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NUTRITIONAL AND LIFESTYLE DETERMINANTS IN THE PATHOGENESIS AND PROGRESSION OF AGE-RELATED MACULAR DEGENERATION

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ABSTRACT

Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss among the elderly, with its global prevalence expected to rise substantially in the coming decades. Given its multifactorial pathogenesis—driven by oxidative stress, retinal pigment epithelium (RPE) dysfunction, and chronic inflammation—identifying modifiable nutritional and lifestyle risk factors has become a central focus in developing preventive strategies. This review article synthesizes current literature retrieved from PubMed and Google Scholar to examine the influence of dietary fatty acids, antioxidants, smoking, and alcohol consumption on the onset and progression of AMD. Key sources include large-scale observational cohorts and randomized controlled trials, notably AREDS and AREDS2. Long-chain omega-3 polyunsaturated fatty acids (PUFAs), specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), primarily obtained from fish, show consistent protective effects against both early and late AMD. In contrast, excessive omega-6 intake and an unfavorable omega-6 to omega-3 ratio may promote retinal inflammation. Antioxidants and zinc significantly reduce the risk of disease progression, particularly in individuals with intermediate AMD. Lutein and zeaxanthin offer additional benefits. Smoking is one of the strongest modifiable risk factors, with persistent effects even after cessation. Moderate to heavy alcohol consumption correlates with early-stage AMD. Robust evidence supports the implementation of public health strategies focused on smoking cessation, reducing alcohol intake, and promoting nutrient-rich diets to lower AMD incidence and progression. Integrating nutritional counseling into routine ophthalmologic care represents a biologically plausible and cost-effective approach to preserving vision and improving long-term outcomes in at-risk populations.

KEYWORDS

Macular Degeneration, Retinal Pigment Epithelium, Fatty Acids, Carotenoids, Smoking, Zinc

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1. Introduction

Age-related macular degeneration (AMD) represents one of the most prevalent ocular conditions contributing to visual impairment and irreversible eyesight loss among individuals aged above 50 years. This disease is defined by the gradual deterioration of the macula, the central portion of the retina essential for proper visual function, and is estimated to affect around 8.7% of the global population.[1,2]

A substantial number of epidemiological researches have analyzed the prevalence and incidence of AMD across various populations worldwide. One large-scale cohort study demonstrated notable ethnic differences in the incidence of early AMD, reporting the highest rates among White individuals (5.3%), followed by Chinese (4.5%) and Spanish populations (3.3%), with the lowest incidence observed in Black individuals (1.6%). A similar trend was observed for late-stage AMD, with incidence rates of 4.1%, 2.2%, 0.8%, and 0.4%, respectively.[3] Meta-analytical data further support a strong age-dependent increase in AMD prevalence. In one analysis of European cohorts, the frequency of early or late AMD rose from merely 0.08% among individuals aged 50–55 years to as high as 20.1% in those aged 90 years and older.[4] A separate meta-analysis focusing on Asian populations aged between 40 and 79 years showed a distribution of nearly 7% for early AMD and 0.56% for the late form. Comparative data from White individuals in the same age range indicated slightly higher values: 8.8% and 0.59%, respectively.[5]

AMD is often divided into two main forms: wet (neovascular) and dry (atrophic) AMD. The atrophic form, often representing the earlier stages of this condition, is distinguished by the accumulation of lipid- and protein-rich layers known as drusen, linking the retinal pigment epithelium (RPE) and Bruch's membrane. These deposits are often accompanied by changes in retinal pigmentation. In contrast, the advanced or wet form of AMD is a sight-threatening disease associated with neovascularization of the choroid, resulting in the formation of irregular blood vessels below the retina.[6,7]

Despite its widespread occurrence and clinical significance, the exact pathophysiological processes underlying AMD remain incompletely elucidated. Current evidence suggests that AMD arises from a multifactorial interplay involving metabolic dysregulation, genetic predisposition, and environmental influences. Numerous studies have investigated potential determinants linked to both the beginning and progression of the disease. Key risk factors, besides increasing age, include smoking, alcohol consumption, lifestyle behaviors, dietary habits, chronic systemic diseases and family history.[1]

Projections by the WHO indicate that, in the lack of successful therapeutic strategies and preventive measures, the worldwide prevalence of AMD may reach nearly 288 million cases by the year 2040.[8] The health and socioeconomic burden of AMD is anticipated to escalate significantly in the upcoming years, driven by limited therapeutic options for the neovascular form and the continually increasing geriatric population. Since patients rarely consume a diet composed of only one nutrient, and dietary habits often change over time, analyses focused solely on individual foods or nutrients, as well as those examining overall dietary patterns, may not fully capture the complex interplay between diet and disease. Nonetheless, identifying nutritional components that are highly likely to influence AMD can offer valuable insights for healthcare professionals, potentially aiding in the development of targeted dietary recommendations and preventive strategies.[8–11] This review aims to synthesize current evidence on modifiable nutritional and lifestyle factors—specifically focusing on dietary fats, antioxidants, alcohol consumption, cigarette smoking, and the potential role of comprehensive dietary approaches—in the pathogenesis and progression of AMD.

Methods

A non-systematic narrative review was conducted to evaluate the role of modifiable dietary and lifestyle factors in the pathogenesis and progression of age-related macular degeneration (AMD). A comprehensive literature search was performed using PubMed, Google Scholar, and Cochrane Library, focusing on articles published in English from 2000 to 2024.

The search terms included combinations of the following keywords:

“age-related macular degeneration”, “AMD”, “diet”, “nutrition”, “omega-3 fatty acids”, “omega-6 fatty acids”, “PUFAs”, “EPA”, “DHA”, “smoking”, “alcohol”, “antioxidants”, “AREDS”, “zinc”, “lutein”, “zeaxanthin”, and “lifestyle factors.”

Priority was given to: randomized controlled trials (RCTs) and meta-analyses, large-scale prospective cohort studies, authoritative reviews and guideline statements (e.g., from the AREDS studies), articles with human subjects

Studies were selected based on their relevance to the topic and their contribution to understanding the relationship between diet, lifestyle, and AMD. Duplicates and articles unrelated to the main topic were excluded. The findings were synthesized to provide a concise overview of current evidence and highlight biologically plausible links between modifiable factors and AMD development or progression.

2. Pathogenesis

2.1. Retinal Architecture and Sites of AMD Damage

The retina, a transparent extension of the CNS lining the interior surface of the posterior eye wall, plays a key role in the process of vision. It comprises multiple specialized layers and cellular components, each contributing to distinct visual functions. The macula is a highly organized, multilayered structure crucial in enabling sharp visual perception. At its center lies the fovea, a critical anatomical area that enables fine visual tasks essential for daily functioning, including reading, driving, and facial recognition.[12]

AMD predominantly affects the outer retinal structures, including the RPE, Bruch’s membrane, choriocapillaris, and the adjacent choroid layer. The RPE performs several critical homeostatic functions, such as nutrient transport, phagocytosis of photoreceptor outer segments, and maintenance of electrolyte balance. The choriocapillaris and choroid constitute a dense vascular network responsible for supplying oxygen and nutrients to the outer retina. Bruch's membrane facilitates bidirectional exchange between the RPE and choriocapillaris and is implicated in the pathogenesis of neovascular lesions characteristic of advanced AMD.[13] The RPE forms the blood–retina barrier, effectively separating the photoreceptor layer from systemic circulation. Rods and cones, which mediate the complex phototransduction essential for vision, rely on this layer for a continuous supply of oxygen and metabolic substrates. Throughout life, the RPE ensures both photoreceptor sustenance and choroidal homeostasis.[14] In AMD, RPE degeneration and atrophy disrupt the structural support of the photoreceptor layer, leading to impaired phototransduction. This disturbance interferes with neural signal transmission from the retina to the visual cortex, ultimately leading to progressive vision

loss. Furthermore, the choroidal vasculature may be adversely affected by microvascular injury associated with systemic conditions such as hypertension and hyperlipidemia.[15,16]

2.2. Oxidative Stress: A Central Driver of Retinal Degeneration

Two primary factors believed to drive the formation of AMD are oxidative stress and choroidal neovascularization (CNV). Due to its exceptionally high oxygen consumption, the retina is particularly vulnerable to oxidative damage, a key contributor to age-related diseases like AMD [1]. The retina's high oxygen demand, combined with light exposure and the abundance of polyunsaturated fatty acids (PUFAs), such as docosahexaenoic acid (DHA) in photoreceptors, promotes oxidative stress in AMD. This leads to an overproduction of reactive oxygen species (ROS), which damages Bruch's membrane, photoreceptors, and the RPE. Impaired RPE function compromises its ability to phagocytose the outer segments of photoreceptors, further exacerbating ROS accumulation and resulting in structural failure. The accumulation of malondialdehyde and carboxyethylpyrrole, markers of oxidative stress, reflects both local and systemic damage. This cascade accelerates the progression of AMD by undermining retinal integrity, leading to lipid and protein deposits, cellular loss, and neovascularization.[17–19]

2.3. Molecular Biomarkers of Oxidative Damage in AMD

Clinical studies involving AMD patients and post-mortem donor eyes have provided compelling evidence of DNA, protein, and lipid biomarkers associated with oxidative stress in the context of AMD. Notably, oxidative DNA damage, including the accumulation of 8-hydroxy-2-deoxyguanosine (8-OHdG), has been detected in AMD donor eyes—particularly in cases of dry AMD characterized by RPE atrophy.[20] Because the outer segments of photoreceptors are enriched in lipids such as DHA, higher levels of carboxyethylpyrrole (CEP) protein adducts—a marker of DHA-related lipid peroxidation—have been detected in Bruch's membrane of AMD donor eyes, indicating increased oxidative vulnerability compared to non-AMD eyes.[21,22] Another investigation demonstrated that, in dry AMD, proteomic and genomic profiling of donor eyes revealed significantly elevated plasma levels of CEP—by approximately 60%—alongside increased expression of ARMS2, CFH, and complement component C3.[23]

2.4. Drusen Formation and Inflammatory Cascade

Cellular damage in AMD contributes to the formation of drusen—extracellular deposits that accumulate between Bruch's membrane and the RPE—triggering local inflammation. The presence of drusen is a hallmark of dry AMD and may represent the earliest detectable sign of the disease, even in asymptomatic individuals. The risk of progression correlates with both the size and number of drusen. Based on their diameter, drusen are classified as small (<63 μm), medium (63–124 μm), and large (≥125 μm). Morphologically, drusen are further categorized as hard or soft: hard drusen are typically small with well-defined borders, whereas soft drusen exhibit indistinct edges and may coalesce into larger lesions, which are associated with a higher risk of disease progression. Drusen are also implicated in the development of CNV observed in wet AMD. The risk of progression from the dry to the wet form increases in the presence of larger and more numerous drusen, particularly when accompanied by pigmentary abnormalities of the RPE.[13,24,25]

2.5. Choroidal Neovascularization and VEGF-Driven Pathology

CNV involves the abnormal growth of new blood vessels from the choroid into the subretinal space. These vessels are fragile and prone to extravascular leakage. As CNV progresses, fluid accumulation or hemorrhage may occur in the subretinal and/or intraretinal layers, ultimately leading to rapid central vision loss.[26] In AMD pathogenesis, vascular endothelial growth factor (VEGF) promotes CNV development and subretinal edema by enhancing the proliferation and permeability of vascular endothelial cells.[27,28]

3. Dietary Fatty Acids and Fish Consumption in AMD

3.1. Role of Omega-3 Fatty Acids

Omega-3 fatty acids are a group of polyunsaturated fats essential for metabolism that cannot be synthesized by the human body and must therefore be supplied through the diet. The main representatives of this group include alpha-linolenic acid (ALA), DHA and eicosapentaenoic acid (EPA). ALA is primarily sourced from plant-derived foods such as flaxseeds, walnuts, and certain vegetable oils. In contrast, EPA and DHA are predominantly obtained from marine sources, especially oily fish like mackerel, sardines, tuna,

anchovies, salmon, and swordfish. Notably, DHA plays a crucial role in visual health, as it is a major structural lipid in retinal photoreceptors and neuronal synapses, where it contributes to proper retinal function.[9]

A 2021 meta-analysis conducted by Jiang et al., which included 21 observational studies, provided strong evidence supporting a protective role of omega-3 PUFAs in the development of AMD. The analysis demonstrated that individuals with higher dietary intake of omega-3 PUFAs had a significantly reduced risk of both early (relative risk [RR]: 0.86; 95% confidence interval [CI]: 0.77–0.96) and late AMD (RR: 0.71; 95% CI: 0.55–0.91). A dose-response relationship was observed, indicating that each additional gram per day of omega-3 PUFA intake correlated with a 6% reduction in early AMD risk and a 22% reduction in late AMD risk. Among the specific fatty acids analyzed, both EPA and DHA were inversely associated with AMD risk, while no significant correlation was found for ALA.[29] These findings are consistent with an earlier systematic review by Chong et al. from 2008, which analyzed data from over 88,000 individuals, including 3,203 AMD cases. That study reported that high omega-3 PUFA intake was associated with a 38% reduction in the risk of late AMD (pooled odds ratio [OR]: 0.62; 95% CI: 0.48–0.82).[30]

3.2. Omega-6 Fatty Acids and the Omega-6/Omega-3 Ratio

In contrast to the anti-inflammatory and protective properties of omega-3 fatty acids, several omega-6 PUFAs—particularly arachidonic acid (AA)—have been associated with proinflammatory activity. Elevated levels of omega-6 PUFAs have been linked to enhanced inflammatory signaling, reduced DHA concentrations, and an increased risk of cardiovascular disease and certain types of cancer. Omega-6 fatty acids compete with omega-3 fatty acids for incorporation into membrane phospholipids, and a high dietary intake of AA has been shown to reduce DHA esterification in cellular membranes, even when dietary DHA is sufficient. Furthermore, since omega-6 and omega-3 PUFAs share the same enzymatic pathways for conversion—specifically from linoleic acid (LA) to AA and from ALA to DHA—an excessive intake of LA may inhibit the biosynthesis of DHA from ALA, potentially exacerbating the imbalance between these two families of fatty acids.[31]

DHA and AA are present in high concentrations in the retina, where they are essential structural components of the outer segments of retinal photoreceptors and vascular tissue. Being modifiable through diet, these nutrients highlight their potential significance in the development and progression of AMD. A study by William G. Christen further emphasizes the relevance of fatty acid balance in AMD pathogenesis. The authors reported that a higher dietary ratio of omega-6 to omega-3 fatty acids (specifically DHA and EPA) was strongly predictive of early AMD. These results support the notion that not only the absolute intake of omega-3 fatty acids but also their ratio relative to omega-6 fatty acids plays a critical role in AMD risk. Moreover, the inverse association between DHA and EPA intake and AMD was more pronounced among individuals with higher omega-6 intake, although the interaction did not reach statistical significance.[32]

Some evidence suggests that a recommended dietary ratio of omega-3 to omega-6 fatty acids should be around 1:5 or lower. However, in modern Western diets, this balance is often heavily skewed toward omega-6 dominance. As highlighted in a systematic review by Naoko A. Chapman, while increasing omega-3 intake remains a key strategy to restore this balance, reducing excessive omega-6 consumption may be an equally important and more effective approach in achieving a healthier omega-3 to omega-6 ratio, particularly in the context of chronic diseases with inflammatory components, including AMD.[9]

3.3. Fish Intake

Regular fish consumption has been repeatedly highlighted as a key dietary source of long-chain omega-3 PUFAs, particularly DHA and EPA. Several studies have suggested that regular fish consumption may act as a protective factor by lowering the risk of AMD, likely due to its high content of long-chain omega-3 PUFAs, which play a crucial role in retinal health.[29,30,32]

A population-based study by Seddon et al. involving a unique cohort of elderly male twins from a national registry provided compelling evidence for the protective role of fish consumption and omega-3 intake in the context of AMD. Importantly, individuals with more frequent fish consumption and higher intake of long-chain omega-3 PUFAs exhibited a reduced risk of AMD, even after controlling for potential confounding factors such as cigarette smoking. Interestingly, this protective association was evident only when LA intake remained below the median, emphasizing the importance of a balanced dietary ratio between omega-3 and omega-6 fatty acids.[33] These findings are consistent with earlier results from different cohorts and underscore the importance of considering overall dietary composition—particularly the omega-6 to omega-3 fatty acid ratio—when formulating nutritional strategies for AMD prevention.[34,35]

4. Other Nutritional Components in AMD

4.1. Zinc and Antioxidants

Since compelling evidence suggests that oxidative stress may play a central role in the pathogenesis of AMD, the scientific community has shown considerable interest in the potential of antioxidants, zinc, and other micronutrients to counteract retinal degeneration and slow disease progression. This focus has been strongly shaped by two landmark clinical trials — the Age-Related Eye Disease Study (AREDS) and its successor, AREDS2 — which have provided critical insights into the role of specific micronutrient formulations in AMD management. The original AREDS trial enrolled over 3600 participants aged 55 to 80 years with varying degrees of AMD severity and evaluated the effect of high-dose supplementation with antioxidants — vitamin C (500 mg), vitamin E (400 IU), and beta-carotene (15 mg) — in combination with zinc (80 mg as zinc oxide) and copper (2 mg as cupric oxide). After a mean follow-up of 6.3 years, the combination of antioxidants and zinc was shown to reduce the risk of progression to advanced AMD by 25% and the risk of moderate vision loss by 27%, compared to placebo. Importantly, the protective effect was most pronounced in individuals at moderate to high risk of progression, such as those with large drusen or noncentral geographic atrophy. These findings established antioxidant and zinc supplementation as a cornerstone in the nutritional management of intermediate and advanced AMD.[36]

However, two significant studies emerged linking beta-carotene supplementation to an increased risk of lung cancer in smokers, raising a critical question as to whether a safer alternative could replace beta-carotene in the original AREDS formulation.[37,38]

4.2. Carotenoids: Lutein and Zeaxanthin

Lutein and zeaxanthin, together with meso-zeaxanthin, accumulate in the inner retinal layers of the macular region, where they are collectively referred to as macular pigment (MP). MP selectively absorbs short-wavelength visible light (400–500 nm), with peak absorption at 460 nm, forming an internal yellow filter that protects cone and central rod photoreceptors from blue light. This filtering function, along with their antioxidant properties, is thought to reduce oxidative stress in the photoreceptor outer segments and the RPE. Empirical evidence suggests that MP contributes to several visual benefits, including reduced glare disability and discomfort, faster photostress recovery, extended visual range, and improved chromatic contrast.[39,40]

Therefore, due to concerns about the potential adverse effects of beta-carotene in smokers, the AREDS2 trial was conducted to determine whether adding lutein, zeaxanthin, DHA, EPA, or both to the original AREDS formulation could further reduce the risk of advanced AMD, as well as to evaluate the effects of eliminating beta-carotene and/or lowering zinc doses. Although the primary analyses of AREDS2 did not demonstrate a statistically significant reduction in the overall risk of progression to advanced AMD with lutein and zeaxanthin supplementation, further exploratory subgroup analyses revealed more nuanced outcomes. Specifically, participants with the lowest dietary intake of these carotenoids at baseline exhibited a significantly lower risk of disease progression when supplemented (hazard ratio [HR] = 0.74; 95% CI: 0.59–0.94; p = 0.01). This suggests that individuals with insufficient carotenoid intake may be more responsive to supplementation. Moreover, post hoc assessments indicated that simultaneous administration of beta-carotene might impair the absorption and systemic availability of lutein and zeaxanthin due to competitive uptake mechanisms. Participants assigned to receive beta-carotene displayed significantly lower serum concentrations of lutein and zeaxanthin compared to those who were not, which implies there is an interaction between these compounds. Among those not receiving beta-carotene, lutein and zeaxanthin were associated with additional protective effects. These findings support replacing beta-carotene with lutein and zeaxanthin in supplement formulations —particularly in light of the elevated risk of lung cancer linked to beta-carotene in smokers and former smokers. While no enhancement in visual acuity was observed and omega-3 fatty acids (DHA/EPA) did not significantly affect AMD progression, the AREDS2 results underscore the importance of baseline nutritional status and nutrient-nutrient interactions in determining therapeutic efficacy.[41]

4.3. Dietary Intake vs. Supplementation

Equally important to investigating the effects of micronutrient and antioxidant supplementation is understanding the role of their natural dietary intake. It is crucial since the bioavailability, synergistic interactions with other dietary components, and long-term safety profiles may differ substantially between natural and supplementary intake. This is crucial, as the bioavailability, synergistic interactions with other dietary components, and long-term safety profiles may differ substantially between naturally consumed nutrients and those provided through supplementation. Additionally, habitual dietary patterns might reflect

broader lifestyle behaviors that influence disease risk beyond isolated nutrient effects. Various epidemiological studies have explored these associations, offering insights into the potential protective role of higher dietary intake of lutein and zeaxanthin against AMD.[42]

Among the key investigations into the impact of dietary intake on AMD risk is the study by Sangiovanni et al., conducted within the framework of AREDS. The objective of this cross-sectional analysis was to evaluate the association between the intake of dietary carotenoids and the prevalence of AMD among participants aged 60 to 80 years. The analysis revealed that individuals with the highest dietary intake of lutein and zeaxanthin exhibited a markedly reduced probability of having neovascular AMD (OR = 0.65; 95% CI: 0.45–0.93), geographic atrophy (OR = 0.45; 95% CI: 0.24–0.86), and large or extensive intermediate drusen (OR = 0.73; 95% CI: 0.56–0.96), compared to those in the lowest intake group. These associations remained robust after adjusting for total energy consumption and non-nutritional confounders, indicating an independent protective effect of these carotenoids. In contrast, other evaluated nutrients—such as vitamin A, vitamin C, and alpha-tocopherol—did not show statistically significant associations with AMD phenotypes.[43]

Substantial contributions to the understanding of dietary influences on AMD have also been made by Seddon and colleagues. Substantial contributions to the understanding of dietary influences on AMD have been made by Seddon and colleagues. In her 1994 study, Seddon identified a potentially beneficial effect of dietary intake of carotenoids such as lutein and zeaxanthin on the risk of developing AMD. After adjusting for various confounding factors, the study demonstrated that individuals in the highest quintile of total carotenoid consumption had a 43% lower likelihood of developing AMD compared to those in the lowest quintile (OR = 0.57; 95% CI: 0.35–0.92; P for trend = .02). The strongest protective association was observed for lutein and zeaxanthin, primarily sourced from dark green, leafy vegetables, with a highly significant trend (P = .001). Notably, frequent consumption of spinach or collard greens was linked to a markedly reduced risk (P for trend < .001). In contrast, no significant associations were found for preformed vitamin A (retinol), vitamin E, or total vitamin C, though a possible benefit of higher dietary vitamin C intake—especially from natural sources—was suggested.[44]

One of Seddon's more recent studies, published in 2024, further explored the role of diet in the progression of AMD through a prospective longitudinal analysis. The study assessed the impact of dietary intake of green leafy vegetables, fish, lutein/zeaxanthin, and omega-3 fatty acids on AMD progression. The analysis, which included 2,697 eyes, revealed that 23% exhibited progression to a higher severity group. Notably, individuals with the highest intake of green leafy vegetables (≥2.7 servings per week) had a significantly lower risk of progression compared to those who consumed none (HR = 0.75; 95% CI: 0.59–0.96; P = 0.02). A similarly protective effect was observed for higher fish consumption (≥ two 4-ounce servings per week), which was linked to a reduced risk of disease progression (HR = 0.79; 95% CI: 0.65–0.95; P = 0.01). In nutrient-specific models, greater dietary intake of lutein/zeaxanthin (≥2 mg/day) was significantly associated with a lower progression risk (HR = 0.76; 95% CI: 0.60–0.96; P = 0.02). While the association between omega-3 fatty acid intake and progression did not reach statistical significance, a trend toward benefit was observed (HR = 0.85; 95% CI: 0.71–1.01; P = 0.06).[42]

These findings reinforce the potential role of nutritional strategies—particularly those involving lutein and zeaxanthin-rich vegetables and omega-3-rich fish—in mitigating the advancement of early-stage AMD.

5. Smoking and Alcohol Consumption

5.1. Smoking as a Major Modifiable Risk Factor

Among the various modifiable risk factors implicated in AMD, smoking and alcohol consumption are among most frequently discussed lifestyle-related contributors. A recent systematic review and meta-analysis by Asiamah et al. underscores the substantial association between smoking and AMD development. Current smokers were found to have up to a 12-fold increased risk of developing AMD compared to those who have never smoked, with an OR of 11.93 (95% CI: 4.40–32.33) and a RR of 7.45 (95% CI: 4.09–13.57). Furthermore, the risk remains elevated even after smoking cessation, as evidenced by an OR of 7.09 (95% CI: 4.79–10.51) for former smokers.[45]

While the results from another meta-analysis conducted by Raghad Babaker were not as high as those reported by Asiamah, they still identified smoking as a statistically significant predictor for AMD occurrence, with an OR of 1.86 (95% CI: 1.33–2.60; p = 0.0003), confirming its relevance as a modifiable risk factor.[8] Similar results were reported in a meta-analysis focused on the the Iranian population, where smoking was associated with a significantly increased risk of AMD (OR: 1.78; 95% CI: 1.15–2.76). Notably, all participants included in the analyzed studies were over 40 years old.[46]

5.2. Alcohol consumption in AMD

As previously mentioned in this review, the retina is particularly susceptible to oxidative damage, which provides a biological rationale for considering alcohol consumption as a potential modifiable risk factor in AMD. Numerous observational studies have examined this relationship; however, the findings have been inconsistent, with some suggesting increased risk, others showing no effect, and a few even indicating potential protective effects. To clarify these discrepancies, Zhang et al. conducted a meta-analysis that evaluated early and late AMD separately and assessed the impact of different levels of alcohol intake. This analysis, which included seven studies encompassing 4,566 cases of early AMD and 440 cases of late AMD, revealed that moderate and heavy alcohol consumption were significantly associated with an increased risk of early AMD, with pooled effect estimates of 1.19 (95% CI: 1.03–1.37) and 1.24 (95% CI: 1.10–1.39), respectively. In contrast, light alcohol consumption was not significantly associated with early AMD, and no level of alcohol intake showed a significant relationship with late AMD. Importantly, a linear dose–response relationship was identified, indicating that each 10 g/day increase in alcohol consumption elevated the risk of early AMD by 14% (pooled estimate: 1.14; 95% CI: 1.08–1.21; $p < 0.05$).[47]

Another recent study investigating global trends in the incidence, progression, and risk factors of AMD found that smoking was an independent risk factor for both early and late stages of the disease. Additionally, the study identified alcohol consumption as a significant risk factor for early AMD specifically, which aligns with the findings of the aforementioned meta-analysis.[48] These findings emphasize the critical role of tobacco exposure and alcohol consumption in the pathogenesis of AMD.

6. Conclusions

AMD remains a leading cause of irreversible vision loss among aging populations worldwide, with its prevalence expected to rise substantially in the coming decades.[1,2] Given the multifactorial etiology of AMD, identifying modifiable lifestyle and nutritional risk factors is essential for implementing effective preventive strategies. This review highlights the growing body of evidence linking dietary components—particularly specific types of fat intake, antioxidants, alcohol consumption, and smoking habits—to the development and progression of AMD.[1,8,41] The findings underscore the potential of targeted lifestyle modifications to mitigate AMD risk, particularly in its early stages, where intervention may be most effective.[36,41,43]

Recent advances in our understanding of AMD pathogenesis have emphasized the central role of oxidative stress, RPE dysfunction, and inflammatory processes in retinal degeneration. The disease primarily affects the outer retinal layers, where cumulative oxidative damage, driven by high metabolic activity and exposure to light, initiates a cascade of molecular events that disrupt photoreceptor-RPE-choroid homeostasis. The accumulation of lipid peroxidation products, mitochondrial DNA damage, and inflammatory mediators contributes to drusen formation and promotes the progression to choroidal neovascularization in advanced cases. These pathophysiological insights underscore the biological plausibility of nutritional and lifestyle interventions aimed at reducing oxidative stress and preserving retinal structure and function.[16,20,21,25]

Among the most promising modifiable factors highlighted in the literature are dietary fatty acids—particularly omega-3 PUFAs—and fish consumption, both of which have demonstrated potential in the primary prevention of AMD. Numerous studies strongly support the protective role of long-chain omega-3 fatty acids, especially EPA and DHA, in lowering the risk of both early and late AMD, highlighting their importance as key dietary components in vision-preserving strategies.[9,29,30]

Unlike the well-established anti-inflammatory and protective effects of omega-3 fatty acids, certain omega-6 PUFAs—notably AA—have been implicated in proinflammatory processes. Accumulating evidence suggests that both a high dietary intake of omega-6 PUFAs and an unfavorable omega-6 to omega-3 ratio may contribute to retinal inflammation and oxidative stress, potentially increasing the risk of AMD development and progression.[31]

Epidemiological findings support the notion that the relative balance between these fatty acids is critical. For instance, research by Christen et al. highlighted that a higher dietary omega-6 to omega-3 ratio was strongly predictive of early AMD, and the protective association between DHA/EPA intake and AMD risk appeared more pronounced in individuals with high omega-6 consumption. While some studies observed a stronger inverse association between omega-3 intake and AMD in the context of elevated omega-6 levels, these interactions did not consistently reach statistical significance. Conversely, other analyses have shown that the benefits of fish consumption were only evident when LA intake was below the population median—implying that a high omega-6 to omega-3 ratio may attenuate the protective effects of long-chain omega-3 PUFAs.[32–35]

Antioxidants and zinc, as demonstrated by the AREDS trial, significantly reduce the progression of intermediate to advanced AMD. However, due to the increased risk of lung cancer associated with beta-carotene in smokers, its replacement with lutein and zeaxanthin is now preferred, as supported by AREDS2 findings. Although the overall effect of these carotenoids on AMD progression was modest, individuals with low baseline intake benefited most.[36,41,43]

Dietary intake of lutein and zeaxanthin from leafy greens and fish appears more effective than supplementation alone, offering a broader spectrum of long-term protective effects. Epidemiological and prospective studies consistently associate higher consumption of these foods with reduced risk of AMD onset and progression. Therefore, nutritional strategies emphasizing whole-food sources of protective compounds—especially in individuals with low dietary intake—may play a crucial role in slowing AMD progression.[42–44]

Cumulative evidence from multiple meta-analyses highlights smoking as one of the strongest modifiable risk factors for AMD, with both current and former smokers exhibiting a significantly elevated risk. The association persists across diverse populations and remains statistically significant even after smoking cessation. In contrast, alcohol consumption demonstrates a dose-dependent relationship with early AMD, where moderate to heavy intake is linked to increased risk, while light consumption appears neutral. Notably, no consistent association has been found between alcohol and late-stage AMD.[45–48]

Taken together, the current body of evidence strongly supports the implementation of public health strategies focused on smoking cessation, moderation of alcohol intake, and promotion of nutrient-rich diets to reduce AMD incidence and progression. Nonetheless, further high-quality, longitudinal, and interventional studies are warranted to establish definitive dietary guidelines and to clarify the impact of complex nutrient interactions. Integrating nutritional counseling into routine ophthalmologic care may ultimately serve as a cost-effective and biologically plausible approach to preserve vision and improve long-term outcomes in individuals at risk for AMD.

Main Points

1. Oxidative stress, retinal pigment epithelium dysfunction, and inflammation are central to AMD pathogenesis and provide biologically plausible targets for prevention.
2. Long-chain omega-3 fatty acids (EPA and DHA), especially from fish, are strongly associated with reduced AMD risk.
3. A high dietary omega-6 to omega-3 ratio may counteract protective effects and promote retinal inflammation.
4. Antioxidants, zinc, lutein, and zeaxanthin can slow AMD progression, particularly in individuals with low baseline intake.

Smoking and excessive alcohol intake remain among the strongest modifiable risk factors for AMD development.

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