Risk Factors for Age-related Macular Degeneration

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Abstract

Although the pathogenesis of age-related macular disease (ARMD) is still not fully understood, genetic and environmental factors are implicated. Epidemiological studies have found conflicting findings between ARMD development and many potential risk factors. This review provides an up-to-date account of modifiable and non-modifiable risk factors associated with ARMD development, with potential mechanisms between risk factors and ARMD development described. Age, smoking and genetic factors appear to be consistently associated with an increased risk of developing ARMD. However, ageing and genetic disposition cannot be currently modified, leading to increased interest as to how other modifiable factors may reduce the risk of ARMD.

Keywords

Macular degeneration, risk, nutritional supplements, age related, smoking, genetics

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Age-related macular disease (ARMD) is a degenerative disease of the macula, most common over the age of 50 years.[1] It is the leading cause of visual loss within western industrialised countries.[2–4] The number of blind registrations attributable to the disease increased by 30–40 % between 1950 and 1990[3] and the number of cases each year is continuing to rise[4–6] as these populations have an increasing longevity.

Definition of Age-related Macular Disease

The international age-related maculopathy group has defined an international classification system for quantifying and defining the different subgroups of ARMD in an attempt to permit easier comparison of research findings between groups.[1]

Age-related maculopathy (ARM) is a disorder of the macular area most apparent after age 50 and is characterised by the following:

- Areas of drusen which are external to the neuroretina and retinal pigment epithelium (RPE). They are soft and distinct or soft and indistinct. Hard drusen are not characteristic of ARM. Drusen are discrete white-yellow spots containing abnormal extracellular lipoprotein deposits that accumulate between the RPE basal lamina and the inner collagenous layer of Bruch's membrane.[7]
- Hyperpigmentation in the outer retina or choroid with drusen.
- Hypopigmentation of the RPE with drusen.

This early stage of the condition may not affect vision, but can predispose patients to visual loss (see *Figure 1*).

Later stages of the condition are classified as 'wet' or 'dry' age-related macular degeneration (AMD). These forms of the disease can occur with or without the involvement of new blood vessel growth. If new vessels are not involved (dry AMD), clinical presentation is a sharply defined round or oval area of hypopigmentation where choroidal vessels are more visible than the surrounding area, with a diameter greater than 175 µm[1] (see *Figure 2*). This is also known as geographic atrophy (GA).

The term 'wet AMD', also known as disciform AMD, exudative AMD or neovascular AMD refers to the development of choroidal neovascularisation (see *Figure 3*) and has numerous manifestations, including:

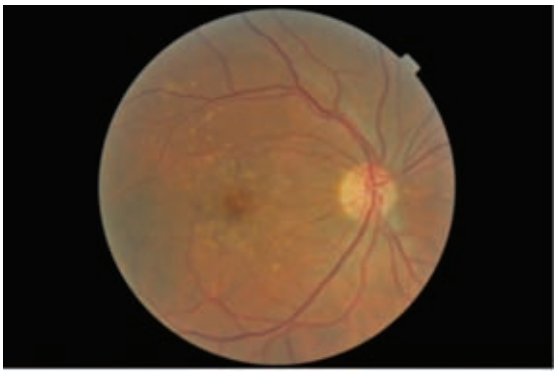
- choroidal neovascularisation (CNV);
- RPE detachment(s);
- subretinal or sub-RPE neovascular membrane(s);
- deposition of scarring, glial tissue or fibrin-like material within the epiretinal, intraretinal, subretinal or sub-RPE layers;
- subretinal haemorrhages (without other retinal vascular cause); and
- hard exudates (formed from lipid) associated with the above manifestations (without other retinal vascular cause).

This article uses the terms ARM, AMD and ARMD as per the international classification system described.

Physiology of Age-related Macular Disease

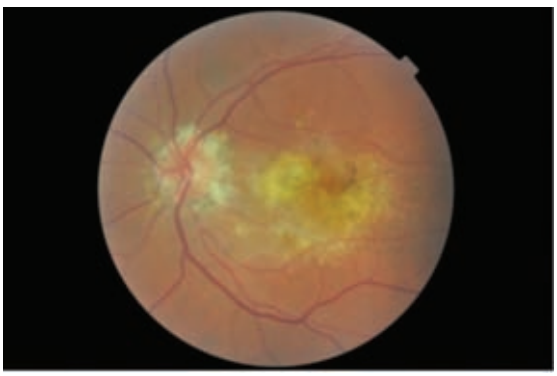
The RPE rests on Bruch's membrane and separates the neural retina from the choriocapillaris. The RPE phagocytoses the outer segment discs of the photoreceptors and is a point of metabolite and waste exchange, which is considered crucial to retinal function.[8] The initial signs of ARMD are variations within and below the RPE, seen as alterations in the pigmentation of the RPE, with or without the occurrence of drusen.[9] Drusen are discrete white-yellow spots containing abnormal extracellular lipoprotein deposits that accumulate between the RPE basal lamina and the inner collagenous

Figure 1: Age-related Maculopathy Showing Drusen



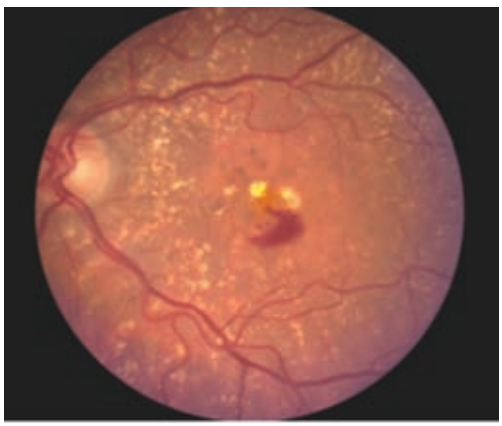
Source: author's own photo.

Figure 2: Age-related Macular Degeneration with Geographic Atrophy



Source: author's own photo.

Figure 3: Exudative Age-related Macular Degeneration



Source: Webvision, with permission.

layer of Bruch's membrane.[7] Within the ageing eye a build up of lipofuscin granules can be seen in the RPE,[10] possibly caused by a reduced ability of the RPE's phagocytic-lysosomal system to efficiently digest photoreceptor outer segment membranes,[11] leading to an accumulation of lipids from this material in Bruch's membrane reducing membrane permeability. This in turn may interrupt the supply of nutrients from the choroid to the retina ultimately leading to photoreceptor atrophy.[12] Oxidative stress causes injury and inflammation to the RPE and choriocapillaris which may lead to an altered extracellular matrix. This affects nutrient supply to the RPE and retina, possibly thus further damaging the RPE and retina, leading to the retinal atrophy seen in the later stages of ARMD.[13]

Aetiology of Age-related Macular Disease

Although the precise aetiology of ARMD is currently unknown, there are several hypotheses that have been postulated.

Oxidative Stress

Ageing is associated with cumulative oxidative damage.[14] The retina is constantly under high oxygen tension and is thus susceptible to this damage. Reactive oxygen intermediates (ROIs), a term used to describe hydrogen peroxide, singlet oxygen and free radicals, are synthesised as byproducts of phototransduction and cell metabolism.[15] Phagocytosis of photoreceptor outer segments by the RPE produces ROIs, increasing oxidative stress. Outer segments of photoreceptors contain polyunsaturated fatty acids and vitamin A. Under high oxygen tension and light irradiation the outer segments undergo lipid peroxidation, especially within the macular area.[16] Light irradiation induces photoreceptor damage.[17] It is suggested that lipid peroxidation may be involved in the cause of light induced retinal degeneration.[18] A healthy RPE is required for the correct functioning of the retina[19] but RPE changes occur with age as lipofuscin granules accumulate within RPE cells. Lipofuscin is composed of vitamin A metabolites and lipid peroxides, and is constantly exposed to visible light (400–700 nm) and high oxygen tension (~70 mmHg),[20] which cause reactive oxygen species synthesis and possible RPE membrane damage. Lipofuscin accumulates in the human RPE from approximately 20 years of age and continues throughout life.[21] Lipofuscin is a photosensitiser that may increase the risk of retinal photodamage and contribute to the development of ARMD.[22] There are differing thoughts as to whether RPE melanosomes provide a protective effect to the RPE by scavenging reactive free radicals.[23] Therefore their decline within the RPE with increasing age[24] may reduce free radical scavenging by these cells. However, an increase in phototoxic melanin–lipofuscin complexes (melanolipofuscin) also occur with increasing age and may have a detrimental effect to the RPE as their accumulation more closely reflects the onset of AMD than lipofuscin accumulation alone.[25]

Genetics

Although knowledge about the role of genetic variants in ARMD is currently rudimentary, many genes have been identified as providing either deleterious or protective effects against the disease.[26,27] Several genes have been associated with an increased risk of developing ARMD and have been verified in further studies.[28] The LOC387715 variant[29] and complement factor H gene polymorphisms (Y402H) predispose people to an increased risk of developing ARMD.[30] Protective genes have also been identified such as the complement factor B and complement component 2 gene, although current knowledge is limited and continued genetic research may yield further information.[31] Although the extent of heritability and the number of genes involved in ARMD is presently unknown[32] there has been evidence to suggest increased risk of disease development with a positive family history of the disease.[33–36] Many studies have assessed familial predisposition to ARMD by looking at monozygotic and dizygotic twins,[34,37–41] with monozygotic twins showing a stronger concordance than dizygotic twins. The higher prevalence of ARMD in first-degree relatives of those with the disease than those without the disease further strengthens the case that genetic factors may play a part in ARMD pathogenesis.[42–44] More may be learnt over time as genetic marker testing becomes

increasingly sophisticated, identifying greater numbers of genes associated with ARMD. It appears likely that a combination of exposure to environmental stimuli and genetic predisposition to ARMD are implicated in the pathogenesis of the disease.[3,45]

Deterioration of Ruysch's Complex

Ruysch's complex consists of the RPE, Bruch's membrane and choriocapillaris. The hydraulic conductivity of Bruch's membrane reduces with increasing age.[9,46,47] Bruch's membrane collagen solubility decreases with increasing age particularly at the posterior pole and is thought to interfere with the function of the RPE[48] whose cell attachment rates are decreased on an aged Bruch's membrane.[49] Cross-linking of collagen fibres within Bruch's membrane increases with increasing age and a rise in ultraviolet absorbance and fluorescence also occurs within the membrane.[50]

In ARMD, deposition of long-space collagen and basement membrane proteins can be observed between the RPE plasma membrane and RPE basement membrane.[51] These deposits are termed basal laminar deposits (BlamD). Basal linear deposits (BlinD) are found between the basement membrane of RPE cells and Bruch's membrane (soft drusen) mostly comprising membranous debris.[52] Histopathologically, ARMD is characterised by occurrence of both deposits.[52,53] The presence of BlamD is strongly associated with the presence of AMD,[54] which compromises photoreceptor cell function,[55] and BlinD are also specific for AMD.[52] Histopathological studies have correlated BlamD with CNV[56,57] and a severely compromised RPE.[51]

With increasing age Bruch's membrane progressively accumulates lipid content[58,59] and fluid diffusion is slowed.[46] It is thought that the debris within Bruch's membrane is derived from RPE metabolic activity[58] and this rise in lipid and protein quantity within Bruch's membrane reduces permeability, thus impeding flow of macromolecules between the RPE and choroid.[60] This may lead to slowed regeneration of photopigment due to retinoid deficiency, ultimately causing photoreceptor loss.[61] Bruch's membrane thickens with increasing age,[62] which is associated with a decline in phagocytosis of photoreceptor outer segments by RPE cells[63] and increases the distance for oxygen transport between the choriocapillaris and outer retina, reducing the oxygen to the outer retina.[64] In the normally functioning RPE, angiogenic growth factors such as vascular endothelial growth factor (VEGF) and anti-angiogenic factors like pigment-epithelium derived factor are optimally balanced within the RPE. Oxidative stress and the accumulation of deposits within the RPE and Bruch's membrane may disrupt this balance[65,66] upregulating VEGF, which increases vascular permeability and angiogenesis, contributing to the development of CNV.[67–69]

There is evidence that choroidal circulation attenuation may be responsible for development of ARMD. Ninety per cent of the oxygen requirement of the photoreceptors is provided by the choroidal circulation[70] and reduced choroidal blood flow has been associated with ARMD.[71,72] Choriocapillaris density and lumen diameter reduce with age,[73] which may decrease oxygen to the RPE and photoreceptors and reduce clearance of waste products from Bruch's membrane, leading to its thickening with age.[13] Retinal hypoxia increases the release of VEGF within Ruysch's complex leading to CNV.[74] Vascular deficits are further advanced in AMD75 with a linear relationship between reduced choroidal blood flow and increased risk for development of CNV.[76] Retinal hypoxia drives the synthesis of VEGF, which gives rise to the angiogenesis seen in CNV.[77]

Factors Associated with an Increased Risk of Age-related Macular Disease Development

There are many modifiable and non-modifiable risk factors that have been linked with an increased risk of developing ARMD. When reporting risk, many studies use either the odds ratio (OR) or the relative risk (RR). The OR is the ratio of the odds of a disease occurring in people exposed to a risk factor to the odds of it occurring in people not exposed to a risk factor. The RR is a ratio of the probability of a disease occurring in a risk factor exposed group versus a non-exposed group. The hazard ratio (HR) is a ratio of the chance of events occurring in people exposed to a risk factor compared with people not exposed to a risk factor. Estimates of OR, RR or HR greater than 1.0 are statistically significant and suggest a positive association or increased risk of developing a disease. If described in the literature, statistically significant OR, RR and HR are reported in this article.

Modifiable Risk Factors

Smoking

Smoking is the one modifiable risk factor that has been largely consistently associated with an increased risk of developing ARMD.[78–86] The Rotterdam study found that the higher the pack-years smoked, the higher the risk of developing neovascular AMD, with a 6.6-fold increase in risk for developing neovascular AMD compared with non-smokers.[87] The Pathologies Oculaires Liees a l'Age (POLA) study found an increased risk of neovascular AMD and GA in people who smoked for more than 20 years (OR 3.0 for 20–39 pack-years and 5.2 for 40 pack-years). The risk remained elevated until 20 years after smoking cessation.[88] Smoking was not associated with risk for ARM development in this study. Increase of ARMD development risk with increase in smoking was also demonstrated in a study by Seddon et al.[89] in a 12-year prospective study of 31,843 women with a RR of 2.4 for developing AMD compared with women who never smoked. This was echoed in a 12-year prospective study of 21,157 males by Christen et al.,[90] showing a RR of 2.46. The Rotterdam study results are echoed in a study on Japanese men with an OR of 2.97 in smokers compared with non-smokers of developing neovascular AMD.[91] All of these studies show that even previous smokers who had ceased smoking still had an elevated risk of ARMD development compared with non-smokers, but not as elevated as current smokers. A study undertaking pooled and separate analysis of 14,752 participants from the Beaver Dam eye study, the Rotterdam study and the Blue Mountains eye study showed that apart from age, smoking was the only consistent risk factor associated with any form of ARMD (OR 3.12).[92] This pooled study was taken from three different continents (North America, Europe and Australia). Another study based on 3,271 Australians also highlighted this consistent association for AMD and smoking (OR 2.39).[93] A review of the literature in conjunction with New Zealand morbidity and smoking prevalence data estimated that 26.8 % of all AMD cases were attributable to current and past smoking in New Zealand.[94] In the UK, a two-fold risk of ARMD has been associated with smoking when compared with non-smoking in 28,000 individuals (OR 2.15).[95] Cigar smoking in India has also been linked with a higher risk for developing AMD (OR 3.29).[96] A study of Latino subjects also demonstrated an association between smoking and AMD in the Hispanic population (OR 2.4).[97] The effects of passive smoking on AMD risk have been examined in a UK study comparing 435 people with end-stage AMD with 280 healthy controls. The results showed an OR of 1.87 in passive smoking exposure in non-smokers.[98] This prolific evidence across continents and differing ethnicities suggests that smoking is highly toxic to the retina, although the pathogenic mechanisms between smoking and retinal toxicity still remain unclear.

There are approximately 4,000 toxic components in cigarette smoke, one of which is nicotine. A study assessing the effects of nicotine on the vascular smooth muscle cells confirmed that nicotine increases CNV size and severity in laser-induced CNV in the mouse eye model.[99] Nicotine attaches to nicotinic acetylcholine receptors on photoreceptors, bipolar, horizontal and ganglion cells.[100] Tar within cigarette smoke contains hydroquinone – an oxidant that in the mouse eye has been shown to encourage sub-RPE deposits and thickening of Bruch's membrane.[101] Cadmium is another toxic oxidant found in cigarette smoke; higher urinary levels in smokers have been linked with an increased risk of AMD.[102] It accumulates at levels 2.5 times higher in the choroid–RPE complex of smokers compared with non-smokers[103] and increases reactive oxygen species, alters RPE cell morphology and decreases cell survival.[104] Studies on mice eyes have demonstrated that chronic exposure to smoke causes changes to the RPE similar to those observed in AMD, with RPE apoptosis, increased oxidative damage,[105] DNA damage to the RPE and increased inflammatory activity.[106]

The effects of the combination of smoking and genetics of ARMD have been analysed in many studies. An additive effect of smoking for increased risk of developing ARMD has been shown when there is a genetic disposition for the disease.[107–111]

Alcohol Intake

Studies assessing the association between ARMD risk and alcohol intake have shown inconsistent findings.[85,112,113] A relationship between beer consumption and risk for CNV has been identified in the Beaver Dam eye study (OR 1.41), although no such relationship was seen with wine or spirit consumption.[114] This was echoed in subjects from the Latino community with beer consumption (OR 2.9) and high alcohol intake (OR 5.8) being linked with a greater risk of developing the disease.[97] Conversely, no association between any type of alcohol and ARMD risk has been shown in other studies.[97,115–117] Interestingly, moderate wine consumption has been associated with a decreased risk of developing AMD (OR 0.86)[118] and in the Reykjavik eye study alcohol consumption decreased the risk for drusen formation (OR 0.34),[119] suggesting a protective effect of alcohol against ARMD. Chronic, heavy alcohol consumption is linked with an increased accumulation of ethyl esters and an increase in laser-induced CNV of 28 % within the rat choroid models.[120] Ethanol is the key component of alcohol. When photoreceptor outer segments of zebrafish are exposed to ethanol this leads to inhibited photoreceptor outer segment growth, leading to poor photoreceptor function as demonstrated by reduced a- and b-wave amplitudes of the electroretinogram (ERG).[121] Red wine has a high level of phenolic compounds that increase antioxidant activity, which may reduce oxidative stress and abnormal proliferation of the RPE.[122]

Socioeconomic Factors

Socioeconomic factors have been inconsistently associated with an increased risk of developing ARMD. A Canadian study looking at socioeconomic status and CNV found that the severity of CNV appeared to be associated with lower socioeconomic status, although ORs or RRs were not provided in this study.[123] However, in another Brazilian study assessing AMD in two differing socioeconomic populations no association between AMD and socioeconomic background was seen (p=0.113).[124] No association was demonstrated between ARMD and socioeconomic factors in a case–control study by Hyman et al.[35] or in the Framingham eye study,[125] the Beaver Dam eye study[126] and the third National Health and Nutrition Examination Survey (NHANES) study.[127] Although the underlying reasons for increased risk of ARMD development with lower socioeconomic status have not been determined, possible mechanisms include the underuse of eye care services, poor nutrition and exposure to adverse work and home environments.

Education

The Age-related eye disease study (AREDS) report number three found that people with higher education had a lower risk for developing drusen (OR 0.73), GA (OR 0.45) and CNV (OR 0.44).[128] The Eye Disease Case–Control Study Group (EDCCS) found a similar trend for education and neovascular AMD risk (OR 0.7 when 12 years of education or greater was completed compared with those who completed less than 12 years of education), although no statistical significance was demonstrated in their final multiple regression model.[78] The first NHANES study also demonstrated this association (OR 0.64) but statistical significance was lost on logistic regression modelling.[129] The mechanisms associating risk for ARMD development and educational level are not clear. People with lower educational level are more likely to be unemployed or in lower incomes jobs, leading to poorer socioeconomic status. Lower education may limit the ability to read and comprehend the importance of health literature.

Nutrition

Nutrition as an associated risk factor for developing ARMD has also been subject to conflicting findings in the literature. The first NHANES study found high levels of dietary vitamin A provides a protective effect against AMD (OR 0.74) with no beneficial effect shown with vitamin C.[129] The Beaver Dam eye study found no association between vitamins A, C and E and reduced risk of developing ARM.[130] Another study of serum lycopene in the Beaver Dam eye study showed an increased risk of ARMD with reduced lycopene levels (OR 2.2).[131] However, lower levels of lutein, zeaxanthin and vitamin E were not related to an increased risk for ARMD development in this study. Conversely, higher serum alpha tocopherol was found to be conducive to lower ARMD risk in the Baltimore longitudinal study (OR 0.43).[132] The Physicians Health study and the Blue Mountains eye study did not find a protective effect for vitamin C, E and multivitamins[133] and vitamin E and beta carotene[134] against ARMD, respectively. The EDCCS found a 70 % reduced risk of AMD with high (>0.67 µmol/l) compared with low (0.25 µmol/l) levels of serum carotenoids.[135] A further study from the EDCCS reported that spinach and collards, high in the carotenoids lutein and zeaxanthin, were most strongly associated with a reduced risk for AMD (p<0.001).[136] Collard greens are various loose-leafed vegetables of Brassica oleracea, the same species that produces cabbage and broccoli. They are genetically similar to kale and spring greens. Eyes with intermediate drusen, large drusen and non-central GA of people taking high-dose vitamins C, E, beta carotene and zinc were found to have a lower risk (OR 0.72) of developing advanced AMD in a large trial undertaken by the AREDS group.[137] Improvements in visual function in eyes with ARM or non-exudative AMD were reported in several studies involving carotenoids.[138–141]

High levels of omega-3 fatty acid consumption (≥64.0 mg/day versus <26.0 mg/day) have been shown to provide a protective effect against progression to AMD (HR 0.73).[142] Lowering the dietary glycaemic index with higher omega-3 intake also showed a reduction in AMD progression in this study (p<0.001). The benefits of a low glycaemic diet in reducing ARM risk have been identified in other studies.[142–144] The Blue Mountains eye study found a lower risk of developing ARM

when consuming omega-3 fatty acids in the form of one serving of fish per week (RR 0.69).[145] Consumption of linoleic acid in the form of one to two servings of nuts per week was also associated with reduced ARM risk in this study (RR 0.65). The AREDS studies found a reduction in risk of progression from drusen to GA in people with the highest dietary intake of omega-3 fatty acid (OR 0.45)[146] and reduced risk of developing neovascular AMD (OR 0.61[147] and 0.68[148]) and GA (OR 0.65).[148] It is thought that omega-3 provides a protective role in the retina by inhibiting oxidative stress and reducing inflammation in the retina.[149]

An association between higher trans-unsaturated fat intake and increased prevalence of AMD was reported in a large study of 6,734 people (OR 1.76).[150] Omega-3 fatty acids and olive oil were associated with a reduced prevalence of ARM and AMD in this study (OR 0.85 and 0.48, respectively). However, the third NHANES results showed no association between dietary fat intake and ARM risk in 7,883 people[151] and this was echoed in 3,654 people taking part in the Blue Mountains eye study.[152] Studies of mouse retinae have shown an increase in the accumulation of basal laminar deposits when consuming a high fat and cholesterol diet.[153] Some studies have shown that diets higher in fats have a propensity to be lower in essential nutrients and antioxidants.[130,154]

Body Mass Index

A high body mass index (BMI) has been inconsistently linked with risk for developing ARMD. The Blue Mountains eye study found an OR of 1.78 for risk of early ARM in people with obesity compared with those with a normal BMI.[155] The AREDS group reported that a higher BMI was associated with a risk for developing neovascular AMD[156] and GA (OR 1.93).[157] A 2.29-fold risk of AMD and a 1.54-fold risk of pigmentary abnormalities were demonstrated in the POLA study in people with obesity.[158] The RR was 2.35 for a BMI of 30 or more and 2.32 for a BMI of 25–29 for developing AMD in another study.[159] Larger waist circumference (RR 2.04) and a larger waist–hip ratio (RR 1.84) also increased the risk of progression to AMD.[159] An inverse relationship between BMI and retinal levels of L and Z (often referred to as macular pigment optical density) was reported.[160] The authors also assessed dietary L and Z intake and found that people with the highest BMI consumed lower amounts of L and Z. They concluded that lower dietary intake of L and Z, and/or competition between adipose tissue and retina for L and Z uptake were likely to affect retinal levels of L and Z.[160] Conversely, associations between lean men and dry AMD have been found.[161] A pooled study of 14,752 people from the Beaver Dam eye study, the Rotterdam study and the Blue Mountains eye study did not report any consistent association between BMI and risk for any forms of ARMD[92] and this was echoed in other studies.[86,162]

Cardiovascular Disease

Cardiovascular disease (CVD) has been associated with risk for developing ARMD in several studies and discounted in others. The Beaver Dam eye study showed no association between CVD and neovascular AMD or GA.[163] Arterial stiffness – an indicator for CVD, has been shown to be associated with the presence of AMD.[164] The Blue Mountains eye study did show associations between CVD (RR 1.57) for early incident ARM.[165] C-Reactive protein is an inflammatory marker for CVD. Some studies have shown increased levels of C-reactive protein in ARMD,[166–168] suggesting an inflammatory role in the development of ARMD. Conversely, better cardiovascular health was associated with an increased risk of ARMD in the Cardiovascular Health and Age-Related Maculopathy (CHARM) study (OR 2.54).[169] The POLA study showed a reduced risk (OR 0.72) for developing drusen and no association between AMD and a history of cardiovascular disease.[158] No association between CVD and ARMD risk was reported in the AREDS studies,[128,157] the EDCCS study[78] or Smith et al.'s pooled analysis from the Rotterdam, Blue Mountains and Beaver Dam eye studies.[92] Hyman et al. found a link between ARMD and CVD (OR 1.7)[35] in an earlier study but not in a later study.[170]

Hyman et al. also found an association between moderate to severe hypertension (diastolic >95 mmHg) and risk for developing neovascular AMD (OR 4.4), especially in people receiving antihypertensive medication.[170] The same association was not found for GA and hypertension, leading the authors to suggest that comparable disease processes may occur in neovascular AMD and hypertension.[170] Reduced choroidal blood flow in people with hypertension with neovascular AMD may account for this relationship.[171] The Framingham eye study[125] and the first NHANES study (OR 1.5 for systolic blood pressure≥170 mmHg)[129] reported links between ARMD development risk and hypertension. The AREDS group found increased risk for developing neovascular AMD (OR 1.45) and large drusen (OR 1.19) in people with hypertension and those taking hypertensive treatment,[128] although no association with incident neovascular AMD was seen in a further AREDS study.[157] Hypertensive disease severity has been linked with neovascular AMD, with doubled odds in the severest of hypertension (OR 3.21).[172] The Beaver Dam eye study,[173,174] the Blue Mountains eye study165, the EDCCS[78] and others[175,176] found no evidence to suggest that ARMD development risk and hypertension are linked.

Cholesterol Levels and Treatment

Links between cholesterol levels, cholesterol-lowering treatments and risk of ARMD development have been conflicting. A possible protective effect of statins and lipid-lowering treatments against ARMD has been found in a number of studies (OR 0.14–0.79).[177–181] Some studies have suggested statins protect the vascular endothelium from oxidative damage[182] and reduce basal linear deposit accumulation in Bruch's membrane by reducing cholesterol.[183] Conversely, an article assessing pooled data on the use of statins and lipid-lowering treatments did not show a reduced risk of developing ARMD when using statins.[184] Pooled data analysis of the Beaver Dam, Rotterdam and Blue Mountains eye studies did not report the effects of statins on ARMD risk.[92] Other studies have found no association between statin use and reduced risk for developing ARMD.[158,185–187] Furthermore, an observational study reported an increased risk of ARMD development in people taking statins (OR 1.19).[188] In the EDCCS higher levels of cholesterol were associated with an increased risk of neovascular AMD (≥6.7 mm/l=OR 4.1),78 but no information about statins was presented in this study. The AREDS study also did not provide data about statin use or cholesterol levels.[128] The benefits of statins for reducing heart disease and lowering cholesterol were not largely reported and routinely used until 1994[189] and this is the likely reason for the lack of data before this period. The first NHANES study found no association between cholesterol levels and risk for ARMD development, but again statins were not assessed here as the study results were published in 1988.[129] Higher HDL cholesterol levels were protective for late AMD (RR per standard deviation increase 0.74), and a high total/HDL cholesterol ratio was linked to an increased risk of late AMD (RR per standard deviation increase 1.35) and GA (RR per standard deviation increase 1.63) in the Blue Mountains eye study.[165] Statins (HR 0.51) and aspirin (HR 0.63) were found to be associated with reduced rates of CNV in a retrospective study of 326 patients

as possible mechanisms for increasing AMD risk after cataract extraction.[226] Other studies, such as the AREDS group report 25, found no risk of ARMD progression after cataract surgery.[227,228] It has been postulated that the cataract itself increases the risk of developing ARMD. In pooled findings from three studies severe cataract was associated with a higher prevalence of AMD, although this was not statistically significant.[229] Studies assessing the risk of ARMD development associated with the use of newer intraocular lenses with short-wavelength blue light filtering properties may provide more information in the coming years.

Cognitive Impairment

Evidence from the AREDS group showed a trend between reduced cognitive impairment and increased risk of AMD development ($p<0.01$ for a mental state examination and 0.048 for a logical memory test).[230] This was resonated in people with ARM in the Cardiovascular Health Study (OR 1.38),[231] a weak association in another study (OR 1.6 for ARM)[232] and in people with AMD in an Australian population (OR 2.2).[233] The Rotterdam study demonstrated that tobacco and atherosclerosis may play a role in the pathogenesis of both ARMD and Alzheimer's disease.[234] Amyloid beta peptide is found in the neuritic plaques in Alzheimer's disease and also in drusen. It contributes to inflammatory processes in both of these diseases[235] and in many neurodegenerative diseases of ageing such as Parkinson's disease, arthritis, atherosclerosis and myocardial infarction.[236] Many people with ARMD reduce their physical and mental activity levels, which is associated with cognitive decline.[237] Conversely, no significant relationship was established between Alzheimer's disease and ARMD[238] in 33 people with Alzheimer's disease compared with 24 controls. The authors believe that a small sample size and age differences between the groups may have accounted for the lack of any relationship. They did not specify between ARM or AMD for their study.

Gender

Female gender has been associated with increased risk for development of ARMD, although no consensus seems to prevail. A Croatian study of 6,617 patients found that ARMD incidence was slightly increased in women compared with men (56 versus 46 %).[5] This was echoed by the AREDS group, with ARM being more apparent in women (OR 1.22)[128] and in other work (no OR, RR or HR reported).[216] However this was not replicated in a pooled analysis from the Beaver Dam, Rotterdam and Blue Mountains Eye studies.[92,239] Men were more likely to undergo photodynamic therapy than women for neovascular AMD in an Israeli study (0.21 versus 0.16 %, $p=0.03$)240 and were more likely to have AMD than women in two Japanese studies (statistical significance was not reached in one of the studies, but the other having an OR of 2.97).[241,242] The authors suggest that this may be due to the significantly higher proportion of Japanese men who smoke. A recent study of the Beaver Dam offspring study also showed that being male was associated with ARM (OR 1.65).[86]

Arthritis

An association between arthritis and increased likelihood of ARM was reported in one AREDS study (OR 1.26),[128] whereas another AREDS study suggested a protective effect of anti-inflammatory medications against AMD development (OR 0.22).[157] One study found people with rheumatoid arthritis had less prevalence of AMD and suggested anti-inflammatory agents, commonly used to manage the symptoms of rheumatoid arthritis, provide a protective effect against development of ARMD,[243] since there is some evidence that inflammation may play a role in the development of ARMD.[244] However, environmental and genetic factors may also be relevant as rheumatoid arthritis is commonly a disease of the young and ARMD is more apparent over 50 years of age.[245]

Ethnicity

Higher prevalence of ARMD has been shown in white people compared with black people, although genetics, culture and diet may play a role in these differences. Darker iris pigmentation may also confer some protective effect in the black population.[246] The AREDS group found a higher risk of developing large drusen (OR 1.88) and CNV (OR 4.22) in white people.[128] A further AREDS study echoed these results for incident CNV (OR 6.77).[157] However, no such association was found in a Brazilian study of 107 people with ARMD.[124] In the Salisbury Eye Evaluation project the risk of developing large drusen (OR 2.10) and RPE pigmentation (OR 2.22) was higher in white people than in black people but the risk of developing GA or CNV was no different for white and black people.[247] A south Indian study found a prevalence of AMD in its population similar to other developed countries.[96] A Japanese population study reported similar prevalence of ARM to the white population of the Blue Mountains eye study. This similarity also held true for AMD in Japanese men, but AMD prevalence was lower in Japanese women compared with the Blue Mountains Eye Study population. This disparity was assumed to occur because of a high proportion of Japanese male smokers according to the authors.[241] Another Japanese study compared the incidence of ARMD in the Japanese population with the Beaver Dam eye study, the Blue Mountains eye study (both with a predominantly white population) and the Barbados eye study (a predominantly black population).[242] The authors concluded that the nine-year incidence of ARMD was lower among the Japanese population than among white people, but AMD was higher in the Japanese population than among black people. The prevalence of ARM in South Koreans was also found to be similar to other studies but the prevalence of AMD was lower.[221] Exudative AMD was found to be higher in Chinese people (OR 4.3) compared with white people in a study assessing four different ethnic groups, even when smoking age, gender, pupil size, BMI, alcohol intake, diabetes and hypertension were adjusted for.[248] A putative mechanism for reduced risk of ARMD in black people compared with white people is the protective effect of the darker pigmentation of the iris[246] and higher concentrations of melanin within the choroid of black people compared with white people.[249] Melanin acts as an antioxidant, scavenging free radicals and reducing oxidative stress.[24]

Iris Pigmentation

Iris pigmentation has been inconsistently associated with an increased risk for ARMD with the EDCCS demonstrating no association between iris colour and neovascular AMD,[78,250] incident ARMD[251] or GA.[250] Conversely light irises were associated with increased risk for ARMD in other studies (OR 1.22–5.0).[218,252,253] Blue iris colour was linked with increased risk of both ARM and AMD in the Blue Mountains eye study (OR 1.69).[254] However, five years later, longitudinal data did not support this association. A study of 1,000 Danes also showed no difference between light iris and dark iris colour for AMD.[255]

Hypermetropia

Hypermetropia and its associated shorter axial length have been linked with increased ARMD development risk[35,256–260] (in these studies, either $p<0.05$ or OR 1.54–2.4, depending on the statistics used). An association

with ARMD.[178] Aspirin was not found to be related to an increased risk of ARM or AMD development in the AREDS study,[128] but was positively correlated in a later AREDS study (OR 1.88).[157] It was not linked in other studies[190–192] or its effects were not reported.[35,78,129]

Medication

Conflicting associations between the use of other medication and risk for developing ARMD have been reported. Those with GA were more likely to take antacids (OR 2.13) and those with large drusen or extensive intermediate drusen were more likely to take hydrochlorothiazide diuretics (OR 1.51) in one AREDS report.[128] Antacid use was associated with a reduced risk of developing GA (OR 0.29) in another AREDS group study.[157] This report also highlighted an association between anti-inflammatory medication and reduced incidence of GA (OR 0.22). In a further study assessing the use of antacids and thiazide diuretics in ARMD no relationship was found for increased risk of the disease and either medication.[193] Van Leeuwen et al. found an increased risk for ARM development in people taking antihypertensive treatment (OR 1.3) and a decreased risk in women taking tricyclic antidepressants (OR 0.4).[194]

Hormones

The use of differing hormones has been associated with risk for developing ARMD. Thyroid hormones were associated with an increased risk of GA in the AREDS study (OR 1.99), although the use of oestrogen and progesterone in women was not associated with any form of ARMD in this study.[128] Thyroid and antithyroid hormones were not associated with ARMD in another study.[193] There was also no association between the use of hormone replacement therapy (HRT), hysterectomy or oopherectomy in women and ARMD risk in the POLA study.[195] However, a protective effect of HRT was found in another study, with a 48 % lower risk of developing CNV compared with women who had never used HRT, although no protective effect was found for ARM.[196] A reduced risk of developing ARM was seen in another study in women taking HRT (OR 0.6).[194] A lack of oestrogen was shown to be associated with an increase in basal laminar deposits and thickened Bruch's membranes in mice retinae.[197] The authors postulated that oestrogen downregulated matrix metalloproteinase-2, which is responsible for breaking down Bruch's membrane and RPE basement membranes. Another study demonstrated that a lack of oestrogen upregulates a glycoprotein called YKL-40, leading to CNV. The function of YKL-40 in the retina is unknown.[198]

Type II Diabetes

Inconsistent links between type II diabetes and ARMD risk have been described. The Blue Mountains eye study also found a relationship between type II diabetes and development of GA after 10 years with a RR of 3.89, but no relationship for neovascular AMD.[165] Type II diabetes was associated with an increased risk for developing ARMD compared with type I diabetes ($p<0.001$) and controls ($p<0.005$).[199] The European Eye study (EUREYE) and AREDS group demonstrated a relationship between type II diabetes and risk of neovascular AMD development (OR 1.81 and 1.88, respectively) but not for GA and type II diabetes.[157,200] Conversely, a study assessing the 10-year follow-up of 133 people with newly diagnosed type II diabetes and 144 controls found no significant difference between groups in risk for ARMD development over the 10 years.[201] No relationship between type II diabetes and ARMD was seen in the POLA study,[158] a further Blue Mountains eye study[155] or reported by others.[78,92] The mechanisms for any association between diabetes and ARMD are unknown. Hyperglycaemia in diabetes has been associated with reduced choroidal circulation within the foveal area.[202,203] This may reduce the exchange of oxygen, nutrients and waste products within the outer retina, which may increase susceptibility to ARMD.

Sunlight Exposure

There are contradictory findings in the literature about the relationship between exposure to sunlight and risk for ARMD development. No statistically significant associations were reported in a Brazilian study,[124] an Italian study[204] or studies from other global locations.[78,128,205,206] Intriguingly, two studies demonstrated a protective effect of light against ARMD (OR 0.73 in one study and annual sun exposure of controls at 940 versus 770 hours in those with ARMD, $p=0.0002$).[207,208] However, other studies have shown a detrimental effect of sunlight with increased risk of ARMD development. Blue light exposure was associated with an increased risk of developing GA in a study of 838 watermen (OR 1.36).[209] The Beaver Dam eye study found a relationship between high sunlight exposure and a higher 10-year incidence of ARM (RR 2.20),[210] with sunglasses and headwear providing protection against drusen development (RR 0.55) and RPE depigmentation (RR 0.51). The Blue Mountains eye study found that high (OR 2.54) and low (OR 2.18) skin sensitivity to sunlight was associated with AMD but not ARM.[211] Retinal photochemical injury occurs cumulatively over a long period to tolerable light levels. Sunlight damages the RPE-photoreceptor complex, causing the formation of free radicals that peroxidise the fatty acids within the photoreceptor outer segments, leading to RPE and photoreceptor dysfunction and death.[212] Free radicals also increase the production of lipofuscin in RPE cells. A2E, a major fluorophore of lipofuscin, generates free radicals in response to light, which leads to RPE apoptosis.[213]

Miscellaneous

Other, less reported modifiable risk factors inconsistently associated with ARMD include parity greater than zero. Increased risk of neovascular AMD has been seen with parity greater than zero in the EDCCS study (OR 1.8)[78] but this relationship is not apparent in another study.[214] Conversely, parous women were found to have a 26 % lower risk of developing ARM[196] in a more recent study. Although not clear, hormonal mechanisms such as the effects of oestrogen mentioned previously may play a role.

Non-modifiable Risk Factors

It is well reported that increasing age is strongly linked with a higher risk of developing ARMD[92,96,128,204,215–221] and certain genes have been recognised for their association with disease development, but there are other non-modifiable risk factors for developing the disease that are inconsistent in the literature.

Cataracts and Intraocular Lenses

Cataracts are known to protect the retina by reducing the amount of ultraviolet and blue light entering the eye. Thus, after cataract extraction, the retina is subjected to increased light levels and increased photochemical damage. The Blue Mountains eye study and the Beaver Dam eye study found an increased risk for developing ARMD in eyes that had undergone cataract surgery (OR 1.3–5.7 in these studies).[222–224] This was evident in other work, showing an increased risk of AMD in eyes after cataract extraction, with neovascular AMD developing in 19.1 % of post-cataract surgery eyes compared with 4.3 % of non-operated fellow eyes.[225] Intra-operative photic damage and surgical inflammation have also been discussed

between ARM risk and hypermetropia was found in the Blue Mountains eye study (OR 2.0)[261] and the Rotterdam study (OR 1.20 for advanced hyperopia compared with emmetropia).[262] In a further Blue Mountains eye study no association was found between hypermetropia and the five-year incidence of ARM.[263] Large drusen (OR 1.28) and CNV (OR 2.31) were associated with hypermetropia in the AREDS study.[128] Other studies have reported no effect of hypermetropia on risk for developing ARMD.[124,264] A biological mechanism for increased risk of ARMD with hypermetropia has not yet been elucidated. One study suggests shorter, thicker eyes with increased scleral rigidity decreases choroidal blood flow and thus retinal nutrient and waste exchange, leading to increased oxidative stress.[262]

Miscellaneous

Other, less reported non-modifiable risk factors inconsistently associated with ARMD include hand-grip strength, optic disc appearance and birth weight. A couple of studies have linked decreased hand grip strength to increased risk for AMD (no OR, RR or HR given).[35,125] Unusual optic disc appearance has been associated with ARMD risk (no risk statistics reported)[265] but repealed in other studies.[266,267] Babies with increased birth weight were found to have a higher possibility of developing AMD than those with lower birth weight in one study (OR 1.5)[268] and this was echoed in another study, but only in white people for ARM (OR 1.2), although AMD risk was not assessed in this study.[269]

Summary

There are many risk factors associated with ARMD development, with varying degrees of consistency. Age, smoking and genetics appear to be congruously linked with increased risk for developing the disease. With the costly management of neovascular AMD and limited treatment for dry AMD, the potential for modification of environmental factors in reducing the risk of ARMD development is an important research area. The oxidative stress theory for the aetiology of ARMD provokes interest in how antioxidants may play a role in reducing the risk of disease development and progression. ■

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