**Factors Predicting the Onset and Progression of Pathologic Myopia: Systematic Review and Meta-analysis Protocol**

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\*This protocol is developed in accordance with guidance provided by the Cochrane Prognosis Methods Group (<https://methods.cochrane.org/prognosis/tools>), in conjunction with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist (<https://www.prisma-statement.org/Extensions/Protocols>).

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1. **Background**

**1.1 Description of Pathologic Myopia (PM) and Context**

In one of their seminal works describing pathologic fundus changes secondary to axial elongation, Curtin and Carlin1 noted that “the posterior fundus changes of the myopic eye are as striking as they are unique”. Yet, it is not until 45 years later, in 2015, that an international panel of established myopia researchers and retinal specialists was able to synthesise evidence and agreed upon a common classification framework for PM based on colour fundus photographs (Meta-analysis for Pathologic Myopia or Meta-PM),2 which hitherto had been subjected to considerable inconsistencies in nomenclature. For instance, PM was often used interchangeably (but erroneously) with high myopia, regardless of whether retinal complications characteristic of excessive axial length such as posterior staphyloma were present.3-5

Driven by an inordinately high prevalence of myopia in East Asia,6 PM has long been (i.e. as far back as 1999) a leading cause of visual impairment (VI) among adults in parts of Mainland China,7 Taiwan8 and Japan.9 10 In keeping with a projected steep rise in myopia prevalence worldwide (around 50% by 2050),6 the global prevalence of VI caused by PM is predicted to increase from 0.13% (95% CI 0.07% to 0.34%) in 2015 to 0.57% (95% CI 0.33% to 1.11%) by 2050.11 On top of substantial potential productivity loss (US$2 billion in 2015 based on conservative estimate),12 patient-reported outcomes like quality of life, e.g. mobility, emotional wellbeing, etc., are known to be strongly affected by severe PM — even when the presenting distance visual acuity (VA) is adjusted for, suggesting that its impact reaches far beyond a patient’s spatial resolution.13 14

**1.2 Health Outcomes of Interest: PM Onset & Progression**

Against this backdrop, several observational studies have been set up to shed light on risk factors associated with PM development (onset), i.e. among myopes without PM, and prognostic factors associated with PM progression.15-17 Nonetheless, the classification systems developed in the intervening years following Curtin and Carlin,1 such as Avila et al.,18 Tokoro19 and Hayashi et al.,20 were largely developed in silos and not adopted universally. This precluded the opportunity to synthesise evidence from different studies until recently. Based on META-PM, myopic maculopathy (also known as myopic macular degeneration), which is a prominent feature of PM, is categorised into (with increasing severity) “no myopic retinal lesions” (category 0), “tessellated fundus only” (category 1), “diffuse chorioretinal atrophy” (category 2), “patchy chorioretinal atrophy” (category 3) and “macular atrophy” (category 4).2 Three additional “plus” lesions, i.e. lacquer cracks (LC), myopic choroidal neovascularisation (mCNV) and Fuchs spot (FS), so called because they can either develop from or coexist with any of the myopic maculopathy categories, are also incorporated into META-PM.2 PM is defined as myopic maculopathy equal to or greater than category 2, and/ or the presence of any of the 3 ‘plus’ lesions, and/ or the presence of posterior staphyloma.2 21

**1.3 Why it is Important to do this Review**

A systematic review of risk factors and prognostic factors associated with PM (whether modifiable or unmodifiable) will contribute to the development of evidence-based risk stratification models. Highly myopic patients most at risk of developing mCNV, for instance, can be monitored more closely and treated with anti-VEGF at the earliest opportunity. This will help improve prognosis in the short to medium term (<4 years) at the very least.22 Unfortunately, the long-term prognosis of mCNV — even if treated with anti-VEGF — does not seem particularly favourable at present owing to the potential development of mCNV-related macular atrophy.23-25 Effective treatments are also not yet available for lesions like myopic maculopathy.26

Despite this, knowledge of modifiable risk factors (if present), e.g. smoking, derived from robust evidence synthesis can benefit clinical practice as high myopes (without PM) can be advised of the risk and choose to make appropriate lifestyle changes. Knowledge of modifiable prognostic factors can be used in a similar way to benefit patients already diagnosed with PM. In addition, knowledge of imaging biomarkers, such as those derived from colour fundus photographs, that predict PM onset/ progression may provide insight into the pathogenesis of PM, help generate hypothesis about potential genetic markers responsible for the disease or provide a priori indication of whether deep learning can be used to predict PM onset/ progression from ophthalmic images.

1. **Objectives**

The primary objective is to synthesise evidence from relevant longitudinal observational studies that utilise Meta-PM (from 2015 onwards) to grade fundus images for PM to identify: (1) risk factors associated with the development of PM among myopes without PM and (2) prognostic factors associated with the progression of PM among myopes already diagnosed with PM. The secondary objective is to review the adjusted predictive (concerned with onset) and prognostic (concerned with progression) value of all identified factors; that is, over and above the predictive value and prognostic value of core factors. Core risk factors include baseline age, sex and baseline severity of myopia, since high myopia is already known to be a significant risk factor for PM onset; core prognostic factors include baseline age and sex. Table 1 presents the review questions in the PICOTS format.

Table Review question in PICOTS format

|  |  |
| --- | --- |
| **PICOTS element** | **Description** |
| **P**opulation | 1. **Risk factors:** Individuals with any degree of myopia (spherical equivalent refraction ≤-0.50D) who do not have a diagnosis of PM (Meta-PM definition) at baseline. 2. **Prognostic factors:** Treatment-naive myopes, i.e. not receiving or have not received treatment for PM, who already have a diagnosis of PM at baseline (longitudinal). Other characteristics are same as above. |
| **I**ndex risk/ prognostic factors | All types of risk/ prognostic factors are of interest, i.e. demographic, behavioral, environmental, physiologic and genetic, whether they are modifiable or unmodifiable. |
| **C**omparator risk/ prognostic factors | Comparator factors are to be controlled for to obtain the adjusted predictive/ prognostic value of a given index factor. These comparator (core) risk and prognostic factors are:   1. **Risk factors:** baseline axial length (AL)/ spherical equivalent refraction (SER), baseline age and sex. 2. **Prognostic factors:** baseline age and sex. |
| **O**utcomes | 1. PM Onset: development of myopic maculopathy category≥2 (more severe than “tessellated fundus”), and/ or any of the 3 “plus” lesions, namely LC, mCNV and FS. 2. PM progression: An increase (≥1) in Meta-PM myopic maculopathy category (from category 2 at least), and/ or enlargement of existing chorioretinal atrophy/ “plus” lesion(s), and/ or development of new “plus” lesion(s) among those with a diagnosis of PM. |
| **T**iming | 1. **Risk factors:** measured at least 1 year before the fundus image, from which PM diagnosis is made, is taken. 2. **Prognostic factors:** measured around the same time as when the fundus image, on which PM grading is performed, is taken. There needs to be a minimum time interval of 1 year between baseline (when fundus images are first graded and when prognostic factors are measured) and follow-up. |
| **S**etting | Intended setting is primary care to provide predictive information about myopic patients without PM (especially high myopes) and prognostic information about patients with PM during routine eye examinations. |

1. **Methods**

This section is developed in accordance with the formulated review questions presented in the PICOTS format above (Table 1), in conjunction with the CHARMS checklist.27

**3.1 Inclusion and Exclusion criteria**

**3.1.1 Types of Studies**

To review risk factors for PM onset, we will include any (analytic) longitudinal observational studies, namely (prospective or retrospective) cohort and (nested or not nested) case-control studies. Studies that are purely descriptive (e.g. case series, case report), without full-text articles or not reported in English will be excluded. Only studies conducted in or after the year Meta-PM was developed (2015) will be included. We do not anticipate finding any relevant interventional studies due to obvious ethical and practical challenges.

**3.1.2 Targeted Population**

We will include studies involving individuals aged 7 years or above to reduce the likelihood of including patients with congenital, syndromic form of myopia, e.g. myopia secondary to Marfan’s syndrome, Stickler’s syndrome, etc. Myopia (spherical equivalent refraction, SER ≤-0.50D as per International Myopia Institute definition28) of any severity will be included, as posterior staphyloma is not found exclusively in high myopes.26 We will exclude studies that recruit participants who are receiving/ have received treatment in relation to PM, regardless of whether they are prophylactic or experimental, such as anti-VEGF for mCNV and scleral reinforcement for posterior staphyloma. There are no restrictions to the targeted population in terms of ethnicity and geographic location. We will also not exclude studies based on the setting from which their study population is derived; that is, participants recruited/ sampled from primary care (e.g. community practices), secondary care (e.g. hospital-based high myopia clinic monitoring patients at risk of developing PM), pre-existing cohort studies. We will include studies that derive their study participants from a pre-existing clinical trial as long as the intervention in question is not judged to have any influence on the course of PM development/ progression (if the intervention arm is sampled). If only a subset of participants enrolled in a study meet the inclusion criteria of the present review, we will endeavour to extract data relevant to this subgroup only, if possible. Otherwise, the study will be excluded altogether.

**3.1.3 Types of Risk/ Prognostic Factors**

We will not restrict the present review to any particular type(s) of risk and prognostic factors, whether they are modifiable or unmodifiable — i.e. demographic, environmental, physiologic (e.g. imaging biomarkers) and genetic — nor will we exclude studies based on the method (e.g. contact vs non-contact tonometry) employed to measure a given factor (e.g. intraocular pressure). However, predictive or prognostic model studies that employ any artificial intelligence approaches (e.g. random forest, convolutional neural network), where uncertainty (e.g. 95% CI) of “weight”/ “feature importance”/ “risk” estimates are often unavailable — and hypothesis testing is therefore not/ cannot be attempted — will be excluded.

**3.1.4 Types of Outcomes to be Predicted**

The present review will only include studies that investigate PM onset, PM progression, or a combination of both as their health outcome. PM onset is defined as the development (between baseline and follow-up) of Meta-PM myopic maculopathy category≥2 (more severe than “tessellated fundus”), and/ or any of the 3 “plus” lesions — namely LC, mCNV and FS. PM progression is defined as an increase (≥1) in Meta-PM myopic maculopathy category (from category 2 at least), and/ or enlargement of existing chorioretinal atrophy/ “plus” lesion(s), and/ or development of new “plus” lesion(s) among those with a diagnosis of PM.

Fundus grading needs to be performed on colour fundus photographs — at a minimum — and may be supplemented with other imaging modalities such as OCT and fluorescein angiography. We acknowledge that posterior staphyloma is often best imaged with widefield imaging modalities as opposed to a conventional 30-degree to 50-degree fundus camera because wide macular staphyloma is the predominant subtype of posterior staphyloma.26 As we anticipate few (if any) studies to have access to widefield imaging modalities, and they may therefore choose not to grade posterior staphyloma, we decide not to incorporate posterior staphyloma into our definition of PM onset and progression. However, we will include studies that have posterior staphyloma in their definition of PM onset/ progression. Such studies will be noted explicitly and synthesised separately.

We will exclude studies that do not define PM onset and/ or progression a priori even if the post-hoc definition is similar to ours. We will also exclude studies that only investigate some component(s) of PM onset/ progression, e.g. “plus” lesions are not part of the definition, only mCNV is investigated, etc. Studies that investigate factors associated with PM recurrence or treatment response will be excluded. We will also exclude studies that combine both PM onset and PM progression (as defined in the present review) into one health outcome and analysed as a single event. Finally, we will exclude longitudinal studies that have a time horizon (between measurement of risk/ prognostic factors and PM onset/ progression) of less than 1 year.

**3.2 Search Methods for Identification of Studies**

**3.2.1 Electronic Searches**

We will search MEDLINE (Ovid), EMBASE (Ovid) and Scopus from 1 January 2015 (the year Meta-PM was developed) to the most recent date, while restricting the searches to human studies and publications in English. Search keywords pertaining to PM will include the following and their spelling/ associated variants: “degenerative myopia” (MeSH), “choroidal neovascularization” (MeSH), “myopia” (MeSH), “myopic maculopathy”, “myopic macular degeneration”, “staphyloma”, “lacquer crack”, “fuchs spot”, “tessellated fundus/ retina”, “diffuse/ patchy chorioretinal atrophy”, “macular atrophy”, “pathologic myopia”, etc.

We will apply a validated search filter for prognostic research (Ingui filter),29 which include terms like “validation”, “prediction”, “rule”, “outcome”, “prognosis”, “decision”, “criteria”, “finding”, “score”, “factor”, etc., to the PM keywords above. The full search strategy for MEDLINE using the Ovid interface can be found in Appendix 1.

**3.2.2 Searching Other Resources**

We will handsearch the reference list of each included study to identify relevant publications.

**3.3 Data Collection**

**3.2.2 Selection of Studies**

All studies retrieved by electronic searching of different databases and handsearching will be imported into Covidence (<https://www.covidence.org>) — which is a popular primary screening and data extraction tool. After removing duplicates, titles and abstracts will be screened independently by two reviewers. We will remove studies that clearly do not meet the selection criteria of the present review at this stage. We will then obtain full-text copies of eligible studies and studies whose eligibility cannot be determined adequately at the title/ abstract screening stage. The same reviewers will then apply the selection criteria independently to each retrieved full-text article. Any disagreements will be resolved through discussion between the two reviewers. A third reviewer will be consulted if consensus cannot be reached. We will document the reasons for exclusion during full-text selection.

**3.2.3 Data Extraction and Management**

A data extraction form containing the following items will be built using Covidence.

* General information: last name of first author and publication year.
* Study design: type of study (e.g. retrospective cohort study, nested case-control study, etc.); predictive or prognostic, or both; source of data (e.g. pre-existing cohort, randomised control trial)
* Participants: inclusion criteria; exclusion criteria; recruitment method (e.g. consecutive); country and ethnicity; age range; myopia range; method to determine refractive error (e.g. cycloplegic or non-cycloplegic refraction, objective or subjective, etc.); study dates.
* PM grading: imaging modalities for PM grading, if applicable (e.g. OCT and fluorescein angiography on top of colour fundus photography); definition of PM onset; definition of PM progression; description of grading protocol (e.g. number of assessors, mCNV appearance on fundus photos); whether the same outcome definition is used in all participants; number and duration of follow-up(s).
* Risk/ prognostic factors: number and type of predictors (e.g. demographic, behavioural, physiologic); measurement method and definition of each predictor; timing of predictor measurement (e.g. at patient presentation); whether each predictor assessed is blinded to health outcome (e.g. PM or no PM); whether multivariable adjustment is performed (e.g. accounting for other predictors).
* Sample size: total number of participants
* Missing data: number of participants with any missing value (include predictors and outcomes); number of participants with missing data for each predictor and reasons; handling of missing data (e.g. complete-case analysis, imputation).
* Statistical analysis: method (e.g. logistic regression, cox regression); effect measure (e.g. odds ratio, risk ratio)
* Results: unadjusted and adjusted effect measures (e.g. odds ratio, relative risk, hazard ratio); standard error and 95% CI; p-values.

The form will first be piloted on at least 2 studies by two reviewers and appropriate refinement will be made before performing further data extraction. Two reviewers will carry out data extraction independently, following the same process to resolve any disagreements as above.

**3.2.4 Assessment of Risk of Bias**

We will appraise each included study using the Quality in Prognosis Studies (QUIPS) tool which has 6 domains of assessment: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding as well as statistical analysis and reporting.30 A study is judged to have a low risk of bias if all 6 domains are judged to have low risk; moderate risk of bias if no high-risk domain but at least 1 domain is judged to have moderate risk; high risk of bias if at least 1 domain is judged to have high risk. This will again be carried out independently by two reviewers, following the same process to resolve any disagreements as before.

Given our focus on reviewing all relevant risk/ prognostic factors (i.e. not specifically interested in a single factor), with a specific interest in the predictive/ prognostic value of each factor after adjustment for core (i.e. comparator factors in PICOTS) factors, we will change the domain “study confounding” to “adjustment for core risk/ prognostic factors”, where high risk of bias refers to a total lack of appropriate adjustment for core factors (i.e. for risk factors: baseline degree of myopia, age and sex; for prognostic factors: age and sex). The preliminary risk of bias form can be found in Appendix 2. Where multiple versions of publications are available for a study, we will consider all publications related to that study collectively. Assessors will not be blinded to study authors, institutional affiliations and journal.

**3.2.4 Measures of Association**

We will extract all unadjusted and adjusted measures of association from included studies. As we anticipate all included studies to report dichotomous outcome, we will use odds ratio in the natural log scale as the common measure of associations for meta-analysis purposes owing to its favourable mathematical properties (e.g. unbounded). Where studies report risk ratio (relative risk), conversion to odds ratio will be carried out using an appropriate conversion method. To communicate effect, we will either use risk ratio (relative risk) or risk difference, where possible, since they are relatively easy to understand.

**3.2.5 Dealing with Missing Data**

We will calculate missing odds ratio or relative risk if a 2-by-2 frequency table can be constructed from the raw data. When uncertainty of an effect measure (e.g. standard error, 95% CI) is not reported, we will estimate it from the p-value associated with the effect measure using the approach outlined in Chapter 6 of Cochrane Handbook for Systematic Reviews of Interventions.32 We will attempt to contact the study authors to retrieve relevant missing information, e.g. effect measure, uncertainty, etc., if none of the above is feasible.

**3.2.6 Assessment of Heterogeneity**

We anticipate considerable heterogeneity of included studies in terms of the length of follow-up, depending on the source of data — i.e. prospectively recruited cohort where length may be shorter than if electronic health record of a large hospital is analysed retrospectively — from which the study participants are sampled. We will explore the impact of this potential source of heterogeneity by synthesising associations within different subgroups as defined by the length of follow-up. We do not anticipate any significant amount of heterogeneity arising from outcome measurements, since included studies must use Meta-PM as their PM classification framework.

**3.4 Data Synthesis**

**3.2.1 Data synthesis and Meta-analysis**

We will perform a meta-analysis of the adjusted odds ratio (adjusted for core factors at the very least as outlined in 3.2.4) associated with each risk/ prognostic factor if sufficiently similar studies (n≥2) are available. We define “sufficiently similar” as:

* Follow-up period should not differ by more than 1 year (e.g. 5-year PM progression can be pooled with 6-year progression but not 10-year progression).
* Core risk factors, if applicable, are included in the multivariable analysis, i.e. baseline severity of myopia (expressed as AL or SER), baseline age, sex.
* Core prognostic factors, if applicable, are included in the multivariable analysis, i.e. baseline age and sex.
* Exact same definition of outcome; specifically, whether posterior staphyloma is included in the definition of PM onset or progression.

When judging whether a meta-analysis is appropriate, we will also consider if eligible (i.e. sufficiently similar) studies are reasonably resistant to biases based on QUIPS. If, for example, all eligible studies are found to have high risk of bias, we will not proceed with meta-analysis. The heterogeinty of eligible studies will also be quantified using the I2 statistic which gives the percentage of the observed vairablity in effect estimates due to heterogeneity across studies — above and beyond random chance/ sampling error alone. We will use a cutoff of 90% to decide if meta-analysis is appropriate.

If a meta-analysis is judged to be appropriate, we will pool the estimates separately for risk factors and prognostic factors. The generic inverse-variance method will be used to calculate the weighted average of odds ratio. As prognostic research is known to be a lot more heterogeneous than interventional studies,31 we will use a random-effects model which assumes that different studies are estimating different, yet related, effects.33 Forest plots with the pooled estimates will be used to present meta-analysis results, or without the pooled estimates as a visualisation tool if we only perform narrative synthesis. We will use RevMan 5.4.1 to perform meta-analysis and to produce forest plots.

**3.2.2 Rating of Certainty of Evidence and Summary of Findings**

We will use a modified version of Grades of Recommendation, Assessment, Development and Evaluation (GRADE),34 i.e. specifically adapted to suit reviews of prognostic factor studies, to assess the overall quality and certainty in evidence for the summary estimates (odds ratio) for each risk/ prognostic factor. Two reviewers will carry out the assessment independently and resolve any disagreements through discussion or involve a third reviewer if necessary. We will produce a different summary of findings table for risk factors and prognostic factors. We will interpret the results in light of GRADE assessment.

**References**

1. Curtin BJ, Karlin DB. Axial length measurements and fundus changes of the myopic eye. I. The posterior fundus. *Trans Am Ophthalmol Soc* 1970;68:312-34.

2. Ohno-Matsui K, Kawasaki R, Jonas JB, et al. International photographic classification and grading system for myopic maculopathy. *Am J Ophthalmol* 2015;159(5):877-83.e7. doi: 10.1016/j.ajo.2015.01.022 [published Online First: 20150126]

3. Fredrick DR. Myopia. *BMJ* 2002;324(7347):1195-9. doi: 10.1136/bmj.324.7347.1195

4. Paluru PC, Nallasamy S, Devoto M, et al. Identification of a novel locus on 2q for autosomal dominant high-grade myopia. *Invest Ophthalmol Vis Sci* 2005;46(7):2300-7. doi: 10.1167/iovs.04-1423

5. Young TL, Ronan SM, Alvear AB, et al. A second locus for familial high myopia maps to chromosome 12q. *Am J Hum Genet* 1998;63(5):1419-24. doi: 10.1086/302111

6. Holden BA, Fricke TR, Wilson DA, et al. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. *Ophthalmology* 2016;123(5):1036-42. doi: 10.1016/j.ophtha.2016.01.006 [published Online First: 20160211]

7. Xu L, Wang Y, Li Y, et al. Causes of blindness and visual impairment in urban and rural areas in Beijing: the Beijing Eye Study. *Ophthalmology* 2006;113(7):1134.e1-11. doi: 10.1016/j.ophtha.2006.01.035 [published Online First: 20060502]

8. Hsu WM, Cheng CY, Liu JH, et al. Prevalence and causes of visual impairment in an elderly Chinese population in Taiwan: the Shihpai Eye Study. *Ophthalmology* 2004;111(1):62-9. doi: 10.1016/j.ophtha.2003.05.011

9. Iwase A, Araie M, Tomidokoro A, et al. Prevalence and causes of low vision and blindness in a Japanese adult population: the Tajimi Study. *Ophthalmology* 2006;113(8):1354-62. doi: 10.1016/j.ophtha.2006.04.022

10. Yamada M, Hiratsuka Y, Roberts CB, et al. Prevalence of visual impairment in the adult Japanese population by cause and severity and future projections. *Ophthalmic Epidemiol* 2010;17(1):50-7. doi: 10.3109/09286580903450346

11. Fricke TR, Jong M, Naidoo KS, et al. Global prevalence of visual impairment associated with myopic macular degeneration and temporal trends from 2000 through 2050: systematic review, meta-analysis and modelling. *Br J Ophthalmol* 2018;102(7):855-62. doi: 10.1136/bjophthalmol-2017-311266 [published Online First: 20180426]

12. Naidoo KS, Fricke TR, Frick KD, et al. Potential Lost Productivity Resulting from the Global Burden of Myopia: Systematic Review, Meta-analysis, and Modeling. *Ophthalmology* 2019;126(3):338-46. doi: 10.1016/j.ophtha.2018.10.029 [published Online First: 20181017]

13. Fenwick EK, Ong PG, Sabanayagam C, et al. Assessment of the psychometric properties of the Chinese Impact of Vision Impairment questionnaire in a population-based study: findings from the Singapore Chinese Eye Study. *Qual Life Res* 2016;25(4):871-80. doi: 10.1007/s11136-015-1141-1 [published Online First: 20150929]

14. Wong YL, Sabanayagam C, Ding Y, et al. Prevalence, Risk Factors, and Impact of Myopic Macular Degeneration on Visual Impairment and Functioning Among Adults in Singapore. *Invest Ophthalmol Vis Sci* 2018;59(11):4603-13. doi: 10.1167/iovs.18-24032

15. Chen SJ, Cheng CY, Li AF, et al. Prevalence and associated risk factors of myopic maculopathy in elderly Chinese: the Shihpai eye study. *Invest Ophthalmol Vis Sci* 2012;53(8):4868-73. doi: 10.1167/iovs.12-9919 [published Online First: 20120724]

16. Asakuma T, Yasuda M, Ninomiya T, et al. Prevalence and risk factors for myopic retinopathy in a Japanese population: the Hisayama Study. *Ophthalmology* 2012;119(9):1760-5. doi: 10.1016/j.ophtha.2012.02.034 [published Online First: 20120510]

17. Liu HH, Xu L, Wang YX, et al. Prevalence and progression of myopic retinopathy in Chinese adults: the Beijing Eye Study. *Ophthalmology* 2010;117(9):1763-8. doi: 10.1016/j.ophtha.2010.01.020 [published Online First: 20100505]

18. Avila MP, Weiter JJ, Jalkh AE, et al. Natural history of choroidal neovascularization in degenerative myopia. *Ophthalmology* 1984;91(12):1573-81. doi: 10.1016/s0161-6420(84)34116-1

19. Tokoro T. Types of Fundus Changes in the Posterior Pole. Atlas of Posterior Fundus Changes in Pathologic Myopia. Tokyo: Springer-Verlag 1998:5-22.

20. Hayashi K, Ohno-Matsui K, Shimada N, et al. Long-term pattern of progression of myopic maculopathy: a natural history study. *Ophthalmology* 2010;117(8):1595-611, 611.e1-4. doi: 10.1016/j.ophtha.2009.11.003 [published Online First: 20100305]

21. Ohno-Matsui K, Lai TY, Lai CC, et al. Updates of pathologic myopia. *Prog Retin Eye Res* 2016;52:156-87. doi: 10.1016/j.preteyeres.2015.12.001 [published Online First: 20160106]

22. Ohno-Matsui K, Ikuno Y, Lai TYY, et al. Diagnosis and treatment guideline for myopic choroidal neovascularization due to pathologic myopia. *Prog Retin Eye Res* 2018;63:92-106. doi: 10.1016/j.preteyeres.2017.10.005 [published Online First: 20171028]

23. Kasahara K, Moriyama M, Morohoshi K, et al. SIX-YEAR OUTCOMES OF INTRAVITREAL BEVACIZUMAB FOR CHOROIDAL NEOVASCULARIZATION IN PATIENTS WITH PATHOLOGIC MYOPIA. *Retina* 2017;37(6):1055-64. doi: 10.1097/IAE.0000000000001313

24. Ruiz-Moreno JM, Montero JA, Araiz J, et al. INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY FOR CHOROIDAL NEOVASCULARIZATION SECONDARY TO PATHOLOGIC MYOPIA: SIX YEARS OUTCOME. *Retina* 2015;35(12):2450-6. doi: 10.1097/IAE.0000000000000632

25. Sarao V, Veritti D, Macor S, et al. Intravitreal bevacizumab for choroidal neovascularization due to pathologic myopia: long-term outcomes. *Graefes Arch Clin Exp Ophthalmol* 2016;254(3):445-54. doi: 10.1007/s00417-015-3076-1 [published Online First: 20150618]

26. Ohno-Matsui K, Wu PC, Yamashiro K, et al. IMI Pathologic Myopia. *Invest Ophthalmol Vis Sci* 2021;62(5):5. doi: 10.1167/iovs.62.5.5

27. Moons KG, de Groot JA, Bouwmeester W, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Med* 2014;11(10):e1001744. doi: 10.1371/journal.pmed.1001744 [published Online First: 20141014]

28. Flitcroft DI, He M, Jonas JB, et al. IMI - Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiologic Studies. *Invest Ophthalmol Vis Sci* 2019;60(3):M20-M30. doi: 10.1167/iovs.18-25957

29. Ingui BJ, Rogers MA. Searching for clinical prediction rules in MEDLINE. *J Am Med Inform Assoc* 2001;8(4):391-7. doi: 10.1136/jamia.2001.0080391

30. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013;158(4):280-6. doi: 10.7326/0003-4819-158-4-201302190-00009

31. Riley RD, Moons KGM, Snell KIE, et al. A guide to systematic review and meta-analysis of prognostic factor studies. *BMJ* 2019;364:k4597. doi: 10.1136/bmj.k4597 [published Online First: 20190130]

32. Higgins J, Li T, Deeks J. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins J, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions* version 63, 2022.

33. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7(3):177-88. doi: 10.1016/0197-2456(86)90046-2

34. Huguet A, Hayden JA, Stinson J, et al. Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. *Syst Rev* 2013;2:71. doi: 10.1186/2046-4053-2-71 [published Online First: 20130905]

**Appendix 1: Full Search Strategy**

**Database: Ovid MEDLINE(R) <1946 to November Week 1 2022>**

**Search Strategy:**

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1 Myopia, Degenerative/ (1604)

2 Choroidal Neovascularization/ (6606)

3 Myopia/ (18920)

4 2 and 3 (231)

5 1 or 4 (1831)

6 (myopi\* adj2 (maculopathy or (macula\* adj2 degenerat\*))).mp. (393)

7 (staphyloma and myopia).mp. (347)

8 (lacquer crack\* and myopia).mp. (119)

9 ((fuch\* adj2 spot\*) and myopia).mp. (32)

10 (myopi\* adj2 choroid\* adj2 neovascular\*).mp. (343)

11 ((tessellat\* adj2 (fundus or retina\*)) and myopia).mp. (42)

12 (((diffuse or patch\*) adj2 (chorioretina\* adj2 atroph\*)) and myopia).mp. (58)

13 ((macula\* adj2 atroph\*) and myopia).mp. (81)

14 (pathologi\* adj2 myopi\*).mp. (755)

15 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (2527)

16 (validat\* or predict\* or rule\*).mp. (2279170)

17 (predict\* and (outcome\* or risk\* or model\*)).mp. (1056215)

18 ((History or variable\* or criteria or scor\* or characteristic\* or finding\* or factor\*) and (predict\* or model\* or decision\* or identif\* or prognos\*)).mp. (4129742)

19 decision\*.mp. and ((model\* or clinical\*).mp. or Logistic Models/) (242345)

20 ((prognos\* or risk\*) and (history or variable\* or criteria or scor\* or characteristic\* or finding\* or factor\* or model\*)).mp. (2520078)

21 Risk Factors/ or (risk adj2 factor\*).mp. (1229733)

22 16 or 17 or 18 or 19 or 20 or 21 (6297753)

23 15 and 22 (778)

24 exp animals/ not humans.sh. (5059735)

25 23 not 24 (767)

26 limit 25 to english language (728)

27 limit 26 to yr="2015 -Current" (435)

**Appendix 2: Preliminary (23 Nov 2022) QUIPS Risk of Bias Form**

|  |  |  |
| --- | --- | --- |
| Domains | Signaling Items | Risk of Bias Ratings |
| 1. Study participation | (a) Adequate participation in the study by eligible persons (b) Description of the target population or population of interest (c) Description of the baseline study sample (d) Adequate description of the sampling frame and recruitment (e) Adequate description of the period and place of recruitment (f) Adequate description of inclusion and exclusion criteria | **High:** *the relationship between the PF and outcome is very likely to be different for participants and eligible non-participants*  **Moderate:** *the relationship between the PF and outcome may be different for participants and eligible non-participants*  **Low:** *the relationship between the PF and outcome is unlikely to be different for participants and eligible non-participants* |
| 1. Study attrition | (a) Adequate response rate for study participants (b) Description of attempts to collect information on participants who dropped out (c) Reasons for loss to follow-up are provided (d) Adequate description of participants lost to follow-up (e) There are no important differences between participants who completed the study and those who did not | **High:** *the relationship between the RF/ PF and outcome is very likely to be different for completing and non-completing participants*  **Moderate:** *the relationship between the PF and outcome may be different for completing and non-completing participants*  **Low:** *the relationship between the RF/ PF and outcome is unlikely to be different for completing and non-completing participants* |
| 1. Risk/ prognostic factor measurement | (a) A clear definition or description of the RF/PF is provided (b) Method of RF/ PF measurement is adequately valid and reliable (c) Continuous variables are reported or appropriate cutpoints are used (d) The method and setting of measurement of RF/PF is the same for all study participants (e) Adequate proportion of the study sample has complete data for the RF/PF (f) Appropriate methods of imputation are used for missing RF/PF data | **High**: *the measurement of the RF/ PF is very likely to be different for different levels of the outcome of interest*  **Moderate**: *the measurement of the RF/ PF may be different for different levels of the outcome of interest*  **Low**: *the measurement of the RF/ PF is unlikely to be different for different levels of the outcome of interest* |
| 1. Outcome measurement | (a) A clear definition of the outcome is provided (b) Method of outcome measurement used is adequately valid and reliable (c) The method and setting of outcome measurement is the same for all study participants | **High**: *the measurement of the outcome is very likely to be different related to the baseline level of the RF/ PF*  **Moderate**: *the measurement of the outcome may be different related to the baseline level of the RF/ PF*  **Low**: *the measurement of the outcome is unlikely to be different related to the baseline level of the RF/ PF* |
| 1. Adjustment for core risk/ prognostic factors | (a) All other core RFs/PFs are measured, i.e. for RFs (baseline severity of myopia measured either as AL or SER, baseline age and sex); for PFs (baseline age and sex). (b) Measurement of all core RFs/ PFs is adequately valid and reliable (c) The method and setting of RF/ PF measurement are the same for all study participants (d) Appropriate methods are used to deal with missing values of core RFs/ PFs, such as multiple imputation (e) Core RFs/ PFs are accounted for in the analysis | **High**: *the observed effect of the PF on the outcome is very likely to be distorted by another factor related to RF/ PF and outcome*  **Moderate**: *the observed effect of the PF on outcome may be distorted by another factor related to RF/ PF and outcome*  **Low**: *the observed effect of the RF/ PF on outcome is unlikely to be distorted by another factor related to RF/ PF and outcome* |
| 1. Statistical analysis and reporting | (a) Sufficient presentation of data to assess the adequacy of the analytic strategy (b) Strategy for model building is appropriate and is based on a conceptual framework or model (c) The selected statistical model is adequate for the design of the study (d) There is no selective reporting of results | **High**: *the reported results are very likely to be spurious or biased related to analysis or reporting*  **Moderate**: *the reported results may be spurious or biased related to analysis or reporting*  **Low**: *the reported results are unlikely to be spurious or biased related to analysis or reporting* |