Prognostic factors for predicting progression of open angle glaucoma in adults: Cochrane Prognostic Review Protocol

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Prognostic factors for predicting progression of open angle glaucoma in adults

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (prognosis). The objectives are as follows:

Primary objective

To identify prognostic risk factors for progression of functional visual outcomes of primary open angle glaucoma (POAG) and pseudoexfoliation glaucoma (PXFG) in adults.

Table 1. PICOTS of the primary objective

Population	Adults ≥ 18 years of age of any ethnicity with open angle glaucoma (restricted to POAG and PXFG types) diagnosed as having open angle and evidence of glaucomatous damage. We will exclude studies evaluating risk factors on those who have already undergone surgical treatment for glaucoma.
Index prognostic factors	Prognostic factors associated with the progression of open angle glaucoma (restricted to POAG and PXFG types), evaluated in primary studies. Specific prognostic factors of interest will include, but are not restricted to: patient demographic information, such as age, sex, ethnicity, and socio-economic status; clinical data, such as comorbidities (presence or absence of cardiovascular disease, diabetes, hypothyroidism, obstructive sleep apnoea, etc.) and variations in systemic blood pressure (diastolic blood pressure, systolic blood pressure, mean arterial pressure); and functional and structural biomarkers in the prognostic context of the POAG or PXFG. We will also consider the stage of glaucoma at baseline (mild, moderate, severe types). We expect that prognostic factors will generally be measured at the time that participants enter the study, and after the diagnosis of POAG or PXFG has been made.
Comparator	Not applicable

Outcomes	Primary outcome: progression of glaucoma that has been ascertained by visual fields (VF) (functional assessment), or by VF plus imaging test (e.g. OCT) will be the main outcome of interest for the primary objective. We will exclude studies that have assessed structural outcomes using optical coherence tomography (OCT) only.
Timing	We will include studies that present the above outcome with at least 2 years follow-up after diagnosis. Ideally, the period of follow-up should be 5 years or more.
Setting	We will include studies undertaken in any care setting, with no geographical limitations.

Secondary objectives

To identify prognostic risk factors for progression of structural outcomes of POAG and PXFG in adults.

Table 2. PICOTS of the secondary objective

Population	Adults ≥ 18 years of age of any ethnicity with open angle glaucoma (restricted to POAG and PXFG types) diagnosed as having open angle and evidence of glaucomatous damage. We will exclude studies evaluating risk factors on those who have already undergone surgical treatment for glaucoma.
Index prognostic factors	We anticipate that there will be fewer studies that have assessed glaucoma progression using OCT. However, the prognostic factors that we will consider and expect to be measured in the included studies are similar to those for the primary objective.
Comparator	Not applicable
Outcomes	Progression of glaucoma that has been ascertained by OCT or any other imaging test (structural assessments) will be the outcome of interest for the secondary objective.
Timing	We will include studies that present the above outcome with at least 2 years follow-up after diagnosis. Ideally, the period of follow-up should be 5 years or more.
Setting	Studies undertaken in any care setting, with no geographical limitations.

Investigation of sources of heterogeneity between studies

We anticipate between-study heterogeneity relating to two key areas in this review:

- Clinical heterogeneity including characteristics of the participants such as ethnicity/race; primary interventions such as medical treatment, or laser treatment, or both for POAG or PXFG; concurrent interventions such as phacoemulsification +/- intraocular implantation in study cohorts.
- Methodological heterogeneity generated from different study designs and how robustly studies are conducted and their approach to analysis.

We will visually explore these potential sources of heterogeneity by grouping studies on forest plots. If a meta-analysis is possible and sufficient data are available, we will further investigate using subgroup analyses or meta-regression.

BACKGROUND

Description of the health condition and context

Health condition

Glaucoma is a chronic optic nerve disease that can lead to loss of vision if not identified and treated early. The global prevalence of glaucoma amongst the population aged 40 to 80 years is 3.54% (95% credible interval [CrI] 2.09 to 5.82). The number of people with glaucoma is predicted to increase to 111.8 million by the year 2040 (Tham 2014), as its prevalence increases with age. Glaucoma is the leading cause of irreversible blindness worldwide, and the second leading cause of blindness in high-income countries (Flaxman 2017). Early in the disease, glaucoma impairs the peripheral vision, which can affect quality of life. Glaucoma sight-loss is preventable by early detection and treatment. People with the condition are typically monitored in hospital eye-care services. Lifelong treatment entails reduction of intraocular pressure (IOP) by using eye drops on a daily basis, having laser treatment or surgery, or both.

There are various types of glaucoma, which are usually classified based on the appearance of the irido-corneal angle i.e. open angle and angle closure glaucomas. Primary open angle glaucoma (POAG) is the most common type of glaucoma and is characterised by a normal appearance of the anterior chamber angle. The global prevalence of POAG is highest in Africa (4.20%, 95% CrI 2.08 to 7.35) (Tham 2014). It is recognised that POAG is a multifactorial disorder, and the pathogenesis of POAG is characterised by progressive loss of retinal ganglion cells and optic nerve damage that leads to irreversible damage to the visual field (VF) (Chen 2019); however, early stages are asymptomatic. Pseudoexfoliation syndrome is an identifiable disease entity, frequently associated with open angle glaucoma (OAG), known as pseudoexfoliation glaucoma (PXFG). PXFG is the most common type of secondary OAG worldwide and its prevalence increases markedly with age (Ritch 1994; Tekin 2019).

Treatment

Appropriate management of glaucoma is crucial considering the cost of interventions and associated complications. Patients with glaucoma seek care at varying degrees of disease severity. One major concern in glaucoma management decision-making is the likelihood of the disease progressing to an advanced stage (De Moraes 2017). The rate of progression varies greatly across individuals. Identification of people at high risk of disease progression is important to individualise management decisions.

The first-line approach in managing POAG is usually through topical medications, preferably a prostaglandin analogue (European Glaucoma Society 2021) aiming to lower IOP (Conlon 2017). Laser trabeculoplasty can also be considered as a first-line treatment. When medical and laser treatments fail to control the disease, surgical management such as trabeculectomy is often considered (Bicket 2021; Sayyad 2012).

Moment of prognostication

The 'moment of prognostication' is considered as any time after a person has been diagnosed as having POAG and prior to the occurrence of changes in perimetry, associated with or without structural changes in optical coherence tomography (OCT) or other imaging tests. Currently, there is no definition of a 'clinically significant glaucoma level' in the evidence base to clearly define the moment of prognostication.

Clinical context

Glaucoma is an asymptomatic condition until it progresses to an advanced stage. Therefore, central visual acuity is preserved until the disease progresses to an advanced stage. The diagnostic evaluation of glaucoma is a complex process. An accurate clinical diagnosis of glaucoma entails meticulous assessment of physical signs of anterior segment and optic nerve head supported by clinical tests, such as perimetry and OCT.

Close monitoring of VFs is necessary to determine whether treatment is effective and that glaucoma is stable during the follow-up of a patient. In addition, assessing structural properties, such as appearance of the optic nerve head and thickness of nerve fibre layers, can also help to detect disease progression. Regular follow-up is required throughout the lifespan of a patient.

Description of the existing clinical pathway and identification of patients with the problem

Open angle glaucoma is asymptomatic at early stages. Patients do not generally seek eye care early in the disease, and it is not uncommon to diagnose glaucoma at advanced stages. Once glaucoma is diagnosed, patients are typically managed in secondary care. Usually treatment is effective to reduce the risk of rapid disease progression (Hollands 2013). However, there is uncertainty about how best to identify people at higher risk of progression and visual loss. Risk stratification, aligned with identified prognostic risk factors would help to individualise monitoring strategies, e.g. different tests and frequency of testing and eventually help prevent sight loss. It also would be cost-effective for service providers and payers.

Description of the prognostic factors and predictive models based on primary studies

This Cochrane Prognostic Review will focus on identifying prognostic factors for progression of glaucoma as defined according to VF functional or OCT structural changes. Some known risk factors from landmark primary studies and systematic literature reviews are described below.

There is a large volume of literature on potential risk factors for glaucoma and for glaucoma progression. The main risk factors associated with prevalence of progression of glaucoma are older age (Rudnicka 2006), elevated IOP (Sommer 1991), African ancestry (Cole 2021), positive family history of glaucoma (McMonnies 2017), low diastolic blood pressure (Tielsch 1995), and high myopia (Alward 2000; Kwon 2009; Marcus 2011). Evidence in landmark studies such as the Advanced Glaucoma Intervention Study (AGIS) (AGIS 2000), Collaborative Initial Glaucoma Treatment Study (CIGTS) (Musch 2009), Early Manifest Glaucoma Trial (EMGT) (Heijl 2002), and United Kingdom Glaucoma Treatment Study (UKGTS) (Garway-Heath 2015) has shown that lowering IOP results in preservation of VF in patients with POAG. Studies also show that factors, such as socio-economic status, may affect the prognosis of the disease. However, evidence is scarce on how these and other factors affect disease progression.

Description of prognostic factors and predictive models based on reviews/systematic reviews

Kim 2020 explored the association between ocular perfusion pressure (OPP) and the risk of POAG. Their findings suggested that in patients with high baseline IOP, who already have a higher risk of glaucoma, low OPP might be another risk factor for progression. Bowe 2015 reported that there was no difference in mean systolic or diastolic diurnal and nocturnal blood pressure between patients with or without progressive VF loss (nocturnal dips > 10% in systolic blood pressure odds ratio (OR) 3.32, 95% confidence interval (CI) 1.84 to 6.00, and diastolic blood pressure OR 2.09, 95% CI 1.20 to 3.64). Zhang 2019 reported that focal loss measured by Fourier Domain OCT (FD-OCT) or VF along with central corneal thickness (CCT) are strong baseline predictors for the rate of glaucoma progression.

A systematic review by Ernest 2013 found that factors such as age, baseline VF loss, baseline IOP, and exfoliation syndrome were clearly associated with glaucomatous VF progression. They concluded that association was unlikely for family history of glaucoma, atherosclerosis, systemic hypertension, sex, systolic blood pressure, and myopic refractive error, which contradicts the risk factors described in the current evidence base. This clearly highlights the gaps in evidence and the need for a comprehensive prognostic systematic review on this topic. Currently, IOP is the only modifiable risk factor for glaucoma; thus, identifying other modifiable risk factors will lead to better outcomes in disease management. The following risk factors have been generally identified and described in individual studies.

Higher intraocular pressure (IOP)

The UKGTS reported higher IOP as a risk factor for deterioration of glaucoma (hazard ratio (HR) 1.07 per mmHg, 95% CI 1.02 to 1.12, P = 0.008) (Founti 2020). Similarly, IOP was identified as a risk factor (OR 1.22, 95% CI 1.18 to 1.25) in a national level survey conducted in Nigeria by Kyari 2016. Kelly 2020, in another UK study, reported that IOP lowering therapy was associated with lower risk of conversion of OHT to POAG (HR 0.45, 95% CI 0.35 to 0.57, P < 0.001). Pleet 2016 reported poor control of IOP as a major risk factor for becoming blind due to POAG.

Age

An analysis of medical records of 45,309 patients in the UK by Kelly 2020 identified older age as a risk factor for conversion of ocular hypertension (OHT) to POAG (HR 1.35 per decade, 95% CI 1.22 to 1.50, P < 0.001). Older age was reported as a risk factor in VF worsening by Kim 2019. A similar finding (OR 1.04, 95% CI 1.03 to 1.05) was observed in a national level survey conducted by Kyari 2016.

Cardiovascular disease

Chan 2017 studied rapidly progressing patients and found that cardiovascular disease is an important risk factor for rapid disease progression, irrespective of the level of IOP control. They observed that patients with cardiovascular disease were 2.33 times more likely to develop rapidly progressive glaucoma. Lee 2020 reported that low blood pressure identified during follow-up was correlated with structural progression of eyes with normotension glaucoma. Similarly, Martínez 2010 identified other risk factors, such as lower diastolic blood pressure, lower mean arterial pressure, and lower end-diastolic velocity in the ophthalmic artery.

Additional risk factors

Current evidence shows that there are other possible risk factors, such as obstructive sleep apnoea (Bahr 2020), high fasting plasma glucose level (Choi 2020), and dietary factors (Mylona 2020; Na 2020). However, there is no strong evidence base showing an association with progression of POAG.

Health outcomes

Progression of POAG and PXFG amongst newly diagnosed participants, evaluated by VF data with or without OCT measures.

Measures of disease progression or health outcomes

Glaucoma progression can be assessed using functional measure i.e. with VF testing, or structural tests (such as OCT), or both. The time-points for the evaluation of health outcomes in POAG or PXFG will be at least 2 years of follow-up after diagnosis. Ideally, the period of follow-up should be 5 years or more.

Visual field progression

Standard automated perimetry is the standard test used routinely to detect and measure disease progression from the functional point of view. There are different types of perimeters and, in addition, there are different ways of analysing glaucoma progression using VF tests, most commonly event analyses (designed to answer whether the VF has progressed or not) or trend analyses (designed to quantify the rate of progression over time).

Common technologies used in glaucoma are the Humphrey and Octopus perimeters, typically evaluating the central 24 or 30 degrees of the VF. Linear regression of changes of global indices, such as mean defect (MD) in Octopus, or mean deviation (MD) or visual field index (VFI) in Humphrey are widely used. Other statistical approaches evaluating changes in the different locations of the VF, such as glaucoma progression analysis (GPA) in Humphrey, are also available. In Octopus local defect (LD) can be used to identify presence of local progression.

Gard 2018 reported that the presence of central VF (24-2) damage at baseline is significantly associated with more rapid global progression and this aids risk stratification in order to provide closer surveillance of aggressive treatment. De Moraes 2012 validated a risk assessment model for patients with treated glaucoma and concluded that this prediction model showed moderate level of accuracy in estimating the future VF outcomes in an independent population with glaucoma. De Moraes 2017 conducted a literature review and reported that decreasing the rate of VF progression by 30% can have significant effects on health-related quality of life. Also, we should note that some people with glaucoma who are not found to be progressing by VF testing alone, may actually have changes detected by combined evaluation of structure and function.

In a non-interventional cohort study, Aptel 2015 showed that rate of progression and severity of the disease can be assessed by MD and VFI. The reported rate of progression in this study was -0.32 dB/year (-0.83% VFI/year) in eyes with early glaucoma, -0.52 dB/year (-1.81% VFI/year) in moderate glaucoma, -0.54 dB/year (-2.35% VFI/year) in advance glaucoma and -0.45 dB/year (-1.97% VFI/year) in

severe glaucoma. Summarising these type of rates of VFIs will be useful in developing a model for assessing prognostic risk factors.

Structural progression by imaging tests, including optical coherence tomography (OCT)

Visual field measurements alone may not be sufficient to detect disease progression. Therefore, it may be useful to conduct the structural evaluation, especially in the early stages of the disease. Trend and event analyses can be used to define structural progression. Daneshvar 2019 reported that baseline structural OCT measures predicted subsequent VF progression in contrast to semi-quantitative optic disc measures. They have suggested that OCT-based structural measures should be included in prognostic models of glaucomatous VF deterioration.

Why it is important to do this review

This Cochrane Review will consider prognostic factor studies only (restricted to POAG and PXF types).

Understanding prognostic factors is useful for clinicians and patients to estimate the risk of disease progression. However, at present it is difficult to interpret all available information. To our knowledge, there are currently no systematic reviews specifically on prognostic factors for the progression of glaucoma. Understanding risk factors of progression is also helpful for designing glaucoma services and prioritising resources for those at higher risk of visual loss. A Cochrane Prognostic Review on this topic would be invaluable for decision-makers, healthcare professionals, service providers, and policymakers, as well as for service users and their families. The findings of this review could help clinicians to counsel patients and provide advice regarding modifiable and unmodifiable factors, determine treatment and follow-up package in a more personalised manner, and consider early surgical intervention in high-risk groups.

The review's findings may help guide the design and analysis of future interventional clinical trials, and to identify areas where further research is required.

In 2017, the UK National Institute for Health and Care Excellence (NICE) glaucoma guidelines identified risk prediction tools to predict risk of developing chronic open angle glaucoma and risk of sight loss as a top research recommendation (NICE 2017). Our review aims to address this research priority by identifying prognostic factors that could be considered in future risk prediction tools. This will be useful in designing glaucoma management plans and public health strategies in the future. In addition, review findings may be useful in facilitating development of predictive models specifically for POAG.

OBJECTIVES

Primary objective

To identify prognostic risk factors for progression of functional visual outcomes of primary open angle glaucoma (POAG) and pseudoexfoliation glaucoma (PXFG) in adults.

Table 1. PICOTS of the primary objective

Population	Adults ≥ 18 years of age of any ethnicity with open angle glaucoma (restricted to POAG and PXFG types) diagnosed as having open angle and evidence of glaucomatous damage. We will exclude studies evaluating risk factors on those who have already undergone surgical treatment for glaucoma.
Index prognostic factors	Prognostic factors associated with the progression of open angle glaucoma (restricted to POAG and PXFG types), evaluated in primary studies. Specific prognostic factors of interest will include, but are not restricted to: patient demographic information, such as age, sex, ethnicity, and socio-economic status; clinical data, such as comorbidities (presence or absence of cardiovascular disease, diabetes, hypothyroidism, obstructive sleep apnoea, etc.) and variations in systemic blood pressure (diastolic blood pressure, systolic blood pressure, mean arterial pressure); and functional and structural biomarkers in the prognostic context of the POAG or PXFG. We will also consider the stage of glaucoma at baseline (mild, moderate, severe types). We expect that prognostic factors will generally be measured at the time that participants enter the study, and after the diagnosis of POAG or PXFG has been made.
Comparator	Not applicable
Outcomes	Primary outcome: progression of glaucoma that has been ascertained by visual fields (VF) (functional assessment), or by VF plus imaging test (e.g. OCT) will be the main outcome of interest for the primary objective. We will exclude studies that have assessed structural outcomes using optical coherence tomography (OCT) only.
Timing	We will include studies that present the above outcome with at least 2 years follow-up after diagnosis. Ideally, the period of follow-up should be 5 years or more.

Setting	We will include studies undertaken in any care setting, with no geographical limitations.

Secondary objectives

To identify prognostic risk factors for progression of structural outcomes of POAG and PXFG in adults.

Table 2. PICOTS of the secondary objective

Population	Adults ≥ 18 years of age of any ethnicity with open angle glaucoma (restricted to POAG and PXFG types) diagnosed as having open angle and evidence of glaucomatous damage. We will exclude studies evaluating risk factors on those who have already undergone surgical treatment for glaucoma.
Index prognostic factors	We anticipate that there will be fewer studies that have assessed glaucoma progression using OCT. However, the prognostic factors that we will consider and expect to be measured in the included studies are similar to those for the primary objective.
Comparator	Not applicable
Outcomes	Progression of glaucoma that has been ascertained by OCT or any other imaging test (structural assessments) will be the outcome of interest for the secondary objective.
Timing	We will include studies that present the above outcome with at least 2 years follow-up after diagnosis. Ideally, the period of follow-up should be 5 years or more.
Setting	Studies undertaken in any care setting, with no geographical limitations.

Investigation of sources of heterogeneity between studies

We anticipate between-study heterogeneity relating to two key areas in this review:

- Clinical heterogeneity including characteristics of the participants such as ethnicity/race; primary interventions such as medical treatment, or laser treatment, or both for POAG or PXFG; concurrent interventions such as phacoemulsification +/- intraocular implantation in study cohorts.
- Methodological heterogeneity generated from different study designs and how robustly studies are conducted and their approach to analysis.

We will visually explore these potential sources of heterogeneity by grouping studies on forest plots. If a meta-analysis is possible and sufficient data are available, we will further investigate using subgroup analyses or meta-regression.

METHODS

Criteria for considering studies for this review

We will include studies that have assessed prognostic factors of POAG of PXFG according to the PICOTS parameters described in Table 1 and Table 2.

Types of studies

Inclusion criteria

Eligible study designs will include population-based studies cohort and case-control studies involving patients who have not had previous treatment for glaucoma by surgeries. We will also include randomised controlled trials (RCTs) that evaluated medical, laser, or surgical therapeutic interventions to prevent glaucoma progression where one comparison group was untreated. We will include studies based on longitudinal registry data and hospital records. It is essential that included studies must have evaluated prognostic factors for the progression of glaucoma.

Exclusion criteria

We will exclude any study with less than 2 years follow-up. In addition, we will exclude case reports, editorials, letters to editors, and conference abstracts as those not being completed research studies.

Targeted population

The targeted population will consist of adults (≥ 18 years of age) of any gender with glaucoma (restricted to POAG and PXFG types), diagnosed as having open angle and evidence of glaucomatous damage. We will include studies involving participants of all ethnicities from any geographical location and socioeconomic background.

Those who have been previously medically treated or treated with laser for glaucoma; or are currently undergoing medical or laser treatment, or both; are eligible for inclusion.

Population exclusion criteria

We will exclude studies involving participants who have other types of glaucoma other than POAG and PXFG types.

Types of prognostic/predictive factor(s) or model(s)

We will consider prognostic factors associated with the progression of open angle glaucoma (restricted to POAG and PXFG types), evaluated in primary studies.

We aim to identify prognostic factors that are associated with progression of POAG and PXFG. These prognostic factors of interest will include: patient demographic information, such as age, sex, ethnicity, and socio-economic status; clinical data, such as comorbidities (presence or absence of cardiovascular disease, diabetes, hypothyroidism, obstructive sleep apnoea, etc.); functional and structural ocular or systemic biomarkers in the context of the progression of open angle glaucoma.

It is expected that prognostic factors will generally be measured at the time that participants enter the study, and at the time or shortly after the diagnosis of POAG or PXFG has been made. We anticipate that these potential prognostic factors had been measured using standard methods/clinical procedures in the primary studies (i.e. IOP using tonometry recorded in mmHg etc.). We will also consider the stage of glaucoma at baseline based on the reported VF findings (Humphrey VF MD: stratified by mild, or moderate, or both < -12dB, severe > -12dB). We will also accept VF measurements from other types of perimeters, such as MD in Octopus. However, we anticipate that it is unlikely to have sufficient data for within study subgroups, and it would be more feasible to conduct between study comparisons using MD across studies.

Types of outcomes to be predicted

We plan to assess the health outcomes of: progression of open angle glaucoma amongst newly diagnosed participants (restricted to POAG and PXFG), functional outcomes evaluated by progressive VF data with or without OCT measures, and structural outcomes evaluated by OCT or other measures.

The time-points for the evaluation of health outcomes in this review will be at least 2 years of follow-up after diagnosis. Ideally, the period of follow-up should be 5 years or more. We understand that it may not be sensible to assess the outcomes based on time-points at individual level but study level i.e. time-points are more likely to be related to the study design characteristics and not the participant characteristics at the baseline. We will consider different duration of follow-up i.e. 2 years, 3 to 5 years, long term > 5 years, if primary data are available. If not, we will accept and present other time points.

Electronic searches

The search strategy will include the following key concepts: POAG, PXFG, study design terms, prognostic factors, and risk factors. The Cochrane Eyes and Vision (CEV) Information Specialist will search the following electronic databases. There will be no restrictions to language or date of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL; latest issue) (which contains the CEV Trials Register) in the Cochrane Library (Appendix 1).
- MEDLINE Ovid (1946 to present) (Appendix 2).
- Embase Ovid (1980 to present) (Appendix 3).
- US National Institutes of Health Ongoing Trials Register - ClinicalTrials.gov (www.clinicaltrials.gov) (Appendix 4).
- World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp) (Appendix 5).

Searching other resources

We will supplement the search by screening reference lists of eligible articles. We will not include grey literature in this review because we do not expect these will be sufficiently informative to justify the extra resources required in conducting the searches.

Data collection

Selection of studies

We will pilot test the inclusion criteria, to assess agreement amongst the review authors and begin the screening process after getting a substantial level of agreement between review authors. Two review authors (MPP and QD) will independently assess the titles and abstracts of articles identified by the search strategy, and will classify as either potentially eligible or ineligible. We will use the Covidence screening package for this purpose, and will obtain the full-text articles of potentially eligible studies. Two review authors (MPP and QD) will independently classify the full-text articles as either eligible or ineligible. We will resolve discrepancies by discussion or by consulting an arbitrator if necessary (AAB or GV). We will graphically report the selection process of studies in a PRISMA flow diagram and document the reasons for exclusions at full text in a 'Characteristics of excluded studies' table.

Data extraction and management

We will use the items of CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS-PF) (Moon 2014) to guide data extraction (Appendix 6). We will extract data using a pre-piloted data extraction form on the Covidence platform.

To assess the potential sources of heterogeneity, we will extract data in two stages. In the first stage we will map studies based on the study design, prognostic factors evaluated, severity of disease, type of treatment, follow-up time, and type of analysis. We will collect first stage data using Extraction 2.0 in Covidence and then import into RevMan Web 2022. In the second stage, we will extract specific prognostic factor data of interest from relevant studies, which have been identified during the stage one as having common factors and variables appropriate for meta-analysis. We will collect these more detailed data for analysis into a pilot-tested MS Excel spreadsheet designed based on Cochrane guidelines.

Two review authors (MPP and QD) will independently extract data. We will resolve any disagreements through discussion, by involving a third review author (AAB or GV), or by consensus of the review author team if necessary.

We will extract the data, if available, and enter according to the following categories.

- Study
  - Title
  - Authors' contact details
  - Sources of funding

- Year of publication
- Source of data
  - Type of study (prospective or retrospective cohort or case-control studies, RCTs evaluating therapeutic interventions)
  - Sources of data (e.g. hospital, other study, etc.) if not prospective
  - Setting (e.g. primary, secondary, tertiary)
- Participants
  - Eligibility and recruitment method
  - Participant description (e.g. baseline characteristics)
  - Details of treatments received (e.g. doses, durations, specific treatment type/name etc.)
  - Study dates and period of follow-up
- Outcomes to be predicted
  - Definition and method of measurement of progression
  - Types of outcomes
  - Time of outcome occurrence
- Prognostic factors
  - Number and type of prognostic factors
  - Definition and method for measurement
  - Timing of prognostic factor measurement
- Sample size
  - Sample size calculation
  - Number of patients and number of outcomes
  - Outcomes per variable
- Missing data
  - Number missing by treatment group
  - Any differences in missingness by treatment group
  - Method of handling missing data
- Analysis
  - Modelling method
- Results
  - Unadjusted and adjusted prognostic effect estimates (e.g. risk ratio [RR], OR, HR, or mean difference) for each prognostic factor of interest and corresponding measure of uncertainty (e.g. standard errors, variances, or CIs)
  - For each extracted adjusted prognostic effect estimate of interest, the set of adjusted factors

Assessment of risk of bias in included studies

We will utilise the Quality in Prognosis Studies (QUIPS) tool to assess the risk of bias of included studies (Appendix 7; Riley 2019). We will pilot test the QUIPS tool to ensure similar approach and assessment across the review author team. Two review authors (MPP and QD) will independently assess the risk of bias and a third review author (AAB or GV) will arbitrate discrepancies.

We will consider following domains for each eligible study:

- Study participation: is the study sample representative of the population of interest?
- Study attrition: is the sample data available representative of the study sample?
- Prognostic factor measurement: is the prognostic factor of interest measured similarly for all participants?
- Outcome measurement: is the outcome of interest measured similarly for all participants?
- Adjustment for other prognostic factors: are potentially confounding factors appropriately accounted for?
- Statistical analysis and reporting: is the statistical analysis appropriate, and are all primary outcomes reported?

Each risk of bias domain will be assessed as low, moderate, or high, and we will provide descriptions as to the reasoning for our assessments.

Measures of association or predictive performance measures to be extracted

We will extract estimates of prognostic effect, including HRs, RRs, ORs, or mean differences for each factor of interest, with a measure of their uncertainty (i.e. standard errors, variances, or CIs). We will also document adjusted prognostic effect estimates and the set of adjustment factors used.

Dealing with missing data

We will contact study authors if we require further information, primary data, or clarification.

Assessment of heterogeneity

We anticipate that there will be statistical heterogeneity due to clinical and methodological differences between studies. Since the I^2 statistic may not be appropriate in certain situations, given the different models and factors that may be used and adjusted for across studies, we will quantify heterogeneity using Tau^2. Where there is an appropriate number of studies included in a meta-analysis, we will also present 95% prediction intervals (Rücker 2008).

Assessment of reporting deficiencies

We will assess small-study effects using contour-enhanced funnel plots when 10 or more studies are included in a meta-analysis. We anticipate variation in effect measures and length of follow-up, and therefore expect to include few studies in each meta-analysis. Consequently, we do not plan to perform funnel plot asymmetry tests given the low power of such tests when studies are few (Debray 2017).

Data synthesis

Data synthesis and meta-analysis approaches

We will conduct meta-analysis in clinically-relevant groups using a random-effects approach. We will analyse the effect in their original measures, unless the data are available in such a way as to permit conversion to the most common measure of association in the studies included in meta-analysis. Specifically, we will meta-analyse the OR as common measure of association, given that most study types we have specified for inclusion are observational and retrospective in nature. For different effect measures that cannot be converted, we will present those (i.e. HR or mean differences) on separate subfigures for the comparison. Similarly, unadjusted and adjusted associations will be meta-analysed and reported separately. Our primary analyses will focus on unadjusted estimates, and we will present adjusted estimates as secondary analysis to prevent correlated/entangled effects. If we determine that conducting a meta-analysis is inappropriate due to heterogeneity, we will report a narrative or tabulated summary. We will use 95% CIs and prediction intervals throughout.

Subgroup analysis and investigation of heterogeneity

We will initially undertake subgroup analysis, if appropriate, given by visual examination of forest plots (with or without meta-analysis) depending on the quantity and quality of data available. We will formally explore reasons for heterogeneity using meta-regression if meta-analysis is possible and given the quality and quantity of data available.

We propose to keep the number of subgroup analyses to a minimum to prevent generating potentially misleading results and to minimise the risk of spurious statistical findings. We will undertake subgroup analysis based on the study methodology and study features, such as different outcome measurement (e.g. trend analysis versus event analysis), different definitions used to assess the progression, differences in categorising the disease severity (mild, or moderate, or both VF MDv < -12dB and severe VF MDv > -12dB), and duration of follow-up (e.g. 2 years, 3 to 5 years, long term > 5 years).

Sensitivity analysis

We will assess the effects of unmeasured confounding through a sensitivity analysis provided adequate data are available. We will perform sensitivity analyses to explore the impact of studies with high risk bias and retrospective studies on effect sizes.

Conclusions and summary of findings

We will provide the summary of prognostic estimates table assessing the certainty of the evidence using the GRADE modified tool for prognostic factors studies (Foroutan 2020). Two review authors will independently perform this assessment, and we will resolve any disagreement by consensus amongst the review author team. We will describe the factors that influence the certainty of the evidence generated in this Cochrane Review under domains of risk of bias, imprecision, inconsistency, indirectness, and publication bias. We will use the summary of prognostic estimates table to clearly identify the factors with the most significant prognostic influence on the development and progression of POAG.

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APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Glaucoma, Open-Angle] explode all trees
#2 open NEAR/2 angle NEAR/2 glaucoma*
#3 OAG or POAG
4low NEAR/2 tension NEAR/2 glaucoma*
#5 low NEAR/2 pressure NEAR/2 glaucoma*
#6 normal NEAR/2 tension NEAR/2 glaucoma*
#7 normal NEAR/2 pressure NEAR/2 glaucoma*
#8 MeSH descriptor: [Exfoliation Syndrome] this term only
#9 exfoliat* NEAR/2 syndrome*
#10 exfoliat* NEAR/2 glaucoma*
#11 pseudoexfoliat* NEAR/2 syndrome*
#12 pseudoexfoliat* NEAR/2 glaucoma*
#13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#14 MeSH descriptor: [Cohort Studies] this term only
#15 MeSH descriptor: [Case-Control Studies] this term only
#16 MeSH descriptor: [Follow-Up Studies] this term only
#17 MeSH descriptor: [Longitudinal Studies] this term only
#18 MeSH descriptor: [Prospective Studies] this term only
#19 MeSH descriptor: [Retrospective Studies] this term only
#20 MeSH descriptor: [Observational Study] this term only
#21 (cohort or longitudinal) NEAR/3 (stud* or trial*)
#22 case NEAR/1 control* NEAR/3 (stud* or trial*)
#23 follow NEAR/1 up NEAR/3 (stud* or trial*)
#24 case NEAR/2 series
#25 hospital NEAR/2 record*
#26 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25

#27#13 AND #26
#28 MeSH descriptor: [Randomized Controlled Trial] this term only
#29 random*
#30 #28 OR #29
#31 untreat* or placebo
#32 no NEAR/2 (treat* or intervention*)
#33 #31 OR #32
#34 #30 AND #33
#35 #13 AND #34
#36 #27 OR #35
#37 MeSH descriptor: [Prognosis] this term only
#38 MeSH descriptor: [Disease Progression] this term only
#39 MeSH descriptor: [Risk Factors] this term only
#40 (prognostic or prognosis or predict* or prevent*) NEAR/4 (glaucoma* or factor or factors or disease* or model* or progress*)
#41 risk NEAR/4 (progress* or predict* or factor or factors or disease*)
#42(progress* or severity) NEAR/4 (glaucoma* or disease*)
#43 (structural* or function* or baseline or predict*) NEAR/4 progress*
#44 (rate or rates or detect*) NEAR/4 (change* or worse* or loss*)
#45 visual NEAR/2 field NEAR/2 (loss* or progress* or change* or decreas* or deteriorat*)
#46 conversion NEAR/3 (POAG or OAG or glaucoma*)
#47 natural NEAR/1 history
#48 #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47
#49 MeSH descriptor: [Aged] explode all trees
#50 elderly
#51 old* NEAR/2 age*
#52 MeSH descriptor: [Intraocular Pressure] this term only
#53 (ocular or intra-ocular or intraocular) NEAR/2 pressure
#54 MeSH descriptor: [Ocular Hypertension] this term only
#55 ocular NEAR/2 hypertens*
#56 IOP or OHT
#57 #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56
#58 prognostic or prognosis or progression or risk*
#59# 37 OR #38 OR #39 OR #58
#60 central NEAR/2 cornea* NEAR/2 thick*
#61 CCT
#62 high NEAR/2 myopia
#63 ocular NEAR/2 blood NEAR/2 flow*
#64 ocular NEAR/2 perfusion NEAR/2 pressure*
#65 MeSH descriptor: [Blacks] explode all trees
#66 MeSH descriptor: [Africa, Western] explode all trees
#67 MeSH descriptor: [Caribbean Region] explode all trees
#68 Afr* NEAR/2 Caribbean*
#69 Afr* NEAR/2 American*
#70 west NEAR/2 (india* or indies)
#71 MeSH descriptor: [Family Health] this term only
#72 MeSH descriptor: [Age of Onset] this term only
#73 MeSH descriptor: [Delayed Diagnosis] this term only
#74 family NEAR/3 history NEAR/4 risk
#75 MeSH descriptor: [Genetic Association Studies] this term only
#76 MeSH descriptor: [Genetic Predisposition to Disease] this term only
#77 MeSH descriptor: [Genetic Variation] this term only
#78 MeSH descriptor: [Genome-Wide Association Study] this term only
#79 MeSH descriptor: [Genotyping Techniques] this term only
#80 genetic or genetics or genome or genotyp*
#81 MeSH descriptor: [Cardiovascular Diseases] explode all trees
#82 (cardiovascular or heart) NEAR/2 disease*
#83 MeSH descriptor: [Hypotension] this term only
#84 hypotension or hypotensive
#85 MeSH descriptor: [Hypertension] explode all trees
#86 hypertension or hypertensive
#87 blood NEAR/2 pressure*
#88 MeSH descriptor: [Blood Glucose] explode all trees

#89 (glucose or glycem*) NEAR/3 blood*
#90 MeSH descriptor: [Diet] explode all trees
#91 MeSH descriptor: [Feeding Behavior] this term only
#92 diet* or nutrition or eat or eating or lifestyle*
#93 MeSH descriptor: [Carbohydrates] this term only
#94 MeSH descriptor: [Vitamins] explode all trees
#95 MeSH descriptor: [Dietary Supplements] this term only
#96 (nutrition* or diet*) NEAR/2 supplement*
#97 vitamin*
#98 MeSH descriptor: [Carbohydrates] this term only
#99 MeSH descriptor: [Caffeine] this term only
#100 MeSH descriptor: [Alcoholic Beverages] this term only
#101 carbohydrate* or meat or salt or caffeine or coffee or alcohol*
#102 MeSH descriptor: [Sleep Apnea Syndromes] explode all trees
#103 apnea
#104 #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103
#105 36 AND 48
#106 36 AND 57 AND 59
#107 36 AND 104
#108105 OR 106 OR 107
#109 MeSH descriptor: [Incidence] this term only
#110 MeSH descriptor: [Mortality] explode all trees
#111 MeSH descriptor: [Follow-Up Studies] this term only
#112 prognos*
#113] predict*
#114 course*
#115 MeSH descriptor: [Prognosis] this term only
#116 diagnosed
#117 cohort*
#118 death
#119 MeSH descriptor: [Models, Statistical] explode all trees
#120# 109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119
#121 #13 AND #120
#122 #108 OR #121

Appendix 2. MEDLINE Ovid search strategy

1.exp glaucoma open angle/
2.(open adj2 angle adj2 glaucoma$).tw.
3.(OAG or POAG).tw.
4.(low adj2 tension adj2 glaucoma$).tw.
5.(low adj2 pressure adj2 glaucoma$).tw.
6.(normal adj2 tension adj2 glaucoma$).tw.
7.(normal adj2 pressure adj2 glaucoma$).tw.
8.exfoliation syndrome/
9.(exfoliat$ adj2 syndrome$).tw.
10.(exfoliat$ adj2 glaucoma$).tw.
11.(pseudoexfoliat$ adj2 syndrome$).tw.
12.(pseudoexfoliat$ adj2 glaucoma$).tw.
13.or/1-12
14.cohort studies/
15.case-control studies/
16.follow-up studies/
17.longitudinal studies/
18.prospective studies/
19.retrospective studies/
20.observational study/
21.((cohort or longitudinal) adj3 (stud$ or trial$)).tw.
22.(case adj1 control$ adj3 (stud$ or trial$)).tw.
23.(follow adj1 up adj3 (stud$ or trial$)).tw.

24.(case adj2 series).tw.
25.(hospital adj2 record$).tw.
26.or/14-25
27.13 and 26
28.randomized controlled trial/
29.random$.tw.
30.or/28-29
31.(untreat$ or placebo).tw.
32.(no adj2 (treat$ or intervention$)).tw.
33.or/31-32
34.30 and 33
35.13 and 34
36.27 or 35
37.prognosis/
38.disease progression/
39.risk factors/
40.((prognostic or prognosis or predict$ or prevent$) adj4 (glaucoma$ or factor or factors or disease$ or model$ or progress$)).tw.
41.(risk adj4 (progress$ or predict$ or factor or factors or disease$)).tw.
42.((progress$ or severity) adj4 (glaucoma$ or disease$)).tw.
43.((structural$ or function$ or baseline or predict$) adj4 progress$).tw.
44.((rate or rates or detect$) adj4 (change$ or worse$ or loss$)).tw.
45.(visual adj2 field adj2 (loss$ or progress$ or change$ or decreas$ or deteriorat$)).tw.
46.(conversion adj3 (POAG or OAG or glaucoma$)).tw.
47.(natural adj1 history).tw.
48.or/37-47
49.exp Aged/
50.elderly.tw.
51.(old$ adj2 age$).tw.
52.Intraocular Pressure/
53.((ocular or intra-ocular or intraocular) adj2 pressure).tw.
54.exp Ocular Hypertension/
55.(ocular adj2 hypertens$).tw.
56.(IOP or OHT).tw.
57.or/49-56
58.(prognostic or prognosis or progression or risk$).tw.
59.37 or 38 or 39 or 58
60.(central adj2 cornea$ adj2 thick$).tw.
61.CCT.tw.
62.(high adj2 myopia).tw.
63.(ocular adj2 blood adj2 flow$).tw.
64.(ocular adj2 perfusion adj2 pressure$).tw.
65.exp african continental ancestry group/
66.exp africa, western/
67.exp caribbean region/
68.(Afr$ adj2 Caribbean$).tw.
69.(Afr$ adj2 American$).tw.
70.(west adj2 (india$ or indies)).tw.
71.Family Health/
72.Age of Onset/
73.Delayed Diagnosis/
74.(family adj3 history adj4 risk).tw.
75.Genetic Association Studies/
76.Genetic Predisposition to Disease/
77.Genetic Variation/
78.Genome-Wide Association Study/
79.Genotyping Techniques/
80.(genetic or genetics or genome or genotyp$).tw.
81.exp Cardiovascular Diseases/
82.((cardiovascular or heart) adj2 disease$).tw.
83.exp Hypotension/
84.(hypotension or hypotensive).tw.
85.exp Hypertension/

86.(hypertension or hypertensive).tw.
87.(blood adj2 pressure$).tw.
88.exp blood glucose/
89.((glucose or glycem$) adj3 blood$).tw.
90.exp Diet/
91.Feeding Behavior/
92.(diet$ or nutrition or eat or eating or lifestyle$).tw.
93.Carbohydrates/
94.exp Vitamins/
95.Dietary Supplements/
96.((nutrition$ or diet$) adj2 supplement$).tw.
97.vitamin$.tw.
98.Carbohydrates/
99.Caffeine/
100.Alcoholic Beverages/
101.(carbohydrate$ or meat or salt or caffeine or coffee or alcohol$).tw.
102.exp Sleep Apnea Syndromes/
103.apnea.tw.
104.or/60-103
105.36 and 48
106.36 and 57 and 59
107.36 and 104
108.105 or 106 or 107
109.incidence.sh.
110.exp mortality/
111.follow up studies.sh.
112.prognos$.tw.
113.predict$.tw.
114.course$.tw.
115.prognosis/
116.diagnosed.tw.
117.cohort$.mp.
118.death.tw.
119.exp models, statistical/
120.or/109-119
121.13 and 120
122.108 or 121

Appendix 3. Embase Ovid search strategy

1.glaucoma open angle/
2.(open adj2 angle adj2 glaucoma$).tw.
3.(OAG or POAG).tw.
4.(low adj2 tension adj2 glaucoma$).tw.
5.(low adj2 pressure adj2 glaucoma$).tw.
6.(normal adj2 tension adj2 glaucoma$).tw.
7.(normal adj2 pressure adj2 glaucoma$).tw.
8.pseudoexfoliation/
9.(exfoliat$ adj2 syndrome$).tw.
10.(exfoliat$ adj2 glaucoma$).tw.
11.(pseudoexfoliat$ adj2 syndrome$).tw.
12.(pseudoexfoliat$ adj2 glaucoma$).tw.
13.or/1-12
14.cohort analysis/
15.case control study/
16.follow up/
17.longitudinal study/
18.prospective study/
19.retrospective study/
20.observational study/
21.((cohort or longitudinal) adj3 (stud$ or trial$)).tw.
22.(case adj1 control$ adj3 (stud$ or trial$)).tw.

23.(follow adj1 up adj3 (stud$ or trial$)).tw.
24.(case adj2 series).tw.
25.(hospital adj2 record$).tw.
26.or/14-25
27.13 and 26
28.randomized controlled trial/
29.random$.tw.
30.or/28-29
31.(untreat$ or placebo).tw.
32.(no adj2 (treat$ or intervention$)).tw.
33.or/31-32
34.30 and 33
35.13 and 34
36.27 or 35
37.prognosis/
38.disease course/
39.risk factor/
40.((prognostic or prognosis or predict$ or prevent$) adj4 (glaucoma$ or factor or factors or disease$ or model$ or progress$)).tw.
41.(risk adj4 (progress$ or predict$ or factor or factors or disease$)).tw.
42.((progress$ or severity) adj4 (glaucoma$ or disease$)).tw.
43.((structural$ or function$ or baseline or predict$) adj4 progress$).tw.
44.((rate or rates or detect$) adj4 (change$ or worse$ or loss$)).tw.
45.(visual adj2 field adj2 (loss$ or progress$ or change$ or decreas$ or deteriorat$)).tw.
46.(conversion adj3 (POAG or OAG or glaucoma$)).tw.
47.(natural adj1 history).tw.
48.or/37-47
49.exp aged/
50.elderly.tw.
51.(old$ adj2 age$).tw.
52.Intraocular Pressure/
53.((ocular or intra-ocular or intraocular) adj2 pressure).tw.
54.exp intraocular hypertension/
55.(ocular adj2 hypertens$).tw.
56.(IOP or OHT).tw.
57.or/49-56
58.(prognostic or prognosis or progression or risk$).tw.
59.37 or 38 or 39 or 58
60.(central adj2 cornea$ adj2 thick$).tw.
61.CCT.tw.
62.(high adj2 myopia).tw.
63.(ocular adj2 blood adj2 flow$).tw.
64.(ocular adj2 perfusion adj2 pressure$).tw.
65.Black person/
66.exp africa/
67.Caribbean/
68.(Afr$ adj2 Caribbean$).tw.
69.(Afr$ adj2 American$).tw.
70.(west adj2 (india$ or indies)).tw.
71.family health/
72.onset age/
73.delayed diagnosis/
74.(family adj3 history adj4 risk).tw.
75.genetic association study/
76.genetic predisposition/
77.genetic variation/
78.genome-wide association study/
79.genotyping/
80.(genetic or genetics or genome or genotyp$).tw.
81.exp cardiovascular disease/
82.((cardiovascular or heart) adj2 disease$).tw.
83.exp hypotension/
84.(hypotension or hypotensive).tw.

85.exp hypertension/
86.(hypertension or hypertensive).tw.
87.(blood adj2 pressure$).tw.
88.glucose blood level/
89.((glucose or glycem$) adj3 blood$).tw.
90.exp diet/
91.feeding behavior/
92.(diet$ or nutrition or eat or eating or lifestyle$).tw.
93.Carbohydrate/
94.vitamin/
95.dietary supplement/
96.((nutrition$ or diet$) adj2 supplement$).tw.
97.vitamin$.tw.
98.carbohydrate/
99.caffeine intake/
100.alcoholic beverage/
101.(carbohydrate$ or meat or salt or caffeine or coffee or alcohol$).tw.
102.sleep disordered breathing/
103.apnea.tw.
104.or/60-103
105.36 and 48
106.36 and 57 and 59
107.36 and 104
108.105 or 106 or 107
109.incidence.sh.
110.exp mortality/
111.follow up studies.sh.
112.prognos$.tw.
113.predict$.tw.
114.course$.tw.
115.prognosis/
116.diagnosed.tw.
117.cohort$.mp.
118.death.tw.
119.statistical model/
120.or/109-119
121.13 and 120
122.108 or 121
123.limit 122 to conference abstract status
124.122 not 123

Appendix 4. Clinicaltrials.gov search strategy

(open angle glaucoma) AND (prognosis OR progression OR risk)

Appendix 5. WHO ICTRP search strategy

open angle glaucoma AND prognosis OR open angle glaucoma AND progression OR open angle glaucoma AND risk

Appendix 6. CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS-PF) - list of data extraction items

Main domain	Study characteristics
Study design	Source of data (e.g. cohort, case-control, randomised trial, or registry data)
	Time period (dates)
Participants	Participant eligibility and recruitment method (e.g. consecutive participants, location, number of centres, setting, inclusion and exclusion criteria)

(Continued)

	Participant description
	Details of treatment received, if relevant
Outcomes to be predicted	Definition of outcome
	Method of measurement
	Time of outcome occurrence
Prognostic factors (index and comparator)	Type of prognostic factors
	Definition and method of measurement for prognostic factors
	Timing of prognostic factor measurement
	Handling of prognostic factors in the analysis
Sample size	Was a sample size calculation conducted, and if so, how?
	Number of participants
	Number of outcomes
	Number of outcomes in relation to number of candidate prognostic factors (outcomes per variable)
Missing data	Number of participants with missing data for each prognostic factor of interest
	Details of attrition and, for time-to-event outcomes, number of censored observations
	Handling of missing data
Analysis	Modelling method of analysis
	How modelling assumptions were checked: in particular, for time-to-event outcomes and the analysis of hazard ratios (HRs), the method for assessing non-proportional hazards (non-constant HRs over time)
	Method for selection of prognostic factors for inclusion in multivariable modelling (e.g. all candidate prognostic factors considered, preselection of established prognostic factors, retain only those significant from univariable analysis)
	Method for selection or exclusion of prognostic factors (including those of interest and those used as adjustment factors) during multivariable modelling (e.g. backward or forward selection, or full model approach including all factors regardless) and criteria used for any selection or exclusion (e.g. P value, Akaike information criterion)
Results	Unadjusted and adjusted prognostic effect estimates (e.g. risk ratios, odds ratios, HRs, mean differences) for each prognostic factor of interest, and the corresponding 95% confidence interval (or variance or standard error)
	For each extracted adjusted prognostic effect estimate of interest, the set of adjustment factors used

Appendix 7. Quality in Prognostic Studies (QUIPS) tool

QUIPS – list of signalling items and risk of bias ratings

Domains	Signalling items	Risk of bias ratings
1. Study participation	(a) Adequate participation in study by eligible individuals	Relationship between prognostic factor (PF) and outcome
	(b) Description of target population	High: very likely to be different for participants and eligible non-participants
	(c) Description of baseline study sample	Moderate: may be different for participants and eligible non-participants
	(d) Adequate description of recruitment process	Low: unlikely to be different for participants and eligible non-participants
	(e) Adequate description of period and place of recruitment	
	(f) Adequate description of inclusion/exclusion criteria	
2. Study attrition	(a) Adequate response rate for study participants	Relationship between PF and outcome
	(b) Description of process for collecting information on participants who dropped out	High: very likely to be different for completing and non-completing participants
	(c) Reasons for loss to follow-up provided	Moderate: may be different for completing and non-completing participants
	(d) Adequate description of participants lost to follow-up	Low: unlikely be different for completing and non-completing participants
	(e) No important differences between participants who completed the study and those who dropped out	
3. PF measurement	(a) Clear definition of PF provided	Measurement of PF
	(b) Method of PF measurement is adequately valid and reliable	High: very likely to be different for different levels of outcome of interest
	(c) Continuous variables are reported	Moderate: may be different for different levels of outcome of interest

(Continued)

	(d) Method and setting of measurement of PF is identical for all participants	Low: unlikely to be different for different levels of outcome of interest
	(e) Adequate proportion of study sample has complete data for PF	
	(f) Appropriate methods of imputation used for missing PF data	
4. Outcome measurement	(a) Clear definition of outcome provided	High: outcome measurement very likely to be different related to baseline level of PF
	(b) Method of outcome measurement is adequately valid and reliable	Moderate: outcome measurement may be different related to baseline level of PF
	(c) Method and setting of outcome measurement is identical for all participants	Low: outcome measurement unlikely to be different related to baseline level of PF
5. Adjustment for other prognostic factors	(a) All other important PFs measured	Observed effect of PF on outcome
	(b) Clear definitions of important PFs measured provided	High: very likely to be distorted by another factor related to PF and outcome
	(c) Measurement of all important PFs adequately valid and reliable	Moderate: may be distorted by another factor related to PF and outcome
	(d) Measurement and setting of PF measurement identical for all participant	Low: unlikely to be distorted by another factor related to PF and outcome
	(e) Appropriate methods are used to deal with missing values of PFs	
	(f) Important PFs accounted for in study design	
	(g) Important PFs accounted for in analysis	
6. Statistical analysis and reporting	(a) Sufficient presentation of data to assess adequacy of analytic strategy	Reported results
	(b) Strategy for model building appropriate and based on a conceptual framework or model	High: very likely to be spurious or biased related to analysis or reporting

(Continued)

	(c) Selected statistical model adequate for design of study	Moderate: may be spurious or biased related to analysis or reporting
	(d) No selective reporting of results	Low: unlikely to be spurious or biased related to analysis or reporting

Abbreviations: PF: prognostic factor

WHAT'S NEW

Date	Event	Description
3 November 2022	Amended	Correction of author byline

HISTORY

Protocol first published: Issue 11, 2022

CONTRIBUTIONS OF AUTHORS

MPP developed the initial draft of the protocol under the guidance of AAB and GV. AAB, GV, RQ, TL, YT, MPP, and QD contributed to developing and revising the protocol. All protocol authors provided input to the planned methodological aspects of the review, and approved the final draft for publication.

DECLARATIONS OF INTEREST

QD: none to declare
MPP: none to declare
RQ: none to declare
TL: none to declare
YT: none to declare
GV: none to declare
AAB: none to declare

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