

# Prevention of age-related macular degeneration

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**Abstract** Age-related macular degeneration (AMD) is one of the leading causes of blindness in the developed world. Although effective treatment modalities such as anti-VEGF treatment have been developed for neovascular AMD, there is still no effective treatment for geographical atrophy, and therefore the most cost-effective management of AMD is to start with prevention. This review looks at current evidence on preventive measures targeted at AMD. Modalities reviewed include (1) nutritional supplements such as the Age-Related Eye Disease Study (AREDS) formula, lutein and zeaxanthin, omega-3 fatty acid, and berry extracts, (2) lifestyle modifications, including smoking and body-mass-index, and (3) filtering sunlight, i.e. sunglasses and blue-blocking intraocular lenses. In summary, the only proven effective preventive measures are stopping smoking and the AREDS formula.

**Keywords** AREDS · Age-related macular degeneration · AMD · Vitamin E · Beta-carotene · Neovascular AMD · Yellow IOL · Sunlight filtration · Prevention

## Introduction

Age-related macular degeneration (AMD) is one of the leading causes of blindness in developed countries [1–3]; currently 11.5% of the population in the United States is affected [1]. The exact pathogenesis of AMD remains unknown [4], but one of the main components is thought to be oxidative stress [5, 6]: the retina, because of its high oxygen concentration and intense light exposure, is susceptible to damage by oxidative stress [6]. Early stages of AMD can be asymptomatic but can cause severe impairment of central vision in late stages. Details of the most up-to-date classification of AMD are given in Table 1. There have been some promising new treatments in recent years since the emergence of anti-vascular endothelial growth factor (anti-VEGF) agents, and numerous pivotal studies have proven their effectiveness in controlling neovascular AMD [7]. However, at the moment, costs for these drugs are high and patients may have to undergo multiple injections.

Taking in consideration the ever-growing population, the incidence of AMD will only increase. In the United States alone, it is thought that the incidence may double in the next 20 years [1], and so will the resources and effort spent in the area. Even if anti-VEGF agents are made cheaper and more available, more and more patients will have to rely on them, and as a result the burden on the healthcare system will be increased [8]. It may be more economical to tackle AMD with prevention. Studies done on AMD prevention usually

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**Table 1** Categorization of age-related macular degeneration (AMD) according to the Age-Related Eye Disease Study (AREDS) guidelines

	Brief description	Clinical features	Visual acuity
Category 1	Free of AMD in both eyes	<5 small drusen in one or both eyes	20/32 or better in both eyes
Category 2	Mild to borderline AMD in one or both eyes	Multiple small or intermediate drusen in one or both eyes Pigment abnormalities in one or both eyes	20/32 or better in both eyes
Category 3	Absence of advanced AMD in both eyes	Intermediate or large drusen Geographical atrophy Features not involving central macular	20/32 or better in better eye
Category 4	Advanced AMD in one eye	Advanced AMD or geographical atrophy in worse eye No such features in better eye	20/32 or better in better eye

*Key:* Small drusen, <63  $\mu\text{m}$  in diameter (disc diameter around 1500  $\mu\text{m}$ ); intermediate drusen, 63–124  $\mu\text{m}$  in diameter; large drusen, >125  $\mu\text{m}$  in diameter; pigment abnormalities refer to either hyperpigmentation or depigmentation

fall into one of three areas: (1) nutritional supplements, (2) lifestyle modifications, (3) filtering sunlight. It is vital that ophthalmologists and general practitioners be aware of the latest and updated evidence. In this article we hope to provide an overview of current opinions on the prevention of AMD.

## Methods

An evidence-based approach was adopted in the review process. The literature up to December 2009 was searched for keywords ‘age-related macular degeneration’, ‘macular’, ‘AMD’, ‘antioxidants’, ‘mineral supplements’, ‘dietary supplements’, and ‘prevention’. We used the databases Medline, The Cochrane Library, Embase.com, Web of Knowledge, and Google Scholar. The search was limited to studies in human subjects, in English. Strength of evidence and rating of recommendation were assessed according to the method described previously [9], and are summarized in Table 3.

## Evidence synthesis

### Nutritional supplements

Most studies focused on four types of supplements:

1. AREDS or AREDS-like formulas,
2. Lutein and zeaxanthin,

3. Omega-3 fatty acids,
4. Berry extracts.

### *AREDS or AREDS-like formulas*

The Age-Related Eye Disease Study (AREDS) was designed to investigate whether active treatment with supplements such as vitamins and minerals can reduce the risk of advanced AMD. The main components of the formula were vitamin A (as beta-carotene), vitamin C, vitamin E, and zinc. These ingredients were thought to exert a protective effect on retinal cells by counteracting oxidative stresses [10–15]. The formula was a type of active treatment and therefore the dosages of ingredients were much higher than the Dietary Reference Intake (DRI), which is a system of nutrition recommendations from the Institute of Medicine of the USA National Academy [16]. For instance, the amount of vitamin C included in the AREDS formula was 500 mg per day, whereas the DRI for an adult is only 90 mg per day (a medium-sized orange contains around 70 mg of vitamin C, and therefore one has to eat almost seven or eight oranges to obtain 500 mg of vitamin C). A detailed comparison of nutrient contents between the AREDS formula and common fruits is given in Table 2.

Subjects were categorized initially according to the suggested grading system [17], and then were asked to take either the supplements or placebo on twice a day. The progress of 3,640 subjects was

**Table 2** Dosages of the Age-Related Eye Disease Study (AREDS) type formulas compared with common fruit items

Nutrient	AREDS [17]	DRI <sup>a</sup>	Orange <sup>b</sup>	Apple <sup>b</sup>	Blueberry <sup>b</sup>	Banana <sup>b</sup>	Mango <sup>b</sup>	Strawberry <sup>b</sup>	Watermelon <sup>b</sup>
Vitamin A <sup>c</sup> (IU)	5000	3000	225	54	22	64	765	18	569
Vitamin C (mg)	500	90	53.2	4.6	0.7	8.7	27.7	13.7	8.1
Vitamin E (mg)	400	15	0.1	0.18	0.23	0.10	1.12	0.1	0.05
Zinc (mg)	80	11	0.07	0.04	0.1	0.15	0.04	0.06	0.1
Copper (mg)	2	0.9	0.045	0.027	0.12	0.078	0.11	0.03	0.042
Lutein/zeaxanthin (µg)	None	No data	129	29	33	22	0	9	8

<sup>a</sup> Dietary Reference Intakes from the Institute of Medicine [16]

<sup>b</sup> Nutrient contents of common fruit items are measured per 100 g

<sup>c</sup> Vitamin A as beta-carotene

monitored for an average of 6.3 years. In essence, the results showed a 25% reduction in risk of progression to advanced AMD if recommended doses of antioxidants and zinc were taken daily. However, this was seen in category 3 or 4 patients only, probably because of the higher natural risk of progression to advanced AMD. Results were not significant for category 2 or 1, i.e. those with small drusen only (the 5-year risk of progression to advanced AMD in category 2 was only 1.3% and in category 1 <1%).

However, in the USA 80% of people over age 70 fall into category 1 or 2, and hence most people would probably not benefit from the AREDS formula. Therefore it was only recommended to high-risk patients (i.e. category 3 or 4). For low risk patients (i.e. category 1 or 2), recommendation was deferred until indicated [17].

Potential risks of the AREDS formula include kidney stones from vitamin C; fatigue, muscle weakness, decreased thyroid function, and increased hemorrhagic stroke risk from vitamin E; increased lung cancer risk in smokers and yellow discoloration of skin from beta-carotene; and anemia, decreased serum high-density lipoprotein cholesterol, and stomach upset from zinc [18]. Despite numerous potential side effects, the only documented statistically significant ones were increased genitourinary symptoms, increased self-reported anemia, and yellow discoloration of skin. Although there was an increase in self-reported anemia, no significant change in blood hematocrit level was found. Smokers were discouraged from taking pills containing beta-carotene, so an increased risk of lung cancer with beta-carotene was not addressed in the AREDS, but it has already been

established in two other trials [19, 20]. Nevertheless, the few side effects were minor and the formula was otherwise considered safe. In any case, patients should always be informed of the risks and when significant contraindications exist (smoking, vascular diseases, hyperlipidemia, risk of hemorrhage, etc.), they should be discouraged from taking the formula.

Instead of an active supplementation formula, some have proposed an enriched diet alone. The Rotterdam Study investigated the effect of a vitamin- and mineral-rich diet alone in the prevention of AMD [21]. In comparison to the AREDS, no active interventions were given. Baseline dietary content was assessed, and followed up for possible development of AMD. The study found that an above-median intake of vitamin C and E, beta-carotene, and zinc was associated with a striking 35% decrease in incident AMD [21]. They concluded that such a diet should be recommended to those with early signs of AMD or those with a strong family history.

A recent meta-analysis carried out by the Cochrane Collaboration reviewed the evidence and concluded that both these recommendations were sound but patients should nevertheless be warned of potential harmful effects, particularly those who smoke or who have vascular diseases [22]. Since patients take these pills on a prophylactic basis, it is undesirable to have complications arising.

#### *Lutein and zeaxanthin*

Also of great interest is the antioxidant balance among macular pigments, mainly lutein and its stereo-isomer, zeaxanthin. These carotenoids exist

in high concentrations in the macula, hence its yellowish color. In vitro studies have shown that both protect the retina from oxidative stress [23]. These carotenoids act in biological systems as (1) an important structural molecule in cell membranes, (2) a short-wavelength light filter, (3) a keeper of the redox balance, and (4) a modulator in signal transduction pathways [24, 25]. However, the human body is not capable of lutein synthesis; it can only be obtained from diet. Hence, supplementing the body with lutein may offer protection against AMD. However, these were not included in the AREDS because neither of the two substances was ready for manufacturing as a research formula [18].

The Carotenoids in Age-Related Eye Disease Study (CAREDS) followed 1,787 American women aged 50–79 for 4–7 years [26]. Subjects were divided according to their average intake of dietary lutein and zeaxanthin, but here were no statistical differences between the amount of lutein and zeaxanthin they took and the risk of development of AMD.

Conversely, two other studies were in favor of the hypothesis. The cohort Pathologies Oculaires Liées à l'Age (POLA) measured actual plasma carotenoids levels from 899 subjects and correlated them with risk of AMD. A striking reduction in risk was found in those with a high plasma level: the odds ratios were 0.31 and 0.07 for lutein and zeaxanthin, respectively [27]. This was in agreement with another similar study in the UK, where a high plasma zeaxanthin was associated with a 50% reduction in risk of AMD [28].

The US Food and Drug Administration (FDA) denied a link between the carotenoids and AMD protection after reviewing some interventional and observational randomized studies [29]. In view of the contradicting results, the National Eye Institute (Bethesda, Maryland, USA) launched the Age-Related Eye Disease Study 2 (AREDS2) in autumn of 2006, hoping to answer this question. As well as carotenoids, it also studies omega-3 [30, 31]. It also modifies the original formula by eliminating beta-carotene, which increases the risk of lung cancer in smokers. The proposed study end time is late 2012. In the meantime, no evidence-based conclusion can be reached.

Although not yet proven for benefits, many manufacturers have been including lutein and zeaxanthin in their supplements, many of which are

available over the counter. In 2006, the Council for Responsible Nutrition (CRN) in Washington DC reviewed the risk profile of lutein and concluded that the only documented side effect is yellow discoloration of skin, characterized by high dermal carotenoid levels. This condition is reversible and benign and there were no other adverse events [32]. The CRN also suggested a daily lutein upper level of supplementation (ULS) of 20 mg. Lutein and zeaxanthin carry potential benefits, and have minimal side effects. For those who are keen and are at risk of AMD, they may offer some protection.

### *Omega-3 fatty acids*

The role of omega-3 fatty acids in reducing the incidence of cardiovascular diseases and strokes has been well established [33]. For instance, the American Heart Association recommends the intake of omega-3 fatty acids in the form of either fish or fish oil capsule supplements for cardiovascular benefits [34]. Recently, its role in AMD has also been investigated. Docosahexaenoic acid (DHA) is a type of omega-3 fatty acid present in high concentration in the photoreceptor segment of the retina. It is constantly being shed and reformed in the normal visual cycle, and has been shown to reduce inflammation and regulate autoimmune responses [35–40], which in turn prevents AMD. Hodge et al. carried out a meta-analysis and concluded that evidence so far was inconsistent and not randomized [41]. Larger randomized controlled trials are needed before conclusions can be drawn.

More recently, the US Twin Study of Age-Related Macular Degeneration (USTS) investigated the relationship among 681 twins, and found that fish consumption and omega-3 fatty acid intake reduced the risk of AMD [42], by an estimated 22% if omega-3 was high. However, the study was not randomized and hence its impact is limited.

Because of the potential antithrombotic effect of fish oil, the risk of hemorrhagic stroke is potentially increased [43]. Clinical studies have demonstrated that even with concurrent administration of agents like warfarin and aspirin, a high dose of fish oil does not significantly increase the risk of bleeding [44–46]. Another safety concern is environmental contaminants such as mercury, which is commonly

found in fish; high consumption of fish or fish oil capsules may pose potential health threats. The FDA issued an advisory statement recommending that pregnant women, breast-feeding mothers and children avoid eating certain types of seafood high in mercury [47]. The risk is still low and is limited to certain types of fish such as golden bass, shark, king mackerel, and swordfish [33]. Fish oil supplements are generally considered safe because most industrial purification processes eliminate these toxins [48, 49].

The risk of taking omega-3 fatty acids either from dietary fish or fish oil supplements is low, and the potential benefits outweigh the risks. With the proven cardiovascular benefits, consumption of fish or fish oil supplements remains a reasonable and safe recommendation.

#### *Berry extracts*

The interest in berry extracts grew from their antioxidant properties. Probably the most notable member of the berry family is blueberry, which ranked first in antioxidant properties among 100 common food items published by the United States Department of Agriculture assays [50]. As far as ophthalmology is concerned, its antioxidant strength helps reduce risk of AMD, and improves night vision. Many berry extract products claim to protect eyes from AMD. Another berry, wolfberry, better known as ‘goji berry’, which has been long used in Traditional Chinese Medicine (TCM), is also known for its eye-protecting properties [51].

Anthocyanin is commonly present, and in plant studies it was found to absorb blue-green light and protect cells from light stress [52]. Other laboratory studies have shown that it can theoretically protect eyes from degenerative diseases like AMD [53–55]. Others also suggested anti-angiogenic and anti-cancer properties in anthocyanin [53, 56, 57]. However, at the moment evidence is limited to the laboratory level. The precise dosage and frequency remains uncertain, and potential toxicity and long-term side effects still require exploration.

Currently there are no legal requirements for quality control of these extracts. Most of these products need not disclose their exact content and production method. At the moment, berry extracts should not be recommended.

## Lifestyle modifications

### *Smoking cessation*

The only established causative factor for AMD is smoking, which has been linked to increased oxidative stress, platelet aggregation, higher fibrinogen level, and reduced plasma high-density lipoprotein and antioxidant levels [58–60].

In AREDS Report No. 19, subjects who smoke were found to have a higher risk of progression to advanced AMD. For 10 pack-years or higher smokers, the odds ratio for advanced AMD was 1.55 [61]. Results of the US Twin Study showed that current smokers had a 1.9-fold increased risk of having AMD, and ex-smokers still had a 1.7-fold increased risk [42]. If smokers take supplements containing beta-carotene, the risk of lung cancer is further increased [19, 20]. All smokers should be advised to stop.

### *Body mass index (BMI)*

In the AREDS, a higher risk of the geographical atrophy type of AMD was seen in subjects with higher BMI [19, 20, 61]. The odds ratio was 1.93 in obese individuals (obese BMI  $\geq 30$  kg/m [2], normal BMI 18.5–24.9 kg/m [2]). Another study by Seddon et al. also produced similar results [62].

## Reducing light exposure

### *Sunglasses*

Some studies have suggested that sunlight exposure may contribute to AMD [63–73]. The Beaver Dam Eye Study (BDES) was a population-based cohort study measuring the amount of sunlight exposure and incidence of AMD in 2,764 subjects over a 10-year period [74]. The BDES found that extended sunlight exposure was associated with higher incidence of early AMD. However, the protective effect of sunglasses was only marginal, and the data were reported on a subjective basis.

More supporting evidence comes from reports on the incidence of AMD after cataract surgery and intraocular lens (IOL) implantation [75–77]. Human crystalline lens turns yellow with age and has been proven to protect the retina from harmful ultraviolet

(UV) blue or blue-green phototoxicity [78, 79]. When the crystalline lens is removed during surgery, the implanted IOL does not provide equivalent theoretical protection in vivo [79]. For those who have had cataract surgery, wearing sunglasses in outdoor areas may provide protection in this regard.

### Spectral filtering IOLs

A theoretical link has been proposed between phototoxicity and cataract extraction [80]. Most modern-day IOLs mimic the crystalline lens in filtering the harmful UV spectrum of 300–400 nm [78, 81]. The human crystalline lens turns yellow with age, thereby blocking blue light (400–500 nm), while IOLs tend to be transparent [82].

In the Chesapeake Bay Watermen Study, a significant correlation between blue or visible light exposure and AMD was found [68]. In fact, after cataract extraction, blue light exposure is greater than at any other point in life [83].

Among the blue-light blocking properties of modern IOLs (better known as ‘Yellow IOLs’), transmittance

mimics that of a human adult crystalline lens. One example is the AcrySof® Natural IOL by Alcon (Fort Worth, Texas, USA), which partially attenuates violet light (400–440 nm) [84], and blocks 50% of blue light at 450 nm and 25% at 480 nm [85]. In contrast, conventional transparent IOLs transmit 90% of light >400 nm [82]. Therefore these yellow IOLs may theoretically protect the macula from phototoxicity.

Concerns have been raised that these yellow IOLs attenuate visual performances under scotopic conditions (defined as lighting levels as experienced on a moonless night with only starlight), because blue light, which is more informative in this environment, is being partially filtered [82]. Furthermore, some raised the issue of possible differences in color perception. For instance, driving at night is considered a mesopic task [86], which refers to lighting conditions under a quarter of a full moon [87]. Even under scotopic conditions, contrast sensitivity is greatest around the 507 nm wavelength, and the AcrySof Natural IOL transmits 85% of light at this wavelength, as compared to 90% with conventional transparent IOLs, and only around 60% in a young

**Table 3** Summary of recommendations

Category	Study	Recommendation	Strength of evidence <sup>a</sup>	Rating of recommendation <sup>a</sup>
Nutritional supplements				
AREDS formula	AREDS	Regular intake may reduce risk of neovascular AMD	I	B
	Cochrane [22]	Regular intake may reduce risk of neovascular AMD	I	A
Lutein and zeaxanthin	AREDS2	Not yet available	n/a	n/a
	CAREDS	No difference	II	C
	POLA	Higher lutein and zeaxanthin reduced risk of AMD	II	C
Omega-3	Gale et al. [28]	Higher lutein and zeaxanthin reduced risk of AMD	II	C
	AREDS2	Not yet available	n/a	n/a
Berry extracts	USTS	Higher omega-3 intake reduced risk of AMD	II	C
	None	n/a	n/a	n/a
Life style				
Smoking	AREDS	Smokers had higher risk of AMD	I	B
	USTS	Smokers had higher risk of AMD	II	C
BMI	AREDS	Higher BMI was associated with higher risk of AMD	I	B
Sunlight filtering				
Sunglasses	BDES	Benefit of sunglasses use against AMD marginal	II	C
Yellow IOLs	None	n/a	n/a	n/a

n/a data not available, AREDS Age-Related Eye Disease Study [17], AREDS2 Age-Related Eye Disease Study 2 [31], CAREDS Carotenoids in Age-Related Eye Disease Study [26], POLA ‘Pathologies Oculaires Liées à l’Age’ study [27], USTS United States Twins Study [42], BDES Beaver Dam Eye Study [66]

<sup>a</sup> Strength of evidence and rating of recommendation rated according to method described previously [9]

adult natural crystalline lens [78]. In fact, some studies even reported increased contrast sensitivity with the yellow IOLs [88–90].

Cionni used the Farnsworth 100-Hue test in subjects who had undergone bilateral yellow IOL implantation, and found no significant changes in terms of color perception [91]. Comparison was also made with those who had a yellow IOL implanted in one eye, and a transparent IOL in the other, and found no significant alternations [92]. Hence for most patients a yellow IOL may offer theoretical protection from AMD.

## Summary and conclusions

A systematic review of evidence on the prevention of age-related macular degeneration was made. A summary of recommendations is given in Table 3. The AREDS formula remains the only A-rated recommendation so far. When dealing with patients, it is the responsibility of the practitioner to fully explain the nature of supplements and potential side effects from long-term regular intake, especially the increased risk of lung cancer in smokers. Any misconceptions should be addressed and rectified. It is also necessary to remind patients that even when taking the AREDS formula, AMD can still occur. Patients should be taught self-monitoring methods and undergo regular fundal examinations by qualified ophthalmologists. The importance of this cannot be over-emphasized.

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