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Chapter 1

# AMD: Epidemiology and Risk Factors

Jane Khan

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## 1. Introduction

Age-related maculopathy (ARM) and age-related macular degeneration (AMD) are stages in a process of degeneration of the central macular region of the retina defined as occurring over the age of 50. This chapter examines the evidence for environmental and genetic risk factors for developing AMD.

## 2. Epidemiology

### 2.1. Burden and impact of disease

*2.1.1. Incidence*

Incidence rates for all ARM lesions increases significantly with age. In the Blue Mountains Eye Study (BMES) Mitchell et al found overall 5-year incidence of late ARM lesions (combined geographic atrophy and neovascular ARM), was 1.1%. Age specific rates were 0.0%, 0.6%, 2.4%, and 5.4% for participants aged 60 years and younger, 60 to 69 years, 70 to 79 years, and 80 years and older at baseline, respectively [1]. After excluding participants with either early or late ARM in either eye at baseline, the overall 5-year incidence of early ARM was 8.7%, (3.2%, 7.4%, 18.3%, and 14.8% for the corresponding age. The findings parallel those in the Beaver Dam Eye Study (BDES) where it was noted those 75 years of age or older have significantly higher 5-year incidence of exudative macular degeneration (1.8% vs. 0%), and pure geographic atrophy (1.7% vs. 0%) than people 43 to 54 years of age [2].

Individual ARM fundus signs that predict best the development of AMD are large drusen (> or =125 microm) [3], 10% or more of the grid area covered by drusen [3], soft indistinct drusen [2] and focal hyperpigmentation [2;4]. There is a high risk of second eye involvement with

annual incidence of CNV occurring in the second eye of patients with CNV in the first eye reported as between 6-15% [5;6].

*2.1.2. Prevalence*

Age-related macular degeneration is the third largest world cause of visual impairment, and in Western countries it is often the leading cause of blindness. In the UK and USA for example it is the leading cause of blind registration [7;8 9;10] accounting for nearly 50% of blind and partial sight registrations in all age groups and nearly 55% in the over 65 age group. There is evidence to suggest the incidence of AMD is increasing. Evans and Wormald examined data from the Office of Population censuses and Surveys in the UK and compared available data for the years 1950, 1960, 1970 1980 and 1990 [11] and were able to demonstrate an increase in percentage registrations due to AMD by 30%. Population studies give prevalence figures of 2-10% for ARM in the age range 50-75. Thereafter, the frequency rapidly increases to figures of around 15% and nearing 50% in those over the age of 85. These prevalence figures vary according to the diagnostic criteria used hence the studies performed to date, with the exception of those using the International or Wisconsin grading systems, are difficult to compare. Whether or not the incidence is increasing there is no doubt that with the ageing population, the prevalence is increasing and the impact on the individual to be able to live independently will also have an indisputable impact on society.

**2.2. Impact of AMD on the individual**

*2.2.1. Mortality*

There is some evidence to suggest that poor vision is associated with increased mortality and co-morbidity in elderly people [12;13]; although interestingly those with much more severe visual impairment may actually live longer, perhaps due to leading more 'sheltered lives' [14]. However recent data suggest that AMD in itself is not associated with increased mortality but acts as a marker for other diseases which do [15].

*2.2.2. Mental health, quality of life and well-being*

Visual impairment has been shown to be more age-related than any other disability [7] and visually impaired elders may be at more risk of affective disorders, particularly depression [16]. Williams et al assessed the impact of AMD on quality of life and well-being [17]. The authors found significantly poorer ratings for quality of life and emotional distress in patients with AMD compared with age-matched adults and the rates were comparable with those reported for chronic illnesses (e.g. arthritis, bone marrow transplantees, chronic obstructive airways disease) [18]. Unpublished data (Jan Mitchell BSc, Royal Holloway, University of London) indicates that the Macular Disease Society Quality of Life questionnaire, incorporating the 12-item Well-being questionnaire [19], in addition to questions specifically designed to measure the impact of macular disease, showed a greater negative impact on most aspects of quality of life in macular degeneration compared with diabetes. In addition, attitudes of physicians was shown to add to the stress such a diagnosis may have on an individual by giving an impression of lack of concern or interest

in their patients and by inadequate dissemination of information about the condition or services available to aid their rehabilitation [18]. In a study by Lee et al, blurred vision caused greater decrement in functioning and well-being than many other medical conditions including heart disease, diabetes, hypertension, indigestion and headaches. Only shortness of breath had a greater impact on these parameters than blurred vision [20]. The quality of life of community-dwelling elderly people has been shown to be significantly linked to sensory impairment. Mood level and social relationships are particularly affected by visual impairment [21]. A survey, using the VCM1 questionnaire [22] (a questionnaire designed to measure vision-related quality of life) lead to an estimate of more than 550,000 individuals in England with substantial vision-related quality of life impairment [23].

*2.2.3. Falls and functional ability*

Falls among the elderly are a major cause and result of morbidity and studies indicate that 30% of persons over the age of 65 may suffer a fall each year, increasing to 40% in those over 80 [24]. Tinetti et al demonstrated that although visual impairment was not the single most common cause of falls in the elderly it had a significant additive effect in this multifactorial condition [25]. Other studies have been able to show a significant positive association between reduced contrast sensitivity, reduced visual acuity and self-reported visual impairment [26;27] and falls. Older people tend to need to rely more on vision to maintain vertical posture [28]. Hip-fracture is clearly a serious consequence of falls in the elderly and has provided an objective outcome measure in assessing the relationship between poor vision and falls in the elderly. Cummings et al performed a detailed prospective study of 9516 white women over 65 years of age and found that poor contrast sensitivity and reduced depth perception were independent risk factors for hip fracture [29]. The Blue Mountains Eye Study has subsequently confirmed that measured visual impairment is associated with both falls and hip-fracture [30].

*2.2.4. Driving and independence*

Independence is an important measure of quality of life for older people. Being able to continue driving is often seen as the most valuable means of maintaining this independence. Macular degeneration and macular haemorrhage were found in one study to be among the six most frequent medical conditions for driving cessation in community-based ambulatory individuals over the age of 70 [31]. Evidence exists to show that older drivers with visual impairment and/or a constriction in the size of the useful field of view to be at greater risk for vehicle crashes than those without these problems [32]. Studies have also been able to show in more general terms loss of independence for example, in a survey by Branch et al of self-reported vision loss in those over the age of 65 Activities of Daily Living needs such as housekeeping, grocery shopping, and food preparation were largely unmet [16] and Williams et al found that people with macular degeneration were more likely to need help with daily activities [17].

### 2.3. Impact of AMD on society

It is difficult to quantify the financial burden of AMD disease on society and there have been few studies specifically addressing this complex subject. In the UK for example, the

National Health Service (NHS) spends more than £20 billion per year on long-term, residential and home care and it can be envisaged that redirecting a fraction of this sum towards helping people maintain independence such as by the provision of inexpensive low vision aids may save billions of pounds per year [33]. Scuffham et al [34] examined the cost of injurious falls associated with visual impairment in the UK and showed that the National Health Service currently spends £1.7 billion per year treating hip fracture resulting from falls and given that older people with sight problems are more likely to fall than non-visually impaired older people this sum might be significantly reduced by attending to visual impairment. Studies have also looked at individual ocular diseases in order to quantify the cost-effectiveness of treatment verses no treatment which is an important consideration with an ever increasing financial burden of healthcare [35]. Photodynamic therapy (PDT) and the use of Anti-Vascular endothelial growth factor (VEGF) treatments have highlighted this controversy and rationing in health care has, as yet, prevented this treatment from being made available to all. Sharma et al determined the cost-effectiveness of PDT for the treatment of subfoveal choroidal neovascularisation (CNV) in patients with disciform degeneration in one eye and who's second and better-seeing eye develops visual loss secondary to predominantly classic subfoveal CNV. The authors concluded that PDT can be considered to be a treatment that is of only minimal cost-effectiveness for AMD patients who have subfoveal CNV in their second and better-seeing eyes and who have good presenting visual acuity at baseline and is a cost-ineffective treatment for AMD patients who have poor visual acuities in their affected better-seeing eyes [36]. However the same authors also examined the expected gain in quality of life-adjusted life-years (QALYs) associated with photodynamic therapy for the treatment of subfoveal CNV. Photodynamic therapy was associated with a relative increase in QALYs of 11.3% compared with placebo [36]. This example alone highlights the problems of attempting to cost quality of life.

Epidemiological data for many of the issues outlined here is often scarce and may be non-comparable between studies, however epidemiological studies remain an important tool for assessing the distribution and determinants of disease in a population and can be used to evaluate interventions.

## 3. Risk factors for AMD

The search for modifiable risk factors for AMD has gained impetus over the past two decades and this has largely stemmed from the development of clearer definitions of disease. The advent of appropriate grading scales [37;38], knowledge of natural history and progression and the identification of sub-types of AMD, enables comparison and corroboration of data between studies, adding weight to putative risk associations. However, some of the data can be conflicting due to the large numbers of possible risk factors assessed. Despite the limitations of these studies, there has been consensus that age, smoking and genetic make-up are risk factors for developing AMD.

### 3.1. Demographics

#### *3.1.1. Age*

Age is the strongest risk factor for AMD and ARM. An age of 50 yrs was taken to be the minimum criteria for the findings of drusen and other changes to be described as ARM in the International Classification System of age related maculopathy [37] and this has generally been accepted as the cut-off for defining maculopathy as being age-related. In a meta-analysis all studies found a strong association with increasing age [39]. Population studies universally show increasing prevalence with age [9;40-43]. A meta-analysis of three large population studies by Smith et al gives age-specific prevalence of sub-groups of ARM and AMD [44]. The authors reviewed the findings from the Beaver Dam, Rotterdam and Blue Mountains eye studies. All these studies used the Wisconsin grading system for ARM and AMD enabling direct comparisons between prevalence rates. The AMD lesions, namely geographic atrophy (GA) or choroidal neovascularisation (CNV) were found to have an overall prevalence of 1.63% in the populations when combined (note: the age range was from 43-99 years overall but in the analysis by Smith et al they only reviewed the data on the age range common to all three studies which was 55-86). These specific AMD lesions were not found in anyone below the age of 55 years in any of the populations. The incidence of AMD rises with age being 0.21% in those 55-64, 0.85% in those 60-74 then a dramatic rise to 4.59% in those 75-84 and 13.05% of those aged 85+ [45]. The average age at which wet AMD develops is 75 years [46]. Incidences of drusen, RPE changes, geographic atrophy, and exudative disease all increase, as exemplified by the 8- to 17-fold increased risk of developing AMD demonstrated between ages 50 and 90.

#### *3.1.2. Gender*

The evidence is conflicting for gender as a risk factor. The Beaver Dam eye study indicates both a higher incidence of early ARM in women over the age of 75(ratio 2.2:1) [2] and a higher incidence of exudative AMD in this same age group (ratio 2.6:1) [9]. This difference was not explained by selective mortality. Other studies have not been able to demonstrate this clear sex prevalence. In the Rotterdam study presence of hypo- or hyperpigmentation was higher in men but there was no difference in the sex ratio for atrophic (GA) or neovascular AMD [41]. Mitchell et al in the Blue Mountains Eye Study found consistently higher rates for AMD in women in each 10-year age-group but this difference was found not to be significant when adjusting for age in a logistic regression. They also used the same statistic on the figures from the Beaver Dam eye study using an age-adjusted relative risk of 1.27 and found the sex difference to be non-significant. Smith et al [44] found there to be no difference in the age-specific prevalence of AMD between men and women in the Beaver Dam, Rotterdam and Blue Mountains studies. Evans summarises this well and concludes that, although more studies have demonstrated a slight increased risk in women in the older age-groups, it could not be confirmed that all age-effects and health-seeking behaviours were taken into account [47]. The meta-analysis by Chakratharty et al suggests that there is no significant association between female gender and late AMD. In the case control studies included in the analysis, the overall

OR for female gender was 1.00 (95% CI 0.83 - 1.21). In the cross-sectional studies, it was 1.06 (95% CI 0.78 - 1.44) and in the prospective studies, it was 1.01 (95% CI 0.89 - 1.16) [39].

*3.1.3. Ethnicity*

Several studies have looked at incidence and prevalence by ethnicity and there are established differences. Comparison of the three large population studies from Holland, the US and Australia demonstrated a lower prevalence of neovascular AMD in the Dutch population [44]. All late forms of AMD appear to be more common in the White population as compared to Black and Hispanic populations [48;49]. However the highest frequency for exudative AMD appeared to be in Chinese (age- and gender-adjusted odds ratio, 4.30; 95% confidence interval, 1.30-14.27) compared with whites [50]. Choroidal melanin has been hypothesized to have a protective effect on the RPE, photoreceptors, and Bruch's membrane, perhaps through an antioxidant effect or an ability to absorb light rays that damage the posterior layers of the retina [51]. However, in most of these studies that included both whites and blacks, there were too few blacks with neovascular AMD to examine the reason for these racial differences. Although the incidence of neovascular AMD in blacks is lower, it is not negligible. Data from one recent study, the Salisbury Eye Evaluation, showed that the prevalence of choroidal neovascularization was 1.1% in blacks, compared with 1.7% in whites [52].

When examining specific features of age-related macular change, the Baltimore Eye Survey found large drusen (>125 microm), pigment abnormalities and AMD were more common among older whites compared with blacks. The prevalence of AMD was 2.1 % among whites over 70 years of age. No cases of AMD were detected among 243 black subjects in this age group [53]. In addition the spectrum of neovascular maculopathy in black Americans was found to differ from that typically seen in whites, both clinically and demographically. In a retrospective review of over 100 angiograms for AMD, CNV in blacks was more commonly juxtapapillary and more had CNV in the absence of drusen or other known predisposing conditions. Disciform-stage CNV in blacks was associated with a greater degree of pigment proliferation than that typically noted in whites. Demographically, there was a significant female predominance of CNV in blacks (87%) compared with population studies [54]. In Vancouver a total of 88 ethnic Chinese patients were identified among 10,000 angiograms. Pigment epithelial detachments were more than twice as common in the overall group of ethnic Chinese patients as in their counterparts of European ancestry (OR 2.6, 95% CI 0.7 to 10.1). The relative prevalence of the two main late AMD subtypes (GA and CNV) varies according to the population studied. In the Beaver Dam [9], Rotterdam [41] and Blue Mountains [42] eye studies the overall ratio of GA to CNV was 1:2. Whereas in the Reykjavik eye study [55] the ratio is reversed with an overall relative prevalence of GA to CNV of 4.5:1 (3: 1 in those 70+) but it was noted that a common ancestor was found in those with GA only 6 generations back compared with the norm of 12 generations in the Icelandic population. In Japan there is evidence that AMD is increasing quite dramatically which would refute the idea of a racial component to the disease and would imply that lifestyle factors may be more important. The number of exudative AMD patients in all ophthalmology departments throughout Japan was estimated to be 14,400 in 1993. This number was estimated to have almost doubled over the six year

period since the initial survey in 1987 [56]. In Greenland an unusual form of AMD is described as retino-choroidal atrophy (RCA). The clinical picture of RCA is peripapillary and central retino-choroidal atrophy and sclerosis. In 1997 Ostenfeld-Akerblom et al examined 22 patients with AMD and of these 12 patients had RCA, which was the most common type of AMD in this Greenlandic investigation. All were severely visually handicapped with a visual acuity less than or equal to Snellen 6/60 [57]. Similarly, in African-Americans and Asians the pattern of disease does appear to be different with polypoidal chorio-vasculopathy (PCV) being more common [58].

#### *3.1.4. Geography*

It is difficult to separate the effects of geography from race and there is little evidence to suggest that geography per-say has an influence. However it has been shown that the prevalence in immigrants tends towards that of the native population and the assumption is that diet and lifestyle influences disease presentation [59;60].

#### *3.1.5. Socioeconomics*

It has been shown that visual impairment reflects socioeconomic status [61] and there is limited research specifically looking at the socio-demographics of people with age-related macular degeneration. However after controlling for smoking, age, sex and less vitamin supplementation Klein et al [62] found incidence of early ARM was highest in those in the service industries and blue collar workers and in those with less formal education. The association of early and late ARM with less education was also demonstrated in the AREDS study [63] and the EDCCS demonstrated an association of less education with CNV [64]. The Beijing eye study shows conflicting evidence with an early report noting early ARM was statistically associated with living in a rural region ($p<0.001$; 95% CI: 0.17 to 0.49) and lower level of education ($p = 0.01$; 95% CI: 1.07 to 1.65) [65] but a later report showing no statistical association [66]. In another Chinese study, high educational background was a protective factor for AMD (OR: 0.761, 95% CI: 0.51-0.98) [67]. However other studies have not been able to show an association [48;68-71]. The difficulty of establishing a link with socioeconomic status is that in itself it comprises many facets and confounders are thus difficult to quantify but the majority of cross-sectional studies appear to support an association with lower levels of education.

### 3.2. Personal characteristics

#### *3.2.1. Hair colour / skin sun-sensitivity*

Although sun-exposure might in itself be a risk for AMD, it is recognised that sun-sensitivity and sun-avoidance may be confounding factors [72]. In the case-control study by Darzins et al [73] they were able to demonstrate significantly poorer tanning ability (skin types I or II) in cases with AMD in chi-squared analysis. However, age and smoking as well as sun-exposure are all possible confounders and were not included in the analysis. Data from the Blue mountains study [72] indicated greater skin sun-sensitivity in those with AMD but also reduced skin sun-sensitivity; possibly explained by increased biological risk in those with

sensitive skin but overridden by sun avoidance in those with average tanning skin and but increased sun exposure in the darker skin category. Khan et al found no association between skin sun-sensitivity and late AMD [74]. Hair colour may be associated with ocular pigmentation and has also been postulated as a possible identifiable risk factor for AMD, however no association was found in either the Blue Mountains Eye Study or the case-control study by Khan et al [72;74].

*3.2.2. Iris colour*

Four case-control studies have demonstrated an association between light iris colour and macular degeneration [75-78]. Three of these studies looked at cases with a broad definition of macular degeneration, which included cases of ARM as well as AMD [75-78], and all appeared to shown an association of AMD with lighter iris pigment. However, the control groups are not clearly defined in two of the studies [76;77], the studies did not always define a specific grading protocol for iris colour and did not look at potential confounding factors such as smoking and age in a logistic regression approach. Khan et al, in a study of well-defined GA and CNV with adjustment for potential confounders, showed that whilst there was a trend for lighter iris colour to be associated more frequently with geographic atrophy type AMD, this did not reach clinical significance. In a case series, Sandberg et al suggest that light iris colour may be associated with more severe neovascular AMD with more extensive retinal degeneration [79] than might occur in patients with darker irides. Holz [80] demonstrated that iris colour per-say may not be linked to ARM but that a change in iris colour with loss of stromal pigmentation may be associated with increased risk of ARM. The grouping of different phenotypes of AMD in some studies may have diluted any association of iris colour and AMD and hence it is difficult to be certain if there is any true association. Iris colour has also been explored in population studies [64] however, the numbers of late AMD may have been too small to detect any association. In the Blue Mountains eye study [72] an association was detected for blue iris colour alone when compared with all other iris colours, in both late AMD and early ARM and this was using a multiple logistic regression approach correcting for confounders of smoking, age, gender and family history of AMD. Lighter-coloured irides were associated with GA (OR, 5.0; 95% CI, 1.0, 25.3) in the Latinos Los-Angeles eye study [81]. On balance, whilst there may be a small association between lighter iris colour and AMD, the effect appears to be small and other risk factors are likely to outweigh any effect of iris pigmentation.

*3.2.3. Refractive error and axial length*

Several authors have demonstrated a relationship between hyperopia and AMD, more specifically CNV. Sandberg and co-workers found patients with unilateral neovascular AMD had an average spherical equivalent that was 1.0 diopter (D) more hyperopic than that of patients with the bilateral dry form. Patients with a refractive error of +0.75 D or greater were more likely to have the neovascular form compared with patients with other refractive errors [82]. A number of case-control and population cross-sectional studies also confirm an association with shorter axial length and AMD [83 63;84 85]. In the Beijing eye study, hyperopic refractive error, besides age was the single most important risk factor for ARM in adult Chinese

[65]. It is thought that hyperopia might cause secondary changes in the choroidal vasculature, predisposing them to choroidal neovascularization [86].

### 3.3. Genetics

The first information assessing genetic risk was demonstrated in twin and familial aggregation studies. Candidate gene studies then attempted to associate putative disease-causing polymorphisms with disease, but this relied on scarce knowledge of gene function and disease pathways. Thus initial studies examined known monogenic macular dystrophies as potential candidate genes. Non-retinal disease-causing genes then began to be explored and with the discovery of an association of APOE variants with AMD. This opened up new avenues for exploring other 'house-keeping' genes as potential candidates in AMD.

Major breakthroughs then came with family-based linkage studies of affected siblings, which identified a number of genetic loci. Thus genes known genes in these regions could be targeted and case-control association studies initially also played a role in discovering the major genetic variants for AMD. In 2010, several large-scale genome-wide association studies (GWAS) identified genes that had not been previously identified.

#### *3.3.1. Family history and twin studies*

There is strong support now for a genetic basis to AMD and ARM [87](major review). Evidence arises from a number of sources. Initially twin studies [88-92] demonstrated concordance in Monozygotic twins, greater than in dizygotic twins. Population [93-95]. There have been relatively few studies quantifying the influence of family history [75;93;94; 96-99], with estimates of the odds ratio for a positive family history conferring risk of AMD ranging from 2 to 27 [75;93;94;96;97;100].

#### *3.3.2. Linkage studies and genome-wide association studies*

Genetic linkage studies [101-103] have identified genes in large families which associate with disease. Two major disease susceptibility loci have been confirmed in a number of studies; chromosomes 1q32, which includes the gene that encodes complement factor H [CFH] and chromosome 10q26 [104;105](meta-analysis), (includes PLEKHA1, hypothetical gene LOC387715, and HTRA1). In one study genetic variation in VEGF showed evidence of linkage (HLOD = 1.32) [106] and this has been confirmed in other studies [107]. Further novel variants have been found in the TNXB-FKBPL-NOTCH4 region of chromosome 6p21 in a recent genome-wide association study and this requires further exploration.

#### *3.3.3. Candidate gene studies*

A number of autosomal genes associated with hereditary retinal dystrophies have been isolated with the majority assessed as potential candidate genes for AMD (RetNet Retinal Information Network at http://www.sph.uth.tmc.edu/retnet/). Attention has focused on those with phenotypic similarity to AMD. Stargardt disease and Best macular dystrophy commonly result in high levels of retinal pigment epithelial autofluorescence and macular atrophy.

Drusen are a prominent feature of Doyne honeycomb retinal dystrophy (autosomal dominant radial drusen; Malattia Leventinese) followed later by the development of CNV, which is also a common feature of Sorsby fundus dystrophy.

Genes associated with hereditary retinal dystrophies are not the only candidate genes for AMD. Data on environmental risk factors suggest other pathogenic processes to be explored. Positive associations have been found for proteins involved in the biological infrastructure such as the extracellular matrix [108], and the RPE [109]. Genetic polymorphisms in genes controlling angiogenesis have also been investigated [110;111]. Genes controlling lipid and cholesterol transport [112-116] have also been implicated. Apolipoprotein E (ApoE), a major lipid transporter, has two alleles of interest: ε2 and ε4. ApoE ε4 was the first gene identified that appeared to confer resistance to the disease (OR 0.43; 95% CI 0.21-0.88) [113;114]. Conversely, ApoE ε2 confers susceptibility to AMD.

The inflammation and immune response has been examined in greater detail since linkage studies revealed common variants found in complement factor H (1q) [117-119] associated with disease. CFH is a major regulator of complement cascade which is part of the innate immune system. Risk of developing AMD is associated with an allele of CFH in which a histidine residue is encoded in place of a tyrosine residue at amino acid position 402. The increased risk ranges between 2- to 4-fold for heterozygote carriers and 3- to 7-fold for homozygotes. In addition, multiple other polymorphisms, many of which are in non-coding regions of CFH or in nearby genes encoding other complement factors, demonstrate equal or stronger association with disease susceptibility than does the CFH Y402H variant [120;121 122]. No single polymorphism accounts for the entire contribution of CFH to disease susceptibility and there appears to be a number of polymorphisms, some conferring risk, others reducing risk [123;124]. At 10q26, a number of genes have been implicated. A single nucleotide polymorphism (SNP) in the promoter of the HTRA1 gene was associated with a population attributable risk of 49.3% and a 10-times greater risk of developing CNV [125]. Another susceptibility locus PLEKHA1/ LOC387715 also mapped to chromosome 10q26 [126;127]. In the study by Jakobsdottir, the association of either a single or a double copy of the high-risk allele within the PLEKHA1/LOC387715 locus accounts for an odds ratio of 5.0 (95% confidence interval 3.2-7.9) for ARM and a population attributable risk as high as 57%.

### 3.4. Systemic disease

Epidemiological studies have primarily investigated hypertension and hyperlipidaemia, and the clinical manifestations of CVD such as myocardial infarctions and angina [128], although some other chronic diseases have also been investigated. Although the overall number of participants in these studies is large, there may be low prevalence of end-stage cases and in the longitudinal population studies, few incident cases. Therefore the power to test for statistically significant associations is weak, unless the relative risk is very high. Failure to find associations may also be due to the insensitivity of some of the risk factor measurements or due to selective survival. Conversely, some of the relations reported may be due to chance, bias, and unadjusted confounding.

*3.4.1. Cardiovascular disease*

Risk factors for cardiovascular disease (such as age, smoking, hypertension, hypercholesterolemia, post-menopausal estrogen use, diabetes, and dietary intake of fats, alcohol and antioxidants) have been associated with AMD in some studies. This raises the possibility that the causal pathways for cardiovascular disease and AMD may share similar risk factors [129]. However, few studies have looked at cardiovascular disease as a risk factor in its own right. In one case-control study there was a statistically significant association between coronary artery disease and AMD [83], but in the prospective case-control Age-Related Eye Disease Study (AREDS) study of 776 subjects there was no increased incident AMD with mean 6.3 years follow-up with a history of angina as a measure of cardiovascular disease [130]. A large population study, the National Health and Nutrition Examination Survey (NHANES) III showed dry AMD was with myocardial infarctions in non-Hispanic white subjects [48]. Other population-based studies have not found an association [44;131-139]. A retrospective study of Medicare records investigated the relationship between AMD and myocardial infarctions, diabetes mellitus, and hypertension [140]. They used a five percent random sample of 2000 to 2003 Medicare enrolees which included 134,246 people with dry AMD and 32,788 people with wet AMD. All three diseases were associated with AMD, particularly wet AMD, and baseline AMD was significantly associated with the development of incident myocardial infarction from which they suggest the possibility of shared common antecedents between myocardial infarction and AMD.

*3.4.2. Blood pressure*

A number of population-based cross-sectional and case-control studies have found an association between systemic hypertension and AMD [63;69;83;140-143]. The relationship appears to be complex, with the association was significant only for wet AMD in two of the studies63;143 and the association became statistically non-significant when dry and wet AMD were analysed separately in another [83]. The Beaver Dam Eye Study (BDES) found that systemic hypertension was associated with incident AMD and wet AMD at 10-year follow-up [135]. There were differences noted in this study between the association of systolic and diastolic blood pressure, with systolic BP showing a positive association with both wet AMD and RPE depigmentation while diastolic BP was inversely associated with incident early ARM. An inverse relationship between systolic BP and wet AMD was reported by the Women's Health Initiative Sight Exam Ancillary Study [139]. Other case-control and population studies have not been able to detect a statistically significant relationship between AMD and hypertension which may reflect uncontrolled factors such as treatment for or duration of hypertension [44;75;130-134;136-138;144-149].

*3.4.3. Atherosclerosis*

The Atherosclerosis Risk in Communities Study (ARIC) and the Rotterdam Study have investigated relationship of atherosclerosis as a risk factor for AMD [128;133;150] using ultrasound measurements of the common carotid intima-media thickness and to assess the presence of atherosclerotic plaques. carotid artery plaque (odds ratio, 1.77; 95% confidence

interval, 1.18-2.65) and focal retinal arteriolar narrowing (odds ratio, 1.79; 95% confidence interval, 1.07-2.98) were associated with retinal pigment epithelial depigmentation only in the ARIC study but no association was detected for AMD. In the Rotterdam Study atherosclerosis was noted to be associated with a 2.5 to 4.7 times increased risk of AMD [150], suggesting there may be similar pathways in the disease process or that it might directly influence pathogenesis due to altered ocular blood flow.

*3.4.4. Haematological- lipids/ Inflammatory markers*

Cholesterol has been found in drusen deposits [151], and dyslipidemia, being an established risk factor for atherosclerosis might also be a risk factor for AMD. Two 10-year follow-up reports of population-based cohort studies and a case-control study have found a significant association for HDL and AMD, however both protective and adverse effects have been reported. The prospective studies also found an increasing trend of elevated total/HDL cholesterol ratio with AMD, and pure geographic atrophy [135;152]. In contrast, population-based cohort studies have not demonstrated a significant association between inflammatory markers and AMD [152;153].Other biochemical risk factors for CVD that have been investigated for their association to AMD are serum lipids, fibrinogen and C-reactive protein (CRP). Fibrinogen and CRP are inflammatory biomarkers shown to predict CAD [154]. Most studies have not found any association between serum total cholesterol, HDL and LDL cholesterol, or triglyceride levels and AMD [44;48;69;132;134;141;155 156;157]. Fibrinogen was positively associated in the baseline analysis of the BMES population, however this relationship became non-significant at the 10-year follow-up [132;152]. Seddon *et al* reported that CRP was positively associated with progression of AMD in a clinic-based cohort. Similarly, cross-sectional and case-control studies have shown positive relationships [48;132;153;158]. These findings support an inflammatory aetiology for AMD pathogenesis with a minor, if at all, contribution from serum lipids.

*3.4.5. Stroke*

Most studies have been unable to find an association between stroke and AMD [131 132 48 44; 133;134 135;136;139]. In the ARIC study early ARM predicted incident stroke in middle-aged persons, however there were too few cases of late AMD to establish any association [159]. This finding is supported with incident early ARM predicted by stroke in the Blue mountains eye study [152]. Thus far, an association between late AMD and stroke has not been established.

*3.4.6. Body mass index*

There have been some positive associations noted between high BMI and early AMD. [135;139;152;160-162]. In the AREDS study, greater body mass was found to be associated with higher risk of incident GA after mean follow-up of 6.3 years [130]. Also Seddon et al specifically evaluated progression from early or intermediate AMD to advanced AMD and demonstrated an increased risk with higher BMI. [160]. However, pooled analyses of 3 large population cohort studies have found no association between BMI and AMD [44;136]. In fact, in some of these studies there has been shown an association of lean body mass with increased risk of GA

[132;135;161] this association was not found in the AREDS. It therefore appears the association is not yet universally established.

*3.4.7. Diabetes*

Diabetes may theoretically be a risk factor for AMD by influencing choroidal blood flow [163] and increased plasma fibrinogen which may independently be associated with AMD [132]. Associations have been made between diabetes and wet AMD in some studies [130;139;140;163]. But there is little evidence of an association with dry AMD [130, 139, 140]. Interestingly, the BMES found no association with wet AMD, but a significant relationship with dry AMD [164]. In a meta-analysis, estimates from four prospective cohort studies demonstrated the presence of diabetes to be associated with an increased risk of late AMD (RR 1.66; 95% CI 1.05 - 2.63) [147;152;165;166] and similarly meta-analysis of data from two cross-sectional studies [167] associations were non-significant (OR 1.09; 95% CI 0.61 - 1.92). One case control study [148] showed non- significant association with diabetes (OR 0.55; 95% CI 0.06 - 4.87). Certainly the evidence points to only a weak association between diabetes and AMD.

*3.4.8. Other chronic diseases*

Some diseases which have been postulated to have common pathogenesis with AMD include Alzheimer's disease (AD), gout and emphysema. In the Beaver Dam Eye Study, a history of emphysema at baseline was associated with the incidence of retinal pigment epithelial depigmentation (RR = 2.84; 95% CI, 1.40-5.78), increased retinal pigment (RR = 2.20; 95% CI, 1.11-4.35), and exudative macular degeneration (RR = 5.12; 95% CI, 1.63-16.06). A history of gout was associated with the incidence of pure geographic atrophy (RR = 3.48; 95% CI, 1.27-9.53) [168]. Whilst in the Rotterdam population based study, although advanced age-related maculopathy at baseline showed an increased risk of incident Alzheimer's disease (relative risk = 2.1), this risk decreased after additional adjustment for smoking and atherosclerosis (relative risk = 1.5). In a further population study, cognitive scores were lower in those with AMD even after correcting for education although Alzheimer disease was not associated with AMD. Other investigators have looked at the relationship between the CFH Y402H polymorphism (now considered a major risk gene for AMD) and Alzheimer disease but the association in one study was null [169]. Whilst in a further study, although an increased frequency of the CFH AMD-risk polymorphism was noted in those with AD, subgroup analysis showed that the association between CFH C allele and AD was only evident for individuals carrying the APOE epsilon4 allele indicating a possible association between these genes and disease phenotypes. Conversely a Hungarian study, whilst supporting the findings of others of an association between the AMD-protective and AD-risk with APOE epsilon4, found that AMD is rare in those with AD which is logical if the ApoE is a major determinant of risk in this population.

**3.5. Lifestyle**

Along with identifying disease and co-morbidity as potential modifiable risk factors for AMD there has also been extensive investigation of environmental and social risk factors. Smoking

is the single consistent factor identified by the majority of studies. Evaluation of dietary factors and sun-exposure has been less consistent, which may partly be due to the complexity of measuring these factors.

*3.5.1. Smoking*

Of the many environmental factors investigated in relation to AMD, smoking is the one most consistently found to be associated with increased risk. Several case-control and population based studies have reported odds ratios typically in the range 2–5 [44;170;171,63;64;134;144;170-174]. However this has not been completely consistent finding with a few smaller studies showing no association [69;75;83;148;175;176]. McCarty et al11 argued that total length of time of smoking was the most significant factor for development of AMD rather than pack years or current or former smoking status. However, Khan et al demonstrated that, whilst a loose definition of smoker or non-smoker did not show a statistically significant relationship with AMD, when careful calculation of pack-years of smoking was measured, this showed a strong association with both CNV and GA. Risk was also influenced by living with a smoker which highlights an important public health message in demonstrating the likely increased risk with passive smoking [177]. Stopping smoking was associated with reduced odds of AMD in this study and the risk in those who had not smoked for over 20 years was comparable to non-smokers. Studies have also shown that ceasing smoking reduces risk even in those older smokers (over age 80) [178]. In the recent Eureye study, bilateral disease was associated with increased odds of heavier smoking in the preceding 25 years [179].

Experimental evidence also supports smoking as a risk factor for AMD. The foveal region of the retina has a yellow pigmentation composed primarily of the carotenoids lutein and zeaxanthin. A variety of evidence suggests that this macular pigment protects the macula from actinic damage both passively (by screening potentially harmful short-wave light) and actively as an antioxidant (by quenching reactive oxygen species). Studies have shown that cigarette smoking depresses carotenoid concentration in the blood [180]. In a study by Hammond et al [181] macular pigment density and smoking frequency were inversely related ($r = -0.498$ $P < 0.001$) in a dose-response relationship. Smoking also has an established role in upregulating inflammatory mediators [182,183] and contains the pro-oxidant hydroquinone [184] causing further oxidative damage.

*3.5.2. Sun exposure*

Logically increased sun-exposure could increase the exposure of the retina to oxidative processes. In experimental studies photic injury is frequently used as a model of oxidative stress. In epidemiological studies, the measurement of sun-exposure generally relies on recall diaries so evidence from epidemiological and basic scientific investigations unfortunately gives somewhat conflicting results.

Experimental evidence to suggest sunlight as a risk factor is given by in-vitro studies. In the retina, lipofuscin is located within the pigment epithelium where it is exposed to high oxygen

and visible light, a prime environment for the generation of reactive oxygen species. It has been demonstrated that retinal lipofuscin is a photo-inducible generator of reactive oxygen species and this may translate into cell damage via several mechanisms. The position of lipofuscin within the lysosome implies that irradiated lipofuscin is liable to cause oxidative damage to either the lysosomal membrane or the lysosomal enzymes. One study group found that that illumination of lipofuscin with visible light is capable of extragranular lipid peroxidation, enzyme inactivation, and protein oxidation. The authors postulate that lipofuscin may compromise retinal cell function by causing loss of lysosomal integrity and that this may be a major contributory factor to the pathology associated with retinal light damage and diseases such as age-related macular degeneration [185]. It has also been shown that lipofuscin-loaded RPE cells are considerably more sensitive to visible blue light than unloaded control cells. The loaded cells showed lysosomal membrane destabilization with ensuing leakage of lytic enzymes and eventually cell death [186]. Macular pigment, consisting of lutein and zeaxanthin, through its ability to filter light and by direct antioxidative properties, has been proposed as the most effective protective factor in the central retina ("natural sun glasses") and could be important to reduce light-induced oxidative retinal damage. The observation, that with age and especially in eyes with AMD, lower concentrations of macular pigment could be found, can be interpreted that low macular pigment concentrations may be associated with higher risk for AMD. Through dietary intake and eventually with supplementation the concentration of macular pigment can be increased, and analysis of the correlation between macular pigment and AMD may be important to characterise a possible modifiable AMD risk factor [187].

One of the first studies to examine the relationship of AMD to sun exposure was a case-controls study by Hyman et al [75] of 228 cases; no association with AMD demonstrated. A larger study of the Chesapeake Bay Waterman [176] found that even with high levels of UV-B or UV-A exposure, there was no evidence of increased risk of age-related macular degeneration [176]. However a further report from the same study calculated that compared with age-matched controls, patients with advanced age-related macular degeneration (geographic atrophy or disciform scarring) had significantly higher exposure to blue or visible light over the preceding 20 years (odds ratio, 1.36 [95% CI 1.00 to 1.85]). The data suggests that high levels of exposure to blue or visible light may cause ocular damage, especially later in life, and may be related to the development of age-related macular degeneration [188]. Cross-sectional data from the BDES also suggests that the amount of leisure time spent outdoors in summer was significantly associated with exudative macular degeneration (OR, 2.26; 95% CI, 1.06 to 4.81) and late maculopathy (OR, 2.19; 95% CI, 1.12 to 4.25). Whereas, wearing eyeglasses was inversely associated with increased retinal pigment and the use of hats and sunglasses was inversely associated with soft indistinct drusen [189]. Data from the Blue Mountains Eye Study [72] indicated increased risk of late AMD associated with both high (OR, 2.54) and low (OR, 2.18) skin sun sensitivity; possibly explained by increased biological risk in those with sensitive skin but increased sun-exposure in the darker skin category. It was postulated that there may be significant confounding by skin sensitivity and sun avoidance.

No support was found for sunlight exposure as a risk factor for AMD in several other case-control studies [64;73;74;144;167]. Subjects In the POLA Study who had used sunglasses

regularly had a decreased risk of soft drusen (OR = 0.81; 95% CI, 0.66-1.00) but the study did not support a deleterious effect of sunlight exposure in ARMD [167]. In a study of 3271 people in 9 randomly selected urban clusters and 4 randomly selected rural clusters in Victoria, Australia, lifetime sunlight exposure and UV-B exposure was not associated with AMD [144]. In the Newcastle (Australia) study, after stratifying by tanning ability, the median annual sun exposure of control subjects exceeded that of cases and after adjusting for age and sun-sensitivity sun-exposure was negatively associated with AMD. The authors concluded that sun-sensitivity confounds study of the postulated AMD-sunlight link [73]. The evidence is thus still lacking to support a definite link between AMD and sun-exposure.

*3.5.3. Micronutrients*

A significant role for vitamin C in the retina has been indicated by laboratory experiments in animals. Tso et al showed that under conditions of continuous light exposure, the levels of ascorbic acid in the retina fell [190]. The same group also demonstrated that ascorbic acid may protect the retina from light damage [191]. Retinal degeneration can be induced specifically by anti-oxidant (E and A) vitamin deficiency in monkeys [192]. Zinc is found in high concentrations in the RPE and pathological lesions have been observed in animals deprived of zinc [193]. Vitamin E and selenium play key roles in preventing in vitro lipid peroxidation and free radical damage to retinal tissues. Rats fed on diets deficient in vitamin E and/or selenium and subsequently exposed to hyperbaric oxygen show diminished ERG amplitudes and evidence of photoreceptor cell necrosis [194]. Carotenoids are vegetable products which are essential to the health of the eye and are concentrated at the macula- in particular zeaxanthin (found mainly in maize) and lutein (found mainly in spinach); they may also act as anti-oxidants to scavenge free radicals.

In light of these experimental findings the EDCCS examined the relationship of micronutrients to neovascular age-related macular degeneration [64;195]. Serum levels of carotenoids (Lutein/Zeaxanthin, beta-carotene, alpha-carotene, cryptoxanthin, lycopene), vitamins C and E, selenium (glutathione peroxidase is selenium dependent and theoretically may reduce the amount of macular damage from oxidative insult) and zinc in 421 patients with neovascular age-related macular degeneration and 615 controls were compared. Although no statistically significant protective effect was found for vitamin C or E or selenium individually, an antioxidant index that combined all four micronutrient measurements showed statistically significant reductions of risk with increasing levels of the index. No support was found for serum zinc levels as a risk factor for neovascular AMD. In a further report dietary intake was examined in this same study group using food frequency questionnaires. A higher dietary intake of carotenoids was associated with a 43% lower risk for AMD. Lutein and zeaxanthin were most strongly associated [196].

Other population studies have not been able to demonstrate a protective effect of the antioxidant micronutrients. In the Beaver Dam Eye Study a protective effect of higher zinc intake in early but not late ARM was demonstrated but there was no association with intake of other antioxidant micronutrients [197]. The study's main failing may have been with the use of diet recall from 10 years prior; hence recall bias is likely to be a major factor limiting the ability to

detect an association. Similarly the third national health and nutrition examination survey study did not find a link with serum levels of lutein/ zeaxanthin or dietary intake and AMD in the sample as a whole but only in those with young onset AMD [198]. Again recall bias is likely to be a major factor influencing the likelihood of detecting an association.

Results from a large clinical trial have indicated that high-dose vitamin supplementation may reduce vision loss from AMD [199]. The Age-related Eye Disease Study Research Group developed a double-masked clinical trial in patients with AMD. Treatment with zinc with or without antioxidant vitamins reduced the risk of progression to advanced AMD in the groups with more severe AMD at the outset (more specifically these groups were those with extensive intermediate-sized drusen, large drusen or non-central GA in one or both eyes, or advanced AMD in one eye). Relative risk estimates suggest a reduced risk of 21% if zinc is taken alone and 17% for antioxidants the reduced risk if both are taken is 25%. In the less severe AMD groups at outset the incidence of progression to advanced AMD at 5 years was too low to establish any effect of supplementation and there was no effect of supplementation on delaying progression from the less severe groups to more severe groups during the study.

At the time of writing, a multi-center, randomized trial of supplementation with Lutein, Zeaxanthin, and Omega-3 Long-Chain Polyunsaturated Fatty Acids (the AREDS 2 study) is underway, with results expected in 2013 [200].

### *3.5.4. Dietary fat*

The major drusen component is neutral lipid and this is also deposited in Bruch's membrane. Theories therefore propose AMD as having a similar pathway to atherosclerosis. However, since the lipid is esterified, it implies the fat arises secondary to being transported out of RPE cells and does not arise from plasma cholesterol. By contrast, the lipoprotein constituent of drusen is plasma derived. There are epidemiological studies to support this theory. In one study dietary linoleic acid (the major fatty-acid component of drusen [151]) was associated with increased risk of AMD [201]. Generally the epidemiological studies show conflicting results for dietary fat which may be in part due to the difficulty inherent in food-frequency questionnaires and associated recall bias or may be further evidence that there is no association as might be expected from the underlying biology. There appears to be limited evidence for an association between saturated fatty acid intake and AMD [202]. Seddon *et al* suggest an increased risk of AMD prevalence and progression with higher vegetable fat intake [203;204], and it is hypothesised that this may be due to high levels of trans-fatty acids in some margarines. Whilst in the BMES there was a reduction of incident AMD with increasing intake of polyunsaturated fats after 5 years follow-up [205]. Omega-3 fatty acids may protect against AMD [206;207] and the AREDS2 study is currently underway to further investigate this [200].

### *3.5.5. Alcohol*

There is experimental evidence to suggest alcohol may increase the risk of AMD. A study of alcohol-fed rats showed that heavy alcohol intake was associated with both an increased accumulation of ethyl esters in the choroid and an exacerbation of the CNV induced by laser

treatment [208]. A number of clinical studies have investigated the role of alcohol consumption and risk of AMD and among these there are studies demonstrating no association [209-211], weak positive associations for some forms of ARM/ AMD [212-217], or even an inverse association [146;218]. In a recent systematic review of the literature pooled results showed that heavy alcohol consumption was associated with an increased risk of early AMD (pooled odds ratio, 1.47; 95% confidence interval, 1.10 to 1.95), whereas the association between heavy alcohol consumption and risk of late AMD was inconclusive. There were insufficient data to evaluate a dose-response association between alcohol consumption and AMD or the association between moderate alcohol consumption and AMD. The authors conclude that although this association seems to be independent of smoking, residual confounding effects from smoking cannot be excluded completely [219].

## 4. Summary

AMD creates a huge burden on society, being the third largest cause of blindness world-wide. The impact is far reaching in terms of quality of life to the individual as well as financial and social burdens on society as a whole. AMD appears to have greater representation in white, Caucasian populations but it is becoming apparent that the prevalence in other ethnic populations is substantial. There are differences in the sub-type presentation of disease in different populations.

It appears that AMD is caused by environmental factors triggering disease in genetically susceptible individuals. Identifying modifiable risk factors is a vital part of defining the pathogenesis of AMD and enabling appropriate targeting of treatment strategies. Whilst age is the strongest risk factor for AMD, a number of environmental risk factors have been proposed and the adverse effect of smoking is well-established.

The data demonstrate a clear association between the risk of AMD and pack-years of cigarette smoking with odds ratios in some studies demonstrating a dose-related effect. Both types of AMD show a similar relationship in most studies. Stopping smoking is associated with reduced odds of AMD. This provides strong support for a causal relationship between smoking and age-related macular degeneration. Axial length and refractive error also appear to play a role with most studies indicating increased prevalence associated with hyperopia. Other possible risk factors include blue iris colour, poor skin tanning or abnormal skin sensitivity to sunlight but generally the studies show null or only weak association. Hypertension and other cardiovascular risk factors do seem to play a role but the associations appear weaker than for smoking and genetic factors. Dietary factors associations are notoriously difficult to establish but in general there appears to be reduced risk in those with diets higher in antioxidants and fish but there is only weak evidence for an association with increased dietary fat intake. Dietary antioxidant supplements such as carotenoids and zinc may be protective for progression in the later stages of AMD and other dietary supplements are currently being investigated.

Genes associated with hereditary retinal dystrophies have been isolated but few appear to show association with AMD. However, non-retina specific genes appear to be significantly associated with risk, in particular those involved in complement activation, extracellular matrix composition, angiogenesis and lipid transport which provides vital evidence for developing targeted therapy.

## Author details

Jane Khan[1,2,3,4]

1 Centre for Ophthalmology and Visual Science, University of Western Australia, Australia

2 Royal Perth Hospital, Western Australia, Australia

3 Department of Medical Technology and Physics, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia

4 Western Eye, Perth, Western Australia, Australia

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