

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The prevalence and risk factors of epiretinal membranes: a systematic review and meta-analysis of population-based studies
AUTHORS	Xiao, Wei; Chen, Xiaoyun; Yan, William; Zhu, Zhuoting; He, Mingguang

VERSION 1 - REVIEW

REVIEWER	Ning Cheung Singapore Eye Research Institute / Singapore National Eye Centre
REVIEW RETURNED	10-Nov-2016

GENERAL COMMENTS	<p>This paper is well-written and organised, with adequate methodology and analysis.</p> <p>Page 13, last paragraph: Not all the OCT studies showed lower prevalence. The BDES OCT study did show higher prevalence of ERM (>30%). Was this study included in Table 3? Any hypothesis for these differences?</p> <p>For Table 3 and 4, it might be more informative to reference the studies included in the Studies (n) column, so that one can more easily check which studies were included.</p> <p>How about pooled odds ratios for factors associated with primary and secondary ERMs? Or for other subtypes of ERM (CMR and PMF)? It is known that PMF is more "clinically significant" because it is likely to be associated with visual impairment. The small number of cases in individual studies limit their ability to assess risk factors, and therefore this pooled analysis may be better suited to look at this if possible.</p>
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REVIEWER	Akhiro Kakehashi Saitama Medical Center, Jichi Medical University Japan
REVIEW RETURNED	17-Jan-2017

GENERAL COMMENTS	<p>General Comments</p> <p>This article is a meta-analysis of idiopathic epiretinal membranes (ERMs) that investigated the prevalence and risk factors for idiopathic ERMs. The authors reported that ERMs are relatively common in the aging population and only greater age and female gender are correlated with a significantly higher risk of development of ERMs. The results are just as we had imagined.</p> <p>Specific Comments</p>
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	As the authors mentioned, optical coherence tomography (OCT) is necessary to diagnose ERMs. However, of the 13 articles included in the meta-analysis, OCT was used in only two to diagnose the ERMs. I think that quite a few cases with a cellophane macular reflex (CMR) do not have an ERM but have a shallow posterior vitreous detachment (PVD) around the fovea. This is typically observed on OCT images in cases with an idiopathic macular hole with a CMR. Macular hole cases with a CMR do not have a ERM but have a shallow PVD around the macular hole. It is possible that the CMR disappears when a biomicroscopic PVD develops in some case with a CMR. I think the authors should mention this phenomenon.
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REVIEWER	Neil Scott Medical Statistics Team, University of Aberdeen, UK
REVIEW RETURNED	10-Feb-2017

GENERAL COMMENTS	<p>This review has generally been conducted to a high standard.</p> <p>I don't think the methodology used to conduct meta-analysis is clear enough and more details should be added. Were age-standardised prevalences reported in each paper or did these have to be calculated from stratified data that were presented in each?</p> <p>The surveys did not cover younger people. Does this mean that the prevalence in these groups was assumed to be zero when calculating age-standardised rates? I am not a clinician so don't know if this is sensible or not.</p> <p>Similarly, I did not find it clear how the results in Table 4 had been obtained. Is this pooling of adjusted odds ratios as reported in the papers or did you manage to obtain individual patient data?</p> <p>Why is I2 only reported for some tables? Nearly all analyses have extremely high heterogeneity but this does not seem to be commented on.</p> <p>Although the standard of written English is generally very good, I think this needs to be reviewed carefully to correct errors.</p> <p>P.9, line 20: Doesn't Singapore count as a South-East Asian country?</p> <p>P.9, line 47: I was confused between "any ERM" and "all ERM" in this paragraph. Is this correct?</p> <p>P.14, line 22: "associations between age and sex". I understand the meaning but the wording does not seem correct.</p>
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REVIEWER	Colm McAlinden University Hospitals Bristol, NHS Foundation Trust, Bristol, UK
REVIEW RETURNED	08-Apr-2017

GENERAL COMMENTS	Impressive and novel study with a large sample size. Good contribution to knowledge.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Ning Cheung

Institution and Country: Singapore Eye Research Institute / Singapore National Eye Centre

Please state any competing interests: None declared

This paper is well-written and organised, with adequate methodology and analysis.

Page 13, last paragraph: Not all the OCT studies showed lower prevalence. The BDES OCT study did show higher prevalence of ERM (>30%). Was this study included in Table 3? Any hypothesis for these differences?

[Response] With the introduction of SD-OCT, the 20-year BDES follow-up study indeed documented an extremely high prevalence of ERMs (34.1%). It was much higher than all the studies included in our analysis. Several factors might account for such differences. First, as a survival cohort, age of the participants (range: 63-102 years, mean 74.1 years) in BDES follow-up study was much greater than those in other cross-sectional studies (generally 40-80 years with mean age 50 years). Second, the percentage of subjects with positive history of cataract surgery was much higher in BDES follow-up study (24.5%) than the other ones. Cataract surgery was well documented as a risk factor for secondary ERMs. Owing to these features, we believed that BDES follow-up study may not properly represent the general population, thus we did not include this study either.

For Table 3 and 4, it might be more informative to reference the studies included in the Studies (n) column, so that one can more easily check which studies were included.

[Response] It is a very good point. In the revised Table 2 and 4, we have added a column to list all relevant references.

How about pooled odds ratios for factors associated with primary and secondary ERMs? Or for other subtypes of ERM (CMR and PMF)? It is known that PMF is more "clinically significant" because it is likely to be associated with visual impairment. The small number of cases in individual studies limit their ability to assess risk factors, and therefore this pooled analysis may be better suited to look at this if possible.

[Response] Actually, we at first attempted to pool the risks for CMR and PMF. Nevertheless, there were only two studies (i.e. BMES and MESA) reported their odds ratios separately. The paucity of literature would made the aggregated data less reliable, so we finally had to give up doing analysis for ERM subtypes.

Reviewer: 2

Reviewer Name: Akhiro Kakehashi

Institution and Country: Saitama Medical Center, Jichi Medical University, Japan

Please state any competing interests: None declared

General Comments

This article is a meta-analysis of idiopathic epiretinal membranes (ERMs) that investigated the prevalence and risk factors for idiopathic ERMs. The authors reported that ERMs are relatively common in the aging population and only greater age and female gender are correlated with a significantly higher risk of development of ERMs. The results are just as we had imagined.

Specific Comments

As the authors mentioned, optical coherence tomography (OCT) is necessary to diagnose ERMs. However, of the 13 articles included in the meta-analysis, OCT was used in only two to diagnose the ERMs. I think that quite a few cases with a cellophane macular reflex (CMR) do not have an ERM but have a shallow posterior vitreous detachment (PVD) around the fovea. This is typically observed on

OCT images in cases with an idiopathic macular hole with a CMR. Macular hole cases with a CMR do not have a ERM but have a shallow PVD around the macular hole. It is possible that the CMR disappears when a biomicroscopic PVD develops in some case with a CMR. I think the authors should mention this phenomenon.

[Response] We sincerely thank the reviewer's valuable comments. It is definitely possible that OCT helped to discriminate CMR and posterior vitreous detachment (PVD), which were quite similar to each other in colour retinal images. We have added it into the discussion section. Please refer to page 14.

Reviewer: 3

Reviewer Name: Neil Scott

Institution and Country: Medical Statistics Team, University of Aberdeen, UK

Please state any competing interests: None declared

This review has generally been conducted to a high standard.

I don't think the methodology used to conduct meta-analysis is clear enough and more details should be added. Were age-standardised prevalences reported in each paper or did these have to be calculated from stratified data that were presented in each?

[Response] Although several studies (e.g. HES and Jiangning Study) reported age-standardised prevalence from their national population statistics, majority of the studies only reported crude rates. To improve the comparability of studies, all age-standardised prevalence of each study in Table 1 were calculated by projecting the crude prevalences to the WHO world standard age-structure.

The surveys did not cover younger people. Does this mean that the prevalence in these groups was assumed to be zero when calculating age-standardised rates? I am not a clinician so don't know if this is sensible or not.

[Response] Epiretinal membrane (ERM) generally affects the elderly, typically those older than 40 years. Accordingly, almost all population-based surveys only covered that age group. When we calculated age-standardised rates, the prevalence in population younger than 40 was assumed to be zero unless otherwise provided.

Similarly, I did not find it clear how the results in Table 4 had been obtained. Is this pooling of adjusted odds ratios as reported in the papers or did you manage to obtain individual patient data?

[Response] Adjusted odds ratios in Table 4 were directly obtained from individual studies, not calculated by using individual patient data. We have specified this issue in the Method section (page 8). Besides, to make it clearer, we have added a column to list the relevant references in Table 4.

Why I² is only reported for some tables? Nearly all analyses have extremely high heterogeneity but this does not seem to be commented on.

[Response] It is good advice to report the heterogeneity values in all tables. We have added I² into Table 2. Indeed, great heterogeneity, especially for prevalence aggregation, was a clear limitation of this study. We sought to figure out the sources of heterogeneity through subgroup analysis. However, several key factors, like ethnicity, retinal image acquisition and grading methods, can only partly explain the heterogeneity. Pooled prevalences in each subgroup were still remarkably heterogeneous (all I² > 50%, Table 2 and 3), that is, unknown factors may affect the prevalence variation across studies. We have commented on this issue in Discussion section (page 15).

Although the standard of written English is generally very good, I think this needs to be reviewed carefully to correct errors.

[Response] We thank the reviewer's advice. One of our co-author (William Yan), who is a native English speaker, have read through the manuscript and corrected some errors.

P.9, line 20: Doesn't Singapore count as a South-East Asian country?

[Response] According to the WHO region classification, Singapore is actually categorized as a Western Pacific country (<http://www.who.int/about/regions/en/>, accessed on 29 May, 2017). This definition was widely used in recent epidemiological studies and meta-analysis (e.g. references with the following PMIDs: 20445186, 19043456, 24285620).

P.9, line 47: I was confused between "any ERM" and "all ERM" in this paragraph. Is this correct?

[Response] ERMs are divided into primary and secondary subtype according to its etiology. In this paper, "all ERM" means an individual with either primary or secondary ERM. According to the features on retinal images, both primary and secondary ERMs can be classified into two stages - CMR and PMF. The term "any ERM" was to represent subjects with any features of ERM (either CMR or PMF) in retinal images. These similar concepts were also used in some of our included literatures, such as SINDI, HES and Jiangning study. Moreover, we have clarified their definitions as the footnote under Table 2.

P.14, line 22: "associations between age and sex". I understand the meaning but the wording does not seem correct.

[Response] Thanks for the reviewer's comment. We have changed the wording, and it goes now as "...our data showed that only age and sex were significantly associated the risk of any ERMs".

Reviewer: 4

Reviewer Name: Colm McAlinden

Institution and Country: University Hospitals Bristol, NHS Foundation Trust, Bristol, UK

Please state any competing interests: None

Impressive and novel study with a large sample size.

Good contribution to knowledge.

VERSION 2 – REVIEW

REVIEWER	Akihiro Kakehashi Jichi Medial University, Saitama Medical Center Japan
REVIEW RETURNED	22-Jun-2017

GENERAL COMMENTS	This meta-analysis study of idiopathic epiretinal membrane (ERM) showed that ERMs are relatively common among aged population and only greater age and female significantly conferred a higher risk of ERMs. The results are just as we had imagined. The manuscript has improved after revision. I think this article can be published in BMJ open.
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REVIEWER	Neil Scott University of Aberdeen, UK
REVIEW RETURNED	13-Jun-2017

GENERAL COMMENTS	Thank you for responding to the reviewers' comments. Most of these have now been addressed. Although I think the methods for performing the analysis are now
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	<p>clearer, I still think that it should be made clearer in the statistical analysis section what methodologies have been used for Tables 2-3 and Table 4: meta-analysis of age-standardised prevalence followed by prognostic meta-analyses. There are still no references for the meta-analysis methods used and no justification for pooling prevalences when there is clearly a large amount of variability in the results. I could not find literature on meta-analysis of age-standardised prevalences to confirm this method is appropriate so it would be really useful to provide references.</p> <p>Some of the English in the added text needs careful review as the wording is still not quite correct (p.15: "fourth" instead of "forth" is just one example).</p> <p>Otherwise, I am happy for the article to be published.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Akihiro Kakehashi

Institution and Country: Jichi Medical University, Saitama Medical Center, Japan

Please state any competing interests: None declared

This meta-analysis study of idiopathic epiretinal membrane (ERM) showed that ERMs are relatively common among aged population and only greater age and female significantly conferred a higher risk of ERMs. The results are just as we had imagined. The manuscript has improved after revision. I think this article can be published in BMJ open.

[Response] We sincerely thank the reviewer's effort.

Reviewer: 3

Reviewer Name: Neil Scott

Institution and Country: University of Aberdeen, UK

Please state any competing interests: None declared

Although I think the methods for performing the analysis are now clearer, I still think that it should be made clearer in the statistical analysis section what methodologies have been used for Tables 2-3 and Table 4: meta-analysis of age-standardised prevalence followed by prognostic meta-analyses. There are still no references for the meta-analysis methods used and no justification for pooling prevalences when there is clearly a large amount of variability in the results. I could not find literature on meta-analysis of age-standardised prevalences to confirm this method is appropriate so it would be really useful to provide references.

[Response] Thanks for the reviewer's comments. We have further clarified the methodology of statistical analysis, and added relevant references in the revised manuscript. As for the method of age-standardizing prevalence, we adopted it from several previous systematic reviews and meta-analysis, which generated the pooled prevalence of some major eye diseases, including age-related macular degeneration (PMID. 20110127), diabetic retinopathy (PMID. 22301125) and retinal vein occlusion (PMID. 20022117).

Some of the English in the added text needs careful review as the wording is still not quite correct (p.15: "fourth" instead of "forth" is just one example).

[Response] We apologize for such spelling errors. The authors have carefully read through the manuscript, and have corrected such kind of mistakes.