Prevalence and Associations of Epiretinal Membranes in a Rural Chinese Adult Population: The Handan Eye Study

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PURPOSE. To determine the prevalence and association of epiretinal membranes (ERMs), as assessed by retinal photography and optical coherence tomography (OCT), in a Chinese population.

METHODS. The Handan Eye Study is a population-based study of eye disease in rural Chinese aged 30+ years. Eligible residents underwent a detailed ophthalmic examination including retinal photography and Stratus OCT. ERMs were defined by a combination of retinal photographs and OCT and classified as cellophane macular reflex (CMR) or preretinal macular fibrosis (PMF) based on retinal photographs characteristics.

RESULTS. Of the 6830 persons examined, 6565 (96.1%) had gradable retinal photographs and/or OCT. The mean age was 51.7 ± 11.6 years. ERMs were present in 3.4% (95% CI: 2.9%–3.8%) of participants, bilateral in 20.3% of the cases. CMR was present in 2.2% and PMF in 0.7%, and ERMs were unclassified in 0.5% (detected by OCT only). ERM prevalence was similar in women and men (3.6% vs. 3.1%), strongly associated with increasing age (P for trend < 0.001). After adjustment for age and sex, primary ERM was associated positively with myopia (OR: 1.58, 95% CI: 1.12–2.23) and inversely with current smoking (OR: 0.61, 95% CI: 0.38–0.97, versus never smoked). Best corrected visual acuity was significantly worse in eyes with primary ERMs (mean LogMAR score lower by 0.07, 95% CI: 0.05–0.10) than eyes without ERMs, after adjustment for age, sex, and lens status.

CONCLUSIONS. ERMs affect 3.4% of the population 30+ years of age and living in rural China. Idiopathic ERMs were associated with myopia, decreased visual acuity, and inversely associated with smoking. (Invest Ophthalmol Vis Sci. 2009;50:2018–2023) DOI:10.1167/iovs.08-2624

Epiretinal membranes (ERMs) are common conditions that may affect vision in older individuals.¹–⁶ ERMs are known to be associated with past cataract surgery, retinal detachment, retinal vein occlusions, and diabetic retinopathy (termed secondary ERMs).⁷–¹¹ Many, however, have no known causes, and are termed idiopathic ERMs. The early form of ERMs, cellophane macular reflex (CMR), is usually asymptomatic.¹²–¹⁴ The more severe form, preretinal macular fibrosis (PMF) or macular pucker, can cause significant visual symptoms.¹⁵–²¹ Other associations of ERMs include abnormal retinal vascular tortuosity,²² cystoid macular edema, and lamellar macular holes.²³–²⁵ Surgical removal of ERMs restores structure, but there is frequently residual loss of visual function.²⁶–²⁷

Previous population-based studies documenting the prevalence and associations of ERMs in various populations show substantial racial and ethnic variations.¹²–¹⁴,²⁸–³¹ The highest prevalence (18.5%) reported has been in U.S. Latinos³¹ and the lowest (2.2%) in Chinese.³⁰ However, all these studies have relied solely on retinal photographs to define ERMs and may thus underdiagnose early-stage cases not seen on retinal photographs. OCT is increasingly used in the clinical setting to define and monitor early ERMs.

The purpose of this study was to describe the prevalence and associated factors of ERMs in a Chinese population, defined based on retinal photographs and/or optical coherence tomography (OCT).

METHODS

Study Population

The Handan Eye Study (HES) was designed to provide population-based prevalence estimates of eye disorders in rural adult Chinese. Residents of Yongnian County, Handan, Hebei Province, aged 30+ years, were randomly selected using a clustered sampling technique with probabilities proportionate to the size of population in each cluster. Of the 458 villages in the Yongnian County, 13 were randomly selected to achieve a target sample size of 5105. The sampling frame for selection was a list of the persons living in the town, obtained from the Household Resident Register Record office of the local police stations. All residents in the 13 selected villages who were 50+ years of age were invited to participate. In addition, to study individuals 30...
to 49 years of age, the study team randomly selected 6 of the 13 villages with probabilities proportionate to the size, where all residents 30 to 49 years of age were also invited.

A total of 8653 individuals were selected and their permanent residency in the villages was confirmed in a door-to-door census conducted by the study team. A person was considered ineligible if he had moved out of the village, had not lived there in the past 6 months, was deceased, or was terminally ill with a life expectancy estimated at less than 5 months. Of the 8653 individuals, 7557 were considered eligible. Participants were requested to visit Yongnian County Hospital for a detailed examination. Those who declined to visit the hospital were offered a simplified evaluation at a temporary study site established in the village, and those who further declined to visit the temporary study site were offered a limited examination conducted at home. The survey was conducted from October 2006 to October 2007. Details of the study design, sampling plan, and baseline data are reported elsewhere. The Beijing Tongren Hospital Ethics Committee approved the study protocol, and written informed consent was obtained from all participants examined in the hospital, in village sites, and at home. All study procedures adhered to the principles outlined in the Declaration of Helsinki for research involving human subjects.

Retinal Photography and OCT

Digital 45° color retinal photographs (CR-DiG Non-mydriatic Retinal Camera; Canon Inc. Medical Equipment Group, Tokyo, Japan, or TRC-NW6S/7SF Non-mydriatic Retinal Camera, Topcon Corp., Tokyo, Japan) of ETDRS Standard Field 13 (centered on the optic disc, stereoscopic), ETDRS Standard Field 2 (centered on the macula, nonstereoscopic), and OCT (Stratus OCT; Model 3000, Carl Zeiss Meditec, Jena, Germany) were performed in participants after 20 minutes of adequate pupil dilation or dark adaptation with the pupil naturally dilated. The photographers were trained and certified by specialists in Singapore Eye Research Institute according to the protocol for the Singapore Malay Eye Study.34 Samples of photographs were sent to Centre for Eye Research Australia, University of Melbourne for an assessment of quality. OCT operators were trained and certified by retinal specialists and OCT operators in Beijing Tongren Eye Center, Beijing Tongren Hospital. The photographers were masked to all participant details. The OCT operators were not masked so that they could take additional images of the retina when ERMs or other retinal diseases were observed by the examining physician that were noted to be outside the prearranged line scans of the OCT device.

OCT was performed by an experienced examiner who was aware of the clinical findings of ERMs and diagnosis with the OCT software (Stratus ver. 4.0.1. Carl Zeiss Meditec). Line scan images 5 mm in length were acquired through the center of the macula along horizontal and/or vertical axes; a fast macular thickness map composed of six radial 6-mm-long scans of each operated eye were also taken. Additional OCT images were taken if any lesions were found outside the macular fields. Most of the OCT images of the macula were centered on the patient’s fixation point. Manual positioning of the macula by moving the fixation LED or using the external fixation was used when visual acuity in the participant’s eye to be scanned was too poor to provide stable fixation or to bring another particular pathologic portion of the retina away from the macula into view or into the center of view. To help in orienting the images, part of the optic disc was included at the edge of the video images.

Definitions and Classification of ERMs

ERMs were diagnosed with fundus photographic and OCT images graded by the same reader (XRD). In indeterminate cases, a panel of ophthalmologists (XRD, GLW, WBW) reassessed the photographs and the OCT images to arrive at a final grade by consensus.

For the photographic grading, two types of ERMs were identified as described by Klein et al.22 The first- or early-stage (CMR) was defined as present when a patch or patches of irregular increased reflection were seen on the inner surface of the retina. The second or more severe stage (PMF) was defined as present when an opaque and gray membrane lined the inner retina with the presence of superficial retinal folds or traction lines. Subjects were classified according to the most severe stage that was present in one or two eyes.

In OCT images, ERMs were defined as thin, highly reflective bands either anterior to the neurosensory retina with focal areas of macular attachments or globally adherent to the retinal surface. In the globally adherent group (where a separation was invisible), the ERMs were detected by a steepened foveal contour (pseudohole), contrast in reflectivity between the membrane and the retina, and/or the presence of a membrane tuft or edge contiguous with the retinal surface.23 Cases with ERMs detected by OCT only were those with poor photographic quality and thus no attempt was made to classify CMR or PMF. ERMs were subdivided as primary or secondary. Secondary ERMs were defined as those occurring in eyes that had undergone cataract surgery or had retinal vein occlusion, retinal detachment, or diabetic retinopathy. Primary ERMs were cases without apparent disease or cause.

Definitions of Other Variables

A detailed interview was conducted to determine information regarding ocular and medical histories and various risk factors. The visual acuity (VA) of each participant was measured with a log of the minimum angle of resolution (logMAR) chart at a distance of 4 m. Automated refraction was performed (Auto Refractometer KR 8800, Topcon Corp.), followed by subjective refraction performed by a trained optometrist on subjects with vision worse than 1.0 (≤20/20) in either eye (best corrected VA [BCVA]). Lens opacification was graded at the slit lamp by trained ophthalmologists according to the Lens Opacities Classification System III (LOCS III).35,36 Pseudophakia and aphakia were documented during the examination.

Blood pressure, height, weight, and Perkins applanation intraocular pressure were measured, as well as ankle brachial pressure index (ABI), toe brachial pressure index (TBI), and pulse wave velocity (PWV) (BP-203RPE II, VP-1000; Colin Medical Technology Corp., Komaki, Japan). Fasting plasma glucose, serum ura, creatinine, cholesterol, high-density (HDL) and low-density (LDL) lipoprotein cholesterol, and triglycerides were tested in 83.7% participants.

Diabetes mellitus was diagnosed from self-reported history of medication and/or fasting plasma glucose ≥7.0 mM. Hypertension was defined as having a history of hypertension on medication or elevated blood pressure when measured in the examination (diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg). Refractive error was defined by spherical equivalent (SE, sum of spherical power and half of the cylinder power, in diopters). Emmetropia was defined as an SE between −0.50 D and +0.50 D, hyperopia as an SE greater than +0.50 D, myopia as an SE less than −0.50 D.37 Persons with diabetes mellitus were classified as having diabetic retinopathy (DR). Characteristic DR lesions were graded using protocol developed in the Multi-ethnic Study of Atherosclerosis,46 which followed the Early Treatment for Diabetic Retinopathy (ETDRS) severity scale modified from the Airlie House Classification system.

Data Handling and Statistical Analysis

Data were entered into computer databases. Commercial software (Statistical Analysis System, ver. 9.1.3; SAS Institute Inc, Cary, NC) was used for tabulations and statistical analyses. Statistical analyses included χ² analyses, general linear model, and logistic regression analyses. Logistic regression was used to investigate the association of the presence of binary dependent variables versus the absence of ERMs with continuous (age, intraocular pressure, spherical equivalent, and biochemical parameters) and dichotomous (hypertension, diabetes, smoking, and other indices of systemic disease status) variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported.
RESULTS

Of the 7557 eligible subjects, 6830 took part in the study (90.4% response rate), 142 (1.9%) declined to participate, and 448 (5.9%) were temporarily outside of Yongnian County. Of the 6830 participants, 5909 (86.5%) were examined in the hospital clinic, 807 (11.8%) in a temporary study site at the village, and 114 (1.7%) at home. Subjects examined in the hospital clinic had both retinal photographs and OCT, subjects examined in the temporary study site had retinal photographs only, and subjects examined at home had no images taken.

Of the 6830 participants, 6649 (97.3%) had retinal photographs, and 6356 (95.6%) had photographs in at least one eye that weregradable for ERMs (3932 with the Canon camera and 2424 with the Topcon camera). Of the 474 participants excluded from this analysis, 181 had no photographs taken and 293 had ungradable photographs because of poor quality or dense media opacities.

Of the 5881 (86.1%) participants who underwent OCT, 5824 (99.0%) had OCT images from at least one eye that were consideredgradable for ERMs. Of the 1006 participants excluded, 949 had no OCT taken (807 had examinations conducted in the village, 114 had home visits, and 85 could not be imaged), and 57 had OCT images considered ungradable because of poor quality or dense media opacities.

Thus, there were 6565 participants with gradable retinal photographs and/or OCT images included in this report. Of those, 6439 (98.1%) participants were photographed after pupil dilation in at least one eye, and 126 (1.9%) were photographed without dilation. The mean age of these participants was 51.7 ± 11.6 years and 3502 (55.3%) were women.

Prevalence and Characteristics of ERMs

Based on retinal photograph grading only, ERMs were observed in 229 eyes of 191 participants, giving a prevalence of 3.0% (95% CI: 2.6%–3.4%). CMR was present in 2.3% (95% CI: 1.9%–2.7%) and PMF in 0.7% (95% CI: 0.5%–0.9%). In participants 40+ years of age, the prevalence of any ERMs was 3.5% (95% CI: 3.0%–4.0%), 217 eyes of 181 participants), of CMR 2.7% (95% CI: 2.2%–3.1%), and of PMF 0.8% (95% CI: 0.6%–1.1%).

When the diagnosis of ERMs included retinal photographs and OCT, ERMs were detected in 264 eyes of 221 participants, giving a prevalence of 3.4% (95% CI: 2.9%–3.8%). There were 35 eyes of 30 participants (0.5%; 95% CI: 0.3%–0.6%) detected by OCT only. The number of cases and eyes diagnosed by retinal photographs only, OCT only and both retinal photographs and OCT are shown in Table 1. The prevalence of ERMs was similar in right (2.1%, 133/6432) and left (2.0%, 131/6434, P = 0.90) eyes. The prevalence of any ERMs, as well as CMR and PMF separately, increased significantly with increasing age (P for trend<=0.001 for all). Bilateral ERMs were assessed in participants with ERMs with gradable photographs or OCT images in both eyes (n = 212) and were found in 45 (20.3%) of the 212 participants with ERMs.

Table 1. The Number of Cases Diagnosed by Each Method

<table>
<thead>
<tr>
<th>Diagnostic Methods</th>
<th>Gradable Images, n (%)</th>
<th>ERM Cases, n (%)</th>
<th>ERM Eyes, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal photographs only</td>
<td>741 (11.3)</td>
<td>115 (52.0)</td>
<td>140 (53.0)</td>
</tr>
<tr>
<td>OCT Only</td>
<td>209 (3.2)</td>
<td>30 (13.6)</td>
<td>35 (13.3)</td>
</tr>
<tr>
<td>Both photographs and OCT</td>
<td>5615 (85.5)</td>
<td>76 (3.4)</td>
<td>89 (33.7)</td>
</tr>
<tr>
<td>Total</td>
<td>6565</td>
<td>221</td>
<td>264</td>
</tr>
</tbody>
</table>

After adjustment for age, no significant differences were found in the overall prevalence of ERMs (3.6% vs. 3.1%, OR: 1.2, 95% CI: 0.9–1.6) or CMR (2.2% vs. 2.3%; OR: 1.0, 95% CI: 0.7–1.4) between the women and men. However, the women were more likely to have PMF than the men were (0.9% vs. 0.4%; OR: 2.2, 95% CI: 1.1–4.2).

Primary and Secondary ERMs

In the 264 eyes of 221 participants with ERMs diagnosed either by retinal photographs or by OCT, primary ERMs were observed in 227 eyes of 188 subjects, and secondary ERMs in 37 eyes of 33 subjects. The age-specific prevalences of primary and secondary ERMs are presented in Table 2. The prevalence of secondary ERMs in subjects with DR, retinal vein occlusion, and a history of cataract surgery was 7.9% (95% CI: 3.8%–12.0%, 13/165), 14.3% (95% CI: 5.6%–22.9%, 9/63), and 24.0% (95% CI: 12.2%–35.8%, 12/50), respectively. Full-thickness macular holes were seen in four eyes of four persons.

ERMs and Visual Acuity

BCVA was assessed in the worse eye of subjects with primary ERMs compared to subjects without ERMs. After adjusting for age, sex and lens status, mean BCVA was significantly lower (by 0.07 logMAR score, 95% CI: 0.05–0.10) in eyes with primary ERMs and with PMF (lower by 0.15, 95% CI: 0.09–0.21). CMR was not significantly associated with BCVA (difference of 0.03, 95% CI: −0.01 to +0.06). Visual impairment was present in 20 of 188 participants with primary ERMs. After adjustment for age, sex, and lens opacities, eyes with idiopathic ERMs had a higher prevalence of visual impairment (< 20/60, according to World Health Organization [WHO] criteria; OR: 3.23, 95% CI: 1.87–5.58). This result was due to a higher prevalence of visual impairment in those with PMF (OR: 5.70, 95% CI: 2.10–15.43), not those with CMR (OR: 1.25, 95% CI: 0.49–3.19).

Associations with Idiopathic ERMs

After adjustment for age and sex, current smoking was inversely associated with primary ERMs (OR: 0.61, 95% CI: 0.38–0.97). However, neither cigarette quantity smoked per day, nor smoking years for current smokers was significantly associated with ERMs. Myopia was significantly associated with primary ERMs (OR: 1.58, 95% CI: 1.12–2.23, Table 3).

Other characteristics assessed including intraocular pressure, diabetes (history or blood), hypertension (history or examination), body mass index, ABI, TBI, PWV, fasting plasma glucose, serum cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, urea, creatinine, alcohol intake (past or current), and level of education. After adjustment for age and sex, none of these previously suggested risk factors was significantly associated with ERMs in our study (OR: 0.54–1.25, all P > 0.05).

DISCUSSION

In this large rural Chinese population of participants 30+ years of age, we report an overall prevalence of ERMs of 3.4% (2.2% for CMR, 0.7% for PMF, and 0.5% unclassified, because these
cases were detected by OCT only). In participants 40+ years of age, the prevalence was 4.0% after age and sex standardization to the 2000 Chinese national census. This rate is higher than that reported in the Beijing Eye Study (2.2%), which was conducted in the urban and economically well-developed city of Beijing, with ERM detected by using retinal photographs only. After age-standardization to the 2000 world population, our ERM prevalence in participants 40+ years of age was 4.5% when diagnosed by either or both photographs and OCT, or 4.2% when diagnosed by retinal photographs only. Compared with other population-based eye studies in which ERMs were diagnosed by retinal photography only, this rate is higher than that observed in a Japanese sample in the Hisayama study, but similar to the rate seen in a sample of whites from higher than that observed in a Japanese sample in the Hisayama study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractive error (D)</td>
<td>0.97</td>
<td>0.91-1.05</td>
</tr>
<tr>
<td>Myopia</td>
<td>1.58</td>
<td>1.12-2.23*</td>
</tr>
<tr>
<td>Emmetropia</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Hyperopia</td>
<td>1.40</td>
<td>0.99-1.96</td>
</tr>
<tr>
<td>Smoking habits (past or current)</td>
<td>0.61</td>
<td>0.39-0.95†</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.61</td>
<td>0.38-0.97†</td>
</tr>
<tr>
<td>Past smoker</td>
<td>0.60</td>
<td>0.29-1.28</td>
</tr>
<tr>
<td>Cigarette quantity of current smoker</td>
<td>0.98</td>
<td>0.71-1.36</td>
</tr>
<tr>
<td>Smoking years of current smoker</td>
<td>1.15</td>
<td>0.75-1.78</td>
</tr>
</tbody>
</table>

Data are adjusted for age and sex.  
* P < 0.01.  
† P < 0.05.
Singapore Malay Eye Study (30.7%),
but is slightly higher than (15%),
thus, differences in the prevalence of myopia is in the Latinos (16.8%) and Blue Mountains Eye Study valuable skill and support.

Acknowledgments

The authors thank the staff and participants in the HES Study for their valuable skill and support.

Several studies have described the prevalence of ERMs in Asian ethnic groups,
and reported that Chinese has lower prevalence of ERMs compared with Malays, whites, and Latinos. Our study findings from this Chinese population confirmed this previous observations, despite the additional use of OCT to detect ERMs. The underlying explanation for these racial/ethnic variations is unclear. The prevalence of myopia in our study (19.4% in participants 40 years old) is lower than in the Beaver Dam Eye Study (26.2%) and the Singapore Malay Eye Study (30.7%),
but is slightly higher than in the Latinos (16.8%) and Blue Mountains Eye Study (15%).
thus, differences in the prevalence of myopia is unlikely to explain the lower prevalence of ERMs in our population. One intriguing possibility is the higher rates of smoking in the Chinese. Smoking rates are reportedly higher in China and Japan than in Singapore, Australia, and the United States. Because of the apparent inverse association between smoking and ERMs, the higher prevalence of cigarette smoking may explain the lower rates of ERMs in our study. Such a hypothesis has to be verified.

The strengths of our study include a large sample size with a high response rate in a population-based sample, and the use of OCT to complement retinal photographic diagnosis of ERMs. There are some limitations to this study. First, we took nonstereoscopic fundus photographs, which could miss subtle retinal abnormalities and subtle ERMs. It is conceivable that this could have resulted in an underestimation of the true ERM prevalence; however, our use of OCT very likely minimized this possibility. Second, ERM cases diagnosed by OCT only could not be further classified into CMR or PMF. This may have influenced the ratio of CMR to PMF, although the number diagnosed by OCT alone was small in this group.

In conclusion, we report the prevalence of ERMs in a population-based sample of Chinese subjects across a wide age range and provide unique data on the epidemiology of ERMs detected from photographs and OCT. We confirmed that ERMs are less common in Chinese than in similarly aged whites in Western countries. Besides age, myopia, and cigarette smoking, no other systemic or ocular factors were found to be significantly associated with the presence of idiopathic ERM. Primary ERM was significantly associated with poorer visual acuity.

References


TABLE 4. Comparison of the Age-Standardized Prevalence of Epiretinal Membranes in the Handan Eye Study and Other Population-Based Eye Studies Using the 2000 World Population Census

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Year(s) Conducted</th>
<th>Age Range (y)</th>
<th>Population at Risk</th>
<th>Prevalence (%)</th>
<th>Age-Standardized Rate (% 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beaver Dam Eye Study1,12</td>
<td>USA</td>
<td>1988–1990</td>
<td>43–84</td>
<td>4802</td>
<td>11.8</td>
<td>Not available</td>
</tr>
<tr>
<td>Blue Mountains Eye Study1,13</td>
<td>Australia</td>
<td>1992–1994</td>
<td>40</td>
<td>3490</td>
<td>7.0</td>
<td>5.6 (4.9–6.3)</td>
</tr>
<tr>
<td>Melbourne VIP2,5</td>
<td>Australia</td>
<td>1992, 1997</td>
<td>40</td>
<td>4513</td>
<td>6.0</td>
<td>4.8 (4.2–5.4)</td>
</tr>
<tr>
<td>Hiayama Study28</td>
<td>Japan</td>
<td>1998</td>
<td>40</td>
<td>1765</td>
<td>4.0</td>
<td>2.8 (2.3–3.5)</td>
</tr>
<tr>
<td>Los Angeles Latino Eye Study1,15</td>
<td>USA</td>
<td>2000–2003</td>
<td>40</td>
<td>5982</td>
<td>18.5</td>
<td>18.9 (17.7–20.0)</td>
</tr>
<tr>
<td>Beijing Eye Study30</td>
<td>China</td>
<td>2001</td>
<td>40</td>
<td>4378</td>
<td>2.2</td>
<td>Not available</td>
</tr>
<tr>
<td>Singapore Malay Eye Study1,16</td>
<td>Singapore</td>
<td>2004–2006</td>
<td>40–80</td>
<td>3265</td>
<td>7.9</td>
<td>9.1 (8.2–10.0)</td>
</tr>
<tr>
<td>Handan Eye Study1,17</td>
<td>China</td>
<td>2006–2007</td>
<td>40</td>
<td>5136</td>
<td>3.5</td>
<td>4.2 (3.6–4.8)*</td>
</tr>
</tbody>
</table>

* Age-standardized prevalence of the ERMs diagnosed by retinal photographs only in participants aged 40+ years.
† Age-standardized prevalence of the ERMs diagnosed by retinal photographs or OCT in participants aged 40+ years.
Prevalence of Epiretinal Membranes in Rural China

2023


