Ethnic Variation in Early Age-Related Macular Degeneration Lesions Between White Australians and Singaporean Asians

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Purpose. We compared early age-related macular degeneration (AMD) lesion characteristics between white Australians and Singaporean Asians.

Methods. Participants of the Blue Mountains Eye Study (BMES; whites, $n = 3508$) and the Singapore Epidemiology of Eye Disease Study (SEED; Malay, $n = 3280$, Indian, $n = 3400$, and Chinese, $n = 3353$) underwent examinations, including retinal photography. The AMD lesions were assessed following the Wisconsin AMD grading protocol by the same photographic grader. Prevalence and characteristics of early AMD lesions were compared between the BMES and the SEED. The associations between ethnicity and early AMD lesion types were analyzed using logistic regression models adjusting for age, sex, smoking status, lipids, and genetic polymorphisms associated with AMD.

Results. After age-standardization to the BMES population, the prevalence of distinct soft drusen was significantly higher in Singaporeans compared to Australians (23.9%, 95% confidence interval [CI] 22.9–25.0 vs. 6.2%, 95% CI 5.3–7.0), with an adjusted odds ratio (OR) of 4.6 (95% CI 3.4–6.0). In contrast, the prevalence of indistinct soft or reticular drusen was significantly lower in Singaporeans compared to Australians (6.5%, 95% CI 5.9–7.1 vs. 8.3%, 95% CI 7.4–9.3, with nonsignificant adjusted OR of 1.2, 95% CI 0.8–1.7). Soft drusen of any type were present frequently at the inner and outer macula (within a zone $\geq$500 to $<$3000 μm radius from the foveal center) among Singaporeans, while among Australians soft drusen were present more frequently at the central macula ($<$500 μm radius).

Conclusions. Singaporean Asians had a milder spectrum of early AMD lesions and lesion characteristics (predominantly distinct soft drusen and noncentral location) compared to white Australians.

Keywords: age-related macular degeneration, AMD, Asian, Australian, early AMD, late AMD, drusen, pigment

Differences in the prevalence of early and late signs of age-related macular degeneration (AMD) and specific AMD lesions, between whites and blacks residing in the United States long have been observed and documented; these findings have been suggested to reflect underlying ethnic predisposition to AMD.[1–3] For example, larger drusen and retinal pigmentary abnormalities have been reported to be present more frequently, and the advanced forms of AMD more prevalent, in whites compared to blacks.[1,3]

Emerging data on AMD in Asians now are available.[4,5] Although it was suggested that AMD was not common in Asians,[4] the pooled prevalence of early (6.8%) and late AMD (0.56%) in four Asian populations in a meta-analysis was comparable to the prevalence of early (8.8%) and late AMD (0.59%) in white populations,[6] challenging this previous assumption that AMD is less frequent in Asians than in whites.[7] However, these previous studies comparing differences in prevalence of AMD between white and Asian populations have focused only on the overall prevalence of any, early, or late AMD. The prevalence of individual early AMD lesions in particular, may exhibit ethnic variability. Similar to white populations, the type and frequency of different early AMD lesions in Asians may indicate a certain risk of progression to late AMD, for example, eyes with indistinct soft drusen having a higher risk of developing late AMD compared to those with distinct soft drusen, in mainly Caucasian populations.[8,9] Few studies have assessed the differences in specific AMD lesion characteristics and distributions between different ethnic

groups.[10,11] Such information may yield further insights into the early pathogenesis and presentation of AMD in diverse ethnic groups.

In this report, we aimed to compare directly the frequencies of different types of early AMD lesions, bilateral involvement, and lesion location between population-based samples of white Australians and Asians living in Singapore.

Methods

Study Populations

The Blue Mountains Eye Study (BMES). The BMES is a longitudinal population-based study of vision and eye disease in a predominantly white population aged 49 years and older residing in the Blue Mountains region, west of Sydney Australia. Details of the study methods and procedures have been described previously.[12,13] Briefly, of 4433 eligible persons identified in a door-to-door census of the study area, 3654 (82.4%) persons participated in the baseline study conducted from 1992 to 1994 (BMES I). Of these, 2334 participants (75.8% of survivors) were examined 5 years later, from 1997 to 1999 (BMES II-a). An additional 1378 eligible permanent residents were identified following a second door-to-door census in 1999. This included residents who had moved into the study area or had reached 49 years of age between BMES I and II. Of these newly eligible persons, 1174 participated in the study (85.2%, BMES II-b). Prevalence of AMD was derived from BMES II survey sample with a total number of 3508 participants from BMES II-a and b.

The Singapore Epidemiology of Eye Disease (SEED) Study. The SEED studies include three population-based studies, the Singapore Malay Eye Study (SiMES), the Singapore Indian Eye Study (SINDI), and the Singapore Chinese Eye Study (SCES), which are cross-sectional studies of the Malay, Indian, and Chinese populations aged 40+ years residing in southwestern Singapore. Detailed study methods for the SiMES, SINDI, and SCES have been reported previously.[14,15] Briefly, age-stratified random sampling was used to select 5600 Malay, 6350 Indian, and 6752 Chinese names from the Ministry of Home Affairs. From the number of eligible persons, a total of 3280 Malays[16] participated in the SiMES, 3400 Indians[17] participated in the SINDI, and 3353 Chinese[18] participated in the SCES from 2004 to 2006, 2007 to 2009, and 2009 to 2011, respectively.

Examinations of the BMES were approved by the Western Sydney Area Health Service and University of Sydney, and adhered to the tenets of the Declaration of Helsinki. The SEED (SiMES, SINDI, and SCES) study protocols were approved by the SingHealth Institutional Review Board, and all examinations were conducted at the Singapore Eye Research Institute in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before examinations of each study.

Examination Procedures

Each participant in the BMES and the SEED study cohort underwent a comprehensive ocular examination and completed a detailed largely identical interviewer-administered questionnaire pertaining to their socio-demographic and lifestyle factors, and medical history. The SEED cohort questionnaires and examination protocols were adapted from the BMES questionnaire.

In the BMES, 30° stereoscopic retinal fundus photographs of both eyes of each participant were taken using a Zeiss FF3 fundus camera (Carl Zeiss Meditec, Oberkochon, Germany) and processed on color film (Kodachrome; Eastman Kodak, Rochester, NY, USA). Similarly, in the SEED cohort, 45° digital retinal fundus photographs of the macular and optic disc were taken with a Canon CR-DGi with a 10D SLR digital camera backing (Canon Tokyo, Japan) after dilation.

Blood samples were collected from 3222 BMES and 9670 SEED participants at examination. Total cholesterol and high density lipoprotein (HDL) concentrations (mmol/L) were measured on a Reflotron reflectance photometric analyzer (Roche Diagnostics, Manheim, Germany) in the BMES, or were obtained from the biochemistry tests conducted at the Singapore National University Hospital Reference Laboratory. Blood samples collected also were used for genotyping.

AMD Grading and Definitions

Retinal photographs taken from participants of the BMES and SEED studies were graded by a single senior grader (MM) using a masked manner at the Centre for Vision Research, University of Sydney, Australia, and closely followed the Wisconsin Age-Related Maculopathy Grading System (WARMGS) protocol.[19] Adjudication of early AMD lesions was provided by a senior researcher (JJW). All late AMD cases were confirmed by a retinal specialist (PM). Briefly, the presence and location of AMD lesions were graded using the WARMGS grid containing three concentric circles corresponding to a distance of 500, 1000, and 3000 μm radius from the foveal center, superimposed over the macula. Lesion area was graded using the WARMGS standard circles with defined diameters of 63, 125, 250, 375, and 660 μm, and 0.5 and 1 disc area (DA).

Late AMD was defined as the presence of any sign of neovascular AMD (pigment epithelial or neurosensory subretinal detachment, retinal or subretinal hemorrhage, subretinal fibrosis, or old atrophic disciform scars, or photocoagulation scars) as described in the International Age-Related Maculopathy classification[20] or geographic atrophy (GA). Early AMD lesions were defined by the same classification system. Distinct soft drusen were distinguished as discrete whitish-yellow nodules >125 μm in diameter with uniform density and sharp edges. Indistinct soft drusen were described as >125 μm in diameter with decreasing density from center outwards to the periphery and fuzzy edges. Confluent indistinct soft drusen with the appearance of broad interlacing ribbons were distinguished as reticular drusen. The retinal pigment epithelial (RPE) depigmentation was defined as faded, but sharply demarcated areas of the RPE without visible choroidal vessels underneath. Granules of gray or black pigment within the retina were distinguished as hyperpigmentation.[19] In this report, early AMD was defined as the presence of either large (>125 μm diameter) indistinct soft or reticular drusen, or distinct soft drusen with retinal pigmentary abnormalities (RPE depigmentation and hyperpigmentation). In the following analyses we have included reticular drusen under the broader category of indistinct soft drusen.

Macular areas involved by early AMD lesions were categorized as small, intermediate, and large areas for each lesion type; and location of early AMD lesions categorized as within the central macula, inner macula, outer macula, or outside the macula area, as shown in Table 1.

Bilateral involvement of early or late AMD was defined among persons with early or late AMD, respectively. Participants with early AMD in one eye and late AMD in the fellow eye were considered bilateral for any AMD, but unilateral for early or late AMD. If maculopathy data were missing in one eye, the study subject was excluded from analysis of bilateral involvement.

Table 1. Definitions of the Area and Location of the Early AMD Lesions Assessed

Area and Location	Definitions
Drusen area	
Small	None or <375 μm in diameter
Intermediate	≥375 μm to <0.5 disc area in diameter
Large	≥0.5 disc area in diameter
RPE depigmentation area	
Small	None or <375 μm in diameter
Intermediate	≥375 μm to <2 disc area in diameter
Large	≥2 disc area in diameter
Hyperpigmentation area	
Small	None or <64 μm in diameter
Intermediate	≥64 to <660 μm in diameter
Large	≥660 μm in diameter
Location (all lesions)	
Central macula	<500 μm radius from the foveal center
Inner macula zone	≥500 to <1500 μm radius from the foveal center
Outer macula zone	≥1500 to <3000 μm radius from the foveal center
Outside macula	≥3000 μm radius from the foveal center

Genotyping

In the BMES, genotyping of the *complement factor H* (*CFH*) single nucleotide polymorphism (SNP) *rs1061170* and the *age-related maculopathy susceptibility gene 2* (*ARMS2*) SNP *rs10490924* was performed using TaqMan assays (Applied Biosystems, Foster City, CA, USA) and restriction fragment length polymorphism analysis, respectively. Both SNPs also were imputed using the BMES genome wide association scan data. Genome wide genotyping was first performed using an Illumina Human 670-Quad custom array version 1; Illumina, Inc., San Diego, CA, USA and stringent quality control applied. Imputation was then performed using the 1000 Genomes penal and IMPUTE 2.0 (Department of Statistics, University of Oxford, Oxford, UK). In the SEED, genotyping was performed using the Illumina Human 610-Quad array (Illumina, Inc.). Similar quality control procedures were applied in the SEED as in the BMES before analysis. Imputation then was performed using the 1000 Genomes penal and IMPUTE 2.0 (Department of Statistics, University of Oxford).

Definitions of Other Variables

Smoking status was obtained from the interviewer-administered questionnaire in the BMES and the SEED cohort. Participants categorized as nonsmokers were those who answered "no" to smoking regularly. If participants answered "yes," but had stopped smoking ≥1 year before the examination they were categorized as past smokers. Participants who currently smoked or had stopped smoking <1 year before the examination were categorized as current smokers. In the BMES, hypertension was considered present if participants were taking antihypertensive medication at the time of examination, or blood pressure was ≥140 mm Hg, or diastolic blood pressure was ≥90 mm Hg at examination. In the SEED, hypertension was considered present if systolic blood pressure was ≥140 mm Hg, diastolic blood pressure was ≥90 mm Hg, or with previous physician diagnosis reported by the participant. Body mass index (BMI) was calculated from weight and height measurements taken at examination.

Statistical Analyses

The program SAS (version 9.3; SAS Institute, Inc., Cary, NC, USA) was used for all analyses. We included participants aged 50 years or older only, with 3508 from the BMES, 2453 from the SiMES, 2427 from the SINDI, and 2633 from the SCES. The worse eye prevalence of late and early AMD in the BMES were compared to worse eye prevalence estimates of the SiMES, SINDI, and SCES, respectively, after direct age-standardization to the BMES population. Comparisons also were performed within subgroups stratified by smoking status after age-standardization to the BMES population. Differences in the frequencies of bilateral involvement of early AMD lesions between the ethnic groups were assessed using Fisher's exact test. Logistic regression models adjusted for age, sex, smoking, lipids, hypertension, BMI, and the *CFH* and *ARMS2* polymorphisms were used to estimate association magnitudes between each Asian ethnicity, and the presence of distinct soft drusen and indistinct soft drusen, with reference to the BMES.

Early AMD lesion characteristics, including the areas involved by the lesions and location of the lesions within the central, inner, and outer zones were compared between the BMES and the Singaporean Asian samples combined. Data of both eyes and generalized estimating equation (GEE) models were used in these analyses.

Results

Table 2 shows the characteristics of participants without AMD and with early AMD in the BMES compared to the SiMES, SINDI, SCES, or these Asian samples combined. Among participants with and without early AMD, the mean age and frequency of women were lower in the three Asian populations combined compared to the BMES ($P < 0.0001$ for age and sex). There was a lower frequency of past smokers and higher frequency of current smokers in the combined Singaporean Asian sample compared to the BMES (both $P < 0.0001$). The mean ages of participants with early AMD were higher than participants without any AMD across all the study samples (Table 2). The frequency of participants with 1 or 2 risk alleles of *CFH* was significantly lower in the SiMES, SINDI, and SCES compared to the BMES, whereas there was a higher frequency of 2 risk alleles for *ARMS2* across the Singaporean Asian samples compared to the BMES sample (all $P < 0.0001$). Mean cholesterol, high density lipoprotein, and BMI were significantly lower in the Asian samples compared to the BMES in both subgroups with and without early AMD lesions (Table 2).

The crude prevalence of AMD in each study population is presented in Table 3 and age-standardized prevalence is presented in Table 4. After direct age-standardization, late AMD prevalence was nonsignificantly lower in the combined Asian sample compared to the BMES, whereas the prevalence of early AMD was significantly higher in the combined Asian samples compared to the BMES.

The prevalence of distinct soft drusen was substantially higher in each of the Asian samples or in the combined Asian samples, compared to the BMES. In contrast, the prevalence of indistinct soft drusen was significantly lower in SiMES and SCES, or in the combined Asian samples, compared to the BMES sample. The prevalence of indistinct soft drusen in SINDI was similar to the BMES, after age-standardization to the BMES sample (Table 4). There was no difference in the prevalence of retinal pigmentary abnormalities in the combined Asian samples compared to the BMES sample.

Table 2. Characteristics in Participants Without AMD and With Early AMD in the BMES Compared to Participants of the SiMES, SINDI, SCES, and the Three Asian Samples Combined

Characteristic	BMES, $n = 2867$	SiMES, $n = 1746$	*P* Value*	SINDI, $n = 1806$	*P* Value*	SCES, $n = 2046$	*P* Value*	Combined Asian, $n = 5598$	*P* Value†
	% Participants With No AMD								
Mean age, y (SD)	65.1 (8.7)	61.2 (8.1)	<0.0001	60.0 (7.8)	<0.0001	60.9 (8.2)	<0.0001	60.7 (8.0)	<0.0001
Sex, female	56.5	51.7	0.002	48.3	<0.0001	52.2	0.003	50.8	<0.0001
Smoking status									
Nonsmoker	49.2	62.3	<0.0001‡	73.1	<0.0001‡	74.8	<0.0001‡	70.4	<0.0001‡
Past smoker	40.1	18.5		12.6		12.9		14.5	
Current smoker	10.8	19.2		14.3		12.4		15.1	
Hypertension, present	75.5	75.3	0.9	62.7	<0.0001	61.9	<0.0001	66.3	<0.0001
CFH, rs1061170-BMES/ rs1080155-SiMES, SINDI, SCES									
No risk alleles	38.4	83.0	<0.0001‡	54.0	<0.0001‡	93.7	<0.0001‡	75.7	<0.0001‡
1 risk allele	47.3	15.8		37.9		6.2		21.0	
2 risk alleles	14.4	1.2		8.1		0.1		3.4	
ARMS2, rs10490924-BMES/ rs3750847-SiMES, SINDI, SCES									
No risk alleles	62.6	37.8	<0.0001‡	40.8	<0.0001‡	31.5	<0.0001‡	37.1	<0.0001‡
1 risk allele	32.7	47.4		47.7		49.3		48.0	
2 risk alleles	4.8	14.8		11.5		19.2		14.9	
Mean total cholesterol, mmol/L (SD)	5.8 (1.1)	5.7 (1.2)	<0.0001	5.2 (1.1)	<0.0001	5.5 (1.1)	<0.0001	5.5 (1.1)	<0.0001
Mean HDL, mmol/L (SD)	1.5 (0.4)	1.4 (0.3)	<0.0001	1.1 (0.3)	<0.0001	1.3 (0.4)	<0.0001	1.3 (0.4)	<0.0001
Mean BMI, kg/m^2 (SD)	27.8 (4.9)	26.4 (4.9)	<0.0001	26.3 (4.7)	<0.0001	23.7 (3.7)	<0.0001	25.4 (4.6)	<0.0001
	% Participants With Early AMD								
	$n = 284$	$n = 147$		$n = 166$		$n = 219$		$n = 532$	
Mean age, years (SD)	75.1 (8.4)	67.6 (7.8)	<0.0001	67.0 (8.6)	<0.0001	66.9 (8.1)	<0.0001	67.1 (8.2)	<0.0001
Sex, female	62.7	39.5	<0.0001	44.0	0.0001	39.3	<0.0001	40.8	<0.0001
Smoking status									
Nonsmoker	53.0	57.9	0.01‡	68.7	0.0002‡	69.9	<0.0001‡	66.2	<0.0001‡
Past smoker	38.8	26.9		19.9		18.7		21.3	
Current smoker	8.2	15.2		11.5		11.4		12.5	
Hypertension, present	82.0	85.7	0.3	78.9	0.4	78.1	0.3	80.5	0.6
CFH, rs1061170-BMES/ rs1080155-SiMES, SINDI, SCES									
No risk alleles	26.6	80.5	<0.0001‡	52.0	<0.0001‡	90.3	<0.0001‡	74.6	<0.0001‡
1 risk allele	50.0	19.5		35.0		9.0		20.8	
2 risk alleles	23.4	0.0		13.0		0.8		4.6	
ARMS2, rs10490924-BMES/ rs3750847-SiMES, SINDI, SCES									
No risk alleles	48.8	32.7	<0.0001‡	43.9	<0.0001‡	20.2	<0.0001‡	31.9	<0.0001‡
1 risk allele	47.3	41.6		37.4		54.5		44.9	
2 risk alleles	4.0	25.7		18.7		25.4		23.2	
Mean total cholesterol, mmol/L (SD)	5.9 (1.0)	5.6 (1.2)	0.01	4.8 (1.1)	<0.0001	5.3 (1.1)	<0.0001	5.2 (1.2)	<0.0001
Mean HDL, mmol/L (SD)	1.5 (0.4)	1.4 (0.4)	<0.0001	1.1 (0.3)	<0.0001	1.3 (0.4)	<0.0001	1.3 (0.4)	<0.0001
Mean BMI, kg/m^2 (SD)	27.0 (4.5)	26.1 (5.5)	0.09	26.2 (4.8)	0.1	23.2 (3.7)	<0.0001	24.9 (4.8)	<0.0001

* *P* value for comparison between participants of the BMES and SiMES or SINDI or SCES.
† *P* value for comparison between participants of the BMES and participants of the SiMES, SINDI, and SCES combined.
‡ Unadjusted tests for heterogeneity used to calculate *P* values.

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TABLE 3. Comparison of the Crude Prevalence of AMD in the BMES to the SiMES, SINDI, and SCES Samples, and the three Asian Samples Combined

Lesion	BMES	SiMES		SINDI		SCES		Combined Asian	
	Prevalence % (No. Affected/ Total No.)	Prevalence % (No. Affected/ Total No.)	P Value*	Prevalence % (No. Affected/ Total No.)	P Value*	Prevalence % (No. Affected/ Total No.)	P Value*	Prevalence % (No. Affected/ Total No.)	P Value*
Any late AMD	1.76 (60/3410)	0.97 (20/2060)	0.02	0.54 (13/2427)	<0.0001	0.95 (25/2633)	0.008	0.81 (58/7120)	<0.0001
Pure GA	0.67 (23/3410)	0.39 (8/2060)	0.2	0.00 (0/2427)	<0.0001	0.19 (5/2633)	0.006	0.18 (13/7120)	<0.0001
Neovascular AMD	1.09 (37/3409)	0.58 (12/2059)	0.06	0.54 (13/2427)	0.02	0.76 (20/2633)	0.2	0.63 (45/7119)	0.01
Any early AMD	9.01 (284/3152)	7.76 (147/1894)	0.1	8.42 (166/1972)	0.5	9.67 (219/2265)	0.4	8.68 (532/6132)	0.6
Any large drusen†	13.06 (412/3154)	20.62 (398/1930)	<0.0001	21.11 (422/1999)	<0.0001	26.83 (620/2311)	<0.0001	23.07 (1440/6241)	<0.0001
Soft distinct drusen	6.00 (194/3235)	17.02 (326/1915)	<0.0001	17.54 (348/1984)	<0.0001	24.12 (556/2305)	<0.0001	19.82 (1230/6205)	<0.0001
Soft indistinct or reticular drusen	7.65 (241/3149)	4.35 (82/1886)	<0.0001	4.33 (85/1964)	<0.0001	3.63 (82/2258)	<0.0001	4.08 (249/6109)	<0.0001
Any pigment abnormality	15.08 (487/3229)	15.65 (323/2064)	0.6	14.98 (319/2129)	0.9	16.04 (385/2400)	0.3	15.57 (1027/6594)	0.5
RPE depigmentation	9.34 (301/3221)	11.49 (236/2054)	0.01	7.91 (169/2136)	0.07	7.71 (185/2398)	0.03	8.95 (590/6589)	0.5
Hyperpigmentation	14.33 (463/3230)	11.25 (231/2053)	0.001	12.71 (270/2124)	0.09	14.11 (338/2395)	0.8	12.76 (839/6573)	0.03

* P value for crude prevalence comparison between participants of the BMES and the SiMES, SINDI, SCES, or Combined Asian sample.
† Includes soft distinct, soft indistinct, and reticular drusen.

Compared to the BMES, the combined Singaporean Asian sample had a lower frequency of bilateral late AMD (17.24% vs. 58.33%, $P < 0.0001$) and bilateral early AMD (30.31% vs. 48.13%, $P < 0.0001$). Bilateral retinal pigment abnormalities also were less frequent in the SiMES, SINDI, and SCES compared to the BMES (all $P < 0.0001$). However, there was no difference in the frequencies of bilateral reticular drusen or other soft drusen between the Asian and BMES samples (all $P > 0.05$, data not shown).

After stratifying by smoking status, the age-standardized prevalence of early AMD was not significantly different between the combined Singaporean Asian and BMES sample in each category of nonsmokers and current smokers. However, there was a significantly higher prevalence of early AMD in past smokers in the combined Asian sample compared to the BMES (Table 5). Distinct soft drusen prevalence remained significantly higher in all three Asian ethnicities compared to the BMES, regardless of smoking status, whereas indistinct soft drusen prevalence remained significantly lower in the combined Asian samples compared to the BMES in the nonsmoking subgroup. In the two subgroups of past smokers and current smokers, the differences in the prevalence of indistinct soft drusen between the combined Asian samples and the BMES were nonsignificant (Table 5).

Table 6 presents a comparison of the areas and location of early AMD lesions in right eyes, between the BMES and the combined Singaporean Asian samples, shown with age-adjusted P values. Larger areas of soft drusen were more frequent in the SiMES, SINDI, and SCES than in the BMES (age-adjusted $P < 0.0001$). The frequencies of larger areas involved by RPE depigmentation were similar in Australian and Singaporean Asian samples, while large areas involved by hyperpigmentation were less frequent in the Asian compared to the BMES sample (6.7% vs. 9.6%, age-adjusted $P = 0.01$). Singaporean Asians were more likely to have eyes with drusen located only at the inner and outer macula zones, but significantly less likely to have eyes with drusen located at the central macula compared to the BMES sample (age-adjusted $P < 0.0001$, see Fig.). Noncentral location for hyperpigmentation was more likely in the Singaporean Asians than in the BMES (age-adjusted $P < 0.0001$).

The associations between ethnicity and soft drusen types were assessed further after adjusting for age, sex, smoking status, total cholesterol, HDL, hypertension, BMI, and the *CHF* SNPs *rs1061170* and *rs1080155*, and *ARMS2* SNPs *rs10490924* and *rs3750847* (Table 7). With reference to Australians, there was a significantly higher likelihood of having distinct soft drusen in Malays, Indians, or Chinese (ORs 4.0, 4.6, and 7.0, respectively). By comparison, there was a lower likelihood of having indistinct soft or reticular drusen among Malays, Indians, and Chinese compared to the Australian population (OR's 1.1, 1.1, and 1.3, respectively), though these associations were not significant (Table 7).

DISCUSSION

In this study, we found a significantly lower prevalence of distinct soft drusen in Australians compared to Asians (Malays, Indians, and Chinese). In contrast, we found a higher prevalence of indistinct soft drusen in Australians compared to Malays and Chinese, while Indians had a similar prevalence of indistinct soft drusen to Australians. The similarity between Indians and whites could be explained by their relatively close genetic make-up, compared to less similarity in the genome between whites and other Asian ethnicities.

Similar to the previous report by Kawasaki et al.[6] of a meta-analysis of findings from nine Asian population-based samples

Table 4. Prevalence of AMD lesions in the SiMES, SINDI, SCES, and Combined Asian Eye Study Samples Age-Standardized to the BMES

Lesion	Age-Standardized Prevalence % (95% CI)				
	BMES	SiMES	SINDI	SCES	Combined Asian
Any late AMD	1.76 (1.32–2.20)	1.09 (0.64–1.54)	0.76 (0.42–1.11)	1.52 (1.05–1.99)	1.3 (1.04–1.56)
Pure GA	0.68 (0.40–0.95)	0.43 (0.15–0.72)	0.00 (0.00–0.00)	0.28 (0.08–0.48)	0.26 (0.15–0.38)
Neovascular AMD	1.09 (0.74–1.43)	0.66 (0.31–1.01)	0.76 (0.42–1.11)	1.24 (0.82–1.67)	1.03 (0.80–1.27)
Any early AMD	9.72 (8.69–10.76)	10.98 (9.57–12.38)	13.53 (12.02–15.04)	13.01 (11.63–14.40)	12.51 (11.69–13.34)
Any large drusen*	13.88 (12.68–15.09)	26.72 (24.75–28.69)	28.35 (26.37–30.33)	32.36 (30.45–34.26)	28.84 (27.72–29.96)
Soft distinct drusen	6.15 (5.32–6.98)	22.73 (20.85–24.60)	21.75 (19.94–23.57)	28.76 (26.91–30.60)	23.93 (22.87–24.99)
Soft indistinct or reticular drusen	8.32 (7.35–9.28)	4.92 (3.94–5.90)	8.36 (7.14–9.59)	5.20 (4.28–6.11)	6.52 (5.91–7.14)
Any pigment abnormality	15.52 (14.27–16.77)	15.76 (14.19–17.34)	18.02 (16.39–19.65)	18.50 (16.95–20.06)	17.62 (16.70–18.54)
RPE depigmentation	9.63 (8.61–10.65)	10.35 (9.03–11.66)	9.07 (7.85–10.28)	7.65 (6.59–8.72)	8.97 (8.28–9.66)
Hyperpigmentation	14.78 (13.56–16.01)	12.03 (10.62–13.44)	15.64 (14.10–17.19)	16.74 (15.24–18.23)	15.06 (14.20–15.93)

* Includes soft distinct, soft indistinct, and reticular drusen.

aged 40 to 79 years, we found a 1.76% prevalence of late AMD in the BMES population to be comparable to the 1.30% prevalence in the combined Asian samples of Malays, Indians, and Chinese, all aged 50 years or older. The age-standardized prevalence of early AMD was slightly lower in Australians and Malays compared to that of Indians or Chinese (9.72% and 10.98% vs.13.53% and 13.01%, respectively).

The early AMD prevalence of 10.98% and 13.53% found in our study contrasts with previously published prevalence of 3.5% and 4.5% for the same Singaporean population of Malays[21] and Indians,[22] respectively. These differences are likely due to the age of the populations under investigation: ≥50 years in our study versus 40 to 80 years in the previous study, and age-standardization to the BMES in our study versus age-standardization to the Singapore population at the 2000 Singapore census.[21,22] Our finding also contrasts with another study of a different multiethnic cohort of Singaporean Malays, Indians, and Chinese aged 40+ years that reported similar prevalence of any AMD among the three ethnic groups (5.7%–7.7%),[11] which was comparable to white populations around the world.

Though the overall prevalence of early AMD was found to be similar between Australians and Singaporean Asians in our study, the frequency of various lesions forming early AMD were different. Malays and Chinese predominantly presented with a milder spectrum of lesions, such as distinct soft drusen and a lower frequency of advanced lesions, including indistinct soft drusen, compared to Australians. Of a few studies that have specifically investigated the prevalence of the individual lesions of late and early AMD, our observation is consistent with previous findings from the Multi-Ethnic Study of Atherosclerosis (MESA) that found higher prevalence of

Table 5. Comparison of the Age-Standardized Prevalence of Early AMD by Smoking Status in the BMES to the SiMES, SINDI, SCES, and the Three Asian Samples Combined

AMD Lesion	Age-Standardized Prevalence (95% CI)				
	BMES	SiMES	SINDI	SCES	Combined Asian
Nonsmoker					
Any early AMD	10.41 (8.88–11.94)	10.49 (8.74–12.25)	13.41 (11.64–15.17)	12.77 (11.18–14.37)	12.20 (11.22–13.18)
Any large drusen	14.72 (12.94–16.49)*	25.03 (22.57–27.48)*	28.42 (26.10–30.74)*	32.48 (30.26–34.70)*	28.86 (27.51–30.20)*
Soft distinct drusen	6.71 (5.48–7.95)*	19.64 (17.37–21.90)*	22.54 (20.39–24.70)*	29.03 (26.87–31.18)*	24.18 (22.90–25.45)*
Soft indistinct or reticular drusen	8.66 (7.25–10.07)*	6.40 (4.99–7.80)	7.69 (6.31–9.07)	4.98 (3.94–6.02)*	6.15 (5.43–6.87)*
Any pigment abnormality	15.74 (13.94–17.54)	13.49 (11.62–15.37)	18.96 (17.02–20.91)	16.51 (14.79–18.24)	16.31 (15.25–17.38)
RPE depigmentation	9.33 (7.89–10.77)*	7.87 (6.39–9.35)	8.38 (7.00–9.75)	5.94 (4.84–7.04)*	7.27 (6.52–8.02)
Hyperpigmentation	14.74 (12.99–16.50)*	10.77 (9.07–12.47)*	16.47 (14.63–18.32)	15.36 (13.68–17.04)	14.27 (13.26–15.28)
Past Smoker					
Any early AMD	9.44 (7.81–11.07)*	13.46 (9.94–16.98)	15.53 (11.14–19.93)*	14.57 (10.61–18.54)	14.30 (12.04–16.55)*
Any large drusen	13.77 (11.85–15.68)*	26.60 (22.09–31.11)*	28.42 (26.10–30.74)*	33.12 (27.94–38.30)*	29.92 (27.01–32.83)*
Soft distinct drusen	6.27 (4.94–7.61)*	21.29 (17.09–25.50)*	22.54 (20.39–24.70)*	29.78 (24.74–34.82)*	24.93 (22.17–27.69)*
Soft indistinct or reticular drusen	8.10 (6.58–9.62)	7.73 (4.97–10.50)	9.27 (5.74–12.80)	5.07 (2.61–7.54)	7.07 (5.42–8.73)
Any pigment abnormality	14.44 (12.50–16.37)*	22.07 (18.00–26.13)*	20.50 (15.76–25.23)	22.58 (18.04–27.11)*	21.74 (19.19–24.29)*
RPE depigmentation	9.15 (7.56–10.74)*	17.14 (13.43–20.85)*	12.80 (8.89–16.72)	12.29 (8.74–15.84)	14.26 (12.10–16.42)*
Hyperpigmentation	14.12 (12.20–16.03)	16.30 (12.66–19.94)	17.86 (13.37–22.36)	19.27 (14.99–23.55)	17.63 (15.27–19.99)
Current Smoker					
Any early AMD	7.66 (4.78–10.55)	7.85 (5.06–10.64)	7.86 (4.69–11.04)	10.66 (7.03–14.29)	8.82 (6.98–10.66)
Any large drusen	10.68 (7.34–14.03)*	22.77 (18.46–27.08)*	20.85 (16.08–25.61)*	30.67 (25.32–36.03)*	24.82 (22.04–27.60)*
Soft distinct drusen	3.60 (1.60–5.60)*	17.11 (13.23–20.98)*	17.44 (12.98–21.90)*	27.03 (21.86–32.21)*	20.32 (17.72–22.91)*
Soft indistinct or reticular drusen	7.37 (4.54–10.20)	5.63 (3.23–8.02)	4.24 (1.87–6.61)	5.24 (2.61–7.87)	5.21 (3.77–6.66)
Any pigment abnormality	18.99 (14.78–23.31)	19.45 (15.48–23.42)	16.37 (12.12–20.62)	21.74 (17.03–26.46)	19.42 (16.92–21.91)
RPE depigmentation	12.51 (8.96–16.07)	15.98 (12.30–19.65)	10.58 (7.06–14.10)	13.17 (9.30–17.03)	13.44 (11.29–15.59)
Hyperpigmentation	17.81 (13.70–21.92)	13.13 (9.73–16.53)	12.92 (9.07–16.77)	17.81 (13.41–22.20)	14.72 (12.48–16.96)

* Indicates significant difference between the BMES and SiMES, SINDI, SCES, or the Combined Asian samples.

Table 6. Area and Location of Drusen and Pigmentary Abnormalities in the BMES Compared to the Combined Asian Samples (SiMES, SINDI, and SCES Combined)

Early AMD Lesion Characteristics	% Eyes BMES	% Eyes Combined Asian Samples*	Age-Adjusted *P* Value†	Odds Ratio (95% CI)‡
AREA				
Drusen				
None or <375 μm in diameter	92.4	91.8		1.0
≥375 μm in diameter	7.7	8.2	<0.0001	1.8 (1.6–2.1)
RPE Depigmentation				
None or <375 μm in diameter	96.3	96.7		1.0
≥375 μm in diameter	3.7	3.3	0.9	1.0 (0.9–1.2)
Hyperpigmentation				
None or <64 μm in diameter	90.5	93.3		1.0
≥64 μm in diameter	9.6	6.7	0.01	0.9 (0.8–1.0)
Location				
Drusen				
Central macula	87.5	59.3		1.0
Inner and outer macula zone	12.5	40.7	<0.0001	5.8 (2.7–12.3)
RPE depigmentation				
Central macula	58.4	62.4		1.0
Inner and outer macula zone	41.6	37.6	0.7	0.9 (0.5–1.5)
Hyperpigmentation				
Central macula	80.8	63.6		1.0
Inner and outer macula zone	19.2	36.4	0.03	2.0 (1.1–4.0)

Location definitions: central macula, <500 μm radius from foveal center; inner macula zone, ≥500 to <1500 μm radius from the foveal center; outer macula zone, ≥1500 to <3000 μm radius from the foveal center.

* SiMES, SINDI, and SCES samples combined.

† Unadjusted tests for heterogeneity used to calculate *P* values.

‡ ORs estimated with BMES as reference group, using generalized estimating equation models and both eyes from each participant.

distinct soft drusen among Chinese compared to black, white, or Hispanic participants.[2]

The BMES consists of participants with predominantly European ancestry and has found comparable early and late AMD prevalence and incidence to other population-based epidemiological studies, including the Beaver Dam Eye Study and the Rotterdam Eye study.[12,23–26] Singaporeans consist of many different Asian ethnicities; however, the three ethnic groups captured in the SEED study were the three predominant ethnic groups of Asians.[14,15] Similar estimates of early and late AMD prevalence were found between Singaporean Indians and Indians living in India.[22]

The SNPs at the CFH and ARMS2 loci are significant risk factors for early AMD, though they present a weaker risk for early than for late AMD, as shown in a recent genome-wide association study (GWAS) meta-analysis.[27] The differences in early AMD lesion prevalence between Australians and Asians could be explained partly by genetic differences.[27–31]

The bilateral involvement of early, late, and any AMD were shown to be comparable between the Malay and Australian populations in a previous report.[10] In the current analysis, we found that the frequency of bilateral late and early AMD was significantly lower in Malays, Indians, and Chinese compared to Australians. The higher frequencies of bilateral involvement of late and early AMD in Australians compared to Singaporean Asians in our study could have been partly due to differences in age ranges of the samples, as age-standardization was not performed in the comparison of bilateral involvement, due to small numbers. The lower frequency of bilateral early AMD in Asians also may be explained by the lower prevalence of the *CFH Y402H* polymorphism in Asian populations,[32,33] which has been found to be associated with bilateral early AMD involvement.[34,35]

In addition to increasing age, smoking is an established risk factor for AMD in many white populations.[36–38] Similar associations between smoking and an increased AMD risk also have been documented in Asians.[39–41] Among past and current smokers, we found no difference in the age-standardized prevalence of indistinct soft and reticular drusen between Australians and Singaporean Asians. This could have been due to reduced numbers of subjects in these smoking subgroups.

A higher risk of developing late AMD has been associated with a more central location of drusen and more advanced

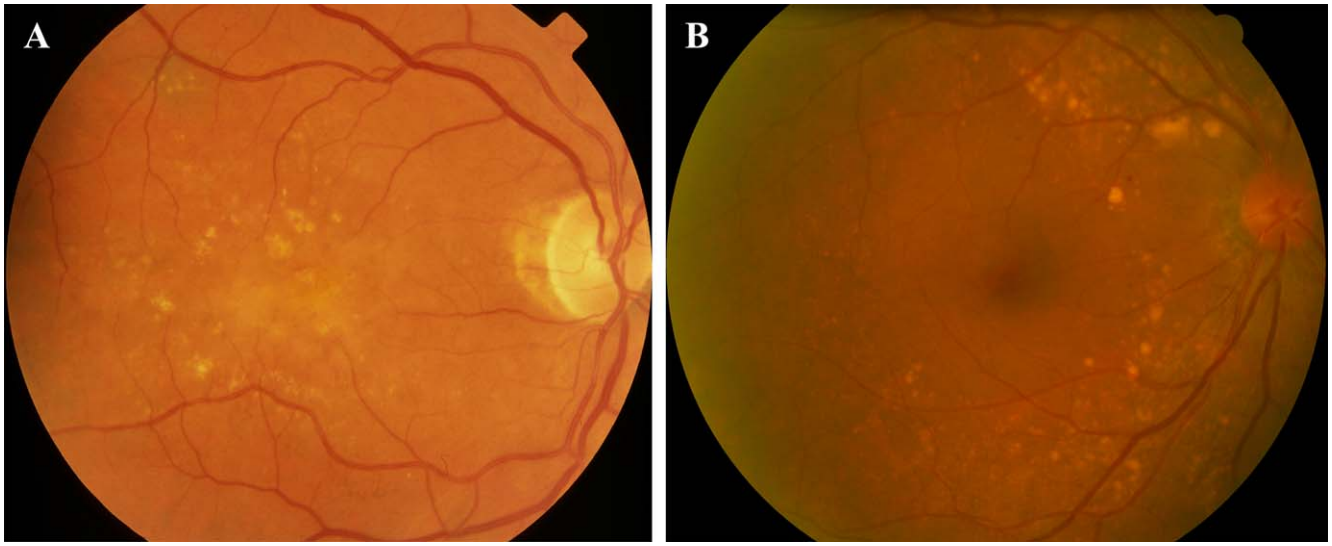

Figure. Examples of the different distribution of early AMD lesions in white Australians and Singaporean Asians. Central location of drusen in an Australian participant (**A**), compared to the more peripheral location of drusen in an Asian participant (**B**).

Table 7. The Association Between Asian Ethnicity (SiMES, SINDI, SCES, and Combined Asian sample) and the Prevalence of Soft Drusen, With Reference to Whites (the BMES Population), Shown as ORs With 95% CIs

	Soft Drusen Type	
	Distinct Soft	Indistinct Soft and Reticular
Ethnic Group	Multivariable Adjusted OR* (95% CI)	Multivariable Adjusted OR* (95% CI)
BMES (reference group)	1.0	1.0
SiMES	4.0 (3.0, 5.4)†	1.1 (0.7, 1.7)
SINDI	4.6 (3.4, 6.3)†	1.1 (0.7, 1.8)
SCES	7.0 (5.1, 9.6)†	1.3 (0.7, 2.2)
Combined Asian sample	4.6 (3.4, 6.0)†	1.2 (0.8, 1.7)

* Adjusted for age, sex, smoking, cholesterol, high density lipoprotein, hypertension, BMI, and the *CFH* and *ARMS2* risk alleles as categorical variables.

† Indicates significant differences.

stages of early AMD lesions.[9,42] Our findings of a predominantly distinct soft drusen pattern among early AMD lesions, and relatively high prevalence of drusen and retinal pigmentary changes located away from the foveal center in Singaporean Asians compared to white Australians, reinforce the impression that Asians present a milder spectrum of early AMD lesions than whites, despite the overall lack of a substantive difference in the prevalence of early and late AMD between the Singaporean Asians and white Australians.

The strengths of this study included the large sample size of each ethnic group, and the direct comparison of AMD lesion and lesion characteristics among the studies. All studies used the same standardized grading protocol to determine AMD lesions and lesion characteristics, with AMD grading performed by the same grader (MM), adjudicated by the same senior researcher (JJW) and ophthalmologist (CY), with all late AMD cases confirmed by the same retinal specialist (PM). Limitations of the study included the small sample size in some groups when bilaterality and area and location of early AMD lesions were assessed, where it was not possible to obtain an age-standardized frequency. There is a difference in examination time between the BMES II study and the three Asian studies conducted in succession of each other, and this may have influenced the comparison between the studies if there was a temporal change in the prevalence of AMD.[10] This does not seem likely given the relatively narrow time interval. The difference in types of fundus photographs taken between the BMES and the three Asian studies (35-mm color film versus color digital images, 30° vs. 45° photographs, and stereo versus nonstereo, respectively), however, could have had subtle effects on the quantitative measurements of lesion area and location, but is unlikely to have affected the assessment of the prevalence of different AMD lesions.

In conclusion, we found that overall, Asians (from the three major Asian ethnic groups, Malays, Indians, and Chinese) living in Singapore, had a predominantly milder spectrum of early AMD lesions compared to whites living in Australia, after age standardization. Further studies of environmental and genetic risk factors, and their associations with early AMD lesions and lesion characteristics may elucidate insights into the similarities and dissimilarities in mechanisms that lead to AMD occurring in either Asians or whites.

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