• Investigation •

Insights into risk factors and interactive effects on epiretinal membrane development from the National Health and Nutrition Examination Survey

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Abstract

● **AIM:** To assess risk factors for epiretinal membranes (ERM) and examine their interactions in a nationally representative U.S. dataset.

● **METHODS:** Data from the 2005–2008 National Health and Nutrition Examination Survey (NHANES) were analyzed, a nationally representative U.S. dataset. ERM was identified *via* retinal imaging based on the presence of cellophane changes. Key predictors included age group, eye surgery history, and refractive error, with additional demographic and health-related covariates. Weighted univariate and multiple logistic regression models were used to assess associations and interaction effects between eye surgery and refractive error.

● **RESULTS:** Totally 3925 participants were analyzed. Older age, eye surgery, and refractive errors were significantly associated with ERM. Compared to those under 65y, the odds ratio (OR) for ERM was 3.08 for ages 65–75y (P=0.0014) and 4.76 for ages 75+ years (P=0.0069). Eye surgery increased ERM risk (OR=3.48, P=0.0018). Moderate to high hyperopia and myopia were also associated with ERM (OR=2.65 and 1.80, respectively). A significant interaction between refractive error and eye surgery was observed (P<0.0001). Moderate to high myopia was associated with ERM only in those without eye surgery (OR=1.92, P=0.0443). Eye surgery was most strongly associated with ERM in the emmetropic group (OR=3.60, P=0.0027), followed by the moderate to high myopia group (OR=3.01, P=0.0031).

● **CONCLUSION:** ERM is significantly associated with aging, eye surgery, and refractive errors. The interaction between eye surgery and refractive error modifies ERM risk and highlights the importance of considering combined effects in clinical risk assessments. These findings may help guide individualized ERM risk assessment that may inform personalized approaches to ERM prevention and management.

● **KEYWORDS:** epiretinal membranes; National Health and Nutrition Examination Survey; logistic regression models; risk factors

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INTRODUCTION

Epiretinal membrane (ERM) is a condition affecting the vitreomacular interface that can cause visual impairment. ERM vary widely in their clinical presentation, ranging from asymptomatic cases found during routine exams to symptomatic cases with metamorphopsia, macropsia, photopsia, decreased visual acuity, or central vision loss[1]. Early-stage ERM, also called cellophane macular reflex, are usually asymptomatic, while the advanced form, pre-retinal macular fibrosis, can cause significant vision impairment[2]. It is estimated that approximately 30 million individuals within the United States present with ERM in at least one ocular structure[3-6].

In recent years, numerous studies have explored the risk factors associated with ERM[2,5-7]. One study conducted among a multi-ethnic population investigated racial disparities in ERM prevalence, revealing a significantly higher prevalence among Chinese individuals compared to other racial groups[3], whereas other studies have indicated lower ERM prevalence among Asians compared to Whites[8-10]. Additionally, advancing age has emerged as a significant factor linked to an increased prevalence of ERM. Prevalence rates rise from 1.9% in individuals under 60 years old to 7.2% in those aged 60–69y, and further to 11.6% in those over 70 years old[6,11-12]. Sex does not seem to exert a significant association, with studies demonstrating similar prevalence rates between males and females[13-14] or slightly lower rates in males[11,15-16]. While some studies have suggested associations between ERM and myopia[17] and hyperopia[13], these associations have not been consistently observed across all studies. Additionally, cataract surgery[11,14,18], diabetic retinopathy[14,19-20], and retinal vein occlusion[11,16] have been significantly associated with ERM development. However, research on ERM risk factors in the US population is limited, and there is a significant gap in understanding how these risk factors interact.

The diagnostic approach to ERM has seen a notable evolution in its methodology. For many years, the standard for diagnosis and grading was based on clinical funduscopic examination. This approach led to foundational classification systems, such as the one described by Gass, which categorized membranes based on their visible characteristics like translucency and the extent of retinal wrinkling[21]. This system provided a framework for understanding the clinical presentation of ERM. Subsequently, the introduction of optical coherence tomography provided a new modality for retinal imaging[1]. By providing high-resolution, cross-sectional views of the retinal microstructure, optical coherence tomography (OCT) allowed for the direct visualization of the membrane and its relationship with the underlying retinal layers. This additional anatomical information prompted the development of new staging systems based on tomographic findings. A prominent example is the four-stage classification, which characterizes ERM based on morphological features seen on OCT, such as the foveal contour and the integrity of specific retinal layers, adding further detail to the clinical picture[21-22].

The aim of this study is to analyze the risk factors, including demographic, socioeconomic status, and medical conditions, within the adult population of the United States. Furthermore, we seek to assess the interaction effects among these significant risk factors. Understanding the contributors to ERM among US adults is crucial for directing interventions aimed at mitigating visual impairment. Through identifying high-risk groups and examining interaction effects, this study endeavors to improve clinical practice and inform public health policy to enhance visual health outcomes.

PARTICIPANTS AND METHODS

Ethical Approval Institutional Review Board approval was not required as the data is de-identified and publicly available.

Sample Participants Data from a total of 3925 participants were collected from the National Health and Nutrition Examination Survey (NHANES), spanning the years 2005 to 2008. This dataset has been successfully used in both earlier and more recent studies to investigate various ocular conditions[23-24]. NHANES surveys are designed to represent the non-institutionalized civilian population in the United States[25]. Each two-year cycle provides a subset representative of the entire population, with appropriate weighting calculated to adjust for differences in sample selection probability and non-response rates. Initially, 6796 participants with responses regarding cellophane or traction changes in the worse eye were extracted from the NHANES database. After excluding individuals with missing values for cellophane or traction changes (n=1099) and other covariates (n=1772), the final analytical sample for this study comprised 3925 participants. Chi-squared tests were conducted for each variable to assess whether their distributions changed significantly before and after exclusion; no significant changes were detected.

Dependent Variable The dependent variable, ERM, was evaluated based on the presence or absence of cellophane or traction changes in the worse eye. Absence was designated as "No", while presence was categorized as "Yes" or "Yes", in center. ERM was categorized as "Beginner-Level" if cellophane macular reflex was present without retinal traction (Gass Grades 0–1), and "Severe" if retinal traction was present (Gass Grade 2). Cellophane or traction changes were identified through retinal imaging examinations conducted using an ophthalmic digital imaging system. The assessment of ERM was conducted through the analysis of non-mydriatic, 45-degree digital color fundus photographs acquired with a Canon CR6-45NM retinal camera. As part of the standardized study protocol, these images were transmitted to the University of Wisconsin Fundus Photograph Reading Center for evaluation. At this central facility, trained and certified graders, who were masked to all participant and clinical data, systematically reviewed the retinal images. Two independent retina specialists, each with at least 5y of experience in retinal image evaluation and 3 years of experience in ERM surgery, were selected from the Centers for Disease Control and Prevention (CDC) to perform the diagnoses and exclude difficult-to-evaluate photographs. The grading protocol for ERM involved a classification based on photographic evidence, which distinguished between an early-stage "cellophane macular reflex", identified by an irregular, glistening sheen on the inner retinal surface without retinal folds, and a more advanced "preretinal macular fibrosis", characterized by an opaque membrane causing discernible wrinkling of the retinal surface and tortuosity of the macular vasculature. The inter-rater reliability was 0.82 for 2005–2006 and 0.85 for 2007–2008. Additional information about the procedure can be found in NHANES[26].

Independent Variables The independent variables investigated in this study comprised age group (under 65y, 65–75y, and ≥75y), history of myopia or cataract surgeries (yes, no), and refractive error (emmetropia, moderate-to-high hyperopia, low, mild myopia, and moderate/high myopia).

Refractive error was assessed using the mean spherical equivalent (MSE) of the worse eye, with specific ranges defining distinct categories[27-28]. The spherical equivalent (SE) was calculated using the formula: SE=S+C/2, where S represents the sphere power [in diopters (D)] and C represents the cylinder power (D). Based on standard definitions, myopia was categorized by SE as mild (-0.75≥SE>-3 D), moderate (-3>SE>-6 D), or high (≤-6 D)[29]. Hyperopia was categorized as mild (SE≤+2 D), moderate (+2<SE≤+5.00 D), or high (>+5 D)[30]. For the purpose of our analysis, these classifications were consolidated into five groups: emmetropia (-0.75>SE>0.5 D), mild myopia, moderate/high myopia, mild hyperopia, and moderate/high hyperopia. Additional covariates considered included sex (male, female), race (Non-Hispanic White, Non-Hispanic Black, Hispanic, and other), usual place for healthcare (yes, no), education level (less than high school, high school graduate, some college or associate's degree, college graduate or above), poverty income ratio (PIR<1.3, 1.3–3.5, ≥3.5), obesity status (normal, overweight, obesity), presence of diabetes (yes, no), cardiovascular disease (CVD; yes, no), retinopathy (yes, no), and high cholesterol (yes, no).

Statistical Analysis Sample characteristics were delineated in terms of sample size and weighted proportions, depicted as percentages for the entire sample and stratified by ERM groups. Proportions were weighted to ensure national representativeness. To examine the association between independent variables and ERM, both univariate and multiple logistic regression models were employed and reported. The univariate logistic regression model assessed one independent variable at a time, while multiple logistic regression models included all predictor variables of interest along with all other covariates described above. The statistical significance of interaction effects between surgery and refractive error was assessed by incorporating the interaction term in the multiple logistic regression model. Specifically, Type III tests of effects were used to evaluate the statistical significance of the interaction terms between surgery and refractive error in the multiple logistic regression model[28]. Subsequently, the main effects of surgery and refractive error on ERM were assessed within strata defined by the other variable, allowing for examination of how the effect of one factor varies across the subgroups defined by the other factor. A *P*-value below 0.05 was considered statistically significant. All logistic regression models were weighted using jackknife repeated replication. The analyses were performed using R software version 4.3.2[31].

RESULTS

Table 1 presents the demographic characteristics of the participants categorized by the presence or absence of ERM. Individuals with ERM exhibited a significantly higher proportion of participants aged 65 years or older (62.4% in ERM *vs* 23% in non-ERM, *P*=0.0001), non-Hispanic White ethnicity (88.6% in ERM *vs* 80.2% in Non-ERM, *P*=0.0484), a PIR between 1.3 and 3.5 (48.5% in ERM *vs* 32.2% in Non-ERM, *P*=0.0387), and those who had undergone eye surgery (41.1% in ERM *vs* 9.7% in non-ERM, *P*=0.0003). Sex (*P*=0.8515) and education attainment (*P*=0.9356) did not exhibit statistically significant associations with ERM.

Table 1 Sample characteristics in total sample and grouped by ERM

n (%)

Parameters	Total	Non-ERM	ERM	*P*
Age group (y)				
<65	2567 (76.2)	2539 (77.0)	28 (37.6)	0.0001
65–75	828 (15.5)	787 (15.2)	41 (30.8)	
75+	530 (8.3)	490 (7.8)	40 (31.6)	
Race				
Non-Hispanic White	2273 (80.3)	2197 (80.2)	76 (88.6)	0.0484
Mexican American	490 (3.9)	480 (3.9)	10 (2.5)	
Non-Hispanic Black	797 (8.8)	782 (8.9)	15 (5.7)	
Other	365 (7.0)	357 (7.0)	8 (3.2)	
Sex				
Female	2005 (53.7)	1952 (53.7)	53 (52.4)	0.8515
Male	1920 (46.3)	1864 (46.3)	56 (47.6)	
Education				
Less than high school	928 (14.4)	899 (14.4)	29 (15.5)	0.9356
High school grad	973 (25.1)	944 (25.0)	29 (28.1)	
Some college or AA	1073 (29.6)	1051 (29.7)	22 (25.6)	
College grad. or above	951 (30.8)	922 (30.8)	29 (30.9)	
Poverty income ratio				
<1.3	804 (11.9)	788 (12.0)	16 (6.5)	0.0387
1.3–3.5	1487 (32.6)	1595 (32.2)	39 (48.5)	
≥3.5	1634 (55.5)	1433 (55.8)	54 (44.9)	
Eye surgery				
No	3444 (89.6)	3380 (90.3)	64 (58.9)	0.0003
Yes	481 (10.4)	436 (9.7)	45 (41.1)	

ERM: Epiretinal membrane; Non-ERM: Participants without ERM detected; AA: Associate of arts; Total: All participants; *n*: The raw frequency counts of the sample; weighted %, the proportion of each category, accounting for sampling weights.

Table 2 presents the results from logistic regression models examining the relationship between ERM and various independent variables, encompassing demographics, medical conditions, and access to healthcare. In unadjusted models, where predictors were evaluated individually without considering other variables, age group, eye surgery, refractive error, race, routine access to healthcare provider, PIR, and high cholesterol level were all significantly linked to ERM. However, after adjusting for all covariates in multiple logistic regression models, only age group, eye surgery, and refractive error retained statistical significance, albeit with slightly attenuated odds ratios (ORs). Age group demonstrated a positive association with ERM, with OR of 3.08 [95%CI: 1.89, 5.01, *P*=0.0014] for ages 65–75 and 4.76 (95%CI: 1.98, 11.45, *P*=0.0069) for ages 75 and older. Participants

Table 2 Associations between ERM and independent variables using univariate and multiple logistic regression models

Parameters	Crude models OR (LCL, UCL)	*P*	Adjusted models OR (LCL, UCL)	*P*
Age group (y)				
<65	Ref.			
65–75	4.15 (2.37, 7.25)	<0.0001	3.08 (1.89, 5.01)	0.0014
75+	8.32 (3.95, 17.53)	<0.0001	4.76 (1.98, 11.45)	0.0069
Eye surgery				
No	Ref.			
Yes	6.46 (3.96, 10.55)	<0.0001	3.48 (1.99, 6.08)	0.0018
Refractive error				
Emmetropia	Ref.			
Moderate-to-high hyperopia	2.87 (1.49, 5.52)	0.004	2.65 (1.29, 5.42)	0.0258
Moderate/high myopia	1.80 (1.11, 2.91)	0.023	1.80 (1.15, 2.82)	0.0303
Race				
Non-Hispanic White	Ref.			
Mexican American	0.58 (0.36, 0.96)	0.041	1.09 (0.63, 1.87)	0.7722
Non-Hispanic Black	0.58 (0.28, 1.21)	0.16	0.84 (0.38, 1.82)	0.6606
Other	0.41 (0.16, 1.04)	0.071	0.59 (0.22, 1.60)	0.3305
Routine place for healthcare				
No	Ref.			
Yes	8.86 (2.02,38.79)	0.007	5.58 (1.25, 24.83)	0.0505
Sex				
Female	Ref.			
Male	1.06 (0.6, 1.86)	0.85	1.29 (0.66, 2.52)	0.4759
Education				
Less than high school	Ref.			
High school graduate	1.05 (0.46, 2.38)	0.914	1.16 (0.50, 2.71)	0.7432
Some college or AA	0.80 (0.40, 1.61)	0.54	1.09 (0.59, 2.03)	0.7799
College grad. or above	0.93 (0.50, 1.76)	0.832	1.29 (0.58, 2.88)	0.5448
Poverty income ratio				
<1.3	Ref.			
1.3–3.5	2.77 (1.33, 5.79)	0.011	1.95 (0.97, 3.94)	0.0941
≥3.5	1.48 (0.93, 2.38)	0.111	1.67 (0.93, 3.01)	0.1227
Obesity status				
Normal	Ref.			
Overweight	0.76 (0.48, 1.20)	0.248	0.68 (0.41, 1.13)	0.1735
Obesity	0.84 (0.45, 1.59)	0.605	0.99 (0.49, 2.01)	0.9874
Diabetes				
No	Ref.			
Yes	1.3 (0.76, 2.23)	0.351	0.72 (0.37, 1.41)	0.3653
CVD				
No	Ref.			
Yes	1.8 (1.02, 3.2)	0.052	0.79 (0.46, 1.36)	0.4189
Retinopathy				
No	Ref.			
Yes	2.31 (0.59, 9.05)	0.239	1.99 (0.36, 10.90)	0.4467
High cholesterol				
No	Ref.			
Yes	1.81 (1.16, 2.81)	0.013	1.48 (0.96, 2.29)	0.106

Crude model: Univariate logistic regression model; Adjusted model: Multiple logistic regression model that includes all independent variables; Ref.: Reference level of a categorical variable; OR: Odds ratio; LCL: 95% lower confidence limit; UCL: 95% upper confidence limit; CVD: Cardiovascular disease; AA: Associate of arts degree.

Table 3 Multiple logistic regression model by surgery status

Parameters	Eye surgery=Yes OR (LCL, UCL)	*P*	Eye surgery=No OR (LCL, UCL)	*P*
Age group (y)				
<65	Ref.		Ref.	
65–75	4.43 (1.44, 13.61)	0.0154	2.94 (1.32, 6.56)	0.0135
75+	4.25 (1.32, 13.67)	0.0228	7.10 (3.09, 16.31)	0.0001
Emmetropia	Ref.		Ref.	
Moderate/high hyperopia	0.97 (0.12, 7.94)	0.9756	1.75 (1.00, 3.05)	0.0617
Low myopia	1.65 (0.75, 3.61)	0.2204	1.69 (0.70, 4.11)	0.257
Moderate/high myopia	1.40 (0.66, 2.95)	0.3859	1.92 (1.05, 3.54)	0.0443

The model was adjusted for all other covariates including sex, race, routine place for healthcare, poverty income ratio, obesity, diabetes, cardiovascular disease, retinopathy, and high cholesterol. OR: Odds ratio; UCL: 95% upper confidence limits; LCL: 95% lower confidence limits; Ref.: Reference categories.

Table 4 Multiple logistic regression model by refractive error status

Parameters	Emmetropia OR (LCL, UCL)	*P*	Moderate/high myopia OR (LCL, UCL)	*P*
Age group (y)				
<65	Ref.		Ref.	
65–75	4.81 (1.88, 12.28)	0.003	2.83 (1.52, 5.27)	0.0031
75+	7.09 (3.00, 16.73)	0.0001	3.85 (1.67, 8.87)	0.004
Eye surgery				
No	Ref.		Ref.	
Yes	3.60 (1.69, 7.65)	0.0027	3.01 (1.56, 5.84)	0.0031

The model was adjusted for all other covariates including sex, race, routine place for healthcare, poverty income ratio, obesity, diabetes, cardiovascular disease, retinopathy, and high cholesterol. OR: Odds ratio; UCL: 95% upper confidence limits; LCL: 95% lower confidence limits; Ref: Reference categories.

who underwent eye surgery exhibited a significantly higher likelihood of ERM, with an OR of 3.48 (95%CI: 1.99, 6.08, *P*=0.0018). Additionally, compared to emmetropia or normal vision, refractive error categories such as moderate to high hyperopia and moderate to high myopia were significantly associated with an increased probability of ERM, with ORs of 2.65 (95%CI: 1.29, 5.42, *P*=0.0258) for hyperopia and 1.80 (95%CI: 1.15, 2.82, *P*=0.0303) for myopia, respectively.

Type III effect tests were conducted to examine the interaction terms between age group, refractive error, and eye surgery in the multiple logistic regression models. The analysis revealed that the interaction between eye surgery and refractive error was statistically significant (*P*<0.0001), indicating that the association of refractive error on ERM may differ significantly between participants with and without eye surgeries. Consequently, subgroup analyses were performed separately for participants with and without eye surgeries (Table 3). Among participants without eye surgeries, moderate to high myopia remained significantly associated with a higher likelihood of ERM (OR=1.92, with a 95%CI: 1.05, 3.54, *P*=0.0443). However, among participants who had undergone eye surgery, moderate to high myopia did not exhibit a statistically significant effect on ERM. Similarly, logistic regressions were conducted for emmetropia and moderate to high myopia groups separately to assess the effect of eye surgery on ERM (Table 4). It was found that having undergone eye surgery was associated with a higher OR in the emmetropia group (OR=3.60, with a 95%CI: 1.69, 7.65) compared to the moderate to high myopia group (OR=3.01, with a 95%CI: 1.56, 5.84).

DISCUSSION

The formation of an ERM is a complex process driven by cellular and molecular events at the vitreoretinal interface. A key initiating step involves the activation of glial cells, primarily Müller cells and astrocytes, in response to posterior vitreous detachment or other retinal stimuli[32]. These activated glial cells can migrate to the retinal surface and undergo a myofibroblastic transformation, a critical step in which they acquire contractile properties similar to smooth muscle cells. This transformation is largely orchestrated by cytokines, with the transforming growth factor-beta (TGF-β) pathway playing a central role in promoting this pathogenic cellular differentiation[33-34]. Concurrently, these newly formed myofibroblasts, along with other cell types like retinal pigment epithelial cells, contribute to the excessive deposition of extracellular matrix (ECM) components. This leads to an accumulation of collagen, particularly type I, and fibronectin, which form the scaffold of the contractile membrane[35-38]. The integrity of this newly formed tissue is further influenced by genetic predispositions. For instance, polymorphisms in genes encoding matrix metalloproteinases (MMPs) can alter ECM remodeling, and variations in collagen-related genes such as *COL1A1* and lysyl oxidase-like 1 (*LOXL1*) have been associated with a compromised vitreoretinal interface, potentially increasing the susceptibility to ERM development[39-42].

Our research investigated the association of various potential risk factors on ERM using a representative sample from the United States. Initially, our unadjusted models demonstrated statistically significant effects among certain variables, including race (Mexican American *vs* Non-Hispanic White), routine place for healthcare, PIR (1.3–3.5 *vs* <1.3), and high cholesterol, alongside the three primary risk factors: age, eye surgery, and refractive error. However, upon adjusting for all covariates, our multiple logistic regression models revealed that only age, eye surgery, and refractive error were significantly associated with a heightened probability of ERM occurrence. This indicates that these three factors stand out as the primary independent risk factors for ERM based on the available data in our survey.

The factors that showed significance in crude models but not in adjusted models may suggest that their effects could be associated by other variables. For example, hypercholesterolemia and BMI were found to be linked to ERM solely in the univariate (crude model) analysis but not in the multivariate analysis (adjusted models)[13]. Similarly, although previous studies have indicated that education is significantly associated with a higher prevalence of ERM[42] this association was not significant in our study. It is possible that differences in educational systems between the US and China contribute to varying effects on ERM, as Chinese students generally dedicate more time to academic studies[43]. Additionally, while a study utilizing the Singapore Malay Eye Study reported that females were significantly associated with a higher prevalence of ERM[16], we did not find this association to be significant in our study.

Among all the potential risk factors examined, three factors remained significant even after adjusting for other covariates. Consistent with numerous previous studies[3,5,15,42,44-45], advancing age emerges as an independent predictor significantly linked to an elevated likelihood of ERM. Cataract surgery has also been consistently reported as a significant factor[3,8,11,46], aligning with our findings indicating that the odds of ERM occurrence in eyes that underwent surgery beforehand are 3.48 times higher compared to those without surgery. Moreover, our study aligns with existing literature in demonstrating that increasing myopic refraction is significantly associated with primary ERM[15,17,45]. Additionally, hyperopia is also associated with a higher prevalence of ERM[44]. It is worth noting that hyperopic patients may exhibit stiffer posterior segments and altered extracellular matrix (ECM) dynamics. These factors could potentially contribute to a predisposition for ERM development, particularly following eye surgery. Further research into the specific mechanisms linking hyperopia, ECM fragility, and postoperative ERM risk is warranted.

In multivariate logistic regression models, both refractive errors and surgery demonstrated significant effects, with their interaction effects on ERM also proving significant. Hence, the correlation of one of these factors on ERM may vary significantly depending on the status of the other factor. We observed that in the group without eye surgery, patients with moderate or high myopia exhibited a notably higher OR (1.92) for developing ERM, whereas this association was weakened for patients who underwent surgery. It is possible that the alteration of ocular anatomy or the healing process linked with eye surgery could alter the relationship between refractive errors and the onset of ERM, thereby reducing the observed association among patients who have had surgery. Furthermore, when evaluating the effects of eye surgery on ERM within refractive error groups, both the emmetropia and moderate/high myopia groups displayed significant associations between surgery and ERM. While in the emmetropia group, eye surgery showed higher OR than in moderate or high myopia group. Eye surgery in emmetropic eyes showed a higher OR (3.6) for ERM development compared to moderate or high myopia (OR=3.01). This indicates that prior eye surgery significantly elevates ERM risk, even in individuals with initially normal vision, a crucial consideration for clinicians. Given the increased risk of ERM after eye surgery, especially in emmetropic patients (OR=3.60), more intensive post-operative monitoring, including detailed retinal imaging, may be warranted. Patient education should specifically address the increased risk of ERM after surgery, even in those with previously normal vision, and emphasize the importance of reporting any visual changes. Tailoring this education based on refractive error status could further enhance patient understanding and compliance with follow-up care.

Combining these pieces of evidence, we can infer that while eye surgery may weaken the association between refractive errors and the development of ERM, it does not completely eliminate the risk posed by either factor. This suggests that eye surgery acts as a moderator in the relationship between refractive errors and the development of ERM. The alteration of ocular anatomy or the healing process associated with eye surgery likely modifies this relationship, leading to a reduction in the observed association among patients who have undergone surgery. However, it is evident that refractive errors still play a significant role in the development of ERM, regardless of surgical status. Such insights are crucial for optimizing patient management strategies and improving visual outcomes in individuals at risk of ERM. To our best knowledge, this is the first study to investigate the interaction effect between refractive errors and eye surgery on the development of ERM among this population.

Strengths and Limitations This study has several notable strengths. First, it is the first to investigate the interaction effects between the risk factors of refractive error and surgery on ERM. Additionally, we utilized a weighted logistic regression model for analysis, considering that the NHANES database comprises multi-stage complex sampling data, and we adjusted for other covariates, thereby enhancing the accuracy and reliability of the conclusions drawn in this study. Furthermore, we analyzed nationally representative survey data spanning a 4-year period, and the relatively large sample size of NHANES enabled us to conduct adequate subgroup analyses. NHANES employed standardized and validated protocols. However, this study is not without limitations. First, the analysis was based on cross-sectional datasets, which may hinder the determination of any temporal association, thus limiting the ability to establish causality. Additionally, some variables in this study were derived from questionnaires and self-reports, rendering them susceptible to bias.

Historically, ERM were identified via clinical observation and fundus photography. The advent of optical coherence tomography (OCT) revolutionized diagnosis, providing high-resolution imaging for increased reliability and specificity, even in early stages. Today, OCT-based criteria are used for ERM classification, significantly improving our understanding of ERM. Our study's reliance on fundus photography, while methodologically rigorous, is a limitation, as it is less sensitive than modern OCT for detecting subtle ERM. This may have led to an underestimation of ERM prevalence. The images, captured on a Canon ophthalmic system and assessed by trained graders, provide a reliable analysis of the NHANES 2005–2008 cohort. While we recommend future studies incorporate OCT, our findings still offer a valuable contribution to the understanding of ERM epidemiology in the US.

In summary, our study investigated significant risk factors for ERM using a large dataset, offering insights into the interaction effects between two key factors: refractive error and history of eye surgery. Our findings suggest that eye surgery might act as a potential moderator of refractive error status in the development of ERM. Further investigation is necessary to fully comprehend the mechanisms behind this interaction and its implications for clinical management. For example, longitudinal studies that monitor intraocular transcription factors before and after eye surgery across varying degrees of refractive errors could offer valuable insights into the temporal relationships and causal pathways linking refractive errors, eye surgery, and the development of ERM. Such research could ultimately inform targeted strategies to prevent and manage ERM effectively.

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