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The Prevalence and Risk Factors of Epiretinal Membranes: Pooled Data from Population-Based Studies

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Running head: The prevalence and risk factors of ERM

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Abstract

Objective: The prevalence and risk estimates of epiretinal membranes (ERMs) are largely heterogeneous. The objective of this study was to aggregate the prevalence and risks of ERMs, and determine the possible causes of the varied estimates.

Design: Systematic review and meta-analysis.

Data sources: The search strategy was designed prospectively. We searched PubMed, Embase and Web of Science databases and reviewed reference lists of the literature selected.

Study selection: Surveys published in any language were included if they had a population-based design, and reported the prevalence of ERM from retinal photography with or without optical coherence tomography (OCT). Eligibility evaluation was conducted independently by two investigators.

Data extraction: The literature search generated 2,144 records, and thirteen population-based studies comprising 49,697 subjects were finally included.

Results: The pooled age-standardised prevalence estimates of earlier ERM (cellophane macular reflex, CMR), advanced ERM (preretinal macular fibrosis, PMF) and any ERM were 6.5% (95%CI: 4.2 to 8.9), 2.6% (95%CI: 1.8 to 3.4), and 9.1% (95%CI: 6.0 to 12.2), respectively. In the subgroup analysis, race and photography modality contributed to the variation in the prevalence estimates of PMF, while the WHO regions and image reading methods were associated with the varied prevalence of CMR and any ERM. Meta-analysis showed that only greater age and female significantly conferred a higher risk of ERMs.

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Conclusions: Our findings suggest that ERMs are relatively common among aged population. Race, image taking and reading methodology may play important roles in influencing the large variability of ERM prevalence estimates.

***Keywords**:* Epiretinal membranes, Prevalence, Risk factors, Meta-analysis, Population-based

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Strengths and limitations of this study

- This study is the first systematic review and meta-analysis that pools the age-standardised prevalence of epiretinal membrane (ERM) from population-based studies.
- The investigators strictly adhered to the guidelines for systematic review and meta-analysis. All included surveys were of desirable quality and large-scale.
- We aggregated not only the prevalence of ERM but also its subtype estimates (CMR and PMF).
- Lack of studies from the African and European continents makes it difficult to project ERM prevalence estimates worldwide.
- We are unable to aggregate the data on the relationship between ERM prevalence and visual acuity impairment due to lack of studies on their association.

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INTRODUCTION

Epiretinal membranes (ERMs) are common retinal conditions that can impair visual acuity in old persons. ERMs may occur without any antecedent ocular conditions or surgical procedures, termed idiopathic or primary ERM. Those associated with other eye diseases (e.g. retinal vascular occlusion, diabetic retinopathy), trauma or surgery are referred to as secondary ERMs. Under ophthalmoscopy, earlier stage ERMs present as increases of the light reflex from the retina inner surface, which is called cellophane macular reflex (CMR). As the membrane progresses, it can contract and create superficial retinal folds. Massive folds make the retinae appear with gray linear reflexes, which are termed preretinal macular fibrosis (PMF). For most cases at the advanced stage, fibrotic membranes generate tangential traction on the macula, causing macular oedema, metamorphopsias and central vision impairment[1].

After the landmark study Beaver Dam Eye Study (BDES) reported the prevalence of ERM in 1994[2], several large-scale population-based studies investigated the epidemics of ERMs in Singapore[3 4], Japan[5], Australia[6 7] and China[8 9]. Most of these surveys introduced retinal photography, and the same classification scheme for ERMs as that in BDES. However, considerable variation in ERM epidemiology across races and regions has been noted. For example, in the population-based Multi-Ethnic Study of Atherosclerosis (MESA)[10], ERM was as prevalent as 39.0% in Chinese, 27.5% in Caucasian, 26.2% in Africans, and 29.3% in Hispanics. These estimates were much higher than those in the Handan Eye Study in North China (3.4%)[8], the Blue Mountains Eye Study (BMES) in Australia (7%)[7], and the Los Angeles Latino Eye

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Study in the US (19.9%)[11]. Reasons for such variability may be complex, but it has been considered to be associated with the differences in study design, population characteristics, as well as the definition of cases. Moreover, some studies did not compute the age-standardised estimates of prevalence, making direct comparisons between studies difficult.

Estimating the prevalence and risk of ERM is perhaps the first step to better clinical management, and understanding the burden of this disease. Therefore, we conducted the present analysis to synthesise data from population-based studies to estimate the prevalence of ERMs, to identify underlying factors causing prevalence variability as well as major risk factors for ERMs.

METHODS

In this study, we followed the preferred reporting items for systematic reviews and meta-analyses (the PRISMA statement, see Supplementary Information)[12].

Search strategy and selection criteria

The search strategy was designed prospectively. We searched all reports on population-based studies for the prevalence of ERMs using PubMed, Embase and Web of Science from inception to July 2016. All English language articles were retrieved using pre-specified search terms. The search terms and strategies were showed in detail in Supplementary information. The reference lists of all included articles were reviewed, and the full texts of potentially related papers were examined.

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We designed a set of inclusion and exclusion criteria for literature screening. Studies included were those population-based surveys in which ERMs were diagnosed on the basis of retinal color photography or a combination of optical coherence tomography (OCT). Studies without population-based (e.g., hospital- or specific population-based) design were excluded. Eligibility evaluation was conducted independently by two investigators (W.X and X.Y.C) using pre-designed forms. Any disagreements were resolved by consensus.

Quality assessment and data extraction

There were no consensus guidelines on evaluating cross-sectional surveys, so we adopted the quality assessment criteria by de Weerd et al[13] and Rogers S et al[14]. The criteria were designed to cover the following four aspects (Supplementary): 1) Representing the general population. To achieve this, studies should be undertaken using population registries, inhabitants of a specific area, or people registered with a general practice. 2) Appropriately recruiting the population. Recruitment was considered appropriate if it was performed randomly or consecutively rather than for convenience or from volunteers. 3) Adequate response rate (>70%). 4) Objective documentation of the outcomes. That means documentation of ERMs by retinal photography according to standardised protocols and graded according to standard definitions. Fulfillment of 3 or 4 points was considered adequate quality. Quality of all included studies was assessed independently by two investigators (W.X and X.Y.C) using quality assessment forms based on the aforementioned criteria.

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For included studies, data were extracted independently by two reviewers on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, Washington, USA). Discrepancies were resolved by consensus. We extracted the following data from each study: country, year, sample size, age range, race/ethnicity, examination methods, crude prevalence of ERM and odds ratios (ORs) of risk factors. Our key outcomes of interest were the prevalence and risk factors of ERM.

Data synthesis and statistical analysis

Study-specific and pooled-data estimates of the prevalence of any ERM, CMR and PMF were directly age-standardised to WHO World Standard age-structure[15]. A random effect model was adopted to calculate pooled prevalence and odds ratios (ORs) for the risk of ERM. Statistical analysis was performed with STATA software (version 13.0, StataCorp LP, TX, USA). The I^2 statistic was used to estimate heterogeneity in pooled studies, and to further explore potential sources of heterogeneity by subgroup analysis.

RESULTS

Figure 1 exhibits the results of the search strategy. The systematic searches yielded 2,144 records. After removing 906 duplications, 1,238 studies were screened through titles and abstracts. Among them, we ruled out 1,186 irrelevant articles and reviewed the left 52 studies in full text. Finally, we identified 13 studies[2 3 5-11 16-18] that were eligible for inclusion (Table 1). Across the 13 studies, sample sizes ranged from

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1,543[5] to 6,565[8], including 49,697 individuals at risk of ERMs. Two studies (Funagata and Hisayama) scored 3 points in the quality assessment owing to their relatively low response rate, while the others all scored 4 points (see Supplementary Information). The Beixinjing Study[18] reported specifically on the prevalence of primary (idiopathic) ERM, whereas the other 12 study documented the prevalence of any ERM (i.e. both idiopathic and secondary ERM). Geographically, the WHO regions of Western Pacific Region and the Americas were heavily represented, with all the 13 studies done in these two regions. No studies had been done in the European, Africa, South-East Asian or Eastern Mediterranean regions. Of these 13 studies, 12 studies (all except Funagata[5]) assessed ERM using both eyes of each participant; 9 studies performed photography after pharmacologic mydriasis. The methods of photography varied between studies, with 4 studies using stereo-photographing (vs. 9 using non-stereo photography), 4 studies using 30-degree camera (vs. 9 using 45-degree camera) and 6 using film photography (vs. 7 using digital photography). Retinal images were graded at the reading centres at the University of Wisconsin-Madison (3 studies), the University of Sydney (7 studies) or by independent ophthalmologists/trained graders (4 studies). Characteristics of the included studies are summarised in Table 1.

Analyses of the 12 studies concerning any ERM (except the Beixinjing Study exclusively on idiopathic ERM) showed that the overall age-standardised prevalence of CMR was 6.5% (95% CI 4.2-8.9), PMF was 2.6% (95% CI 1.8-3.4), and any ERM was 9.1% (95% CI 6.0-12.2) (Table 2). Specific to primary ERM, the pooled prevalence of CMR, PMF and any primary ERM were 7.1% (95%CI 3.3-10.8), 2.0%

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(95%CI 1.3-2.8) and 9.2% (95%CI 4.7-13.8), respectively. Six studies reported the prevalence of secondary ERM, and all explicitly defined the population at-risk as those with other ocular conditions (e.g. retinal vascular disease, retinal detachment) and cataract surgery. The aggregated data showed the prevalence of secondary CMR, PMF and any ERM were 11.4% (95%CI 4.4-18.5), 5.1% (95%CI 3.5-6.6) and 16.6% (95%CI 9.7-23.6), respectively.

The age-standardised prevalence of ERMs by subgroups of interest was shown in Table 3. The aggregated prevalence of any ERM varied according to the WHO regions, different image acquisition and grading method. Three studies from the Americas in which retinal images were also graded by the reading centre at the University of Wisconsin-Madison[2 10 11] documented a much higher prevalence (14.4%) than those from Western Pacific region (8.5%). Of note, this trend was attributed to the increased prevalence of CMR in the Americas (14.3% vs. 4.0% in Western Pacific region). For the more advance stage of CMR, studies in which film photography was used (1.5%) synthesised a lower prevalence PMF than that used digital photography (3.1%). PMF was slightly more prevalent in Asians (3.6%) than in Caucasians (2.5%). There were two studies from China introduced OCT to confirm ERM[8 9]. Intriguingly, studies with a combination of OCT demonstrated lower prevalence in both CMR (3.4% vs. 7.2% without OCT) and PMF (1.8% vs. 2.8% without OCT).

As expected, individuals with greater age were more likely to have any ERM (OR=1.19 per year increase, 95%CI 1.13-1.26). Compared to males, females had a

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higher risk of ERM (OR=1.34, 95%CI 1.17-1.53). Smokers had an unexpected lower risk of ERM compared to non-smokers (OR=0.67, 95%CI 0.58-0.78). Other factors analysed, including myopia, hyperopia, hypertension, diabetes, alcohol intake, early age-related macular degeneration, body mass index and hyperlipidemia, were not associated with the risk of any ERM (Table 4).

DISCUSSION

This study provides estimates for the prevalence of ERMs and its two stages using data from most appropriate population-based studies in the literature. Using data from 13 studies with 49,697 participants, we estimated the age-standardised prevalence of any ERM to be as high as 9.1%, with CMR and PMF as 6.5% and 2.6%, respectively. Race, retinal image taking and grading method were responsible for the variation of the prevalence estimates. Of the risk factors analysed, greater age and female sex were significantly associated with higher risk of ERMs.

The prevalence of ERM has been documented over the last 30 years in several population-based surveys. However, these estimates have varied considerably across studies. For example, the prevalence of any ERM has been estimated to be 35.7% in Latinos aged 70 to 79 years[11], while among Japanese of the same age it has been reported to be 6.8%[17]. There is a need to synthesise the existing data to form an age-standardised estimate of this prevalence and to explore possible sources of heterogeneity. In this review, we identified 13 eligible studies with favorable quality, but they were largely conducted in Pacific Rim countries (the USA, Australia, Japan,

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Singapore and China). Further study is warranted in European and African regions to generate an accurate projection of worldwide ERM prevalence, and as such it falls beyond the scope of this review.

Previously, ERM susceptibility has been reported to vary between ethnic groups. MESA[10] was the only study that directly compared the racial and ethnic differences of ERM prevalence within the same cohort. It reported a significantly higher prevalence rate for Chinese ethnicity (39.0%), followed by Hispanic (29.3%), Caucasian (27.5%), and African (26.2%) ethnicity. However, the sample sizes of each ethnic group were relatively small, particularly in the Chinese subgroup (n=724). However, our data found ethnicity to be less likely associated with ERM prevalence disparities. Our pooled data showed the prevalence difference between Asians and Caucasians for CMR and any ERM was negligible, indicating that race/ethnicity may have a limited role in ERM prevalence.

Our review shows that the differences in ERM prevalence between studies may be partly attributed to their methodological characteristics. Although all included studies consistently adopted the same classification scheme for ERM as that in the Beaver Dam Eye Study[2], their retinal images were graded in different fashions: 3 studies were read by the grading centre of the UW-Madison in the US, 6 at the grading centre at the University of Sydney, and the others graded by ophthalmologists or independently trained graders. In our subgroup analysis, three studies graded at the reading centre at UW-Madison pooled an extremely high prevalence of CMR and any

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ERM (14.3% and 14.4%, respectively). Due to all three studies from the Americas, differences in image reading patterns directly led to the regional differences in CMR and any ERM prevalence estimates. Taken account of the minimal difference in the synthesised PMF prevalence across reading centres, we could speculate that the substantial differences in estimated overall ERM prevalence originated from the systematic differences in grading CMR from retinal images. Accordingly, there is insufficient evidence to conclude whether the regional difference in ERM prevalence is attributable to the difference in geographical location *per se* or to the grading methodology. To address this issue, universal criteria for grading CMR and differentiation from normal fundus manifestations may need to be further standardised.

Interestingly, for more advanced stages of ERM, the pooled prevalence of PMF from different reading centres and regions were quite similar, but this prevalence was more likely to be affected by race and photography modality (film vs. digital). Asians had a slightly higher prevalence of PMF (3.6% vs. 2.0% in Caucasians). Furthermore, digital photography seemed to be better in detection of PMF compared to film photography.

Optical coherence tomography (OCT) has been applied as the gold standard in diagnosing vitreoretinal interface diseases in recent epidemiological studies[19-21]. An unexpected finding to comment on was that two studies using OCT produced much lower prevalence rates of CMR, PMF or any ERM compared to the others without it. In clinical practice, OCT was superior to retinal photography in screening epiretinal

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irregularities[22] and detecting subtle ERMs among special cases, such as those with uveitis[23]. It follows that theoretically; studies using both photography and OCT should detect more persons with ERMs. A hypothesis explaining this apparent contradiction may be that OCT may exclude ERM suspects based on color retinal images. It follows that further research is needed to assess the performance and cost-effectiveness of OCT in diagnosing ERMs prior to its adoption as the gold-standard test for epidemiological studies across the board.

For pooled risk estimates, our data showed that only the associations between age and sex, and the risk of any ERM were significant. Older and female individuals had higher risk of ERM from the meta-analysis (OR=1.19 and 1.34, respectively). Owing to the clear increase in the prevalence of ERMs with increasing age of the population, ERM needs to be considered in a similar vein as age-related macular degeneration, a condition that significantly affects an aging population. In terms of systemic and ophthalmic risk factors, no significant association was found between ERM and diabetes, hypertension, hyperlipidemia, BMI, myopia and early AMD.

Cigarette smoking, an important public health problem, is a well-documented risk factor for several eye diseases, including age-related macular degeneration[24] and thyroid-associated ophthalmopathy[25]. However, smoking can also serve as a protective factor against the development of pterygium[26]. Although our analysis found a negative association of ERM and smoking, this may be explained by a survival bias

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among smokers that cannot be excluded from cross-sectional analysis, and should not discredit the importance of smoking cessation across populations.

Strengths of the present study include the large sample size, specific and inclusive nature of criteria for population-based studies, and the inclusion of ERM subtype estimates (CMR and PMF). The pooled data provide a precise estimate of the ERM age-standard prevalence in the American and Asian-pacific population. However, our study contains several limitations as well: firstly the lack of studies from the African and European continents makes it difficult to project these prevalence estimates worldwide. Second, samples from different study designs had considerably different inclusion criteria, participant selection processes, and study protocols. For example, sample populations were found to have considerably differences in proportions of subjects with cardiovascular disease or diabetes complications[9-11]. Third, although ERM, especially PMF, can cause moderate to severe visual impairment and metamorphopsias[4], most studies did not quantitatively analysed the association between ERM and visual acuity. In this study, we are consequently unable to aggregate the data on their relationship.

CONCLUSIONS

In conclusion, our current study provides the first estimate of ERM and its different subtypes based on a pooled analysis of more than 40,000 participants from 13 studies in the US and the Western Pacific region. Our study shows that 9.1% of general population had some form of ERM, 6.5% had CMR, and that 2.6% had the

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advanced form of PMF. These data suggest that ERMs have the potential to be a major cause of visual impairment. In some specific regions, such as Europe and Africa, robust evidence for the prevalence and risk of ERM is absent. To address these gaps in the evidence, high quality epidemiological research is needed that focuses specifically on these countries using standardised measures of diseases. Finally, we confirmed the significance and impact of two major risk factors, being age and sex, on the risk of any form of ERM.

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Acknowledgments

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Author Contributions

Author MGH conceived and designed the study; Authors WX and XYC performed the literature search, study selection, data extraction and synthesis. Author WX prepared the draft manuscript; Authors WY, ZTZ and MGH were involved in the revision and final preparation of the manuscript.

Competing financial interests

The Authors have no competing financial interests to report.

Data Sharing Statement

No additional unpublished data are available

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Table 1. Characteristics of included studies

Study	Country	Year	N(%male)	Age range	Race/Ethnicity	Eye examined	Pupil dilation	Fundus photography	Image grading	OCT used
BDES	USA	1987-88	4802	43-84	Caucasian	Both	Yes	30-degree; stereo; ≥3 fields; film	Reading center at University of Wisconsin	No
Beixinjing*	China	2010-11	3326 (44.5)	50-98	Asian	Both	Yes	45-degree; non-stereo; 2 fields; digital	Ophthalmologists	No
BMES	Australia	1992-93	3490 (43.8)	≥49	Caucasian	Both	Yes	30-degree; stereo; 6 fields; film	Reading center at University of Sydney	No
Funagata	Japan	2000-02	1543 (43.4)	≥35	Asian	Right eye	No	45-degree; non-stereo; 1 field; film	Reading center at University of Sydney	No
HES	China	2006-07	6565 (46.7)	≥30	Asian	Both	Part of*	45-degree; non-stereo; 2 fields; digital	Ophthalmologists	Yes
Hisayama	Japan	1998	1765 (38.5)	≥40	Asian	Both	Yes	45-degree; non-stereo; 1 field; film	Ophthalmologists	No
Jiangning	China	2012-13	2005 (43.7)	≥50	Asian	Both	No	45-degree; non-stereo; ≥2 fields; digital	Trained graders	Yes
LALES	USA	2000-03	5982 (42.0)	≥40	Hispanic	Both	Yes	30-degree; stereo, 3 fields; film	Reading center at University of Wisconsin	No
MESA	USA	2002-04	5960 (47.9)	45-84	White, Black; Asian; Hispanic	Both	No	45-degree; non-stereo; 2 fields; digital	Reading center at University of Wisconsin	No
SCES	Singapore	2009-11	3353	40-80	Asian	Both	Yes	45-degree; non-stereo; 2	Reading center at	No

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								fields; digital	University of Sydney	
SiMES	Singapore	2004-06	3265 (48.1)	40-80	Asian	Both	Yes	45-degree; non-stereo; 2 fields; digital	Reading center at University of Sydney	No
SINDI	Singapore	2007-09	3328 (50.2)	40-80	Asian	Both	Yes	non-stereo; 2 fields; digital	Reading center at University of Sydney	No
VIP	Australia	1992-97	4313 (47.0)	≥40	Caucasian	Both	Yes	30-degree; stereo; 2 field; film	Reading center at University of Sydney	No

* Data only available for primary ERMs.

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Table 2. Age-standardised prevalence of epiretinal membrane by study

Study	Year	N at-risk	Crude prevalence (%)			Age-standardised prevalence (%, 95%CI)		
			CMR	PMF	Any ERM	CMR	PMF	Any ERM
All ERM								
BDES	1987-88	4802	-	-	-	4.8 (4.3-5.4)	1.7 (1.3-2.0)	6.4 (5.8-7.1)
BMES	1992-93	3490	4.8	2.7	7.0	3.8 (3.2-4.4)	1.7 (1.3-2.1)	5.5 (4.8-6.2)
Funagata	2000-02	1543	4.0	1.5	5.4	2.7 (1.9-3.4)	1.1 (0.6-1.5)	3.7 (2.8-4.6)
HES	2006-07	6565	2.2	0.7	3.4	2.3 (1.8-2.8)	0.6 (0.4-0.7)	3.5 (2.9-4.0)
Hisayama	1998	1765	3.2	0.9	4.0	2.2 (1.6-2.9)	0.5 (0.2-0.8)	2.8 (2.1-3.5)
Jiangning	2012-13	2005	5.0	3.4	8.4	4.5 (3.7-5.4)	3.1 (2.4-3.9)	7.6 (6.5-8.7)
LALES	2000-03	5982	16.3	2.2	18.5	16.6 (15.7-17.6)	2.5 (2.0-2.9)	19.0 (18.0-20.0)
MESA	2002-04	5960	25.1	3.8	28.9	21.5 (20.1-22.5)	3.0 (2.6-3.4)	24.5(23.4-25.6)
SiMES	2004-06	3265	5.8	5.9	11.8	4.7 (4.0-5.3)	4.6 (4.0-5.3)	9.3 (8.3-10.2)
SCES	2009-11	3353	-	-	-	7.0 (6.1-7.9)	7.5 (6.6-8.3)	13.0 (11.9-14.2)
SINDI	2007-09	3328	5.4	4.8	10.2	4.7 (4.0-5.3)	4.1 (3.4-4.7)	8.8 (7.9-9.7)
VIP	1992-97	4313	4.8	1.7	6.0	3.8 (3.3-4.4)	1.4 (1.1-1.8)	4.9 (4.4-5.5)
Pooled estimates	**NA**	**46371**	**-**	**-**	**-**	**6.5 (4.2-8.9)**	**2.6 (1.8-3.4)**	**9.1 (6.0-12.2)**
Primary ERM								

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BDES	1987-88	4125	-	-	-		4.5 (3.9-5.1)	1.3 (1.0-1.6)	5.8 (5.1-6.5)
Beixinjing	2010-11	3326	0.6	0.6	1.0		0.6 (0.3-0.9)	0.4 (0.2-0.6)	1.0 (0.6-1.3)
HES	2006-07	6196	2.0	0.5	3.0		2.1 (1.6-2.6)	0.4 (0.3-0.6)	3.1 (2.6-3.7)
Jiangning	2012-13	1854	4.6	3.1	7.7		4.3 (3.4-5.2)	3.0 (2.2-3.7)	7.3 (6.1-8.4)
LALES	2000-03	5631	15.6	1.9	17.5		16.1 (15.2-17.1)	2.2 (1.8-2.6)	18.4 (17.3-19.4)
MESA	2002-04	4761	22.7	3.3	26.1		20.2 (19.1-21.3)	2.7 (2.3-3.1)	23.0 (21.7-24.1)
SiMES	2004-06	2734	5.1	4.5	9.5		4.5 (3.7-5.2)	3.8 (3.2-4.5)	8.3 (7.3-9.3)
SINDI	2007-09	2324	3.8	2.7	6.5		4.3 (3.4-5.2)	2.8 (2.1-3.5)	7.0 (5.9-8.2)
Pooled estimates	**NA**	**30951**	**-**	**-**	**-**		**7.1 (3.3-10.8)**	**2.0 (1.3-2.8)**	**9.2 (4.7-13.8)**
Secondary ERM									
HES	2006-07	269	7.1	3.7	12.3		6.7 (1.9-11.5)	3.7 (0-7.8)	11.1 (5.0-17.3)
Jiangning	2012-13	151	10.6	6.6	17.2		7.0 (3.4-10.7)	3.9 (1.2-6.6)	10.9 (6.6-15.2)
LALES	2000-03	345	27.0	7.5	34.5		19.8 (14.4-25.2)	6.1 (2.9-9.3)	25.9 (20.0-31.9)
MESA	2002-04	1199	34.3	5.8	40.1		25.1 (22.2-28.1)	3.4 (2.5-4.4)	28.6 (25.6-31.6)
SiMES	2004-06	531	9.8	13.6	23.4		5.3 (2.5-8.1)	7.1 (5.2-9.0)	12.4 (9.1-15.7)
SINDI	2007-09	1004	9.1	9.8	18.8		5.1 (3.6-6.5)	6.0 (4.2-7.8)	11.0 (8.8-13.3)
Pooled estimates	**NA**	**3499**	**-**	**-**	**-**		**11.4 (4.4-18.5)**	**5.1 (3.5-6.6)**	**16.6 (9.7-23.6)**

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Table 3. Age-standardised prevalence of epiretinal membranes by subgroups of interest

	CMR			PMF			Any ERM		
	Studies (n)	Prevalence (%, 95%CI)	I^2 (%)	Studies (n)	Prevalence (%, 95%CI)	I^2 (%)	Studies (n)	Prevalence (%, 95%CI)	I^2 (%)
Race/ethnicity									
Caucasian	4	8.9 (4.6-13.2)	99.4	4	2.0 (1.4-2.7)	88.8	4	11.0 (5.9-16.1)	99.5
Asian	8	6.5 (4.6-8.5)	98.2	8	3.6 (2.2-4.9)	98.7	8	10.5 (7.2-13.8)	99.1
WHO Regions									
The Americas	3	14.3 (3.6-25.0)	99.8	3	2.4 (1.6-3.2)	91.6	3	14.4 (5.6-23.2)	99.7
Western Pacific	9	4.0 (3.1-4.9)	94.2	9	2.7 (1.7-3.7)	98.3	9	8.5 (4.7-8.4)	98.2
Testing method									
Photography only	10	7.2 (4.2-10.1)	99.5	10	2.8 (1.9-3.7)	97.8	10	9.1 (6.0-12.2)	99.3
Photography + OCT	2	3.4 (1.2-5.5)	94.8	2	1.8 (0-3.7)	97.6	2	5.5 (1.5-9.5)	97.7
Photography									
Film	6	5.6 (2.5-8.8)	99.3	6	1.5 (0.9-2.0)	92.2	6	7.0 (3.4-10.7)	99.4
Digital	6	7.4 (3.2-11.7)	99.5	6	3.8 (1.9-5.7)	99.0	6	10.0 (5.7-14.3)	99.3
Image graded by									
RC at UW–Madison[#]	3	14.3 (3.6-25.0)	99.8	3	2.4 (1.6-3.2)	91.6	3	14.4 (5.6-23.2)	99.7
RC at USYD[##]	6	4.4 (3.5-5.4)	92.3	6	3.4 (1.9-4.9)	98.1	6	7.5 (5.1-9.9)	98.1
Ophthalmologists or trained raters	3	3.0 (1.7-4.2)	90.9	3	2.6 (1.8-3.4)	98.1	3	4.6 (2.3-6.8)	96.4

#: Reading center at University of Wisconsin-Madison;

##: Reading center at University of Sydney.

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Table 4. Pooled odds ratios for risk of any epiretinal membrane

Risk factors		Studies	OR (95%CI)	I^2 (%)
Age (per year)		5	**1.19 (1.13, 1.26)**	95.1
Sex (female)		6	**1.34 (1.17, 1.53)**	24.8
Myopia (present)		4	1.21 (0.67, 2.19)	88.9
Hyperopia (present)		3	1.23 (0.78, 1.94)	83.8
Hypertension (present)		6	1.04 (0.90, 1.20)	11.2
Diabetes (present)		6	1.13 (0.92, 1.38)	17.1
Smoking (present)		7	**0.67 (0.58, 0.78)**	0
Alcohol intake (present)		3	0.97 (0.75, 1.25)	0
Early AMD (present)		3	0.96 (0.63, 1.47)	60.7
BMI (per kg/m^2)		5	0.99 (0.98, 1.01)	0
Hyperlipidemia (present)		4	1.05 (0.99, 1.11)	62.0

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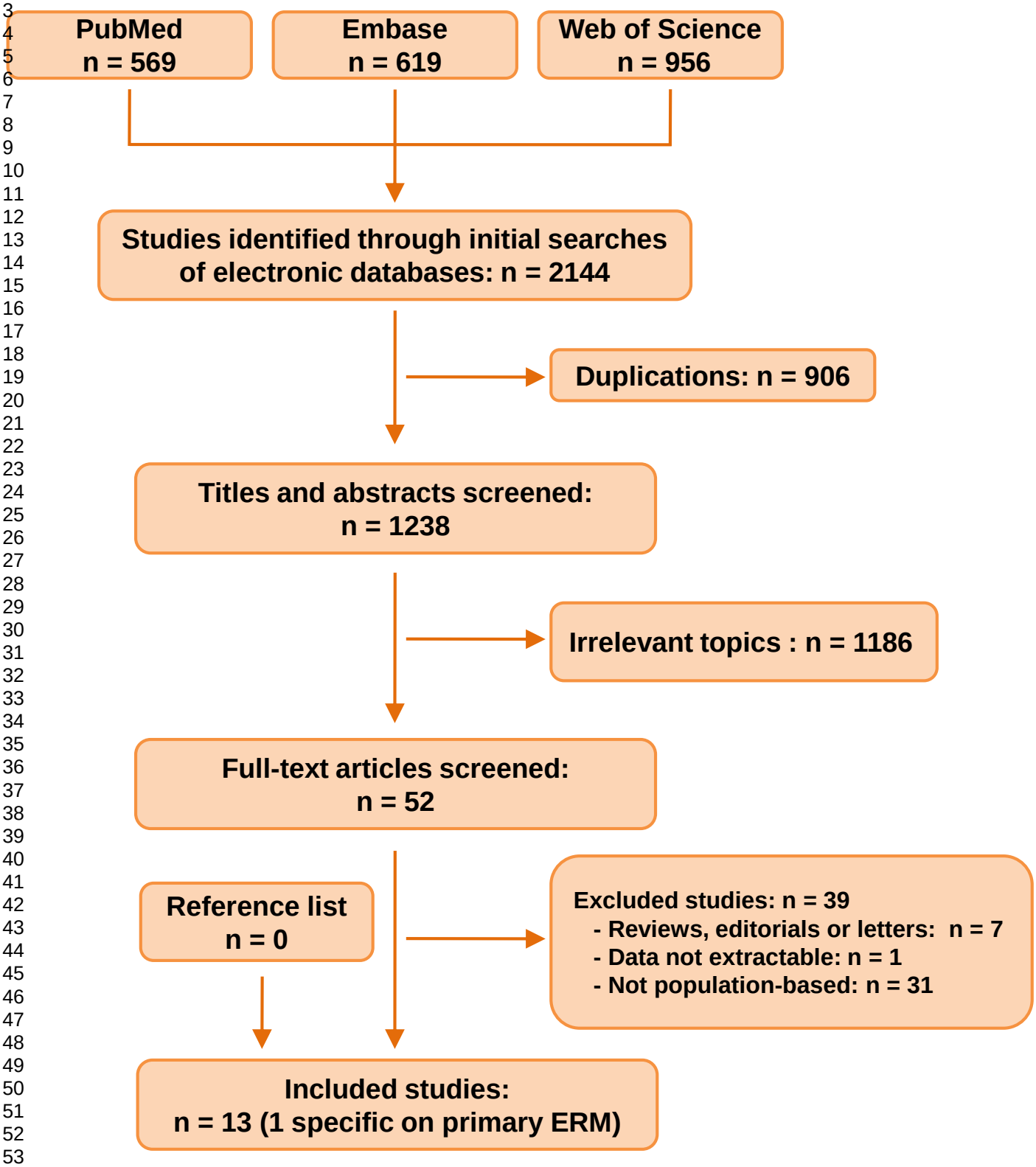
PubMed
n = 569
Embase
n = 619
Web of Science
n = 956
Studies identified through initial searches of electronic databases: n = 2144
Duplications: n = 906
Titles and abstracts screened:
n = 1238
Irrelevant topics : n = 1186
Full-text articles screened:
n = 52
Reference list
n = 0
Excluded studies: n = 39
- Reviews, editorials or letters: n = 7
- Data not extractable: n = 1
- Not population-based: n = 31
Included studies:
n = 13 (1 specific on primary ERM)

The Prevalence and Risk Factors of Epiretinal Membranes: Pooled Data from Population-Based Studies

Wei Xiao, Xiaoyun Chen, William Yan, Zhuoting Zhu, Mingguang He

Supplementary information

Note. Literature search strategy

Terms

1. prevalence, epidemiology, epidemic*, risk
2. epiretinal membrane*; erm*; ierm*; cellophane macular reflex; preretinal macular fibrosis

Search strategy

PubMed (up to July 11, 2016)

#1	prevalence Fields: Title/Abstract	459388
#2	epidemiology Fields: Title/Abstract	143403
#3	epidemic* Fields: Title/Abstract	80597
#4	risk Fields: Title/Abstract	1507737
#5	#1 OR #2 OR #3 OR #4	1973101
#6	epiretinal membrane* Fields: Title/Abstract	2259
#7	ERM Fields: Title/Abstract	3126
#8	iERM Fields: Title/Abstract	23
#9	cellophane macular reflex Fields: All fields	18
#10	preretinal macular fibrosis Fields: All fields	69
#11	#6 OR #7 OR #8 OR #9 OR #10	4935
#12	#5 AND #11	569

Embase (up to July 11, 2016)

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#1	prevalence Fields: ti, ab	609473
#2	epidemiology Fields: ti, ab	144993
#3	epidemic* Fields: ti, ab	89089
#4	risk Fields: ti, ab	2059117
#5	#1 OR #2 OR #3 OR #4	2622649
#6	epiretinal membrane* Fields: ti, ab	2491
#7	ERM Fields: ti, ab	3555
#8	iERM Fields: ti, ab	22
#9	cellophane macular reflex Fields: All fields	18
#10	preretinal macular fibrosis Fields: All fields	75
#11	#6 OR #7 OR #8 OR #9 OR #10	5570
#12	#5 AND #11	619

Web of Science (All Databases, 1980 to Jun 20, 2015)

All languages, all document types

#1	TS = prevalence	684438
#2	TS = epidemiology	1440407
#3	TS=epidemic*	100419
#4	TS=risk	2386116
#5	#1 OR #2 OR #3 OR #4	3597103
#6	TS=epiretinal membrane*	3045
#7	TS=ERM	369
#8	TS=iERM	21
#9	TS=cellophane macular reflex	17
#10	TS=preretinal macular fibrosis	67
#11	#6 OR #7 OR #8 OR #9 OR #10	6344
#12	#5 AND #11	956

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Table S1. Appraisal criteria for study methodology

Quality Criteria	Maximum score
1. Representing the general population	1
2. Appropriately recruiting the population	1
3. Adequate response rate (>70%)	1
4. Objective documentation of the outcomes	1

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Table S2. Quality score of included studies

Study	Representing the general population	Appropriately recruiting the population	Adequate response rate (>70%)	Objective documentation of the outcomes	Total score
BDES	1	1	1	1	4
Beixinjing	1	1	1	1	4
BMES	1	1	1	1	4
Funagata	1	1	0	1	3
HES	1	1	1	1	4
Hisayama	1	1	0	1	3
Jiangning	1	1	1	1	4
LALES	1	1	1	1	4
MESA	1	1	1	1	4
SCES	1	1	1	1	4
SiMES	1	1	1	1	4
SINDI	1	1	1	1	4
VIP	1	1	1	1	4

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PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not available
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6, Suppl. info
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

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PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10, table2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	table 2-4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11, table3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1, 19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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The Prevalence and Risk Factors of Epiretinal Membranes: Pooled Data from Population-Based Studies

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The Prevalence and Risk Factors of Epiretinal Membranes: Pooled Data from Population-Based Studies

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Running head: The prevalence and risk factors of ERM

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Abstract

Objective: This study was to aggregate the prevalence and risks of ERMs, and determine the possible causes of the varied estimates.

Design: Systematic review and meta-analysis.

Data sources: The search strategy was designed prospectively. We searched PubMed, Embase and Web of Science databases from inception to July 2016. Reference lists of the included literatures were reviewed as well.

Study selection: Surveys published in English language from any population were included if they had a population-based design, and reported the prevalence of ERM from retinal photography with or without optical coherence tomography (OCT). Eligibility and quality evaluation was conducted independently by two investigators.

Data extraction: The literature search generated 2,144 records, and thirteen population-based studies comprising 49,697 subjects were finally included. The prevalence of ERM, and the odds ratios of potential risk factors (age, sex, myopia, hypertension, etc.) were extracted.

Results: The pooled age-standardised prevalence estimates of earlier ERM (cellophane macular reflex, CMR), advanced ERM (preretinal macular fibrosis, PMF) and any ERM were 6.5% (95%CI: 4.2 to 8.9), 2.6% (95%CI: 1.8 to 3.4), and 9.1% (95%CI: 6.0 to 12.2), respectively. In the subgroup analysis, race and photography modality contributed to the variation in the prevalence estimates of PMF, while the WHO regions and image reading methods were associated with the varied prevalence of CMR and any ERM. Meta-analysis showed that only greater age and female significantly conferred a higher risk of ERMs.

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Conclusions: Our findings suggest that ERMs are relatively common among aged population. Race, image taking and reading methodology may play important roles in influencing the large variability of ERM prevalence estimates.

***Keywords**:* Epiretinal membranes, Prevalence, Risk factors, Meta-analysis, Population-based

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Strengths and limitations of this study

- This study is the first systematic review and meta-analysis that pools the age-standardised prevalence of epiretinal membrane (ERM) from population-based studies.
- The investigators strictly adhered to the guidelines for systematic review and meta-analysis. All included surveys were of desirable quality and large-scale.
- We aggregated not only the prevalence of ERM but also its subtype estimates (CMR and PMF).
- Lack of studies from the African and European continents makes it difficult to project ERM prevalence estimates worldwide.
- We are unable to aggregate the data on the relationship between ERM prevalence and visual acuity impairment due to lack of studies on their association.
- We only included literatures in English for the analysis.

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INTRODUCTION

Epiretinal membranes (ERMs) are common retinal conditions that can impair visual acuity in old persons. ERMs may occur without any antecedent ocular conditions or surgical procedures, termed idiopathic or primary ERM. Those associated with other eye diseases (e.g. retinal vascular occlusion, diabetic retinopathy), trauma or surgery are referred to as secondary ERMs. Under ophthalmoscopy, earlier stage ERMs present as increases of the light reflex from the retina inner surface, which is called cellophane macular reflex (CMR). As the membrane progresses, it can contract and create superficial retinal folds. Massive folds make the retinae appear with gray linear reflexes, which are termed preretinal macular fibrosis (PMF). For most cases at the advanced stage, fibrotic membranes generate tangential traction on the macula, causing macular oedema, metamorphopsias and central vision impairment[1].

After the landmark study Beaver Dam Eye Study (BDES) reported the prevalence of ERM in 1994[2], several large-scale population-based studies investigated the epidemics of ERMs in Singapore[3 4], Japan[5], Australia[6 7] and China[8 9]. Most of these surveys introduced retinal photography, and the same classification scheme for ERMs as that in BDES. However, considerable variation in ERM epidemiology across races and regions has been noted. For example, in the population-based Multi-Ethnic Study of Atherosclerosis (MESA)[10], ERM was as prevalent as 39.0% in Chinese, 27.5% in Caucasian, 26.2% in Africans, and 29.3% in Hispanics. These estimates were much higher than those in the Handan Eye Study in North China (3.4%)[8], the Blue Mountains Eye Study (BMES) in Australia (7%)[7], and the Los Angeles Latino Eye

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Study in the US (19.9%)[11]. Reasons for such variability may be complex, but it has been considered to be associated with the differences in study design, population characteristics, as well as the definition of cases. Moreover, some studies did not compute the age-standardised estimates of prevalence, making direct comparisons between studies difficult.

Estimating the prevalence and risk of ERM is perhaps the first step to better clinical management, and understanding the burden of this disease. Therefore, we conducted the present analysis to synthesise data from population-based studies to estimate the prevalence of ERMs, to identify underlying factors causing prevalence variability as well as major risk factors for ERMs.

METHODS

In this study, we followed the preferred reporting items for systematic reviews and meta-analyses (the PRISMA statement[12], see Supplementary Information).

Search strategy and selection criteria

The search strategy was designed prospectively. We searched all reports on population-based studies for the prevalence of ERMs using PubMed, Embase and Web of Science from inception to July 2016. All English language articles were retrieved using pre-specified search terms. The search terms and strategies were showed in detail in Supplementary information. The reference lists of all included articles were reviewed, and the full texts of potentially related papers were examined.

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We designed a set of inclusion and exclusion criteria for literature screening. Studies included were those population-based surveys in which ERMs were diagnosed on the basis of retinal color photography with or without a combination of optical coherence tomography (OCT). Studies without population-based (e.g., hospital- or specific population-based) design were excluded. Eligibility evaluation was conducted independently by two investigators (W.X and X.Y.C) using pre-designed forms. Any disagreements were resolved by consensus.

Quality assessment and data extraction

There were no consensus guidelines on evaluating cross-sectional surveys, so we adopted the quality assessment criteria by de Weerd et al[13] and Rogers S et al[14]. The criteria covered the following four aspects (Supplementary Information): 1) Representing the general population. To achieve this, studies should be undertaken using population registries, inhabitants of a specific area, or people registered with a general practice. 2) Appropriately recruiting the population. Recruitment was considered appropriate if it was performed randomly or consecutively rather than for convenience or from volunteers. 3) Adequate response rate (>70%). 4) Objective documentation of the outcomes. That means documentation of ERMs by retinal photography according to standardised protocols and graded according to standard definitions. Fulfillment of 3 or 4 points was considered adequate quality. Quality of all included studies was assessed independently by two investigators (W.X and X.Y.C) using quality assessment forms based on the aforementioned criteria.

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For included studies, data were extracted independently by two reviewers (W.X and X.Y.C) on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, Washington, USA). Discrepancies were resolved by consensus. We extracted the following data from each study: country, year, sample size, age range, race/ethnicity, examination methods, crude prevalence, and odds ratios (ORs) of risk factors (including age, gender, refractive error, hypertension, diabetes, smoking status, alcohol intake, early AMD, body mass index and hyperlipidemia). Our key outcomes of interest were the prevalence and risk factors of ERM.

Data synthesis and statistical analysis

Age-standardised prevalence of ERMs were calculated by projecting study-specific estimate to the WHO World Standard age-structure[15]. A random effect model was adopted to calculate pooled prevalence and odds ratios (ORs) for the risk of ERM. The I^2 statistic was used to estimate heterogeneity in pooled studies. Potential sources of heterogeneity were explored by subgroup analysis. All statistical analysis was performed with STATA software (version 13.0, StataCorp LP, TX, USA).

RESULTS

Figure 1 exhibits the procedure of literature searching and screening. The systematic searches yielded 2,144 records. After removing 906 duplications, 1,238 studies were screened through titles and abstracts. Among them, we ruled out 1,186 irrelevant articles and reviewed the left 52 studies in full text. Finally, we identified 13 studies[2 3]

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[5-11 16-18] that were eligible for inclusion (Table 1). Across the 13 studies, sample sizes ranged from 1,543[5] to 6,565[8], including 49,697 individuals at risk of ERMs. Two studies (Funagata and Hisayama) scored 3 points in the quality assessment owing to their relatively low response rate (<70%), while the others all scored 4 points (see Supplementary Information). The Beixinjing Study[18] reported specifically on the prevalence of primary (idiopathic) ERM, whereas the other 12 study documented the prevalence of any ERM (i.e. both primary and secondary ERM). Geographically, the WHO regions of Western Pacific Region and the Americas were heavily represented, with all 13 studies done in these two regions. In other words, no studies had been done in the European, Africa, South-East Asian or Eastern Mediterranean regions. Of these 13 studies, 12 studies (all except Funagata[5]) assessed ERM using both eyes of each participant; 9 studies performed photography after pharmacologic mydriasis. The methods of photography varied between studies, with 4 studies using stereo-photographing (vs. 9 using non-stereo photography), 4 studies using 30-degree camera (vs. 9 using 45-degree camera) and 6 using film photography (vs. 7 using digital photography). Retinal images were graded at the reading centres at the University of Wisconsin-Madison (3 studies), at the University of Sydney (7 studies), or by independent ophthalmologists/trained graders (4 studies). Characteristics of the included studies are summarised in Table 1.

Analyses of the 12 studies concerning any ERM (except the Beixinjing Study exclusively on primary ERM) showed that the overall age-standardised prevalence of CMR was 6.5% (95% CI 4.2-8.9), PMF was 2.6% (95% CI 1.8-3.4), and any ERM

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was 9.1% (95% CI 6.0-12.2) (Table 2). Specific to primary ERM, the pooled prevalence of CMR, PMF and all primary ERM were 7.1% (95%CI 3.3-10.8), 2.0% (95%CI 1.3-2.8) and 9.2% (95%CI 4.7-13.8), respectively. Six studies reported the prevalence of secondary ERM, and all explicitly defined the population at-risk as those with other ocular conditions (e.g. retinal vascular disease, retinal detachment) or cataract surgery. The aggregated data showed the prevalence of secondary CMR, PMF and any ERM were 11.4% (95%CI 4.4-18.5), 5.1% (95%CI 3.5-6.6) and 16.6% (95%CI 9.7-23.6), respectively.

The age-standardised prevalence of ERMs by subgroups of interest was shown in Table 3. The aggregated prevalence of any ERM varied according to the WHO regions, different image acquisition and grading method. Three studies from the Americas, in which retinal images were also graded by the reading centre at the University of Wisconsin-Madison[2 10 11], documented a much higher prevalence (14.4%) than those from Western Pacific region (8.5%). Of note, this trend was potentially attributed to the extremely high prevalence of CMR in the Americas (14.3% vs. 4.0% in Western Pacific region). For PMF, the advanced stage of ERM, studies using film photography synthesised a much lower prevalence than that using digital photography (1.5% vs. 3.1%). PMF was slightly more prevalent in Asians than in Caucasians (3.6% vs. 2.5%). There were only two studies from China introduced OCT to confirm ERM cases[8 9]. Intriguingly, studies with a combination of OCT demonstrated lower prevalence in both CMR (3.4% vs. 7.2% without OCT) and PMF (1.8% vs. 2.8% without OCT).

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As expected, individuals with greater age were more likely to have any ERM (OR=1.19 per year increase, 95%CI 1.13-1.26). Compared to males, females carried higher risk of ERM (OR=1.34, 95%CI 1.17-1.53). Smokers had an unexpected lower risk of ERM compared to non-smokers (OR=0.67, 95%CI 0.58-0.78). Other factors analysed, including myopia, hyperopia, hypertension, diabetes, alcohol intake, early age-related macular degeneration, body mass index and hyperlipidemia, were not associated with the risk of any ERM (Table 4).

DISCUSSION

This study provides estimates for the prevalence of ERMs and its two stages using data from most appropriate population-based studies in the literature. Using data from 13 studies with 49,697 participants, we estimated the age-standardised prevalence of any ERM (both primary and secondary) to be as high as 9.1%, with CMR and PMF as 6.5% and 2.6%, respectively. Race, retinal image taking and grading method were responsible for the variation of the prevalence estimates across studies. Among the factors analysed, greater age and female sex were significantly associated with higher risk of developing ERMs.

The prevalence of ERM has been documented over the last 30 years in several population-based surveys. However, these estimates have varied considerably across studies. For example, the prevalence of any ERM has been estimated to be 35.7% in Latinos aged 70 to 79 years[11], which was five-fold more prevalent than that

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in the same age Japanese (6.8%)[17]. To form an age-standardised estimate of ERM prevalence, and further to explore possible sources of heterogeneity, we conducted this study to synthesise the best available data. In this review, we identified 13 eligible studies with favorable quality, but they were predominantly carried out in Pacific Rim countries (the USA, Australia, Japan, Singapore and China). Further study is warranted in European and African regions so that we can generate the global prevalence, and magnitude of this disease.

Previously, ERM susceptibility has been reported to vary between ethnic groups. MESA[10] was the only study that directly compared the racial and ethnic differences of ERM prevalence within the same cohort. It reported a significantly higher prevalence rate for Chinese ethnicity (39.0%), followed by Hispanic (29.3%), Caucasian (27.5%), and African (26.2%) ethnicity. However, the sample sizes of each ethnic group were relatively small, particularly in the Chinese subgroup (n=724). However, our aggregated data of large sample size showed that ethnicity was less likely to be associated with ERM prevalence disparities. The prevalence difference between Asians and Caucasians for CMR and any ERM was negligible, indicating that race/ethnicity may have a limited role in ERM prevalence.

Our review shows that the variations in ERM prevalence between studies may be partly attributed to their methodological characteristics. In terms of image grading protocol, although all included studies consistently adopted the same classification

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scheme as that in the Beaver Dam Eye Study[2], retinal images were graded in different fashions: 3 studies were read by the grading centre of the UW-Madison in the US, 6 at the grading centre at the University of Sydney, and the others graded by ophthalmologists or independently trained graders. In our subgroup analysis, three studies graded at the reading centre at UW-Madison pooled an extremely high prevalence of CMR and any ERM (14.3% and 14.4%, respectively). Due to all three studies from the Americas, differences in image reading patterns directly led to the regional differences in CMR and any ERM prevalence estimates. Taken account of the minimal difference in the synthesised PMF prevalence across reading centres, we could speculate that the substantial differences in estimated overall ERM prevalence originated from the systematic differences in grading CMR from retinal images. Accordingly, there is insufficient evidence to conclude whether the regional difference in ERM prevalence is attributable to the difference in geographical location *per se* or to the grading methodology. To address this issue, universal criteria for grading CMR and differentiation from normal fundus manifestations may need to be further standardised.

Interestingly, unlike CMR and any ERM, the pooled prevalence of PMF across regions were quite similar, but this prevalence was more likely to be affected by race and photography modality (film vs. digital). Asians had a slightly higher prevalence of PMF (3.6% vs. 2.0% in Caucasians), and digital photography seemed to detect more PMF cases than film photography (3.8% vs. 1.5%).

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Optical coherence tomography (OCT) has been applied as the "gold standard" in diagnosing vitreoretinal interface diseases in recent epidemiological studies[19-21]. In clinical practice, OCT was superior to retinal photography in screening epiretinal irregularities[22] and detecting subtle ERMs among special cases, such as those with uveitis[23]. It follows that theoretically; studies using both photography and OCT should detect more persons with ERMs. However, we unexpectedly found that two studies using OCT produced much lower prevalence rates of CMR, PMF and any ERM than the others without using it. A hypothesis explaining this apparent contradiction might be that OCT may exclude ERM suspects based on color retinal images. For example, OCT is capable of differentiating ERM from posterior vitreous detachment (PVD), another condition which frequently affect the elderly and resemble CMR on colour retinal images. Further research is needed to assess the performance and cost-effectiveness of OCT in diagnosing ERMs prior to its adoption as the gold-standard test for epidemiological studies across the board.

For pooled risk estimates, our data showed that only age and sex were significantly associated the risk of any ERMs. Older and female individuals had higher risk of ERM from the meta-analysis (OR=1.19 and 1.34, respectively). With increasing age of the global population, ERM needs to be considered in a similar vein as age-related macular degeneration, a condition that significantly affects the aging population. In terms of systemic and ophthalmic risk factors, no significant association was found between ERM and diabetes, hypertension, hyperlipidemia, BMI, myopia and early AMD.

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Cigarette smoking, on one hand, is a well-documented risk factor for several eye diseases, including age-related macular degeneration[24] and thyroid-associated ophthalmopathy[25]. On the other, smoking can also serve as a protective factor against the development of pterygium[26]. Our analysis convinced a negative association of ERM and smoking as well. This may be explained by a survival bias of smokers that cannot be excluded from cross-sectional analysis. So these findings should not discredit the importance of smoking cessation across populations.

Strengths of the present study include the large sample size, specific and inclusive nature of criteria for population-based studies, and the inclusion of ERM subtype estimates (CMR and PMF). The pooled data provide a precise estimate of the ERM age-standard prevalence in the American and Asian-pacific population. However, our study contains several limitations as well. First, significant heterogeneity across studies existed in most of our analysis. Although we found that retinal image acquisition and grading methods might partly account for the heterogeneity, pooled prevalence estimates in each subgroup were still heterogeneous (all $I^2 > 50\%$, Table 2 and 3). Second, the lack of studies from the African and European continents makes it difficult to estimate the global prevalence and magnitude of ERM. Third, samples from different study designs had considerably different inclusion criteria, participant selection processes, and study protocols. For example, sample populations were found to have considerably differences in proportions of subjects with cardiovascular disease or diabetes complications[9-11]. Forth, although ERM,

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especially PMF, can cause moderate to severe visual impairment and metamorphopsias[4], most studies did not quantitatively analysed the association between ERM and visual acuity. In this study, we are consequently unable to aggregate the data on their relationship.

CONCLUSIONS

In conclusion, our current study provides the first estimate of ERM and its different subtypes based on a pooled analysis of more than 40,000 participants from 13 studies in the US and the Western Pacific region. Our study shows that 9.1% of general population had some form of ERM, 6.5% had CMR, and 2.6% had the advanced form of PMF. These data suggest that ERMs have the potential to be a major cause of visual impairment. In some specific regions, such as Europe and Africa, robust evidence for the prevalence and risk of ERM is absent. To address these gaps in the evidence, high quality epidemiological research is needed that focuses specifically on these countries using standardised measures of diseases. Finally, we confirmed the significance and impact of two major factors, being age and sex, on the risk of ERM.

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Acknowledgments

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Author Contributions

Author MGH conceived and designed the study; Authors WX and XYC performed the literature search, study selection, data extraction and synthesis. Author WX prepared the draft manuscript; Authors WY, ZTZ and MGH were involved in the revision and final preparation of the manuscript.

Competing financial interests

The Authors have no competing financial interests to report.

Data Sharing Statement

No additional unpublished data are available

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Table 1. Characteristics of included studies

Study	Country	Year	N(%male)	Age range	Race/Ethnicity	Eye examined	Pupil dilation	Fundus photography	Image grading	OCT used
BDES	USA	1987-88	4802	43-84	Caucasian	Both	Yes	30-degree; stereo; ≥3 fields; film	Reading center at University of Wisconsin	No
Beixinjing*	China	2010-11	3326 (44.5)	50-98	Asian	Both	Yes	45-degree; non-stereo; 2 fields; digital	Ophthalmologists	No
BMES	Australia	1992-93	3490 (43.8)	≥49	Caucasian	Both	Yes	30-degree; stereo; 6 fields; film	Reading center at University of Sydney	No
Funagata	Japan	2000-02	1543 (43.4)	≥35	Asian	Right eye	No	45-degree; non-stereo; 1 field; film	Reading center at University of Sydney	No
HES	China	2006-07	6565 (46.7)	≥30	Asian	Both	Part of*	45-degree; non-stereo; 2 fields; digital	Ophthalmologists	Yes
Hisayama	Japan	1998	1765 (38.5)	≥40	Asian	Both	Yes	45-degree; non-stereo; 1 field; film	Ophthalmologists	No
Jiangning	China	2012-13	2005 (43.7)	≥50	Asian	Both	No	45-degree; non-stereo; ≥2 fields; digital	Trained graders	Yes
LALES	USA	2000-03	5982 (42.0)	≥40	Hispanic	Both	Yes	30-degree; stereo, 3 fields; film	Reading center at University of Wisconsin	No
MESA	USA	2002-04	5960 (47.9)	45-84	White, Black; Asian; Hispanic	Both	No	45-degree; non-stereo; 2 fields; digital	Reading center at University of Wisconsin	No
SCES	Singapore	2009-11	3353	40-80	Asian	Both	Yes	45-degree; non-stereo; 2	Reading center at	No

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								fields; digital	University of Sydney	
SiMES	Singapore	2004-06	3265 (48.1)	40-80	Asian	Both	Yes	45-degree; non-stereo; 2 fields; digital	Reading center at University of Sydney	No
SINDI	Singapore	2007-09	3328 (50.2)	40-80	Asian	Both	Yes	non-stereo; 2 fields; digital	Reading center at University of Sydney	No
VIP	Australia	1992-97	4313 (47.0)	≥40	Caucasian	Both	Yes	30-degree; stereo; 2 field; film	Reading center at University of Sydney	No

* Data only available for primary ERMs.

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Table 2. Age-standardised prevalence of epiretinal membrane by study

Study	Year	N at-risk	Crude prevalence (%)				Age-standardised prevalence (%, 95%CI)		
			CMR	PMF	Any ERM [#]		CMR	PMF	Any ERM [#]
All ERM [##]									
BDES	1987-88	4802	-	-	-		4.8 (4.3-5.4)	1.7 (1.3-2.0)	6.4 (5.8-7.1)
BMES	1992-93	3490	4.8	2.7	7.0		3.8 (3.2-4.4)	1.7 (1.3-2.1)	5.5 (4.8-6.2)
Funagata	2000-02	1543	4.0	1.5	5.4		2.7 (1.9-3.4)	1.1 (0.6-1.5)	3.7 (2.8-4.6)
HES	2006-07	6565	2.2	0.7	3.4		2.3 (1.8-2.8)	0.6 (0.4-0.7)	3.5 (2.9-4.0)
Hisayama	1998	1765	3.2	0.9	4.0		2.2 (1.6-2.9)	0.5 (0.2-0.8)	2.8 (2.1-3.5)
Jiangning	2012-13	2005	5.0	3.4	8.4		4.5 (3.7-5.4)	3.1 (2.4-3.9)	7.6 (6.5-8.7)
LALES	2000-03	5982	16.3	2.2	18.5		16.6 (15.7-17.6)	2.5 (2.0-2.9)	19.0 (18.0-20.0)
MESA	2002-04	5960	25.1	3.8	28.9		21.5 (20.1-22.5)	3.0 (2.6-3.4)	24.5(23.4-25.6)
SiMES	2004-06	3265	5.8	5.9	11.8		4.7 (4.0-5.3)	4.6 (4.0-5.3)	9.3 (8.3-10.2)
SCES	2009-11	3353	-	-	-		7.0 (6.1-7.9)	7.5 (6.6-8.3)	13.0 (11.9-14.2)
SINDI	2007-09	3328	5.4	4.8	10.2		4.7 (4.0-5.3)	4.1 (3.4-4.7)	8.8 (7.9-9.7)
VIP	1992-97	4313	4.8	1.7	6.0		3.8 (3.3-4.4)	1.4 (1.1-1.8)	4.9 (4.4-5.5)
Pooled estimates	**NA**	**46371**	**-**	**-**	**-**		**6.5 (4.2-8.9)**	**2.6 (1.8-3.4)**	**9.1 (6.0-12.2)**
I^2							99.3	98.2	99.5

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Primary ERM									
BDES	1987-88	4125	-	-	-		4.5 (3.9-5.1)	1.3 (1.0-1.6)	5.8 (5.1-6.5)
Beixinjing	2010-11	3326	0.6	0.6	1.0		0.6 (0.3-0.9)	0.4 (0.2-0.6)	1.0 (0.6-1.3)
HES	2006-07	6196	2.0	0.5	3.0		2.1 (1.6-2.6)	0.4 (0.3-0.6)	3.1 (2.6-3.7)
Jiangning	2012-13	1854	4.6	3.1	7.7		4.3 (3.4-5.2)	3.0 (2.2-3.7)	7.3 (6.1-8.4)
LALES	2000-03	5631	15.6	1.9	17.5		16.1 (15.2-17.1)	2.2 (1.8-2.6)	18.4 (17.3-19.4)
MESA	2002-04	4761	22.7	3.3	26.1		20.2 (19.1-21.3)	2.7 (2.3-3.1)	23.0 (21.7-24.1)
SiMES	2004-06	2734	5.1	4.5	9.5		4.5 (3.7-5.2)	3.8 (3.2-4.5)	8.3 (7.3-9.3)
SINDI	2007-09	2324	3.8	2.7	6.5		4.3 (3.4-5.2)	2.8 (2.1-3.5)	7.0 (5.9-8.2)
Pooled estimates	**NA**	**30951**	**-**	**-**	**-**		**7.1 (3.3-10.8)**	**2.0 (1.3-2.8)**	**9.2 (4.7-13.8)**
I^2							99.6	97.9	99.7
Secondary ERM									
HES	2006-07	269	7.1	3.7	12.3		6.7 (1.9-11.5)	3.7 (0-7.8)	11.1 (5.0-17.3)
Jiangning	2012-13	151	10.6	6.6	17.2		7.0 (3.4-10.7)	3.9 (1.2-6.6)	10.9 (6.6-15.2)
LALES	2000-03	345	27.0	7.5	34.5		19.8 (14.4-25.2)	6.1 (2.9-9.3)	25.9 (20.0-31.9)
MESA	2002-04	1199	34.3	5.8	40.1		25.1 (22.2-28.1)	3.4 (2.5-4.4)	28.6 (25.6-31.6)
SiMES	2004-06	531	9.8	13.6	23.4		5.3 (2.5-8.1)	7.1 (5.2-9.0)	12.4 (9.1-15.7)
SINDI	2007-09	1004	9.1	9.8	18.8		5.1 (3.6-6.5)	6.0 (4.2-7.8)	11.0 (8.8-13.3)

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Pooled estimates	**NA**	**3499**	**-**	**-**	**-**		**11.4 (4.4-18.5)**	**5.1 (3.5-6.6)**	**16.6 (9.7-23.6)**
I^2							97.0	69.4	95.4

#: Any ERM: both CMR and PMF.

##: All ERM: both primary and secondary ERM.

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Table 3. Age-standardised prevalence of epiretinal membranes by subgroups of interest

	CMR			PMF			Any ERM			Reference
	Studies (n)	Prevalence (%, 95%CI)	I^2 (%)	Studies (n)	Prevalence (%, 95%CI)	I^2 (%)	Studies (n)	Prevalence (%, 95%CI)	I^2 (%)	
Race/ethnicity										
Caucasian	4	8.9 (4.6-13.2)	99.4	4	2.0 (1.4-2.7)	88.8	4	11.0 (5.9-16.1)	99.5	2, 6, 7, 10
Asian	8	6.5 (4.6-8.5)	98.2	8	3.6 (2.2-4.9)	98.7	8	10.5 (7.2-13.8)	99.1	3, 4, 5, 8, 9, 10, 16, 17
WHO Regions										
The Americas	3	14.3 (3.6-25.0)	99.8	3	2.4 (1.6-3.2)	91.6	3	14.4 (5.6-23.2)	99.7	2, 10, 11
Western Pacific	9	4.0 (3.1-4.9)	94.2	9	2.7 (1.7-3.7)	98.3	9	8.5 (4.7-8.4)	98.2	3, 4, 5, 6, 7, 8, 9, 16, 17
Testing method										
Photography only	10	7.2 (4.2-10.1)	99.5	10	2.8 (1.9-3.7)	97.8	10	9.1 (6.0-12.2)	99.3	2, 3, 4, 5, 6, 7, 10, 11, 16, 17
Photography + OCT	2	3.4 (1.2-5.5)	94.8	2	1.8 (0-3.7)	97.6	2	5.5 (1.5-9.5)	97.7	8, 9
Photography										
Film	6	5.6 (2.5-8.8)	99.3	6	1.5 (0.9-2.0)	92.2	6	7.0 (3.4-10.7)	99.4	2, 5, 6, 7, 11, 17
Digital	6	7.4 (3.2-11.7)	99.5	6	3.8 (1.9-5.7)	99.0	6	10.0 (5.7-14.3)	99.3	3, 4, 8, 9, 10, 16
Image graded by										

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RC at UW–Madison[#]		3	14.3 (3.6-25.0)	99.8		3	2.4 (1.6-3.2)	91.6		3	14.4 (5.6-23.2)	99.7	2, 10, 11
RC at USYD[##]		6	4.4 (3.5-5.4)	92.3		6	3.4 (1.9-4.9)	98.1		6	7.5 (5.1-9.9)	98.1	3, 4, 5, 6, 7, 16
Ophthalmologists or trained raters		3	3.0 (1.7-4.2)	90.9		3	2.6 (1.8-3.4)	98.1		3	4.6 (2.3-6.8)	96.4	8, 9, 17

#: Reading center at University of Wisconsin-Madison;

##: Reading center at University of Sydney.

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Table 4. Pooled odds ratios for risk of any epiretinal membrane

Risk factors		Studies	OR (95%CI)	I^2 (%)	Reference
Age (per year)		5	**1.19 (1.13, 1.26)**	95.1	3, 4, 5, 9, 10, 16
Sex (female)		6	**1.34 (1.17, 1.53)**	24.8	3, 4, 5, 9, 16, 17
Myopia (present)		4	1.21 (0.67, 2.19)	88.9	6, 8, 9, 16
Hyperopia (present)		3	1.23 (0.78, 1.94)	83.8	6, 8, 16
Hypertension (present)		6	1.04 (0.90, 1.20)	11.2	4, 5, 6, 9, 16, 17
Diabetes (present)		6	1.13 (0.92, 1.38)	17.1	4, 5, 6, 9, 16, 17
Smoking (present)		7	**0.67 (0.58, 0.78)**	0	3, 4, 5, 6, 8, 16, 17
Alcohol intake (present)		3	0.97 (0.75, 1.25)	0	6, 9, 17
Early AMD (present)		3	0.96 (0.63, 1.47)	60.7	2, 5, 6
BMI (per kg/m^2)		5	0.99 (0.98, 1.01)	0	4, 5, 6, 9, 17
Hyperlipidemia (present)		4	1.05 (0.99, 1.11)	62.0	4, 5, 9, 17

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Figure legends:

Figure 1. Flow chart of studies identified, included, and excluded.

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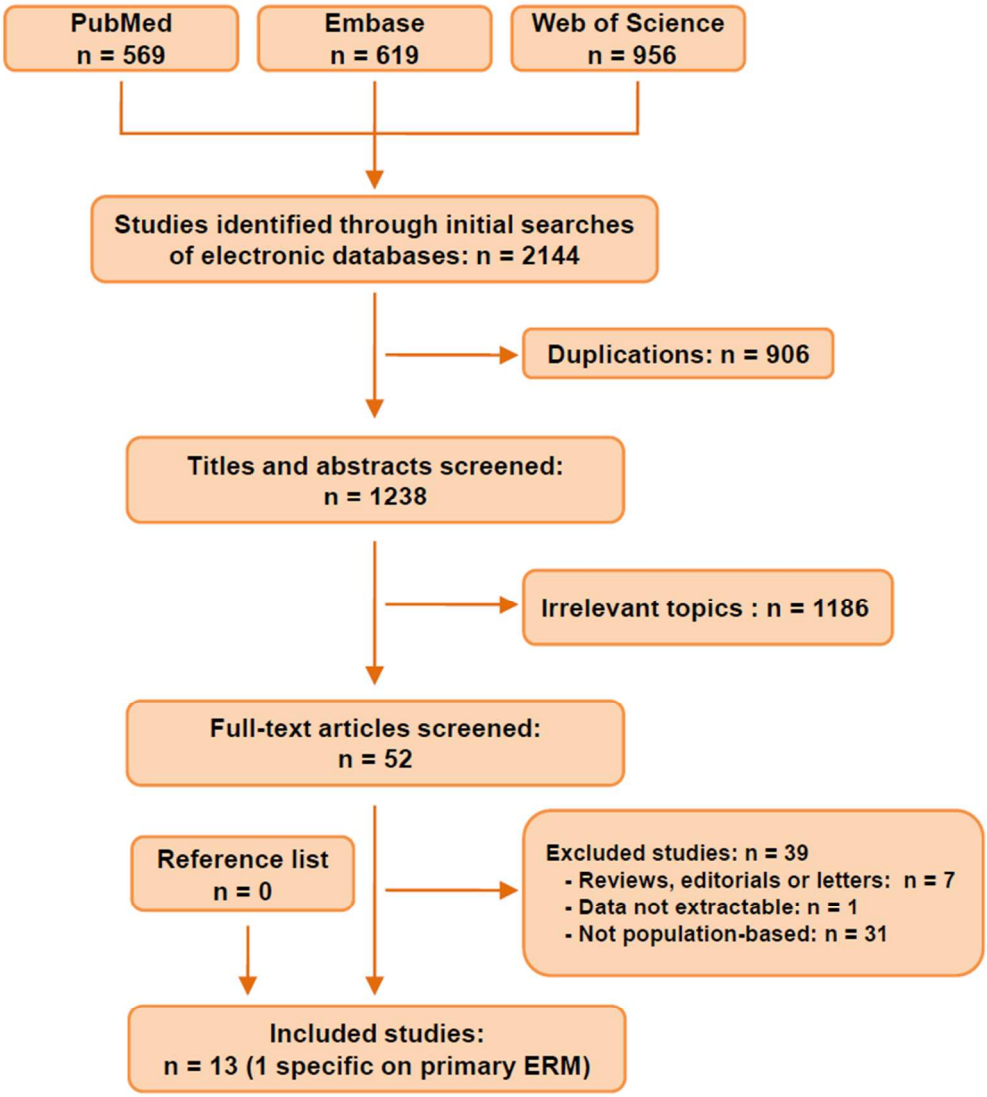

Flow chart of studies identified, included, and excluded

69x77mm (300 x 300 DPI)

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The Prevalence and Risk Factors of Epiretinal Membranes: Pooled Data from Population-Based Studies

Wei Xiao, Xiaoyun Chen, William Yan, Zhuoting Zhu, Mingguang He

Literature search strategy

Terms

1. prevalence, epidemiology, epidemic*, risk
2. epiretinal membrane*; erm*; ierm*; cellophane macular reflex; preretinal macular fibrosis

Search strategy

PubMed (up to July 11, 2016)

#1	prevalence Fields: Title/Abstract	459388
#2	epidemiology Fields: Title/Abstract	143403
#3	epidemic* Fields: Title/Abstract	80597
#4	risk Fields: Title/Abstract	1507737
#5	#1 OR #2 OR #3 OR #4	1973101
#6	epiretinal membrane* Fields: Title/Abstract	2259
#7	ERM Fields: Title/Abstract	3126
#8	iERM Fields: Title/Abstract	23
#9	cellophane macular reflex Fields: All fields	18
#10	preretinal macular fibrosis Fields: All fields	69
#11	#6 OR #7 OR #8 OR #9 OR #10	4935
#12	#5 AND #11	569

Embase (up to July 11, 2016)

#1	prevalence	609473

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	Fields: ti, ab	
#2	epidemiology Fields: ti, ab	144993
#3	epidemic* Fields: ti, ab	89089
#4	risk Fields: ti, ab	2059117
#5	#1 OR #2 OR #3 OR #4	2622649
#6	epiretinal membrane* Fields: ti, ab	2491
#7	ERM Fields: ti, ab	3555
#8	iERM Fields: ti, ab	22
#9	cellophane macular reflex Fields: All fields	18
#10	preretinal macular fibrosis Fields: All fields	75
#11	#6 OR #7 OR #8 OR #9 OR #10	5570
#12	#5 AND #11	619

Web of Science (All Databases, 1980 to July 11, 2016)

All languages, all document types

#1	TS = prevalence	684438
#2	TS = epidemiology	1440407
#3	TS=epidemic*	100419
#4	TS=risk	2386116
#5	#1 OR #2 OR #3 OR #4	3597103
#6	TS=epiretinal membrane*	3045
#7	TS=ERM	369
#8	TS=iERM	21
#9	TS=cellophane macular reflex	17
#10	TS=preretinal macular fibrosis	67
#11	#6 OR #7 OR #8 OR #9 OR #10	6344
#12	#5 AND #11	956

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Table S1. Appraisal criteria for study methodology

Quality Criteria	Maximum score
1. Representing the general population	1
2. Appropriately recruiting the population	1
3. Adequate response rate (>70%)	1
4. Objective documentation of the outcomes	1

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Table S2. Quality score of included studies

Study	Representing the general population	Appropriately recruiting the population	Adequate response rate (>70%)	Objective documentation of the outcomes	Total score
BDES	1	1	1	1	4
Beixinjing	1	1	1	1	4
BMES	1	1	1	1	4
Funagata	1	1	0	1	3
HES	1	1	1	1	4
Hisayama	1	1	0	1	3
Jiangning	1	1	1	1	4
LALES	1	1	1	1	4
MESA	1	1	1	1	4
SCES	1	1	1	1	4
SiMES	1	1	1	1	4
SINDI	1	1	1	1	4
VIP	1	1	1	1	4

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PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not available
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6, Suppl. info
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

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PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10, table2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	table 2-4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11, table3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1, 19

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The prevalence and risk factors of epiretinal membranes: a systematic review and meta-analysis of population-based studies

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Running head: The prevalence and risk factors of ERM

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Abstract

Objective: This study was to aggregate the prevalence and risks of ERMs, and determine the possible causes of the varied estimates.

Design: Systematic review and meta-analysis.

Data sources: The search strategy was designed prospectively. We searched PubMed, Embase and Web of Science databases from inception to July 2016. Reference lists of the included literatures were reviewed as well.

Study selection: Surveys published in English language from any population were included if they had a population-based design, and reported the prevalence of ERM from retinal photography with or without optical coherence tomography (OCT). Eligibility and quality evaluation was conducted independently by two investigators.

Data extraction: The literature search generated 2,144 records, and thirteen population-based studies comprising 49,697 subjects were finally included. The prevalence of ERM, and the odds ratios of potential risk factors (age, sex, myopia, hypertension, etc.) were extracted.

Results: The pooled age-standardised prevalence estimates of earlier ERM (cellophane macular reflex, CMR), advanced ERM (preretinal macular fibrosis, PMF) and any ERM were 6.5% (95%CI: 4.2 to 8.9), 2.6% (95%CI: 1.8 to 3.4), and 9.1% (95%CI: 6.0 to 12.2), respectively. In the subgroup analysis, race and photography modality contributed to the variation in the prevalence estimates of PMF, while the WHO regions and image reading methods were associated with the varied prevalence of CMR and any ERM. Meta-analysis showed that only greater age and female significantly conferred a higher risk of ERMs.

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Conclusions: Our findings suggest that ERMs are relatively common among aged population. Race, image taking and reading methodology may play important roles in influencing the large variability of ERM prevalence estimates.

***Keywords**:* Epiretinal membranes, Prevalence, Risk factors, Meta-analysis, Population-based

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Strengths and limitations of this study

- This study is the first systematic review and meta-analysis that pools the age-standardised prevalence of epiretinal membrane (ERM) from population-based studies.
- The investigators strictly adhered to the guidelines for systematic review and meta-analysis. All included surveys were of desirable quality and large-scale.
- We aggregated not only the prevalence of ERM but also its subtype estimates (CMR and PMF).
- Lack of studies from the African and European continents makes it difficult to project ERM prevalence estimates worldwide.
- We are unable to aggregate the data on the relationship between ERM prevalence and visual acuity impairment due to lack of studies on their association.
- We only included literatures in English for the present analysis.

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INTRODUCTION

Epiretinal membranes (ERMs) are common retinal conditions that can impair visual acuity in old persons. ERMs may occur without any antecedent ocular conditions or surgical procedures, termed idiopathic or primary ERM. Those associated with other eye diseases (e.g. retinal vascular occlusion, diabetic retinopathy), trauma or surgery are referred to as secondary ERM. Under ophthalmoscopy, earlier stage ERMs present as increases of the light reflex from the retina inner surface, which is called cellophane macular reflex (CMR). As the membrane progresses, it can contract and create superficial retinal folds. Massive folds make the retina appear with gray linear reflexes, which are termed preretinal macular fibrosis (PMF). For most cases at the advanced stage, fibrotic membranes generate tangential traction on the macula, causing macular oedema, metamorphopsias and central vision impairment[1].

After the landmark study Beaver Dam Eye Study (BDES) reported the prevalence of ERM in 1994[2], several large-scale population-based studies investigated the epidemics of ERMs in Singapore[3 4], Japan[5], Australia[6 7] and China[8 9]. Most of these surveys introduced retinal photography, and the same classification scheme for ERMs as that in BDES. However, considerable variation in ERM epidemiology across races and regions has been noted. For example, in the population-based Multi-Ethnic Study of Atherosclerosis (MESA)[10], ERM was as prevalent as 39.0% in Chinese, 27.5% in Caucasian, 26.2% in Africans, and 29.3% in Hispanics. These estimates were much higher than those in the Handan Eye Study in North China (3.4%)[8], the Blue Mountains Eye Study (BMES) in Australia (7%)[7], and the Los Angeles Latino Eye

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Study in the US (19.9%)[11]. Reasons for such variability may be complex, but it has been considered to be associated with the differences in study design, population characteristics, as well as the definition of cases. Moreover, some studies did not compute the age-standardised estimates of prevalence, making direct comparison between studies difficult.

Estimating the prevalence and risk of ERM is perhaps the first step to better clinical management, and understanding the burden of this disease. Therefore, we conducted the present analysis to synthesise data from population-based studies to estimate the prevalence of ERMs, to identify underlying factors causing prevalence variability as well as major risk factors for ERMs.

METHODS

In this study, we followed the preferred reporting items for systematic reviews and meta-analyses (the PRISMA statement[12], see Supplementary Information).

Search strategy and selection criteria

The search strategy was designed prospectively. We searched all reports on population-based studies for the prevalence of ERMs using PubMed, Embase and Web of Science from inception to July 2016. All English language articles were retrieved using pre-specified search terms. The search terms and strategies were showed in detail in Supplementary information. The reference lists of all included articles were reviewed, and the full texts of potentially related papers were examined.

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We designed a set of inclusion and exclusion criteria for literature screening. Studies included were those population-based surveys in which ERMs were diagnosed on the basis of retinal colour photography with or without a combination of optical coherence tomography (OCT). Studies without population-based (e.g., hospital- or specific population-based) design were excluded. Eligibility evaluation was conducted independently by two investigators (W.X and X.Y.C) using pre-designed forms. Any disagreements were resolved by consensus.

Quality assessment and data extraction

There were no consensus guidelines on evaluating cross-sectional surveys, so we adopted the quality assessment criteria used by de Weerd et al[13] and Rogers S et al[14]. The criteria covered the following four aspects (Supplementary Information): 1) Representing the general population. To achieve this, studies should be undertaken using population registries, inhabitants of a specific area, or people registered with a general practice. 2) Appropriately recruiting the population. Recruitment was considered appropriate if it was performed randomly or consecutively rather than for convenience or from volunteers. 3) Adequate response rate (>70%). 4) Objective documentation of the outcomes. That means documentation of ERMs by retinal photography according to standardised protocols and graded according to standard definitions. Fulfillment of 3 or 4 points was considered adequate quality. Quality of all included studies was assessed independently by two investigators (W.X and X.Y.C) using quality assessment forms based on the aforementioned criteria.

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For included studies, data were extracted independently by two reviewers (W.X and X.Y.C) on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, Washington, USA). Discrepancies were resolved by consensus. We extracted the following data from each study: country, year, sample size, age range, race/ethnicity, examination methods, image grading approach, crude prevalence with 95% confidence interval (95%CI), and odds ratios (ORs) with 95%CI for risk factors (including age, gender, refractive error, hypertension, diabetes, smoking status, alcohol intake, early AMD, body mass index and hyperlipidaemia). Our key outcomes of interest were the prevalence and risk factors of ERM.

Data synthesis and statistical analysis

Age-standardised prevalence of ERMs in each study was calculated by projecting its crude prevalence rates to the WHO world standard age-structure[15]. This method has been adopted to estimate the regional and global prevalence and burden of several major eye diseases, such as age-related macular degeneration[16], diabetic retinopathy[17] and retinal vein occlusion[14]. The I^2 statistic was used to estimate heterogeneity between studies with a value greater than 50% as significantly heterogeneous. Due to the marked difference between studies, pooled prevalence was synthesised using random-effect models[18]. Sources of heterogeneity were explored by conducting subgroup analysis accordingly to race/ethnicity, WHO regions, testing method (photography with or without OCT), photography technique (digital or film), and image grading approach (centralised grading centre vs. independently

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trained graders). To aggregate odds ratios (ORs) for potential risk factors, random-effect models were used if included studies were significantly heterogeneous ($I^2 \geq 50\%$); otherwise, fixed-effect models were used. All statistical analysis was performed with STATA software (version 13.0, StataCorp LP, TX, USA).

RESULTS

Figure 1 exhibits the procedure of literature searching and screening. The systematic searches yielded 2,144 records. After removing 906 duplications, 1,238 studies were screened through titles and abstracts. Among them, we ruled out 1,186 irrelevant articles and reviewed the left 52 studies in full text. Finally, we identified 13 studies[2 3 5-11 19-21] that were eligible for inclusion (Table 1). Across the 13 studies, sample sizes ranged from 1,543[5] to 6,565[8], including 49,697 individuals at risk of ERMs. Two studies (Funagata and Hisayama) scored 3 points in the quality assessment owing to their relatively low response rate (<70%), while the others all scored 4 points (see Supplementary Information). The Beixinjing Study[21] reported specifically on the prevalence of primary (idiopathic) ERM, whereas the other 12 study documented the prevalence of any ERM (i.e. both primary and secondary ERM). Geographically, the WHO regions of Western Pacific Region and the Americas were heavily represented, with all 13 studies done in these two regions. In other words, no studies had been done in the European, Africa, South-East Asian or Eastern Mediterranean regions. Of these 13 studies, 12 studies (all except Funagata[5]) assessed ERMs using both eyes of each participant; 9 studies performed photography after pharmacologic mydriasis. The methods of photography varied between studies, with 4 studies using

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stereo-photographing (vs. 9 using non-stereo photographing), 4 studies using 30-degree camera (vs. 9 using 45-degree camera) and 6 using film photography (vs. 7 using digital photography). Retinal images were graded at the reading centres at the University of Wisconsin-Madison (3 studies), at the University of Sydney (7 studies), or by independent ophthalmologists/trained graders (4 studies). Characteristics of the included studies were summarised in Table 1.

Analyses of the 12 studies concerning any ERM (except the Beixinjing Study exclusively on primary ERM) showed that the overall age-standardised prevalence of CMR was 6.5% (95% CI 4.2-8.9), PMF was 2.6% (95% CI 1.8-3.4), and any ERM was 9.1% (95% CI 6.0-12.2) (Table 2). Specific to primary ERM, the pooled prevalence of CMR, PMF and all primary ERM were 7.1% (95%CI 3.3-10.8), 2.0% (95%CI 1.3-2.8) and 9.2% (95%CI 4.7-13.8), respectively. Six studies reported the prevalence of secondary ERM, and all explicitly defined the population at-risk as those with other ocular conditions (e.g. retinal vascular disease, retinal detachment) or cataract surgery. The aggregated data showed the prevalence of secondary CMR, PMF and any ERM were 11.4% (95%CI 4.4-18.5), 5.1% (95%CI 3.5-6.6) and 16.6% (95%CI 9.7-23.6), respectively.

The age-standardised prevalence of ERMs by subgroups of interest was shown in Table 3. The aggregated prevalence of any ERM varied according to the WHO regions, different image acquisition and grading method. Three studies from the Americas, in which retinal images were also graded by the reading centre at the

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University of Wisconsin-Madison[2 10 11], documented a much higher prevalence (14.4%) than those from Western Pacific region (8.5%). Of note, this trend was potentially attributed to the extremely high prevalence of CMR in the Americas (14.3% vs. 4.0% in Western Pacific region). For PMF, the advanced stage of ERM, studies using film photography synthesised a much lower prevalence than that using digital photography (1.5% vs. 3.1%). PMF was slightly more prevalent in Asians than in Caucasians (3.6% vs. 2.5%). There were only two studies from China introduced OCT to confirm ERM cases[8 9]. Intriguingly, studies with a combination of OCT demonstrated lower prevalence in both CMR (3.4% vs. 7.2% without OCT) and PMF (1.8% vs. 2.8% without OCT).

As expected, individuals with greater age were more likely to have any ERM (OR=1.19 per year increase, 95%CI 1.13-1.26). Compared to males, females carried higher risk of ERM (OR=1.34, 95%CI 1.17-1.53). Smokers had an unexpected lower risk of ERM compared to non-smokers (OR=0.67, 95%CI 0.58-0.78). Other factors analysed, including myopia, hyperopia, hypertension, diabetes, alcohol intake, early age-related macular degeneration, body mass index and hyperlipidaemia, were not associated with the risk of any ERM (Table 4).

DISCUSSION

This study provides estimates for the prevalence of ERMs and its two stages using data from most appropriate population-based studies in the literature. Using data from 13 studies with 49,697 participants, we estimated the age-standardised prevalence of

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any ERM (both primary and secondary) to be as high as 9.1%, with CMR and PMF as 6.5% and 2.6%, respectively. Race, retinal image taking and grading method were responsible for the variation of the prevalence estimates across studies. Among the factors analysed, greater age and female sex were significantly associated with higher risk of developing ERMs.

The prevalence of ERM has been documented over the last 30 years in several population-based surveys. However, these estimates have varied considerably across studies. For example, the prevalence of any ERM has been estimated to be 35.7% in Latinos aged 70 to 79 years[11], which was five-fold more prevalent than that in the same age Japanese (6.8%)[20]. To form an age-standardised estimate of ERM prevalence, and further to explore possible sources of heterogeneity, we conducted this study to synthesise the best available data. In this review, we identified 13 eligible studies with favorable quality, but they were predominantly carried out in Pacific Rim countries (the USA, Australia, Japan, Singapore and China). Further study is warranted in European and African regions so that we can generate the global prevalence, and magnitude of this disease.

Previously, ERM susceptibility has been reported to vary between ethnic groups. MESA[10] was the only study that directly compared the racial and ethnic differences of ERM prevalence within the same cohort. It reported a significantly higher prevalence rate for Chinese ethnicity (39.0%), followed by Hispanic (29.3%), Caucasian (27.5%), and African (26.2%) ethnicity. However, the sample sizes of each ethnic group were

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relatively small, particularly in the Chinese subgroup (n=724). However, our aggregated data of large sample size showed that ethnicity was less likely to be associated with ERM prevalence disparities. The prevalence difference between Asians and Caucasians for CMR and any ERM was negligible, indicating that race/ethnicity may have a limited role in ERM prevalence.

Our review shows that the variations in ERM prevalence between studies may be partly attributed to their methodological characteristics. In terms of image grading protocol, although all included studies consistently adopted the same classification scheme as that in the Beaver Dam Eye Study[2], retinal images were graded in different fashions: 3 studies were read by the grading centre of the University of Wisconsin-Madison in the US, 6 at the grading centre at the University of Sydney, and the others graded by ophthalmologists or independently trained graders. In our subgroup analysis, three studies graded at the reading centre at University of Wisconsin-Madison pooled an extremely high prevalence of CMR and any ERM (14.3% and 14.4%, respectively). Due to all three studies from the Americas, differences in image reading patterns directly led to the regional differences in CMR and any ERM prevalence estimates. Taken account of the minimal difference in the synthesised PMF prevalence across reading centres, we could speculate that the substantial differences in estimated overall ERM prevalence originated from the systematic differences in grading CMR from retinal images. Accordingly, there is insufficient evidence to conclude whether the regional difference in ERM prevalence is

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attributable to the difference in geographical location *per se* or to the grading methodology. To address this issue, universal criteria for grading CMR and differentiation from normal fundus manifestations may need to be further standardised.

Interestingly, unlike CMR and any ERM, the pooled prevalence of PMF across regions were quite similar, but this prevalence was more likely to be affected by race and photography modality (film vs. digital). Asians had a slightly higher prevalence of PMF (3.6% vs. 2.0% in Caucasians), and digital photography seemed to detect more PMF cases than film photography (3.8% vs. 1.5%).

Optical coherence tomography (OCT) has been applied as the "gold standard" in diagnosing vitreoretinal interface diseases in recent epidemiological studies[22-24]. In clinical practice, OCT was superior to retinal photography in screening epiretinal irregularities[25] and detecting subtle ERMs among special cases, such as those with uveitis[26]. It follows that theoretically; studies using both photography and OCT should detect more persons with ERMs. However, we unexpectedly found that two studies using OCT produced much lower prevalence rates of CMR, PMF and any ERM than the others without using it. A hypothesis explaining this apparent contradiction might be that OCT may exclude ERM suspects based on colour retinal images. For example, OCT is capable of differentiating ERM from posterior vitreous detachment (PVD), another condition which frequently affect the elderly and resemble CMR on colour retinal images. Further research is needed to assess the performance and

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cost-effectiveness of OCT in diagnosing ERMs prior to its adoption as the gold-standard test for epidemiological studies across the board.

For pooled risk estimates, our data showed that only age and sex were significantly associated the risk of any ERMs. Older and female individuals had higher risk of ERM from the meta-analysis (OR=1.19 and 1.34, respectively). With increasing age of the global population, ERM needs to be considered in a similar vein as age-related macular degeneration, a condition that significantly affects the aging population. In terms of systemic and ophthalmic risk factors, no significant association was found between ERM and diabetes, hypertension, hyperlipidaemia, BMI, myopia and early AMD.

Cigarette smoking, on one hand, is a well-documented risk factor for several eye diseases, including age-related macular degeneration[27] and thyroid-associated ophthalmopathy[28]. On the other, smoking can also serve as a protective factor against the development of pterygium[29]. Our analysis convinced a negative association of ERM and smoking as well. This may be explained by a survival bias of smokers that cannot be excluded from cross-sectional analysis. So these findings should not discredit the importance of smoking cessation across populations.

Strengths of the present study include the large sample size, specific and inclusive nature of criteria for population-based studies, and the inclusion of ERM subtype estimates (CMR and PMF). The pooled data provide a precise estimate of the ERM

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age-standard prevalence in the American and Asian-pacific population. However, our study contains several limitations as well. First, significant heterogeneity across studies existed in most of our analysis. Although we found that retinal image acquisition and grading methods might partly account for the heterogeneity, pooled prevalence estimates in each subgroup were still heterogeneous (all I^2 > 50%, Table 2 and 3). Second, the lack of studies from the African and European continents makes it difficult to estimate the global prevalence and magnitude of ERMs. Third, samples from different study designs had considerably different inclusion criteria, participant selection processes, and study protocols. For example, sample populations were found to have considerably differences in proportions of subjects with cardiovascular disease or diabetes complications[9-11]. Fourth, although ERMs, especially PMF, can cause moderate to severe visual impairment and metamorphopsias[4], most studies did not quantitatively analysed the association between ERMs and visual acuity. In this study, we are consequently unable to aggregate the data on their relationship.

CONCLUSIONS

In conclusion, our current study provides the first estimate of ERM and its different subtypes based on a pooled analysis of more than 40,000 participants from 13 studies in the US and the Western Pacific region. Our study shows that 9.1% of general population had some form of ERMs, 6.5% had CMR, and 2.6% had the advanced form of PMF. These data suggest that ERMs have the potential to be a major cause of visual impairment. In some specific regions, such as Europe and

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Africa, robust evidence for the prevalence and risk of ERMs is absent. To address these gaps in the evidence, high quality epidemiological research is needed that focuses specifically on these countries using standardised measures of diseases. Finally, we confirmed the significance and impact of two major factors, being age and sex, on the risk of ERMs.

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Author Contributions

Author MGH conceived and designed the study; Authors WX and XYC performed the literature search, study selection, data extraction and synthesis. Author WX prepared the draft manuscript; Authors WY, ZTZ and MGH were involved in the revision and final preparation of the manuscript.

Competing financial interests

The Authors have no competing financial interests to report.

Data Sharing Statement

No additional unpublished data are available

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Table 1. Characteristics of included studies

Study	Country	Year	N(%male)	Age range	Race/Ethnicity	Eye examined	Pupil dilation	Fundus photography	Image grading	OCT used
BDES	USA	1987-88	4802	43-84	Caucasian	Both	Yes	30-degree; stereo; ≥3 fields; film	Reading centre at University of Wisconsin	No
Beixinjing*	China	2010-11	3326 (44.5)	50-98	Asian	Both	Yes	45-degree; non-stereo; 2 fields; digital	Ophthalmologists	No
BMES	Australia	1992-93	3490 (43.8)	≥49	Caucasian	Both	Yes	30-degree; stereo; 6 fields; film	Reading centre at University of Sydney	No
Funagata	Japan	2000-02	1543 (43.4)	≥35	Asian	Right eye	No	45-degree; non-stereo; 1 field; film	Reading centre at University of Sydney	No
HES	China	2006-07	6565 (46.7)	≥30	Asian	Both	Part of*	45-degree; non-stereo; 2 fields; digital	Ophthalmologists	Yes
Hisayama	Japan	1998	1765 (38.5)	≥40	Asian	Both	Yes	45-degree; non-stereo; 1 field; film	Ophthalmologists	No
Jiangning	China	2012-13	2005 (43.7)	≥50	Asian	Both	No	45-degree; non-stereo; ≥2 fields; digital	Trained graders	Yes
LALES	USA	2000-03	5982 (42.0)	≥40	Hispanic	Both	Yes	30-degree; stereo, 3 fields; film	Reading centre at University of Wisconsin	No
MESA	USA	2002-04	5960 (47.9)	45-84	White, Black; Asian; Hispanic	Both	No	45-degree; non-stereo; 2 fields; digital	Reading centre at University of Wisconsin	No
SCES	Singapore	2009-11	3353	40-80	Asian	Both	Yes	45-degree; non-stereo; 2	Reading centre at	No

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								fields; digital	University of Sydney	
SiMES	Singapore	2004-06	3265 (48.1)	40-80	Asian	Both	Yes	45-degree; non-stereo; 2 fields; digital	Reading centre at University of Sydney	No
SINDI	Singapore	2007-09	3328 (50.2)	40-80	Asian	Both	Yes	non-stereo; 2 fields; digital	Reading centre at University of Sydney	No
VIP	Australia	1992-97	4313 (47.0)	≥40	Caucasian	Both	Yes	30-degree; stereo; 2 field; film	Reading centre at University of Sydney	No

BDES, the Beaver Dam Eye Study; BMES, the Blue Mountains Eye Study; Funagata, the Funagata study; HES, the Handan Eye Study; Hisayama, the Hisayama study; Jiangning, the Jiangning Eye Study; LALES, the Los Angeles Latino Eye Study; MESA, the Multi-Ethnic Study of Atherosclerosis; SiMES, the Singapore Malay Eye Study; SCES, the Singapore Chinese Eye Study; SINDI, the Singapore Indian Eye study; VIP, the Visual Impairment Project; OCT, optical coherence tomography.

* Data only available for primary ERMs.

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Table 2. Age-standardised prevalence of epiretinal membrane by study

Study	Year	N at-risk	Crude prevalence (%)			Age-standardised prevalence (%, 95%CI)		
			CMR	PMF	Any ERM #	CMR	PMF	Any ERM #
All ERM ##								
BDES	1987-88	4802	-	-	-	4.8 (4.3-5.4)	1.7 (1.3-2.0)	6.4 (5.8-7.1)
BMES	1992-93	3490	4.8	2.7	7.0	3.8 (3.2-4.4)	1.7 (1.3-2.1)	5.5 (4.8-6.2)
Funagata	2000-02	1543	4.0	1.5	5.4	2.7 (1.9-3.4)	1.1 (0.6-1.5)	3.7 (2.8-4.6)
HES	2006-07	6565	2.2	0.7	3.4	2.3 (1.8-2.8)	0.6 (0.4-0.7)	3.5 (2.9-4.0)
Hisayama	1998	1765	3.2	0.9	4.0	2.2 (1.6-2.9)	0.5 (0.2-0.8)	2.8 (2.1-3.5)
Jiangning	2012-13	2005	5.0	3.4	8.4	4.5 (3.7-5.4)	3.1 (2.4-3.9)	7.6 (6.5-8.7)
LALES	2000-03	5982	16.3	2.2	18.5	16.6 (15.7-17.6)	2.5 (2.0-2.9)	19.0 (18.0-20.0)
MESA	2002-04	5960	25.1	3.8	28.9	21.5 (20.1-22.5)	3.0 (2.6-3.4)	24.5(23.4-25.6)
SiMES	2004-06	3265	5.8	5.9	11.8	4.7 (4.0-5.3)	4.6 (4.0-5.3)	9.3 (8.3-10.2)
SCES	2009-11	3353	-	-	-	7.0 (6.1-7.9)	7.5 (6.6-8.3)	13.0 (11.9-14.2)
SINDI	2007-09	3328	5.4	4.8	10.2	4.7 (4.0-5.3)	4.1 (3.4-4.7)	8.8 (7.9-9.7)
VIP	1992-97	4313	4.8	1.7	6.0	3.8 (3.3-4.4)	1.4 (1.1-1.8)	4.9 (4.4-5.5)
Pooled estimates	**NA**	**46371**	**-**	**-**	**-**	**6.5 (4.2-8.9)**	**2.6 (1.8-3.4)**	**9.1 (6.0-12.2)**
I^2						99.3	98.2	99.5

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Primary ERM									
BDES	1987-88	4125	-	-	-		4.5 (3.9-5.1)	1.3 (1.0-1.6)	5.8 (5.1-6.5)
Beixinjing	2010-11	3326	0.6	0.6	1.0		0.6 (0.3-0.9)	0.4 (0.2-0.6)	1.0 (0.6-1.3)
HES	2006-07	6196	2.0	0.5	3.0		2.1 (1.6-2.6)	0.4 (0.3-0.6)	3.1 (2.6-3.7)
Jiangning	2012-13	1854	4.6	3.1	7.7		4.3 (3.4-5.2)	3.0 (2.2-3.7)	7.3 (6.1-8.4)
LALES	2000-03	5631	15.6	1.9	17.5		16.1 (15.2-17.1)	2.2 (1.8-2.6)	18.4 (17.3-19.4)
MESA	2002-04	4761	22.7	3.3	26.1		20.2 (19.1-21.3)	2.7 (2.3-3.1)	23.0 (21.7-24.1)
SiMES	2004-06	2734	5.1	4.5	9.5		4.5 (3.7-5.2)	3.8 (3.2-4.5)	8.3 (7.3-9.3)
SINDI	2007-09	2324	3.8	2.7	6.5		4.3 (3.4-5.2)	2.8 (2.1-3.5)	7.0 (5.9-8.2)
Pooled estimates	**NA**	**30951**	**-**	**-**	**-**		**7.1 (3.3-10.8)**	**2.0 (1.3-2.8)**	**9.2 (4.7-13.8)**
I^2							99.6	97.9	99.7
Secondary ERM									
HES	2006-07	269	7.1	3.7	12.3		6.7 (1.9-11.5)	3.7 (0-7.8)	11.1 (5.0-17.3)
Jiangning	2012-13	151	10.6	6.6	17.2		7.0 (3.4-10.7)	3.9 (1.2-6.6)	10.9 (6.6-15.2)
LALES	2000-03	345	27.0	7.5	34.5		19.8 (14.4-25.2)	6.1 (2.9-9.3)	25.9 (20.0-31.9)
MESA	2002-04	1199	34.3	5.8	40.1		25.1 (22.2-28.1)	3.4 (2.5-4.4)	28.6 (25.6-31.6)
SiMES	2004-06	531	9.8	13.6	23.4		5.3 (2.5-8.1)	7.1 (5.2-9.0)	12.4 (9.1-15.7)
SINDI	2007-09	1004	9.1	9.8	18.8		5.1 (3.6-6.5)	6.0 (4.2-7.8)	11.0 (8.8-13.3)

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Pooled estimates	**NA**	**3499**	**-**	**-**	**-**		**11.4 (4.4-18.5)**	**5.1 (3.5-6.6)**	**16.6 (9.7-23.6)**
I^2							97.0	69.4	95.4

ERM, epiretinal membrane; CMR, cellophane macular reflex; PMF, preretinal macular fibrosis; BDES, the Beaver Dam Eye Study; BMES, the Blue Mountains Eye Study; Funagata, the Funagata study; HES, the Handan Eye Study; Hisayama, the Hisayama study; Jiangning, the Jiangning Eye Study; LALES, the Los Angeles Latino Eye Study; MESA, the Multi-Ethnic Study of Atherosclerosis; SiMES, the Singapore Malay Eye Study; SCES, the Singapore Chinese Eye Study; SINDI, the Singapore Indian Eye study; VIP, the Visual Impairment Project. #: Any ERM: both CMR and PMF. ##: All ERM: both primary and secondary ERM.

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Table 3. Age-standardised prevalence of epiretinal membranes by subgroups of interest

	CMR			PMF			Any ERM			Reference
	Studies (n)	Prevalence (%, 95%CI)	I^2 (%)	Studies (n)	Prevalence (%, 95%CI)	I^2 (%)	Studies (n)	Prevalence (%, 95%CI)	I^2 (%)	
Race/ethnicity										
Caucasian	4	8.9 (4.6-13.2)	99.4	4	2.0 (1.4-2.7)	88.8	4	11.0 (5.9-16.1)	99.5	2, 6, 7, 10
Asian	8	6.5 (4.6-8.5)	98.2	8	3.6 (2.2-4.9)	98.7	8	10.5 (7.2-13.8)	99.1	3, 4, 5, 8, 9, 10, 19, 20
WHO Regions										
The Americas	3	14.3 (3.6-25.0)	99.8	3	2.4 (1.6-3.2)	91.6	3	14.4 (5.6-23.2)	99.7	2, 10, 11
Western Pacific	9	4.0 (3.1-4.9)	94.2	9	2.7 (1.7-3.7)	98.3	9	8.5 (4.7-8.4)	98.2	3, 4, 5, 6, 7, 8, 9, 19, 20
Testing method										
Photography only	10	7.2 (4.2-10.1)	99.5	10	2.8 (1.9-3.7)	97.8	10	9.1 (6.0-12.2)	99.3	2, 3, 4, 5, 6, 7, 10, 11, 19, 20
Photography + OCT	2	3.4 (1.2-5.5)	94.8	2	1.8 (0-3.7)	97.6	2	5.5 (1.5-9.5)	97.7	8, 9
Photography										
Film	6	5.6 (2.5-8.8)	99.3	6	1.5 (0.9-2.0)	92.2	6	7.0 (3.4-10.7)	99.4	2, 5, 6, 7, 11, 20
Digital	6	7.4 (3.2-11.7)	99.5	6	3.8 (1.9-5.7)	99.0	6	10.0 (5.7-14.3)	99.3	3, 4, 8, 9, 10, 19
Image graded by										
RC at UW–Madison[#]	3	14.3 (3.6-25.0)	99.8	3	2.4 (1.6-3.2)	91.6	3	14.4 (5.6-23.2)	99.7	2, 10, 11
RC at USYD[##]	6	4.4 (3.5-5.4)	92.3	6	3.4 (1.9-4.9)	98.1	6	7.5 (5.1-9.9)	98.1	3, 4, 5, 6, 7, 19
Ophthalmologists or	3	3.0 (1.7-4.2)	90.9	3	2.6 (1.8-3.4)	98.1	3	4.6 (2.3-6.8)	96.4	8, 9, 20

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trained raters												

ERM, epiretinal membrane; CMR, cellophane macular reflex; PMF, preretinal macular fibrosis; OCT, optical coherence tomography.

#: Reading centre at University of Wisconsin-Madison; ##: Reading centre at University of Sydney.

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Table 4. Pooled odds ratios for risk of any epiretinal membrane

Risk factors		Studies	OR (95%CI)	I^2 (%)	Reference
Age (per year)		5	**1.19 (1.13, 1.26)**	95.1	3, 4, 5, 9, 10, 19
Sex (female)		6	**1.34 (1.17, 1.53)**	24.8	3, 4, 5, 9, 19, 20
Myopia (present)		4	1.21 (0.67, 2.19)	88.9	6, 8, 9, 19
Hyperopia (present)		3	1.23 (0.78, 1.94)	83.8	6, 8, 19
Hypertension (present)		6	1.04 (0.90, 1.20)	11.2	4, 5, 6, 9, 19, 20
Diabetes (present)		6	1.13 (0.92, 1.38)	17.1	4, 5, 6, 9, 19, 20
Smoking (present)		7	**0.67 (0.58, 0.78)**	0	3, 4, 5, 6, 8, 19, 20
Alcohol intake (present)		3	0.97 (0.75, 1.25)	0	6, 9, 20
Early AMD (present)		3	0.96 (0.63, 1.47)	60.7	2, 5, 6
BMI (per kg/m^2)		5	0.99 (0.98, 1.01)	0	4, 5, 6, 9, 20
Hyperlipidaemia (present)		4	1.05 (0.99, 1.11)	62.0	4, 5, 9, 20

AMD, age-related macular degeneration; BMI, body mass index; OR, odds ratio.

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Figure legends:

Figure 1. Flow chart of studies identified, included, and excluded.

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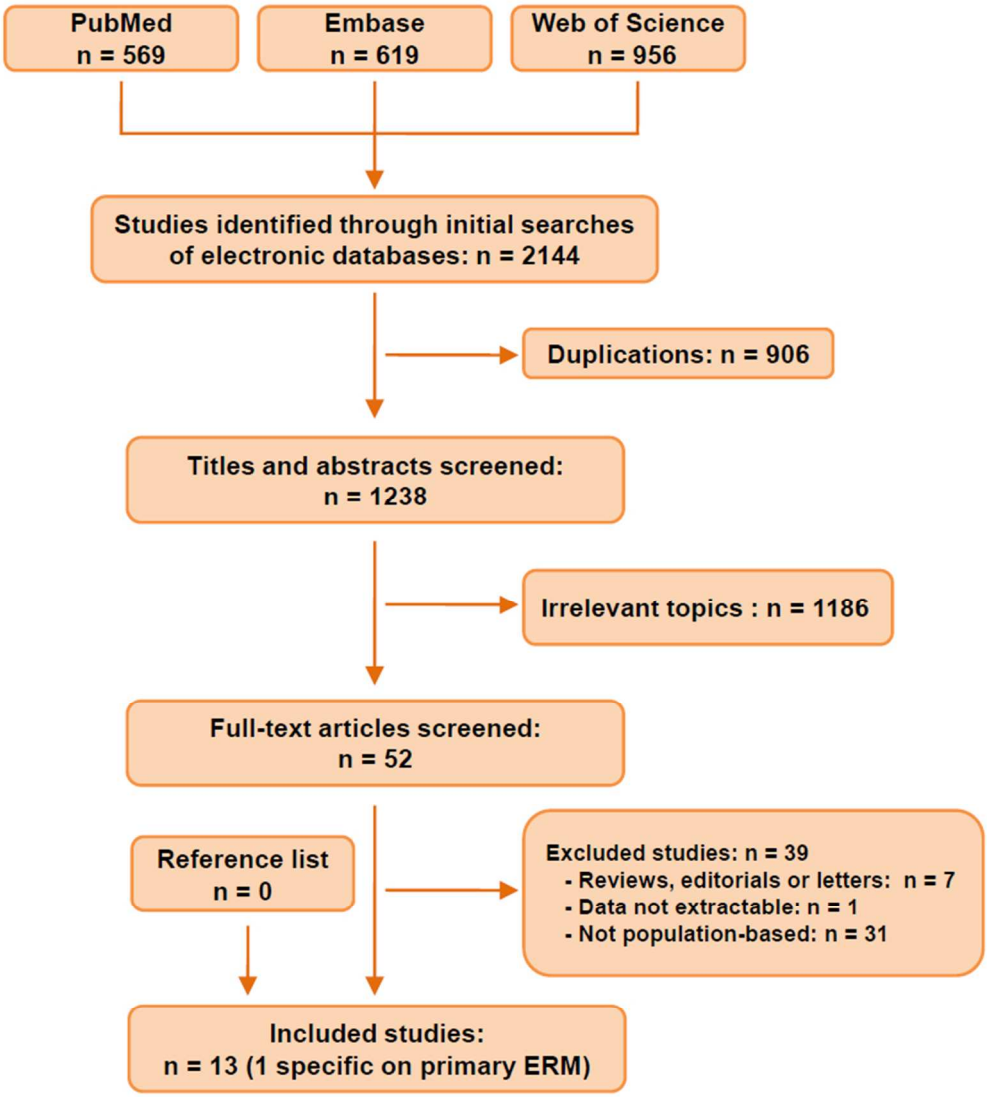

Flow chart of studies identified, included, and excluded.

69x77mm (300 x 300 DPI)

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The prevalence and risk factors of epiretinal membranes: a systematic review and meta-analysis of population-based studies

Wei Xiao, Xiaoyun Chen, William Yan, Zhuoting Zhu, Mingguang He

Literature search strategy

Terms

1. prevalence, epidemiology, epidemic*, risk
2. epiretinal membrane*; erm*; ierm*; cellophane macular reflex; preretinal macular fibrosis

Search strategy

PubMed (up to July 11, 2016)

#1	prevalence Fields: Title/Abstract	459388
#2	epidemiology Fields: Title/Abstract	143403
#3	epidemic* Fields: Title/Abstract	80597
#4	risk Fields: Title/Abstract	1507737
#5	#1 OR #2 OR #3 OR #4	1973101
#6	epiretinal membrane* Fields: Title/Abstract	2259
#7	ERM Fields: Title/Abstract	3126
#8	iERM Fields: Title/Abstract	23
#9	cellophane macular reflex Fields: All fields	18
#10	preretinal macular fibrosis Fields: All fields	69
#11	#6 OR #7 OR #8 OR #9 OR #10	4935
#12	#5 AND #11	569

Embase (up to July 11, 2016)

#1	prevalence	609473

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	Fields: ti, ab	
#2	epidemiology Fields: ti, ab	144993
#3	epidemic* Fields: ti, ab	89089
#4	risk Fields: ti, ab	2059117
#5	#1 OR #2 OR #3 OR #4	2622649
#6	epiretinal membrane* Fields: ti, ab	2491
#7	ERM Fields: ti, ab	3555
#8	iERM Fields: ti, ab	22
#9	cellophane macular reflex Fields: All fields	18
#10	preretinal macular fibrosis Fields: All fields	75
#11	#6 OR #7 OR #8 OR #9 OR #10	5570
#12	#5 AND #11	619

Web of Science (All Databases, 1980 to July 11, 2016)

All languages, all document types

#1	TS = prevalence	684438
#2	TS = epidemiology	1440407
#3	TS=epidemic*	100419
#4	TS=risk	2386116
#5	#1 OR #2 OR #3 OR #4	3597103
#6	TS=epiretinal membrane*	3045
#7	TS=ERM	369
#8	TS=iERM	21
#9	TS=cellophane macular reflex	17
#10	TS=preretinal macular fibrosis	67
#11	#6 OR #7 OR #8 OR #9 OR #10	6344
#12	#5 AND #11	956

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Table S1. Appraisal criteria for study methodology

Quality Criteria	Maximum score
1. Representing the general population	1
2. Appropriately recruiting the population	1
3. Adequate response rate (>70%)	1
4. Objective documentation of the outcomes	1

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Table S2. Quality score of included studies

Study	Representing the general population	Appropriately recruiting the population	Adequate response rate (>70%)	Objective documentation of the outcomes	Total score
BDES	1	1	1	1	4
Beixinjing	1	1	1	1	4
BMES	1	1	1	1	4
Funagata	1	1	0	1	3
HES	1	1	1	1	4
Hisayama	1	1	0	1	3
Jiangning	1	1	1	1	4
LALES	1	1	1	1	4
MESA	1	1	1	1	4
SCES	1	1	1	1	4
SiMES	1	1	1	1	4
SINDI	1	1	1	1	4
VIP	1	1	1	1	4

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PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not available
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6, Suppl. info
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

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PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10, table2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	table 2-4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11, table3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1, 19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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