A health promotion protocol to prevent Age-Related Macular Degeneration progression: The Roles of Vitamin D and Polyphenols

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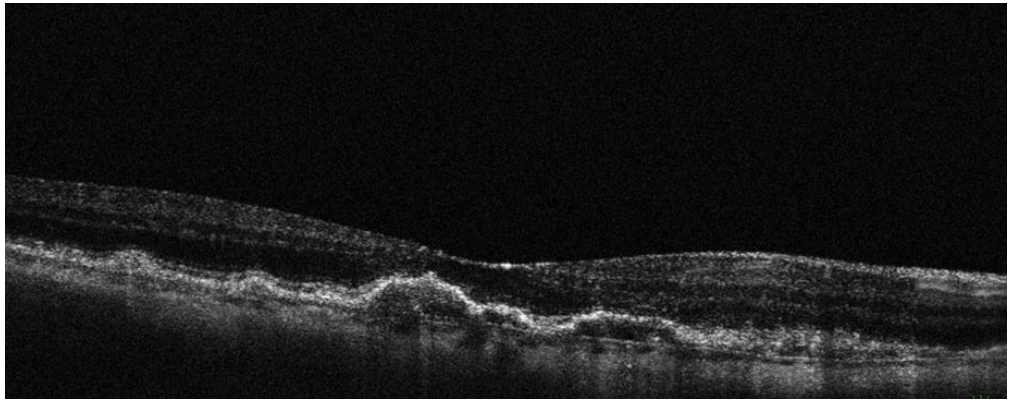
The author states that she has no conflict of interest with the subject matter addressed in the presentation or with any ophthalmologic equipment/software or dietary supplements mentioned during the presentation.

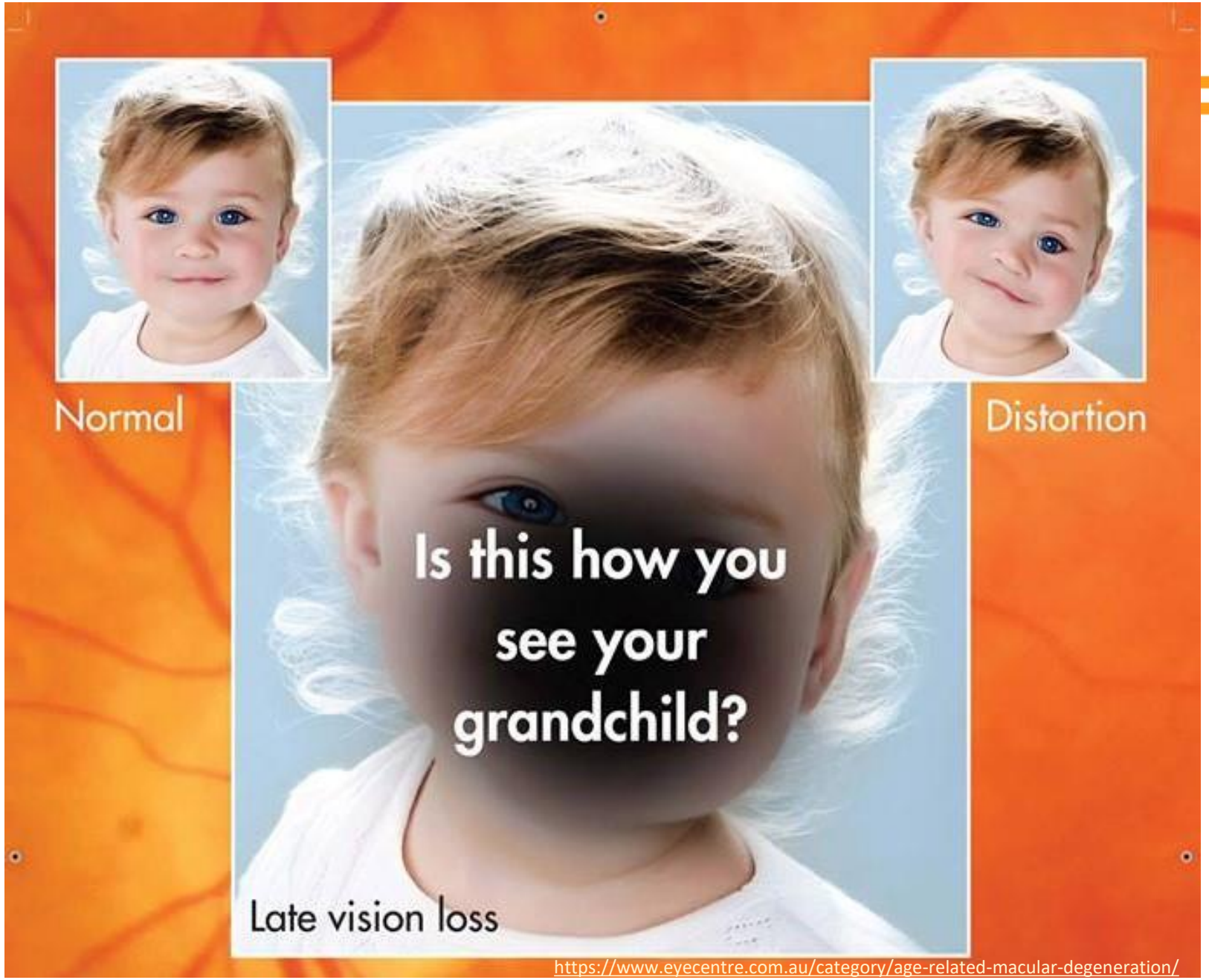
Age-related Macular Degeneration (AMD)

- Chronic progressive ocular disease that causes central vision loss;
- Responsible for 8.7% of blindness worldwide, and it is the main cause of visual impairment in developed countries in individuals aged over 60 years;
- Incidence is variable: late AMD is higher in Europe (0.14%) and in America(0.35%).



Wong, W.L.; Su, X.; Li, X.; Cheung, C.M.; Klein, R.; Cheng, C.Y.; Wong, T.Y. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: A systematic review and meta-analysis. Lancet Glob. Health 2014, 2, e106–e116.

Zhou, M.; Duan, P.C.; Liang, J.H.; Zhang, X.F.; Pan, C.W. Geographic distributions of age-related macular degeneration incidence: A systematic review and meta-analysis. Br. J. Ophthalmol. 2021, 105, 1427–1434.



https://www.eyecentre.com.au/category/age-related-macular-degeneration/

Central vision loss

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Negative impact on daily living activities

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- Reading ability
- Face recognition
- Detailed vision loss

↓

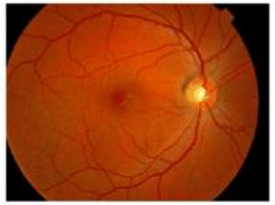
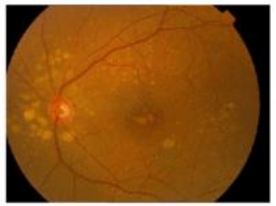
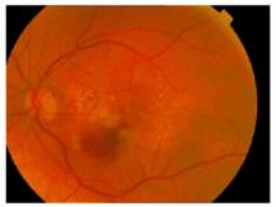
Loss of well-being and quality of life

The prevalence of AMD is increasing due to the growth of the aging population. Thus, **health promotion and preventive medicine are essential tools to reduce the risk of visual impairment**.

Martinez, A.; Pizzimenti, J.J.; Lem, D.W.; Davey, P.G. Health Promotion for AMD and the Role of Nutrition. In Recent Advances and New Perspectives in Managing Macular Degeneration; IntechOpen: London, UK, 2022.

Age-Related Eye Disease Studies (AREDS) classification

AMD can be divided into four categories based on ocular fundus examination and the existence of drusen, retinal pigment epithelium changes, atrophy, and neovascularization.

Classification	Category	Clinical signs	
No AMD	1		0–5 small drusen (<63 μm in diameter)
Early AMD	2		Multiple small drusen or a few intermediate-sized (63–124 μm in diameter) drusen, or macular pigmentary changes
Intermediate AMD	3		Extensive intermediate drusen or at least one large (≥125 μm) drusen, or GA not involving the foveal center
Advanced AMD	4		GA involving the foveal center or any evidence of choroidal neovascularization[a]

Note: [a]Subretinal hemorrhage, serous retinal or RPE detachments, lipid exudates, or fibrovascular scar.
Abbreviations: AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; GA, geographic atrophy; RPE, retinal pigment epithelium.

Al-Zamil, W. M., & Yassin, S. A. (2017). Recent developments in age-related macular degeneration: A review. In *Clinical Interventions in Aging* (Vol. 12, pp. 1313–1330). Dove Medical Press Ltd. https://doi.org/10.2147/CIA.S143508

Elsharkawy, M.; Elrazzaz, M.; Ghazal, M.; Alhalabi, M.; Soliman, A.; Mahmoud, A.; El-Daydamony, E.; Atwan, A.; Thanos, A.; Sandhu, H.S.; et al. Role of optical coherence tomography imaging in predicting progression of age-related macular disease: A survey. Diagnostics 2021, 11, 2313.

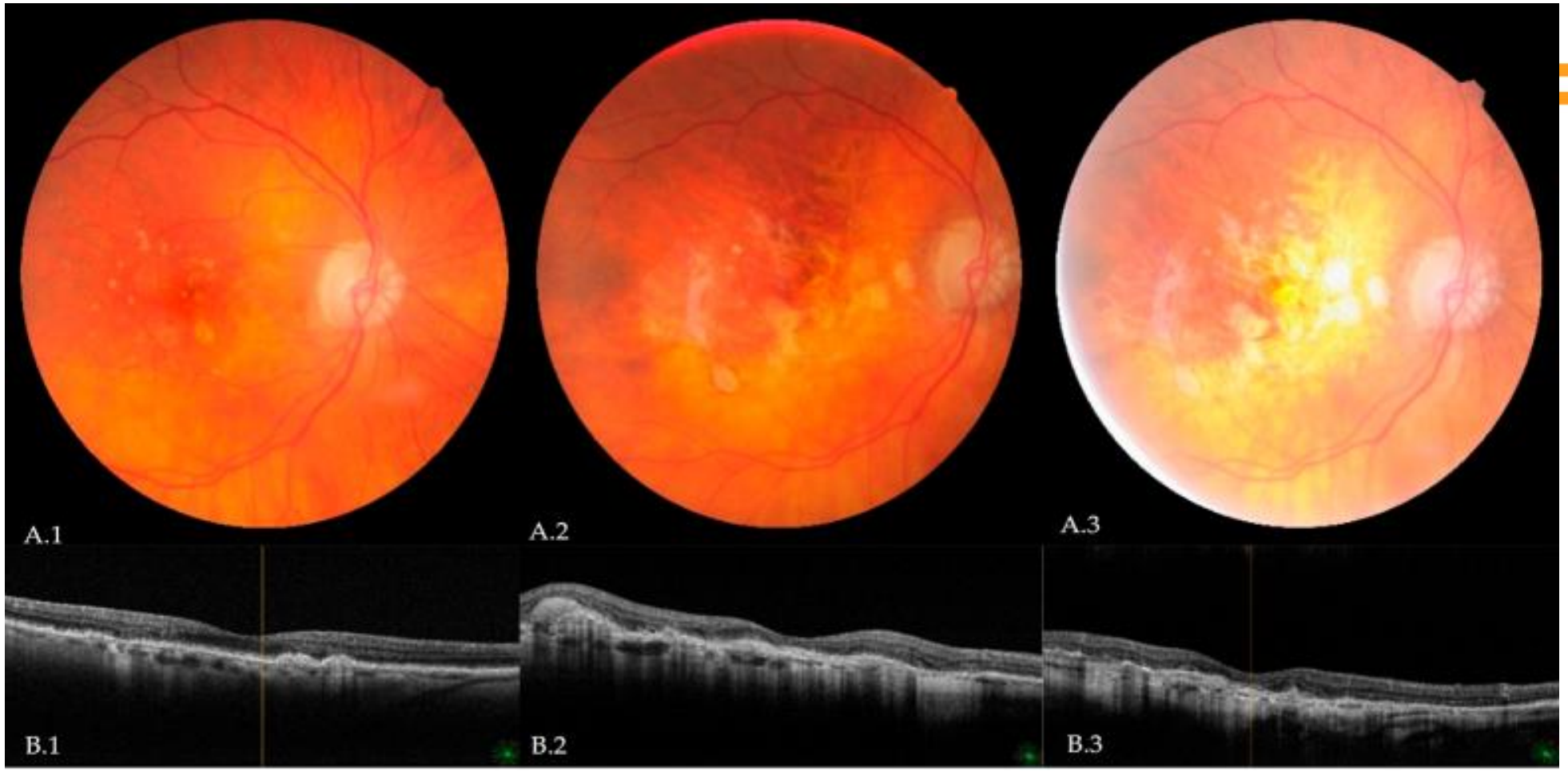


Figure 1. Ocular fundus retinography (**A.1**–**A.3**) and spectral domain—optical coherence tomography (**B.1**–**B.3**) showing the progression from intermediate to advanced AMD; from left to right: (**A.1**,**B.1**) large, confluent, soft drusen in high risk intermediate AMD, retinal pigment epithelium (RPE) migration and pericentric geographic atrophy; (**A.2**,**B.2**) occult choroidal neovascularization, pigmentary clumping, and RPE serous detachment with a tear in an advanced stage; (**A.3**,**B.3**) end-stage AMD with disciform scar (Araujo, M. e Fernandes, N. courtesy).

Fernandes, N., Araújo, M. C., & Lança, C. (2023). The Roles of Vitamin D and Polyphenols in the Management of Age-Related Macular Degeneration: A Narrative Review. *Future Pharmacology*, *3*(1), 317–328. https://doi.org/10.3390/futurepharmacol3010020

Pathogenesis of AMD

- Oxidative stress has an important role, but the exact causal mechanism is not clear yet.
- The overproduction of reactive oxygen species (ROS) and the appearance of free radical-mediated oxidative damage with consequent hypoxia, leads to a chronic inflammatory process.
- Retinal regeneration decreases with age. Additionally, ROS increases with an improper diet.

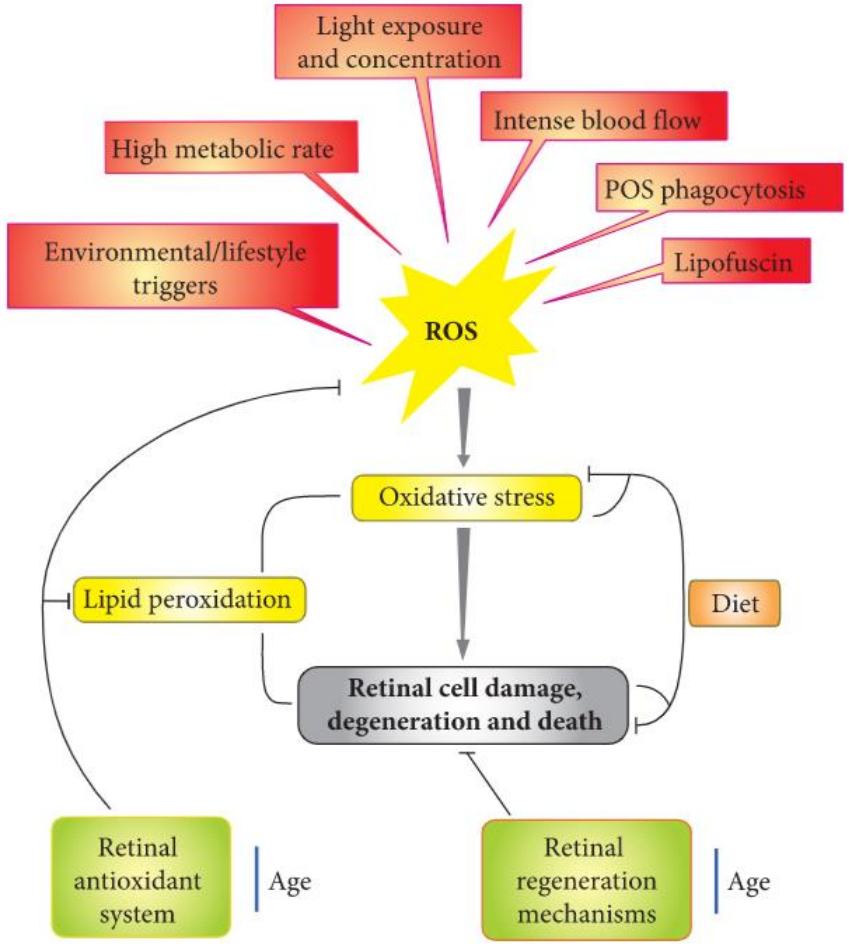


Figure 3 | Dietary Polyphenols in Age-Related Macular Degeneration: Protection against Oxidative Stress and Beyond (hindawi.com)

Parodi, M.B.; Brunoro, A.; Tomasso, L.; Scuderi, G. Benefits of micronutrient supplementation for reducing the risk of wet age-related macular disease and diabetic retinopathy: An update. Eur. J. Ophthalmol. 2020, 30, 780–794.

Hodži´c, N.; Kenjeri´c, D.; Hodži´c, Z.; Nadarevi´c-Voden˘carevi´c, A. Age-related Macular Degeneration (AMD), supplements and nutrition - What does the evidence tell us? Food Health Dis. Sci.-Prof. J. Nutr. Diet. 2021, 10, 14–23.

AMD Risk Factors

A multifactorial disease affected by:

- non-modifiable (age, family history, genetics, and ethnicity)
- **modifiable risk factors** (**health status**, smoking habits, **low antioxidant diet**, sedentary lifestyles, and exposure to ultraviolet [240–300nm] and blue light [415–455nm].

Elsharkawy, M.; Elrazzaz, M.; Ghazal, M.; Alhalabi, M.; Soliman, A.; Mahmoud, A.; El-Daydamony, E.; Atwan, A.; Thanos, A.; Sandhu, H.S.; et al. Role of optical coherence tomography imaging in predicting progression of age-related macular disease: A survey. Diagnostics 2021, 11, 2313.

The potential benefit of identifying these risk factors is the ability to prevent or delay the onset of the disease and slow the progression of AMD by acting on modifiable risk factors

Mediterranean diet
the most indicated type of diet to reduce the risk of developing advanced AMD

Antioxidants and Micronutrition
Dietary supplements aid in the prevention and to slow the progression to late stages of AMD

Heesterbeek, T. J., Lorés-Motta, L., Hoyng, C. B., Lechanteur, Y. T. E., & den Hollander, A. I. (2020). Risk factors for progression of age-related macular degeneration. In *Ophthalmic and Physiological Optics* (Vol. 40, Issue 2, pp. 140–170). Blackwell Publishing Ltd. https://doi.org/10.1111/opo.12675

AREDS formulation

	AREDS2
Vitamin C	500 mg[a]
Vitamin E	273 mg (400 IU)[a]
Beta-carotene	–
Lutein	10 mg
Zeaxanthin	2 mg
Zinc	25 mg[a]
Copper	2 mg

Benefits of micronutrient supplementation for reducing the risk of wet age-related macular disease and diabetic retinopathy (sagepub.com)

- Nutritive supplements with antioxidant properties;
- Carotenoids are the main components of the macular pigment, and their protective role relies on antioxidant properties;
- Some of them also contain vitamin D (Vit D) and polyphenols that contribute to improving retinal antioxidant defence.

Hodži´c, N.; Kenjeri´c, D.; Hodži´c, Z.; Nadarevi´c-Voden˘carevi´c, A. Age-related Macular Degeneration (AMD), supplements and nutrition - What does the evidence tell us? Food Health Dis. Sci.-Prof. J. Nutr. Diet. 2021, 10, 14–23.

Mediterranean diet

- A systematic review conducted by Pameijer et al. (2022) found moderate certainty of evidence regarding a high intake of fruit, vegetables, grains, nuts, fish, red wine, and olive oil and limited consumption of red meat, it may be a recommended approach to AMD management, associated with a lower risk of AMD progression;
- The use of antioxidant supplements with this kind of diet was also associated with a reduced risk of progression.

Pameijer, E.M.; Heus, P.; Damen, J.A.; Spijker, R.; Hooft, L.; Ringens, P.J.; Imhof, S.M.; van Leeuwen, R. What did we learn in 35 years of research on nutrition and supplements for age-related macular degeneration: A systematic review. Acta Ophthalmol. 2022, 100, e1541–e1552.

Vit D and Polyphenols – What are the benefits?

- Anti-oxidative and anti-inflammatory properties that impact AMD pathogenesis - Vit D3 (cholecalciferol), as well as some polyphenols, such as flavonoids, resveratrol, and curcumin, are included in some nutritional supplements together with the AREDS 2 formulation;

- Investigate the effects of Vit D and polyphenols on AMD progression through a narrative review based on references of evidence-based reviews/meta-analyses and practice guidelines, with selected RCTs and observational studies published between 2017 and 2022.

Nutritional management of AMD Progression

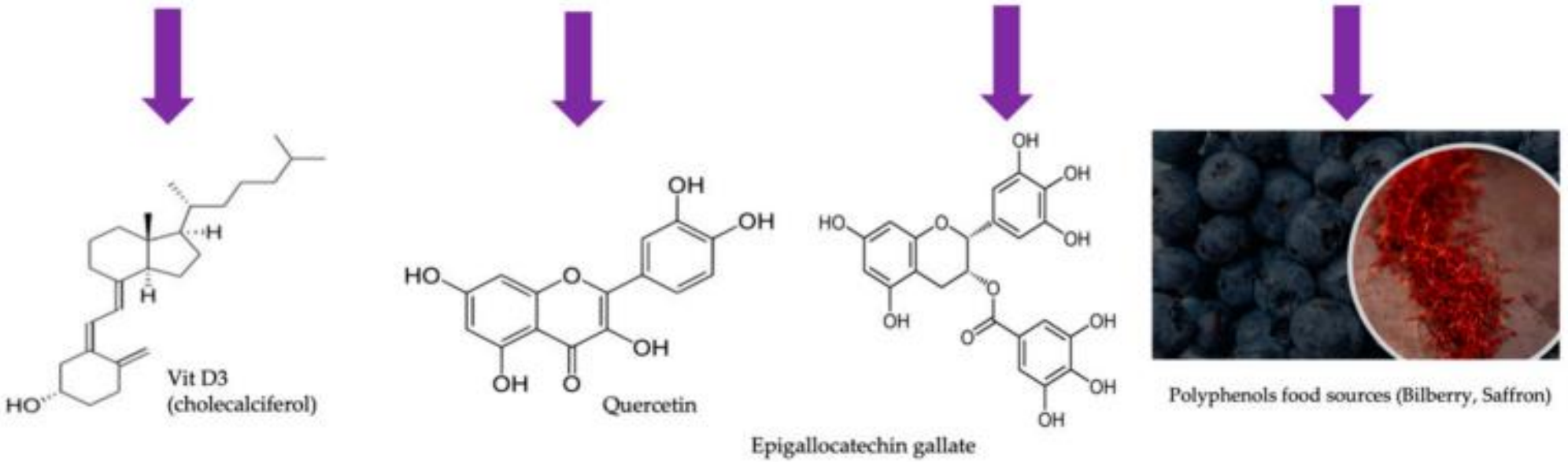


Figure 2. Vitamin D and polyphenols: molecular structure and food sources.

Fernandes, N., Araújo, M. C., & Lança, C. (2023). The Roles of Vitamin D and Polyphenols in the Management of Age-Related Macular Degeneration: A Narrative Review. *Future Pharmacology*, *3*(1), 317–328. https://doi.org/10.3390/futurepharmacol3010020

Vitamin D and AMD

- Vit D deficiency may be a risk factor for AMD, and its receptors have been shown to be present in retinal vascular and choroidal endothelial cells;
- Lower Vit D serum levels (25(OH) D3 deficiency) may contribute to the incidence of choroidal neovascularization-related diseases, increasing the risk of neovascular AMD.

Öncül, H.; Alakus, M.F.; Ça ˘glayan, M.; Öncül, F.Y.; Dag, U.; Arac, E. Changes in choroidal thickness after vitamin D supplementation in patients with vitamin D deficiency. Can. J. Ophthalmol. 2020, 55, 486–491.
Kabata¸s, N.; Do ˘gan, A. ¸S.; Yılmaz, M.; Kabata¸s, E.U.; Biçer, T.; Çalı¸skan, S.; Çelikay, O.; Uçar, F.; Gürdal, C. Association Between Age-Related Macular Degeneration And 25(Oh) Vitamin D Levels In The Turkish Population. Arq. Bras. Oftalmol. 2022, 85, 7–12

Table 1. Association between vitamin D levels and AMD.

Study Design, Country	Vitamin D (Mean Serum 25(OH)D Levels ng/mL)	N (Group I e II)	Age (Mean ± SD)	Association between Vit D and Retinal-Choroidal Structure/AMD	Author(s) Study, Year
Case-Control	Group I: deficiency = 7.61	82	37.29 ± 12.76	Deficient Vit D levels affected macular perfusion with lower retinal vascular density values. Central macular volume and RNFL were not significantly different.	Icel, et al., 2022 [20]
	Group II: control = 25.29	50	39.1 ± 11.59		
Case-Control	AMD group = 14.4 ± 9.6; (wet-type AMD = 11.4 ± 5.1 dry-type AMD = 15.3 ± 10.9)	114 (64/50)	71.5 ± 7.9	Significant correlation between vit D deficiency and AMD progression.	Kabatas et al., 2022 [10]
	Control group = 29.4 ± 14.6	102 (57/45)	69.4 ± 10.1		
Cross-sectional	AMD group = 15 ± 10	93 (57/36)	78.96 ± 8.5	Deficient Vit D levels (<30 ng/mL) were found in 89.2% of the AMD group and 50.5% had higher prevalence of Vit D deficiency comparatively with controls 31.2%.	Serena, et al., 2022 [21]
	early AMD = 12.5 ± 7.3	(10)			
	intermediate AMD = 15 ± 11	(12)			
	advanced aAMD = 15 ± 8	(19)			
	advanced nAMD = 17 ± 11.5	(52)			
	Control group = 21 ± 14	93 (54/39)	78.8 ± 8.4		

OCT: optical coherence tomography; Vit D: vitamin D; 25(OH)D: 25-hydroxyvitamin D; CT: choroidal thickness; AMD—age macular degeneration; RNFL—retinal nerve fiber layer thickness; SD: standard deviation.

Vitamin D or 25-hydroxyvitamin D [25(OH)D]

- An inverse relationship between Vit D plasma levels and early AMD or late atrophic and/or neovascular AMD have been showed by observational studies, but the results of the systematic review and meta-analysis conducted by Ferreira et al. do not confirm the possible inverse association between Vit D levels and AMD. However, there was a trend for advanced AMD in people with serum Vit D < 50 nmol/L.

Layana, A.G.; Minnella, A.M.; Garhöfer, G.; Aslam, T.; Holz, F.G.; Leys, A.; Silva, R.; Delcourt, C.; Souied, E.; Seddon, J.M. Vitamin D and Age-Related Macular Degeneration. Nutrients 2017, 9, 1120.

Ferreira, A.; Silva, N.; Furtado, M.J.; Carneiro, Â.; Lume, M.; Andrade, J.P. Serum vitamin D and age-related macular degeneration: Systematic review and meta-analysis. Surv. Ophthalmol. 2021, 66, 183–197.

Flavonoids

- Decreasing oxidative stress and inflammatory processes, and by producing angiogenesis inhibitors;
- The median dietary intake of total flavonoids 875 mg/d was associated with reduced prevalence of different AMD stages, mainly quercetin (a flavanol) and hesperidin (flavanone).

Sun, M.; Yu, T.; Zhao, J.; Zhu, X.; Xin, W.; Zhang, F.; Zhang, L. Role of flavonoids in age-related macular degeneration. Biomed. Pharmacother. 2023, 159, 114259

Gopinath, B.; Liew, G.; Kifley, A.; Flood, V.M.; Joachim, N.; Lewis, J.R.; Hodgson, J.M.; Mitchell, P. Dietary flavonoids and the prevalence and 15-y incidence of age-related macular degeneration. Am. J. Clin. Nutr. 2018, 108, 381–387.

Saffron (*Crocus sativus*)

- Phytochemical with 150 compounds: carotenoids, crocin, and crocetin are the most organically active elements;
- Open-label longitudinal studies and double-blind RCTs demonstrated that saffron reduces progression of dry, mild-to-moderate, and advanced stages of AMD.

Wong, K.-H.; Nam, H.-Y.; Lew, S.-Y.; Naidu, M.; David, P.; Kamalden, T.A.; Hadie, S.N.H.; Lim, L.-W. Discovering the Potential of Natural Antioxidants in Age-Related Macular Degeneration: A Review. Pharmaceuticals 2022, 15, 101.

Resveratrol

- Promising agent that can improve the anti-VEGF therapy in neovascular AMD and a reduction in anti-VEGF injections' side effects;
- Decreases inflammatory processes and increases glutathione production;
- Future research to investigate the synergetic effects of resveratrol and anti-VEGF in neovascular AMD may be relevant to reducing the complications of this treatment.

Pawlowska, E.; Szczepanska, J.; Koskela, A.; Kaarniranta, K.; Blasiak, J. Dietary polyphenols in age-related macular degeneration: Protection against oxidative stress and beyond. Oxidative Med. Cell. Longev. 2019, 2019, 9682318.

Ikonne, E.U.; Ikpeazu, V.O.; Ugbogu, E.A. The potential health benefits of dietary natural plant products in age related eye diseases. Heliyon 2020, 6, e04408

Wong, K.-H.; Nam, H.-Y.; Lew, S.-Y.; Naidu, M.; David, P.; Kamalden, T.A.; Hadie, S.N.H.; Lim, L.-W. Discovering the Potential of Natural Antioxidants in Age-Related Macular Degeneration: A Review. Pharmaceuticals 2022, 15, 101.

Curcumin (*Curcuma longa*)

- Curcumin is a polyphenolic compound with an antioxidant property which could be combined with resveratrol;
- In a meta-analysis conducted by Csader et al. (2022), demonstrated that curcumin was associated an improvements in function, with no significant changes in macular structure, and a reduction in the number of anti-VEGF injections.

Csader, S.; Korhonen, S.; Kaarniranta, K.; Schwab, U. The Effect of Dietary Supplementations on Delaying the Progression of Age-Related Macular Degeneration: A Systematic Review and Meta-Analysis. Nutrients 2022, 14, 4273.

Supplementation and dietary intake´s effect on AMD

- Simultaneous administration of different compounds influences intestinal absorption and may influence AMD prevention and progression;
- It is also relevant to investigate if Vit D, dietary polyphenols compounds, and other micronutrients and vitamins have a synergistic effect that contributes to improvements in AMD management;
- A structure and function evaluation seems to be an interesting tool for assessing changes in the retina and choroid after supplementation.

Table 2. Vitamin D and polyphenol supplementation and dietary intake's protective effects against AMD.

Compounds	Study Design, Country	Doses or Natural Source/Follow-Up	Age in Years (Mean ± SD)	Summary of Findings	AMD Type	Author(s), Year
Vit D3 (cholecalciferol)	Prospective Switzerland	300.000 IU/month Follow-up: 3 months	28.4 ± 6.74—group I (Vit D deficiency) 30.2 ± 6.25—group II (Normal Vit D levels)	CT values measured in OCT increased significantly after vit D supplementation.	Absence of AMD	Öncül et al., 2020 [9]
Macumax® (bilberry, saffron extract)	RCT India	Bilberry extract: 40 mg/day Follow-up: 3 months	58.97 ± 7.5	Significant improvement in functional vision in early stages of dry AMD with no structural AMD progression. Significant decrease of vision distortion and increased distance vision and dark adaptation. No structural changes were observed in OCT.	Dry Early-stage	Majeed et al., 2021 [23]
Dietary Flavonoids Intake	Cohort Study Australia	Intake of total flavonoids (median) 287.59 mg/day: Follow-up: 12 months	78.7 ± 9.1	Higher intake of flavanols (quercetin) and flavan-3-ols (epigallocatechin-3-gallate and epigallocatechin) contributed to better treatment outcomes with anti-VEGF therapy in neovascular AMD. Significantly better BCVA associated with lower IRF in OCT (flavanols and flavan-3-ols).	Neovascular (anti-VEGF therapy)	Detaram et al., 2021 [25]

RCT: randomized clinical trial; CT: choroidal thickness; OCT: optical coherence tomography; Vit D: vitamin D; AMD—age macular degeneration; IU—international unit; BCVA—better corrected visual acuity; IRF—intra-retinal fluid.

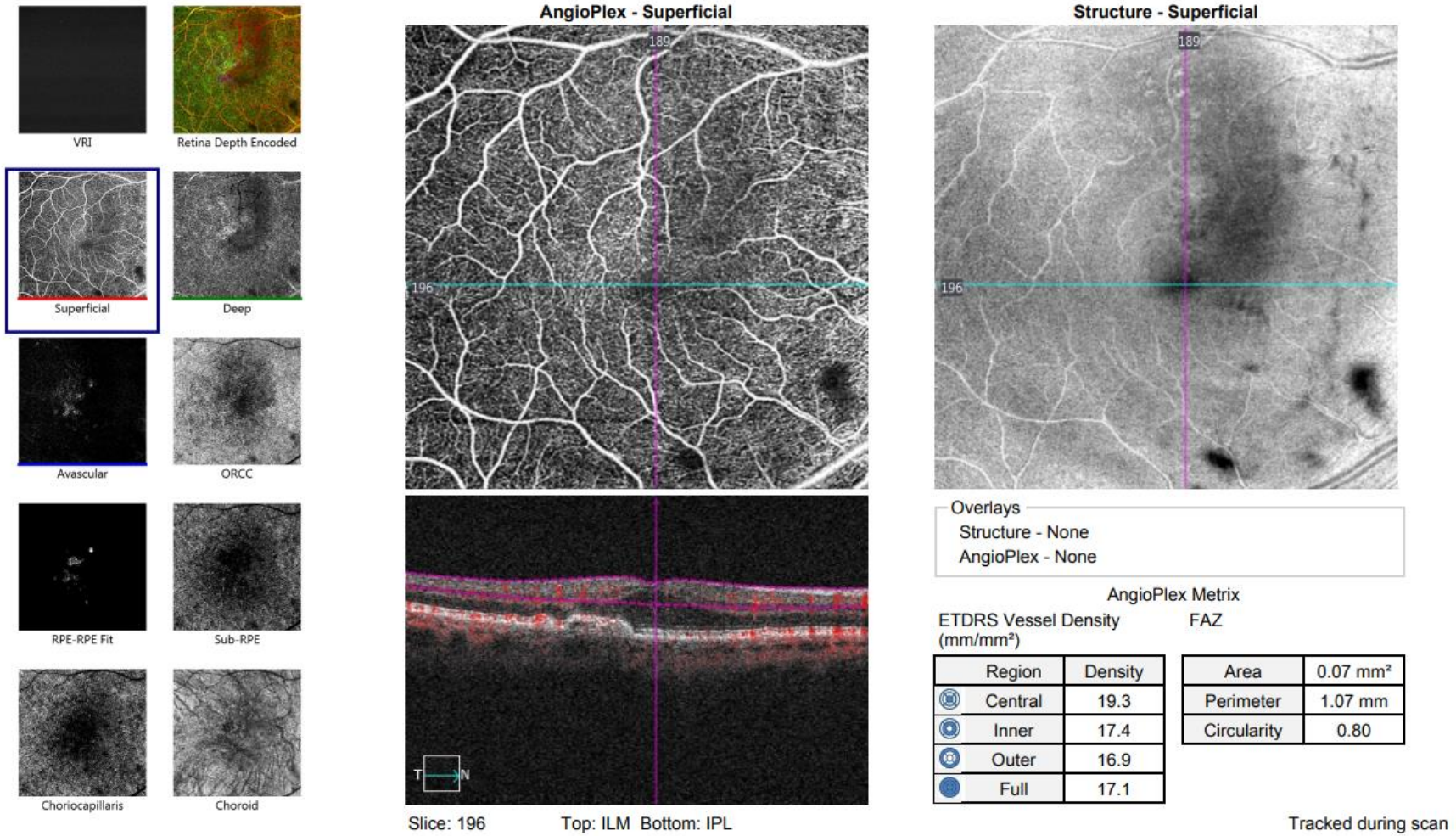


Figure 3: OCT-A could play an important role in different stages of AMD, allowing the evaluation of blood flow perfusion through vessel density. Exploring the choriocapillaris map could be important in follow-up after vitamin D supplementation. (Carvalho, T. courtesy)

The Gut-Retina axis

- With aging, the composition of the microbiome changes, and several degenerative diseases are associated with microbiome aging;
- There is a potential interaction between the immune system modulation, inflammation, and diet on the gut microbiota. Thus, gut microbes and their metabolites may play a key role in AMD.

Singh, R.K.; Chang, H.W.; Yan, D.; Lee, K.M.; Ucmak, D.; Wong, K.; Abrouk, M.; Farahnik, B.; Nakamura, M.; Zhu, T.H.; et al. Influence of diet on the gut microbiome and implications for human health. J. Transl. Med. 2017, 15, 73.

Vision Impairment (VI) in elderly and General Health

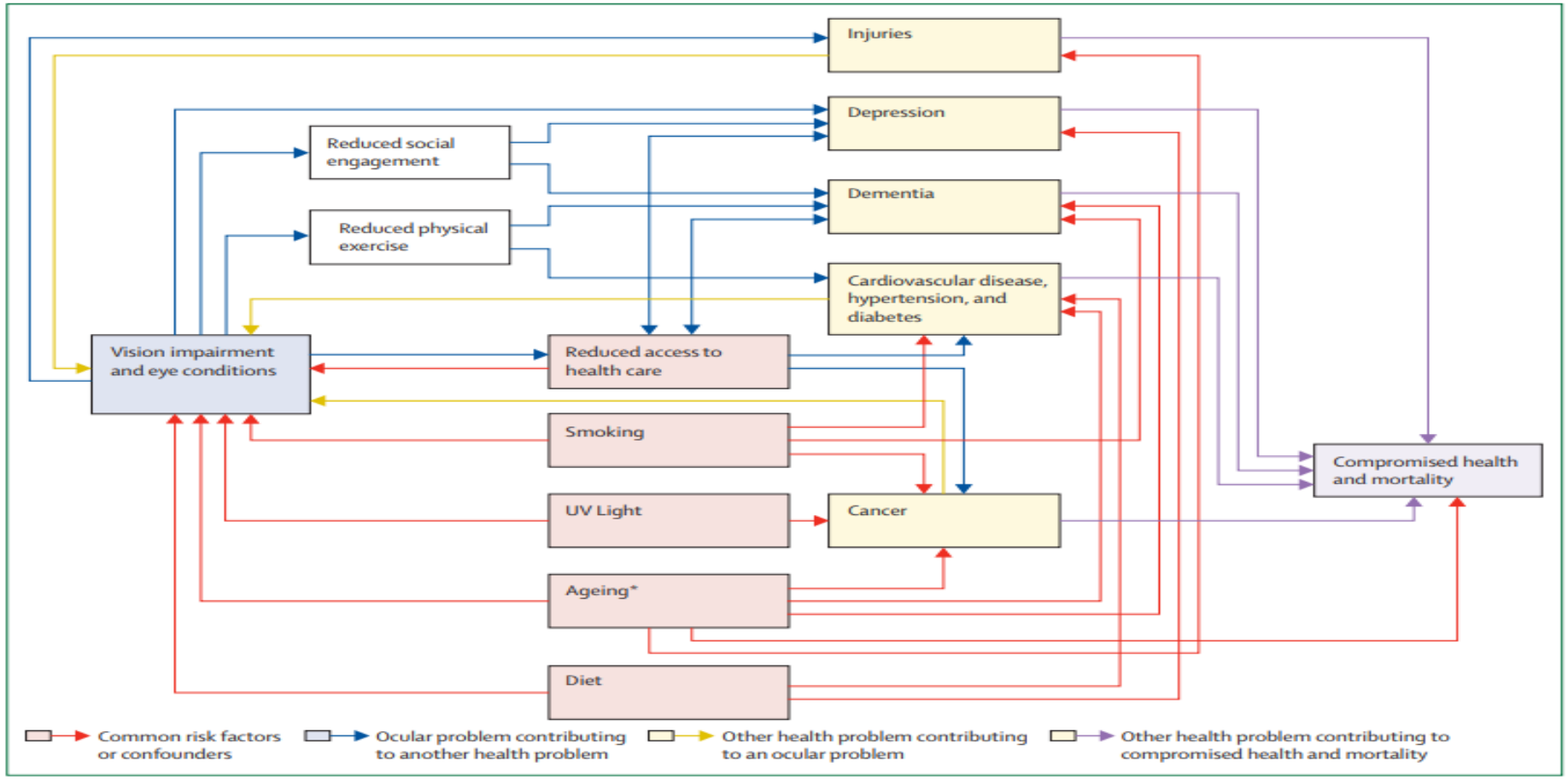


Figure 5: **Relationships between vision impairment and general health**
These associations are derived from multiple literature reviews done by this Commission. *Hypothetical common degenerative pathways.

Burton, M. J., Ramke, J., Marques, A. P., Bourne, R. R. A., Congdon, N., Jones, I., Ah Tong, B. A. M., Arunga, S., Bachani, D., Bascaran, C., Bastawrous, A., Blanchet, K., Braithwaite, T., Buchan, J. C., Cairns, J., Cama, A., Chagunda, M., Chuluunkhuu, C., Cooper, A., … Faal, H. B. (2021). The Lancet Global Health Commission on Global Eye Health: vision beyond 2020. In *The Lancet Global Health* (Vol. 9, Issue 4, pp. e489–e551). Elsevier Ltd. https://doi.org/10.1016/S2214-109X(20)30488-5

Health Promotion and Integrative Protocol to VI and Prevent AMD Progression

- ***Ophthalmological treatment of eye health conditions;***
- ***Education about healthy eating behaviours to promote macular health;***
- ***AREDS 2 formulation + Vitamin D + Polyphenols even in advanced AMD stages;***
- ***Increase antioxidants and omegas intakes to improve functional and cognitive vision;***
- ***Monitoring Ocular and General health status by a specialist;***
- ***Low Vision Rehabilitation to improve quality of life in daily living activities namely, to improve reading ability.***

Take-home messages

- Studies with longer follow-ups are necessary to confirm these results, along with the role of each compound in improving macular function;
- Vit D3 and polyphenolic supplementation of AMD patients may contribute to better functional outcomes. Efficient dosage, safety, and pharmacodynamics for treatment should also be further evaluated;
- There is some evidence that some polyphenolic groups affect vascular health through improved endothelial function and vascular function, thereby possibly improving the management of AMD;

Take-home messages

- Mediterranean diet may be a recommended approach to AMD management, and it is associated with a lower risk of AMD progression;
- Furthermore, the use of antioxidant supplements with this kind of diet was also associated with a reduced risk of progression;
- Potential benefit in intervention on unhealthy behaviors to reduce the prevalence of visual impairment and improve eye health.

future pharmacology

MDPI

Review

The Roles of Vitamin D and Polyphenols in the Management of Age-Related Macular Degeneration: A Narrative Review

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Abstract: Age-related macular degeneration (AMD) is a chronic progressive ocular disease and the main cause of severe visual impairment in the elderly. Vitamin D deficiency may be a risk factor for AMD. Additionally, current evidence suggests dietary advice of increasing consumption of polyphenols, which may have antioxidant and anti-inflammatory properties. The aim of this review was to describe the roles of vitamin D levels and polyphenols in the management of AMD. The results of this review showed mixed evidence regarding the protective effect of vitamin D against AMD. Polyphenols (flavonoids group, curcumin and resveratrol) seem to play an important role as angiogenesis inhibitors, but their effect on AMD is still unclear. Vitamin D and polyphenols may both play an important role as nutritional modifiable protective factors that reduce the risk of AMD progression. However, more research is necessary to better understand the roles of vitamin D and polyphenols in different stages of the disease.

Keywords: age macular degeneration; vitamin D; 25-hydroxyvitamin D serum; polyphenols; nutrition; eye healthcare; retina; choroid

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REABILITAÇÃO VISUAL
E SAÚDE DA VISÃO

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THANK YOU