Increased Caucasian Prevalence of Medium and Large Drusen, Focal Pigment Abnormalities, and Advanced Age-related Macular Degeneration

a report by
Sharon D Solomon, MD *and* **Susan B Bressler, MD**

Wilmer Eye Institute, Johns Hopkins University *DOI: 10.17925/USOR.2007.03.00.57*

Over the past 35 years, a number of large population-based studies have concentrated on the epidemiology of age-related macular degeneration (AMD), the leading cause of irreversible vision loss in persons aged 65 years and older in the US and other developed nations.[1] Recent advances in effective therapies slow the progression of intermediate AMD to advanced AMD and decrease the risk for moderate vision loss associated with the development of choroidal neovascularization (CNV). However, epidemiological investigations remain important to identify possible risk factors for the development or progression of AMD, to recognize susceptible individuals and populations, to promote screening, education, and prevention tools, and to generate hypotheses for disease pathogenesis. For instance, the strongest and most consistent association between incident and prevalent AMD and a modifiable risk factor has been tobacco use.[2] It is theorized that hypoxia stimulates vascular endothelial growth factor (VEGF) production, which in turn upregulates retinal endothelial cell proliferation, which fosters the development of CNV.[3] Smoking may potentiate hypoxic retinal conditions, thus contributing to the pathogenesis and progression of AMD. Identifying patients with this modifiable risk factor and educating them about the potential benefits of tobacco cessation may have a significant long-term impact on lowering the incidence and progression of AMD.

Many of the landmark epidemiological studies concentrating on AMD have employed a standardized approach to identify 'cases' of AMD. Case recognition has involved the use of high-quality stereoscopic color fundus photographs, obtained by certified photographers adhering to a protocol, which are then graded by trained and experienced readers with systematic application of standard definitions and reference photographs to generate levels of specific AMD features and levels of disease. As many studies have used similar means of generating their data, pooling of databases has been facilitated and some comparisons can be made between studies to partially overcome the limitation that only a few investigations have involved populations with heterogeneous ethnic backgrounds. While there are minor distinctions from one population-based study to the next in terms of the characterization of specific ocular features that comprise the early, intermediate, and advanced stages of AMD, the descriptions that follow are generally accepted, and the prevalence of each level of AMD has repeatedly been shown to be age-related.

The label 'early' AMD requires that an eye has, as its most advanced feature, the presence of at least one medium-sized druse, with a linear dimension that is at least 64µm and up to 125µm (including 125µm in some studies) within 3,000µm (two standard disc diameters) of the foveal center.[4] The number of medium-sized drusen required may vary between studies. Progressing along a severity scale, the label 'intermediate' AMD requires that the most advanced AMD feature is the presence of at least one large druse, manifesting a diameter of 125µm (or >125µm in some studies) within the same region of the posterior pole. As graded in the Age-Related Eye Disease Study (AREDS), intermediate AMD was also defined as the presence of extensive, medium-sized drusen, approximately 20 in number, soft and indistinct, measuring ≥63 and <125µm in diameter.[5]

The presence of retinal pigment epithelium (RPE) abnormalities—either focal hyperpigmentation or depigmentation (also known as non-geographic atrophy [non-GA])—may be variably present in either early or intermediate AMD. Frequently, RPE abnormalities may be restricted to the central 1,500µm radius of the foveal center to avoid considering non-specific RPE alterations in the peripapillary area as manifestations of AMD.[4,5] Advanced AMD is also referred to as late AMD and requires the presence of either CNV or GA. Studies vary as to whether GA must involve the foveal center to be considered advanced AMD compared with intermediate AMD.[1,4,5]

Sharon D Solomon, MD, is the Katharine Graham Professor of Ophthalmology at the Wilmer Eye Institute, Johns Hopkins University. She is a Principal Investigator at Wilmer on a number of National Institutes of Health (NIH)-sponsored clinical trials through the Diabetic Retinopathy Clinical Research Network (DRCRN), and a Principal Investigator of the Anecortave Acetate Risk Reduction Trial. Dr Solomon is a diplomate of the American Board of Ophthalmology (ABO), and a member of Alpha Omega Alpha (AOA), the Society of Heed Fellows (HEED), the American Academy of Ophthalmology (AAO), the Association for Research in Vision and Ophthalmology (ARVO), the American Society of Retina Specialists (ASRS), and the Macula Society.

E: ssolomon1@jhmi.edu

Susan B Bressler, MD, is a Professor of Ophthalmology at the Wilmer Eye Institute, Johns Hopkins University, and the inaugural recipient of the Julia G Levy, PhD, Professor of Ophthalmology. She has received the Rosenthal Award from the Macula Society, the Olga Keith Wiess Scholar Award from Research to Prevent Blindness, a 'Woman to Watch' Award from *Jewish Women International Magazine*, a Senior Achievement Award from the American Academy of Ophthalmology (AAO), and the Gertrude Pyron Award and the Senior Honor Award from the American Society of Retina Specialists (ASRS), and was the inaugural recipient of the Neil Miller Medical Student Teaching Award at the Johns Hopkins University School of Medicine. Dr Bressler has served on the Editorial Board of the *American Journal of Ophthalmology*, the *Survey of Ophthalmology*, *Retina*, *EyeNet Magazine*, *Health After 50: The Johns Hopkins Medical Letter*, and the *Wilmer Retina Update*.

Table 1: Racial Differences in the Prevalence of Age-related Macular Degeneration and Specific Fundus Manifestations of Age-related Macular Degeneration

Study Name	BES	MESA	SEE	NHANES	AREDS	ARIC
Participants (n)	5,308	6,176	2,520	4,007	4,519	11,532
Race/Ethnicity (%)						
B	45	27	26	23	N/A	22
W	55	39	74	54	96	78
H	N/A	22	N/A	23	N/A	N/A
C	N/A	12	N/A	N/A	N/A	N/A
O	N/A	N/A	N/A	N/A	4	N/A
Prevalence of Drusen by Size and Race (%)						
64–125µm	B: 13.7	B: 2.1	B: 54	B: 10.7	O: 1.4	B: 3.4
	W: 13.2	W: 4.8	W: 56	W: 14	W: 22	W: 4.6
		H: 4		H: 13.1		
		C: 3.6				
>125µm	B: 6.2		B: 11		O: 1.4	
	W: 7.1		W: 16		W: 33.3	
Pigmentary Abnormalities by Race (%)						
	B: 1.9	B: 2.1	B: 4.3	B: 3.7	O: 1.4	B: 0.8
	W: 3.5	W: 4.8	W: 7.5	W: 6.3	W: 22	W: 2.9
		H: 4		H: 2.9		
		C: 3.6				
GA by Race (%)						
	B: 0.1	B: 0.3	B: 0.3	B: 0.2	O: 0	B: 0
	W: 2.5	W: 0.6	W: 1.8	W: 0.4	W: 2.6	W: 0.2
		H: 0.2		H: 0		
		C: 1				
Neovascular AMD by Race (%)						
	B: 0.1	B: 0.3	B: 1.1	B: 0.2	O: 0.3	B: 0
	W:1.8	W: 0.6	W: 1.7	W: 0.3	W: 14.3	W: 0.2
		H: 0.2		H: 0.1		
		C: 1				

BES = Baltimore Eye Survey; MESA = Multi-ethnic Study of Atherosclerosis; SEE = Salisbury Eye Evaluation; NHANES = National Health and Nutrition Examination Survey; AREDS = Age-Related Eye Disease Study; ARIC = Atherosclerosis Risk in Communities Study; B = black; W = white; H = Hispanic; C = Chinese; O = other; GA = geographic atrophy; AMD = age-related macular degeneration.

Data from population-based epidemiological studies have shown significant variation in the prevalence of AMD and specific fundus manifestations of AMD among various ethnic groups, which will be the focus of this article.

Racial Differences in the Prevalence of Age-related Macular Degeneration and Specific Fundus Manifestations of Age-related Macular Degeneration

Baltimore Eye Survey

The Baltimore Eye Survey (BES) reported cross-sectional population-based data on the prevalence of various eye diseases following examination of approximately equal numbers of black and white participants from the same community in East Baltimore (Maryland). The sample consisted of 5,308 participants, 40 years of age or older, who underwent ophthalmic examinations that included dilation and 30° stereoscopic color fundus film photographs that were graded by a centralized reading center for the presence and severity of drusen, pigmentary abnormalities, GA, and CNV associated with AMD. The median age of white participants was in the 60–69 years of age range, whereas the median age range for blacks was 50–59 years.

Although the age-adjusted prevalence of any drusen within one disc diameter of the fovea that was at least 64µm was roughly 20% and similar among both blacks and whites in all age groups in the BES, larger drusen (at least 125µm) were significantly more common among whites compared with blacks in participants over 70 years of age (15.2 versus 9%; p=0.02).[6] The age-adjusted rate for focal abnormalities of the RPE was higher among whites than among blacks (2.5 versus 0.9%; p<0.001), and this was particularly pronounced in individuals over 70 years of age (7.9 versus 0.4%; p≥0.001).[6] No differences were detected for prevalence of RPE hypopigmentation between the two racial subgroups, with age-adjusted prevalence around 1.7%. Note that prevalence rates for any pigmentary abnormalities were substantially lower than those for drusen in each racial group, a common finding for every cohort reporting AMD features. GA within one disc diameter of the fovea, but not necessarily under the foveal center, was more prevalent among whites than blacks (age-adjusted prevalence 2.5 versus 0.1%; p<0.001). Similarly, neovascular AMD was more common among whites than blacks (age-adjusted prevalence 1.8 versus 0.1%; p=0.02). Combining rates of GA and CNV to evaluate advanced AMD, logistic regression adjustments for age and gender demonstrated an odds ratio (OR) of 4.1 (95% confidence interval [CI] 1.4–11.6) for whites compared with blacks.[6] Among the 2,395 black participants, only four cases of advanced AMD were observed, two manifested GA, and two were classified as AMD-associated CNV. Thirty-five cases of advanced AMD were identified among the 2,913 white participants

followed in the BES. Of these 35 white subjects, 15 had CNV and 20 had GA in the central macula.[6]

The important conclusions from the BES are that although drusen are common in both black and white adults 40 years of age and older, the more severe forms of AMD represented by large drusen, pigment abnormalities, and late features of AMD appear to be more prevalent among whites, particularly at the older end of the age spectrum.

A major strength of BES, relative to many of the other population studies, is the simultaneous assessment of nearly equivalent fractions of a sizable number of black and white participants from the same community, with the result that there is no difference in study design or definitions when comparing AMD among these two racial groups. In addition, photographs were read in a masked fashion, which minimizes bias in interpreting the level of AMD present in subjects of different racial backgrounds. Furthermore, the prevalence rates, adjusted for age, for drusen in the central macula among whites in the BES are consistent with prevalence rates reported in other large population-based studies, such as the Rotterdam Study (RS), the Beaver Dam Eye Study (BDES), and the Blue Mountains Eye Study (BMES), where the populations studied were homogeneously white.[7–9] Similarly, the age-adjusted rates of drusen ≥64µm in the BES were similar to those in the Barbados Eye Study, which evaluated Caribbean blacks.[10] This adds to the confidence we have in accepting the prevalence values for these specific AMD manifestations in black and white participants within this community. However, whites in the BES appeared to have lower rates of RPE abnormalities in the central macula than whites in the BDES (3.5 versus 9.8%), and blacks in the BES had lower rates of pigment abnormalities than those identified in the Barbados Eye Study (2 versus 2.8%).[6,8,10] These differences may represent methodological differences and/or innate differences (genetic and/or environmental) between these different populations.

Multi-ethnic Study of Atherosclerosis

The Multi-ethnic Study of Atherosclerosis (MESA) was a 10-year longitudinal study consisting of 6,176 men and women 45–84 years of age at time of study entry recruited from field centers in Baltimore (MD), Chicago (IL), Los Angeles (CA), New York City (NY), St Paul (MN), and Forsyth County (NC). This prospective cohort study incorporated fundus photographs at the first follow-up exam, which included 2,438 whites (39%), 1,677 blacks (27%), 1,334 Hispanics (22%), and 727 Chinese (12%). The mean age of participants was approximately 62 years. The methods to obtain fundus images differed in this study in that a 45° non-mydriatic digital camera was used and pupils were dark-adapted rather than pharmacologically dilated. Photographs were graded at a centralized reading center for the presence and severity of drusen, pigmentary abnormalities, GA, and CNV within 3,450µm of the fovea. AMD was reported as early AMD (any soft drusen ≥63µm in diameter with pigment abnormalities or large, soft drusen ≥125µm in diameter with a drusen area >500µm diameter circle) or late AMD (GA in any location, pigment epithelial detachment, or CNV).

While the prevalence of early and advanced AMD in the MESA generally increased with age within each of the four ethnic groups evaluated, the crude prevalence of early AMD was lower in blacks (2.1%) relative to whites (4.8%), although no difference was seen for Chinese (3.6%) or Hispanics (4%) compared with whites.[11] Age- and gender-adjusted OR for early AMD was only significantly different for the comparison of blacks with whites (OR 0.45, 95% CI 0.30–0.67). Similar comparisons for the OR (95% CI) of large drusen (0.74 [0.58–0.94]), increased retinal pigment (0.22 [0.12–0.40]), and RPE depigmentation (0.13 [0.04–0.44]) showed significant reductions in blacks relative to whites. In addition, Hispanics had lower rates of increased pigment and RPE depigmentation compared with whites, but no apparent difference when assessing large drusen.[11] The estimated prevalence of advanced AMD (utilizing crude rates) in the MESA was lower in blacks (0.3%) and Hispanics (0.2%) compared with whites (0.6%), and highest in the Chinese cohort (1%).[11] However, there were only 27 total late AMD events, and comparisons between each group with whites did not yield any significant differences when controlling for gender and age.

> Data from population-based epidemiological studies have shown significant variation in the prevalence of age-related macular degeneration (AMD) and specific fundus manifestations of AMD among various ethnic groups.

The overall prevalence of any AMD in the MESA varied from 2.4% in blacks to 4.2% in Hispanics, 4.6% in Chinese, and 5.4% in whites.[11] While the lower frequency of all stages of AMD in blacks compared with whites is consistent with data from other studies, the frequencies of AMD reported in the MESA were lower than those reported in other studies in which 30° stereoscopic fundus film photographs were obtained on subjects with dilated pupils.[6,8]

Salisbury Eye Evaluation

The Salisbury Eye Evaluation (SEE) was a cross-sectional population-based study of 2,520 older participants, 65–84 years of age (mean 73.5 years), from a racially heterogeneous community in Salisbury, Maryland. Stereoscopic 30° color fundus film photographs were obtained through dilated pupils on 1,854 white participants and 666 black participants. Two years following the initial assessment the cohort was re-evaluated to develop incidence data. A centralized reading center, masked to preclude race from the findings, graded the photographs from each visit for the presence and extent of specific AMD features within two disc diameters of the foveal center.

As with several of these observational studies, at the initial examination drusen of any size were common in both blacks and whites, being present in 93% of the cohort.[4] Drusen that were at least medium in size were moderately prevalent in each racial group (56% whites, 54% blacks), whereas large drusen were less frequent and more commonly identified in whites relative to blacks (16 versus 11%; p=0.005). The differences in specific AMD features between white and black participants were most pronounced within the central macula zone (within 1,500µm of the fovea). This included higher prevalence rates for large drusen, confluent drusen, area occupied by drusen, and focal hyperpigmentation in whites versus blacks.[2,4] Non-GA was uncommon in the population, occurring in only 1.4% overall, and no racial differences were observed.[4]

Neovascular AMD was observed in 1.6% of SEE participants, with observed rates of 1.7% among white participants and 1.1% among black participants, which did not statistically differ from one another.[4] Half (15/30) of the white participants with CNV had bilateral involvement, whereas only one of seven affected black participants had bilateral CNV. White participants also had a higher prevalence of GA compared with black participants (1.8 versus 0.3%; age- and sex-adjusted p=0.02).[4] Similar to other population-based studies, the limited number of late AMD cases leads to imprecise estimates for the prevalence of these features of AMD within the population.

At the follow-up examination, the observed rates of progression from early AMD 1 (at least one medium-sized druse 64–125µm in diameter) to early AMD 2 (at least one large druse >125µm in diameter or RPE abnormalities within 1,500µm of the foveal center) and progression from early AMD 1 or early AMD 2 to late AMD (GA or CNV) were greater in whites than in blacks, although the differences were not statistically significant.[2] Race was a significant univariate risk factor for incident focal pigmentation within 3,000µm of the foveal center (3.6% in whites versus 1.6% in blacks; p=0.006).[2]

> When data are compared across studies important differences in study design may occur, such as means of acquiring the retinal images and definitions used to classify disease.

The SEE data suggest that blacks have similar rates of non-neovascular AMD features in the pericentral macular zone (area between one and two disc diameters of the fovea) compared with whites, but do not manifest the high-risk AMD features of large drusen and focal pigment, especially within the central macular zone, which is often observed in whites. This may explain why blacks appear to progress to the late forms of AMD less frequently than whites.

The Third National Health and Nutrition Examination Survey

The Third National Health and Nutrition Examination Survey (NHANES III) was a periodic, national survey of whites, blacks, and Mexican Americans 40 years of age and older conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control (CDC). AMD characteristics among 4,007 participants were based on a reading center assessment of a single, 45° non-mydriatic film fundus photograph of a single eye of the individual. The median age of the cohort was in the 50–59-year-old strata, but there were more whites 70 years of age and older than blacks or Mexicans.

In 1995, NHANES III reported prevalence rates of any AMD as 9.3% in whites compared with 7.4% in blacks and 7.1% in Mexican Americans.[12] While whites 60 years of age and older had a consistently lower prevalence of any drusen in the macula compared with blacks and Mexican Americans, whites in this age group had a consistently higher prevalence of soft drusen and early AMD compared with their counterparts. Consistent with other population-based studies, the rates of advanced AMD were considerably lower than early AMD in all three groups but still highest in whites at 0.5% compared with 0.4% in blacks and 0.1% in Mexican Americans.[12]

Age-adjusted frequencies of both early and late AMD for whites in the NHANES III were lower than those observed for whites in the BDES.[8] One possible explanation may be related to differences in study design. The NHANES III photographed fundus features of only one eye, quite possibly missing features of AMD in the fellow eye, and utilized non-stereoscopic fundus photographs through undilated pupils, which possibly could have made detection of AMD features more difficult.

Age-Related Eye Disease Study

AREDS evaluated the natural history of AMD and treatment effects of nutritional supplements among subjects recruited from tertiary retinal care centers. Within AREDS, a case-control study of 4,519 individuals (4,318 whites and 201 non-whites) 60–80 years of age was performed to explore relationships between entry AMD status and potential risk factors, including race. Stereoscopic 30° color fundus film photographs of the macula of each eye of participants were interpreted by a centralized reading center to classify participants by the AMD status of the more severely affected eye. Individuals were considered controls if they had fewer than 15 small drusen.

Similar to observations made in BES and SEE, AREDS found little difference between whites and non-whites in the odds of manifesting small drusen or non-extensive intermediate drusen within two disc diameters of the fovea.[13] As in the BES, AREDS observed that the presence of one or more large drusen or extensive intermediate drusen was associated with white race, with an OR of 1.88 (95% CI 1.34–2.64) for whites compared with non-whites.[13] Neovascular AMD was also associated with white race (OR 4.22 [2.23–7.99])[13] as previously found in the BES and suggested in NHANES III. Of individuals with early or intermediate AMD at baseline with a median follow-up of 6.3 years in the AREDS, incident neovascular AMD occurred more commonly (age- and gender-adjusted OR 6.77, 95% CI 1.24–36.9]) in whites versus blacks.[14]

Atherosclerosis Risk in Communities Study

The Atherosclerosis Risk in Communities (ARIC) Study was a biracial population-based study of 11,532 adults ranging from 48 to 72 years of age and comprising 8,984 whites and 2,548 blacks living in Forsyth County (NC), Jackson (MS), Minneapolis (MN), and Washington County (MD). Fundus lesions consistent with AMD were identified by obtaining non-stereoscopic 45° color fundus photographs of one eye from each undilated participant. The median age strata for the white participants was 60–64 years, whereas blacks tended to be younger, with a median age strata of 55–59 years.

The overall prevalence of any AMD lesions (soft drusen, RPE abnormalities, CNV, or GA within 3,450µm of the fovea) in the ARIC study was lower in blacks than in whites: crude rates of 3.7 versus 5.6%.[15] Age- and gender-controlled OR for any AMD in blacks compared with whites was 0.73 (95% CI 0.58–0.91). The overall prevalence of late AMD was relatively low in the ARIC cohort, possibly due to the methodological differences in photography protocols used in this study compared with other studies

such as BDES.[8,15] For example, ARIC investigators estimate that approximately 36% of participants with early AMD and 26% with late AMD may have been missed because the affected eye may not have been selected for photography.[15] As the event rate for late AMD was only 0.1% (15/11,532), statistical comparisons between whites and blacks in this study are not possible.

Conclusion

What factors could explain why several epidemiological studies, performed in different regions over the last few decades, have found whites to have a similar prevalence of early AMD (small drusen) but a higher prevalence of intermediate AMD (large drusen) and advanced AMD (CNV and GA) compared with non-whites? Some of the data on which this question is founded arise from a comparison of AMD prevalence between studies, as there are a limited number of studies that evaluate multiple racial groups within a community or project. When data are compared across studies important differences in study design may occur, such as means of acquiring the retinal images and definitions used to classify disease. For example, NHANES III and ARIC classified participants based on a single non-stereoscopic 45° fundus image of one eye obtained through an undilated pupil. This design likely leads to underestimates of disease prevalence and severity. Many other studies utilized 30° stereoscopic fundus photographs of both eyes through dilated pupils to classify the level of AMD in their subjects. This provides greater magnification to identify small and subtle lesions, increases the possibility of detecting subtle signs of neovascular AMD, and provides more images per participant so that the proportion of participants with gradable images is generally higher. However, these methodological differences between studies are more likely to explain absolute differences in the prevalence rates observed for early, intermediate, and advanced AMD between races from one study to another, but they are less likely to influence findings within those investigations that have evaluated more than one race within their study design.

Another possible explanation is that the absolute number of intermediate and particularly advanced AMD cases identified within population-based AMD studies remains relatively small, making it difficult to precisely identify point estimates for prevalence rates and to generate sufficient power to evaluate differences between racial groups, particularly for the late manifestations of AMD.[4] The SEE population-based study focuses on an older cohort to try to minimize this limitation, but still has a small number of advanced cases of AMD. AREDS has the advantage of large numbers of participants with intermediate and late AMD, but may be biased due to the evaluation of participants within a clinical trial recruited at tertiary care centers.

If there is a genuine disparity in the prevalence rates of advanced AMD between the races, it may be the result of survivor bias.[6] For instance, in the BES, no cases of advanced AMD were observed in blacks over 70 years of age, whereas a few cases were identified in subjects between 50 and 69 years of age. [6] Is it possible that blacks who develop advanced AMD are more likely to die than their white counterparts? Or could the explanation for a disparity between races be due to other confounding variables that have not yet been recognized to be the culprit?

The most likely explanation for an increased prevalence of intermediate and advanced AMD among whites relative to other races is that whites are genetically predisposed to develop more severe maculopathy than non-whites, or at least to develop these more advanced manifestations at a different tempo. Investigators theorize that increased melanin in the RPE cells of non-whites may offer protection to the RPE cells, Bruch's membrane, and the outer retina by acting as a filter for ultraviolet radiation or by serving as free radical scavengers, reducing the chances of developing large drusen and pigmentary abnormalities. The SEE has longitudinally followed racial groups and found that white participants were significantly more likely than blacks to develop large drusen and focal pigmentation and to progress from medium to large drusen or to pigment abnormalities within the macular zone.[2] Future studies are needed to confirm these observations and ask what factors are promoting progression of high-risk AMD features in whites while limiting this development in blacks, as this may be the explanation as to why late AMD appears to be more common in whites relative to other racial groups. ■

Could the explanation for a disparity between races be due to other confounding variables that have not yet been recognized to be the culprit?

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