Prevalence and Risk Factors of Epiretinal Membrane in Asian Indians

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PURPOSE. To describe the prevalence of epiretinal membrane (ERM) and its risk factors in an Indian population and compare the findings with other populations.

METHODS. The Singapore Indian Eye Study is a population-based survey of 3400 Asian Indians aged between 40 and 80 years. A comprehensive ophthalmic examination, standardized interviews, and laboratory blood tests were performed. Digital retinal fundus photographs were assessed for the presence of ERM following the definitions used in the Blue Mountains Eye Study (BMES). ERM was classified into a less severe form termed “cellophane macular reflex” (CMR) and a more severe form termed “preretinal macular fibrosis” (PMF) and also as primary and secondary (if it was associated with retinal pathology or cataract surgery).

RESULTS. A total of 3328 persons (mean age 57.8 ± [SD] 10.1 years, and 50.2% male) provided data in this study. The age-standardized prevalence of ERM was 7.6% (95% confidence interval [CI], 6.8–8.6), CMR 4.1% (95% CI, 3.5–4.9), and PMF 3.5% (95% CI, 2.9–4.2). Older age (odds ratio [OR], 1.09; 95% CI, 1.07–1.11, per year increase), increasing myopic refraction (OR, 1.14; 95% CI, 1.07–1.22, per diopter decrease), and narrower retinal arteriolar diameter (OR, 1.02; 95% CI, 1.00–1.03, per µm decrease) were significantly associated with primary ERM.

CONCLUSIONS. The age-standardized prevalence of ERM in the Indian population in Singapore was 7.6%. This is similar to Malays in Singapore (8.0%) and higher than the prevalence in whites in Australia (4.7%). Significant factors associated with primary ERM were older age, myopia, and narrower retinal arteriolar diameter. (Invest Ophthal Vis Sci. 2012;53: 1018–1022) DOI:10.1167/iovs.11-8557

Epiretinal membrane (ERM) is a common retinal pathology resulting in mild to moderate visual impairment with impact on quality of life.1–3 ERM can be classified as primary “idiopathic” or secondary to ocular pathology such as diabetic retinopathy, retinal vein occlusion, trauma, or after surgery. For primary ERM, the only consistent risk factor identified is older age.4

There are few population-based studies on ERM, with reported prevalence rates varying by ethnicity. For example, the Singapore Malay Eye Study (SiMES) reported a higher prevalence of ERM in Asian Malays living in Singapore than among white persons in the Blue Mountains Eye Study (BMES) in Australia.5 In the United States, the Multi-Ethnic Study of Atherosclerosis (MESA)6 reported a higher prevalence of ERM in the American-Chinese population compared with the white, black, and Hispanic populations. It is difficult to directly compare these rates due in part to variations related to methodology differences in the definition of ERM and its imaging and assessment.

India has one of the largest populations in the world with over a billion people (17% of the world’s population). To our knowledge, there has been no study that has reported on the prevalence of ERM in the Indian population. We aimed to study the prevalence of ERM and its risk factors in the Indian population in Singapore, and compare our results with the Asian Malay population in Singapore (SiMES) and the white population in Australia (BMES), because all three studies used the same grading standardized protocols, and the same assessor.

METHODS

Study Population

The Singapore Indian Eye (SINDI) study is a population-based, cross-sectional study aimed at collecting systemic and ocular data from 3400 Indian adults aged 40 to 80 years in Singapore. The SINDI methodology was described in detail elsewhere.7 In brief, residents of Indian ethnicity and aged between 40 and 80 years residing in the southwestern part of Singapore were randomly selected based on an age-stratified random sampling strategy. Out of an initial 12,000 Indian residents, a final sampling frame of 4,497 subjects was derived (Fig. 1). Of these, 3,400 (75.6% response) subjects were examined between 2007 and 2009. This study adhered to the principles of the Declaration of Helsinki with ethics approval obtained from the Singapore Eye Research Institute (SERI) Institutional Review Board. All participants agreed to a written informed consent.

Ophthalmic Examination

Best-corrected visual acuity (VA) was measured using a logarithm of the minimum angle of resolution (LogMAR) number chart. Lens status was assessed for nuclear, cortical, and posterior subcapsular cataract following the Lens Opacities Classification System (LOCS III).8 Central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) was calculated using standardized methods described elsewhere.9

Retinal Imaging and Grading

A digital nonmydriatic retinal camera (Canon CR-DGi with a 20 Dioptre SLR back; Canon, Tokyo, Japan) was used to obtain color photo-
graphs of Early Treatment for Diabetic Retinopathy Study (ETDRS) standard field 1 (centered on the optic disc) and standard field 2 (centered on the fovea) of each eye after pupil dilation. The fundus photographs were assessed in the Centre for Vision Research, University of Sydney, Australia, for the presence of ERM and other retinal diseases which followed the definitions used in the BMES. Fundus photographs were assessed initially by trained graders, and all pathologies were adjudicated by either or both a senior researcher (JW) and a retinal specialist (PM).

Of the 3400 participants, 3328 (97.9%) had fundus photographs with sufficient quality for grading of ERM. Two stages of ERM were identified: a less severe form termed ‘cellophane macular reflex’ (CMR) was defined as having glinting, water-silk, and shifting light reflex without visible retinal folds; and a more severe form termed ‘preretal macular fibrosis’ (PMF) was defined as having retinal folds with more opaque, grayish appearance on the inner retinal surface. ERM outside the 3000 μm radius grid on macula were not assessed. When both CMR and PMF were found within the same eye, it was categorized as having the more severe stage, PMF. The term ‘any ERM’ was defined to include subjects with either CMR or PMF.

The graders also assessed retinal diseases other than ERM using similar standardized grading protocols. Diabetic retinopathy was graded using the modified Airlie House Classification, as used in the Early Treatment Diabetic Retinopathy study. Age-related macular degeneration was defined following the modification of the Wisconsin Age-Related Maculopathy Grading System. Retinal vein occlusion was classified as either present or absent based on fundus photographs.

Secondary ERM was defined as ERM associated with retinal diseases (diabetic retinopathy, age-related macular degeneration, and retinal vein occlusion) or previous cataract surgery in the same eye; all other were classified as primary ERM.

Physical Examination and Laboratory Tests
A comprehensive physical examination, laboratory tests, and interview were performed following standardized protocols as described elsewhere. Blood pressure was measured in a standard manner with a digital automatic sphygmomanometer after 5 minutes rest. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or physician’s diagnosis. Diabetes mellitus was defined as the finding of a random glucose ≥11.1 mmol/L, or self-reported history of diabetes and use of diabetic medication. A detailed interviewer-administered questionnaire was used to collect information about medical history, cigarette smoking (defined as current, past, and never), alcohol consumption, current medication use, and socioeconomic status.

Statistical Analysis
All analyses were performed using a statistical software package (Statistical Package for Social Science; SPSS, version 17.0, Chicago, IL). Age- and sex-specific prevalence rates for CMR, PMF, and any ERM (both CMR and PMF) were calculated, and then age-standardized to the Indian population from the 2010 Singapore Census. These age-standardized rates were compared with previous population data from SIMES and BMES. Risk factors were classified as either binary traits (e.g., any previous cataract surgery) or as continuous parameters (e.g., age). Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for age and sex, and for likely possible risk factors associated with primary and secondary ERM. Using multivariate analyses, a model was constructed for primary and secondary ERM that included independent risk factors adjusting for age, sex, and significant risk factors and other known associations.

RESULTS
A total of 3400 (75.6% response) Indian participants aged between 40 and 80 years had data available for analysis. The mean ± SD for age was 57.8 ± 10.1 years, 50.2% were male, spherical equivalent refraction was −0.081 ± 2.15 diopters (D), and intraocular pressure was 15.8 ± 3.0 mm Hg. A history of cataract surgery was given by 14.8%, 34.2% had diabetes mellitus, 8.2% had diabetic retinopathy, and 6.1% had age-related macular degeneration (AMD). After excluding 72 (2.1%) subjects with ungradable fundus photographs due to poor quality, a total of 3328 persons were included for analysis.

In our study, of the 3328 Indian persons, 339 (10.2%) had ERM; 179 (5.4%) had CMR, and 160 (4.8%) had PMF. Of these 339 subjects, 99 (29.2%) and 240 (70.8%) subjects, respectively, had bilateral and unilateral ERM. The age-standardized prevalence of ERM in this Indian sample based on the 2010 census Singapore population was 7.6% (95% CI, 6.8–8.6)—4.1% (95% CI, 3.5–4.9) had CMR and 3.5% (95% CI, 2.9–4.2) had PMF (Table 1). Table 1 also showed that the prevalence of both CMR and PMF was significantly age-related (P < 0.001).

The age-standardized prevalence of ERM (based on the 2010 Singapore population census) in the SIMES and BMES were 8.0% (7.1%–9.0%) and 4.7% (4.0%–5.5%) respectively (Table 2). Figure 2 showed the comparison of CMR, PMF, and any ERM between all three populations. Compared with SINDI, the prevalence of ERM is similar to SIMES but significantly higher than BMES. Further analysis of primary and secondary ERM showed that the prevalence of secondary ERM were similar across all three populations but primary ERM was significantly more prevalent in SINDI and SIMES. Under primary ERM, the prevalence of PMF was significantly higher in SINDI and SIMES compared with BMES but the prevalence of CMR was similar across the three studies.

The LogMAR (Snellen equivalent) VA of eyes with and without ERM was 0.187 (20/30) ± SD 0.31 and 0.081 (20/24) ± SD 0.20 respectively (P < 0.001). Compared with uninvolved eyes, the VA of eyes with CMR was 0.128 (20/24) ± 0.176 (P = 0.044) and for eyes with PMF, 0.262 (20/36) ± 0.416 (P < 0.001). Of eyes with ERM, the VA differences between eyes with CMR and PMF were statistically significant (P < 0.001).

Of the 339 subjects with ERM, 150 (44.2%) were classified as primary and 189 (55.8%) as secondary. Comparing the primary (n = 2328) and secondary (n = 1004) ERM group, a higher proportion of ERM was found in the secondary ERM group compared with the primary ERM group (18.8% vs. 6.5% respectively, P < 0.001). Comparing the proportion of CMR and PMF, there was no difference between the primary and secondary ERM groups (41.3% vs. 51.9% PMF respectively, P = 0.054). In the 189 eyes with secondary ERM, past history of cataract surgery was the most frequent association (80.4%; 152/189).

Table 3 shows the associations between primary and secondary ERM with systemic and ocular parameters. For primary
Secondary ERM is defined as any eye with diabetic retinopathy, retinal vein occlusion, age-related macular degeneration, or history of cataract surgery. Primary ERM are the eyes without the named risk factors.

ERM, after multivariate analysis adjusting for age, sex, and systolic blood pressure, older age (OR, 1.08; 95% CI, 1.07–1.10, per year increase), myopic refraction (OR, 1.09; 95% CI, 1.02–1.15; per diopter decrease), and narrower retinal arteriolar diameter (OR, 1.01; 95% CI, 1.003–1.020, per μm decrease) were significantly associated with primary ERM.

For secondary ERM, older age (OR, 1.07; 95% CI, 1.05–1.10), lower blood triglyceride level (OR, 1.29; 95% CI, 1.04–1.58), and lower blood triglyceride level (OR, 1.10; 95% CI, 1.04–1.16, per mmol increase) were significantly associated with secondary ERM.

### Table 1. Prevalence of ERM by Age and Sex

<table>
<thead>
<tr>
<th>Age Groups (y)</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 to 49</td>
<td>1669</td>
<td>1659</td>
<td>3328</td>
</tr>
<tr>
<td>50 to 59</td>
<td>189</td>
<td>187</td>
<td>376</td>
</tr>
<tr>
<td>60 to 69</td>
<td>368</td>
<td>366</td>
<td>734</td>
</tr>
<tr>
<td>70 to 80</td>
<td>520</td>
<td>518</td>
<td>1038</td>
</tr>
</tbody>
</table>

### Table 2. Age-Standardized Prevalence of Epiretinal Membranes across Studies Using the Indian 2010 Census Singapore Population as the Standard Population

<table>
<thead>
<tr>
<th>SIMES</th>
<th>SINDI</th>
<th>BMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>All ERM</td>
<td>3265</td>
<td>3328</td>
</tr>
<tr>
<td>Cellophane macular reflex</td>
<td>190 (5.8)</td>
<td>179 (5.4)</td>
</tr>
<tr>
<td>Preretinal macular fibrosis</td>
<td>194 (5.9)</td>
<td>160 (4.8)</td>
</tr>
<tr>
<td>Any ERM signs</td>
<td>384 (11.8)</td>
<td>339 (10.2)</td>
</tr>
<tr>
<td>Primary ERM</td>
<td>2734</td>
<td>2324</td>
</tr>
<tr>
<td>Cellophane macular reflex</td>
<td>138 (5.1)</td>
<td>88 (3.8)</td>
</tr>
<tr>
<td>Preretinal macular fibrosis</td>
<td>122 (4.5)</td>
<td>62 (2.7)</td>
</tr>
<tr>
<td>Any ERM signs</td>
<td>260 (9.5)</td>
<td>150 (6.5)</td>
</tr>
<tr>
<td>Secondary ERM</td>
<td>531</td>
<td>1004</td>
</tr>
<tr>
<td>Cellophane macular reflex</td>
<td>52 (9.8)</td>
<td>91 (9.1)</td>
</tr>
<tr>
<td>Preretinal macular fibrosis</td>
<td>72 (13.6)</td>
<td>98 (9.8)</td>
</tr>
<tr>
<td>Any ERM signs</td>
<td>124 (23.4)</td>
<td>189 (18.8)</td>
</tr>
</tbody>
</table>

Secondary ERM is defined as any eye with diabetic retinopathy, retinal vein occlusion, age-related macular degeneration, or history of cataract surgery. Primary ERM are the eyes without the named risk factors.

* Age-standardized prevalence using the 2010 Census Singapore population.
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Figure 2. Comparison of CMR, PMF, and any ERM across SINDI, SiMES, and BMES.

1.59), previous cataract surgery (OR, 1.71; 95% CI, 1.08–2.70), and age-related macular degeneration (OR, 1.68; 95% CI, 1.01–2.80) were significantly associated with secondary ERM. Supplemental analysis (not shown) was performed and showed no significant association between ERM and hypertension, diabetes mellitus, smoking, and alcohol intake.

Discussion

Our study showed that the prevalence rate of ERM in older Asian Indians to be 7.6%, which is similar to Asian Malays in Singapore and more common than in whites in Australia. While previous population studies generally showed that ERM are less common in Asians than whites,10,14–18 direct comparison of these population studies has been limited by inconsistent methodology and definitions. In a multiethnic population study based in the United States, Chinese had the highest prevalence of ERM.5 A key strength of our study is that all the retinal photographs in SINDI, SiMES, and BMES were assessed by the same team of graders using standardized protocols. Our findings thus confirmed that the prevalence of ERM in Asian eyes is higher than in Caucasian eyes. Interestingly, our study showed that bilateral ERM was present in 29.2% of subjects with ERM, close to the BMES (31%) but relatively higher than the CMR (31%) across all three studies was similar. Compared with BMES findings, the CMR (early ERM) prevalence was significantly higher in the Malay and Indian eyes than in whites. One factor to consider may be the differential retinal pigmentation in Asian eyes compared with the whites. It is conceivable to think that the retina in the Indian and Malay eyes is more heavily pigmented which could have improved the contrast and thus resulted in a higher detection rate for CMR.16 Alternatively, the brighter retinal reflex in the Asian eyes may be wrongly classified as CMR and thus the true prevalence of ERM could have been overestimated.

Our study also showed that myopia and increasing axial length were significant risk factors for ERM, in contrast to reports in SiMES and BMES. There are, however, several reasons for an association between ERM and either myopia or longer axial length. Firstly, longer axial length is associated with posterior vitreous detachment which is a known risk factor for ERM. Secondly, a longer axial length may be associated with increased vitreoretinal traction predisposing to ERM formation. This association between myopia and ERM could become increasingly important in Asia as the prevalence and severity of myopia increases.19,20 Our study also showed that narrower retinal arteriolar diameter was associated with ERM, which was consistent with data from SiMES. This may either be a result of ERM disturbing the retinal surface making the retinal arterioles appear narrower or there could be a vascular etiology to the development of ERM. The BDES reported the association of arteriovenous nicking with ERM10 but more studies will be needed to examine this causative relationship.

Hypercholesterolemia was previously reported to be associated with ERM in populations studies based in United States and Japan.6,21 It was suggested that lipids may act as a chemotactant inducing glial cell migration and proliferation. However, our results showed that lower blood triglyceride level was a significant risk factor for secondary ERM in the Indian population which could have been a chance finding as the study examined a large number of variables.

Our study showed that despite previous reports suggesting that visual acuity in eyes with ERM is relatively unaffected; there was significant worsening in VA for eyes with ERM. Compared with CMR, the VA is also worse for eyes with PMF where there are more obvious retinal striae over the macula. As shown by Fraser-Bell et al.4 in a longitudinal study of the BMES, nearly one-third of eyes with pre-existing ERM progressed in severity with time. In our cross-sectional study, we showed that worse VA is associated with increasing severity of ERM and patients should be aware of this.

The strengths of our study include its large sample size and high response rate. All the fundus photographs were graded using standardized protocols at the same center used in both the BMES and SiMES, and by the same group of graders led by a senior researcher (JJW) and retinal specialist (PM). The sample of subjects included was a good representation of the vast Asian immigrant populations found worldwide and thus our results could potentially be extended to these populations. There are also limitations to be considered. Firstly, our study did not include all potential risk factors so that residual confounding may exist.
Acknowledgments

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References