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

**Brief introduction**

Pathologic myopia (PM) is characterised by structural changes in the posterior segment of the eye as a result of excessive axial elongation.1 It has long been a leading cause of visual impairment in parts of East Asia where myopia prevalence is high.2-5 A systematic review of risk factors and prognostic factors associated with PM onset and progression has not been possible until very recently thanks to the development of a common, widely used classification framework for PM based on colour fundus photographs — Meta-analysis for Pathologic Myopia (Meta-PM) — in 2015.6 Prior to this, PM was subjected to considerable inconsistencies in nomenclature. For example, authors often conflated PM with high myopia in the absence of any structural complications.7-9 Observational studies aiming to identify PM risk/ prognostic factors before the introduction of Meta-PM, such as Chen et al.,10 Asakuma et al.,11 Liu et al.,12 etc., all used different definitions of PM, thereby precluding the opportunity for evidence synthesis.

**Preliminary Search**

From our preliminary search on MEDLINE (Ovid), at least 8 longitudinal studies published between 2018 and 2022 — all aimed to identify risk/ prognostic factors for PM — adopted the Meta-PM classification framework for PM.13-20 Follow-up length ranges from 5 to 18 years, involving 122 to 4439 participants from East Asia and Western Europe. This creates a good opportunity to synthesise evidence.

**Objectives**

We aim to perform the first systematic review of prognostic studies to:

1. Identify risk factors associated with PM onset among myopes (spherical equivalent refraction, SER≤-0.50D as per International Myopia Institute definition).21 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 lacquer cracks (LC), myopic choroidal neovascularization (mCNV) and Fuchs spot (FS).
2. Identify prognostic factors associated with PM progression among myopes (SER≤-0.50D) already diagnosed with PM at baseline. 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).

**Selection Criteria**

We will include (analytic) longitudinal observational studies with a follow-up period of at least 1 year that involve 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 of any severity will be included, given that PM is not found exclusively in high myopes.1 All types of risk/ prognostic factors, whether they are modifiable or unmodifiable, i.e. demographic, environmental, physiologic (e.g. imaging biomarkers) and genetic, will be considered. However, predictive or prognostic model studies that employ any artificial intelligence approaches (e.g. convolutional neural network), where uncertainty (e.g. 95% CI) of “weight”/ “feature importance”/ “risk” estimates are often not available, will be excluded. Studies that investigate factors associated with PM recurrence or treatment response will also be excluded.

**Search strategy**

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),22 which include terms like “validation”, “prediction”, “rule”, “outcome”, “prognosis”, “decision”, “criteria”, “finding”, “score”, “factor”, etc., to the PM keywords above.

**Data Synthesis**

We will assess the risk of bias of each included study using the Quality in Prognosis Studies (QUIPS) tool.23 We will perform a meta-analysis of the adjusted odds ratio associated with each risk/ prognostic factor if at least 2 included studies are found to be sufficiently homogeneous, e.g. similar follow-up length (difference not more than 1 year), risk factors adjusted for (at the very least) core factors which include baseline age, sex and baseline severity of myopia, etc., and if all eligible studies are reasonably resistant to biases (based on QUIPS assessment).

If a meta-analysis is judged to be appropriate, we will pool the estimates (odds ratio) 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,24 we will use a random-effects model which assumes that different studies are estimating different, yet related, effects.25 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.

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

We will use a modified version of Grades of Recommendation, Assessment, Development and Assessment (GRADE),26 i.e. specifically adapted to suit reviews of prognostic factor studies, to assess the overall quality and certainty in evidence for the summary estimates for each risk/ prognostic factor. We will produce a different summary of findings table for risk factors and prognostic factors. The results will be interpreted in light of GRADE assessment.

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