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REVIEW ARTICLE

Epidemiology of geographic atrophy and its precursor features of intermediate age-related macular degeneration

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Abstract

Globally age-related macular degeneration (AMD) is a leading cause of blindness with a significant impact on quality of life. Geographic atrophy (GA) is the atrophic late form of AMD and its prevalence increases markedly with age with around 1 in 5 persons aged 85 and above having GA in at least one eye. Bilateral GA leads to severe visual impairment thus posing a significant burden on patients, careers and health providers. The incidence and prevalence of GA varies across different geographic regions, with the highest rates in those of European ancestry. Although heterogeneity in definitions of GA and reporting strategy can explain some of the discrepancies, the data overall are consistent in showing a lower prevalence in other ethnicities such as those of Asian heritage. This is at present unexplained but thought to be due to the existence of protective factors such as differences in eye pigmentation, diet, environmental exposures and genetic variability. This review covers key aspects of the prevalence and incidence of the ocular precursor features of GA (large drusen, pigmentary abnormalities and reticular pseudo-drusen), the late stage of GA and factors that have been known to be associated with modifying risk including systemic, demographic, environment, genetic and ocular. Understanding the global epidemiology scenario is crucial for the prevention of and management of patients with GA.

KEYWORDS

age-related macular degeneration, drusen, epidemiology, geographic atrophy, reticular pseudo-drusen, risk factors

1 | INTRODUCTION AND HISTORICAL CONTEXT

The evolution of our understanding of age-related macular degeneration (AMD) and its associated nomenclature which has changed dramatically and markedly over time has been elegantly described in a recent exposition by de Jong (De Jong, 2016). Descriptions of the degenerative changes that occur in the macular retina of older adults appear in the works of Donders in 1855 (Donders, 1855). Donders found whitish flecks in the fundus of the eye which he detected through the use of the earliest ophthalmoscope and indeed this was a notable and impressive observation and likely the first description of drusen. Subsequently, Nettleship in 1884 published a description of an *areolar atrophy of the choroid* which probably represents for the first time an appreciation of the condition which we now know as atrophic macular degeneration (Nettleship, 1884). The studies of Junius and Kuhnt and later Duke Elder led to the description of *senile disciform macular degeneration* and thus through the most part of the last century, it became an accepted term in the history of ocular disorders (Duke-Elder & Dobree, 1967; Junius & Kuhnt, 1926). That neovascularization was responsible for the disciform lesion was identified by Gass and appears in his Stereoscopic Atlas (Gass, 1967). In the 1970s, it became apparent that disciform degeneration and a confluent atrophy of the retinal pigment epithelium (RPE) both of which localized to the macula were part of the same disorder. Reports began to appear show that eyes with a high drusen load were at risk of developing regions of RPE atrophy with scalloped well-defined margins creating an appearance similar to a geographic map leading to the use of the

term geographic atrophy (GA) (Blair, 1975; Willerson & Aaberg, 1978). The clinicopathological proof came from the studies of Sark and co-workers who showed that drusen were the precursors to both disciform neovascular scars and GA (Sarks, 1976, 1982; Sarks et al., 1988). This was soon followed by cohort studies of patients with bilateral drusen and prognosis in terms of progression to late AMD (Smiddy & Fine, 1984). Following on from these seminal observations of the condition which we now term AMD, the need to accurately document its prevalence and incidence became clear particularly since AMD was identified as one of the leading causes of blindness in the twentieth century across many countries.

2 | CURRENT NOMENCLATURE, AMD DEFINITIONS AND STAGING SYSTEMS

The earliest epidemiological studies were focused on the context of visual loss and reported prevalence as they understood it in terms of senile macular degeneration (Gibson et al., 1985; Kahn et al., 1977). As a consequence, there was no appreciation of the role played by the early manifestations of AMD and neither was a separation made of neovascular AMD from GA. However, with increasing recognition of the varied spectrum of fundus features which we now term AMD, which includes precursor lesions of drusen and pigmentary irregularities and the two late-stage manifestations of neovascularization and GA, later studies began to employ a more systematic approach to understanding its epidemiology (Klein et al., 1991, 1992).

Table 1 shows the earliest systematic approach to grading of the precursor features of AMD and the definitions used in the identification of these features.

Histologically drusen are yellow-whitish deposits between the basal lamina of the RPE and the inner collagenous layer of Bruch's membrane (BrM) (Spaide & Curcio, 2010; van der Schaft et al., 1992). Drusen are dynamic structures with cycles of increase and decrease in volume, but overall drusen load increases steadily over time until atrophy or neovascularization becomes established in the macular retina (Schlanitz et al., 2017; Yehoshua et al., 2011).

Drusen are the hallmark of AMD and were observed to be highly pleiomorphic and hence attempts were made to classify them by size (<63 μm, 63–<125 μm, and ≥125 μm) benchmarked to a diameter of a retinal blood vessel at the optic disc which was measured to be 125 μm (Figure 1). Other characteristics of drusen that have influenced their descriptions in the literature include their contours and margins (hard, soft colloid confluent) and clinical characteristics such as the presence of refractile crystals (calcified drusen) flat ribbon-shaped distribution of yellowish material (reticular pseudo-drusen), basal laminar (cuticular drusen) (Figure 1). Pigmentary changes in the macula were also recognized as part of the spectrum of AMD and separated into either hyperpigmentation representing clumped dark pigment or hypopigmentation consisting of focal regions with loss of pigment and with these features grouped under the umbrella term of pigmentary irregularities. The dysfunction of the RPE in AMD leads to a decreased phagocytic capacity compared to normal RPE from age-matched human donors. This accumulation of waste deposits like drusen leads to the accumulation of innate immune system cells, which can cause chronic inflammation and contribute to the progression of AMD (Inana et al., 2018; Wong et al., 2022).

As merely reporting the prevalence of AMD precursor fundus features and the manifestations of late-stage disease is clearly insufficient, researchers banded them together to derive pragmatic severity scales and staging systems (Table 2). This type of approach was required as combinations of these features were observed to increase the risk of progression to later stages notably neovascular AMD and GA (Figure 2). Longer-term follow-up in the Rotterdam Eye Study has validated this strategy as eyes that exhibit only small hard drusen were shown not to progress to late AMD, whereas those with large drusen and pigmentary irregularities that fall into a more severe category, progress more rapidly to late-stage AMD (Klaver et al., 2001). In this context, the more complex 9-step severity grading scheme was developed during the large age-related eye disease study (AREDS), which has also validated the strategy of classifying eyes into severity groups based on the early AMD features. The AREDS scale was subsequently simplified and revealed that the probability of progression steadily increased when the severity scale took into consideration features of AMD from both eyes. Notably, when late-stage AMD was detected in one eye along with the presence of precursor lesions (large drusen and hyperpigmentation) in the fellow eye, the probability of progression to late AMD in the fellow eye rose dramatically with around 50% developing nAMD or GA within 5 years. These findings confirmed that large soft drusen were the most important of the precursor lesions for progression to late AMD and the term intermediate AMD was coined to distinguish soft from small hard drusen.

While these staging systems were applied along with the more granular approaches to the grading of precursor lesions into early and intermediate AMD, most epidemiological and cohort studies continued to combine nAMD and GA together as late AMD (Klein et al., 1992; Mitchell et al., 1995; Vingerling et al., 1995). This led to a systematic under-reporting of GA because of two reasons. First, when GA and nAMD occur in the same patient but with one eye exhibiting GA and the other nAMD, these cases are reported as nAMD. Second, when both late stages occur in the same eye, nAMD takes precedence over GA. Although the literature is replete with systematic reviews and meta-analyses that have used data from population-based studies, clinical cohorts as well as visual impairment and blindness registries, few provide the prevalence and incidence of GA and nAMD separately and those that have reported on risk factors specifically related to GA are scant (Deng et al., 2021).

Therefore, to utilize the available information optimally, we focus in subsequent sections specifically on those features of intermediate AMD of particular relevance to GA and consider the prevalence and incidence estimates of large drusen, reticular pseudo-drusen (RPD) and RPE pigmentary irregularities because these

TABLE 1 Feature definitions used in earliest epidemiological studies.

	Features graded		Definition	How used
WARMGS Colour photos. Circles of known size C_0, C_1 and C_2 (C referring to the central section of the Wisconsin Grid) of 63 μm, 125 μm and 250 μm, respectively, were used to categorize drusen. Other circles I_1, I_2, O_1, O_2 representing Inner and outer subfields of the grid occupy 1.6% and 6.3% of the respective subfields. Klein et al. (1991)	Drusen. *Note drusen less than 63 μm are hard. If ≥63 μm but ≤125 μm may be hard or soft. If ≥125 μm are always soft.*	Drusen Hard Drusen Hard or Soft but distinct Drusen soft only if ≥125 μm	≤63 μm diameter 63–≤125 μm ≥125–≤250 μm	Each feature in each eye is graded on maximum dimension and textural characteristics of the margins distinct or indistinct. Features are localized to the sector of the grid central, inner and outer (see column 1) The area covered by drusen is also reported as proportion of a subfield occupied within the WARMGS grid. The frequency of the most severe feature is reported.
	Hypopigmentation	Based on pallor	Focal areas of pallor without elevation on stereoscopic examination	
	Hyperpigmentation	Based on the detection of black or black/brown pigment that has clumped together	Focal areas of increased pigmentation	
	RPE degeneration	Based on drusen	Patches of confluent drusen with fading (drusen substance has disappeared)	
	Neovascular AMD	Features associated with fluid leakage into the macular retina	Serous detachment of the retina, pigment epithelial detachment, hard exudate, haemorrhage, fibrous tissue, retinal thickening	
	Geographic atrophy	Based on the detection of confluent areas of depigmentation	Area of partial or complete depigmentation of the RPE with round or oval shape, sharp margins and visibility of the choroidal vessels	

are the precursor lesions that are strongly associated with progression to GA. We also direct our attention to studies where GA by itself was the focus of the report or when the prevalence and incidence of the two late stages were provided separately.

3 | PREVALENCE AND INCIDENCE OF LARGE DRUSEN AND PIGMENTARY IRREGULARITIES (COLLECTIVELY REFERRED TO AS INTERMEDIATE AMD) AND RETICULAR PSEUDO-DRUSEN (RPD)

3.1 | Prevalence

In Table 3, we summarize studies with robust prevalence estimates. Three major epidemiological studies were conducted during the 1980s and 1990s in the US, Europe and Australia and provided prevalence estimates of intermediate AMD features across three continents (Klein et al., 1992; Mitchell et al., 1995; Vingerling et al., 1995). The Beaver Dam Eye Study (BDES) reported a prevalence of 24.0%, 0.7% and 26.6%, for large soft drusen ≥125 μm, pseudo-drusen and RPE irregularities respectively (Klein et al., 1992). A few years later the Blue Mountain Eye Study (BMES), in Australia, found lower prevalence compared to BDES in large soft drusen (13%, 95% CI, 12.2%–14.4%) and RPE pigmentary irregularities (12.6%, 95% CI, 11.5%–13.7%) but higher for RPDs 1.95% (Mitchell et al., 1995). In Europe, the Rotterdam study (Vingerling et al., 1995) reported the prevalence of large soft drusen (≥125 μm) and RPDs as 17.5% and 4.9% respectively, which was similar to that of the BMES study. However, the occurrence of pigmentary irregularities was lower than that of the BMES (7.2%). Reasons for discrepancies in the prevalence of drusen and pigmentary changes between these populations might have arisen due to disparities in definitions of the features of

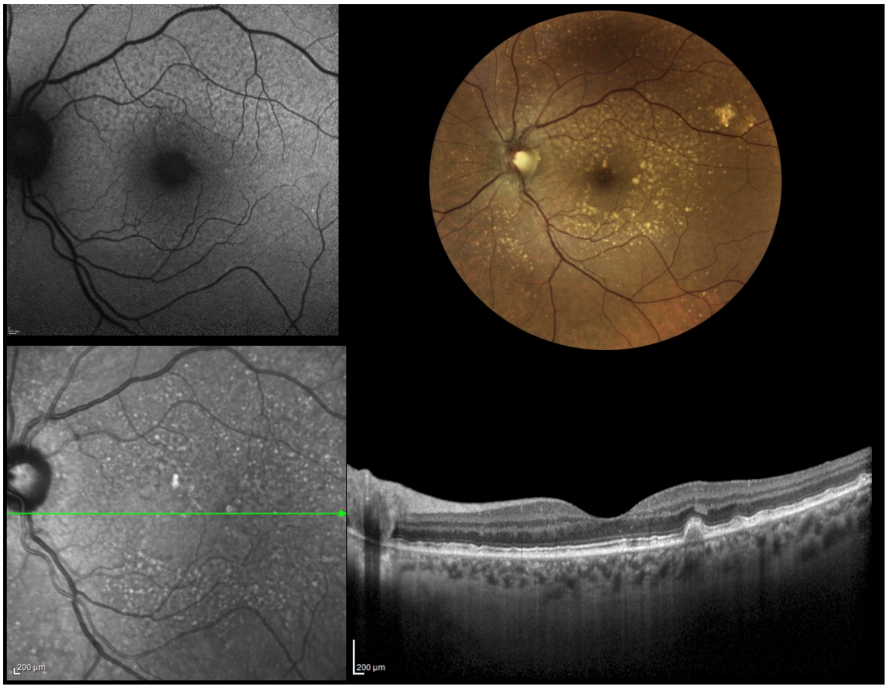

FIGURE 1 Left eye with multimodal imaging blue light autofluorescence (BAF), colour fundus and near-infrared with SD-OCT B scan through the fovea. The enface images show features of intermediate AMD (large soft drusen in the macula). In addition, there are multiple dot-like drusen (reticular pseudo-drusen) mainly located along the vascular arcades and on SD OCT can be seen as subretinal drusenoid deposits.

AMD, use of monoscopic instead of stereoscopic images and alternatively represent true differences.

Later roughly contemporaneous studies in European and Indian populations (Augood et al., 2006; Krishnan et al., 2010) using identical grading methodology published estimates of intermediate AMD features. In the EUREYE study conducted in 7 locations in Europe, large soft drusen were found in 15.41% of participants (95% CI, 13.61%–17.21%) (Augood et al., 2006). By contrast, in the INDEYE study, the prevalence of large soft drusen was 8.9% in South India and 6.3% in North India (Krishnan et al., 2010). More severe features of intermediate AMD (Rotterdam eye study stage 3) comprising soft indistinct with pigment abnormalities were low in India compared to Europe 2.4% (95% CI, 1.8–3.1) in EUREYE and 0.2% (95% CI, 0–0.5) in INDEYE (Augood et al., 2006; Krishnan et al., 2010) (Table 3). However, the high number of ungradable images due to cataracts in the oldest age groups of the Indian population may have led to an underestimation of these more severe manifestations.

Subsequent studies have shown widely varying estimates of the prevalence of RPD. The Melbourne collaborative study found a prevalence of 0.78% which is markedly lower than previous reports from Europe. Further findings of interest from the Melbourne study were the recognition that RPDs tend to develop much later in life than large soft drusen and that their association with late AMD was mainly with GA (Finger et al., 2016) (Table 3).

The Alienor study which used multimodal imaging and was conducted during the same period reported a higher detection rate of 13.4% for RPD and a strong association was found between this drusen phenotype and central large soft drusen (OR: 1.67; 95% CI = 1.16–2.42) (Chan et al., 2016). The Alstar study recruited a cohort in routine care and reported that RPDs were highly prevalent in 52% of patients with AMD. This drusen type was found in 49% of eyes with early AMD, rising to 79% in intermediate AMD. However, this prevalence decreased and was 1.48% when using only colour fundus photography (Zarubina et al., 2016).

Very recently, the Northern Ireland Cohort study of longitudinal Aging (NICOLA) published the prevalence of early and intermediate AMD features in a community-based randomly selected sample of adults aged 55 and above. Any drusen were found in 28.9% (95% CI, 27.4, 30.4) with prevalence rising steadily with increasing age (Table 3) (Hogg et al., 2022). The prevalence of large drusen increased from 1.3% in the youngest age group to 9.6% in those >85 years. Interestingly, pseudo-drusen also rose from 1.3% to 12.0% from the youngest to the oldest age band.

Overall, the evidence is supportive of higher prevalence rates of large soft drusen in European populations compared to Asian. However, data on the prevalence of RPD even in those of European ancestry is limited to the more recent epidemiological studies and scant in other racial groups making it difficult to speculate on its role in promoting progression to late AMD in different populations. Furthermore, data are confounded by variations in the imaging methods employed, definitions used in the detection of the features of AMD, population characteristics and the time course of the studies which are spread over many decades.

3.2 | Incidence

While many reports have investigated the prevalence of intermediate and late AMD worldwide, few have focused on its incidence (Colijn et al., 2017; Klein et al., 2006;

TABLE 2 Staging systems used in AMD studies.

Study	Definition of the spectrum of AMD	Grading	Nomenclature and staging
International Classification System (Bird et al., 1995)	Age-related maculopathy (ARM) is a degenerative disorder of the macular area in persons ≥50 years of age characterized by abnormalities in the macular area	Based on WARMGS definitions, soft drusen ≤63 mm, hyperpigmentation or hypopigmentation and exudative features.	Early ARM • drusen and or pigmentary irregularities Late ARM • Geographic atrophy • Neovascular AMD
Rotterdam Eye Study Staging System (Klaver et al., 2001)	Age-related maculopathy is a degenerative disorder of the macular area in persons >50 years of age characterized by abnormalities in the macular area. Age-related macular degeneration is the end-stage of the disease	Based on WARMGS definitions and International Classification and Grading System **Grading features** Stage O: a. No signs of ARM at all b. Hard drusen (<63 μm) only Stage 1: a. Soft distinct drusen (≥63 μm) only b. Pigmentary abnormalities only, no soft drusen (≥63 μm) Stage 2: a. Soft indistinct drusen (≥125 μm) or reticular drusen only b. Soft distinct drusen (≥63 μm) with pigmentary abnormalities Stage 3: Soft indistinct (≥125 μm) or reticular drusen with pigmentary abnormalities Stage 4: Atrophic or neovascular AMD	Early ARM (are stages 2–3) • Soft distinct drusen (≥63 μm) with hyperpigmentation and/or hypopigmentation of RPE or soft indistinct or reticular drusen with or without pigment irregularities Late ARM /AMD (stage 4 only and includes both GA and nAMD) • Atrophic AMD: round/ oval area without RPE larger than 175 μm with visible choroidal vessels • Neovascular AMD: serous/ hemorrhagic RPE detachment and/or subretinal neovascular membrane and/or subretinal haemorrhage and/or periretinal fibrous scar
Beckman classification of AMD (Ferris 3rd et al., 2013)	Age-related Macular Degeneration (AMD) single term encompassing all stages from early through intermediate and late.	Small drusen ≤63 μm Medium drusen >63 μm and ≤125 μm Large drusen ≥125 μm Hyperpigmentation Hypopigmentation Exudative features	No apparent ageing changes • No drusen • No AMD pigmentary abnormalities* Normal ageing changes • Only small drusen ≤63 μm • No AMD pigmentary abnormalities* Early AMD • Medium drusen >63 μm and ≤125 μm • No AMD pigmentary abnormalities* Intermediate AMD • Large drusen ≥125 μm and/or any AMD pigmentary abnormalities* Late AMD • Neovascular AMD and/or GA

Rudnicka et al., 2012; Wong et al., 2014). In Table 4, we review some of the key studies worldwide with robust incidence estimates. The Beaver Dam Eye Study published data in 2007 that provided one of the most extensive follow-up analyses of AMD incidence, spanning over a period of 15 years (Klein et al., 2007). The incidence of soft drusen was higher in people over the age of 75, and 8% had late AMD (Klein et al., 2007). In this older group, there was a higher occurrence of soft indistinct drusen (18.7%), RPE abnormalities (20.2%) and pure GA (3.2%) over the course of 15 years compared to younger patients (Table 4). Eyes with soft indistinct drusen or RPE pigmentary abnormalities at the beginning of the study were more likely to develop late AMD, during the follow-up than eyes without these lesions (17.8% vs. 1.2% and 12.9% vs. 1.7%, respectively). Additionally, the study revealed that a greater size of large, soft and indistinct drusen raises the likelihood of developing RPE pigmentary abnormalities, and the coexistence of both factors is highly indicative of progression to late-stage AMD. A report in 2008 based on the BDES characterized the effects of RPD over a 15-year period (Klein et al., 2008). The incidence of RPDs in either eye was 3.0% over 15 years, with the occurrence varying with age from 0.4% in those aged 43–54 years, to 6.6% in those aged 75 years or older ($p < 0.001$).

In the 10-year follow-up of the Blue Mountains Eye Study in Australia, findings on the incidence of intermediate AMD were similar to the BDES (Wang et al., 2007) (Table 4). Data presented in this study were in accord with previous observations that the occurrence of late AMD was closely linked to the severity of the intermediate AMD lesions observed at the beginning of the study.

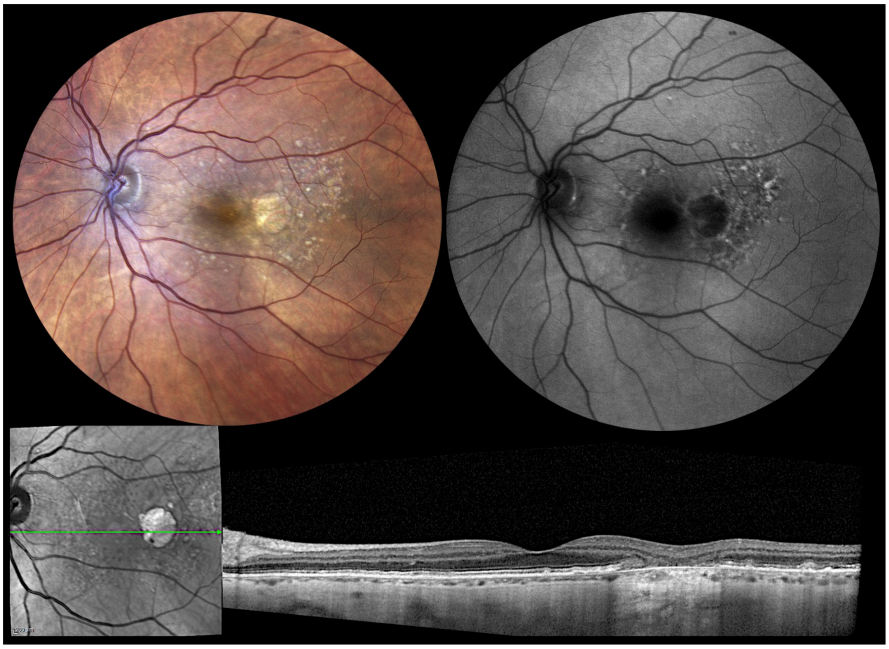

FIGURE 2 Multimodal imaging of left eye with geographic atrophy (GA). There is a region of hypo autofluorescence representing the region with GA with abnormal autofluorescence surrounding the area of GA. There are multiple small and large drusen seen on color temporal to the GA lesion. The area of GA on AF corresponds on SD OCT to a region seen on the B scan where there is complete loss of the outer retinal layers and a band of hypertransmission of signal.

Between 1986 and 2003, longitudinal data became available from the studies conducted in European populations with a follow-up period ranging from 5 to 14 years which permitted the determination of the incidence rates of intermediate and late AMD (Buch, Vinding, et al., 2005; Jonasson et al., 2005; Klein et al., 2014; van Leeuwen et al., 2003). In the Rotterdam Study at 6½ years, the occurrence of large drusen (≥125 m) was 8.6%, and that of pigmentary abnormalities was 9.3%, which was marginally lower than the BDES (van Leeuwen et al., 2003) (Table 4). In the Reykjavik study and in the Copenaghen Study the incidence of large drusen and pigmentary abnormalities were higher than in the Rotterdam Study and BDES (Buch, Vinding, et al., 2005; Jonasson et al., 2005; van Leeuwen et al., 2003).

The Hisayama Study conducted in Japan was a population-based cohort in which the 5-year incidence and risk factors were investigated. The 5-year incidence of early AMD was 8.5% and 0.8% for late AMD (Miyazaki et al., 2005). Features that set this study apart from European and other Asian cohorts was the very high incidence of large drusen (54%). However, both prevalence and incidence of late AMD were lower in the Japanese compared to white populations. Potential explanations for these discrepancies may include differences in grading methodology as well as racial and genetic factors. It is also possible that the very high levels of antioxidants in the typical Japanese diet may be protective against AMD but this is not supported by the high prevalence of large drusen (Table 4). Furthermore, the Singapore Malay Eye Study reported that the 5-year incidence rate for early AMD was 6.13% which is considerably lower than that of RES, BDES and BMES (Cheung et al., 2017). These findings clearly indicate a lower incidence of precursor features of GA in Asian populations and are consistent with the low prevalence and incidence of late AMD in Asian populations (Cheung et al., 2017).

4 | LATE AMD

4.1 | GA prevalence

Table 3 shows the prevalence of late AMD by GA and nAMD when these were reported separately by major epidemiological studies. As with features of intermediate AMD the prevalence rates vary widely by study and by geographical location This heterogeneity in prevalence is reflected in the most recent and most comprehensive work on the population-based global prevalence of AMD which estimated that the combination of the two late stages (nAMD and GA) was around 0.37% (95% CI, 0.18–0.77) (Wong et al., 2014). However, there were considerable differences both by ethnicity and geographic region. The same report also found that the overall prevalence of GA was 0.44% (CrI 0.15%–1.36%). However, most of the studies that contributed to this part of the meta-analyses were made on populations of European ancestry in whom the prevalence of late AMD is much higher (Augood et al., 2006; Klein et al., 2006, 2011; Vingerling et al., 1995; Yang et al., 2011). On examining the frequencies of GA by ethnicity there were significant differences in prevalence 1.11% European, 0.21% Asian, 0.16% Hispanic and 0.14% African.

A pooled analysis of the prevalence of GA based on 5 large studies (Beaver Dam Eye Study, Blue Mountain Eye Study, Copenhagen City Eye Study, Melbourne Visual Impairment Project, Rotterdam Eye Study) in those aged 65 to 79 years was 0.53% (95% CI, 0.37–0.68) (Rudnicka et al., 2012). This meta-analysis

TABLE 3 Prevalence of large drusen and pigmentary irregularities (constituting intermediate AMD features) and reticular psuedo-drusen (RPD).

Study	Period of study	Size of sample	Age of sample	Large drusen (≥125)	Pigmentary irregularities	Reticular psuedo-drusen	GA	nAMD
Beaver Dam Eye Study. Klein et al. (1992)	1987–1988 Wisconsin (USA)	4926	43–86 years (>75 years)	24.0%*	26.6%*	0.7%*	2.0%*	5.2%*
Rotterdam Study. Vingerling et al. (1995)	1990–1993 Rotterdam (Netherlands-Europe)	6251	55–98 years	17.5%*	7.2%*	4.9%*	3.7%*	7.4%*
Blue Mountain Eye Study. Mitchell et al. (1995)	1991–1993 Sydney (Australia)	3654	≥49 years	13% (95% CI, 12.2%–14.4%)	12.6% (95% CI, 11.5%–13.7%)	1.95%*	9/71*	22/71*
Melbourne Collaborative Study. Finger et al. (2016)	2003–2007 Melbourne (Australia)	21 130	48–86 years	11.2%* (2370/21 130)	5.7%* (1202/21 130)	0.78%*	0.4%* 87/21 130	0.26%* 55/21 130
European EYE Study. Augood et al. (2006)	2003–2005 Europe (7 countries)	5040	≥65 years	15.41% (95% CI, 13.61%–17.21%)	NA	NA	1.2% (95% CI, 0.8%–1.7%)	2.3% (95%, CI, 1.7%–2.9%)
India Eye Study. Krishnan et al. (2010)	2005–2007 India (two sites)	4266	≥60 years	8.9% (95% CI, 7.6–10.1) South India 6.3% (95% CI, 4.3–8.3) North India	39.5% (95% CI, 37.4–41.6)	0.2% (95% CI, 0–0.5)	1.2% (95% CI, 0.9–1.6)	1.2% (95% CI, 0.9–1.6)
Singapore Eye Study. Cheung et al. (2017)	2004–2014 Singapore	10 033	40–79 years	Early AMD defined as soft indistinct or reticular drusen or soft distinct drusen with pigmentary irregularities. 5.1% (95% CI, 4.6–5.5)		NA	0.25%	0.25%
Alienor Study. Chan et al. (2016)	2011–2012 Bordeaux, Dijon, Montpellier (France-Europe)	494	≥77 years	84.8%* (823/970)	69%* (670/970)	13.4%*	6.9%* (late AMD)	6.9%* (late AMD)
ALSTAR. Zarubina et al. (2016)	2009–2011 Alabama (USA)	651	≥60 years	NA	NA	Overall SDD was found at a frequency of 32% SDD occurred at a frequency of 49% in early and 79% in intermediate AMD. With colour CFP 1.97% had RPD	NA	NA

Abbreviations: AMD, Age-related macular degeneration; CI, Confidence Interval; NA, not available; SDD, subretinal drusenoid deposit.

*CI data, not available.

TABLE 4 Incident intermediate AMD and late stages (GA and nAMD).

Study	Period of study	Follow-up (yrs)	Size of sample	Age of sample	Large drusen (≥125)	Pigmentary irregularities	Reticular pseudo-drusen	GA	nAMD
Copenhagen City Eye Study (Denmark-Europe) Buch, Vinding, et al. (2005)	1986–2002	14	946–359	60–80 yrs	22%–34.7%[a]	25.7%[a]	NA	4.9%–12.5%[a]	12%–28.1%[a]
BDES (Wisconsin-USA) Klein et al. (2007, 2008)	1988–2005	15	3917	43–86 yrs	18.7%[a]	20.2%[a]	6.6%[a]	3.2%[a]	4.4%[a]
Rotterdam Study Rotterdam (Netherlands-Europe) van Leeuwen et al. (2003), Klein et al. (2014)	1989–1995 (1997–1999)	6 1/2	6418	≥55 yrs	8.6%[a]	9.3%[a]	NA	0.0%–3.2% (95% CI, 1.6%–6.4%)	1.1%[a]
BMES (Sydney-Australia) Wang et al. (2007)	1992–2002	10	3654	≥49 yrs	21.3%[a]	12.1%[a]	11.7%[a]	1.7%[a]	2.2%[a]
Reykjavik Study Reykjavik (Iceland-Europe) Jonasson et al. (2005)	1996–2001	5	1379	≥50 yrs	1.1%–17% (95% CI, 0.0%–28.6%) (95% CI, 1.5%–55.6%)	9.9%–31.3% (95% CI, 6.3%–13.6%) (95% CI, 5.7–56.8)	NA	4.6% (95% CI, 1.2%–7.9%)	0%[a]
Hisayama Study Fukuoka (Japan) Miyazaki et al. (2005)	1998–2003	5	1482	40–79 yrs	54%[a]	13%[a]	15%[a]	3%[a]	5%[a]
Singapore Malay Eye Study Cheung et al. (2017)	2006–2013	6	1901	≥40 yrs	Early AMD definition was soft indistinct drusen or soft distinct plus pigmentary irregularities (thus representing intermediate AMD) 5.89 (95% CI, 4.81–7.16)		NA	CNV and GA reported together 0.98%	

Abbreviations: CI, Confidence Interval; GA, geographic atrophy; NA, not available; nAMD, neovascular age-related macular degeneration; yrs, years.

[a]CI data, not available.

also estimated the prevalence of GA by age groups in those aged 80–84, 85–89 and 90+ and these were 4.65% (3.49%–6.05%), 6.99% (4.73%–9.88%) and 11.27% (6.58%–17.65%) respectively. These confidence limits reveal the degree of uncertainty in terms of the true prevalence of GA and it is worth noting that they are based on the detection of features of GA in at least one eye (Rudnicka et al., 2012). In the European Eye Study that enrolled participants aged 65 and older across 7 countries prevalence of GA was 1.2% (95% CI, 0.75–1.65) (Augood et al., 2006).

The best estimate of the age-specific prevalence of GA in a European country (the UK) comes from the work of Owen et al. using a novel approach (Owen et al., 2003). They first established a pooled prevalence by age in an analogous white population from countries with robust epidemiological data on late AMD. The pooled prevalence of GA rose from 0.03% in the 55 to 59 age group to 10.56% after the age of 90 years. Population growth predictions for the UK over a contemporaneous 10-year period were obtained and the pooled prevalence estimates were applied to derive figures for prevalent late AMD resulting in calculations that estimated that the number of persons with GA was likely to be of the order of 276 000 (CrI. 188 000–396 000) (Owen et al., 2003).

4.2 | GA incidence

Data are lacking on the global incidence of pure GA. However, there are a number of epidemiological studies that have reported the incidence over a 5-year period (Table 4). In a population from Rotterdam aged 50, the incidence of all late AMD (GA and nAMD combined) has been reported to be around 1.8% (95% CI, 1.3–2.4), rising from 0.0% in the age group 55–59 years to 6.8% (95% CI, 4.2–11.0) in those aged 80 and older. For GA alone the incidence rose from 0.0% in the age group of 55–59 to 3.2% (95% CI, 1.6–6.4) in the age group 80 and older (van Leeuwen et al., 2003). In another contemporaneously recruited cohort in Australia that enrolled participants aged 49 and older, the 15-year incidence of GA was 3.6% (95% CI, 2.7–4.7) but after accounting for the competing risk of death and following age standardization, the incidence was estimated to be 1.8% (95% CI, 1.2–2.4). The highest incidence of GA despite only 5 years of follow-up comes from the Reykjavik Eye Study at 4.6% (95% CI, 1.2–7.9) and has been attributed to diet and genetic differences in this population (Jonasson et al., 2005).

Other epidemiological facts of importance on GA development and progression are scant but a recent analysis of combined data from prospective studies of similar design has yielded useful knowledge (Colijn et al., 2021; Joachim et al., 2013). Researchers used figures from 4 population-based cohorts that were collected across three decades. The average age at first diagnosis of GA was 82.6 years. The 10-year cumulative incidence was 2.8% in the Rotterdam cohort in which enrolment commenced in 1990 and it was 3.6% in the Australian cohort in which enrolment commenced in 1992. Interestingly the mean size of prevalent GA was larger than the mean size when detected at incidence. The mean size of GA when calculated at incidence in successive cohorts continued to reduce. These data suggest improving trends in population eye health which may be associated with cessation of smoking and adoption of healthier diets and lifestyle in the more recent decades. One inexplicable finding is the faster enlargement rates found in incident GA although the lesion sizes were smaller (1.16 mm^2 per year in incident GA compared to 1.03 mm^2 per year for prevalent GA) and this is not in accord with what is known on GA enlargement as larger lesions having larger perimeters tend to expand faster (Sunness, 1999). It is possible that the square root transformation which adjusts for differences in GA starting area may account for this observation.

In terms of absolute numbers of incident GA, the only source of information comes from the UK which was estimated in 2001 to be 43 700 (95% Crl 27 000 to 71 200) cases.

5 | RISK FACTORS

The preceding sections have specifically addressed the prevalence and incidence of intermediate AMD lesions and the late stage of GA. However the risk factor profiles for the precursor lesions of intermediate AMD and the late-stage manifestations of nAMD and GA overlap.

Therefore we review the systemic, environmental, genetic and ocular risk factors for intermediate and both late stages of AMD together. Nonetheless, when risk factors show differential associations with these different stages of AMD we draw out these distinctions.

5.1 | Systemic risk factors

Hypertension: for a long time, researchers have studied the relationship between hypertension and the progression of AMD, as well as the potential protective effects of anti-hypertensive medication. However, the results have been unclear. While hypertension may be a risk factor, it is unlikely to be a significant contributor to the appearance and progression of AMD (Choudhury et al., 2011; Tan et al., 2007).

Cardiovascular disease: initially, reports from the Beaver Dam Eye Study Group (Klein et al., 1992, 2003), the Rotterdam Study (Klaver et al., 2001) and the Blue Mountains Eye Study (Mitchell et al., 1995) did not observe any significant association between late AMD and cardiovascular disease (CVD). However, recent studies have investigated the relationship between CVD, systemic blood pressure, and lipid metabolism in a variety of ethnic populations (Erke et al., 2014; Fraser-Bell et al., 2008; Hogg et al., 2008; Hyman et al., 2000; Tan et al., 2008; Taniguchi et al., 2015; Thomas et al., 2015; Vassilev et al., 2015; Wu et al., 2014; Yang et al., 2014).

Hyman et al. were the first to report a significant association between CVD and AMD and subsequent studies have continued to provide additional evidence (Hogg et al., 2008; Hyman et al., 2000; Vassilev et al., 2015). In this context, Hogg et al. showed that a history of CVD

was a strong risk factor for nAMD (OR 7.53, CI, 2.78, 20.41) and Vassilev et al. found an association between AMD and myocardial infarction (MI). In a large meta-analysis published in 2014, patients with both early and late AMD had an increased risk of CVD and coronary heart disease (Pennington & DeAngelis, 2016; Wu et al., 2014). However, data are not always consistent in this regard as Nguyen-Khoa et al. described a lower incidence of MI and cerebrovascular accidents in patients affected by neovascular AMD than in controls (Nguyen-Khoa et al., 2008).

Cholesterol and lipid metabolism: Research conducted since 1992 has successfully identified a link between both advanced forms of AMD and high HDL levels, and dietary cholesterol intake but the associations are particularly strong for nAMD (Hyman et al., 2000; The Eye Disease Case–Control Study Group, 1992).

Several reports documented a positive link between total serum cholesterol levels and GA incidence, however, in early AMD no significant association with HDL, LDL triglycerides, and total cholesterol was observed (Klein et al., 1992; Mitchell et al., 1995). High triglyceride levels were found to be a significant risk factor for small hard macular drusen (defined as >20 small drusen) (Munch et al., 2013).

Diabetes: The role of diabetes in the development of AMD remains unclear. Several studies have found increasing risk of AMD in persons with diabetes mellitus (Age-Related Eye Disease Study Research Group et al., 2005; Wang et al., 2016). Hyperglycemia and dyslipidemia of diabetes were thought to be responsible for the development and progression of AMD through induction of oxidative stress and the associated parainflammation both of which are pathophysiological processes that are known to occur in AMD (Zhang et al., 2011). On the other hand, there are studies that have shown no correlation between diabetes mellitus and AMD (Saunier et al., 2018; Seddon et al., 2003; Tomany et al., 2004), while others have reported lower rates of progression both from no AMD to intermediate AMD and from intermediate to late in patient populations with diabetes (Chakravarthy et al., 2020).

Hyperthyroidism: research shows that in cases of hyperthyroidism, elevated levels of T4 (but not TSH) can cause an increase in basal metabolism and oxidative stress. This can lead to damage of RPE cells and photoreceptors, raising the risk of developing AMD (Chaker et al., 2015; Duncan et al., 1999; Ma et al., 2014; Tsai et al., 2007).

Oxidative stress and inflammation: Compared to healthy subjects, case–control studies report higher levels of products of oxidation in peripheral blood and ocular fluids in AMD patients (Kersten et al., 2018). The macula is susceptible to oxidative stress due to its high metabolic activity and the presence of polyunsaturated fatty acids (PUFAs) in the photoreceptors. In AMD, there is accumulation of lipofuscin in the RPE which is also a significant contributor to the production of reactive oxygen species in the retina. Thus the environment at the photoreceptor RPE interface is at high risk of exposure to products of oxidative stress leading to the onset and progression of AMD (Beatty et al., 2000; Feeney-Burns et al., 1984; Khandhadia & Lotery, 2010).

Gut microbiota: recent studies have supported the concept of a "gut–retina axis" in the pathogenesis of ocular diseases, especially AMD. It is well known that gut microbiota undergoes essential changes after the age of 65 years, reducing absorption capacity, particularly in patients with many systemic diseases. This reduction of macro and micronutrients that is vital for the health of the retina can lead to an increase in the ageing process of the retinal cells (Andriessen et al., 2016; Rinninella et al., 2018).

Periodontal disease (PD): It has been shown that individuals with AMD tend to have more PDs ($p=0.031$), fewer teeth ($p<0.001$), and more alveolar bone loss compared to those without AMD ($p=0.004$) (Karesvuo et al., 2012; Wagley et al., 2015). Because both conditions are common in older age groups it may be purely coincidental but additional data are required to confirm or refute this association (Pockpa et al., 2019).

5.2 | Demographic and environmental risk factors

Age and sex: Age is the most important demographic risk factor for AMD (Joachim et al., 2013; Shim et al., 2016). A recent meta-analysis showed an increase in prevalence from 3.5% in patients with early AMD aged 55–59 years to 17.6% in people older than 85 years. The prevalence increases from 0.1% to 9.8% respectively for late AMD (Colijn et al., 2017). Additionally, age has a slightly stronger association with the progression of GA (Joachim et al., 2013). Although age is a known risk factor for AMD, the impact of sex is still unclear. Certain studies suggest that estrogens may help protect against the development of the disease, putting males at a higher risk (Vingerling et al., 1995). However, other studies have found no evidence to support this claim (Defay et al., 2004).

Ethnicity: A recent study conducted by Zhou et al. revealed that Europeans have the highest annual incidence rate for both early and late AMD (Zhou et al., 2018). However, African people have a high incidence of early AMD but a low incidence of late AMD. This could be due to high ambient UV radiation in Africa (Patton et al., 1999). Compared to Asia, the incidence of early and late AMD is higher in Europe and Oceania, particularly among the White population. One explanation is the lower levels of protective melanin in the retina in White populations as compared to other ethnic groups (Rim Hyungtaek et al., 2020; Wong et al., 2014).

Smoking and air pollution: smoking is the strongest modifiable risk factor for AMD at any stage. It is associated with a faster GA growth (0.33 mm/year in smokers compared to 0.27 mm/year in non-smokers) (Age-Related Eye Disease Study Research Group et al., 2018). Individuals who have quit smoking may yet face a slightly higher risk of disease progression as compared to those who have never smoked (Buch, Vinding, et al., 2005; Merle et al., 2017). Like smoking damage, air pollution may accelerate or worsen AMD, changing homeostasis

and interfering with inflammation, with a consequent increase in lipid metabolism and oxidative stress in the macula (Liu et al., 2022).

Sunlight exposure: A definite correlation between sunlight exposure and the incidence and progression of AMD was not found (Zhou et al., 2018). A significant association was found between blue light exposure and neovascular AMD in patients with low levels of antioxidant products like vitamin C, zeaxanthin, vitamin E and dietary zinc, which were also associated with early stages of AMD (Fletcher et al., 2008). In a recent meta-analysis about sunlight exposure, no significant association was observed by degree of AMD, exposure method and latitude (Zhou et al., 2018).

Body mass index (BMI) and physical activity: Higher BMI and irregular exercise are thought to increase inflammatory and oxidant products and influence the progression of AMD (McGuinness et al., 2016). The elevation of inflammatory factors such as complement and cytokines could interfere with RPE function, leading to the development of AMD (Johnson, 2005).

Diet and macronutrients: maintaining a healthy diet and consuming the right macronutrients can greatly improve the health of the eyes and is an important factor in reducing the risk of AMD and its progression. Recent studies have shown that long-chain polyunsaturated fatty acids (LCPUFAs), as well as vitamins such as C, D and E, zinc, carotenoids, beta carotene and lutein and zeaxanthin (Augood et al., 2008; Layana et al., 2017; Merle et al., 2019), play a significant role in promoting macular health. It was reported that eating oily fish at least once per week could significantly reduce the odds of nAMD (OR = 0.47; 95% CI: 0.33, 0.68, $p = 0.002$) (Augood et al., 2008) and also that low vitamin D status could be a potential risk factor for the development of early and late AMD due to its anti-inflammatory and cell activity modulation properties (Layana et al., 2017).

5.3 | Genetic risk factors

The development of AMD is heavily influenced by genetic susceptibility. Currently, the GWAS Catalogue (https://www.ebi.ac.uk/gwas/) has identified 103 AMD genes or loci associated with this disease. Some of these genes are involved in regulating complement activity, whereas others are linked to lipid metabolism. Two specific genes, CFH and HTRA1, are particularly significant in regulating complement and playing a role in AMD, according to Fritsche et al. (2014). CFH plays a crucial role in regulating the complement pathway. A study conducted in 2010 revealed that there is a connection between a specific variation in the CFH gene, known as a single nucleotide polymorphism (SNP) Y402H, and the prevalence of AMD in the European population (correlation coefficient 0.40). This variation involves the substitution of histidine for tyrosine at codon 42 on the long arm of chromosome 1-region 31 (rs1061170) (Nonyane et al., 2010). This allele causes over-activation of complement and disrupts the transport of oxidative lipids from the RPE layer as well as the regulatory function of CFH (Despriet et al., 2006; Edwards et al., 2005).

There are certain mutations in the complement pathway, such as CFB and CFI, that could either offer protection (rs10033900, rs11728699, rs6854876, rs7439493, rs13117504) or raise the risk for AMD (rs2285714) (Dewan et al., 2006; Hughes et al., 2007; Seddon et al., 2007).

The relationship between genes and environmental factors can impact the onset and progression of AMD. Smoking, for instance, may elevate the likelihood of AMD in individuals with the HTRA1 genotype (Sobrin & Seddon, 2014).

Regarding the genes that are capable of regulating lipid metabolism, the APOE gene plays a vital role in regulating the transportation of lipids and cholesterol in the nervous system and retina. The haplotypes of APOE alleles are thought to contribute to the development of drusen and the advancement of AMD (Li et al., 2006).

Another key genetic locus lies in the ARMS2/HTRA1 gene. Variants at this locus are known to increase the risk of developing early AMD and progression to nAMD and GA. While the exact function of the ARMS 2 gene is unknown it is thought that it is responsible for the synthesis of a protein that has functions in the mitochondria of retinal cells. The HTRA1 gene encodes for a heat shock serine protease and controls the process of neoangiogenesis (Canfield et al., 2017; Grassmann et al., 2015).

5.4 | Ocular risk factors

5.4.1 | Drusen

The pathophysiology and characteristics of drusen in AMD have been covered in the section describing the features of early and intermediate AMD and the development and validation of the AMD staging systems. Studies have shown that the total number of drusen, drusen area and volume are risk factors for progression of intermediate AMD to either GA or nAMD (Age-Related Eye Disease Study Research Group et al., 2005; Gass, 1973; Heesterbeek et al., 2020; Klein et al., 1992; Lei et al., 2017; Mitchell et al., 1995; Ouyang et al., 2013; Schlanitz et al., 2017). Progression is also influenced by drusen location since eyes with drusen near the fovea have a higher probability of developing late forms of AMD compared to eyes with drusen outside the fovea (Joachim et al., 2013; Nathoo et al., 2014; Shim et al., 2016). The use of multimodal retinal imaging techniques enabled to differentiation several subtypes of drusen with different roles in AMD evolution (Lengyel et al., 2015; Schmidt-Erfurth et al., 2017).

Small drusen (hard drusen) are discrete yellow-whitish deposits (<63 μm in diameter) with a clearly defined margin (Khan et al., 2016). In 2013 The Beckman group published guidance in which hard drusen or a few small drusen, called 'druplets', were considered a normal ageing process of the eye, because of the low probability (0.4%) in such eyes of progression to late AMD (Belmouhand et al., 2022; Ferris 3rd et al., 2013; Mitchell et al., 1995). Nevertheless, when small drusen accumulate in number over time, there is an increased risk of progression to intermediate AMD (Ferris 3rd et al., 2013).

Medium drusen (>63 μm and ≤125 μm) and *large drusen* (>125 μm) (soft drusen) represent a later stage in drusen (Sarks et al., 1999) evolution owing to enlargement and fusion of hard drusen. They are abundant in the central macula where a high concentration of cones and Müller cells could serve as upstream drivers of lipoprotein deposit formation (Spaide et al., 2018). Large drusen which are stages of intermediate AMD are associated with a high risk of progression to late AMD and in particular GA (Brader et al., 2013; Joachim et al., 2013; Klein et al., 1992). Drusen of all sizes are easily identified on Spectral Domain OCT (SD-OCT) as focal elevations of the RPE containing medium to highly reflective material (Schmidt-Erfurth et al., 2017). Three extensive studies conducted in Europe between 1986 and 2003 found that a higher risk of more severe AMD lesions and progression at follow-up was associated with larger drusen size, pigmentary changes and the severe drusen type at baseline (Buch, Vinding, et al., 2005; Jonasson et al., 2005; van Leeuwen et al., 2003). Moreover, The Copenhagen Study found that soft indistinct drusen and pigmentary abnormalities at baseline were linked to a high risk of late AMD and visual loss (≤20/200) at follow-up (Buch, Nielsen, et al., 2005) (Table 4).

Calcified or refractile drusen: overtime drusen can undergo a calcification process acquiring a glistening appearance on fundus examination. On SD-OCT refractile drusen appear as hyperreflective dots occasionally shadowing into the deeper structure and with overlying hyperreflective foci (Spaide & Curcio, 2010; Suzuki et al., 2015). It has been shown that patients with calcified drusen are more likely to develop GA than patients without these lesions, with a probability of 26% within 5 years (Armstrong et al., 2006; Oishi et al., 2017). Foci with loss of outer retinal and retinal pigment epithelial layers develop in areas overlying atrophic drusen and when the diameter exceeds 250 μm is considered to be equivalent to GA a diagnosis made on colour imaging or clinical examination (Oishi et al., 2017; Tan et al., 2018).

Cuticular drusen: also called basal laminar drusen are a distinct form of small round drusen that occur in early adulthood, attributed to internal nodularity of the RPE (Russel et al., 2000). Like other drusen, they are localized in the sub-RPE basal laminar compartment. SD-OCT and fundus autofluorescence (FAF) are useful in diagnosing these lesions (Balaratnasingam et al., 2018; Sakurada et al., 2020). Cuticular drusen are ultra-structurally similar to hard drusen but their life cycle and macular complications are similar to soft drusen, with an association to nAMD development in 12.5% and to GA in 25% of the cases over 5 years (Balaratnasingam et al., 2018; Sakurada et al., 2020).

Reticular Pseudo-drusen (RPDs) or subretinal drusenoid deposits (SDD): These were first described by Mimoun et al. in 1990 as drusen best visible with blue light (Mimoun et al., 1990) and termed reticular pseudodrusen owing to their reticular distribution in the fundus. They are visible as ribbon-like sheets on colour images. However, with improved imaging technology they are consistently and easily seen on the spectral domain (SD) OCT in which they appear as hyperreflective material located internal to the RPE and hence termed subretinal drusenoid deposit (SDD) (Schlanitz et al., 2017; Zweifel et al., 2010). In the BDES the risk of developing RPDs was found to be higher in females, current smokers, lower education, B vitamin complex supplement/intake, patients with glaucoma and those with more severe drusen types (e.g. soft indistinct drusen; OR, 1.4). Conversely, people with diabetes at baseline had a decreased risk (OR, 0.1). Eyes with RPDs at baseline had a higher incidence of GA (21% vs. 9%) compared to those with soft indistinct drusen (Klein et al., 2008).

Huisingh et al. analysed a subset of 455 participants from the AREDS cohort with at least one eye, exhibiting SDD at enrolment, and observed that the risk of progression to AMD over 3 years follow-up was 2.24 fold greater than those without SDD (Huisingh et al., 2016). SDD has been also associated with an increased risk of developing outer retinal atrophy, complete outer retinal and RPE atrophy, and choroidal neovascularization. Data from the Geographic Atrophy Progression Study indicate that reticular pseudo-drusen occur in around 62% of eyes with GA (Schmitz-Valckenberg et al., 2011), Interestingly GA is rarely seen prior to the development of reticular drusen (Sarks et al., 2011). It has also been noted that the prevalence of RPDs is up to 90% or more in eyes with GA or type 3 macular neovascularization (Sacconi et al., 2023). Consistent findings have emerged over time as investigators reported correlations between SDD and outer retinal atrophy, decreased choroidal thickness, and altered choroidal vasculature (Spaide, 2013; Velaga et al., 2020). More recently, Hirabayashi et al. described the presence of SDD as a significant risk factor for the development of complete retinal pigment epithelium and outer retinal atrophy (cRORA) at 2 years (RR 2.307, 95% CI, 1.003–5.304) (Hirabayashi et al., 2023).

Peripheral drusen: Since the introduction and use of ultra-widefield (UWF) imaging, it has been possible to evaluate the presence of peripheral lesions as well as the central macular fundus. In 2015 Lengyel et al. documented the presence of wide-ranging AMD-like pathologic changes in the retinal periphery, including drusen, that were present in patients who had no macular changes suggesting a possible influence of the peripheral retina in the onset of AMD. Notably, drusen in the retinal periphery may not be randomly located but some sectors of the retina seem to be more affected, such as the superior sector and in particular the nasal-superior sector with a sparing of the temporal sectors (Corbelli et al., 2020; Lengyel et al., 2015).

Choroid: The choriocapillaris (CC) and choroid exhibit changes which are observed across the entire spectrum of AMD from early through to the late-stage manifestations of GA and nAMD. In 2011 a histologic study demonstrated, for the first time, the involvement of CC and choroid in drusen formation in the earliest stages of AMD (Mullins et al., 2011). More recently, OCT Angiography (OCTA) enabled the visualization and quantification of CC impairment in eyes with drusen. Different patterns and severity of CC flow impairment depending on drusen location and extent and higher number of flow voids in CC in intermediate AMD vs controls were documented (Chatziralli et al., 2018; Vujosevic et al., 2019). In advanced stages of AMD, such as GA, OCTA

highlighted a displacement of larger choroidal vessels in CC under the GA area and an impairment of CC beyond its border even with RPE preservation (Choi et al., 2015; Kvanta et al., 2017; Waheed et al., 2016). Subsequently, different studies demonstrated that the direction of the enlargement of GA could be predicted by CC flow deficit (Alagorie et al., 2020; Sacconi et al., 2021; Thulliez et al., 2019).

Cataract and cataract surgery: Cataracts and AMD frequently occur together and can result in vision loss and blindness in older individuals. In the late 1990s, studies suggested that cataract surgery might increase the risk of AMD progression to late AMD (Cugati et al., 2006; Klein et al., 2002; Wang et al., 2003). The Beaver Dam Study and the Blue Mountains Eye Study reported a higher long-term risk of developing late AMD in eyes that previously had cataract surgery (before the baseline examinations) than in phakic eyes at baseline (RR, 3.81; 95% CI, 1.89–7.69 and RR, 3.3; 95% CI, 1.1–9.9 respectively) (Cugati et al., 2006; Klein et al., 2002). The authors proposed several mechanisms that could lead to AMD progression after cataract surgery. First, the presence of cataracts may have masked signs of exudative and non-exudative AMD; second increased penetration of UV after cataract removal could have accelerated degenerative changes owing to higher exposure to oxidative stress at the macula; third cataract and AMD have shared common risk factors. The BDES found an association between cataract at baseline and incidence of early AMD (RR, 1.30, 95% CI, 1.04–1.63), soft indistinct drusen (RR, 1.38, 95% CI, 1.08–1.75), increased retinal pigment abnormalities (RR, 1.38, 95% CI, 1.08–1.79) and progression of AMD (RR, 1.37, 95% CI, 1.06–1.77). Moreover, in these patients, there was a higher risk of progression to pure GA (RR, 3.18, 95% CI, 1.33–7.60) and nAMD (RR, 4.31, 95% CI, 1.71–10.9) (Klein et al., 2002). However, in recent studies, cataract surgery did not lead to an increased risk of AMD progression (Bhandari & Chew, 2023; Kessel et al., 2015). Bhandari and Chew compared the results of AREDS1 (Chew et al., 2009) and AREDS 2 (Bhandari et al., 2022), with prior population-based longitudinal studies. Significant advances in surgical techniques and better ability to assess macular tissue health through non-invasive imaging even in the presence of medial opacities due to cataracts made these studies feasible. Additionally, increased use of ultraviolet-blocking or blue-filtering intraocular lenses may have addressed potential macular toxicity and eventual AMD progression (Bhandari & Chew, 2023).

5.4.2 | Conclusions

The ageing population is burgeoning worldwide not only because of lower mortality in childhood and early adult life due to vaccination, improvements in health care programs and overall nutritional status but also because of better management of chronic diseases of the elderly. However, longevity has brought with it an increase in GA which now constitutes an important cause of visual impairment and blindness. Worldwide the absolute numbers of visually handicapped people continue to rise despite the small reductions in incident GA that have occurred with improvements in population health. Existing epidemiological data from countries in which the majority of the population is of European ancestry indicate that intermediate AMD and pseudo-drusen (key precursors of GA) are commonly found. In prevalence terms, these characteristic features are uncommon in Asian populations and their incidence rates are also low. With regard to the late stage of AMD namely GA, prevalence varies considerably across studies because of heterogeneity in definitions as well as in reporting strategy. The incidence of GA is even more variable across studies, partially because they are non-contemporaneous and have been performed across several decades. This could have led to differences accounted for by changes in environmental exposure, lifestyle and diet and improved population health. Despite these variations in both prevalence and incidence of GA in European populations, corresponding rates are clearly lower still in Asian populations suggesting the existence of strong protective factors such as genetic variability playing a role. Recent developments in non-invasive imaging permit microscopic level resolution of macular morphology and thus new studies to understand the drivers of progression from normal ageing to early functional and anatomical abnormalities are needed across many geographical locations and with enrolment of populations of different ancestries. Large consortia, federated learning and collaborative working can help piece together a better understanding of the factors that drive progression to GA. Such a program of future work can not only assist in developing strategies for prevention of GA but also help with appropriate resource allocation and planning since new therapeutic modalities with potential to limit GA growth and reduce functional loss are on the horizon.

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