2) **Progression to late AMD**: HR=1.29 (95%CI 1.10 to 1.51) / HR=0.97 (95%CI 0.85 to 1.10) **Progression to geographic atrophy**: HR=1.21 (95%CI 1.01 to 1.46) / HR=1.06 (95%CI 0.86 to 1.31) **Progression to neovascular AMD**: HR=1.25 (95%CI 1.02 to 1.53) / HR=0.95 (95%CI 0.78 to 1.15) *Alcohol intake, in interval (i.e. 5-15 g/day [female] or 10-15 g/day[male]) (AREDS/ AREDS2)* **Progression to late AMD**: HR=0.87 (95%CI 0.75 to 1.01) / HR=0.91 (95%CI 0.81 to 1.02) **Progression to geographic atrophy**: HR=0.83 (95%CI 0.69 to 1.00) / HR=0.85 (95%CI 0.70 to 1.03) **Progression to neovascular AMD**: HR=0.86 (95%CI 0.71 to 1.05) / HR=0.93 (95%CI 0.78 to 1.11) *In all cases, the unit of analysis was the eye and analyses were adjusted for age, sex, smoking, total calorie intake, body mass index (BMI) (for AREDS only), and correlation between eyes.*
• **Visual acuity**	Not reported.
• **Adverse events**	Not reported.
• **Limitations and other comments**	
• **Limitations**	Differences in AREDS and AREDS2 cohorts regarding variables assessed (e.g. BMI), FFQs, in assignment of food items to the modified aMedi components. Population also contains individuals without AMD at baseline (looking at prevention). Moderate risk of bias due to missing data, insufficient information to judge risk of bias due to deviations of the intended interventions, low risk of bias on other ROBINS-I-domains.

Q: quartile; T: tertile

Merle 2017 - Associations Between Vitamin D Intake and Progression to Incident Advanced Age-Related Macular Degeneration	
• **Methods**	
• **Design**	Cohort study
• **Source of funding and competing interests**	Supported by Grants R01-EY011309 (JMS) and R01-EY022445 (BR) from the National Institutes of Health. JMS also received support from the Massachusetts Lions Eye Research Fund, Inc., New Bedford, Massachusetts; Laboratoires Thea, Clermont-Ferrand, France; American Macular Degeneration Foundation, Northampton, MA; and the Age-

	Related Macular Degeneration Research Fund, Ophthalmic Epidemiology and Genetics Service, Tufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts/ J.M. Seddon, Laboratoires Thea. All other authors had nothing to declare.
• **Setting**	Study population of various nationwide genetic and epidemiologic studies (USA).
• **Sample size**	2146 participants (3965 eyes)
• **Study dates**	1988 - end date not reported.
• **Follow-up**	Mean of 9.4 years
• **Patient characteristics**	•
• **Eligibility criteria**	People enrolled in one of the nationwide genetic and epidemiologic studies (participants were derived from clinic population and nationwide referrals) with at least one eye with nonadvanced AMD at baseline.
• **Exclusion criteria**	Participants with advanced disease in both eyes at baseline and participants with less than 1 year of follow-up.
• **AMD definition**	Clinical Age-Related Maculopathy Staging (CARMS) was used. CARMS grades were defined as follows: grade 1 (no AMD, no drusen or only a few small drusen < 63 µm); grade 2 (early AMD, intermediate size drusen 63–124 µm); grade 3 (intermediate AMD, large drusen ≥ 125 µm); grade 4 (advanced dry AMD, or GA, including both central and noncentral forms); and grade 5 (advanced exudative AMD, or NV, with choroidal neovascularization). Progressors were defined as subjects who transitioned from no AMD, early AMD, or intermediate AMD to either GA or NV in at least one eye.
• **Patient & disease characteristics**	*Total study population (n=2146) / Progressors to advanced disease (n=541)* Age: • ≤65 yrs: 26 / 15 • 65.1-73.9 yrs: 41 / 38 • ≥74 yrs: 33 / 47 % Male: 49 / 43 % Smoking: • Never: 42 /41 • Past: 52 / 52 • Current: 6 / 7 % with BMI in kg/m^2 of: • <25: 36 / 37 • 25-29: 43 / 43 • ≥30: 21 / 20

	Race: Not reported. Other ocular pathology: not reported. AMD stage: % with CARMS grade (for both eyes [one eye, other eye]): • No AMD: 1 / 1 • [1,1]; [1,2]; [2,2]: 65 / 21 • [1,3]; [2,3]; [3,3]: 20 / 45 • [1.4]; [2.4]; [3.4]: 2 / 8 • [1.5]; [2.5]; [3.5]: 12 / 25 Visual acuity at baseline: not reported.
• **Interventions**	
• **Determinants**	Vitamin D and Calcium intake assessed using food frequency questionnaire (FFQ) (n=2146). "All dietary data were collected upon enrollment. […] Vitamin D consumption was defined as (1) dietary vitamin D intake from food sources and (2) total vitamin D intake, which is the sum of dietary and supplemental sources. Vitamin D intake was expressed in IU consumed per day. Calcium consumption was also defined according to dietary or total intake, with measurements expressed in milligrams consumed per day. […].Nutritional intake was assessed in g/d for saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), linoleic acid (LA), EPAþDHA, lutein, and folate (lg/d).
• **Results**	
• **Progression of AMD**	*Dietary Vitamin D Intake, per quintile (Model 1 / Model 2*)* **Progression to advanced AMD:** Q1: 163/795; Reference Q2:149/805; HR= 0.89 (95%CI 0.67 to 1.19) / HR= 0.79 (95%CI 0.59 to 1.06) Q3:169/781; HR= 0.98 (95%CI 0.74 to 1.30) / HR= 0.87 (95%CI 0.67 to 1.12) Q4: 136/794; HR= 0.74 (95%CI 0.56 to 0.99) / HR= 0.59 (95%CI 0.43 to 0.80) Q5: 160/790; HR= 0.87 (95%CI 0.65 to 1.16) / HR= 0.60 (95%CI 0.43 to 0.83) **Progression to geographic atrophy**: Q1: 70/795; Reference Q2: 70/805; HR= 0.97 (95%CI 0.65 to 1.47) / HR= 0.88 (95%CI 0.59 to 1.34) Q3: 78/782; HR= 1.05 (95%CI 0.71 to 1.56) / HR= 0.80 (95%CI 0.54 to 1.19) Q4: 66/794; HR= 0.84 (95%CI 0.55 to 1.28) / HR= 0.71 (95%CI 0.46 to 1.10) Q5: 85/790; HR= 1.09 (95%CI 0.73 to 1.62) / HR= 0.83 (95%CI 0.53 to 1.30) **Progression to neovascular disease:** Q1: 104/795; Reference Q2:84/805; HR= 0.76 (95%CI 0.53 to 1.09) / HR= 0.77 (95%CI 0.53 to 1.11)

Q3:101/781; HR= 0.92 (95%CI 0.66 to 1.28) / HR= 0.93 (95%CI 0.66 to 1.30)
Q4: 77/794; HR= 0.64 (95%CI 0.45 to 0.92) / HR= 0.58 (95%CI 0.39 to 0.85)
Q5: 93/790; HR= 0.77 (95%CI 0.55 to 1.09) / HR= 0.59 (95%CI 0.39 to 0.89)

Total Vitamin D Intake, per quintile (Model 1 / Model 3)*

Progression to advanced AMD: Q1: 185/788; Reference
Q2:148/782; HR= 0.79 (95%CI 0.60 to 1.04) / HR= 0.86 (95%CI 0.65 to 1.15)
Q3:162/799; HR= 0.84 (95%CI 0.64 to 1.10) / HR= 0.86 (95%CI 0.66 to 1.13)
Q4: 134/793; HR= 0.74 (95%CI 0.55 to 0.98) / HR= 0.82 (95%CI 0.60 to 1.12)
Q5: 148/803; HR= 0.83 (95%CI 0.63 to 1.10) / HR= 0.89 (95%CI 0.64 to 1.24)

Progression to geographic atrophy: Q1: 94/788; Reference
Q2: 66/782; HR= 0.69 (95%CI 0.47 to 1.01) / HR= 0.73 (95%CI 0.49 to 1.09)
Q3: 67/799; HR= 0.70 (95%CI 0.48 to 1.03) / HR= 0.69 (95%CI 0.47 to 1.03)
Q4: 63/793; HR= 0.69 (95% CI 0.46 to 1.03) / HR= 0.81 (95%CI 0.53 to 1.25)
Q5: 77/803; HR= 0.87 (95%CI 0.60 to 1.26) / HR= 0.87 (95%CI 0.53 to 1.43)

Progression to neovascular disease: Q1: 97/788; Reference
Q2: 95/782; HR= 1.00 (95%CI 0.71 to 1.42) / HR= 1.12 (95%CI 0.79 to 1.61)
Q3:107/799; HR= 1.09 (95%CI 0.78 to 1.52) / HR= 1.08 (95%CI 0.76 to 1.55)
Q4: 80/793; HR= 0.88 (95%CI 0.62 to 1.25) / HR= 0.95 (95%CI 0.63 to 1.41)
Q5: 80/803; HR= 0.88 (95%CI 0.62 to 1.26) / HR= 0.97 (95%CI 0.64 to 1.48)

Dietary calcium Intake, per quintile (Model 1 / Model 2)*

Progression to advanced AMD: Q1: 189/794; Reference
Q2:147/787; HR= 0.74 (95%CI 0.57 to 0.97) / HR= 0.91 (95%CI 0.70 to 1.19)
Q3:141/790; HR= 0.70 (95%CI 0.53 to 0.93) / HR= 1.00 (95%CI 0.76 to 1.32)
Q4: 137/800; HR= 0.74 (95%CI 0.56 to 0.98) / HR= 0.83 (95%CI 0.61 to 1.12)
Q5: 163/794; HR= 0.79 (95%CI 0.60 to 1.04) / HR= 1.01 (95%CI 0.74 to 1.37)

Progression to geographic atrophy: Q1: 95/794; Reference
Q2: 68/787; HR= 0.68 (95%CI 0.47 to 0.99) / HR= 0.80 (95%CI 0.54 to 1.17)

Q3: 55/790; HR= 0.55 (95%CI 0.37 to 0.83) / HR= 0.69 (95%CI 0.45 to 1.05)
Q4: 67/800; HR= 0.73 (95%CI 0.49 to 1.08) / HR= 0.77 (95%CI 0.50 to 1.18)
Q5: 84/784; HR= 0.82 (95%CI 0.56 to 1.20) / HR= 1.00 (95%CI 0.65 to 1.56)

Progression to neovascular disease: Q1: 103/794; Reference
Q2:87/787; HR= 0.83 (95%CI 0.60 to 1.17) / HR= 1.07 (95%CI 0.78 to 1.49)
Q3:93/790; HR= 0.88 (95%CI 0.63 to 1.24) / HR= 1.28 (95%CI 0.90 to 1.82)
Q4: 81/800; HR= 0.80 (95%CI 0.57 to 1.14) / HR= 0.98 (95%CI 0.69 to 1.41)
Q5: 95/794; HR= 0.84 (95%CI 0.60 to 1.18) / HR= 1.05 (95%CI 0.72 to 1.53)

Total calcium Intake, per quintile (Model 1 / Model 3)*

Progression to advanced AMD: Q1: 145/785; Reference
Q2: 172/799; HR= 1.07 (95%CI 0.80 to 1.42) / HR= 1.28 (95%CI 0.95 to 1.72)
Q3: 160/788; HR= 1.14 (95%CI 0.86 to 1.52) / HR= 1.35 (95%CI 0.99 to 1.83)
Q4: 141/784; HR= 0.87 (95%CI 0.64 to 1.17) / HR= 1.11 (95%CI 0.80 to 1.52)
Q5: 159/807; HR= 1.10 (95%CI 0.82 to 1.47) / HR= 1.40 (95%CI 1.02 to 1.92)

Progression to geographic atrophy: Q1: 74/787; Reference
Q2: 81/799; HR= 0.99 (95%CI 0.67 to 1.47) / HR= 1.09 (95%CI 0.73 to 1.63)
Q3: 72/788; HR= 1.01 (95%CI 0.68 to 1.50) / HR= 1.04 (95%CI 0.68 to 1.60)
Q4: 64/784; HR= 0.79 (95% CI 0.52 to 1.20) / HR= 0.95 (95%CI 0.61 to 1.48)
Q5: 78/807; HR= 1.05 (95%CI 0.71 to 1.56) / HR= 1.17 (95%CI 0.75 to 1.84)

Progression to neovascular disease: Q1: 79/787; Reference
Q2: 103/799; HR= 1.17 (95%CI 0.71 to 1.42) / HR= 1.37 (95%CI 0.95 to 1.96)
Q3:101/788; HR= 1.31 (95%CI 0.82 to 1.67) / HR= 1.62 (95%CI 1.12 to 2.33)
Q4: 87/784; HR= 1.00 (95%CI 0.92 to 1.86) / HR= 1.37 (95%CI 0.91 to 2.04)
Q5: 89/807; HR= 1.11 (95%CI 0.77 to 1.60) / HR= 1.40 (95%CI 0.92 to 2.12)

Dietary Intake of combined Vitamin D intake and Calcium intake (Model 1 / Model 2)*

Progression to advanced AMD: Low vitamin D/Low calcium; Reference
Low/High; HR= 1.24 (95%CI 0.92 to 1.66) / HR=1.21 (95%CI 0.89 to 1.65)

	High/Low; HR= 0.73 (95%CI 0.56 to 0.96) /HR=0.67 (95%CI 0.50 to 0.88) **High/High;** HR= 0.91 (95%CI 0.74 to 1.12) / HR=0.81 (95%CI 0.65 to 1.02) *Total Intake of combined Vitamin D intake and Calcium intake (Model 1 / Model 3*)* **Progression to AMD: Low/Low;** Reference **Low/High;** HR= 1.20 (95%CI 0.93 to 1.54) / HR=1.18 (95%CI 0.92 to 1.52) **High/Low;** HR= 1.32 (95%CI 1.01 to 1.73) / HR=1.29 (95%CI 0.98 to 1.69) **High/High;** HR= 1.09 (95%CI 0.88 to 1.36) / HR=1.05 (95%CI 0.84 to 1.31) • ** Model 1: Adjustment for age, sex, and total energy intake.* *Model 2: Adjustment for age, sex, education, smoking, BMI, baseline AMD grade, TEI, supplemental vitamin D use, dietary and supplemental calcium intake, and the dietary intake of EPA+DHA, MUFAs, folate, and lutein.* *Model 3: Adjustment for age, sex, education, smoking, body mass index, AMD grade at baseline in both eyes, total intake of calcium, total energy intake, and dietary intake of folate, lutein, EPA+DHA, and monounsaturated fatty acids.*
• **Visual acuity**	Not assessed.
• **Adverse events**	Not assessed.
• **Limitations and other comments**	
• **Limitations**	• Results are only applicable to Caucasian. • Data collected from FFQs may result in an over- or underestimation of the nutrients consumed. • No clear indication that the study is at serious or critical risk of bias, however there is a lack of information regarding potential bias due to missing data and regarding potential bias due to deviations from intended interventions.

BMI: Body Mass Index; AMD: age-related macular degeneration, TEI: total energy intake; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; MUFAs: monounsaturated fatty acids; Q: quintile

Tisdale 2019 - Association of Dietary and Supplementary Calcium Intake With Age-Related Macular Degeneration. Age-Related Eye Disease Study Report 39
Methods

• **Design**	Secondary analyses of participants enrolled in the Age-Related Eye Disease Study (AREDS).
• **Source of funding and competing interests**	Source of funding: The intramural program funds and contracts AREDS (contract NOI-EY-0-2127) from the National Eye Institute of the National Institutes of Health (NIH); the National Eye Institute; the NIH Medical Research Scholars Program, a public-private partnership supported jointly by the NIH and generous contributions to the Foundation for the NIH from the Doris Duke Charitable Foundation; the American Association for Dental Research; the Howard Hughes Medical Institute, and the Colgate-Palmolive Company, as well as other private donors. Competing interests: None reported.
• **Setting**	11 retinal specialty clinics in the United States.
• **Sample size**	4751
• **Study dates**	November 1992 to 2005.
• **Follow-up**	Not specified, however >10 years.
Patient characteristics	
• **Eligibility criteria**	Adults (aged 55 to 80 years) who had either no AMD, intermediate AMD (bilateral large drusen), and late AMD in 1 eye. Dietary calcium-intake analyses were calorie restricted from 677 to 1994 kcal in female participants and from 794 to 2771 kcal in male participants.
• **Exclusion criteria**	Not reported.
• **AMD definition**	Large drusen was defined as drusen with diameter of 125 µm or more. An eye was considered to have neovascular AMD if any of the following was present: nondrusenoid sub-retinal pigment epithelium detachment, serous hemorrhagic retinal detachment, hemorrhage under the retina or sub-retinal pigment epithelium, and/or sub-retinal fibrosis. An eye was also considered to have neovascular AMD if a clinical center reported treatments for choroidal neovascularization, such as photocoagulation or photodynamic therapy
• **Patient & disease characteristics**	*Total population* Mean age (SD): 69.4 (5.1) % Male: 44.1 Smoking: • % Never smoking: 44.3 • % Former smoking: 47.8 • % Current smoking: 7.9 BMI:

	• % ≤ 25.0 BMI: 32.6 • % >25.0 - ≤30 BMI: 41.8 • % >30 BMI: 25.6 % White non-Hispanic Race: 95.6 Other ocular pathology: not reported. AMD stage: not reported. Visual acuity at baseline: not reported.
Interventions	
• **Determinants**	Baseline dietary calcium intake was determined through food frequency questionnaire, while baseline calcium supplement use was determined through an additional questionnaire. Sex-specific analyses of dietary calcium intake were conducted to account for the differences in daily caloric intake between male and female participants. The amount of dietary calcium intake was energy adjusted. Dietary calcium intake was analysed in quintiles and supplemental calcium intake in tertiles.
Results	
• **Progression of AMD**	*Q5 (highest) vs. Q1 (lowest) on dietary calcium quintiles* **Late AMD:** HR=0.73 (95% CI 0.59 to 0.90) **Neovascular AMD:** HR=0.80 (95% CI 0.63 to 1.01) **Central geographic atrophy (CGA)**: HR=0.64 (95% CI 0.48 to 0.86) **Any geographic atrophy (GA)**: HR=0.80 (95% CI 0.64 to 1.00) **Large drusen**: HR=0.87 (95% CI 0.71 to 1.06) *T3 (highest) vs. none on calcium supplementation* **Late AMD:** event rate not reported. HR=0.78 (95% CI 0.59 to 1.03) **Neovascular AMD:** event rate not reported. HR=0.70 (95% CI 0.50 to 0.97) **Central geographic atrophy (CGA)**: HR=0.88 (95% CI 0.61 to 1.27) **Any geographic atrophy (GA)**: HR=0.89 (95% CI 0.67 to 1.19) **Large drusen**: HR=1.07 (95% CI 0.86 to 1.34) *All analysis models were adjusted for age, sex, smoking, and AREDS treatment group. The models for large drusen,*

	CGA, nAMD, and late AMD were additionally adjusted for race. The models for late AMD, nAMD, CGA, and any GA were adjusted for BMI. The large drusen model was adjusted for nonsteroidal anti-inflammatory drug usage.
• **Visual acuity**	Not assessed.
• **Adverse events**	Not assessed.
Limitations and other comments	
• **Limitations**	AREDS participants were volunteers for the clinical trial, and such volunteers are often healthier and better educated than the general population. The study was at moderate risk of bias due to deviations from the intended intervention. No other indications for bias in this study.

Evidencetabellen van geïncludeerde primaire onderzoeken betreffende voedingssupplementen voor de behandeling van LMD

Akuffo 2017 - The Impact of Supplemental Antioxidants on Visual Function in Nonadvanced Age-Related Macular Degeneration: A Head-to-Head Randomized Clinical Trial	
Methods	
• **Design**	Double-blind, head-to-head, RCT (ISRCTN13894787)
• **Source of funding and competing interests**	Funding: Supported by the European Research Council Grant 281096. Competing interest: none declared.
• **Setting**	The trial was conducted at the Macular Pigment Research Group, Nutrition Research Centre Ireland (Waterford, Ireland).
• **Sample size**	In this study, 121 participants were enrolled at baseline with 98 participants completing final assessment at 24 months.
• **Study dates**	From November 2013 (first visit of first participant) to May 2016 (last visit of last participant).
• **Follow-up**	2-year period
Patient characteristics	

• **Eligibility criteria**	Participants were initially enrolled based on nondetail grading of retinal photographs obtained at screening visit, confirming eligibility by the Moorfields Eye Hospital Reading Centre. Inclusion criteria for the trial were as follows: nonadvanced AMD (1 to 8 on the AREDS 11-step severity scale12 in at least one eye [the study eye], confirmed by the Moorfields Eye Hospital Reading Centre, London, UK, an accredited retinal grading center); best-corrected visual acuity (BCVA) of 6/12 (20/40) or better in the study eye; no more than five diopters spherical equivalent refraction in the study eye; no previous consumption of supplements containing the macular carotenoids; no retinal pathology other than AMD; and no diabetes mellitus (by self-report).
• **Exclusion criteria**	Some participants had AMD grades 8 on the AREDS 11-step severity scale and therefore these participants were excluded based on a decision by the DSMC.
• **AMD definition**	Nonadvanced AMD (1 to 8 on the AREDS 11-step severity scale in at least one eye [the study eye], confirmed by the Moorfields Eye Hospital Reading Centre, London, UK, an accredited retinal grading center).
• **Patient & disease characteristics**	*AREDS 2 plus mesozeaxanthin vs. AREDS 2 only* Mean age (SD): 65.09 (8.59) vs. 64.34 (9.50) % Male: 45 vs. 55 % Smoking: never 50 vs. 50, past 23 vs. 26, current 5 vs. 6 Mean BMI (SD): not reported. Race: not reported. Other ocular pathology: not reported. % AMD stage 1-3: 13 vs. 17 % AMD stage 4-8: 44 vs. 44 Mean (SD) best corrected visual acuity (VAR) at baseline: 100.04 (5.83) vs. 100.08 (5.62)
Interventions	
• **Intervention group**	Age-Related Eye Disease Study (AREDS) 2 formulation with a low dose [25 mg] of zinc and an addition of 10 mg mesozeaxanthin (n=57). AREDS 2 formulation consisted of 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.
• **Control group**	AREDS 2 formulation with a low dose [25 mg] of zinc (n=61).
Results	*Reported as intervention vs. control*
• **Progression of AMD**	**High risk AMD (grades 4-8) after 24 months:** 35/46 vs. 38/50; RR=1.00 (95% CI 0.80 to 1.25) **Advanced AMD after 24 months:** 0/46 vs. 1/50; RR=not estimable.
• **Best corrected Visual acuity**	**Mean (SD) Best corrected visual acuity, VAR (n=51 vs. n=46):** 100.91 (5.80) vs. 101.31 (5.20); MD: -0.40 (95% CI -2.59 to 1.79)
• **Adverse events**	The proportion of participants experiencing any adverse event was statistically similar between interventions: 15

(26%) of 57 from the AREDS 2 plus mesozeaxanthin group and 10 (16%) of 61 from AREDS 2 only (p = 0.187, Pearson chi-squared test). No serious adverse event relating to the study intervention was reported in either intervention group during the course of the study.

Ocular

Watery eyes 1/57 vs 1/61

Transient blurred vision 1/57 vs 0/61

Gritty eyes 1/57 vs 0/61

Ocular pain 1/57 vs NR

Bloodshot eyes 1/57 vs 0/61

Nonocular

Nausea 2/57 vs 3/61

Tiredness 2/57 vs 1/61

Vomiting 3/57 vs 0/61

Itchy skin 1/57 vs 1/61

Metallic taste in mouth 1/57 vs 1/61

Heat rash 0/57 vs 2/61

Irritable bowel syndrome 1/57 vs 0/61

Night-time urination 1/57 vs 0/61

Headaches 1/57 vs 0/61

Weight gain 1/57 vs 0/61

Overactive kidney 0/57 vs 1/61

Leg cramps 1/57 vs 0/61

Knee ache 1/57 vs 0/61

Red and swollen arms and legs 0/57 vs 1/61

Dizziness 1/57 vs 0/61

Neck stiffness 1/57 vs 0/61

Abdominal pains 0/57 vs 1/61

Pancreatitis 0/57 vs 1/61

Palpitations 1/57 vs 0/61

	Sleep disturbance 1/57 vs 0/61 Swollen face 0/57 vs 1/61 Hallucinations 0/57 vs 1/61 Swollen ankle 0/57 vs 1/61 Loss of appetite 0/57 vs 1/61
Limitations and other comments	
• **Limitations**	- A study limitation (albeit slight) is the failure to reach the intended sample size of 56 participants per group; actual samples sizes were 51 and 46. - Another study limitation is the absence of a placebo arm. - Correction for multiple testing was not performed in the current study. It is therefore possible that some of our reported significant results may be attributable to type 1 errors. The study has a high risk of bias for blinding of outcome assessment of subjective outcomes and a low risk of bias for all other domains.

Broadhead 2018 - Saffron therapy for the treatment of mild/moderate age-related macular degeneration: a randomised clinical trial	
Methods	
• **Design**	Prospective, randomised, placebo-controlled, double blind crossover trial
• **Source of funding and competing interests**	No funding was received for this research. No funding was associated with the design, conduct or data analysis of this trial. Dr. Chang has previously acted as a consultant for Novartis, Bayer and Alcon. No authors have any conflicts of interest to declare. One previous researcher associated with this study who had no participant contact, was previously required to withdraw his involvement from the study due to a conflict of interest. This individual is not an author on this manuscript. Preliminary data from this study was presented at the Royal Australian College of Ophthalmologists Annual Congress, Melbourne, Victoria, Australia, November 2016.
• **Setting**	Single tertiary retinal clinic in Australia.
• **Sample size**	100
• **Study dates**	January 2013 to March 2015
• **Follow-up**	3 months
Patient characteristics	

• **Eligibility criteria**	All participants underwent baseline dilated ophthalmic examination and general medical review to confirm the presence of AMD and to assess eligibility under the exclusion/inclusion criteria listed below. Inclusion criteria were as follows: (a) age greater than 50 years, (b) moderate severity AMD (defined as AREDS grade 2 or 3) affecting at least one eye, c) best-corrected visual acuity (BCVA) better than 55 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters (approximately 20/70 Snellen equivalent) in the eye(s) meeting criteria a and b) and (d) ability to provide written consent.
• **Exclusion criteria**	Exclusion criteria were: (a) presence of any confounding visual lesion in the study eye(s), including neovascular AMD, proliferative diabetic retinopathy, macular hole or epiretinal membrane, prior macular off retinal detachment, uncontrolled glaucoma, significant corneal or lenticular opacities or active uveitis; (b) prior macular laser therapy for AMD or other retinal disorders; c) prior or current intravitreal pharmacotherapy and (d) gastric or hepatic disorders altering either absorption or metabolism of orally administered saffron.
• **AMD definition**	The diagnosis of AMD was confirmed by both dilated retinal examination by a retinal specialist (AC) and dilated retinal fundus photography (Zeiss Visucam NM/FA, Zeiss Industries, Dublin). Macular centred fundus photos (45°) were graded according to the AREDS trial criteria.
• **Patient & disease characteristics**	Baseline characteristics not reported per group. Mean age (SD): 73.9 (8.5) % Male: 51 % Non-smoking: 52 % Former smoker: 47 % Current smoker: 1 Mean BMI (SD): not reported. Race: not reported. Other ocular pathology: not reported. AMD stage: not reported. Visual acuity at baseline (ETDRS letters and Snellen equivalent): 81 (20/25+)z ± 7.5 SD
Interventions	
• **Intervention group**	N=50 participants received 20 mg saffron for 3 months (90 days) administered as an unlabeled oral capsule consumed once daily in the morning with meals
• **Control group**	N=50 participants received placebo 3 months (90 days) administered as an unlabeled oral capsule consumed once daily in the morning with meals. Participants were requested to maintain their usual diet throughout the trial, and to continue on any supplements (including AREDS-based therapies) they had been consuming prior to study commencement.
Results	*Reported as intervention vs. control*

• **Progression of AMD**	**Neovascular AMD**: 2/50 vs. 1/50; RR=2.00 (95% CI 0.19 to 21.36)
• **Visual acuity**	"Mean BCVA improved by 0.69 ETDRS letters whilst on saffron compared to placebo (p = 0.001). For those participants already on best-practice supplementation (AREDS equivalent) mean BCVA improved 0.73 letters on saffron compared to placebo after 3 months (p = 0.006)."
• **Adverse events**	"A total of 19 SAEs occurred during the trial, with ten occurring during the saffron supplementation phase and nine during placebo supplementation" *Saffron (n=50) vs. placebo (n=50)* Death (urinary sepsis): 1 vs. 0 Fall: 2 vs. 1 Acute torticollis 0 vs. 1 Self-induced substance overdose 1 vs. 0 SCC requiring excision: 1 vs. 0 Cataract progression: 1 vs. 1 Acutemyocardial infarction: 0 vs. 1 Idiopathic pancreatitis: 1 vs. 0 Hip fracture: 0 vs. 1 Bowel cancer: 1 vs. 1 Bradycardia requiring pacemaker insertion: 0 vs. 1 Incarcerated hernia: 0 vs. 1
Limitations and other comments	
• **Limitations**	The study had an unclear risk of bias for blinding of outcome assessment and a low risk of bias for all other domains.

Forte 2017 - Epilutein for Early-Stage Age-Related Macular Degeneration: A Randomized and Prospective Study	
• **Methods**	
• **Design**	Prospective randomized interventional study
• **Source of funding and competing**	Source of funding was not reported.

interests	The authors declare no conflicts of interests.
• **Setting**	University hospital in Italy.
• **Sample size**	40 (37 after 3 were lost to “run-in” period)
• **Study dates**	Not reported.
• **Follow-up**	First measurement at 1 month (M1), second (final) measurement at 2 months (M2).
Patient characteristics	
• **Eligibility criteria**	Adult patients with early-stage AMD
• **Exclusion criteria**	“Exclusion criteria were the diagnosis of a different stage of AMD (presence of ≥ 5 drusen >125 µm in diameter) within the macula in the studied eye, presence of choroidal neovascularization or geographic atrophy, or signs of any other active retinal disease, such as retinal vascular (i.e., diabetic retinopathy or retinal vein occlusion) or vitreoretinal (i.e., vitreomacular traction syndrome or epiretinal membrane) diseases. Eyes with lens opacities and with best-corrected visual acuity (BCVA) <20/25 were also not included in the study to ensure proper execution of MP density examinations.”
• **AMD definition**	“…early-stage AMD according to the Age-Related Eye Disease Study (AREDS) research group classification...”
• **Patient & disease characteristics**	*Reported as intervention vs. control* Mean age (SD): 69.4 (6.7) vs. 72.0 (6.3) % Male: 38.1 vs. 43.8 % Smoking: 23.8 vs. 25.0 (no former smokers reported) % Underweight: 9.5 vs. 6.3 % Healthy: 81.0 vs. 81.2 % Overweight: 9.5 vs. 12.5 % Obese: 0 vs. 0 Mean macula pigment optical density at baseline (SD), optical density units : 0.203 (0.02) vs. 0.215 (0.03) Max macula pigment optical density at baseline (SD), optical density units: 0.556 (0.07) vs. 0.525 (0.08) Best-corrected visual acuity at baseline (SD), logMar: 0.08 (0.03) vs. 0.06 (0.02) Choroidal thickness at baseline (SD), µm: 207.43 (66.6) vs. 226.6 (62.3) Ganglion cell complex thickness at baseline (SD), µm: 95.14 (7.7) vs. 86.9 (8.2) GCC focal loss volume at baseline (SD), %: 1.25 (0.77) vs. 2.29 (0.69)

	GCC global loss volume at baseline (SD), %: 3.78 (4.17) vs. 3.0 (3.62) Retinal nerve fiber layer thickness at baseline (SD), µm: 110.5 (26.4) vs. 102.6 (16.3)
Interventions	
• **Intervention group**	All-*E*-epilutein plus all-*E*-lutein (n=21). Patients assigned to group 1 were given daily oral treatment with a combination of 8 mg all-*E*-epilutein and 2 mg all-*E*-lutein for 2 months.
• **Control group**	All-*E*-lutein only (n=16). Patients assigned to group 2 were given daily oral treatment of 10 mg all-*E*-lutein for 2 months.
Results	*Reported as intervention vs. control*
• **Progression of AMD**	Not assessed.
• **Visual acuity**	**Mean (SD) Best-corrected visual acuity, log MAR:** 0.08 (0.02) vs. 0.06 (0.04); p=NR
• **Adverse events**	Not assessed.
• **Limitations and other comments**	
• **Limitations**	"Limitations of the present study are the limited number of patients and the short treatment period. The pilot study was planned and performed to assess the potential of epilutein as a new dietary source of eye xanthophylls on the basis of the pharmacokinetic responses and the effect on MPOD. Differences in MPOD between group 1 and group 2 are higher in M1 than in M2, and, therefore, the necessity for a longer study period is indicated. Based on the promising results observed, further studies evaluating the efficacy and safety of epilutein are necessary." Study is powered based on a non-inferiority margin of a HR=1.4, yet their main outcome is MPOD on T=2 months. Hence study may be underpowered. The study has an unclear risk of bias for randomization and allocation concealment and an unclear risk of bias for selective reporting. The study was at low risk of bias for all other domains.

Kim 2020 - Orally Administered Alpha Lipoic Acid as a Treatment for Geographic Atrophy
Methods

• **Design**	Randomized, controlled, double-masked, multicenter phase 2 clinical trial (NCT02613572)
• **Source of funding and competing interests**	Funding: Supported by the BrightFocus Foundation, Clarksburg, Maryland; Cures Within Reach, Chicago, Illinois; the Pennsylvania Lions Eye Research and Sight Conservation Foundation, Harrisburg, Pennsylvania; Research to Prevent Blindness, New York, New York (to the Scheie Eye Institute); the National Institutes of Health, Bethesda, Maryland grant no.: P30 EY01583-26 to the Scheie Eye Institute); and the Paul and Evanina Bell Mackall Foundation Trust, Chicago, Illinois (to the Scheie Eye Institute). Competing interests: The author(s) have made the following disclosure(s): B.J.K.: Consultant Synergy Research, Inc, Apellis Pharmaceuticals, Allergan. P.H.: Consultant Alcon, Allergan, DORC, Genentech, Zeiss; Lecturer Genentech. R.N.K.: Consultant Allergan, Genentech, Regeneron; Financial support: Allergan, Chengdu Kanghong, Clearside Biomedical, Roche, Santen. G.-S.Y.: Consultant Chengdu Kanghong Biotech Ltd, Synergy Research Inc, Ziemer Ophthalmic Systems AG. M.G.M.: Financial support (data monitoring committees) Genentech/Roche.
• **Setting**	Multicenter study in USA
• **Sample size**	53 patients randomised
• **Study dates**	April 2016 to August 2017
• **Follow-up**	18 months
Patient characteristics	
• **Eligibility criteria**	Eligible participants were 55 to 90 years of age with geographic atrophy (GA) resulting from AMD that met the study criteria in one or both eyes. GA was defined on color photographs as 1 or more well-defined patches of loss of the retinal pigment epithelium, typically with exposure of underlying choroidal blood vessels. In addition, the protocol required at least some visible hyperfluorescence at the edge of the GA lesion on fundus autofluorescence imaging. The largest GA lesion needed to be 0.5 to 6.0 disc areas (DA). If the GA was multifocal and the largest lesion was less than 0.5 DA, then at least 3 lesions measuring 250 mm or more in greatest linear diameter were required. This criterion was made to enable enrolment of patients with smaller lesions. Lesions 250 mm or larger are considered gradable, and the presence of 3 small lesions was considered enough to be confident that GA was present that would demonstrate lesion growth. Best-corrected visual acuity (BCVA) needed to be 20/20 to 20/400 in study eyes. Eligibility of eyes with respect to GA was confirmed by a reading center (Scheie Eye Institute Reading Center) based on imaging at a screening visit.
• **Exclusion criteria**	Exclusion criteria for an eye included evidence of ocular disease other than AMD that may affect the study outcomes (e.g., history of myopic degeneration, choroidal neovascularization, central serous chorioretinopathy, severe diabetic retinopathy, macular edema), any history of intravitreal injection for AMD or choroidal neovascularization, history of laser treatment (including photodynamic therapy) to the macula, intraocular surgery within 90 days, and media

	opacity (e.g., corneal scar, cataract) that would prevent adequate fundus imaging. Exclusion criteria for participants included history of involvement in another therapeutic clinical trial for GA; prior use of ALA; and history of gastric ulcer, irritable bowel syndrome, or severe, chronic gastric reflux. Age Related Eye Disease Study vitamins taken at standard doses were not considered an exclusion criterion. Taking antioxidant supplements other than a standard multivitamin (e.g., bilberry, vitamin C that is not part of a multivitamin or taken at higher doses than the Age-Related Eye Disease Study formula, or other similar antioxidants) within 1 month of enrolment or during the study was not allowed
• **AMD definition**	Not reported
• **Patient & disease characteristics**	*Reported as intervention vs. control* Mean age (SD): 80.6 (6.5) vs. 79.0 (7.0) % Male: 31 vs. 41 % Smoking: not reported Mean BMI (SD): not reported % White race: 92 vs. 96 % Bilateral geography atrophy: 88 vs. 89 AMD stage: not reported Visual acuity at baseline (mean number of letters): 62.6 (18.0) vs. 65.8 (15.6)
Interventions	
• **Intervention group**	Patients (n=26) received Alpha lipoic acid (ALA). ALA was provided by Pure Encapsulations (Sudbury, MA) as capsules containing 600 mg racemic ALA and 30 mg ascorbyl palmitate.
• **Control group**	The placebo (n=27 patients) consisted of pharmaceutical-grade capsules containing microcrystalline cellulose plus trace amounts of coloring agents to mimic the appearance and contents of ALA capsules.
Results	*Reported as alpha lipoic acid vs. placebo*
• **Progression of AMD**	Not reported.
• **Visual acuity**	**Mean number of letters (SD) at 18 months:** 57.7 (2.7) vs 58.8 (3.9); MD=-1.2 (95% CI -10.4 to 8.0); p=0.80. **Mean change in number of letters from baseline (SD):** -4.9 (1.1) vs -6.4 (2.2); MD=1.5 (95% CI -3.3 to 6.2); p=0.54
• **Adverse events**	Large amount of different adverse events listed. See below a narrative description. "Five serious adverse events (SAEs) occurred among 4 of 27 participants (15%) in the placebo group, and 10 SAEs

	occurred among 7 of 26 participants (27%) in the ALA group (P = 0.28). No SAEs were related to the gastrointestinal system. Three ocular SAEs were related to vision loss (≥30 letters lost), including 1 in the ALA group for vision loss in a study eye resulting from a conversion to exudative AMD, 1 in the placebo group for vision loss in a nonstudy eye with pre-existing exudative AMD, and 1 in the placebo group for vision loss measured at a nonstudy visit (Snellen acuity without refraction) that improved to near baseline at a subsequent research study visit with refracted BCVA. No SAEs were considered to be related to ALA. One hundred twenty-one non-serious AEs occurred among 24 of 27 (89%) participants in the placebo group, and 171 AEs occurred among 23 of 26 (88%) participants in the ALA group (P= 0.96; Table S6B, available at www.ophthalmologyretina.org). The mean number of AEs per participant was 4.48 (standard deviation [SD], 4.12) in the placebo group and 6.58 (SD, 5.99) in the ALA group (P = 0.12). The most common ocular non-SAE was "visual acuity reduced," and this was reported in 6 of 27 (22.2%) participants in the placebo group and 7 of 26 (26.9%) participants in the ALA group. An expected difference was found in the number of non-SAEs related to the gastrointestinal system, with means of 0.6 and 1.7 gastrointestinal AEs per person in the placebo and ALA groups, respectively (P = 0.004). The most common gastrointestinal AEs in the ALA group were dyspepsia, nausea, and vomiting."
Limitations and other comments	
• **Limitations**	"The average total baseline lesion size of this trial therefore was smaller than that of many other trials." The study had an unclear risk for allocation concealment and a low risk of bias for all other domains.

Piatti 2020 - Effect of 2-year nutritional supplementation on progression of age-related macular degeneration	
Methods	
• **Design**	Multicenter, double-masked, placebo-controlled, prospective randomized clinical study.
• **Source of funding and competing interests**	The author(s) received no financial support for the research, authorship and/or publication of this article./ A.P. received consulting fees from Allergan, Bayer, Novartis and SIFI. D.M. received consulting fees from SIFI. All other authors have nothing to disclose.
• **Setting**	Primary care, 8 centres in Italy
• **Sample size**	80 were randomized, 74 were analysed (n=6 were excluded because only patients without major protocol violations were included in the statistical analysis).
• **Study dates**	Not reported.
• **Follow-up**	24 months

Patient characteristics	
• **Eligibility criteria**	Age of 55–80 years; Diagnosis of intermediate AMD, according to the AREDS Research Group classification; Presence of medium (≥63 µm, <125 µm) and/or large drusens (≥125 µm) and/or small areas of non-central retinal atrophy in both eyes; Best-corrected visual acuity (BCVA) for distance ≥20/32 Snellen decimal (LogMAR 0.2) and a minimum number of 43 letters read at the ETDRS (Early Treatment Diabetic Retinopathy Study) chart; BCVA for near ≥20/32 Snellen decimal (LogMAR 0.2) at the MNREAD chart.
• **Exclusion criteria**	Presence myopia >3 dioptres; Presence of any other disorder of the macula; History of eye surgery in the 3 months prior to enrolment in the study.
• **AMD definition**	Intermediate AMD according to the AREDS Research Group classification
• **Patient & disease characteristics**	*Reported as intervention vs. control* Mean age (SD): 71.4 (6.5) vs. 72.7 (5.5) % Male: 35.4 vs. 23.1 % Smoking: not reported. Mean BMI (SD): not reported. Race: not reported. Other ocular pathology: not reported. AMD stage: not reported. Visual acuity at baseline: 49.4 (4) vs. 47.6 (4.4)
Interventions	
• **Intervention group**	Participants (n=48) received a food supplement for 24 months (1 tablet/daily). The food supplement (Azyr Mega, SIFI S.p.A, Italy) contained a 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).
• **Control group**	Participants (n=26) received a placebo for 24 months (1 tablet/daily).
Results	*Reported as intervention vs. control*
• **Progression of AMD**	**Progression of AMD** (defined as retinography, visual acuity for near and visual acuity for distance worsened): 0/48 vs. 3/26; RR= not estimable
• **Visual acuity**	**Worsening of visual acuity (distance)**: 7/48 vs. 5/26; RR=0.76 (95% CI 0.27 to 2.15) **Stable or improved visual acuity (distance)**: 41/48 vs. 21/26; RR=1.06 (95% CI 0.85 to 1.32) **Worsening of visual acuity (near)**: 8/48 vs. 9/26; RR=0.48 (95% CI 0.21 to 1.10) **Stable or improved visual acuity (near)**: 40/48 vs.17/26; RR=1.27 (95% CI 0.94 to 1.73)

• **Adverse events**	"During the entire study, no significant adverse events were recorded."
Limitations and other comments	
• **Limitations**	The study had an unclear risk of bias for randomization and allocation concealment. Also there is an unclear risk of bias due to incomplete outcome data and a high risk of bias because one or more primary outcomes were not pre-defined. For all other domains, risk of bias was low.

Bijlage 5. Overzicht van de kans op vertekening (risk of bias) in de geïncludeerde onderzoeken

5A. AMSTAR-2 (systematische reviews)

Chapman 2019

Domain	Instructions (Check all that apply)	Judgement	Comments (optional)
PICO components	1. Did the research questions and inclusion criteria for the review include the components of PICO? For Yes: ☒ Population ☒ Intervention ☒ Comparator group ☒ Outcome Optional (recommended) ☐ Timeframe for follow up	☒Yes ☐No	Comparator group: all comparisons.
Protocol	2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☐ review question(s) ☐ a search strategy ☐ inclusion/exclusion criteria ☐ a risk of bias assessment For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan, if appropriate, *and* ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐Yes ☐Partial Yes ☒No	
Study design explanation	3. Did the review authors explain their selection of the study designs for inclusion in the review? For Yes, the review should satisfy ONE of the following: ☐ *Explanation for* including only RCTs ☐ OR *Explanation for* including only NRSI ☒ OR *Explanation for* including both RCTs and NRSI	☒Yes ☐No	
Comprehensive search strategy	4. Did the review authors use a comprehensive literature search strategy?	☐Yes ☒Partial Yes ☐No	

	For Partial Yes (all the following): ☒ searched at least 2 databases (relevant to research question) ☒ provided key words and/or search strategy ☒ justified publication restrictions (e.g. language) For Yes, should also have (all the following): ☒ searched the reference lists / bibliographies of included studies ☐ searched trial/study registries ☐ included/consulted content experts in the field ☐ where relevant, searched for grey literature ☒ conducted search within 24 months of completion of the review		
Duplicate study selection	5. Did the review authors perform study selection in duplicate? For Yes, either ONE of the following: ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	☐Yes ☒No	
Duplicate data extraction	6. Did the review authors perform data extraction in duplicate? For Yes, either ONE of the following: ☐at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	☐Yes ☒No	
Details of excluded studies	7. Did the review authors provide a list of excluded studies and justify the exclusions? For Partial Yes: ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review For Yes, must also have: ☐ Justified the exclusion from the review of each potentially relevant study	☐Yes ☐Partial Yes ☒No	
Description of included studies	8. Did the review authors describe the included studies in adequate detail? For Partial Yes (ALL the following): ☒ described populations	☐Yes ☒Partial Yes ☐No	

	☒ described interventions ☒ described comparators ☒ described outcomes ☒ described research designs For Yes, should also have ALL the following: ☐ described population in detail ☐ described intervention in detail (including doses where relevant) ☐ described comparator in detail (including doses where relevant) ☐ described study's setting ☒ timeframe for follow-up		
Risk of bias assessment (RCTs)	9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? For Partial Yes, must have assessed RoB from ☐ unconcealed allocation, *and* ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality) For Yes, must also have assessed RoB from: ☐ allocation sequence that was not truly random, *and* ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐Yes ☐Partial Yes ☒No ☐Includes only NRSI	Only study design was assessed to determine the quality of the study.
Risk of bias assessment (NRSI)	9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? For Partial Yes, must have assessed RoB: ☐ from confounding, *and* ☐ from selection bias For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, *and* ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐Yes ☐Partial Yes ☒No ☐Includes only RCTs	Only study design was assessed to determine the quality of the study.
Funding sources	10. Did the review authors report on the sources of funding for the studies included in the review? For Yes ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐Yes ☒No	

Meta-analyses (RCTs)	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity	☐Yes ☐No ☒No meta-analysis conducted ☐Includes only NRSI	
Meta-analyses (NRSI)	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐Yes ☐No ☒No meta-analysis conducted ☐Includes only RCTs	
Impact of bias on meta-analysis	12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐Yes ☐No ☒No meta-analysis conducted	
Risk of bias and interpretation results	13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? For Yes: ☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☐Yes ☒No	
Heterogeneity	14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	☐Yes ☒No	

	For Yes: ☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review		
Publication bias	15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐Yes ☐No ☒No meta-analysis conducted	
Conflicts of interest	16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? For Yes: ☒ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☒Yes ☐No	Conflict of interest: None declared Source of funding: None declared

Dinu 2019

Domain	**Instructions (Check all that apply)**	**Judgement**	**Comments (optional)**
PICO components	1. Did the research questions and inclusion criteria for the review include the components of PICO? For Yes: ☒ Population ☒ Intervention ☒ Comparator group ☒ Outcome Optional (recommended) ☐ Timeframe for follow up	☒Yes ☐No	
Protocol	2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☐ review question(s) ☐ a search strategy ☐ inclusion/exclusion criteria ☐ a risk of bias assessment	☐Yes ☐Partial Yes ☒No	

	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan, if appropriate, *and* ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol		
Study design explanation	3. Did the review authors explain their selection of the study designs for inclusion in the review? For Yes, the review should satisfy ONE of the following: ☐ *Explanation for* including only RCTs ☒ OR *Explanation for* including only NRSI ☐ OR *Explanation for* including both RCTs and NRSI	☒Yes ☐No	
Comprehensive search strategy	4. Did the review authors use a comprehensive literature search strategy? For Partial Yes (all the following): ☒ searched at least 2 databases (relevant to research question) ☒ provided key words and/or search strategy ☒ justified publication restrictions (e.g. language) For Yes, should also have (all the following): ☒ searched the reference lists / bibliographies of included studies ☐ searched trial/study registries ☐ included/consulted content experts in the field ☐ where relevant, searched for grey literature ☒ conducted search within 24 months of completion of the review	☐Yes ☒Partial Yes ☐No	
Duplicate study selection	5. Did the review authors perform study selection in duplicate? For Yes, either ONE of the following: ☒ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	☒Yes ☐No	
Duplicate data extraction	6. Did the review authors perform data extraction in duplicate? For Yes, either ONE of the following: ☒at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder	☒Yes ☐No	

	extracted by one reviewer.		
Details of excluded studies	7. Did the review authors provide a list of excluded studies and justify the exclusions? For Partial Yes: ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review For Yes, must also have: ☐ Justified the exclusion from the review of each potentially relevant study	☐Yes ☐Partial Yes ☒No	Provided reasons for exclusion, but not studies themselves.
Description of included studies	8. Did the review authors describe the included studies in adequate detail? For Partial Yes (ALL the following): ☒ described populations ☒ described interventions ☒ described comparators ☒ described outcomes ☒ described research designs For Yes, should also have ALL the following: ☐ described population in detail ☐ described intervention in detail (including doses where relevant) ☐ described comparator in detail (including doses where relevant) ☐ described study's setting ☒ timeframe for follow-up	☐Yes ☒Partial Yes ☐No	
Risk of bias assessment (RCTs)	9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? For Partial Yes, must have assessed RoB from ☐ unconcealed allocation, *and* ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality) For Yes, must also have assessed RoB from: ☐ allocation sequence that was not truly random, *and* ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐Yes ☐Partial Yes ☐No ☒Includes only NRSI	
Risk of bias assessment (NRSI)	9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? For Partial Yes, must have assessed RoB: ☒ from confounding, *and*	☒Yes ☐Partial Yes ☐No ☐Includes only RCTs	

	☒ from selection bias For Yes, must also have assessed RoB: ☒ methods used to ascertain exposures and outcomes, *and* ☒ selection of the reported result from among multiple measurements or analyses of a specified outcome		
Funding sources	10. Did the review authors report on the sources of funding for the studies included in the review? For Yes ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐Yes ☒No	
Meta-analyses (RCTs)	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity	☐Yes ☐No ☐No meta-analysis conducted ☒Includes only NRSI	
Meta-analyses (NRSI)	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? For Yes: ☒ The authors justified combining the data in a meta-analysis ☒ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☒ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☒Yes ☐No ☐No meta-analysis conducted ☐Includes only RCTs	
Impact of bias on meta-analysis	12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? For Yes: ☐ included only low risk of bias RCTs	☐Yes ☒No ☐No meta-analysis conducted	

	☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.		
Risk of bias and interpretation results	13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? For Yes: ☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☐Yes ☒No	
Heterogeneity	14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? For Yes: ☐ There was no significant heterogeneity in the results ☒ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☒Yes ☐No	
Publication bias	15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? For Yes: ☒ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☒Yes ☐No ☐No meta-analysis conducted	
Conflicts of interest	16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? For Yes: ☒ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☒Yes ☐No	

Evans 2017a (prevention)

Domain	**Instructions (Check all that apply)**	**Judgement**	**Comments (optional)**
PICO components	1. Did the research questions and inclusion criteria for the review include the components of PICO? For Yes: ☒ Population ☒ Intervention	☒Yes ☐No	

	☒ Comparator group ☒ Outcome Optional (recommended) ☒ Timeframe for follow up		
Protocol	2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☒ review question(s) ☒ a search strategy ☒ inclusion/exclusion criteria ☒ a risk of bias assessment For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☒ a meta-analysis/synthesis plan, if appropriate, *and* ☒ a plan for investigating causes of heterogeneity ☒ justification for any deviations from the protocol	☒Yes ☐Partial Yes ☐No	
Study design explanation	3. Did the review authors explain their selection of the study designs for inclusion in the review? For Yes, the review should satisfy ONE of the following: ☐ *Explanation for* including only RCTs ☐ OR *Explanation for* including only NRSI ☐ OR *Explanation for* including both RCTs and NRSI	☐Yes ☒No	
Comprehensive search strategy	4. Did the review authors use a comprehensive literature search strategy? For Partial Yes (all the following): ☒ searched at least 2 databases (relevant to research question) ☒ provided key words and/or search strategy ☒ justified publication restrictions (e.g. language) For Yes, should also have (all the following): ☒ searched the reference lists / bibliographies of included studies ☒ searched trial/study registries ☒ included/consulted content experts in the field ☒ where relevant, searched for grey literature ☒ conducted search within 24 months of completion of the review	☒Yes ☐Partial Yes ☐No	
Duplicate study selection	5. Did the review authors perform study selection in duplicate?	☒Yes ☐No	After an initial very broad search for trials

	For Yes, either ONE of the following: ☒ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.		on antioxidant supplements, two reviewers selected a sample to identify trials with eye disease outcomes; thereafter the screening was done in duplicate.
Duplicate data extraction	6. Did the review authors perform data extraction in duplicate? For Yes, either ONE of the following: ☒at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	☒Yes ☐No	
Details of excluded studies	7. Did the review authors provide a list of excluded studies and justify the exclusions? For Partial Yes: ☒ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review For Yes, must also have: ☒ Justified the exclusion from the review of each potentially relevant study	☒Yes ☐Partial Yes ☐No	
Description of included studies	8. Did the review authors describe the included studies in adequate detail? For Partial Yes (ALL the following): ☒ described populations ☒ described interventions ☒ described comparators ☒ described outcomes ☒ described research designs For Yes, should also have ALL the following: ☒ described population in detail ☒ described intervention in detail (including doses where relevant) ☒ described comparator in detail (including doses where relevant) ☒ described study's setting ☒ timeframe for follow-up	☒Yes ☐Partial Yes ☐No	

Risk of bias assessment (RCTs)	9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? For Partial Yes, must have assessed RoB from ☒ unconcealed allocation, *and* ☒ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality) For Yes, must also have assessed RoB from: ☒ allocation sequence that was not truly random, *and* ☒ selection of the reported result from among multiple measurements or analyses of a specified outcome	☒Yes ☐Partial Yes ☐No ☐Includes only NRSI	
Risk of bias assessment (NRSI)	9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? For Partial Yes, must have assessed RoB: ☐ from confounding, *and* ☐ from selection bias For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, *and* ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐Yes ☐Partial Yes ☐No ☒Includes only RCTs	
Funding sources	10. Did the review authors report on the sources of funding for the studies included in the review? For Yes ☒ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☒Yes ☐No	
Meta-analyses (RCTs)	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? For Yes: ☒ The authors justified combining the data in a meta-analysis ☒ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☒ AND investigated the causes of any heterogeneity	☒Yes ☐No ☐No meta-analysis conducted ☐Includes only NRSI	
Meta-analyses (NRSI)	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	☐Yes ☐No	

	For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐No meta-analysis conducted ☒Includes only RCTs	
Impact of bias on meta-analysis	12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? For Yes: ☒ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☒Yes ☐No ☐No meta-analysis conducted	"We had planned to conduct sensitivity analyses to determine the impact of study quality on effect size. Currently there are only high-quality trials included in the review, and therefore, this is not relevant at present."
Risk of bias and interpretation results	13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? For Yes: ☒ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☒Yes ☐No	"Currently there are only high-quality trials included in the review,…."
Heterogeneity	14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? For Yes: ☒ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☒Yes ☐No	"Only five trials are included at present, which means that it is not possible to formally investigate heterogeneity."
Publication bias	15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely	☐Yes ☒No ☐No meta-	"We considered risk of bias, inconsistency,

	impact on the results of the review? For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	analysis conducted	indirectness, imprecision, and publication bias when judging the certainty of the evidence"
Conflicts of interest	16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? For Yes: ☒ The authors reported no competing interests OR ☒ The authors described their funding sources and how they managed potential conflicts of interest	☒Yes ☐No	

Evans 2017b (treatment)

Domain	**Instructions (Check all that apply)**	**Judgement**	**Comments (optional)**
PICO components	1. Did the research questions and inclusion criteria for the review include the components of PICO? For Yes: ☒ Population ☒ Intervention ☒ Comparator group ☒ Outcome Optional (recommended) ☒ Timeframe for follow up	☒Yes ☐No	
Protocol	2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☒ review question(s) ☒ a search strategy ☒ inclusion/exclusion criteria ☒ a risk of bias assessment For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☒ a meta-analysis/synthesis plan, if appropriate, *and* ☒ a plan for investigating causes of heterogeneity ☒ justification for any deviations from the protocol	☒Yes ☐Partial Yes ☐No	
Study design explanation	3. Did the review authors explain their selection of the study designs for inclusion in the review?	☐Yes ☒No	

	For Yes, the review should satisfy ONE of the following: ☒ *Explanation for* including only RCTs ☐ OR *Explanation for* including only NRSI ☐ OR *Explanation for* including both RCTs and NRSI		
Comprehensive search strategy	4. Did the review authors use a comprehensive literature search strategy? For Partial Yes (all the following): ☒ searched at least 2 databases (relevant to research question) ☒ provided key word and/or search strategy ☒ justified publication restrictions (e.g. language) For Yes, should also have (all the following): ☒ searched the reference lists / bibliographies of included studies ☒ searched trial/study registries ☒ included/consulted content experts in the field ☒ where relevant, searched for grey literature ☒ conducted search within 24 months of completion of the review	☒Yes ☐Partial Yes ☐No	
Duplicate study selection	5. Did the review authors perform study selection in duplicate? For Yes, either ONE of the following: ☒ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	☒Yes ☐No	
Duplicate data extraction	6. Did the review authors perform data extraction in duplicate? For Yes, either ONE of the following: ☒at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	☒Yes ☐No	
Details of excluded studies	7. Did the review authors provide a list of excluded studies and justify the exclusions? For Partial Yes: ☒ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	☒Yes ☐Partial Yes ☐No	

	For Yes, must also have: ☒ Justified the exclusion from the review of each potentially relevant study		
Description of included studies	8. Did the review authors describe the included studies in adequate detail? For Partial Yes (ALL the following): ☒ described populations ☒ described interventions ☒ described comparators ☒ described outcomes ☒ described research designs For Yes, should also have ALL the following: ☒ described population in detail ☒ described intervention in detail (including doses where relevant) ☒ described comparator in detail (including doses where relevant) ☒ described study's setting ☒ timeframe for follow-up	☒Yes ☐Partial Yes ☐No	
Risk of bias assessment (RCTs)	9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? For Partial Yes, must have assessed RoB from ☒ unconcealed allocation, *and* ☒ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality) For Yes, must also have assessed RoB from: ☒ allocation sequence that was not truly random, *and* ☒ selection of the reported result from among multiple measurements or analyses of a specified outcome	☒Yes ☐Partial Yes ☐No ☐Includes only NRSI	
Risk of bias assessment (NRSI)	9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? For Partial Yes, must have assessed RoB: ☐ from confounding, *and* ☐ from selection bias For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, *and* ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐Yes ☐Partial Yes ☐No ☒Includes only RCTs	
Funding	10. Did the review authors report on the sources of	☒Yes	

sources	funding for the studies included in the review? For Yes ☒ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐No	
Meta-analyses (RCTs)	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? For Yes: ☒ The authors justified combining the data in a meta-analysis ☒ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☒ AND investigated the causes of any heterogeneity	☒Yes ☐No ☐No meta-analysis conducted ☐Includes only NRSI	
Meta-analyses (NRSI)	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐Yes ☐No ☐No meta-analysis conducted ☒Includes only RCTs	
Impact of bias on meta-analysis	12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐Yes ☒No ☐No meta-analysis conducted	"A sensitivity analysis was not planned"
Risk of bias and interpretation results	13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? For Yes:	☒Yes ☐No	"As the majority of the trials were placebo-controlled, we mostly

	☐ included only low risk of bias RCTs ☒ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results		assessed them as being at low risk of bias. In particular, the two trials that contributed most of the data to this review were judged at low risk of bias."
Heterogeneity	14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? For Yes: ☐ There was no significant heterogeneity in the results ☒ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☒Yes ☐No	"The main clinical heterogeneity was the type of supplement. This was incorporated into the analysis strategy by considering the formulations by type."
Publication bias	15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐Yes ☒No ☐No meta-analysis conducted	"In future versions of this review, when sufficient trials are included in the meta-analyses (10 or more), we plan to examine the funnel plot to assess whether there is any evidence that smaller studies are reporting larger effects, which may indicate publication bias."
Conflicts of interest	16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? For Yes: ☒ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☒Yes ☐No	

Lawrenson 2015

Domain	Instructions (Check all that apply)	Judgement	Comments (optional)
PICO components	1. Did the research questions and inclusion criteria for the review include the components of PICO? For Yes: ☒ Population ☒ Intervention ☒ Comparator group ☒ Outcome Optional (recommended) ☐ Timeframe for follow up	☒Yes ☐No	
Protocol	2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☒ review question(s) ☒ a search strategy ☒ inclusion/exclusion criteria ☒ a risk of bias assessment For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☒ a meta-analysis/synthesis plan, if appropriate, *and* ☒ a plan for investigating causes of heterogeneity ☒ justification for any deviations from the protocol	☒Yes ☐Partial Yes ☐No	Could not find the protocol in the Cochrane Library, but I assume that a Cochrane review of 2015 had one registered with all the required components.
Study design explanation	3. Did the review authors explain their selection of the study designs for inclusion in the review? For Yes, the review should satisfy ONE of the following: ☒ *Explanation for* including only RCTs ☐ OR *Explanation for* including only NRSI ☐ OR *Explanation for* including both RCTs and NRSI	☒Yes ☐No	
Comprehensive search strategy	4. Did the review authors use a comprehensive literature search strategy? For Partial Yes (all the following): ☒ searched at least 2 databases (relevant to research question) ☒ provided key words and/or search strategy ☒ justified publication restrictions (e.g. language) For Yes, should also have (all the following):	☐Yes ☒Partial Yes ☐No	Did not consulted content experts (or at least did not describe that), so judged as 'partially yes'.

	☒ searched the reference lists / bibliographies of included studies ☒ searched trial/study registries ☐ included/consulted content experts in the field ☒ where relevant, searched for grey literature ☒ conducted search within 24 months of completion of the review		
Duplicate study selection	5. Did the review authors perform study selection in duplicate? For Yes, either ONE of the following: ☒ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	☒Yes ☐No	
Duplicate data extraction	6. Did the review authors perform data extraction in duplicate? For Yes, either ONE of the following: ☒at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	☒Yes ☐No	
Details of excluded studies	7. Did the review authors provide a list of excluded studies and justify the exclusions? For Partial Yes: ☒ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review For Yes, must also have: ☒ Justified the exclusion from the review of each potentially relevant study	☒Yes ☐Partial Yes ☐No	
Description of included studies	8. Did the review authors describe the included studies in adequate detail? For Partial Yes (ALL the following): ☒ described populations ☒ described interventions ☒ described comparators ☒ described outcomes ☒ described research designs For Yes, should also have ALL the following: ☒ described population in detail	☒Yes ☐Partial Yes ☐No	

	☒ described intervention in detail (including doses where relevant) ☒ described comparator in detail (including doses where relevant) ☒ described study's setting ☒ timeframe for follow-up		
Risk of bias assessment (RCTs)	9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? For Partial Yes, must have assessed RoB from ☒ unconcealed allocation, *and* ☒ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality) For Yes, must also have assessed RoB from: ☒ allocation sequence that was not truly random, *and* ☒ selection of the reported result from among multiple measurements or analyses of a specified outcome	☒Yes ☐Partial Yes ☐No ☐Includes only NRSI	
Risk of bias assessment (NRSI)	9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? For Partial Yes, must have assessed RoB: ☐ from confounding, *and* ☐ from selection bias For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, *and* ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐Yes ☐Partial Yes ☐No ☒Includes only RCTs	
Funding sources	10. Did the review authors report on the sources of funding for the studies included in the review? For Yes ☒ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☒Yes ☐No	
Meta-analyses (RCTs)	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? For Yes: ☒ The authors justified combining the data in a meta-analysis	☒Yes ☐No ☐No meta-analysis conducted ☐Includes only NRSI	Not a lot of heterogeneity to investigate and not a lot of outcomes to meta-analyse.

	☒ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☒ AND investigated the causes of any heterogeneity		
Meta-analyses (NRSI)	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐Yes ☐No ☐No meta-analysis conducted ☒Includes only RCTs	
Impact of bias on meta-analysis	12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? For Yes: ☒ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☒Yes ☐No ☐No meta-analysis conducted	
Risk of bias and interpretation results	13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? For Yes: ☒ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☒Yes ☐No	
Heterogeneity	14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? For Yes: ☒ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☒Yes ☐No	

Publication bias	15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐Yes ☒No ☐No meta-analysis conducted	There were insufficient numbers of studies to carry out a funnel plot analysis to investigate the relationship between treatment effect and study size.
Conflicts of interest	16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? For Yes: ☒ The authors reported no competing interests OR ☒ The authors described their funding sources and how they managed potential conflicts of interest	☒Yes ☐No	

Waugh 2018

Domain	**Instructions (Check all that apply)**	**Judgement**	**Comments (optional)**
PICO components	1. Did the research questions and inclusion criteria for the review include the components of PICO? For Yes: ☒ Population ☒ Intervention ☐ Comparator group ☒ Outcome Optional (recommended) ☐ Timeframe for follow up	☒Yes ☐No	This review studies any kind of intervention or treatment for AMD. Comparator is not described, but likely all comparators were included.
Protocol	2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☒ review question(s) ☐ a search strategy ☒ inclusion/exclusion criteria ☒ a risk of bias assessment For Yes:	☐Yes ☐Partial Yes ☒No	The review has a PROSPERO registration (CRD42016038708), but the information is very limited.

	As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan, if appropriate, *and* ☐ a plan for investigating causes of heterogeneity ☒ justification for any deviations from the protocol		
Study design explanation	3. Did the review authors explain their selection of the study designs for inclusion in the review? For Yes, the review should satisfy ONE of the following: ☐ *Explanation for* including only RCTs ☐ OR *Explanation for* including only NRSI ☒ OR *Explanation for* including both RCTs and NRSI	☒Yes ☐No	
Comprehensive search strategy	4. Did the review authors use a comprehensive literature search strategy? For Partial Yes (all the following): ☒ searched at least 2 databases (relevant to research question) ☒ provided key words and/or search strategy ☐ justified publication restrictions (e.g. language) For Yes, should also have (all the following): ☒ searched the reference lists / bibliographies of included studies ☒ searched trial/study registries ☒ included/consulted content experts in the field ☒ where relevant, searched for grey literature ☒ conducted search within 24 months of completion of the review	☐Yes ☒Partial Yes ☐No	There was no justification for including only English language articles, but the search strategy was very comprehensive. Search strategy is focused on any intervention and includes no specific terms on supplements.
Duplicate study selection	5. Did the review authors perform study selection in duplicate? For Yes, either ONE of the following: ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	☐Yes ☒No	Titles and abstracts from the full literature search results were screened independently by two reviewers to identify all citations that appeared likely to have met the inclusion criteria. Full manuscripts of relevant studies were then retrieved and assessed for eligibility by one reviewer and checked by a second reviewer.
Duplicate data	6. Did the review authors perform data extraction in	☐Yes	Data were

extraction	duplicate? For Yes, either ONE of the following: ☐at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	☒No	extracted by one reviewer using a standard data extraction form and checked by a second reviewer.
Details of excluded studies	7. Did the review authors provide a list of excluded studies and justify the exclusions? For Partial Yes: ☒ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review For Yes, must also have: ☐ Justified the exclusion from the review of each potentially relevant study	☐Yes ☒Partial Yes ☐No	There is a list of some of the excluded studies, and studies that fulfilled eligibility criteria but were not used in the report.
Description of included studies	8. Did the review authors describe the included studies in adequate detail? For Partial Yes (ALL the following): ☒ described populations ☒ described interventions ☒ described comparators ☒ described outcomes ☒ described research designs For Yes, should also have ALL the following: ☒ described population in detail ☒ described intervention in detail (including doses where relevant) ☒ described comparator in detail (including doses where relevant) ☐ described study's setting ☒ timeframe for follow-up	☒Yes ☐Partial Yes ☐No	
Risk of bias assessment (RCTs)	9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? For Partial Yes, must have assessed RoB from ☒ unconcealed allocation, *and* ☒ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality) For Yes, must also have assessed RoB from: ☒ allocation sequence that was not truly random,	☒Yes ☐Partial Yes ☐No ☐Includes only NRSI	Cochrane risk of bias tool.

	and ☒ selection of the reported result from among multiple measurements or analyses of a specified outcome		
Risk of bias assessment (NRSI)	9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? For Partial Yes, must have assessed RoB: ☒ from confounding, *and* ☒ from selection bias For Yes, must also have assessed RoB: ☒ methods used to ascertain exposures and outcomes, *and* ☒ selection of the reported result from among multiple measurements or analyses of a specified outcome	☒Yes ☐Partial Yes ☐No ☐Includes only RCTs	Newcastle Ottawa Scale.
Funding sources	10. Did the review authors report on the sources of funding for the studies included in the review? For Yes ☒ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☒Yes ☐No	
Meta-analyses (RCTs)	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity	☐Yes ☐No ☒No meta-analysis conducted ☐Includes only NRSI	
Meta-analyses (NRSI)	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not	☐Yes ☐No ☒No meta-analysis conducted ☐Includes only RCTs	

	available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review		
Impact of bias on meta-analysis	12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐Yes ☐No ☒No meta-analysis conducted	
Risk of bias and interpretation results	13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? For Yes: ☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☐Yes ☒No	Risk of bias is discussed, but the impact of it on the results is not.
Heterogeneity	14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? For Yes: ☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☐Yes ☒No	
Publication bias	15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐Yes ☐No ☒No meta-analysis conducted	
Conflicts of interest	16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? For Yes: ☐ The authors reported no competing interests OR ☒ The authors described their funding sources and how they managed potential conflicts of interest	☒Yes ☐No	

5B. Primaire onderzoeken

ROBINS-I beoordelingen van de primaire onderzoeken betreffende voeding voor de preventie van LMD

Chiu 2017

Bias	**Authors' judgement** Low, Moderate, Serious, Critical, NI	**Support for judgement**
Bias due to confounding	Low	Appropriate adjustment for confounders.
Bias in selection of participants into the study	Moderate	Selection of participants into the study was based on participant characteristics observed after the start of intervention.
Bias in classification of interventions	Low	No indications for bias.
Bias due to deviations from intended interventions	Moderate	Changes in diet during follow-up are likely to have occurred, however these were not measured and thus not accounted for.
Bias due to missing data	Moderate	Participants with missing data were excluded, but no information on how many participants were excluded for this reason.
Bias in measurement of outcomes	Low	No indications for bias.
Bias in selection of the reported result	Low	No indications for selective reporting.
Overall bias	Moderate	Moderate risk of bias due to selection of participants, due to deviations from the intervention and due to exclusion of participants with missing values.

De Koning-Backus 2019

Bias	**Authors' judgement** Low, Moderate, Serious, Critical, NI	**Support for judgement**
Bias due to confounding	Low	Appropriate adjustment for confounders.

Bias in selection of participants into the study	Low	No indications for bias.
Bias in classification of interventions	Low	No indications for bias.
Bias due to deviations from intended interventions	Moderate	Changes in diet during follow-up are likely to have occurred, however these were not measured and thus not accounted for.
Bias due to missing data	Serious	Considerable amount of participants excluded in the analysis.
Bias in measurement of outcomes	Low	No indications for bias.
Bias in selection of the reported result	Low	No indications for selective reporting.
Overall bias	Serious	Many participants excluded because of missing data, and there were no repeated measurements of diet. No other indications for bias.

Dighe 2019

Bias	**Authors' judgement** Low, Moderate, Serious, Critical, NI	**Support for judgement**
Bias due to confounding	Low	Appropriate adjustment for confounders.
Bias in selection of participants into the study	Low	No indications for bias.
Bias in classification of interventions	Low	No indications for bias.
Bias due to deviations from intended interventions	Moderate	Many participants excluded because of missing data, and there were no repeated measurements of diet. No other indications for bias.
Bias due to missing data	Serious	Considerable number of participants (almost 80%) not included in the analysis.
Bias in measurement of outcomes	Low	No indications for bias.
Bias in selection of the reported result	Low	No indications for selective reporting.

Overall bias	Serious	Serious risk of bias due to exclusion of more than 80% of participants and there were no repeated measurements of diet.

Gopinath 2018a

Bias	**Authors' judgement** Low, Moderate, Serious, Critical, NI	**Support for judgement**
Bias due to confounding	Low	Appropriate adjustment for confounders.
Bias in selection of participants into the study	Low	No indications for bias.
Bias in classification of interventions	Low	No indications for bias.
Bias due to deviations from intended interventions	Moderate	It is possible that there were changes in diet during follow-up, while there were no repeated measurements taken.
Bias due to missing data	Moderate	Some individuals were excluded due to missing data.
Bias in measurement of outcomes	Low	No indications for bias.
Bias in selection of the reported result	Low	No indications for selective reporting.
Overall bias	Moderate	Not accounted for changes in determinant status over time, some individuals with missing data were excluded.

Gopinath 2018b

Bias	**Authors' judgement** Low, Moderate,	**Support for judgement**

	Serious, Critical, NI	
Bias due to confounding	Low	Authors adjusted for the most important confounding domains.
Bias in selection of participants into the study	Low	No indications for bias.
Bias in classification of interventions	Low	No indications for bias.
Bias due to deviations from intended interventions	Moderate	Diet is likely to have changed over time and there is no measurement and thus no adjustment for this change.
Bias due to missing data	Serious	798 participants (22%) with missing data on the outcome, determinants or covariates were excluded in the analyses of prevalence and a further 819 participants were excluded in the analyses of incidence.
Bias in measurement of outcomes	Low	No indications for bias.
Bias in selection of the reported result	Serious	Many additional analyses for various food groups were performed, but only results for analyses with statistically significant results were presented in the article.
Overall bias	Serious	No repeated measurements of diet. Many participants with missing data were excluded and it is likely this has caused bias. Also there is selective reporting of only statistically significant results.

Gopinath 2020

Bias	**Authors' judgement** Low, Moderate, Serious, Critical, NI	**Support for judgement**
Bias due to confounding	Low	Appropriate adjustment for confounders.
Bias in selection of participants into the study	Low	No indications for bias.
Bias in classification of interventions	Low	No indications for bias.

Bias due to deviations from intended interventions	Moderate	Diet is likely to have changed over time and there is no measurement and thus no adjustment for this change.
Bias due to missing data	Serious	1620 out of 3654 individuals were excluded because of missing data.
Bias in measurement of outcomes	Low	No indications for bias.
Bias in selection of the reported result	Low	No indications for selective reporting.
Overall bias	Serious	No repeated measurements of diet. Many participants with missing data were excluded. No other indications for bias.

Jones 2020

Bias	**Authors' judgement** Low, Moderate, Serious, Critical, NI	**Support for judgement**
Bias due to confounding	Low	Analyses were adjusted for important potential confounders.
Bias in selection of participants into the study	Low	No indications for bias.
Bias in classification of interventions	Low	No indications for bias.
Bias due to deviations from intended interventions	Moderate	Dietary pattern could have been changed over time, for which no measurements or adjustments were done.
Bias due to missing data	Moderate	No proper imputation of missing values was performed.
Bias in measurement of outcomes	Low	Although outcome measurement is subjective, there are no indications for bias.
Bias in selection of the reported result	Low	No indications for bias.
Overall bias	Moderate	Dietary pattern could have been changed over time, for which no measurements or adjustments were done. In addition, proper imputation method was performed.

Lin 2017

Bias	Authors' judgement Low, Moderate, Serious, Critical, NI	Support for judgement
Bias due to confounding	Low	Analyses were corrected for the most important confounders.
Bias in selection of participants into the study	Low	No indications for bias.
Bias in classification of interventions	Low	No indications for bias.
Bias due to deviations from intended interventions	Moderate	Diet is likely to have changed over time and there is no measurement and thus no adjustment for this change.
Bias due to missing data	Moderate	About 10% of participants is excluded due to missing data.
Bias in measurement of outcomes	Low	No indications for bias.
Bias in selection of the reported result	Low	No indications for selective reporting.
Overall bias	Moderate	No repeated measurement of diet. 10% of participants was excluded because of missing data, but unclear whether this has caused bias. No other indications for bias.

Merle 2019

Bias	Authors' judgement Low, Moderate, Serious, Critical, NI	Support for judgement
Bias due to confounding	Low	Appropriate adjustment for confounding.
Bias in selection of participants into the study	Moderate	Participants excluded for various reasons tended to be slightly younger than those included, which might have caused some bias.

Bias in classification of interventions	Low	No indications for bias.
Bias due to deviations from intended interventions	Moderate	There might be some bias as there was no repeated measurement of the determinant and nutritional assessment is time-sensitive.
Bias due to missing data	Moderate	Individuals with incomplete dietary data were excluded.
Bias in measurement of outcomes	Low	No indications for bias.
Bias in selection of the reported result	Low	No indications for selective reporting.
Overall bias	Moderate	There might be some bias because individuals excluded were different from included individuals, exclusion of individuals with missing data and inappropriate adjustment for variation in diet over time.

Tisdale 2019

Bias	**Authors' judgement** Low, Moderate, Serious, Critical, NI	**Support for judgement**
Bias due to confounding	Low	Appropriate adjustment for confounding.
Bias in selection of participants into the study	Low	No indications for bias.
Bias in classification of interventions	Low	No indications for bias.
Bias due to deviations from intended interventions	Moderate	There might be some bias as there was no repeated measurement of the determinant and nutritional assessment is time-sensitive.
Bias due to missing data	Low	Only 0.1% missing values.
Bias in measurement of outcomes	Low	No indications for bias.
Bias in selection of the reported result	Low	No indications for selective reporting.
Overall bias	Moderate	There might be some bias of inappropriate adjustment for variation in diet over time, however no other indications for bias.

Wu 2017

Bias	**Authors' judgement** Low, Moderate, Serious, Critical, NI	**Support for judgement**
Bias due to confounding	Low	The study can be considered to be at low risk of bias due to confounding, as models were adjusted for important potential confounders. In addition, a stratified analyses was performed (pre- and post 2002), because of a change of major food sources to ALA intake around the early 2000s, which would potentially introduce a varying degree of confounding.
Bias in selection of participants into the study	Low	No indication of bias in selecting participants into the study
Bias in classification of interventions	Low	No indication of bias in classification of interventions.
Bias due to deviations from intended interventions	Low	No indication of bias due to deviations from intended interventions. Questionnaires to measure dietary pattern/fat intake were measured every four years.
Bias due to missing data	Moderate	Participants were excluded due to missing data.
Bias in measurement of outcomes	Serious	The diagnosis of intermediate AMD was done by the participant's eye physician in a clinical examination, leading to potential misclassification.
Bias in selection of the reported result	Low	No indication of bias in selection of the reported results.
Overall bias	Serious	Due to excluding participants with missing data / incomplete information about handling of missing values and there is the risk of outcome misclassification.

ROBINS-I beoordelingen van de primaire onderzoeken betreffende voeding voor de behandeling van LMD

Joachim 2018

Bias	**Authors' judgement** Low, Moderate, Serious, Critical, NI	**Support for judgement**
Bias due to confounding	Moderate	There is no adjustment for nutritional supplements so there might be a moderate risk of bias.
Bias in selection of participants into the study	Moderate	Many participants were lost to follow-up.
Bias in classification of interventions	Low	No indications for bias.
Bias due to deviations from intended interventions	Low	No indications for bias.
Bias due to missing data	No information	No information on missing data.
Bias in measurement of outcomes	Low	No indications for bias.
Bias in selection of the reported result	Low	No indications for bias.
Overall bias	Moderate	No information about missing data, moderate risk of bias due to confounding.

Keenan 2020

Bias	**Authors' judgement** Low, Moderate, Serious, Critical, NI	**Support for judgement**
Bias due to confounding	Low	Analyses adjusted for important potential confounders.
Bias in selection of participants into the study	Low	No indication of selection bias
Bias in classification of interventions	Low	No indication of bias in classification of interventions.
Bias due to deviations from intended interventions	No information	No information regarding the distribution of co-interventions (i.e. nutritional supplements) among participants in the various tertiles or quartiles of the

		aMedi score.
Bias due to missing data	Moderate	Participants have been excluded due to missing data on outcome, FFQ and covariates, however, no information on proportion of participants with missing data, nor on the reasons for missing data.
Bias in measurement of outcomes	Low	Low risk of bias in measurement of outcomes due to central grading (at the Fundus Photographic Reading Center (University of Wisconsin))
Bias in selection of the reported result	Low	No indication of bias in selection of the reported result.
Overall bias	Moderate	Moderate risk of bias due to missing data.

Merle 2017

Bias	**Authors' judgement** Low, Moderate, Serious, Critical, NI	**Support for judgement**
Bias due to confounding	Low	Analyses adjusted for important potential confounders.
Bias in selection of participants into the study	Low	All participants who would have been eligible for the target trial were included in the study.
Bias in classification of interventions	Low	Intervention status is well defined. No risk of bias in classification of interventions.
Bias due to deviations from intended interventions	No information	No information on co-interventions or deviations from the assigned intervention regimen.
Bias due to missing data	No information	No information about missing data in the covariates is provided.
Bias in measurement of outcomes	Low	The outcome assessors were unaware of the intervention received by study participants.

Bias in selection of the reported result	Low	Multiple analyses, however, all outcome measurements and analyses are consistent with an a priori plan.
Overall bias	No information	No clear indication that the study is at serious or critical risk of bias, however there is a lack of information regarding potential bias due to missing data and regarding potential bias due to deviations from intended interventions.

Cochrane Risk of Bias tool – beoordelingen van RCTs betreffende voedingssupplementen voor de behandeling van LMD

Akuffo 2017

Bias	**Authors' judgement** Low, unclear, high	**Support for judgement**
Random sequence generation (selection bias)	Low	"Participants were randomly assigned to intervention groups using block randomization (block size: 4 and randomization ratio 1:1). The randomization sequence was generated by the study statistician (J.S.), and a pharmacist (C.K.) performed random allocation to intervention groups based on this randomization sequence at Whitfield Clinic, Waterford, Ireland."
Allocation concealment (selection bias)	Low	"The study investigator (K.O.A.) received, from the pharmacist, a box of supplements for each study participant, labeled only with the participant identification number. Only at study completion, after a masked database review and following direction from the CREST DSMC, was the randomization sequence revealed to the study investigator and other data analysts."
Blinding of participants and personnel (performance bias)	Low	See support for judgement at allocation concealment.
Blinding of outcome assessment (detection bias) Subjective outcomes	High	No blinding in visual acuity possible and authors did not write about the influence on the outcome.
Blinding of outcome assessment (detection bias) Objective outcomes	Low	"Retinal photographs were graded in a masked fashion at the Moorfields Eye Hospital Reading Centre, adhering to the AREDS 11-step severity scale."

Incomplete outcome data (attrition bias) Subjective outcomes	Low	Low rate of patients lost to follow-up (approximately 10%), both intention-to-treat and per-protocol analysis performed, and lost to follow-up reasons are unlikely to be related to true outcome.
Incomplete outcome data (attrition bias) Objective outcomes	Low	Low rate of patients lost to follow-up (approximately 10%), both intention-to-treat and per-protocol analysis performed, and lost to follow-up reasons are unlikely to be related to true outcome.
Selective reporting (reporting bias)	Low	"Details of the CREST design and methodology have been reported elsewhere and are briefly summarized here."
Other bias	Low	No indications of other bias.

Broadhead 2018

Bias	**Authors' judgement** Low, unclear, high	**Support for judgement**
Random sequence generation (selection bias)	Low	"Following enrolment, all participants were consecutively randomised by a pre-determined computerised random number generator sequence to receive either 20 mg saffron (treatment; S) or placebo (P) for 3 months (90 days) administered as an unlabelled oral capsule consumed once daily in the morning with meals."
Allocation concealment (selection bias)	Low	"Both types of capsule were identical in colour and size, and provided in numbered containers."
Blinding of participants and personnel (performance bias)	Low	"Participants, study personnel and statistical analysts were masked to treatment allocation throughout the study period. Capsules were prepared by an independent contractor (Vitex Pharmaceuticals, Eastern Creek, NSW, Australia) who deidentified the containers in which capsules were provided prior to delivery to study personnel."

Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear	Nothing mentioned about blinding of the outcome assessment.
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear	Nothing mentioned about blinding of the outcome assessment.
Incomplete outcome data (attrition bias) Subjective outcomes	Low	Very few patients lost to follow-up (2/50 in saffron group and 1/50 in placebo group).
Incomplete outcome data (attrition bias) Objective outcomes	Low	Very few patients lost to follow-up (2/50 in saffron group and 1/50 in placebo group).
Selective reporting (reporting bias)	Low	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
Other bias	Low	No indications of bias.

Forte 2017

Bias	**Authors' judgement** Low, unclear, high	**Support for judgement**
Random sequence generation (selection bias)	Unclear	"After a 2-week run-in period, patients were randomly assigned to daily oral treatment with.." Method of random sequence generation unclear.
Allocation concealment (selection bias)	Unclear	Method of concealment is not described.
Blinding of participants and personnel (performance bias)	Low	Not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Subjective outcomes	NA	No subjective outcomes.
Blinding of outcome assessment (detection bias)	Low	Not likely to be influenced by lack of blinding.

Objective outcomes		
Incomplete outcome data (attrition bias) Subjective outcomes	NA	No subjective outcomes.
Incomplete outcome data (attrition bias) Objective outcomes	Low	Missingness is small and likely complete at random
Selective reporting (reporting bias)	Unclear	No study protocol could be obtained.
Other bias	Low	The study appears to be free of other sources of bias.

Kim 2020

Bias	**Authors' judgement** Low, unclear, high	**Support for judgement**
Random sequence generation (selection bias)	Low	Random treatment allocation schedules were generated by the coordinating center (Center for Preventive Ophthalmology and Biostatistics, University of Pennsylvania) with a randomized block design and stratified by clinical center.
Allocation concealment (selection bias)	Unclear	No information regarding allocation concealment reported.
Blinding of participants and personnel (performance bias)	Low	The placebo consisted of pharmaceutical-grade capsules containing microcrystalline cellulose plus trace amounts of coloring agents to mimic the appearance and contents of ALA capsules.
Blinding of outcome assessment (detection bias) Subjective outcomes	Low	The reading center and all research coordinators were masked to study drug assignment.
Blinding of outcome assessment (detection bias) Objective outcomes	Low	The reading center and all research coordinators were masked to study drug assignment.
Incomplete outcome data (attrition bias) Subjective outcomes	Low	Loss to follow-up was ~8%. No information reported on amount of missing in the outcomes.
Incomplete outcome data (attrition bias)	Low	Loss to follow-up was ~8%. No information reported on amount of missing in

Objective outcomes		the outcomes.
Selective reporting (reporting bias)	Low	Protocol on clinicaltrials.gov have the same outcomes as the final article.
Other bias	Low	No other sources of bias.

Piatti 2020

Bias	**Authors' judgement** Low, unclear, high	**Support for judgement**
Random sequence generation (selection bias)	Unclear	No information is provided about sequence generation.
Allocation concealment (selection bias)	Unclear	No information is provided about the allocation concealment.
Blinding of participants and personnel (performance bias)	Low	*"An independent reading centre judged all the photographstaken during the clinical trial"*, "*Food supplement and placebo were packaged in identical containers and indistinguishable in terms of external appearance."* and "The statistical analysis was performed by SPARC Consulting S.r.l.", however no information was provided to who was (not) aware of patients receiving treatment/placebo.
Blinding of outcome assessment (detection bias) Subjective outcomes	Low	No blinding of outcome assessment is stated, but it is unlike that the outcome measurement could have been influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Objective outcomes	Low	No blinding of outcome assessment is stated, but it is unlike that the outcome measurement could have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear	No information is provided for individual outcomes, however n=6 were excluded due to major protocol violations. It was unclear to which group they were originally allocated to.
Incomplete outcome data (attrition bias) Objective outcomes	Unclear	No information is provided for individual outcomes, however n=6 were excluded due to major protocol violations. It was unclear to which group they were originally allocated to.

Selective reporting (reporting bias)	High	One or more reported primary outcomes were not pre-specified.
Other bias	Low	No indications for bias.

Bijlage 6. Resultaten

6A. Effect van voeding op het onstaan van LMD

Resultatentabel voor het effect van voeding op het ontstaan van LMD

Comparison	*Reference*	*Outcome Development of…*	*Follow-up*	*Number of studies*	*Result*	*GRADE RoB*	*GRADE inconsistency*	*GRADE imprecision*	*GRADE indirectness*	*GRADE other*	*GRADE overall*
Dietary pattern – mediterranean											
Mediterranean diet score: high (Q4) vs. low (Q1)	Chapman 2019	Neovascular AMD	NA	1 Cross-sectional study	OR=0.53 (95% CI 0.27 to 1.04)	-1	0	-1	0	0	Low
Mediterranean Diet score high vs. low	Merle 2019	Advanced AMD	4 to 10 years	1 Cohort	HR= 0.59 (95% CI 0.37 to 0.95)						
		Atrophic AMD			HR=0.42 (95% CI 0.20 to 0.90)						
		Neovascular AMD			HR= 0.88 (95% CI 0.49 to 1.57)						
Dietary pattern – diverse											
Western diet vs. Asian diet vs. Vegetarian diet	Jones 2020	Any AMD	NR	1 Cohort	"After adjusting for ethnicity, age, sex and smoking, none of these Factor scores was significantly associated with prevalence of any AMD"	-2	0	-2	0	0	Very low
Dietary pattern – western											
Western pattern score tertile 3 vs. tertile 1	Dighe 2019	Any AMD	18 years	1 Cohort	OR=1.43 (95% CI 0.83 to 2.46)	-2	0	-1	0	0	Very low
		Early AMD	18 years	1 Cohort	OR=1.10 (95% CI 0.61 to 2.00)						

Western pattern score high (quintile 5) vs. (quintile 1)	Chapman 2019	Early AMD	NA	1 Cross-sectional study	OR=1.56 (95% CI 1.18 to 2.06)						
Western pattern (≥ median vs. < median)	Dighe 2019	Late AMD	18 years	1 Cohort	OR=3.44 (95% CI 1.33 to 8.87)						
Dietary pattern – oriental											
Oriental pattern score high (quintile 5) vs. low (quintile 1)	Chapman 2019	Early AMD	NA	1 Cross-sectional study	OR=0.74 (95% CI 0.59 to 0.91)	-2	0	-1	0	0	Very low
Dietary pattern – recommended intake											
Recommended intake (Vegetables >200 g/day; fruit >200 g/day; 32 g/day < meat < 71 g/day) vs. Lower intake	De Koning-Backus 2019	Incident AMD (early or late)	9 years	1 Cohort	HR=1.01 (95% CI 0.72 to 1.41)	-2	0	-2	0	0	Very low
Recommended intake (Vegetables >200 g/day; fruit >200 g/day; egg >32 g/day) vs. Lower intake					HR=1.62 (95% CI 0.67 to 3.92)						
Recommended intake (Vegetables >200 g/day; fruit >200 g/day; fish >32 g/day) vs. Lower intake					HR=0.58 (95% CI 0.36 to 0.93)						
Recommended intake (Vegetables >200 g/day; fruit >200 g/day; fish >32 g/day; 32 g/day < meat < 71 g/day) vs. Lower intake					HR=0.74 (95% CI 0.33 to 1.66)						
Recommended intake (Vegetables >200 g/day; fruit >200 g/day; fish >32 g/day; egg or poultry >48 g/day) vs. Lower intake					HR=0.95 (95% CI 0.35 to 2.56)						
Recommended intake (Vegetables >200 g/day; fruit >200					HR=0.96 (95% CI 0.36 to 2.57)						

g/day; fish >32 g/day; egg, poultry, or meat >80 g/day) vs. Lower intake											
Recommended intake (Vegetables >200 g/day; fruit >200 g/day; fish >32 g/day; poultry >16 g/day) vs. Lower intake					HR=0.65 (95% CI 0.36 to 1.18)						
Recommended intake (Vegetables >200 g/day; fruit >200 g/day; poultry >16 g/day) vs. Lower intake					HR=0.81 (95% CI 0.60 to 1.10)						
Recommended intake (Vegetables >200 g/day; fruit >200 g/day; fish >32 g/day; egg, poultry, or meat >80 g/day; dairy 150 g/day; potatoes, legumes, or grains >319 g/day; fat products >15 g/day) vs. Lower intake					HR=0.90 (95% CI 0.22 to 3.64)						
Healthy eating (Alternative Healthy Eating Index [AHEI])	Jones 2020	Any AMD	NR	1 Cohort	"In a multivariable-adjusted logistic regression model, only ethnicity, age, sex and smoking were significantly associated with any AMD, and AHEI scores and calories intake were not"	-2	-1	-1	0	0	Very low
Prudent (healthy) pattern: tertile 3 vs. tertile 1	Dighe 2019	Any AMD	18 years	1 Cohort	OR=0.90 (95% CI 0.56 to 1.46)						
		Early AMD	18 years	1 Cohort	OR=1.00 (95% CI 0.59 to 1.68)						
		Late AMD	18 years	1 Cohort	OR=0.51 (95% CI 0.22 to 1.18)						
High intake of grains, fish, steamed/boiled chicken, vegetables, and nuts (quartile 4) vs. low intake (quartile 1)	Chapman 2019	Advanced AMD	13 years	1 Cohort	OR=0.49 (95% CI0.28 to 0.87)	-1	0	-1	0	0	Low

Calcium											
Low dietary calcium intake (≤565.1mg per day) vs. high dietary calcium intake (≥1247.3 mg per day)	Chapman 2019	Late AMD	15 years	1 Cohort	OR=2.99 (95% CI 1.23 to 7.25)	-1	0	-1	0	0	Low
Carbohydrates											
High-GI diet (quartile 4) vs. low (quartile 1)	Chapman 2019	Any AMD	8 years	1 Cohort	RR=1.05 (95% CI 0.91 to 1.22)	-1	-1	-1	0	0	Very low
		Early AMD	10 years	1 Cohort	RR=1.77 (95% CI 1.13 to 2.78)						
Bread, cereal, and oatmeal (quartile 4) vs. low (quartile 1)		Early AMD	10 years	1 Cohort	RR=0.67 (95% CI 0.44 to 1.02)						
Carotenoids											
α-Carotene high (quintile 5) vs. low (quintile 1) intake	Waugh 2018	Intermediate AMD	24 to 26 years	1 Cohort	RR=0.94 (95% CI 0.79 to 1.12)	-1	-1	-1	0	0	Very low
	Chapman 2019; Waugh 2018	Late AMD	24 to 26 years	1 Cohort	RR=0.69 (95% CI 0.56 to 0.84)						
β-carotene high (quintile 5) vs. low (quintile 1) intake	Waugh 2018	Intermediate AMD	24 to 26 years	1 Cohort	RR=1.03 (95% CI 0.85 to 1.24)	-1	-1	-1	0	0	Very low
	Chapman 2019; Waugh 2018	Late AMD	24 to 26 years	1 Cohort	RR=0.82 (95% CI 0.67 to 1.01)						
	Chapman 2019	Neovascular AMD	NA	1 Case-control study	OR=0.2 (95% CI 0.1 to 0.4)						
Food-sourced β-carotene high (quintile 5) vs. low (quintile 1) intake	Waugh 2018	Intermediate AMD	24 to 26 years	1 Cohort	RR=1.02 (95% CI 0.84 to 1.24)	-1	-2	-1	0	0	Very low
	Chapman 2019; Waugh 2018	Late AMD	24 to 26 years	1 Cohort	RR=0.64 (95% CI 0.52 to 0.79)						

β-Cryptoxanthin high (quintile 5) vs. low (quintile 1) intake	Waugh 2018	Intermediate AMD	24 to 26 years	1 Cohort	RR=0.85 (95% CI 0.72 to 1.02)	-1	0	-1	0	0	Low
	Chapman 2019; Waugh 2018	Late AMD	24 to 26 years	1 Cohort	RR=0.73 (95% CI 0.60 to 0.89)						
Lutein/zeaxanthin high (quintile 5) vs. low (quintile 1) intake	Waugh 2018	Intermediate AMD	24 to 26 years	1 Cohort	RR=0.93 (95% CI 0.78 to 1.12)	-1	-2	-1	0	0	Very low
	Chapman 2019; Waugh 2018	Late AMD	24 to 26 years	1 Cohort	RR=0.59 (95% CI 0.48 to 0.73)						
Lycopene (quintile 5) high vs. low (quintile 1) intake	Waugh 2018	Intermediate AMD	24 to 26 years	1 Cohort	RR=1.04 (95% CI 0.87 to 1.23)	-1	0	-1	0	0	Low
	Waugh 2018	Late AMD	24 to 26 years	1 Cohort	RR=0.93 (95% CI 0.76 to 1.13)						
Food-sourced 'total' carotene high (quintile 5) vs. low (quintile 1) intake	Waugh 2018	Intermediate AMD	24 to 26 years	1 Cohort	RR=0.99 (95% CI 0.82 to 1.19)	-1	-2	-1	0	0	Very low
	Chapman 2019; Waugh 2018	Late AMD	24 to 26 years	1 Cohort	RR=0.64 (95% CI 0.51 to 0.79)						
Food-sourced 'total' carotenoid index (β-carotene + 'total' carotene) high (quintile 5) vs. low intake (quintile 1)	Waugh 2018	Intermediate AMD	24 to 26 years	1 Cohort	RR=0.92 (95% CI 0.77 to 1.10)						
	Chapman 2019; Waugh 2018	Late AMD	24 to 26 years	1 Cohort	RR=0.65 (95% CI 0.53 to 0.80)						
Flavonoids											
Intake of ≥1 serving of oranges per day vs. no intake of oranges	Gopinath 2018b	Late AMD	15 years	1 Cohort	OR=0.39 (95% CI 0.18 to 0.85)	-2	0	-1	0	0	Very low
Intake of total flavanones Q4 vs. Q1	Gopinath 2018b	Early AMD	15 years	1 Cohort	OR=0.82 (95% CI 0.55 to 1.22)	-2	0	-1	0	0	Very low
		Late AMD			OR=0.55 (95% CI 0.27 to 1.09)						
Intake of total flavones Q4 vs. Q1		Early AMD	15 years	1 Cohort	OR=0.75 (95% CI 0.50 to 1.11)						

		Late AMD			OR=1.52 (95% CI 0.66 to 3.49)						
Intake of total hesperidin Q4 vs. Q1		Early AMD	15 years	1 Cohort	OR=0.85 (95% CI 0.57 to 1.26)						
		Late AMD			OR=0.54 (95% CI 0.26 to 1.13)						
Intake of all flavonoids Q4 vs. Q1		Early AMD	15 years	1 Cohort	OR=1.22 (95% CI 0.82 to 1.81)						
		Late AMD			OR=1.00 (95% CI 0.50 to 2.00)						
Homocysteine levels, folic acid and B vitamins											
Serum folate per 1-SD (=9.1 nmol/L) increase	Waugh 2018	Any AMD	5 to 10 years	1 Cohort	OR=0.91 (95% CI 0.77 to 1.07)	-1	0	-1	0	0	Low
		Early AMD			OR=0.93 (95% CI 0.77 to 1.13)						
		Late AMD			OR=0.89 (95% CI 0.66 to 1.20)						
Serum homocysteine per 1-SD (=5.09 mmol/L) increase	Waugh 2018	Any AMD	5 to 10 years	1 Cohort	OR=1.33 (95% CI 1.11 to 1.60)	-1	0	-1	0	0	Low
		Early AMD			OR=1.33 (95% CI 1.09 to 1.63)						
		Late AMD			OR=1.25 (95% CI 0.93 to 1.69)						
Serum vitamin B-12 per 1-SD (=144.9 pmol/L) increase	Waugh 2018	Any AMD	5 to 10 years	1 Cohort	OR=0.73 (95% CI 0.60 to 0.89)	-1	0	-1	0	0	Low
		Early AMD			OR=0.77 (95% CI 0.62 to 0.96)						
		Late AMD			OR=0.66 (95% CI 0.45 to 0.96)						
Vitamin C											
Vitamin C high (quintile 5) vs. low (quintile 1) intake	Chapman 2019	Neovascular AMD	NA	1 Case-control study	OR=0.4 (95% CI 0.2 to 0.8)	-2	0	-1	0	0	Very low
Vitamin D											
Vitamin D high (quintile 5) vs. low (quintile 1) intake	Chapman 2019	Neovascular AMD	NA	1 Case-control study	OR=0.4 (95% CI 0.2 to 0.8)	-2	0	-1	0	0	Very low
α-tocopherol											

α-tocopherol high (quintile 5) vs. low (quintile 1) intake	Chapman 2019	Neovascular AMD	NA	1 Case-control study	OR=0.2 (95% CI 0.1 to 0.3)	-2	0	-1	0	0	Very low
Nitrate											
Total nitrate Q4 vs. Q1	Gopinath 2018a	Early AMD	15 years	1 Cohort	OR=0.74 (95%CI 0.51 to 1.08)	-1	0	-2	0	0	Very low
Total vegetable nitrate Q4 vs. Q1	Gopinath 2018a	Early AMD	15 years	1 Cohort	OR=0.69 (95%CI 0.47 to 1.00)						
Total nonvegetable nitrate Q4 vs. Q1	Gopinath 2018a	Early AMD	15 years	1 Cohort	OR=0.82 (95%CI 0.56 to 1.20)						
Total nitrate Q4 vs. Q1	Gopinath 2018a	Late AMD	15 years	1 Cohort	OR=1.07 (95%CI 0.53 to 2.17)						
Total vegetable nitrate Q4 vs. Q1	Gopinath 2018a	Late AMD	15 years	1 Cohort	OR=1.38 (95%CI 0.65 to 2.94)						
Total nonvegetable nitrate Q4 vs. Q1	Gopinath 2018a	Late AMD	15 years	1 Cohort	OR=0.98 (95%CI 0.51 to 1.88)						
Fatty acids											
EPA + DHA (excluding supplements) high (quintile 5) vs. low (quintile 1) intake	Chapman 2019	Intermediate AMD	24 to 28 years	1 Cohort	HR=0.86 (95% CI 0.72 to 1.02)	-1	-1	0	0	0	Low
Omega-3 fatty acids (ALA+DHA +EPA) high (quartile 4) vs. low (quartile 1) intake	Chapman 2019	Early AMD	12 years	1 Cohort	OR=0.85 (95% CI 0.71 to 1.02)						
Omega-3 fatty acids high (quintile 5) vs. low (quintile 1) intake	Chapman 2019	Neovascular AMD	NA	1 Case-control study	OR=0.2 (95% CI 0.1 to 0.4)						
High vs. low consumption of oils	Dinu 2019	Any AMD	4 to 27 years	2 Cohorts	RR=1.10 (95% CI 0.98 to 1.23)	-1	0	-1	0	0	Low
	Dinu 2019	Early AMD	4 to 27 years	2 Cohorts	RR=1.13 (95% CI 0.93 to 1.37)						
	Dinu 2019	Late AMD	4 to 27 years	1 Cohort	RR=1.05 (95% CI 0.53 to 2.07)						

High vs. low consumption of margarine	Dinu 2019	Any AMD	4 to 27 years	3 Cohorts	RR=1.05 (95% CI 0.91 to 1.21)	-1	0	-1	0	0	Low
	Dinu 2019	Early AMD	4 to 27 years	3 Cohorts	RR=1.07 (95% CI 0.85 to 1.35)						
	Dinu 2019	Late AMD	4 to 27 years	2 Cohorts	RR=0.98 (95% CI 0.56 to 1.70)						
High vs. low consumption of butter	Dinu 2019	Any AMD	4 to 27 years	2 Cohorts	RR=1.04 (95% CI 0.93 to 1.16)	-1	0	-1	0	0	Low
	Dinu 2019	Early AMD	4 to 27 years	2 Cohorts	RR=0.99 (95% CI 0.75 to 1.30)						
	Dinu 2019	Late AMD	4 to 27 years	2 Cohorts	RR=0.85 (95% CI 0.49 to 1.47)						
Recommended (15g/day) vs. lower intake	De Koning-Backus 2019	Incident AMD (early or late)	9 years	1 Cohort	HR=1.00 (95% CI 0.81 to 1.23)	-2	0	-1	0	0	Very low
α-linolenic acid Q5 vs. Q1	Wu 2017	Advanced AMD	24 to 28 years	1 Cohort	HR=1.05 (95% CI 0.85 to 1.30)	-2	0	-1	0	0	Very low
	Wu 2017	Intermediate AMD	24 to 28 years	1 Cohort	HR= 1.28 (95% CI 1.05 to 1.56)						
Q5 vs. Q1 of cumulative average intake of α-linolenic acid before 2002	Wu 2017	Advanced AMD	24 to 28 years	1 Cohort	HR=1.09 (95% CI 0.79 to 1.49)						
	Wu 2017	Intermediate AMD	24 to 28 years	1 Cohort	HR=1.36 (95% CI 1.06 to 1.75)						
Q5 vs. Q1 of cumulative average intake of α-linolenic acid after 2002	Wu 2017	Advanced AMD	24 to 28 years	1 Cohort	HR=0.84 (95% CI 0.65 to 1.10)						
	Wu 2017	Intermediate AMD	24 to 28 years	1 Cohort	HR=0.85 (95% CI 0.64 to 1.13)						
Specific food - alcohol											
High vs. low consumption of alcohol	Dinu 2019	Any AMD	4 to 27 years	12 Cohorts	RR=1.20 (95% CI 1.04 to 1.39)	-1	0	0	0	0	Moderate
High vs. low consumption of	Dinu 2019	Early AMD	4 to 27 years	10	RR=1.29 (95% CI 1.16 to 1.43)						

alcohol				Cohorts							
High vs. low consumption of alcohol	Dinu 2019	Late AMD	4 to 27 years	9 Cohorts	RR=0.98 (95% CI 0.76 to 1.27)						
Specific foods - diverse											
apples, orange juice, tea, red wine, and beer	Gopinath 2018b	AMD	15 years	1 Cohort	"No significant associations were observed between the consumption of apples, orange juice, tea, red wine, and beer with the 15-y incidence of AMD (data not shown)."	-2	0	-2	0	0	Very low
Specific food - fish											
High vs. low consumption of fish	Dinu 2019	Any AMD	4 to 27 years	8 Cohorts	RR=0.82 (95% CI 0.75 to 0.90)	-1	0	-1	0	0	Low
	Dinu 2019	Early AMD	4 to 27 years	5 Cohorts	RR=0.84 (95% CI 0.73 to 0.97)						
	Dinu 2019	Late AMD	4 to 27 years	6 Cohorts	RR=0.79 (95% CI 0.70 to 0.90)						
Consumption of >1 serving baked/broiled fish per week vs. <1 serving of baked/broiled fish per month	Chapman 2019	Neovascular AMD	NA	1 Case-control study	OR=0.65 (95% CI 0.45 to 0.93)						
Fish consumption of ≥1 servings per week vs. fish consumption of <1 serving per week	Chapman 2019	Late AMD	15 y years	1 Cohort	OR=0.48 (95% CI 0.29 to 0.79)						
Consumption of >2 servings of fish per week vs. consumption of <1 servings of fish per month	Chapman 2019	Neovascular AMD	NA	1 Case-control study	OR=0.61 (95% CI 0.37 to 1.00)						
Consumption of ≥2 servings of fish per week vs. <1 serving of fish per week	Chapman 2019	Intermediate and late AMD	NA	1 Case-control study	OR=0.63 (95% CI 0.41 to 0.97)						
Total fatty fish consumption of ≥5/week vs. total fatty fish	Chapman 2019	Intermediate AMD	24 to 28 years	1 Cohort	HR=0.61 (95% CI 0.46 to 0.82)						

consumption of almost never											
Canned tuna consumption of ≥5 per week vs. canned tuna consumption of almost never	Chapman 2019	Intermediate AMD	24 to 28 years	1 Cohort	HR=0.68 (95% CI 0.44 to 1.05)						
Recommended (32g/day) vs. lower intake	De Koning-Backus 2019	Incident AMD (early or late)	9 years	1 Cohort	HR=0.76 (95% CI 0.60 to 0.97)	-2	0	0	0	0	Low
Specific food - dairy products											
High vs. low consumption of dairy products	Dinu 2019	Any AMD	4 to 27 years	3 Cohorts	RR=1.07 (95% CI 0.68 to 1.70)	-1	-1	-2	0	0	Very low
	Dinu 2019	Early AMD	4 to 27 years	2 Cohorts	RR=1.18 (95% CI 0.93 to 1.50)						
	Dinu 2019	Late AMD	4 to 27 years	2 Cohorts	RR=0.97 (95% CI 0.27 to 3.48)						
Reduced/low-fat dairy, low intake of ≤0.00 servings per day vs. high intake of ≥1.18 servings per day	Chapman 2019	Late AMD	15 years	1 Cohort	OR=3.10 (95% CI 1.18 to 8.14)	-1	0	-2	0	0	Very low
Regular fat dairy low, intake of ≤0.17 servings per day vs. high intake of ≥1.53 servings per day	Chapman 2019	Late AMD	15 years	1 Cohort	OR=2.60 (95% CI 1.12 to 6.03)	-1	0	-2	0	0	Very low
Recommended (150g/day) vs. lower intake	De Koning-Backus 2019	Incident AMD (early or late)	9 years	1 Cohort	HR=1.13 (95% CI 0.95 to 1.35)	-2	0	-1	0	0	Very low
Specific food - eggs											
>1 egg/day vs. <1 egg/week	Gopinath 2020	AMD onset at 15 years follow-up	15 years	1 Cohort	OR=0.92 (95% CI 0.10 to 8.21)	-2	0	-2	0	0	Very low
	Gopinath 2020	AMD onset at 5 or 10 year follow-up	5 or 10 years	1 Cohort	OR=0.37 (95% CI 0.04 to 3.21)						
	Gopinath 2020	Early AMD	15 years	1 Cohort	OR=1.25 (95% CI 0.56 to 2.77)						
>1 egg/day vs. <1 egg/week	Gopinath 2020	Late AMD	15 years	1 Cohort	OR=0.63 (95% CI 0.14 to 2.78)						

>1 egg/day vs. <1 egg/week	Gopinath 2020	Neovascular AMD	15 years	1 Cohort	OR=1.21 (95% CI 0.27 to 5.42)						
5-6 eggs/week vs. <1 egg/week	Gopinath 2020	Geographic atrophy	15 years	1 Cohort	OR=0.23 (95% CI 0.05 to 1.11)						
Recommended (16g/day) vs. lower intake	De Koning-Backus 2019	Incident AMD (early or late)	9 years	1 Cohort	HR=1.10 (95% CI 0.67 to 1.78)	-2	0	-1	0	0	Very low
Specific food - fruit											
High vs. low consumption of fruit	Dinu 2019	Any AMD	4 to 27 years	3 Cohorts	RR=0.91 (95% CI 0.82 to 1.01)	-1	0	-1	0	0	Low
	Dinu 2019	Early AMD	4 to 27 years	2 Cohorts	RR=0.92 (95% CI 0.82 to 1.03)						
	Dinu 2019	Late AMD	4 to 27 years	3 Cohorts	RR=0.83 (95% CI 0.62 to 1.12)						
Recommended (200g/day) vs. lower intake	De Koning-Backus 2019	Incident AMD (early or late)	9 years	1 Cohort	HR=1.03 (95% CI 0.89 to 1.20)	-2	0	-1	0	0	Very low
Specific food - grains											
High vs. low consumption of grains	Dinu 2019	Any AMD	4 to 27 years	2 Cohorts	RR=0.84 (95% CI 0.62 to 1.13)	-1	0	-1	0	0	Low
Recommended (175g/day) vs. lower intake	De Koning-Backus 2019	Incident AMD (early or late)	9 years	1 Cohort	HR=1.00 (95% CI 0.83 to 1.20)	-2	0	-1	0	0	Very low
Specific food - legumes											
Recommended (21g/day) vs. lower intake	De Koning-Backus 2019	Incident AMD (early or late)	9 years	1 Cohort	HR=1.11 (95% CI 0.90 to 1.36)	-2	0	-1	0	0	Very low
Specific food - meat											
High vs. low consumption of meat	Dinu 2019	Any AMD	4 to 27 years	6 Cohorts	RR=1.11 (95% CI 0.96 to 1.27)	-1	0	-1	0	0	Very low
	Dinu 2019	Early AMD	4 to 27 years	4 Cohorts	RR=1.17 (95% CI 1.02 to 1.34)						
	Dinu 2019	Late AMD	4 to 27 years	4 Cohorts	RR=0.99 (95% CI 0.70 to 1.39)						
Red meat (fresh) consumption ≥ 6.5 times per week vs. ≤2.5 times per week	Chapman 2019	Intermediate AMD	12 years	1 Cohort	OR=1.31 (95% CI 1.10 to 1.69)						

Red meat (fresh and processed) consumption ≥ 10 times per week vs. ≤4.5 times per week	Chapman 2019	Intermediate AMD	12 years	1 Cohort	OR=1.39 (95% CI 1.09 to 1.78)						
Luncheon meat ≥1 time per week vs. <1 time per month	Chapman 2019	Intermediate AMD	12 years	1 Cohort	OR=1.23 (95% CI 0.97 to 1.57)						
Salami or continental sausage consumption ≥ 1 time per week vs. <1 time per month	Chapman 2019	Early AMD	12 years	1 Cohort	OR=1.45 (95% CI 1.12 to 1.88)						
Salami or continental sausage consumption ≥ 1 time per week vs. <1 time per month	Chapman 2019	Intermediate AMD	12 years	1 Cohort	OR=1.36 (95% CI 1.00 to 1.86)						
Salami or continental sausage consumption ≥ 1 time per week vs. <1 time per month	Chapman 2019	Late AMD	12 years	1 Cohort	OR=2.37 (95% CI 1.05 to 5.37)						
Recommended (32-71g/day) vs. lower intake	De Koning-Backus 2019	Incident AMD (early or late)	9 years	1 Cohort	HR=0.91 (95% CI 0.65 to 1.28)	-2	0	-1	0	0	Very low
Specific food - nuts											
High consumption vs. low consumption of nuts	Dinu 2019	Any AMD	4 to 27 years	3 Cohorts	RR=0.81 (95% CI 0.64 to 1.02)	-1	0	-1	0	0	Low
	Dinu 2019	Early AMD	4 to 27 years	1 Cohort	RR=0.73 (95% CI 0.51 to 1.04)						
	Dinu 2019	Late AMD	4 to 27 years	3 Cohorts	RR=0.83 (95% CI 0.62 to 1.10)						
Specific food - potatoes											
Recommended (114g/day) vs. lower intake	De Koning-Backus 2019	Incident AMD (early or late)	9 years	1 Cohort	HR=0.91 (95% CI 0.78 to 1.06)	-2	0	-1	0	0	Very low
Specific food - poultry											
Recommended (16g/day) vs. lower intake	De Koning-Backus 2019	Incident AMD (early or late)	9 years	1 Cohort	HR=0.92 (95% CI 0.78 to 1.09)	-2	0	-1	0	0	Very low
Specific food - vegetables											
High vs. low consumption of	Dinu 2019	Any AMD	4 to 27 years	4 Cohorts	RR=0.92 (95% CI 0.82 to 1.03)	-1	0	-1	0	0	Low

vegetables	Dinu 2019	Early AMD	4 to 27 years	3 Cohorts	RR=0.92 (95% CI 0.67 to 1.25)						
	Dinu 2019	Late AMD	4 to 27 years	3 Cohorts	RR=0.80 (95% CI 0.76 to 1.00)						
Recommended intake (200gr/day, of which: 56 gr cruciferous & green leafy vegetables; 25g red & yellow veg.; 118g other veg.) vs. lower intake	De Koning-Backus 2019	Incident AMD (early or late)	9 years	1 Cohort	HR=1.01 (95% CI 0.86 to 1.18)	-2	0	0	0	0	Low
Xanthophyll											
Intake of xantophyll Q5 vs. Q1	Lin 2017	Early AMD	6 years	1 Cohort	OR=1.02 (95% CI 0.76 to 1.38)	-1	0	-1	0	0	Low
Zinc											
Zinc high (quintile 5) vs. low (quintile 1) intake	Chapman 2019	Neovascular AMD	NA	1 Case-control study	OR=0.1 (95% CI 0.1 to 0.4)	-2	0	-1	0	0	Very low

AMD: age-related macular degeneration; NA: not applicable; NR: not reported; T: tertile; Q: quartile or quintile

6B. Effect van voedingssupplementen op het onstaan van LMD

Resultatentabel voor het effect van voedingssupplementen op het ontstaan van LMD

Comparison	*Reference*	*Outcome Development of*	*Follow-up*	*Number of studies*	*Result*	*GRADE RoB*	*GRADE inconsistency*	*GRADE imprecision*	*GRADE indirectness*	*GRADE other*	*GRADE overall*
Antioxidants											
Alpha-tocopherol (50 mg/day) vs. beta-carotene (20 mg/day) vs. alpha-tocopherol + beta-caroten vs. placebo	Waugh 2018	All AMD incidence	5-8 years	1 RCT	31.6% vs. 29.1% vs. 28.4% vs. 24.9%; p=0.468	-1	0	-2	0	0	Very low
Alpha-tocopherol (50 mg/day) vs. beta-carotene (20 mg/day) vs. alpha-tocopherol + beta-caroten vs. placebo	Waugh 2018	AMD class I (dry maculopathy, with hard drusen and/or pigmentary changes)	5-8 years	1 RCT	65% vs. 64% vs. 64% vs. 46%	-1	0	-2	0	0	Very low
Alpha-tocopherol (50 mg/day) vs. beta-carotene (20 mg/day) vs. alpha-tocopherol + beta-caroten vs. placebo	Waugh 2018	AMD class II (soft macular drusen)	5-8 years	1 RCT	2% vs. 2% vs. 6% vs. 6%	-1	0	-2	0	0	Very low
Alpha-tocopherol (50 mg/day) vs. beta-carotene (20 mg/day) vs. alpha-tocopherol + beta-caroten vs. placebo	Waugh 2018	AMD class III (disciform degeneration)	5-8 years	1 RCT	6% vs. 2% vs. 2% vs. 0%	-1	0	-2	0	0	Very low
Alpha-tocopherol (50 mg/day) vs. beta-carotene (20 mg/day) vs. alpha-tocopherol + beta-caroten vs. placebo	Waugh 2018	AMD class IV (geographic atrophy)	5-8 years	1 RCT	2% vs. 0% vs. 1% vs. 1%	-1	0	-2	0	0	Very low
Carotenoids											
Beta-carotene (20 mg/day in one study and 50 mg/alternate days in the other) vs. placebo	Evans 2017a	Any AMD	5-8 years and 12 years	2 RCTs	RR=1.00 (95% CI 0.88 to 1.14)						High*
Beta-carotene (20 mg/day in one study and 50 mg/alternate	Evans 2017a	Late AMD	5-8 years and 12	2 RCTs	RR=0.90 (95% CI 0.65 to 1.24)						Moderate*

days in the other) vs. placebo			years								
Beta-carotene (20 mg/day in one study and 50 mg/alternate days in the other) vs. placebo	Evans 2017a	Neovascular AMD	5-8 years	1 RCT	RR=0.61 (95% CI 0.17 to 2.15)						Very low*
Beta-carotene (20 mg/day in one study and 50 mg/alternate days in the other) vs. placebo	Evans 2017a	Geographic atrophy	5-8 years	1 RCT	RR=0.31 (95% CI 0.03 to 2.93)						Very low*
Homocysteine levels, folic acid and B vitamins											
Folic acid (2.5 mg/day), vitamin B6 (50 mg/day), vitamin B12 (1 mg/day) vs. placebo	Waugh 2018	Total AMD (includes neovascular)	7.3 years	1 RCT	RR= 0.66 (95% CI 0.47 to 0.93)	-1	0	-1	0	0	Low
Folic acid (2.5 mg/day), vitamin B6 (50 mg/day), vitamin B12 (1 mg/day) vs. placebo	Waugh 2018	Visually significant AMD, BCVA loss to 20/30 or worse	7.3 years	1 RCT	RR= 0.59 (95% CI 0.36 to 0.95)	-1	0	-2	0	0	Very low
Vitamin C											
Vitamin C (500 mg/day) vs. placebo	Evans 2017a	Any AMD	11.2 years	1 RCT	RR=0.96 (95% CI 0.79 to 1.18)						High*
Vitamin C (500 mg/day) vs. placebo	Evans 2017a	Late AMD	11.2 years	1 RCT	RR=0.94 (95% CI 0.61 to 1.46)						Moderate*
Vitamin E											
Vitamin E (either 50 mg/day, 400 IU/alternate days, 600 IU/alternate days, or 500 IU/day) vs. placebo	Evans 2017a	Any AMD	5-8 years, 11.2 years, 4 years, and unclear	4 RCTs	RR=0.97 (95% CI 0.90 to 1.06)						High*
Vitamin E (either 50 mg/day, 400 IU/alternate days, 600 IU/alternate days, or 500 IU/day) vs. placebo	Evans 2017a	Late AMD	5-8 years, 11.2 years, 4 years, and unclear	4 RCTs	RR=1.22 (95% CI 0.89 to 1.67)						Moderate*
Vitamin E (50 mg/day) vs. placebo	Evans 2017a	Neovascular AMD	5-8 years	1 RCT	RR=3.62 (95% CI 0.77 to 16.95)						Very low*
Vitamin E (50 mg/day) vs. placebo	Evans 2017a	Geographic atrophy	5-8 years	1 RCT	RR=2.71 (95% CI 0.28 to 26.00)						Very low*
Vitamin E (natural-source; 600 IU/alternate days) and low dose aspirin vs. placebo	Waugh 2018	Visually significant AMD	10 years	1 RCT	RR=0.93 (95% CI 0.72 to 1.19)	-1	0	-1	0	0	Low

Multivitamin											
Multivitamin (Centrum Silver: zinc 15 mg, vitamin E 45 IU, vitamin C 60 mg, beta-carotene 5000 IU vitamin A, 20% as beta carotene, folic acid 2.5 mg, vitamin B6 50 mg, vitamin B12 1 mg; daily) vs. placebo	Evans 2017a	Any AMD	11.2 years	1 RCT	RR=1.21 (95% CI 1.02 to 1.43)						Moderate*
Multivitamin (Centrum Silver: zinc 15 mg, vitamin E 45 IU, vitamin C 60 mg, beta-carotene 5000 IU vitamin A, 20% as beta carotene, folic acid 2.5 mg, vitamin B6 50 mg, vitamin B12 1 mg; daily) vs. placebo	Evans 2017a	Late AMD	11.2 years	1 RCT	RR=1.22 (95% CI 0.88 to 1.69)						Moderate*
Multivitamin (no details on dose provided) vs. placebo	Waugh 2018	Visually significant AMD	11.2 years	1 RCT	HR=1.19 (95% CI 0.94 to 1.50)	-1	0	-1	0	0	Low

**GRADE certainty of evidence* level overgenomen uit systematische review

6C. Effect van voeding op de progressie van LMD

Resultatentabel voor het effect van voeding op de progressie van LMD

Comparison	*Reference*	*Outcome - pogression…*	*Follow-up*	*Result*	*GRADE RoB*	*GRADE inconsistency*	*GRADE imprecision*	*GRADE indirectness*	*GRADE other*	*GRADE overall*
Dietary pattern - mediterranean										
High adherence to the Mediterranean diet vs. low adherence to the Mediterranean diet	Chapman 2019	to Advanced AMD	13 years	HR=0.74 (95% CI0.61 to 0.91)	-1	0	0	0	0	Moderate
Mediterranean diet T3 vs. T1	Keenan 2020	to Late AMD	10 years	HR=0.78 (95%CI 0.71 to 0.85)						
		to Neovascular AMD	10 years	HR=0.84 (95%CI 0.75 to 0.95)						
		to Geographic atrophy	10 years	HR=0.71 (95%CI 0.63 to 0.80)						
Dietary pattern - oriental										
High oriental pattern score (quintile 5) vs. low score (quintile 1)	Chapman 2019	to Late AMD	NA*	OR=0.38 (95% CI 0.27 to 0.54)	-2	0	0	0	0	Low
Dietary pattern - western										
High western pattern score (quintile 5) vs. low score (quintile 1)	Chapman 2019	to Late AMD	NA*	OR=3.70 (95% CI 2.31 to 5.92)	-2	0	0	0	0	Low
Calcium (dietary)										
Dietary calcium intake Q5 vs. Q1	Merle 2017	to Advanced AMD	9 years	HR= 1.01 (95%CI 0.74 to 1.37)	-1	0	-1	0	0	Low
	Tisdale 2019	Late AMD	NR	HR=0.73 (95% CI 0.59 to 0.90)						
	Merle 2017	to Geographic atrophy	9 years	HR= 1.00 (95%CI 0.65 to 1.56)						
	Tisdale 2019	Any geographic atrophy	NR	HR=0.80 (95% CI 0.64 to 1.00)						
	Tisdale 2019	Central geographic atrophy	NR	HR=0.64 (95% CI 0.48 to 0.86)						
	Merle 2017	to Neovascular AMD	9 years	HR= 1.05 (95%CI 0.72 to 1.53)						
	Tisdale 2019	Neovascular AMD	NR	HR=0.80 (95% CI 0.63 to 1.01)						
	Tisdale 2019	Large drusen	NR	HR=0.87 (95% CI 0.71 to 1.06)						

Carotenoids										
Intake of lutein and zeaxanthin (mg/d) continuous	Waugh 2018	Increase in AMD severity one or more levels in either eye; or an increase in ≥ 2 steps in the grades of size, total number, area occupied by a lesion, and spread	7 years	OR=1.72 (95% CI 0.78 to 3.78)	-1	-1	-2	0	0	Very low
		Increase in AMD severity one or more levels in the worse affected eye	7 years	OR=2.65 (95% CI 1.13 to 6.22)						
		Qualitative (better, worse, same) from macular photographs	7 years	OR=1.84 (95% CI 0.84 to 4.00)						
Lutein-zeaxanthin intake ≥1 median vs. <median	Joachim 2018	≥1 step progression	10-15 years	RR=0.93 (95% CI 0.68 to 1.28)						
		≥2 step progression	10-15 years	RR=0.88 (95% CI 0.58 to 1.35)						
Homocysteine levels, folic acid and B vitamins										
Folate and vitamin B intake	Waugh 2018	to Geographic atrophy	8.7 years	"After adjustment, progressors had a lower intake of thiamine (p=0.01), riboflavin (p=0.03) and folate (p=0.001) than non-progressors. No statistically significant variation was seen for niacin, vitamin B-6 or vitamin B-12. Multivariate analysis showed a significant trend for a lower risk of progression with increasing folate (p=0.007), a borderline association for thiamine (p=0.053), and no association with riboflavin (p=0.20)."	-1	0	-2	0	0	Very low
Carbohydrates										
High-GI diet vs. low-GI diet	Chapman 2019	Any progression	8 years	RR=1.10 (95% CI 1.00–1.20)	-1	0	-1	0	0	Low
		from early AMD	8 years	RR=1.08 (95% CI 0.91–1.30)						
		from intermediate AMD	8 years	RR=1.17 (95% CI 1.01–1.36)						
Specific food - alcohol										

Alcohol intake, in interval (i.e. 5-15 g/day [female] or 10-15 g/day[male]) vs. outside interval	Keenan 2020 - AREDS 1 cohort	to Geographic atrophy	10 years	HR=0.83 (95%CI 0.69 to 1.00)	-1	0	-1	0	0	Low
	Keenan 2020 - AREDS 2 cohort	to Geographic atrophy	10 years	HR=0.85 (95%CI 0.70 to 1.03)						
	Keenan 2020 - AREDS 1 cohort	to Late AMD	10 years	HR=0.87 (95%CI 0.75 to 1.01)						
	Keenan 2020 - AREDS 2 cohort	to Late AMD	10 years	HR=0.91 (95%CI 0.81 to 1.02)						
	Keenan 2020 - AREDS 1 cohort	to Neovascular AMD	10 years	HR=0.86 (95%CI 0.71 to 1.05)						
	Keenan 2020 - AREDS 2 cohort	to Neovascular AMD	10 years	HR=0.93 (95%CI 0.78 to 1.11)						
Specific food - grains										
Whole grain intake, Q4 vs. Q1	Keenan 2020 - AREDS 1 cohort	to Geographic atrophy	10 years	HR=0.78 (95%CI 0.64 to 0.95)	-1	0	-1	0	0	Low
	Keenan 2020 - AREDS 2 cohort	to Geographic atrophy	10 years	HR=0.96 (95%CI 0.79 to 1.18)						
	Keenan 2020 - AREDS 1 cohort	to Late AMD	10 years	HR=0.86 (95%CI 0.73 to 1.01)						
	Keenan 2020 - AREDS 2 cohort	to Late AMD	10 years	HR=0.99 (95%CI 0.87 to 1.12)						
	Keenan 2020 - AREDS 1 cohort	to Neovascular AMD	10 years	HR=0.98 (95%CI 0.79 to 1.21)						
	Keenan 2020 - AREDS 2 cohort	to Neovascular AMD	10 years	HR=0.97 (95%CI 0.81 to 1.17)						
Specific food – fatty acids										
Consumption of ≥100 mL/week of olive oil vs. consumption of <1 mL/week	Chapman 2019	to Late AMD (or development to late AMD; unclear)	12 years	OR=0.48 (95% CI 0.22 to 1.04)	-1	0	-2	0	0	Very low
Regular use of olive oil vs. no use of olive oil		to Late AMD	6 years	OR=0.44 (95% CI0.21 to 0.91)						
Energy adjusted intake of ω-3 fatty acids(g)	Waugh 2018	Increase in AMD severity one or more levels in either eye; or an increase in ≥ 2 steps in the grades of size, total number, area occupied by a lesion, and spread	7 years	OR=1.58 (95% CI 0.88 to 2.84)	-1	-1	-1	0	0	Very low
		Increase in AMD severity one or more levels in the	7 years	OR=1.82 (95% CI 0.99 to 3.37)						

		worse affected eye								
		Qualitative (better, worse, same) from macular photographs	7 years	OR=1.65 (95% CI 0.92 to 2.96)						
High intake of EPA + DHA vs. low intake	Chapman 2019	to Advanced AMD	24 to 28 years	HR=0.68 (95% CI 0.46–0.99)						
MUFA: SFA (monounsaturated fatty acid : saturated fatty acid) intake, Q4 vs. Q1	Keenan 2020 - AREDS 1 cohort	to Geographic atrophy	10 years	HR=1.21 (95%CI 1.01 to 1.46)	-1	-1	-1	0	0	Very low
	Keenan 2020 - AREDS 2 cohort	to Geographic atrophy	10 years	HR=1.06 (95%CI 0.86 to 1.31)						
	Keenan 2020 - AREDS 1 cohort	to Late AMD	10 years	HR=1.29 (95%CI 1.10 to 1.51)						
	Keenan 2020 - AREDS 2 cohort	to Late AMD	10 years	HR=0.97 (95%CI 0.85 to 1.10)						
	Keenan 2020 - AREDS 1 cohort	to Neovascular AMD	10 years	HR=1.25 (95%CI 1.02 to 1.53)						
	Keenan 2020 - AREDS 2 cohort	to Neovascular AMD	10 years	HR=0.95 (95%CI 0.78 to 1.15)						
High trans-fat consumption (quartile 4) vs. low trans-fat consumption (quartile 1)	Chapman 2019	to Late AMD (or development to late AMD; unclear)	12 years	OR=1.76 (95% CI 0.92–3.37)	-1	0	-1	0	0	Low
Specific food - fish										
Fish consumption ≥1 servings/week vs. <1 servings/week	Joachim 2018	≥1 step progression	10-15 years	RR=1.21 (95% CI 0.88 to 1.67)	-1	-1	-1	0	0	Very low
		≥2 step progression	10-15 years	RR=0.94 (95% CI 0.61 to 1.44)						
Fish Intake, Q4 vs. Q1	Keenan 2020 - AREDS 1 cohort	to Geographic atrophy	10 years	HR=0.69 (95%CI 0.57 to 0.85)						
	Keenan 2020 - AREDS 2 cohort	to Geographic atrophy	10 years	HR=0.77 (95%CI 0.61 to 0.98)						
	Keenan 2020 - AREDS 1 cohort	to Late AMD	10 years	HR=0.69 (95%CI 0.58 to 0.82)						
	Keenan 2020 - AREDS 2 cohort	to Late AMD	10 years	HR=0.92 (95%CI 0.78 to 1.07)						
	Keenan 2020 - AREDS 1 cohort	to Neovascular AMD	10 years	HR=0.71 (95%CI 0.57 to 0.88)						
	Keenan 2020 - AREDS 2 cohort	to Neovascular AMD	10 years	HR=1.00 (95%CI 0.80 to 1.25)						
Specific food - fruit										
Whole fruit intake, Q4 vs. Q1	Keenan 2020 -	to Geographic atrophy	10 years	HR=0.98 (95%CI 0.80 to 1.19)	-1	0	-1	0	0	Low

	AREDS 1 cohort									
	Keenan 2020 - AREDS 2 cohort	to Geographic atrophy	10 years	HR=0.79 (95%CI 0.64 to 0.98)						
	Keenan 2020 - AREDS 1 cohort	to Late AMD	10 years	HR=0.94 (95%CI 0.79 to 1.12)						
	Keenan 2020 - AREDS 2 cohort	to Late AMD	10 years	HR=0.94 (95%CI 0.82 to 1.07)						
	Keenan 2020 - AREDS 1 cohort	to Neovascular AMD	10 years	HR=0.97 (95%CI 0.78 to 1.21)						
	Keenan 2020 - AREDS 2 cohort	to Neovascular AMD	10 years	HR=1.05 (95%CI 0.86 to 1.28)						
Specific food - legumes										
Legume intake, Q4 vs. Q1	Keenan 2020 - AREDS 1 cohort	to Geographic atrophy	10 years	HR=0.95 (95%CI 0.77 to 1.17)	-1	0	-1	0	0	Low
	Keenan 2020 - AREDS 2 cohort	to Geographic atrophy	10 years	HR=0.97 (95%CI 0.77 to 1.23)						
	Keenan 2020 - AREDS 1 cohort	to Late AMD	10 years	HR=0.99 (95%CI 0.84 to 1.18)						
	Keenan 2020 - AREDS 2 cohort	to Late AMD	10 years	HR=0.98 (95%CI 0.85 to 1.14)						
	Keenan 2020 - AREDS 1 cohort	to Neovascular AMD	10 years	HR=1.17 (95%CI 0.94 to 1.46)						
	Keenan 2020 - AREDS 2 cohort	to Neovascular AMD	10 years	HR=0.97 (95%CI 0.79 to 1.20)						
Specific food - nuts										
Nut intake, Q4 vs. Q1	Keenan 2020 - AREDS 1 cohort	to Geographic atrophy	10 years	HR=0.87 (95%CI 0.73 to 1.05)	-1	-1	-1	0	0	Very low
	Keenan 2020 - AREDS 2 cohort	to Geographic atrophy	10 years	HR=1.17 (95%CI 0.95 to 1.44)						
	Keenan 2020 - AREDS 1 cohort	to Late AMD	10 years	HR=0.89 (95%CI 0.76 to 1.04)						
	Keenan 2020 - AREDS 2 cohort	to Late AMD	10 years	HR=1.07 (95%CI 0.94 to 1.22)						
	Keenan 2020 - AREDS 1 cohort	to Neovascular AMD	10 years	HR=0.86 (95%CI 0.70 to 1.05)						
	Keenan 2020 - AREDS 2 cohort	to Neovascular AMD	10 years	HR=0.99 (95%CI 0.81 to 1.19)						
Specific food - red meat										

Red meat intake, Q4 vs. Q1	Keenan 2020 - AREDS 1 cohort	to Geographic atrophy	10 years	HR=1.12 (95%CI 0.90 to 1.39)	-1	0	-1	0	0	Low
	Keenan 2020 - AREDS 2 cohort	to Geographic atrophy	10 years	HR=1.16 (95%CI 0.94 to 1.44)						
	Keenan 2020 - AREDS 1 cohort	to Late AMD	10 years	HR=1.20 (95%CI 1.00 to 1.45)						
	Keenan 2020 - AREDS 2 cohort	to Late AMD	10 years	HR=1.12 (95%CI 0.98 to 1.28)						
	Keenan 2020 - AREDS 1 cohort	to Neovascular AMD	10 years	HR=1.20 (95%CI 0.96 to 1.51)						
	Keenan 2020 - AREDS 2 cohort	to Neovascular AMD	10 years	HR=1.16 (95%CI 0.95 to 1.41)						
Specific food - vegetables										
Vegetable intake, Q4 vs. Q1	Keenan 2020 - AREDS 1 cohort	to Geographic atrophy	10 years	HR=0.82 (95%CI 0.66 to 1.02)	-1	0	-1	0	0	Low
	Keenan 2020 - AREDS 2 cohort	to Geographic atrophy	10 years	HR=0.93 (95%CI 0.74 to 1.17)						
	Keenan 2020 - AREDS 1 cohort	to Late AMD	10 years	HR=0.77 (95%CI 0.65 to 0.93)						
	Keenan 2020 - AREDS 2 cohort	to Late AMD	10 years	HR=0.90 (95%CI 0.78 to 1.04)						
	Keenan 2020 - AREDS 1 cohort	to Neovascular AMD	10 years	HR=0.86 (95%CI 0.69 to 1.08)						
	Keenan 2020 - AREDS 2 cohort	to Neovascular AMD	10 years	HR=0.96 (95%CI 0.78 to 1.19)						
Vitamin D (dietary)										
Dietary Vitamin D Intake Q5 vs. Q1	Merle 2017	to Advanced AMD	9 years	HR= 0.60 (95%CI 0.43 to 0.83)	-1	0	-1	0	0	Low
		to Geographic atrophy	9 years	HR= 0.83 (95%CI 0.53 to 1.30)						
		to Neovascular AMD	9 years	HR= 0.59 (95%CI 0.39 to 0.89)						
Vitamin D and Calcium combined (dietary)										
Dietary intake of combined Vitamin D intake and Calcium high vs. Low	Merle 2017	to Advanced AMD	9 years	HR=0.81 (95%CI 0.65 to 1.02)	-1	0	-1	0	0	Low

Alle resultaten werden gevonden in een enkel cohort- of cross-sectioneel onderzoek

AMD: age-related macular degeneration; NA: not applicable; NR: not reported; T: tertile; Q: quartile or quintile

*Cross-sectional study design

6D. Effect van voedingssupplementen op de progressie van LMD

Resultatentabel voor het effect van voedingssupplementen op de progressie van LMD

Comparison	*Reference*	*Outcome Progression to*	*Follow-up*	*Number of studies*	*Result*	*GRADE RoB*	*GRADE inconsistency*	*GRADE imprecision*	*GRADE indirectness*	*GRADE other*	*GRADE overall*
Combination											
Antioxidant multivitamin and minerals* vs. placebo	Evans 2017b	Late AMD	2 to 6.3 years	3 RCTs	OR=0.72 (95% CI 0.58 to 0.90)						Moderate**
Antioxidant multivitamin and minerals* vs. placebo	Evans 2017b	Neovascular AMD	6.3 years	1 RCT	OR=0.62 (95% CI 0.47 to 0.82)						Moderate**
Antioxidant multivitamin and minerals* vs. placebo	Evans 2017b	Geographic atrophy	6.3 years	1 RCT	OR=0.75 (95% CI 0.51 to 1.10)						Moderate**
Antioxidant multivitamin and minerals* vs. placebo	Evans 2017b	Visual loss	6.3 years	1 RCT	OR=0.77 (95% CI 0.62 to 0.96)						Moderate**
Supplement (carotenoids [10 lutein, 4 mg astaxanthin, 2 mg zeaxanthin], antioxidants [90 mg vitamin C, 30 mg vitamin E, 22.5 mg zinc, 1 mg copper], omega-3 fatty acids [500 mg fish oil with 185 mg EPA and 140 mg DHA]; daily) vs. placebo	Piatti 2020	AMD	2 years	1 RCT	0/48 vs. 3/26	-1	0	-2	0	0	Very low
AREDS 2*** plus mesozeaxanthin (10 mg/day) vs. AREDS 2 only	Akuffo 2017	High risk AMD	2 years	1 RCT	RR=1.00 (95% CI 0.80 to 1.25)	-1	0	-1	0	0	Low
AREDS 2 plus mesozeaxanthin (10 mg/day) vs. AREDS 2 only	Akuffo 2017	Advanced AMD	2 years	1 RCT	0/46 vs. 1/50	-1	0	-2	0	0	Very low
Carotenoids											
Lutein (10 mg/day) and/or zeaxanthin (2 mg/day) vs. placebo	Evans 2017b	Late AMD	5 years	1 RCT	RR=0.94 (95% CI 0.87 to 1.01)						Low**
Lutein (10 mg/day) and/or zeaxanthin (2 mg/day) vs. placebo	Evans 2017b	Neovascular AMD	5 years	1 RCT	RR=0.92 (95% CI 0.84 to 1.02)						Low**

Lutein (10 mg/day) and/or zeaxanthin (2 mg/day) vs. placebo	Evans 2017b	Geographic atrophy	5 years	1 RCT	RR=0.92 (95% CI 0.80 to 1.05)						Low**
Lutein (10 mg/day) and/or zeaxanthin (2 mg/day) vs. placebo	Evans 2017b	Visual loss	5 years	1 RCT	RR=0.98 (95% CI 0.91 to 1.05)						Low**
Triple therapy**** + zeaxanthin (20 mg/day) vs. triple therapy	Waugh 2018	% of fellow eyes that developed CNV	2 years	1 Cohort	6.26% vs. 12.50%; p=0.03	-2	0	-1	0	0	Very low
Omega-3 fatty acids											
Omega-3 (650 mg EPA and 350 mg DHA once daily (and additional original AREDS formula of antioxidant vitamins and zinc) in one RCT and 840 mg DHA and 270 mg EPA daily in other RCT) vs. placebo	Lawrenson 2015	Progression of AMD	5 years	2 RCTs	HR=0.96 (95% CI: 0.84 to 1.10)						High**
Omega-3 (840 mg DHA and 270 mg EPA) vs. placebo	Lawrenson 2015	Choroidal neovascularisation	2 years	1 RCT	RR=1.06 (95% CI: 0.47 to 2.40)						Moderate**
Omega-3 (840 mg DHA and 270 mg EPA) vs. placebo	Lawrenson 2015	Choroidal neovascularisation	3 years	1 RCT	RR=1.12 (95% CI: 0.53 to 2.38)						Moderate**
Omega-3 (840 mg DHA and 270 mg EPA) vs. placebo	Lawrenson 2015	Loss of 3 or more lines of visual acuity	2 years	1 RCT	RR=1.14 (95% CI 0.53 to 2.45)						Moderate**
Omega-3 (840 mg DHA and 270 mg EPA) vs. placebo	Lawrenson 2015	Loss of 3 or more lines of visual acuity	3 years	1 RCT	RR=1.25 (95% CI 0.69 to 2.26)						Moderate**
Vitamin E											
Vitamin E (500 IU/day) vs. placebo	Evans 2017b	Late AMD	4 years	1 RCT	RR=1.36 (95% CI 0.31 to 6.05)						Very low**
Vitamin E (500 IU/day) vs. placebo	Evans 2017b	Visual loss	4 years	1 RCT	RR=1.04 (95% CI 0.74 to 1.47)						Low**
Vitamin E (500 IU/day) vs. placebo	Waugh 2018	Soft distinct or soft indistinct or pigment changes	4 years	1 RCT	RR=1.09 (95% CI 0.84 to 1.42)	-2	0	-1	0	0	Very low
Vitamin E (500 IU/day) vs. placebo	Waugh 2018	Large/soft drusen or nongeographical RPE atrophy	4 years	1 RCT	RR=1.31 (95% CI 0.83 to 2.07)	-2	0	-1	0	0	Very low
Saffron											
Saffron (20 mg/day) vs. placebo	Broadhead 2018	Neovascular AMD	3 months	1 RCT	RR=2.00 (95% CI 0.19 to 21.36)	0	0	-2	0	0	Low
Zinc											
Zinc vs. placebo (most evidence drawn from RCT evaluating daily 80 mg zinc as zinc	Evans 2017b	Late AMD	1 to 6.3 years	3 RCTs	OR=0.83 (95% CI 0.70 to 0.98)						Low**

oxide, copper 2 mg as cupric oxide; zinc sulfate 200mg/day was used in other two RCTs)											
Zinc (daily zinc 80 mg as zinc oxide, copper 2 mg as cupric oxide) vs. placebo	Evans 2017b	Neovascular AMD	6.3 years	1 RCT	OR=0.76 (95% CI 0.62 to 0.93)						Moderate**
Zinc (daily zinc 80 mg as zinc oxide, copper 2 mg as cupric oxide) vs. placebo	Evans 2017b	Geographic atrophy	6.3 years	1 RCT	OR=0.84 (95% CI 0.64 to 1.10)						Moderate**
Zinc vs. placebo Zinc daily 80 mg as zinc oxide, copper 2 mg as cupric oxide in one RCT, zinc sulfate 200mg/day in other)	Evans 2017b	Visual loss	1 to 6.3 years	2 RCTs	OR=0.87 (95% CI 0.75 to 1.00)						Moderate**

* Supplement bestond (in meerderheid van de onderzoeken) uit de AREDS-formule (combinatie van 500 mg vitamine C, 400 IE vitamine E, 15 mg bètacaroteen, zink 80 mg als zinkoxide- en 2 mg koperoxide; per dag)

***GRADE certainty of evidence* level overgenomen uit systematische review

*** AREDS 2 formule met lage dosis zink: 10 mg luteïne, 2 mg zeaxanthine, 500 mg vitamine C, 400 IE vitamine E, 25 mg zink en 2 mg koper; per dag

**** Triple therapy: i) Intravitreal injection of 1.25 mg of bevacizumab at the initial visit, ii) 1000 micrograms of intravitreal dexamethasone within 1week, iii) reduced-fluence photodynamic therapy with verteporfin (PDT), usually within 2 weeks from baseline.

6E. Effect van voedingssupplementen op de visus bij patiënten met LMD

Resultatentabel voor het effect van voedingssupplementen op de visus bij patiënten met LMD

Comparison	*Reference*	*Primary studies*	*Number of participants*	*Outcome*	*Follow-up*	*Results*
Carotenoids and other nutrients						
Lutein (10 mg daily in one RCT and 20 mg 3 months once daily followed by 10 mg 3 months once daily in other RCT) vs. placebo	Waugh 2018	1 RCT	126	Mean (SD) change in visual acuity, ETDRS letters	6 mo	2.1 (0.4) vs. 1 (NR); p=0.07
		1 RCT	84	Mean (SD) visual acuity, logMar	12 mo	0.09 (0.14) vs. 0.09 (0.13); p<0.05
				Mean change in visual acuity, logMar	12 mo	0.01 vs. 0.04; p<0.05
Lutein 10 mg vs. lutein 20 mg vs. lutein 10 mg + Zeaxanthin 10 mg vs. placebo	Waugh 2018	1 RCT	108	Mean (95% CI) best-corrected visual acuity, logMAR	48 wks	-0.04 (-0.11 to 0.03) vs. -0.02 (-0.11 to 0.06) vs. -0.04 (-0.10 to 0.01) vs. -0.00 (-0.06 to 0.05)
	Waugh 2018	1 RCT	112	Mean (SD) best-corrected visual acuity, logMAR	2 yrs	0.26 (0.15) vs. 0.28 (0.16) vs. 0.27 (0.24) vs. 0.30 (0.25)
Lutein 12g + zeaxanthin 2 mg vs. no intervention	Waugh 2018	1 before-after study	56	Mean (SD) best-corrected visual acuity, logMAR	6 mo	0.09 (0.08) vs. 0.14 (0.09); p<0.05
All-E-epilutein plus all-E-lutein vs. All-E-lutein	Forte 2017	1 RCT	40	Mean (SD) Best-corrected visual acuity, logMAR	2 mo	0.08 (0.02) vs. 0.06 (0.04); p=NR
Lutein 20 mg + zeaxanthin 2 mg vs. meso-zeaxanthin 10 mg + lutein 10 mg + zeaxanthin 2 mg vs. meso-zeaxanthin 17 mg + Lutein 3 mg + zeaxanthin 2 mg	Waugh 2018	1 RCT	67	Best-corrected visual acuity, (logMar / Snellen unclear)	3 yrs	"observed effects over time did not differ between the groups"
Zeaxanthin 8 mg vs. zeaxanthin 8 mg + lutein 9 mg vs. lutein 9 mg	Waugh 2018	1 RCT	60	Mean (SE) Colenbrander eye *near high-contrast* visual acuity, ETDRS	12 mo	96.8 (8.35) vs. 92.8 (5.9) vs. 98.9 (5.7); p=NS
Carotenoid-enriched eggs vs. placebo eggs	Waugh 2018	1 RCT	50	Mean (SD) best-corrected visual acuity, ETDRS	8 wks	107.7 (4.45) vs. 105.4 (4.78); p=0.035
Lutein based supplement ((vitamin C 150 mg, cupric oxide 400 µg, vitamin E 15 mg, lutein 12 mg, zeaxanthin 0.6 mg, zinc 20 mg, omega-3 fatty acids 1,080 mg per day) vs. no supplement	Waugh 2018	1 RCT	14	Visual acuity, logMAR	40 wks	"no significant difference between the groups"
Age-Related Eye Disease Study (AREDS) 2 formulation with a low dose [25 mg] of zinc and an addition of 10 mg mesozeaxanthin vs. no addition of 10 mg mesozeaxanthin	Akuffo 2017	1 RCT	121	Mean (SD) Best corrected visual acuity, VAR	2 yrs	100.91 (5.80) vs. 101.31 (5.20); MD: -0.40 (95% CI -2.59 to 1.79)

Supplements (lutein 12mg, zeaxanthin 0.6mg, vitamin E 15mg, vitamin C 150mg, zinc oxide 20 mg, copper 0.4mg; daily dose)vs. placebo	Waugh 2018	1 RCT	433	Mean (SD) best-corrected visual acuity, ETDRS	12 mo	79.7 (8.9) vs. 80.4 (9.8)
Lutein vs. lutein and carotenoids, antioxidants, vitamins, minerals vs. placebo*	Waugh 2018	1 RCT	90	Distance visual acuity change, logMAR, Right eye / Left eye (95% CI)	12 mo	-0.10 (-0.19 to -0.01) / -0.03 (-0.09 to 0.03) vs.-0.03 (-0.12 to 0.07) / -0.06 (-0.14 to 0.03) vs. -0.14 (-0.30 to 0.03) / 0.05 (-0.14 to 0.23); p=0.01 / p=NS A12:C12+A13
				Near visual acuity change, letters (95% CI)	12 mo	5.4 (2.5 to 8.2) vs. 3.5 (1.2 to 5.8) vs. -0.2 (-3.0 to 2.7); p=0.013
10mg lutein, 1mg zeaxanthin, 225mg fish oil [of which 100mg docosahexaenoic acid, DHA, and 30mg eicosapentaenoic acid, EPA], antioxidants [60mg vitamin C, 20mg vitamin E, 10mg zinc, 0.25mg copper] vs. 20mg lutein, 2mg zeaxanthin, 500mg fish oil [of which 200mg DHA, and 60mg EPA], antioxidants [120mg vitamin C, 40mg vitamin E, 20mg zinc, 0.5mg copper] vs. placebo	Waugh 2018	1 RCT	172	Mean (SD) best-corrected visual acuity, logMar	12 mo	0.104 (0.18) vs. 0.064 (0.16) vs. 0.127 (0.16); p=NS
				Mean (SD) best-corrected visual acuity change in reading, ETDRS letters	12 mo	1.46 (2.8) vs. 2.02 (3.1) vs. 0.08 (2.8); p=0.038 for placebo vs. dosage 1; p=0.006 for placebo vs. dosage 2; p=0.354 for dosage 1 vs. dosage 2
Lutein (12 mg), zeaxanthin (0.6 mg), docosahexaenoic acid (DHA; 280 mg)vs. placebo	Waugh 2018	1 RCT	44	Mean (SEM) visual acuity, ETDRS letters	12 mo	74.3 (9.2) vs. 75.9 (5.8); p=NS
Lutein 10 mg vs. Lutein 10 mg + Omega-3 fatty acid (DHA/EPA) 160 mg (ingredients of the supplement in both arms also included: vitamin C 10mg, vitamin E 20 mg, niacin / vitamin B3 10mg, copper 0.25 mg, zinc 10 mg, zeaxanthine 1 mg.)	Waugh 2018	1 RCT	79	Mean (SD) best-corrected visual acuity letter score, ETDRS letters	12 mo	81 (5) vs. 80 (10)
Nutritional supplementation with carotenoids (lutein, zeaxanthin, astaxanthin), oligoelements and antioxidant vitamins vs. no nutritional supplements**	Waugh 2018	1 RCT	145	Mean (SD) best-corrected visual acuity, ETDRS letter score	24 mo	81.4 (7.2) vs. 76.8 (8.9); p=0.003
				Mean (95% CI) change in best-corrected visual acuity, ETDRS letter score	24 mo	–0.02 (–1.42 to 1.36) vs. -4.18 (–7.34 to –1.01); p=0.008
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	Piatti 2020	1 RCT	80	Worsening of visual acuity (distance)	24 mo	7/48 vs. 5/26; RR=0.76 (95% CI 0.27 to 2.15)
				Stable or improved visual acuity (distance)	24 mo	41/48 vs. 21/26; RR=1.06 (95% CI 0.85 to 1.32)

omega-3 fatty acids (fish oil 500 mg, containing EPA 185 mg and DHA 140 mg) vs. placebo				Worsening of visual acuity (near)	24 mo	8/48 vs. 9/26; RR=0.48 (95% CI 0.21 to 1.10)
				Stable or improved visual acuity (near)	24 mo	40/48 vs.17/26; RR=1.27 (95% CI 0.94 to 1.73)
Antioxidant effects of vitamins						
Vitamin E (500 IU [335 mg dα tocopherol] daily) vs. placebo	Waugh 2018	1 RCT	1193	Best corrected visual acuity, logMar	up to 4 years	"no differences between groups"
				Loss of > 9 ETDRS letters (two lines) of visual acuity	up to 4 years	59/587 vs. 57/592; RR=1.04 (95% CI 0.74 to 1.47)
Fatty acids						
Phototrop (100 mg acetyl-L-carnitine, 530 mg n-3 fatty acids, 10 mg co-enzyme Q10) vs. placebo (soy oil)	Waugh 2018	1 RCT	106	Mean visual acuity, Snellen	12 mo	0.6 vs. 0.52
		1 RCT	106	% patients with deterioration in visual acuity at 12 months, Snellen	12 mo	23 vs. 45; p=0.015
		1 RCT	106	Mean (SD) change in visual acuity at 12 months, logMar	12 mo	0.009 (0.23) vs. -0.14; (0.23); p=NS
		1 RCT	106	% patients with deterioration in visual acuity at 12 months, logMAR	12 mo	25 vs. 45; p=0.027
(280mg DHA, 90mg eicosapentaenoic acid, EPA, 2mg vitamin E; 3 times a day)	Waugh 2018	1 RCT	300	Mean (SD) best-corrected visual acuity change at 3 years, logMAR	3 years	-0.155 (0.297) vs. -0.116 (0.258); p=0.311
				% with a decrease of >15 letters on ETDRS at 3 years	3 years	17.8 vs. 14.3; p=0.469
α-lipoic acid (0.2 g) vs. vitamin C (1 g)	Waugh 2018	1 RCT	100	Mean (SD) best-corrected visual acuity at 3 months, logMAR	3 months	0.66 (0.41) vs. 0.63 (0.42); p=NS
Alpha lipoic acid (ALA; 600 mg) vs. placebo	Kim 2020	1 RCT	53	Mean number of letters (SD) at 18 months	18 mo	57.7 (2.7) vs 58.8 (3.9); MD=-1.2 (95% CI -10.4 to 8.0); p=0.80.
Saffron						
Saffron (50 mg in one RCT, 20 mg in other) vs. placebo	Waugh 2018	1 RCT	54	Mean (SD) best-corrected visual acuity, logMAR	12 weeks	0.41 (0.41) vs. 0.65 (0.54); p=0.001
	Waugh 2018	1 RCT crossover	25	Mean (SD) visual acuity at 90 days, Snellen	90 days	0.80 (0.20) vs. 0.72 (0.24); p<0.01
				% visual acuity increased by one line, Snellen	90 days	80 vs. 0
	Broadhead 2018	1 RCT	100	Mean BCVA, ETDRS	3 mo	"Mean BCVA improved by 0.69 ETDRS letters whilst on saffron compared to placebo (p = 0.001). For those participants already on best-

						practice supplementation (AREDS equivalent) mean BCVA improved 0.73 letters on saffron compared to placebo after 3 months (p = 0.006).”

*Dose details lutein 10 mg; 2500 IU vitamin A, 15,000 IUnatural beta carotene, 1,500-mg vitamin C, 400 IU vitamin D3, 500 IU natural vitamin E, 50mg vitamin B1, 10mg vitamin B2, 70mg vitamin B3, 50mg vitamins B5 and B6, 500mcg vitamin B12, 800mcg folic acid, 300mcg biotin, 500mg Calcium, 300mg magnesium, 75mcg iodine, 25mg zinc, 1mg copper, 2mg manganese, 200mcg selenium, 200mcg chromium, 75mcg molybdenum, 600mcg lycopene, 60mg bilberry extract, 150mg alpha lipoic acid, 200mg N-acetyl cysteine, 100mg quercetin; 100mg rutin, 250mg citrus bioflavonoids, 50mg plant enzymes, 5mg black pepper extract, 325mg malic acid, 900mg taurine, 100mg L-glycine,10mg L-glutathione, 2mg; daily

**Dose details: vitamin C (180 mg), vitamin E (30 mg), zinc (22.5 mg), copper (1 mg), lutein (10 mg), zeaxanthin (1 mg), astaxanthin (4 mg); daily

6F. Gecombineerd effect van voeding en voedingssupplementen op de progressie van LMD

Resultatentabel voor het gecombineerde effect van voeding en voedingssupplementen op de progressie van LMD

Comparison	*Reference*	*Outcome Progression to*	*Follow-up*	*Result*	*GRADE RoB*	*GRADE inconsistency*	*GRADE imprecision*	*GRADE indirectness*	*GRADE other*	*GRADE overall*
Calcium (dietary + supplemental)										
Total calcium intake Q5 vs. Q1	Merle 2017	to Advanced AMD	9 years	HR= 1.40 (95%CI 1.02 to 1.92)	-1	0	-1	0	0	Low
		to Geographic atrophy	9 years	HR= 1.17 (95%CI 0.75 to 1.84)						
		to Neovascular AMD	9 years	HR= 1.40 (95%CI 0.92 to 2.12)						
Vitamin D (dietary + supplemental)										
Total Vitamin D Intake Q5 vs. Q1	Merle 2017	to Advanced AMD	9 years	HR= 0.89 (95%CI 0.64 to 1.24)	-1	0	-1	0	0	Low
		to Geographic atrophy	9 years	HR= 0.87 (95%CI 0.53 to 1.43)						
		to Neovascular AMD	9 years	HR= 0.97 (95%CI 0.64 to 1.48)						
Vitamin D and Calcium combined (dietary+supplemental)										
Total intake of combined Vitamin D intake and Calcium high vs. Low	Merle 2017	to Advanced AMD	9 years	HR=1.05 (95%CI 0.84 to 1.31)	-1	0	-1	0	0	Low

Bijlage 7. Overzicht medisch-wetenschappelijke tijdschriften

Medisch wetenschappelijke tijdschriften waarin de voor deze systematische review relevante primaire onderzoeken (n=36) gepubliceerd werden

Medisch wetenschappelijk tijdschrift *(aantal studies, indien meer dan 1)*	Vakgebied
Acta Opthalmologica *(3)*	Oogheelkunde
American Journal of Clinical Nutrition *(2)*	Voeding
American Journal of Ophthalmology	Oogheelkunde
Biomedicine Hub	Algemeen
British Journal of Ophthalmology *(2)*	Oogheelkunde
Clinical & Experimental Ophthalmology	Oogheelkunde
Clinical Nutrition	Voeding
European Journal of Clinical Nutrition	Voeding
European Journal of Ophthalmology	Oogheelkunde
Graefe's Archive for Clinical and Experimental Ophthalmology	Oogheelkunde
International Ophthalmology	Oogheelkunde
Investigative Ophthalmology & Visual Science *(5)*	Oogheelkunde
Irish Journal of Medical Science	Algemeen
JAMA Ophthalmology	Oogheelkunde
Journal of the Academy of Nutrition & Dietetics	Voeding
Journal of the American College of Nutrition	Voeding
Nutrients	Voeding
Nutrition	Voeding
Nutrition Journal	Voeding
Ophthalmic Epidemiology *(2)*	Oogheelkunde
Ophthalmic Research	Oogheelkunde
Ophthalmology *(2)*	Oogheelkunde
Ophthalmology Retina *(2)*	Oogheelkunde
Rawal Medical Journal	Algemeen
Scientific Reports	Algemeen