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Prevalence and Associations of Epiretinal Membrane by OCT in a Japanese Population-Based Cohort: Tohoku Medical Megabank Organization Eye Study

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Purpose: To examine the prevalence of epiretinal membrane (ERM) according to the OCT-based severity scales, and to describe associations focusing on the impact of smoking and axial length of the globe.

Design: Cross-sectional study.

Participants: The baseline examination cohort comprised participants from the Tohoku Medical Megabank community cohort recruited from 2013 to 2017.

Methods: In total, 38 118 eyes of 19 486 participants were classified with ERM staging. The characteristics of ERM severity were analyzed, and the association between the prevalence of ERM and ocular and systemic parameters was investigated using logistic regression models. Cubic spline models were constructed to visualize the relationships with lifetime smoking exposure and axial lengths. Regarding ERM severity, the associations between stage 1 and stage 2 or more were analyzed with multivariate analysis.

Main Outcome Measures: Epiretinal membrane prevalence at each stage determined via OCT and factors associated with ERM presence and severity.

Results: The prevalence of ERM was 2.3% per eye (3.6% per person), with a predominance at stage 1. The presence of severe ERM stages was higher in older individuals. The multivariate logistic analysis revealed that older age, female sex, and long axial length were associated with a higher prevalence of ERM. In a multivariate analysis stratified by sex, glaucoma was also identified as a significant factor associated with the prevalence of ERM in women. In the cubic spline model, no consistent trend was observed between smoking and ERM prevalence. However, a U-shaped relationship was indicated between axial length and ERM prevalence. Epiretinal membrane severity highlighted older age, alcohol consumption, and very long axial length as significantly associated compared with stage 1.

Conclusions: Epiretinal membrane prevalence was significantly associated with older age, female sex, and long axial length.

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Epiretinal membrane (ERM) is one of the most common macular diseases in the elderly population. While ERM is often asymptomatic in its early stages, it can cause progressive metamorphopsia, diplopia, and decreased visual acuity, eventually leading to symptom development and irreversible, moderate visual impairment.[1,2] Epiretinal membrane prevalence in the adult population has been reported in many countries and ranges from 2.2% to 34.1% depending on the age distribution.[3–25]

In population-based studies reported until the 2010s, ERM was categorized using color retinal images into simplified categories of cellophane macular reflex and preretinal macular fibrosis with retinal folds.[26] Recently, ERM has been diagnosed in clinical settings using OCT, influencing epidemiological studies that reported OCT-based prevalence and ERM severity.[20–23] The most widely used OCT-based severity grading is that proposed by Govetto et al,[27] which classifies ERM into 4 severity levels based on the extent of visual loss. The

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prevalence of ERM diagnosed and confirmed via OCT is higher than that reported in studies based on color retinal images, ranging from 7.0% to 34.1%, suggesting that OCT provides a more sensitive detection threshold.[20–25]

Several factors were identified to be potentially associated with ERM, including older age, female sex, history of hypertension, diabetes, dyslipidemia, hypouricemia, retinal vein occlusion, and myopia or longer axial lengths.[11–17,22–24,28] However, the link between cigarette smoking and ERM is controversial. Some cross-sectional studies reported a lower prevalence of ERM in smokers compared with nonsmokers,[5,7,8,24,29] while one longitudinal study suggested that smoking increases the risk of ERM.[30] Regarding axial length, while a long axial length was reported to be significantly associated with ERM prevalence, a consistent positive association between axial length and ERM prevalence has not been reported.[13]

The objective of this study was to ascertain ERM prevalence according to OCT-based severity scales and conduct a comprehensive analysis of exploring factors associated with ERM. We used the Tohoku Medical Megabank (TMM) Community Cohort Study of 23 833 adults with eye examinations that included color retinal photography, and OCT was utilized to investigate the data in-depth, including nonlinear associations. The TMM project primarily targets the Miyagi prefecture and its surrounding areas in Japan and aims to build personalized medicine through large-scale genomic cohort studies following the 2011 Great East Japan Earthquake. The data, including 2 major prospective cohort studies, were collected in community support centers across the Miyagi prefecture.

Methods

Study Population

The TMM Community Cohort Study commenced in 2013 as a community-centric genomic cohort study in the post-2011 Great East Japan Earthquake context.[31] It collected extensive data from population-based participants, including detailed lifestyle surveys, physical examinations, and a comprehensive multiomics analysis of biological samples. The initial phase of data collection spanned from 2013 to 2017.[32,33] The study protocols were approved by the Ethics Committee of Osaka University (approval number: 17014-5) and the TMM Organization in accordance with the Declaration of Helsinki. The participants provided written informed consent. Two prospective cohort studies were established within TMM: the CommCohort Study, which recruited participants at the national health screening program ("specific health checkup program") sites, and the BirThree Cohort Study, which recruited pregnant participants at the obstetric hospital. The enrollment rate with informed consent was approximately 65%. All additional examinations were performed at local community support centers, wherein dedicated health examinations for this project were performed. The more detailed explanation and specific protocols were previously reported on the TMM project.[31] Detailed eye examinations, including measurements of axial length, intraocular pressure, and fundus assessments through color retinal images and OCT, were performed at 7 community support centers located at Kesennuma, Osaki, Ishino-maki, Taga-jo, Iwa-numa, Shiro-ishi, and Sendai in the Miyagi prefecture, Japan.

Retinal Assessment and the Definition of ERM

Digital nonmydriatic color fundus photographs were captured with a CR-2 PLUS Non-Mydriatic Retinal Camera (Canon) and the OCT image with the Spectral Domain OCT (3D OCT-2000; Topcon Medical Systems). Axial length was accurately assessed utilizing the OA-1000 (Tomey), with an average of 10 valid measurements.

The initial screening of ERM cases was performed by 2 retinal specialists (A.S. and R.K.), who identified suspected cases of ERM based on the presence of a cellophane macular reflex or preretinal macular fibrosis. In this screening, the evaluation was conducted by placing OCT and fundus photographs side by side with reference to the method described by Kim et al.[22] The exclusion criteria for fundus photographs were set as images not including the macular region or those where an area of more than one-third of the picture is illegible. Additionally, obvious cases of secondary ERM were also excluded. As the history of ophthalmic conditions was not included in this study, only cases showing chorioretinal atrophy, retinal pigment epithelial atrophy, as well as cases of macular edema, where it was difficult to determine whether the cause was ERM or another disease, were excluded as secondary ERM. These screened cases were subsequently evaluated with OCT images to confirm the presence and severity of ERM according to the classification proposed by Govetto et al as follows:

Stage 1: the presence of the foveal pit and well-defined retinal layers;

Stage 2: the absence of the foveal pit with well-defined retinal layers;

Stage 3: the absence of the foveal pit with well-defined retinal layers and ectopic inner foveal layers; and

Stage 4: the absence of the foveal pit with disrupted retinal layers and ectopic inner foveal layers.[27]

In this study, cases diagnosed as either pseudomacular holes or lamellar macular holes by OCT were grouped together for analysis.

Assessment of Potentially Associated Factors

In the TMM cohort study, nonfasting blood samples were collected using a standardized protocol, and a comprehensive examination of each parameter was conducted. The assessments of high blood pressure, diabetes, hyperlipidemia, and hyperuricemia were based on a questionnaire. High blood pressure was defined as a systolic blood pressure of $\geq$140 mmHg or a diastolic blood pressure of $\geq$90 mmHg or currently receiving treatment. Diabetes was defined as a hemoglobin A1c level of $\geq$6.5% or currently receiving treatment. Hyperlipidemia was defined as the following blood test results: triglyceride $\geq$200 mg/dl or high-density lipoprotein cholesterol $<$40 mg/dl or total cholesterol $\geq$240 mg/dl, or currently receiving treatment. Hyperuricemia was defined as a uric acid level of $\geq$7 mg/dl, if "hyperuricemia" was selected on the questionnaire.

The estimated glomerular filtration rate (eGFR) was calculated using the following formulas: for men, eGFR (ml/min/1.73 m^2) = 194 $\times$ Cr (mg/dl) $^{-1.094}$ $\times$ age $^{-0.287}$; for women, eGFR (ml/min/1.73 m^2) = 194 $\times$ Cr (mg/dl) $^{-1.094}$ $\times$ age $^{-0.287}$ $\times$ 0.739.[34] Smoking habit status and alcohol intake were defined based on self-reported questionnaires. Smoking status was categorized into 3 groups as follows: "current smoker" was defined as individuals who self-reported having smoked $\geq$100 cigarettes in their lifetime and were currently smoking, "past smoker" included individuals who had smoked $\geq$100 cigarettes in their lifetime but were not currently smoking, and "never smoker" comprised individuals who reported having smoked $<$100 cigarettes in their lifetime. The cumulative number of cigarettes smoked was calculated by subtracting the age at smoking initiation from the age at consultation or age at smoking cessation before

multiplying the result by the number of cigarettes smoked per day. Alcohol consumption was divided into the following 3 categories: "current drinker" referred to individuals currently consuming alcohol, "past drinker" included individuals who had consumed alcohol in the past but had ceased drinking at the time of the survey, and "never drinker" was used to refer to those who had never consumed alcohol or were unable to do so.

Axial length was categorized as follows: very long (>26 mm), long (24−26 mm), normal (22−24 mm), and short (<22 mm).[35,36] Glaucoma was also defined as the presence of ≥1 of the following criteria: a cup-to-disc ratio of ≥0.7, thinning of the neural rim, or nerve fiber layer defects.[37]

Statistical Analyses

First, we investigated the linear trend of the characteristics according to ERM severity. Then, to examine the association between the presence and severity of ERM as well as several parameters, including sex, body mass index, smoking, alcohol, hypertension, diabetes, dyslipidemia, hyperuricemia, eGFR, glaucoma, retinal vein occlusion, and axial length, we constructed an age-adjusted logistic regression model with generalized estimating equations to account for the clustering of 2 eyes within a person. Cubic spline models were constructed to visualize the relationships between the lifetime number of cigarettes and prevalence of ERM as well as between axial length and ERM prevalence. The lifetime number of cigarettes was analyzed using log-transformed values. Cubic spline models were used to perform a multivariate analysis with the lifetime number of cigarettes and axial length as independent variables and with ERM prevalence as the dependent variable, incorporating all other factors. In addition to the overall analysis, these cubic splines were categorized by sex and age groups (above and <60 years) to elucidate specific patterns and trends within these subgroups. In ERM severity analysis, logistic regression was performed by dividing ERM into 2 groups: stage 1 of ERM and stages 2 and above, including macular traction syndrome and pseudomacular hole. The covariates were also included in the multivariate analysis. Statistical analyses were performed using the statistical programming language R (The R Foundation for Statistical Computing). A P value <0.05 was considered statistically significant.

Results

A total of 38 118 eyes of 19 486 participants from the original cohort of 23 833 adults were classified according to the ERM staging as shown in Tables S1 and S2 (available at www.ophthalmologyscience.org). The interrater reliability between the 2 graders, as assessed by the Kappa coefficient, was 0.93 (95% confidence interval: 0.91−0.96). A total of 2513 eyes were excluded due to poor fundus photo quality. Among them, ERM was detected on OCT in 65 eyes. Additionally, 761 participants (3.2%) had poor fundus photo quality in both eyes. A total of 6 eyes from 6 individuals (0.03%) were excluded as secondary ERM. Due to the small number of cases in stages 3, 4, macular traction syndrome, and pseudomacular hole, the combined number is shown in Table 3. The prevalence of ERM was 2.3% (864 of 38 118) per eye and 3.6% (703 of 19 486) per person, with ERM stage 1 being the most prevalent. In total, 322 eyes of 161 participants (0.8% per person) had bilateral ERM and 542 eyes of 542 participants had unilateral ERM (2.8% per person). The prevalence of ERM increased with age (Fig 1 and Table 4). Moreover, an examination of the prevalence of ERM stages by age indicated that the proportion of severe ERM stages increased with age, as evidenced by a notable difference in the staging between the young and old groups. In addition to older age, we observed that female sex, never smokers, short axial length (defined as <22 mm), glaucoma, hypertension, diabetes, hyperlipidemia, and low eGFR were associated with a higher prevalence of ERM (Table 3). As shown in Table 5, female sex, smoking, and longer axial length were significantly associated with a higher prevalence of ERM after adjusting for age. In a multivariate analysis, the association between smoking and ERM prevalence was no longer significant, whereas older age, female sex, long axial length, and very long axial length remained significant. When the multivariate logistic regression was analyzed separately by sex, older age and very long axial length were identified as significant factors in men, whereas older age, glaucoma, long axial length, and very long axial length were identified as significant factors in women.

We examined a dose-dependent relationship with a nonlinear shape among ERM prevalence by cubic spline, considering the lifetime number of cigarettes (Fig 2). This approach was chosen because our analysis also demonstrated a lower prevalence with smoking prior to adjustment as observed in previous reports.[5,8,24,29] Among the overall participants, there was no consistent increase in the log odds of ERM prevalence with increasing lifetime number of cigarettes smoked. When stratified by age and sex, the results were similar in males, showing no consistent increase in log odds with an increasing number of cigarettes smoked overall. In women, among those <60 years old, there was a tendency for the odds to decrease with a log lifetime cigarette consumption between 1 and 10; however, among those ≥60 years old, there was a tendency for the odds to increase. On the other hand, the odds of ERM prevalence tend to increase extremely with a log lifetime cigarette smoked of >10 across all age groups in women. As a whole, this cubic spline also showed no consistent increase. Figure 3 shows the cubic spline models regarding axial length. Upon creating a cubic spline for axial length and ERM prevalence, a U-shaped relationship indicating higher prevalence was observed for short and long axial lengths. There was no consistent relationship, necessitating further detailed analysis to examine the threshold axial length by sex and age groups, separately. When classified by sex, men showed an increase in prevalence proportional to axial length, whereas women exhibited a U-shaped relationship similar to the overall trend. Regarding age, those <60 years displayed an increase in prevalence with increasing axial length for both sexes. Conversely, for those aged ≥60 years, ERM prevalence tended to decrease when axial length exceeded 26 mm, both overall and within each sex group.

Table 3. Characteristics of Study Participants According to ERM Stage (per Eye)

Characteristics	Total N = 38 118	None N = 37 254	Any ERM N = 864	Severity and Types of ERM Confirmed by OCT			P Trend
				Stage 1 (n = 621)	*Stage 2 (n = 153)*	*Stage 3 + Stage 4 + MTS + pMH (n = 90)*	
Age, yrs							
Mean (SD)	50.7 (15.5)	50.3 (15.5)	63.8 (9.0)	63.2 (8.9)	64.6 (9.7)	66.4 (7.2)	<0.001
Women							
N, %	24 621 (64.6)	24 025 (64.5)	596 (69.0)	436 (70.2)	101 (66.0)	59 (65.6)	0.051
Smoking							
Current							
Yes, %	4970 (13.0)	4921 (13.2)	49 (5.7)	44 (7.1)	4 (2.6)	1 (1.1)	<0.001
Past							
Yes, %	9222 (24.2)	9006 (24.2)	216 (25.0)	141 (22.7)	50 (32.7)	25 (27.8)	
Never							
Yes, %	23 926 (62.8)	23 327 (62.6)	599 (69.3)	436 (70.2)	99 (64.7)	64 (71.1)	
Alcohol intake							
Current							
Yes, %	23 411 (61.4)	22 905 (61.5)	506 (58.6)	350 (56.4)	97 (63.4)	59 (65.6)	0.27
Past							
Yes, %	1882 (4.9)	1854 (5.0)	28 (3.2)	17 (2.7)	9 (5.9)	2 (2.2)	
Never							
Yes, %	12 825 (33.6)	12 495 (33.5)	330 (38.2)	254 (40.9)	47 (30.7)	29 (32.2)	
Glaucoma							
Yes, %	921 (2.4)	875 (2.3)	46 (5.3)	31 (5.0)	12 (7.8)	3 (3.3)	<0.001
Retinal vein occlusion							
Yes, %	142 (0.4)	137 (0.4)	5 (0.6)	3 (0.5)	2 (1.3)	0 (0)	0.35
Axial length							
Short: <22 mm							
Yes, %	966 (2.5)	929 (2.5)	37 (4.3)	22 (3.5)	10 (6.5)	5 (5.6)	<0.001
Normal: 22–24 mm							
Yes, %	16 843 (44.2)	16 430 (44.1)	413 (47.7)	307 (49.4)	65 (42.5)	41 (45.6)	
Long: 24–26 mm							
Yes, %	15 433 (40.5)	15 125 (40.6)	308 (35.6)	227 (36.6)	53 (34.6)	28 (31.1)	
Very long: >26 mm							
Yes, %	4876 (12.8)	4770 (12.8)	106 (12.3)	65 (10.5)	25 (16.3)	16 (17.8)	
History of hypertension							
Yes, %	10 799 (28.3)	10 425 (28.0)	374 (43.3)	263 (42.4)	66 (43.1)	45 (50.0)	<0.001
History of diabetes							
Yes, %	2229 (5.8)	2159 (5.8)	70 (8.1)	46 (7.4)	15 (9.8)	9 (10.0)	0.002
History of dyslipidemia							
Yes, %	13 446 (35.3)	13 099 (35.2)	347 (40.2)	244 (39.3)	59 (38.6)	44 (48.9)	<0.001
History of hyperuricemia							
Yes, %	3638 (9.5)	3568 (9.6)	70 (8.1)	51 (8.2)	12 (7.8)	7 (7.8)	0.17
eGFR, ml/min/1.73 m^2							
Mean (SD)	85.1 (21.6)	85.3 (21.7)	74.5 (16.2)	75.0 (16.4)	73.8 (16.4)	72.6 (14.1)	<0.001
BMI, kg/m^2							
Mean (SD)	22.8 (3.47)	22.8 (3.5)	23.0 (3.3)	22.9 (3.3)	23.3 (3.4)	23.0 (3.3)	0.09

BMI = body mass index; eGFR = estimated glomerular filtration rate; ERM = epiretinal membrane; MTS = macular traction syndrome; pMH = pseudomacular hole; SD = standard deviation.

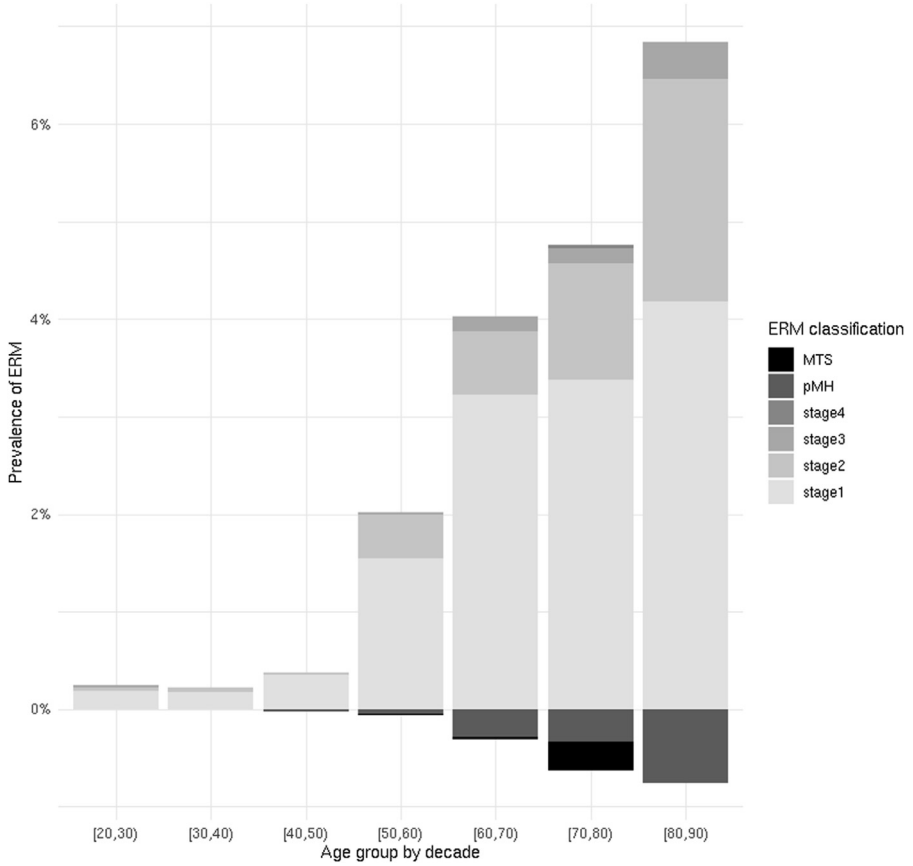

Figure 1. Prevalence of ERM by stages over age categories. ERM = epiretinal membrane; MTS = macular traction syndrome; pMH = pseudomacular hole.

When the forms of stages 2 and above ERM were compared with stage 1 (Table 6), older age, current alcohol intake, and very long axial length were significantly associated with the forms of stages 2 and above ERM.

Discussion

The present study offers a comprehensive descriptive epidemiology of ERM using OCT in a population-based study of participants with a relatively large sample size. In comparison to previous population-based studies in Japan that reported the prevalence of ERM, the Hisayama and Funagata studies reported an age inclusion criteria of ≥40 and ≥35 years, respectively. Restricting out study participants to those aged ≥40 years yielded a prevalence of 5.2%, comparable to that observed in other studies. No significant differences in age-specific prevalence rates of ERM were identified between our study and the 2 reported studies from Japan (data not shown).[9,11]

Herein, we report the prevalence of ERM in younger age groups, including individuals as young as 17 years old. It is

Table 4. Age-Specific Prevalence of ERM by Stages and Types

Age Categories	N	Any ERM (%)	Stage 1 (% Any ERM*)	Stage 2 (% Any ERM)	Stage 3 (% Any ERM)	Stage 4 (% Any ERM)	MTS (% Any ERM)	pMH (% Any ERM)
39 yrs old	12 617	29 (0.2)	23 (76.7)	5 (17.2)	1 (3.4)	0 (0)	0 (0)	0 (0)
40–49 yrs old	4277	17 (0.4)	15 (88.2)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (5.9)
50–59 yrs old	6483	135 (2.1)	100 (74.1)	29 (21.5)	2 (1.5)	0 (0)	1 (0.7)	3 (2.2)
60–69 yrs old	11 133	483 (4.3)	359 (74.2)	72 (14.9)	17 (3.5)	1 (0.2)	2 (0.4)	32 (6.6)
70–79 yrs old	3343	180 (5.4)	113 (62.8)	40 (22.2)	5 (2.78)	1 (0.6)	10 (5.6)	11 (6.1)
80+ yrs old	267	20 (7.5)	11 (55.0)	6 (30.0)	1 (5.0)	0 (0)	0 (0)	2 (10)

ERM = epiretinal membrane; MTS = macular traction syndrome; pMH = pseudomacular hole.
*% Any ERM represents the proportion of each stage of ERM within the total ERM for each age group.

Table 5. Clinical Characteristics Associated with Presence of Any ERM

Characteristics	Age-Adjusted Model		Multivariate Model Total, n = 38 118		Multivariate Model Male, n = 13 497		Multivariate Model Female, n = 24 621	
	OR (95% CI)	P *Value*	*OR (95% CI)*	P *Value*	*OR (95% CI)*	P *Value*	*OR (95% CI)*	P *Value*
Age								
Per 1 yr increase	-	-	**1.08 (1.07–1.09)**	**<0.001**	**1.08 (1.07–1.10)**	**<0.001**	**1.08 (1.07–1.09)**	**<0.001**
Sex								
Females vs. males	**1.26 (1.06–1.49)**	**0.009**	**1.31 (1.05–1.63)**	**0.02**	-	-	-	-
BMI								
Per 1 yr increase	1.00 (0.98–1.03)	0.98	1.01 (0.99–1.04)	0.28	1.02 (0.97–1.07)	0.40	1.01 (0.99–1.05)	0.34
Smoking								
Current/past vs. never	**0.84 (0.702–0.994)**	**0.04**	0.95 (0.77–1.16)	0.62	1.10 (0.80–1.51)	0.56	0.83 (0.61–1.12)	0.22
Alcohol intake								
Current vs. never	0.95 (0.80–1.12)	0.51	1.03 (0.86–1.23)	0.79	1.04 (0.67–1.60)	0.87	1.04 (0.86–1.27)	0.67
Past vs. never	1.03 (0.65–1.62)	0.90	1.14 (0.72–1.81)	0.57	1.66 (0.83–3.33)	0.15	0.79 (0.39–1.62)	0.52
Glaucoma								
Yes vs. no	1.31 (0.91–1.87)	0.14	1.25 (0.87–1.79)	0.23	0.63 (0.29–1.37)	0.25	**1.70 (1.13–2.55)**	**0.01**
RVO								
Yes vs. no	0.68 (0.25–1.90)	0.47	0.70 (0.25–1.97)	0.50	1.22 (0.37–3.98)	0.74	0.28 (0.03–2.36)	0.24
Axial length								
Short vs. normal	1.18 (0.77–1.79)	0.45	1.13 (0.74–1.72)	0.57	0.70 (0.12–3.95)	0.68	1.21 (0.78–1.88)	0.39
Long vs. normal	**1.22 (1.03–1.45)**	**0.02**	**1.28 (1.07–1.53)**	**0.006**	1.05 (0.77–1.43)	0.76	**1.41 (1.14–1.73)**	**0.001**
Very long vs. normal	**1.59 (1.24–2.05)**	**<0.001**	**1.67 (1.29–2.16)**	**<0.001**	**1.75 (1.17–2.61)**	**0.007**	**1.58 (1.12–2.22)**	**0.009**
Hypertension								
Yes vs. no	0.91 (0.77–1.08)	0.26	0.93 (0.78–1.11)	0.44	0.97 (0.72–1.30)	0.84	0.91 (0.74–1.14)	0.42
Diabetes								
Yes vs. no	0.78 (0.59–1.03)	0.08	0.81 (0.61–1.08)	0.15	0.89 (0.59–1.36)	0.59	0.74 (0.50–1.09)	0.13
Dyslipidemia								
Yes vs. no	0.96 (0.82–1.13)	0.65	0.96 (0.82–1.14)	0.65	1.09 (0.80–1.47)	0.59	0.91 (0.75–1.11)	0.35
Hyperuricemia								
Yes vs. no	0.82 (0.62–1.10)	0.19	0.89 (0.65–1.21)	0.45	0.94 (0.66–1.36)	0.75	0.72 (0.38–1.35)	0.30
eGFR								
Per 1 ml/min/1.73 m^2 increase	0.999 (0.994–1.005)	0.78	0.998 (0.993–1.004)	0.53	1.00 (0.99–1.01)	0.94	0.998 (0.991–1.004)	0.52

BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; ERM = epiretinal membrane; OR = odds ratio; RVO = retinal vein occlusion.
Classification of axial length; very long: −26 mm, long: 24 to 26 mm, normal: 22 to 24 mm, short: −22 mm.
Multivariate model included all the characteristics shown in the table. Bold values indicate significant values.

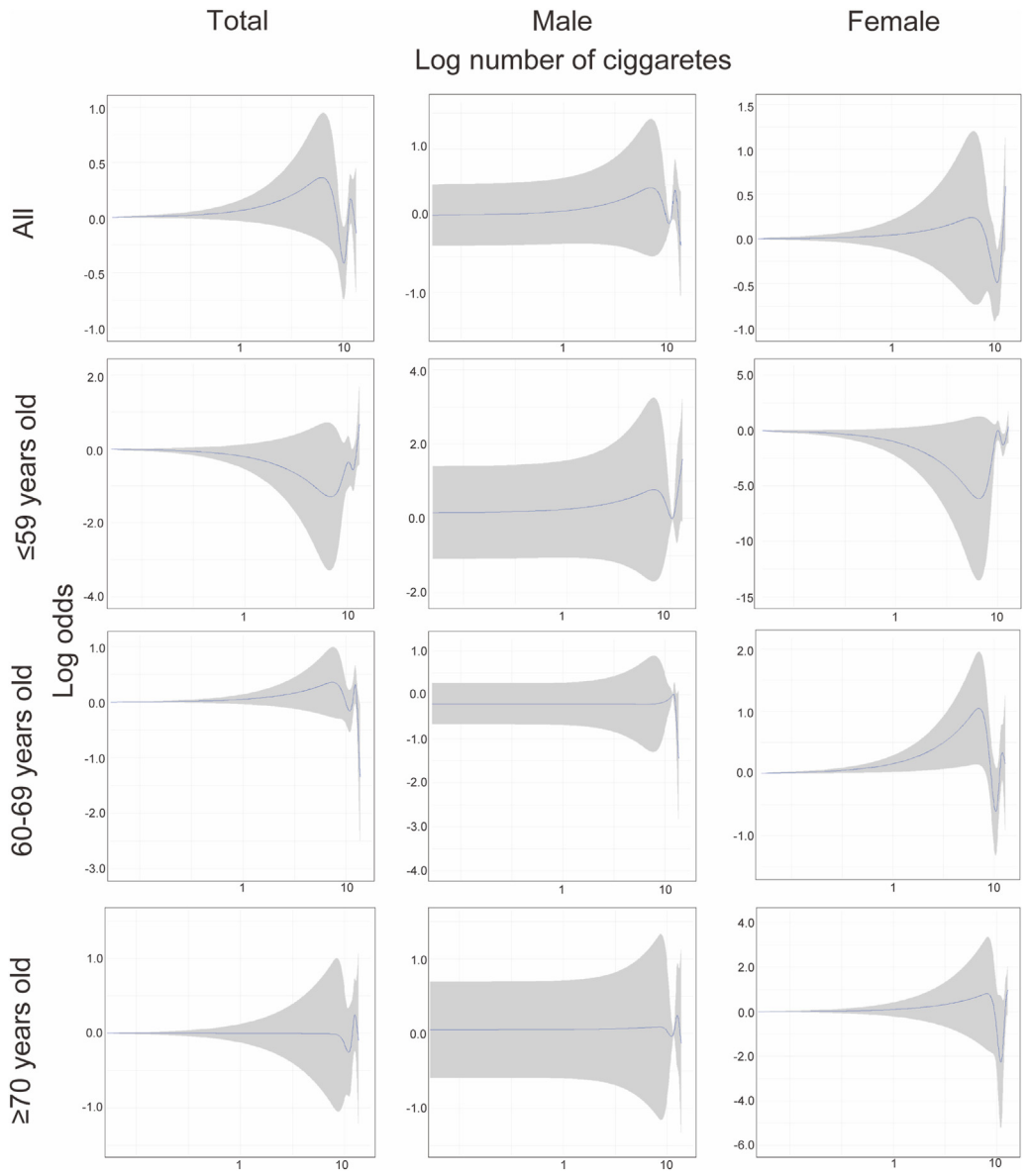

Figure 2. Cubic spline curve of adjusted log odds of the prevalence of epiretinal membrane with cumulative smoking dose over the age and sex categories. (Cumulative smoking dose was defined as the logarithmically transformed value of the lifetime number of cigarettes smoked).

relatively uncommon to encounter patients with idiopathic ERM who are <40 years of age within the context of clinical ophthalmology. However, an unexpected finding in our population-based study was the presence of ERM even in individuals <40 years old. The presence of ERM in individuals <40 years was confirmed on 2 occasions by 2 retina specialists (A.S. and R.K.) and was identified as idiopathic ERM, thus suggesting that ERM can develop in younger age groups.

Stage 1 ERM was the most prevalent stage across all age groups. However, the proportion of more advanced ERMs increased with age (Table 4 and Fig 1). This indicates that aging may be a principal factor contributing to increased severity, which is consistent with the findings presented in Table 6, where older age was associated with ERM severity.

A multivariate analysis stratified by sex revealed a significant association between glaucoma and long axial length exceeding 24 mm with the prevalence of ERM in women. Although previous clinical case series have identified an association between glaucoma and ERM,[38] this study is the first to demonstrate a potential sex-based difference in this association. Specifically, the observed association was limited to women. Regarding axial length, the association is U-shaped, with a higher prevalence of ERM observed for shorter axial lengths (<22 mm). However, this observation was not confirmed in the multivariate analysis. The results for other factors were consistent with previous reports.[3,5,8,9,11–13,15,17,22,25]

It is well-established that smoking causes a range of adverse health outcomes, including cancer and

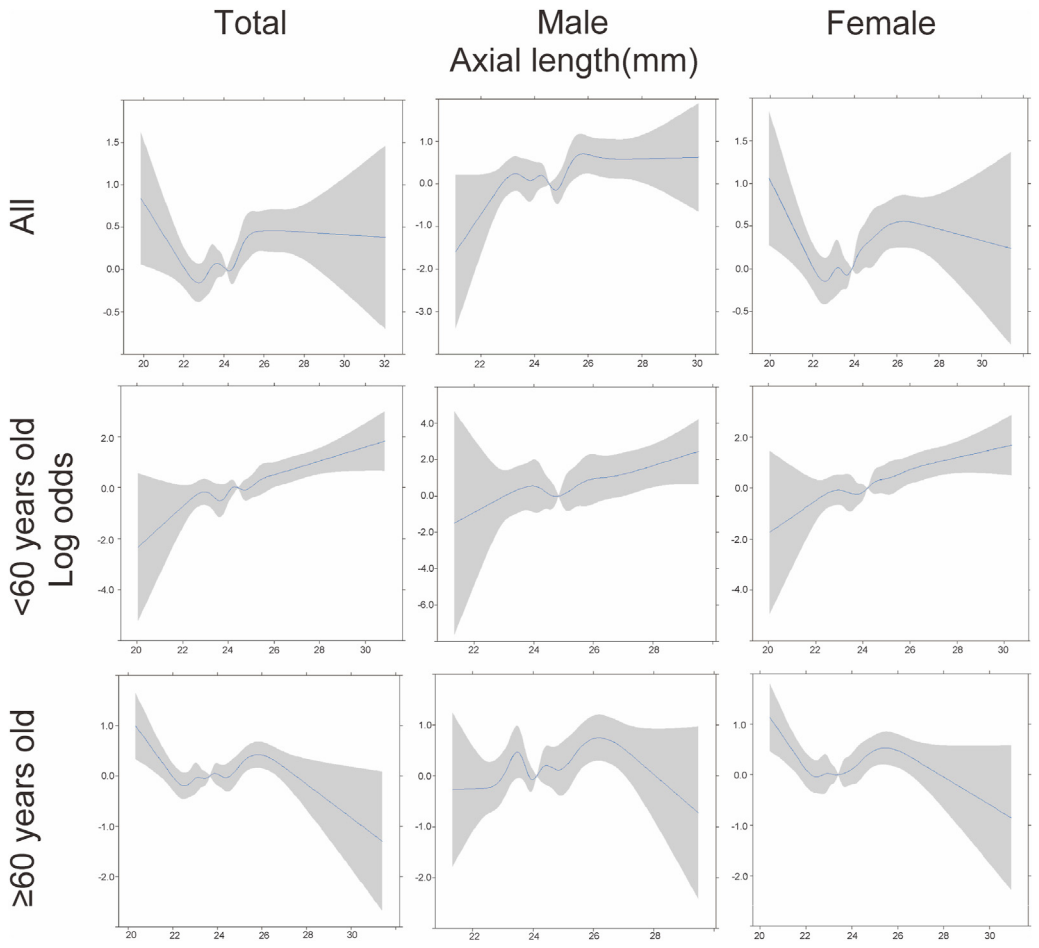

Figure 3. Cubic spline curve of adjusted log odds of the prevalence of epiretinal membrane with the axial length over the age and sex categories.

cardiovascular disease.[39,40] Considering this, it is reasonable to hypothesize that smoking may also increase the risk of ERM via increased inflammation or other mechanisms. In alignment with this hypothesis, a study by Zhu et al[17] reported an association between smoking and increased prevalence of ERM. Conversely, multiple cross-sectional population-based studies indicated a lower prevalence of ERM among smokers.[5,8,24,29] Herein, we observed a negative association between smoking and ERM prevalence after adjusting for age, which diminished in a multivariate adjustment model. No significant association was identified when the data were stratified by sex. However, the point estimate of the odds ratio for women was in the negative direction. To further investigate whether this association is dose-dependent, we applied a cubic spline curve to examine the potential unified correlation between the lifetime number of cigarettes smoked and ERM prevalence. As illustrated in Figure 2, no discernible dose-dependent correlation was observed between the lifetime number of cigarettes smoked and ERM prevalence. In women, ERM prevalence was low in the range of log lifetime cigarette consumption between 1 and 10 in subjects <60 years old. It is postulated that the individuals in this range may have an increased cardiovascular risk, which may be reflected in the observed survivor effect. Indeed, individuals within this range had a higher cardiovascular risk (data not shown). Conversely, in subjects >60 years old, the ERM prevalence in individuals with a log lifetime cigarette consumption of >10 was low because the lower incidences of cardiovascular risk factors compared with those without ERM may indicate that only survivors remain in this group (data not shown). It is evident that establishing causality in cross-sectional studies is not a feasible endeavor. A rare paper reporting the incidence of ERM demonstrated that in individuals >85 years old, smoking was associated with an increased risk of ERM.[30] Considering the findings presented in this study, we concluded that a dose-dependent relationship is an unlikely explanation for the observed phenomenon. To substantiate a causal relationship between smoking and ERM clearly, either in the direction of increased or decreased risk, future studies employing a cohort study design with a large sample size must be performed to demonstrate such a relationship.

This study explored the associations between stage 1 and stage 2 or more, particularly in relation to the staging ERM confirmed by OCT, in a population-based sample. As demonstrated in Table 6, in addition to older age, current alcohol consumption, and an axial length of >26 mm,

Table 6. Clinical Characteristics Associated with the Forms of ERM (Stage 2 or More/MTS/pMH) Compared with Stage 1

Characteristics	Age-Adjusted Model		Multivariate Model	
	OR (95% CI)	*P Value*	*OR (95% CI)*	*P Value*
Age				
Per 1 yr increase	-	-	**1.03 (1.01–1.05)**	**0.01**
Sex				
Females vs. males	0.86 (0.62–1.21)	0.39	1.15 (0.72–1.85)	0.55
BMI				
Per 1 yr increase	1.02 (0.97–1.07)	0.51	1.01 (0.96–1.07)	0.63
Smoking				
Current + past vs. never	1.21 (0.86–1.69)	0.27	1.14 (0.73–1.79)	0.57
Alcohol				
Current vs. never	**1.53 (1.09–2.14)**	**0.01**	**1.52 (1.06–2.19)**	**0.02**
Past vs. never	2.15 (0.87–5.31)	0.10	2.17 (0.83–5.64)	0.11
Glaucoma				
Yes vs. no	1.25 (0.67–2.36)	0.48	1.21 (0.64–2.29)	0.55
RVO				
Yes vs. no	1.55 (0.34–7.06)	0.57	1.92 (0.44–8.42)	0.39
Axial length				
Short vs. normal	1.82 (0.87–3.78)	0.11	1.86 (0.87–3.97)	0.11
Long vs. normal	1.13 (0.79–1.60)	0.50	1.14 (0.79–1.63)	0.49
Very long vs. normal	**2.29 (1.38–3.79)**	**0.001**	**2.32 (1.38–3.92)**	**0.002**
Hypertension				
Yes vs. no	1.01 (0.73–1.39)	0.95	0.94 (0.67–1.32)	0.70
Diabetes				
Yes vs. no	1.33 (0.78–2.26)	0.30	1.30 (0.74–2.29)	0.37
Dyslipidemia				
Yes vs. no	1.05 (0.76–1.44)	0.78	1.01 (0.73–1.41)	0.93
Hyperuricemia				
Yes vs. no	0.92 (0.52–1.63)	0.92	0.74 (0.40–1.38)	0.34
eGFR				
Per 1 ml/min/1.73 m^2 increase	1.00 (0.99–1.01)	0.93	0.997 (0.986–1.01)	0.66

BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; ERM = epiretinal membrane; MTS = macular traction syndrome; OR = odds ratio; pMH = pseudomacular hole; RVO = retinal vein occlusion.
Classification of axial length; very long: −26 mm, long: 24 to 26 mm, normal: 22 to 24 mm, short: −22 mm.
Multivariate model included all the characteristics shown in the table. Bold values indicate significant values.

there was a significantly higher prevalence of stage 2 or more ERMs. Notably, alcohol consumption was unexpectedly found to be associated with more severe forms of ERM, which may be attributed to the increased vascular risk associated with alcohol intake.[41] However, a detailed analysis of alcohol consumption was not available in this study, for which prospective studies are needed in the future. This study presents novel findings regarding ERM, while also confirming some prior observations, as follows:

1. Adoption of an OCT-based grading system: this study validated and applied the OCT-based grading system proposed by Govetto et al to a large population-based cohort for the first time.
2. Identification of new potential associations: we identified not only a U-shaped association between axial length and ERM, but also a novel association between glaucoma in women and ERM.
3. Smoking and ERM: while prior studies have debated whether the association between smoking and ERM is positive or negative, our analysis explored a dose-dependent relationship but found inconsistent results, highlighting the need for large-scale prospective studies to clarify this association.

This study has the following limitations. First, its study design did not allow for the confirmation of a causal association, as detailed information on the timing of exposure and outcome was not available. Second, most participants in this study were of Asian descent. Consequently, further studies involving multiple ethnicities may be necessary to generalize the findings.[15] Third, there is a possibility that some cases of secondary ERM were included. While we excluded obvious secondary ERM based on our exclusion criteria, it is impossible to deny the presence of ERM that cannot be identified through only fundus photography or OCT, including ERM resulting from postuveitis. Because the TMM study did not collect detailed ophthalmic medical history or diagnosis codes, we were unable to completely exclude cases of secondary ERM. Fourth, in this study, the number of stage 3 and stage 4 ERM cases was very small, making comparisons with the ERM group requiring surgical intervention difficult. This represents a limitation of the cross-sectional study design. Therefore,

prospective studies are needed to investigate which factors contribute to the progression of early-stage ERM to stage 3 and stage 4. Fifth, the resolution of this 3D OCT-2000 was significantly lower than that of current OCT devices, making it impossible to identify detailed characteristics, such as microcystic macular changes.

The prevalence of ERM was associated with advanced age, female sex, and longer axial length. Glaucoma was identified as a significant factor associated with the prevalence of ERM in women. There was a suggestion of a U-shaped association between axial length and ERM prevalence. No consistent association was found with smoking, including the cumulative lifetime smoking dose. The stage 2 and above ERM was associated with older age, alcohol intake, and longer axial length compared with stage 1.

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Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. The study protocols were approved by the Ethics Committee of Osaka University (approval number: 17014-5) and the Tohoku Medical Megabank Organization in accordance with the Declaration of Helsinki. The participants provided written informed consent.

No animal subjects were used in this study.

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Obtained funding: N/A

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Abbreviations and Acronyms:
eGFR = estimated glomerular filtration rate; **ERM** = epiretinal membrane; **TMM** = Tohoku Medical Megabank.

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Axial length, Epiretinal membrane, Optical coherence tomography, Prevalence, Smoking.

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