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Piyasena MP, Daka Q, Qureshi R, Roberti G, Michelessi M, Liu SH, Li T, Takwoingi Y, Azuara-Blanco A, Virgili G, supported by the Cochrane Eyes and Vision Group

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[Prognosis Review]

Prognostic factors associated with progression of open-angle glaucoma in adults

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ABSTRACT

Background

Glaucoma is the leading cause of irreversible blindness globally, and the second leading cause of blindness in high-income countries. It is a chronic optic nerve disease that can lead to loss of vision, although it is usually asymptomatic until it progresses (worsens) to an advanced stage. Primary open angle glaucoma (POAG) is the most common type of glaucoma, and it is recognized as a multifactorial disorder. Pseudoexfoliative glaucoma (PXFG) is a common form of secondary open-angle glaucoma and has a higher rate of progression. The understanding of prognostic factors is useful for clinicians to estimate the risk of disease progression and to identify those who are at risk of losing sight early.

Objectives

To identify risk factors associated with disease progression, defined as worsening or deterioration of functional visual outcomes and/or structural outcomes, amongst adults with POAG and PXFG.

Search methods

We searched CENTRAL, Ovid MEDLINE, Ovid Embase, and two trial registries on 15 August 2024. The search was supplemented by checking reference lists of eligible articles. We did not apply any restrictions on language or year of publication.

Selection criteria

We included randomized controlled trials, cohort, and case-control study designs. We excluded any study with less than two years of follow-up and a sample size of < 200. The targeted population consisted of adults ≥ 18 years of age of any sex with glaucoma type restricted to POAG, normal-tension glaucoma (NTG), and PXFG and no previous glaucoma surgery. Two review authors independently screened titles and abstracts, and full-text articles, to determine eligibility. The discrepancies were resolved through discussion with a third reviewer. The time points for the evaluation of outcomes were at a minimum of two years of follow-up.

Data collection and analysis

Two review authors independently extracted data from included studies using pre-piloted data extraction forms in Covidence, SRDR+ and Microsoft Excel. We used the Quality in Prognosis Studies (QUIPS) tool to assess the risk of bias in Covidence. We conducted meta-analyses where homogeneous outcomes were reported, using a random-effects, generic inverse variance model. We reported hazard ratios (HR), odds ratio (OR), and risk ratios (RR) separately for each available prognostic factor and outcome, stratified by different time points and multivariable or univariable prognostic estimates, where possible. We evaluated and reported the certainty of evidence using the GRADE guidelines.

Main results

We screened 16,188 titles and abstracts and retrieved 487 full-text reports from 239 studies for assessment. After full-text screening, we included 123 reports of 22 studies in this review. The 22 studies included 6082 participants. The mean ages of participants ranged from 50 to 78 years across studies. Sixteen of the included studies used visual field (VF) deterioration alone to detect and measure glaucoma progression. In six studies, disease progression was assessed by both functional and structural outcomes (e.g. retinal nerve fiber layer thickness changes by spectral-domain optical coherence tomography). We judged 19 of the 22 (86%) included studies to be at a high risk of bias overall.

We found some prognostic factors had consistent evidence of a relationship with progression. Specifically, presence of disc hemorrhage (adjusted HR 2.03, 95% CI 1.55 to 2.67, 1068 participants, 3 studies; unadjusted HR 1.51, 95% CI 1.12 to 2.02, 961 participants, 3 studies; low certainty), presence of bilateral disease (adjusted HR 1.77, 95% CI 1.35 to 2.32, 771 participants, 2 studies; moderate certainty), and treatment for glaucoma (adjusted HR 0.44, 95% CI 0.31 to 0.61, 961 participants, 3 studies; unadjusted HR 0.56, 95% CI 0.44 to 0.72, 771, 2 studies; low certainty).

The remaining factors had mixed evidence as to their prognostic associations with glaucoma progression, including a few factors that were expected to be important based on other literature. With regard to intraocular pressure (IOP) at baseline, our meta-analysis of the HR had sufficient evidence for an effect (adjusted HR 1.08, 95% CI 1.03 to 1.13, 913 participants, 3 studies, low certainty) while the OR did not (adjusted OR 0.96, 95% CI 0.84 to 1.10, 458 participants, 2 studies, low certainty) and more than half the studies reporting IOP found no evidence of an effect. Similarly, the pooled adjusted HR per 1-year increase in age at baseline was 1.01 (95% CI 0.97 to 1.05; 865 participants, 4 studies) with very low certainty of evidence, and studies had mixed results for its association with progression. Regarding sex, the combined adjusted analyses of two studies suggest females may have a 64% greater hazard of progression than males (HR 1.64, 95% CI 1.15 to 2.34; 961, 3 studies; low certainty). However, other study estimates for sexes that could not be combined were mixed in their directions of effect.

We did not find consistent evidence to suggest that central corneal thickness (adjusted HR 1.13, 95% CI 0.85 to 1.51, 425 participants, 2 studies; unadjusted HR 1.00, 95% CI 1.00 to 1.00, 706 participants, 2 studies, very low certainty), systemic hypertension (adjusted HR 1.33, 95% CI 0.68 to 2.60, 731 participants, 3 studies; unadjusted HR 0.89, 95% CI 0.67 to 1.17, 771 participants, 2 studies; very low certainty), cardiovascular disease (adjusted HR 1.06, 95% CI 0.75 to 1.49, 771 participants, 2 studies; low certainty), migraine (unadjusted HR 1.06, 95% CI 0.75 to 1.49, 961 participants, 3 studies; very low certainty), or Raynaud's syndrome (unadjusted HR 1.21, 95% CI 0.85 to 1.73, 961 participants, 3 studies; very low certainty), have an effect on visual field progression.

Authors' conclusions

There is moderate-certainty evidence to support the finding that bilateral disease is a prognostic factor associated with VF progression in people with glaucoma. There is low-certainty evidence that female sex and the presence of disc hemorrhage are associated with progression, while treatment with pharmacologics is protective of progression. The evidence is uncertain about the associations between progression and all other prognostic factors that we identified. Properly designed prognostic factor research studies are required in the future.

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Registration

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PLAIN LANGUAGE SUMMARY

Factors that affect how fast glaucoma progresses

Key messages

- "Prognostic factors" are characteristics of a person that can be used to predict whether a person's disease will get worse and how quickly. The worsening or deterioration in health is also known as disease progression.

- We found the following factors were important for predicting the progression of glaucoma: (1) the presence of small bleeding and poor blood flow to the retina and back of the eye, (2) abnormal cell structures, (3) having glaucoma in both eyes, and (4) receiving treatment for glaucoma.
- We were uncertain about the strength of the predictive relationship because most of the identified studies were of low quality and reached different conclusions.

What is glaucoma?

Glaucoma is a chronic disease of the optic nerve – the nerve that takes information from the back of the eye to the brain. Glaucoma is a main cause of blindness worldwide, and needs to be managed by specialist doctors. People with glaucoma do not have any symptoms at the early stage. Treatment for glaucoma is effective at stopping or slowing the worsening of the disease.

The most common type of glaucoma is called primary open-angle glaucoma. Another type of glaucoma, pseudoexfoliation glaucoma, can progress more rapidly to a severe stage of the disease. Both of these types were included in this review.

What did we want to find out?

We wanted to find out which personal characteristics are associated with worsening (progression) of glaucoma. Understanding what factors affect faster progression of glaucoma is useful to identify those at higher risk of losing sight. This helps ophthalmologists to identify those who are at risk of losing sight early and helps to guide management and decision-making on the best treatment options.

What did we do?

We looked at different types of studies to identify the factors that are linked to glaucoma progression. Since glaucoma is a chronic condition, we included studies that assessed participants for at least two years. We also required that studies enrolled adults (18 years or over) with a minimum of 200 people to capture sufficient progression events. We critically evaluated the quality of studies and statistically combined the estimates from studies following standard methods.

What did we find?

We identified 16,188 publications and retrieved the full reports of 239 studies for further assessment. After going through the full-text reports, we included 123 reports of 22 studies (6082 participants) in this review. The average age of the participants in these studies was between 50 and 78 years. We found 40 factors with estimates of association with progression of glaucoma across the included studies. Of these 40, most had inconsistent and low-certainty evidence of an association. We reported three prognostic factors with consistent, very low-to-moderate certainty evidence of a positive or negative association with progression — these included the presence of small bleeding in the back of the eye, having glaucoma in both eyes, and receiving treatment for glaucoma. Though previous studies showed that intraocular pressure, thickness of the clear front surface of the eye, age, female sex, high blood pressure, migraine, problems in the blood circulation and blood vessels and heart problems were associated with faster worsening of glaucoma, we did not find consistent evidence of such associations in our review.

What are the limitations of the evidence?

Most (86%) of the included studies were poor in quality. We found a lot of variation in the ways that prognostic factors were defined and assessed for participants, as well as how the outcomes were defined, measured, and included in the analysis. This meant we were unable to combine estimates for most characteristics and were limited to qualitatively describing most of the evidence.

Authors' conclusions

In our review, we identified several factors that were associated with faster worsening of glaucoma and some evidence that treatment helps to slow the worsening of glaucoma, although we are not confident in these findings. We did not find convincing evidence for other known factors such as high blood pressure that could be associated with worsening of the disease. We propose conducting more good-quality research studies on this topic in the future, in order to gather more and better data that will be useful to prevent blindness due to glaucoma.

How up to date are these findings?

We searched and identified published studies up to 15 August 2024.

SUMMARY OF FINDINGS

Summary of findings 1. SoF 1: Demographic prognostic factors associated with progression of glaucoma

Population: Adults of any sex with primary open-angle glaucoma or pseudoexfoliation glaucoma**Prognostic Factors:** Demographic characteristics**Outcome:** Progression (worsening) of open-angle glaucoma assessed by VF data, with or without OCT measures**Timing:** At least two years of follow-up (range: 2 to 6 years)

Prognostic factor	Effect estimates (95% confidence interval (CI)) (I ²) [participants & studies]	Certainty of evidence	Plain text summary
Age at baseline (per year increase)	Adjusted HR = 1.01 (0.97 to 1.05) (I ² = 89%) [865 participants from 4 studies]	Very low a, b, c	Evidence is very uncertain about the effect of age on glaucoma progression.
Female sex (female vs. male)	Adjusted HR = 1.64 (1.15 to 2.34) (I ² = 0%) [774 participants from 2 studies] Unadjusted HR = 1.16 (0.91 to 1.49) (I ² = 0%) [961 participants from 3 studies]	Low a, c (adjusted)	Evidence suggests female sex may be associated with progression of glaucoma in adjusted analyses.

^a Downgraded for risk of bias (-1): at least one contributing study at high risk of bias^b Downgraded for inconsistency (-1): individual study estimates are statistically different on both sides of the null^c Downgraded for indirectness (-1): studies assessed factors over different time periods

Abbreviations:

CI: confidence interval

HR: hazard ratio

I²: I-squared

OCT: optical coherence tomography

VF: visual field

Summary of findings 2. SoF 2: Systemic prognostic factors associated with progression of glaucoma

Population: Adults of any sex with primary open-angle glaucoma or pseudoexfoliation glaucoma**Prognostic Factors:** Systemic characteristics and comorbidities**Outcome:** Progression (worsening) of open-angle glaucoma assessed by VF data, with or without OCT measures**Timing:** At least two years of follow-up (range: 2 to 6 years)

Prognostic factor	Effect estimates (95% confidence interval (CI)) (I ²) [participants & studies]	Certainty of evidence	Plain text summary
Hypertension (present vs. absent)	Adjusted HR = 1.33 (0.68 to 2.60) (I ² = 84%) [731 participants from 3 studies] Unadjusted HR = 0.89 (0.67 to 1.17) (I ² = 0%) [771 participants from 2 studies]	Very low a, b, c, d (adjusted)	Evidence is very uncertain about the effect of hypertension on glaucoma progression.

Cardiovascular disease (present vs. absent)	Unadjusted HR = 1.06 (0.75 to 1.49) ($I^2 = 0\%$) [771 participants from 2 studies]	Low b, d	Evidence suggests cardiovascular disease may be associated with progression of glaucoma.
Migraine history (present vs. absent)	Unadjusted HR = 1.06 (0.67 to 1.67) ($I^2 = 22\%$) [961 participants from 3 studies]	Very low a, b, d	Evidence is very uncertain about the effect of migraines on glaucoma progression.
Raynaud's syndrome (present vs. absent)	Unadjusted HR = 1.21 (0.85 to 1.73) ($I^2 = 0\%$) [961 participants from 3 studies]	Very low a, b, d	Evidence is very uncertain about the effect of Raynaud's syndrome on glaucoma progression.

^a Downgraded for risk of bias (-1): at least one contributing study at high risk of bias

^b Downgraded for imprecision (-1): overall estimate crosses the null

^c Downgraded for inconsistency (-1): individual study estimates are statistically different on both sides of the null

^d Downgraded for indirectness (-1): studies assessed factors over different time periods

Abbreviations:

CI: confidence interval

HR: hazard ratio

I^2 : I-squared

OCT: optical coherence tomography

VF: visual field

Summary of findings 3. SoF 3: Ocular prognostic factors associated with progression of glaucoma

Population: Adults of any sex with primary open-angle glaucoma or pseudoexfoliation glaucoma

Prognostic Factors: Ocular characteristics

Outcome: Progression (worsening) of open-angle glaucoma assessed by VF data, with or without OCT measures

Timing: At least two years of follow-up (range: 2 to 8 years)

Prognostic factor	Effect estimates (95% confidence interval (CI)) (I^2) [participants & studies]	Certainty of evidence	Plain text summary
Intraocular pressure (per 1 mmHg increase)	Adjusted HR = 1.08 (1.03 to 1.13) ($I^2 = 16\%$) [913 participants from 3 studies]	Low a, b	Evidence suggests increased intraocular pressure may be associated with the progression of glaucoma.
Intraocular pressure (per 1 mmHg increase)	Adjusted OR = 0.96 (0.84 to 1.10) ($I^2 = 50\%$) [458 participants from 2 studies]	Low a, b	Evidence is uncertain about the effect of intraocular pressure (odds) on glaucoma progression.
Central corneal thickness (per 30 μm thinner/per 1 μm thicker)	Adjusted HR = 1.13 (0.85 to 1.51) ($I^2 = 80\%$) [425 participants from 2 studies] Unadjusted HR = 1.00 (1.00 to 1.00) ($I^2 = 0\%$) [706 participants from 2 studies]	Very low a, b, c, d (adjusted)	Evidence is very uncertain about the effect of central corneal thickness on glaucoma progression.
Disc hemorrhage (present vs. absent)	Adjusted HR = 2.03 (1.55 to 2.67) ($I^2 = 0\%$) [1068 participants from 3 studies] Unadjusted HR = 1.51 (1.12 to 2.02) ($I^2 = 50\%$)	Low a, b (adjusted)	Evidence suggests the presence of disc hemorrhage may be associated with the progression of glaucoma.

[961 participants from 3 studies]

Bilateral disease (present vs. absent)	Adjusted HR = 1.77 (1.35 to 2.32) ($I^2 = 0\%$) [771 participants from 2 studies]	Moderate ^b	Presence of bilateral disease is likely to be associated with increased glaucoma progression.
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^a Downgraded for risk of bias (-1): at least one contributing study at high risk of bias^b Downgraded for indirectness (-1): studies assessed factors over different time periods^c Downgraded for imprecision (-1): overall estimate crossed the null^d Downgraded for inconsistency (-1): individual study estimates are statistically different on both sides of the null

Abbreviations:

CI: confidence interval

HR: hazard ratio

 I^2 : I-squared

OCT: optical coherence tomography

VF: visual field

Summary of findings 4. SoF 4: Other prognostic factors associated with progression of glaucoma**Population:** Adults of any sex with primary open-angle glaucoma or pseudoexfoliation glaucoma**Prognostic Factors:** Other characteristics**Outcome:** Progression (worsening) of open-angle glaucoma assessed by VF data, with or without OCT measures**Timing:** At least two years of follow-up (range: 2 to 8 years)

Prognostic factor	Effect estimates (95% confidence interval (CI)) (I^2) [participants & studies]	Certainty of evidence	Plain text summary
Treatment with pharmacologics (i.e. intraocular pressure-lowering drugs)	Adjusted HR = 0.44 (0.31 to 0.61) ($I^2 = 37\%$) [961 participants from 3 studies] Unadjusted HR = 0.56 (0.44 to 0.72) ($I^2 = 0\%$) [771 participants from 2 studies]	Low ^{a, b} (adjusted)	Treatment for glaucoma with pharmacologics may be associated with decreased glaucoma progression.

^a Downgraded for risk of bias (-1): at least one contributing study at high risk of bias^b Downgraded for indirectness (-1): studies assessed factors over different time periods

Abbreviations:

CI: confidence interval

HR: hazard ratio

 I^2 : I-squared

OCT: optical coherence tomography

VF: visual field

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 worldwide is predicted to increase to 111.8 million by the year 2040 [1], 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 [2]. Early in the disease, glaucoma impairs peripheral vision, which can affect quality of life. Glaucoma sight-loss can be slowed by early detection and treatment. People with the condition are typically monitored by 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 iridocorneal angle (i.e. open-angle and angle closure glaucomas). Primary open-angle glaucoma (POAG) is the most common type of glaucoma and is characterized by the 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) [1]. It is recognized that POAG is a multifactorial disorder and the pathogenesis of POAG is characterized by progressive loss of retinal ganglion cells and optic nerve damage that leads to irreversible damage to the visual field (VF) [3]; 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 [4, 5].

Treatment

Treatment for glaucoma is usually effective at slowing disease progression, but in some patients, vision deteriorates in spite of treatment. The primary approach to treating glaucoma consists of reducing the IOP. Patients with glaucoma seek care at varying degrees of disease severity, but late presentation is common. One major concern in glaucoma management decision-making is the inability to identify those people who will experience disease progression [6]. The rate of progression varies greatly across individuals. Identification of people at high risk of disease progression is important to individualize management decisions.

The first-line approach to managing POAG is usually through topical medications, preferably a prostaglandin analogue [7, 8] or laser trabeculoplasty [9]. When medical and laser treatments fail to control the disease, or when the disease is severe, surgical management such as trabeculectomy may be considered [10, 11].

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 disease severity. Changes in disease severity are best measured with VF testing, or with structural changes identified by optical coherence tomography (OCT) [12]. 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 usually an asymptomatic condition until it progresses to an advanced stage, because it affects the peripheral vision or visual field. Central visual acuity is commonly preserved until the late stage of the disease. The diagnostic evaluation of glaucoma is a complex process.

An accurate clinical diagnosis of glaucoma entails meticulous assessment of physical signs of the anterior segment and optic nerve head. The function and structure of the nerve should be analyzed by clinical diagnostic tests, such as perimetry and OCT.

Close monitoring of VF 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 through OCT, such as the appearance of the optic nerve head and thickness of nerve fiber layers with macular ganglion layer, is standard practice for monitoring 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

People 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 (i.e. by specialists with the goal of slowing progression as the disease cannot be cured). Although progression may be ongoing, treatment is reasonably effective in reducing the risk of rapid disease progression [13]. However, there is uncertainty about how best to identify people at higher risk of progression and visual loss, amongst both treatment-naïve and treated patients. In theory, a risk-stratification treatment approach (e.g. individualizing the target IOP), aligned with identified prognostic factors, could help to individualize monitoring strategies (e.g. different tests and frequency of testing) and potentially help prevent sight loss. If attainable, it could also lead towards an efficient use of resources by improved targeting of those most likely to benefit from treatment and prevention interventions.

Definition of prognostic research and language in the context of this review

This Cochrane Prognostic Review was designed to identify factors associated with the progression of glaucoma. Conceptually, this review should be considered an exploratory prognostic study as our aim was to explore/identify candidate prognostic factors [14, 15].

In keeping with the current paradigm for prognostic factor research, the most appropriate term for our review is "prognostic factor", which means any measure that is associated with a subsequent clinical outcome (i.e. progression of glaucoma) amongst people with a given condition (i.e. glaucoma) [16]. The term "risk factor" could be considered inappropriate in the context of our review objective because the risk factor suggests a causal relationship, whereas prognostic factors need not be causal [16, 17]. Relatedly, regarding the reporting of results from included studies, "multivariable/univariable" can be better descriptors of the types of analyses conducted in this setting because most exploratory prognostic research is not aiming to try and assess

causal relationships (i.e. prognostic determinants) and eliminate confounding [15]. However, the use of "adjusted/unadjusted" can also be appropriate in certain circumstances, such as assessing the risk of bias using an established tool (e.g. Quality In Prognostic Studies [QUIPS]) [18].

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

There is a large volume of literature on potential prognostic factors for glaucoma and for glaucoma progression. Some prognostic factors from landmark primary studies and systematic literature reviews are already known to be related to the development of glaucoma. The main prognostic factors associated with the prevalence/development of glaucoma are older age [19], elevated IOP [20], African ancestry [21], positive family history of glaucoma [22], low diastolic blood pressure [23], and high myopia [24, 25, 26]. Evidence from landmark studies such as the Advanced Glaucoma Intervention Study (AGIS) [27], Collaborative Initial Glaucoma Treatment Study (CIGTS) [28], Early Manifest Glaucoma Trial (EMGT) [29], and United Kingdom Glaucoma Treatment Study (UKGTS) [30] has shown that lowering IOP results in preservation of VF in people with POAG. Studies also show that factors, such as socioeconomic 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

Several systematic reviews have tried to identify factors associated with glaucoma progression. Kim and colleagues explored the association between ocular perfusion pressure (OPP) and the risk of POAG [31]. Their findings suggest that in people with high baseline IOP, who already have a higher risk of glaucoma, low OPP may be another prognostic factor for progression. Bowe and colleagues reported that there was no difference in mean systolic or diastolic, diurnal and nocturnal blood pressure between people with or without progressive VF loss; however, nocturnal dips > 10% in systolic or diastolic blood pressure were associated with a higher rate of VF deterioration (odds ratio [OR] 3.32, 95% confidence interval [CI] 1.84 to 6.00, and OR 2.09, 95% CI 1.20 to 3.64, respectively) [32]. Zhang and colleagues 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 [33].

A systematic review by Ernest and colleagues found that factors such as age, baseline VF loss, baseline IOP, and exfoliation syndrome were clearly associated with glaucomatous VF progression [34]. They concluded that association was unlikely for a family history of glaucoma, atherosclerosis, systemic hypertension, sex, systolic blood pressure, and myopic refractive error. This clearly highlights the gaps in evidence and the need for a comprehensive prognostic systematic review of this topic. Currently, IOP is the only modifiable prognostic factor for glaucoma; thus, identifying other modifiable prognostic factors may lead to better outcomes in disease management. The following prognostic factors have been generally identified and described in individual studies.

Higher intraocular pressure (IOP)

The UKGTS reported higher IOP as a prognostic factor for deterioration of glaucoma (hazard ratio (HR) 1.07 per mmHg, 95%

CI 1.02 to 1.12, $P = 0.008$) [35]. Similarly, IOP was identified as a prognostic factor (OR 1.22, 95% CI 1.18 to 1.25) for glaucoma development in a national-level survey conducted in Nigeria [36]. In another UK study, Kelly and colleagues reported that IOP-lowering therapy was associated with a lower risk of conversion of ocular hypertension (OHT) to POAG (HR 0.45, 95% CI 0.35 to 0.57, $P < 0.001$) [37]. Pleet and colleagues reported poor control of IOP as a major prognostic factor for becoming blind due to POAG [38].

Age

An analysis of medical records of 45,309 patients in the UK by Kelly and colleagues identified older age as a prognostic factor for conversion of OHT to POAG (HR 1.35 per decade, 95% CI 1.22 to 1.50, $P < 0.001$) [37]. Older age was reported as a prognostic factor in VF worsening by Kim and colleagues [39]. A similar finding (OR 1.04, 95% CI 1.03 to 1.05) was observed in a national-level survey conducted by Kyari and colleagues [36].

Cardiovascular disease

Chan and colleagues studied rapidly progressing patients and found that cardiovascular disease is an important prognostic factor for rapid disease progression, irrespective of the level of IOP control [40]. They observed that patients with cardiovascular disease were 2.33 times more likely to develop rapidly progressive glaucoma [40]. Lea and colleagues reported that low blood pressure identified during follow-up was correlated with structural progression of eyes with normal-tension glaucoma [41]. Similarly, Martinez and colleagues identified other prognostic factors in glaucoma progression, such as lower diastolic blood pressure, lower mean arterial pressure, and lower end-diastolic velocity in the ophthalmic artery [42].

Additional prognostic factors

Current evidence shows that there are other possible prognostic factors for developing glaucoma, such as obstructive sleep apnea [43], high fasting plasma glucose levels [44], and dietary factors [45, 46]. However, there is no strong evidence base showing an association with progression of POAG.

Health outcomes

The relevant outcome for our review in the context of this condition is the progression (worsening) of glaucoma, either POAG and PXFG, evaluated by VF data with or without OCT measurements. We will focus our review on factors assessed at diagnosis.

Measures of disease progression on health outcomes

Glaucoma progression can be assessed using functional measures, 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 were at least two years of follow-up after diagnosis. Ideally, the period for follow-up should be five years or more.

Visual field progression

Standard automated perimetry is the test used routinely to detect and measure disease progression from the functional point of view [47, 48, 49]. There are different types of perimeters and, in addition, there are different ways of analyzing 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 (Carl Zeiss Meditec Inc.) and Octopus perimeters (Interzeag, Schlieren, Switzerland), typically evaluating the central 24 or 30 degrees of the VF. Other technologies may be suitable to detect and quantify disease progression. Linear regression of changes in global indices, such as mean defect 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 the presence of local defects and may help to identify progression.

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 structural evaluation, especially in the early stages of the disease. OCT is the accepted standard for quantitative assessment of glaucoma-related structural changes. With OCT, both trend and event analyses can be used to define structural progression. Daneshvar and colleagues reported that baseline structural OCT measures predicted subsequent VF progression in contrast to semi-quantitative optic disc measures [50].

Why it is important to do this review

Understanding prognostic factors is useful for clinicians and patients to estimate the risk of disease progression and guide disease management. However, at present it is difficult to interpret all available information. To our knowledge, there was no systematic prognostic review that aimed to assess all prognostic factors for the progression of POAG under a single model. A Cochrane Prognostic Review on this topic may be of help to decision-makers, healthcare professionals, service providers, and policymakers, as well as for service users and their families. The findings of this review may help clinicians to counsel patients and provide advice regarding modifiable and unmodifiable factors, determine treatment and follow-up in a more personalized manner, and consider early surgical intervention in high-risk groups.

The review's findings may help guide the design and analysis of future 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 the risk of developing chronic open-angle glaucoma and risk of sight loss as a top research recommendation [51]. Our review will address this research priority by identifying prognostic factors that could be incorporated into future risk prediction tools.

OBJECTIVES

To identify prognostic risk factors for disease progression (worsening) in adult patients with primary open-angle glaucoma (POAG) or pseudoexfoliation glaucoma (PXFG).

METHODS

Differences between protocol and review

In the course of our screening and extraction, we encountered some challenges and came to some conclusions about the quality and value of the evidence, which led us to modify some of our planned approaches. These changes were primarily in the eligibility criteria for studies, which we made more restrictive to narrow the scope of the review and improve the likelihood that the evidence we found would be useful for our purposes. The changes from our protocol to our review are outlined below:

- **Types of studies:** We originally planned to include any population-based cohort and case-control studies, as well as studies based on longitudinal registry data and hospital records. We modified these criteria to exclude studies that were entirely retrospectively assessed from registries or hospital records. As a result, we removed the data extraction items and sensitivity analysis based on retrospective studies.
- **Types of participants:** We did not originally restrict the size of the studies, but changed our eligibility criteria to include only studies with at least 200 participants or eyes.
- **Types of outcomes:** Our protocol specified how essential it was to include studies to evaluate prognostic factors for the progression of glaucoma. However, we have not formalized this in our eligibility criteria. We revised the criteria to exclude any study that did not report at least one prognostic estimate of effect (although this could be quantitative or qualitative). Additionally, related to outcomes, our protocol specified a secondary objective to assess progression via OCT alone or other imaging techniques: we removed this objective as it was not possible to disentangle the population based on OCT or VF alone, and the heterogeneous study definitions for progression used both measures. We plan to examine these in a separate review.
- **Other changes:** We originally specified language as a reason for exclusion; we removed these criteria and accepted all studies, regardless of publication language. We specified some potentially important subgroup and sensitivity analyses. However, we did not have sufficient data to permit these additional analyses (see *Subgroup analysis and investigation of heterogeneity and Sensitivity analysis*).
- **Review title:** We changed the title from “Prognostic factors for predicting progression of open angle glaucoma in adults” to “Prognostic factors associated with progression of open-angle glaucoma in adults” for clarity. The original title was assumed to be more accessible, but feedback during the peer review and editorial process led us to reconsider. Prognosis is the prediction of disease, so “predicting” is redundant.

Criteria for considering studies for this review

We included studies that have assessed prognostic factors of POAG or PXFG according to the PICOTS parameters described in [Table 1](#).

Table 1. PICOTS of the primary objective

Population	Adults ≥ 18 years of age of any ethnicity, newly or recently diagnosed (within the past year) with open-angle glaucoma (restricted to POAG and PXFG types). We excluded studies evaluating risk fac-
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	tors in those who were diagnosed with other types of glaucoma and those who had already undergone surgical treatment for glaucoma when enrolled into the cohort.
Index prognostic factors	We considered any prognostic factors associated with the progression of open-angle glaucoma (restricted to POAG and PXFG types), as evaluated in primary studies. Specific prognostic factors of interest included, but were not restricted to: demographic information, such as age, sex, ethnicity, and socioeconomic status; clinical systemic data, such as comorbidities (presence or absence of cardiovascular disease, diabetes, hypothyroidism, obstructive sleep apnea, etc.) and variations in systemic blood pressure (diastolic blood pressure, systolic blood pressure, mean arterial pressure); and ocular functional and structural biomarkers in the context of the POAG or PXFG. We also considered the stage of glaucoma at baseline (mild, moderate, severe types). We expected that prognostic factors would have generally been measured at the time that participants entered the study, after the diagnosis of POAG or PXFG had 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) was the main outcome of interest for the primary objective. We defined progression as the deterioration or worsening of otherwise healthy structural or functional parameters.
Timing	We included studies that presented the above outcome with at least 2 years' follow-up after enrollment. Ideally, the period for follow-up should be five years or more.
Setting	We included studies undertaken in any care setting, with no geographical limitations.

Types of studies

Inclusion criteria

Eligible study designs were population-based cohort and case-control studies (including those based on longitudinal registry data or hospital records) involving patients who had not had previous treatment for glaucoma by incisional surgery (e.g. MIGS) at the time of entering the cohort. We also included randomized controlled trials (RCTs) that evaluated medical, laser, or surgical interventions to prevent glaucoma progression where at least one comparison group was untreated with surgery. For these RCTs, we used estimates of progression only from the untreated arms. It was essential that included studies had evaluated prognostic factors for the progression of glaucoma.

Exclusion criteria

We excluded any study with less than two years' follow-up or a sample size of < 200 participants or eyes (if their unit of analysis was eyes). The sample size restriction was added to ensure that the studies of prognostic factors were appropriately powered to make inferences about the likelihood of progress, as smaller studies may not have a sufficient number of progression events to evaluate relationships. In addition, we excluded case reports, editorials, and letters to editors. During the full-text screening process, we further added the following exclusion criteria for selecting eligible studies: studies based on purely retrospective designs, studies that only involved participants who have undergone incisional surgical interventions to control disease progression.

Targeted population

The targeted population comprised adults (≥ 18 years of age) of any sex with POAG or PXFG. We expanded our original target population

to also include participants with normal-tension glaucoma (NTG) and studies of progression from glaucoma suspect (defined by the primary studies) to a later stage of glaucoma. As glaucoma is a slowly progressing disease, we included studies in which participants were newly or recently diagnosed, considering a time frame of one year prior to enrollment. We included studies involving participants of all ethnicities from any geographical location and socioeconomic background.

Studies in which participants had been treated (medical, laser, or both) were eligible for inclusion. For studies that included a mixture of participants such that only a subset would be eligible, we included the studies only if the results were presented stratified by population; if we were unable to disentangle the effects amongst eligible and ineligible participants, we excluded the study.

Population exclusion criteria

We excluded studies involving participants who had other types of glaucoma than POAG, PXFG, NTG, or glaucoma suspect. We did not exclude participants with concomitant conditions. Thus, participants in the included studies could have other ocular conditions (e.g. glaucoma and cataracts) depending on the eligibility criteria used in the primary studies.

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

As our review falls within the exploratory stage for prognostic research, we considered all prognostic factors associated with the progression of glaucoma evaluated in primary studies [15, 52]. We anticipated the prognostic factors of interest could be grouped into several categories including: patient demographics, such as age, sex, ethnicity, and socioeconomic status; clinical data, such as comorbidities (e.g. presence or absence of cardiovascular disease,

diabetes, hypothyroidism, obstructive sleep apnea); and functional and structural ocular or systemic biomarkers in the context of the progression of open-angle glaucoma and other eligible glaucomas.

It was expected that prognostic factors had been measured at the time that participants entered the study, and at the time or shortly after the diagnosis of POAG or PXFG had been made. Thus, we consider all prognostic factors to be "at baseline" rather than something that may arise and affect progression if it develops over the course of the disease. We expected that these potential prognostic factors would be measured using standard methods/clinical procedures in primary studies (i.e. IOP uses tonometry recorded in mmHg etc.). We also considered the stage of glaucoma at baseline based on the reported visual field (VF) findings (Humphrey VF MDev: stratified by mild, or moderate, or both < -12dB, severe > -12dB). We also accepted and included VF measurements from other types of perimeters, such as MDef in Octopus. However, we anticipated that it would be unlikely that we would have sufficient data for within-study subgroup comparisons of different measures, and it would be more feasible to conduct between-study comparisons using mean difference (MDiff) across studies. Similarly, we did not stratify our synthesis of prognostic factors by different eligible types of glaucoma because we expected studies would include mixes of types and no clear separation of populations.

Types of outcomes to be predicted

We assessed one outcome: progression of open-angle glaucoma assessed by progressive VF data with or without OCT measures. We originally proposed to also assess structural outcomes evaluated by OCT or other measures but excluded these studies from the review because of the heterogeneity and complexity of the different types of structural outcomes that we encountered. It was not possible to disentangle the population based on OCT or VF alone as the studies reported progression based on both studies. We plan to review these other structural outcomes in a separate review.

The time points for the evaluation of health outcomes in this review were at least two years of follow-up after enrollment and separated into common time periods: two years, three to five years, and over five years. Ideally, studies would assess progression over five years or more and from the time of diagnosis. However, we observed that the outcome assessments were more often related to the study design (i.e. time since enrollment) and not the participants' history of the disease at baseline.

Search methods for identification of studies

Electronic searches

We included the following key concepts in our search strategy: POAG, PXFG, study design terms, prognostic factors, and risk factors. As this was not an intervention review and could not follow the standard PICO framework for combining concepts, we included concepts related to our population, relevant study designs, and prognostic factors, including both generic terminology for "prognostic factors" and specific factors that we expected to find. We worked with a Cochrane Eyes and Vision (CEV) Information Specialist to search the electronic databases below. There were no restrictions on language or date of publication. The search was performed on 15 August 2024.

- Cochrane Central Register of Controlled Trials (CENTRAL; issue 8, 2024) (which contains the CEV Trials Register) in the Cochrane Library ([Supplementary material 1](#)).
- MEDLINE Ovid (1946 to 15 August 2024) ([Supplementary material 1](#)).
- Embase Ovid (1980 to 15 August 2024) ([Supplementary material 1](#)).
- US National Institutes of Health Ongoing Trials Register - ClinicalTrials.gov (www.clinicaltrials.gov) ([Supplementary material 1](#)).
- World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp) ([Supplementary material 1](#)).

Searching other resources

We supplemented the search by checking reference lists of eligible articles. We did not include grey literature in this review because we did not expect this would be sufficiently informative to justify the extra resources required in conducting the searches. Prior to publication, we searched for errata or retractions for reports of included studies in PubMed (www.ncbi.nlm.nih.gov/pubmed) and Retraction Watch (<https://retractiondatabase.org/RetractionSearch.aspx?>). We planned to follow Cochrane guidance had these been identified.

Data collection

Selection of studies

We pilot tested the inclusion criteria to assess agreement amongst the review authors and began the screening process after getting a substantial level of agreement between review authors. Two review authors (MPP and QD) independently assessed the titles and abstracts in Covidence [53], and obtained the full-text articles of potentially eligible studies. Two review authors (MPP and QD) independently classified the full-text articles as either eligible or ineligible for inclusion. We resolved discrepancies by discussion or by consulting an arbitrator if necessary (AAB or GV). We reported the selection process of studies in a PRISMA flow diagram and documented the reasons for exclusions.

Data extraction and management

We used items from the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modeling Studies (CHARMS-PF) [54] to guide data extraction ([Supplementary material 8](#)). We extracted data using a piloted data extraction form developed by Cochrane Eyes and Vision US Project (CEV@US) in Covidence [53].

Two review authors (MPP and QD) independently extracted the data in two stages. In the first stage, we mapped studies based on the study design, prognostic factors evaluated, severity of disease, type of treatment, follow-up time, and type of analysis. We collected first stage data using Extraction 2.0 in Covidence [53]. In the second stage, we extracted more study characteristics (e.g. details about the participants) and specific prognostic factor estimates from included studies. We collected these more detailed descriptive data using SRDR+ and estimates for analysis into a pilot-tested Microsoft Excel spreadsheet designed based on Cochrane guidelines. We resolved any disagreements through discussion, by involving a third review author (AAB or GV), or by consensus of the review author team if necessary.

We extracted the following data items, whenever available, and entered them in RevMan [55].

- Study
 - Title
 - Authors' contact details
 - Sources of funding
 - Year of publication
- Source of data
 - Type of study (prospective cohort or case-control studies, RCTs evaluating therapeutic interventions)
 - Sources of data (e.g. hospital, other studies) 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
 - Moment of prognostication
 - Types of outcomes
 - Time of outcome occurrence
- Prognostic factors
 - Number and type of prognostic factors
- Sample size
 - Sample size calculation
 - Number of participants and eyes
- Missing data
 - Method of handling missing data
- Analysis
 - Modeling method

Several characteristics that we prespecified were not consistently reported in the included studies, and we did not include these in the RevMan data. These include the definition and method of measurement for all prognostic factors, the timing of all prognostic factor measurements, the number of outcomes (i.e. progression events) overall and per variable, and the number of participants missing and reasons for missing by treatment/exposure groups. We extracted all prognostic factor estimates, but due to the number of estimates, we placed these in a repository on the Open Science Framework (OSF) (available at: <https://osf.io/q2tz7/>), rather than including them in the Characteristics of Included Studies table (Supplementary material 2).

Measures of association or predictive performance measures to be extracted

We extracted estimates of prognostic effect, including hazard ratios (HRs), risk ratios (RRs), odds ratios (ORs), or mean differences (MDiff) for each factor of interest, with their measure of their uncertainty (i.e. standard errors [SEs], variances, or CIs) as reported. If reported, we extracted both univariable and multivariable estimates. For multivariable estimates, we also extracted the full set of variables used wherever available.

Assessment of risk of bias in included studies

To assess the risk of bias (RoB) of included studies (Supplementary material 9), we utilized the modified Quality in Prognosis Studies (QUIPS) tool [18, 52]. We pilot tested the tailored signaling questions of QUIPS to ensure a similar approach and assessment across the review author team. Two review authors (MPP, QD, SL) independently assessed the risk of bias and a third review author (RQ or GV) arbitrated discrepancies.

We considered the following domains for each eligible study:

- Study participation: is the study sample representative of the population of interest?
- Study attrition: are 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?

For each domain, the individual studies were assessed as low, moderate, or high. QUIPS is applied at the study level. Therefore, we did not conduct RoB assessments separately for each prognostic factor. Because there were no decision rules for judging the overall risk of bias in QUIPS, we followed a recommended approach: "Low" - if six domains were classified as having low RoB, or five were low with one moderate RoB; "Moderate" - if four domains were classified as having low RoB and two domains have moderate RoB; and "High" - if one or more domains were classified as having high RoB, or at most three domains have low RoB and at least three have moderate RoB [56]. The QUIPS tool does not consider whether there are internal and external validations of the prognostic effects, as studies evaluating prognostic/prediction models would be better assessed by PROBAST (Prediction model Risk of Bias Assessment Tool) [18, 57].

Dealing with missing data

We planned to contact study authors when we required further information, primary data, or clarification. If the authors did not respond to our multiple attempts within two weeks, we used whatever data was available to us.

Assessment of heterogeneity

We anticipated that there would be statistical heterogeneity due to clinical and methodological differences between studies. Since the I^2 statistic was not appropriate in certain situations, given the different models and factors that may be used and included in multivariable analyses across studies, we quantified heterogeneity using Tau² [58]. We planned to also present 95% prediction intervals when there were an appropriate number of studies included in a meta-analysis (i.e. more than four). However, we did not have any meta-analyses that met these criteria, so we only presented 95% confidence intervals [58].

Assessment of reporting deficiencies

We planned to assess small-study effects using contour-enhanced funnel plots when 10 or more studies were included in a meta-analysis. We were able to include only a few studies in each meta-analysis because of variation in effect measures and length of follow-up. Thus, we did not perform any funnel plot asymmetry tests given the low power of such tests when studies were few [59].

Data synthesis

Data synthesis and meta-analysis approaches

We conducted meta-analyses using a contrast-level random-effects approach where possible, given the heterogeneity in prognostic factors, outcomes, and measures of association. The presentation of estimates within studies necessitated a contrast-level approach, rather than entering the number of participants progressing in each group, because most studies assessed multiple prognostic factors using multivariable regression. Relatedly, we analyzed the effects of their original measures, as we were unable to convert any study estimates between measures (e.g. OR to HR) due to the variations in models across studies. Likewise, we assessed and reported all factors separately, as we could not analyze a full or partial set of predictors given the different models used by the included studies. To aid in the summary of the evidence for each factor and following recommended synthesis without meta-analysis (SWiM) methods, we assigned a directionality to each association based on the effect estimate and regardless of the statistical significance: "positive" where more of the factor increased the likelihood of progression and "negative" where more of the factor decreased the likelihood of progression (i.e. was protective). For prognostic factors that had a clear presence/absence (e.g. presence of various comorbidities) or increase/decrease (e.g. age at baseline, central corneal thickness, vessel density), we used the lower values as the reference group. This standardization of directionality was necessary for synthesis because some studies assessed inverse associations, and we needed to have the "direction" oriented the same for all estimates. For example, if one study presented a relative effect size greater than 1.0 for the presence of a characteristic compared to the absence, and another presented a relative effect size less than 1.0 for the absence of a characteristic compared to the presence of the characteristic, we could not simply classify these directions as respectively positive and negative because the comparison had been switched: both associations indicated that presence of the characteristic is positively associated with more of the outcome. For prognostic factors that were categorical without clear reference (e.g. sex), we specified which group we considered to be the reference. We assigned a direction of "null" where the effect estimate was exactly null (e.g. relative effect of 1.0) or not reported (e.g. authors only reported a P value or qualitative statement that there was no association).

We anticipated that the OR would be the most common measure. However, we found that HR had been reported more often in reports from included studies, and the measure had the greatest consistency across prognostic factors and outcomes, permitting meta-analyses for several factors. We converted reported HRs and ORs to the log scale for meta-analyses using standard mathematical transformation (e.g. log transforming the estimate and back-calculating SE from the 95% CI). We analyzed and reported multivariable and univariable associations separately, focusing on multivariable analyses where possible as the preferred

estimates. For prognostic factors with estimates that could not be meta-analyzed due to clinical or methodological heterogeneity, we qualitatively summarized the evidence. We used 95% CIs throughout the results.

Subgroup analysis and investigation of heterogeneity

We anticipated between-study heterogeneity relating to two key areas in this review (clinical and methodological) and planned to conduct subgroup analysis based on the study methodology and study features. Clinically, we expected potential differences in aspects such as ethnicity/race; primary interventions such as medical treatment or laser treatment, or both, for POAG or PXFG; and the presence of concurrent interventions such as phacoemulsification +/- intraocular implantation in study cohorts. Methodologically, we expected potential differences in effect from different outcome measurements (e.g. trend analysis versus event analysis), different definitions used to assess the progression of glaucoma, differences in categorizing the disease severity (mild, or moderate, or both VF MDev < -12dB and severe VF MDev > -12dB), and duration of follow-up (e.g. 2 years, 3 to 5 years, long term > 5 years).

Due to the heterogeneity in the definitions of the predictors, outcomes, measures, and time points, we were not able to conduct any subgroup analyses of the outcomes, other than keeping "multivariable" and "univariable" estimates separate. Duration of follow-up was one particular subgroup that we planned to examine, but instead grouped all estimates where the same measures were used for the same predictors and outcomes, and downgraded the certainty of evidence for indirectness, where applicable.

Sensitivity analysis

We planned to assess the effects of unmeasured confounding (i.e. comparing the associations derived from different multivariable models) through a sensitivity analysis, provided adequate data were available. We also planned to perform sensitivity analyses to explore the impact of studies with high-risk bias on effect sizes. We did not have sufficient data to permit either of these sensitivity analyses.

Conclusions and summary of findings

We provided a summary of the prognostic estimates and assessed the certainty of the evidence using the GRADE modified tool for prognostic factors studies [60]. We highlighted this to the prognostic factors for which we had meta-analytic estimates. We expected the factors most consistently assessed and with the greatest amount of evidence, and therefore the opportunity for meta-analysis, would be the most important for prognostic influence. Ultimately, these factors included: age, female sex, hypertension, cardiovascular disease, migraine history, Reynaud's syndrome, intraocular pressure, central corneal thickness, disc hemorrhage, bilateral disease, and treatment with pharmacologics. We focused on analyses of adjusted estimates for factors for which we had both adjusted and unadjusted measures. As the timing for follow-up was highly variable, we did not stratify or assess our prognostic factors by a specific time range. Thus, our assessment of the certainty of evidence for progression was for at least two years of follow-up (our eligibility criteria for inclusion in the review). Due to this variability in timing, we downgraded all associations for indirectness because glaucoma is a progressive disease and longer follow-up is more likely to capture progression.

Thus, large variation in the timing of assessments may not be directly applicable to the broader glaucoma population.

We added another note for each factor summarizing the qualitative evidence (e.g. the direction of all relevant estimates, regardless of inclusion in meta-analyses). Two review authors independently performed this assessment, and we resolved any disagreement by consensus amongst the review author team. We described the factors that influenced the certainty of the evidence generated in this Cochrane Review under the domains of risk of bias, imprecision, inconsistency, indirectness, and publication bias.

Consumer involvement

We did not have any consumer involvement with the conduct or writing of this review.

RESULTS

Description of studies

Results of the search

We searched electronic databases and identified a total of 22,923 records. We screened 16,188 unique titles and abstracts and retrieved 487 full-text reports of 239 studies for assessment. After full-text screening, we included 22 studies (123 reports) in this review ([Figure 1](#)). We classified one study (2 reports) as awaiting classification and three studies (3 reports) as ongoing ([Supplementary material 4](#); [Supplementary material 5](#)).

Figure 1. PRISMA flow diagram outlining study selection

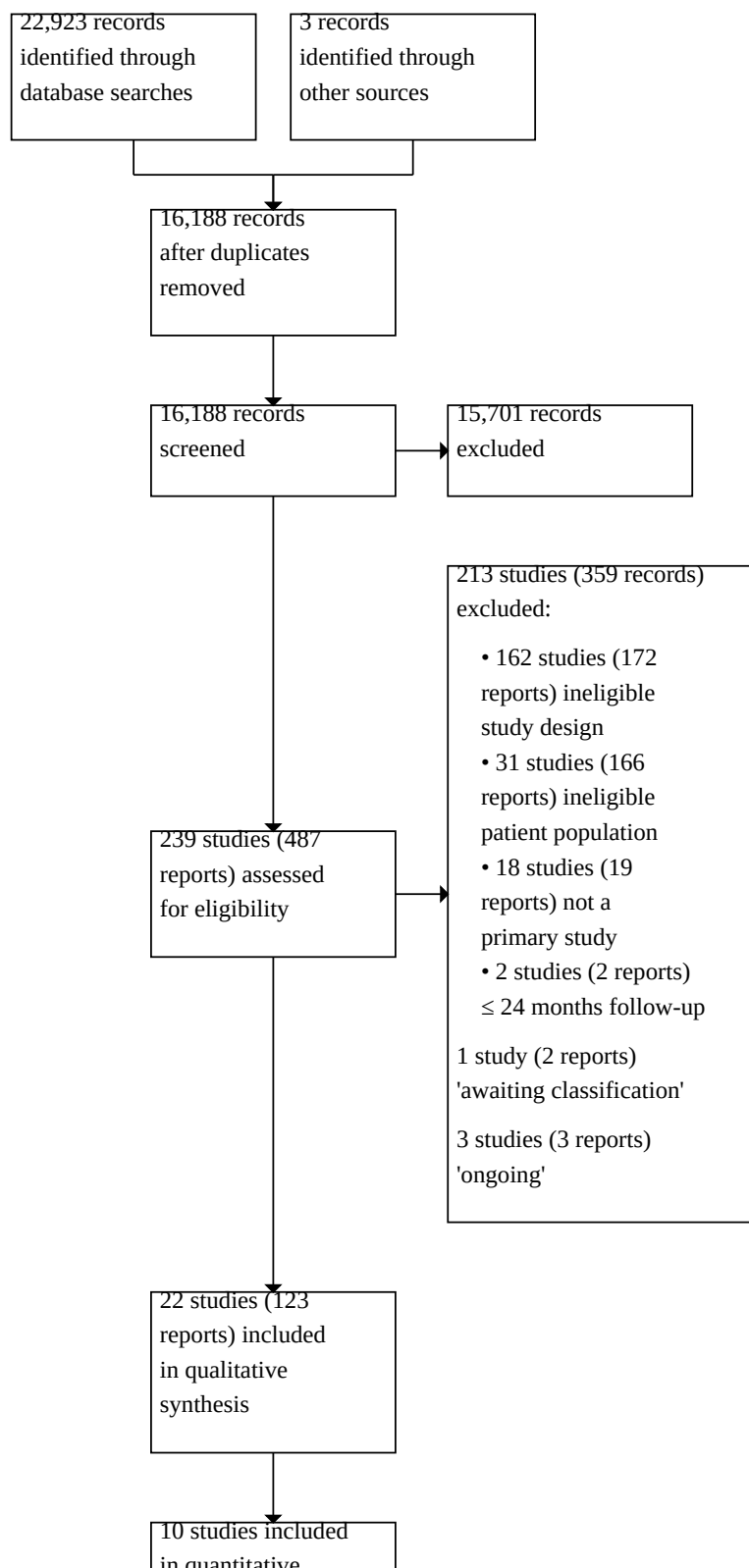


Figure 1. (Continued)

10 studies included
in quantitative
synthesis
(meta-analysis)

We included several major trials and cohort studies which had large numbers of reports, such as The Early Manifest Glaucoma Trial (n = 20), Diagnostic Innovations in Glaucoma Study (n = 20), Laser in Glaucoma and Ocular Hypertension (n = 16), United Kingdom Glaucoma Treatment Study (n = 11), Glaucoma Laser Trial (n = 8), Low Pressure Glaucoma Treatment Study (n = 7), and the Canadian Glaucoma Study (n = 6). The last date of search was 15 August 2024.

Included studies

We included 17 cohort studies (Biswas 2020 [61]; Chauhan 2008 [62, 63, 64, 65, 66, 67]; Dascalu 2021 [68]; Fursova 2022 [69]; Jonas 2004 [70, 71, 72, 73, 74, 75]; Lee 2022 [76]; Lee 2023 [77]; Leung 2009 [78, 79, 80]; Lin 2023 [81]; Medeiros 2009 [82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115]; Pappelis 2019 [116]; Sullivan-Mee 2023 [117]; Wang 2022 [118]; Wilson 2002 [119]; Yoshikawa 2018 [120]; Yu 2016 [121, 122]; Zhang 2016 [123, 124]), and five RCTs (Founti 2020 [125, 126, 127, 128, 129, 130, 131, 132, 133, 134]; Greenfield 2007 [135, 136, 137, 138, 139, 140, 141]; Krug 1995 [142, 143, 144, 145, 146, 147, 148]; Leske 2007 [149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168]; Wright 2020 [169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183]).

These studies were from Canada (Chauhan 2008), Germany (Jonas 2004), Hong Kong (Leung 2009; Lin 2023; Wang 2022; Yu 2016), India (Biswas 2020), Japan (Yoshikawa 2018), Korea (Lee 2022; Lee 2023), the Netherlands (Pappelis 2019), Romania (Dascalu 2021), Russia (Fursova 2022), Sweden (Leske 2007), St. Lucia, the West Indies (Wilson 2002), the United Kingdom (Founti 2020; Wright 2020) and the United States of America (Greenfield 2007; Krug 1995; Medeiros 2009; Sullivan-Mee 2023; Zhang 2016). Eleven studies were conducted at a single center (Biswas 2020; Dascalu 2021; Fursova 2022; Jonas 2004; Lee 2022; Lee 2023; Leung 2009; Lin 2023; Pappelis 2019; Sullivan-Mee 2023; Yoshikawa 2018), and 11 in multiple centers (Chauhan 2008; Founti 2020; Greenfield 2007; Krug 1995; Leske 2007; Medeiros 2009; Wang 2022; Wilson 2002; Wright 2020; Yu 2016; Zhang 2016). They were mainly conducted at a secondary level of care (Biswas 2020; Chauhan 2008; Dascalu 2021; Founti 2020; Fursova 2022; Greenfield 2007; Jonas 2004; Lee 2022; Lee 2023; Leske 2007; Leung 2009; Medeiros 2009; Pappelis 2019; Sullivan-Mee 2023; Wang 2022; Wilson 2002; Yoshikawa 2018; Yu 2016; Zhang 2016), with only two studies conducted at primary level (Krug 1995; Wright 2020) and one at tertiary level (Lin 2023). We summarized other characteristics of the included studies in a detailed tabular format (Supplementary material 2) and the Overview of Synthesis and Included Studies (OSIS) table (Table 1). We did not have any instances where critical information was missing and where contact with authors was necessary.

Participants

The 22 studies included 6082 participants. The mean ages of participants diagnosed with open-angle glaucoma (OAG) ranged from 50 to 78 years across studies, although three studies did not report the age of participants (Fursova 2022; Wilson 2002; Yu 2016). The diagnosis of participants varied between studies: some included other forms of OAG such as PXFG, or pigmentary glaucoma (PG) in addition to POAG (Chauhan 2008; Dascalu 2021; Founti 2020; Jonas 2004; Leske 2007; Medeiros 2009; Pappelis 2019; Wright 2020; Zhang 2016), whereas others included exclusively NTG or in addition to OAG (Greenfield 2007; Jonas 2004; Leske 2007; Leung 2009; Lin 2023; Medeiros 2009; Wang 2022; Yoshikawa 2018) or glaucoma suspects (Medeiros 2009; Pappelis 2019; Sullivan-Mee 2023; Wright 2020; Wilson 2002). The mean percentage of female participants across studies was 49.3%; however, sex was not reported in some studies (Biswas 2020; Leung 2009; Wilson 2002). Most studies did not report race/ethnicity but, where reported, the distribution was over 90% white in two studies (Chauhan 2008; Founti 2020), 45% white and 43% black in another study (Krug 1995), and 51.5 % white and 37.6 % Latin in one study (Sullivan-Mee 2023).

Most studies excluded trials with other ocular morbidities, glaucoma surgery, and visual acuity worse than 20/60 except two studies that included patients with visual acuity at worse than 20/200 (Wilson 2002; Wright 2020) and four studies that did not report on visual acuity (Krug 1995; Leung 2009; Jonas 2004; Pappelis 2019). Some studies specified amongst exclusion criteria also refractive error that varied from +3.0 Dsph to -15.0 Dsph and more than 2.5 Dcyl (Biswas 2020; Chauhan 2008; Founti 2020; Jonas 2004; Lee 2022; Zhang 2016), or patients with advanced glaucomas (Leske 2007) or younger than 18 years old (Leung 2009). Only one study specifically included patients that had glaucoma surgery after the initiation of the study (Sullivan-Mee 2023).

Prognostic factors

Prognostic factors include patient demographic information such as age, sex, and ethnicity (Biswas 2020; Chauhan 2008; Founti 2020; Greenfield 2007; Jonas 2004; Leske 2007; Lee 2023; Lee 2022; Leung 2009; Medeiros 2009; Pappelis 2019; Sullivan-Mee 2023; Wilson 2002; Yu 2016). Prognostic factors were assessed at study baseline for all but two studies (Lee 2023; Yoshikawa 2018) which assessed them at time of diagnosis and six months after diagnosis, respectively.

Other prognostic factors of interest were clinical data, such as comorbidities, and included cardiovascular factors (Dascalu 2021; Founti 2020; Greenfield 2007; Leske 2007; Medeiros 2009), diabetes (Dascalu 2021; Greenfield 2007), peripheral vasospasm (Dascalu 2021; Founti 2020; Greenfield 2007; Leske 2007), BMI (Founti 2020;

Pappelis 2019), sleep apnea (Founti 2020), claudication (Founti 2020), abnormal levels of anticardiolipin antibody (Chauhan 2008), and use of statins (Leung 2009; Pappelis 2019).

Ocular prognostic factors for glaucoma progression (worsening) were the most commonly assessed and included:

- axial length (Biswas 2020; Founti 2020; Lee 2022; Yu 2016);
- BCVA, refractive error, high myopia, spherical equivalent, and lens status (Biswas 2020; Founti 2020; Greenfield 2007; Jonas 2004; Leske 2007; Yoshikawa 2018);
- IOP and family history for glaucoma (Biswas 2020; Chauhan 2008; Founti 2020; Greenfield 2007; Krug 1995; Lee 2022; Leske 2007; Medeiros 2009; Pappelis 2019; Sullivan-Mee 2023; Wilson 2002; Wright 2020; Yoshikawa 2018; Yu 2016; Zhang 2016);
- central corneal thickness and hysteresis (Founti 2020; Greenfield 2007; Leske 2007; Leung 2009; Pappelis 2019; Yoshikawa 2018; Yu 2016; Zhang 2016);
- disc hemorrhage, optic disc measurements and parapapillary atrophy (Founti 2020; Greenfield 2007; Jonas 2004; Krug 1995; Lee 2022; Leske 2007; Leung 2009; Yoshikawa 2018);
- as well as visual field indices (Biswas 2020; Founti 2020; Lee 2022; Leske 2007; Medeiros 2009; Sullivan-Mee 2023; Wang 2022; Wright 2020; Yoshikawa 2018; Yu 2016; Zhang 2016);
- retinal nerve fiber layer (RNFL) thickness and macular ganglion cell parameters (Biswas 2020; Lee 2022; Medeiros 2009; Sullivan-Mee 2023; Yu 2016; Zhang 2016);
- exfoliation glaucoma (Leske 2007);
- receipt of glaucoma treatment (Founti 2020; Leske 2007; Pappelis 2019);
- retinal, choroidal and peripapillary vascular measurements (Fursova 2022; Greenfield 2007; Lee 2023; Lin 2023; Wang 2022);
- glaucoma surgery during the study (Lee 2022); and
- baseline AGIS and CIGTS scores (Wilson 2002).

Outcomes

Our primary outcome for this review was the progression of POAG and PXFG, evaluated by VF data with or without OCT measures. We define progression as the deterioration or worsening of otherwise healthy structural or functional parameters.

Fifteen of the included studies (Chauhan 2008; Founti 2020; Greenfield 2007; Jonas 2004; Krug 1995; Lee 2023; Leung 2009; Pappelis 2019; Sullivan-Mee 2023; Wang 2022; Wilson 2002; Wright 2020; Yoshikawa 2018; Yu 2016; Zhang 2016) used VF deterioration alone to detect and measure glaucoma progression. In six studies (Biswas 2020; Dascalu 2021; Lee 2022; Leske 2007; Lin 2023; Medeiros 2009), disease progression was assessed by both functional and structural outcomes. Leske 2007 and Medeiros 2009 evaluated optic disc changes by stereoscopic photography, whereas Biswas 2020, Dascalu 2021, Lee 2022, and Lin 2023 evaluated retinal nerve fiber layer (RNFL) thickness changes by Spectral-Domain OCT. One study (Fursova 2022) did not specify the definition of glaucoma progression; however, they reported assessing “structural and functional parameters of the optic nerve head during observation.”

In almost all studies, the functional outcome was assessed using Humphrey Field Analyzer perimetry, 24-2 or 30-2, Swedish Interactive Threshold Algorithm, except for Jonas 2004 and Krug

1995 (Octopus perimetry, program 32 or G1) and Dascalu 2021 (Optopol perimetry; Optopol Tech., SA, Poland).

In 11 studies (Chauhan 2008; Founti 2020; Lee 2023; Leske 2007; Lin 2023; Medeiros 2009; Sullivan-Mee 2023; Wang 2022; Wright 2020; Yu 2016; Zhang 2016), event and/or trend-based analysis was applied to measure the disease progression by VF data. In two studies (Greenfield 2007; Jonas 2004), a pointwise linear regression analysis was performed at each test location. Two studies (Pappelis 2019; Yoshikawa 2018) calculated the MDef slope deterioration over time as a measure of disease progression. One study (Wilson 2002) used VF score algorithms developed for the Advanced Glaucoma Intervention Study [27] and the Collaborative Initial Glaucoma Treatment Study [28]. One study (Leung 2009) used criteria for glaucoma progression that is similar to the Collaborative Normal Tension Glaucoma Study [184]. In one study, Fursova 2022, no details were reported.

Amongst studies evaluating OCT RNFL changes over time, Lin 2023 used the Guide Progression Analysis provided by Cirrus HD-OCT (Carl Zeiss Meditec Inc.), whereas Biswas 2020 and Lee 2022 used a linear mixed-model or regression analysis to calculate the rate of change of RNFL thickness per year, by using Cirrus HD-OCT and Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany), respectively.

Time of outcome occurrence was two years for two studies (Founti 2020; Fursova 2022); between three and four years for eight studies (Chauhan 2008; Dascalu 2021; Krug 1995; Lin 2023; Medeiros 2009; Wang 2022; Wright 2020; Zhang 2016); and five or more years for 12 studies (Biswas 2020; Chauhan 2008; Greenfield 2007; Jonas 2004; Lee 2022; Lee 2023; Leske 2007; Pappelis 2019; Sullivan-Mee 2023; Wilson 2002; Yoshikawa 2018; Yu 2016).

Excluded studies

We excluded 213 studies (359 reports) at the full-text stage for several reasons (Supplementary material 3). We excluded 162 studies (76%) with ineligible design characteristics, such as a retrospectively identified cohort or non-prognostic research, or where they did not present any data on prognostic factors. We excluded 31 studies (15%) because the participants did not meet our target population (i.e. requiring glaucoma at the start of the study and no prior surgeries (e.g. trabeculectomy, MIGS). Lastly, we excluded 18 studies (9%) for not being primary studies (i.e. editorial, review, case-report). Lastly, we excluded two studies for having too short follow-up (i.e. < 24 months) (Figure 1). As with our included studies, several excluded studies had many associated publications, all of which were excluded on the basis of the primary study paper being ineligible.

Risk of bias in included studies

Using the modified QUIPS tool, we judged 19 of the 22 included studies (86%) to be at high risk of bias overall with at least one high risk of bias domain or at least three domains at moderate risk of bias. We assessed two studies (Wang 2022; Yu 2016) (9%) to have moderate risk of bias overall and only one study (Leske 2007) (5%) to have low risk of bias (Figure 2). Figure 3 depicts the specific judgments for all studies across the six domains. Detailed assessment results, such as supporting statements for each signaling question, can be accessed on OSF (available at <https://osf.io/q2tz7/>).

Figure 2. Risk of bias for QUIPS domains across included studies

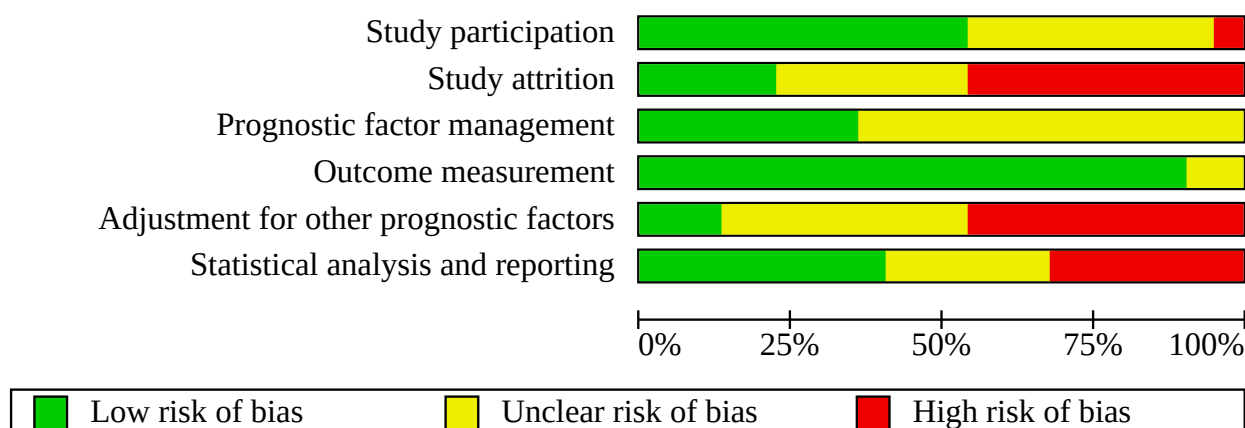


Figure 3. Study specific risk of biases across six QUIPS domains

	Study participation	Study attrition	Prognostic factor management	Outcome measurement	Adjustment for other prognostic factors	Statistical analysis and reporting
Biswas 2020	?	-	+	+	-	+
Chauhan 2008	+	-	?	?	?	+
Dascalu 2021	?	-	?	+	-	-
Founti 2020	+	?	+	+	?	?
Fursova 2022	?	+	?	+	-	-
Greenfield 2007	?	?	?	+	-	?
Jonas 2004	?	?	+	+	-	-
Krug 1995	+	?	+	+	?	?
Lee 2022	+	-	?	+	?	+
Lee 2023	+	-	+	+	+	+
Leske 2007	+	+	+	+	?	+
Leung 2009	?	?	?	+	-	-
Lin 2023	+	-	?	+	+	+
Medeiros 2009	+	-	?	?	-	?
Pappelis 2019	?	?	+	+	?	+
Sullivan-Mee 2023	?	+	+	+	-	?
Wang 2022	+	?	?	+	+	+
Wilson 2002	-	-	?	+	-	-
Wright 2020	+	+	?	+	?	-
Yoshikawa 2018	?	-	?	+	-	-
Yu 2016	+	+	?	+	?	+
Zhang 2016	+	-	?	+	?	?

Domain 1: Study participation

We judged most studies to be at low ($n = 12$, 55%) or moderate ($n = 9$, 41%) risk of bias, with only one study (Wilson 2002) (5%) having a high risk of bias due to study participation as it failed to report any description of the baseline characteristics or sampling frame. We judged studies to have a moderate risk of bias where one or more of the sampling frame, population source, or time period and place of recruitment were not clearly reported.

Domain 2: Study attrition

We judged most studies ($n = 10$, 45%) to be at high risk of bias for study attrition where most details about retention were unclear or there was clearly substantial loss to follow-up from the originally enrolled participants. We judged seven studies (32%) to have moderate risk of bias in this domain where some details were not clearly reported or investigators used inappropriate analyses (e.g. complete case) in the presence of any losses. We judged five studies (Fursova 2022; Leske 2007; Sullivan-Mee 2023; Wright 2020; Yu 2016) (23%) to have low risk of bias in this domain.

Domain 3: Prognostic factor measurement

We judged 12 studies (55%) to have a moderate risk of bias in the measurement of prognostic factors where the descriptions of how the measurement was done and how the management of missing prognostic data were unclear. Nine studies (41%) clearly described their measurements, leading us to judge them as being at low risk of bias. We judged one (5%) study to have a high risk of bias because participants' important prognostic factor data were missing or excluded for no clear reason (Wilson 2002).

Domain 4: Outcome measurement

We found all but two studies (91%) had low risk of bias in the measurement of the outcome. This domain had a low risk of bias for most studies because of the systematic approach and clear definition of progression that was applied to all participants. We judged two studies (9%) to have moderate risk of bias in outcome measurement because it was not clear how progression was measured for those lost to follow-up (Chauhan 2008) or how progression was influenced by abnormal results and diseases other than glaucoma (Medeiros 2009).

Domain 5: Adjustment for other prognostic factors

We found substantial potential for biases in adjustment for other prognostic factors, with 10 studies (45%) being high risk and nine (41%) being moderate risk, largely because studies failed to adjust for important factors in multivariable models or only conducted univariable analyses of prognostic factors. We judged three studies (Lee 2023; Lin 2023; Wang 2022) (13%) to have low risk of bias in this domain as they measured and included important factors in their analyses.

Domain 6: Statistical analysis and reporting

As Domain 6 is closely aligned with Domain 5 but further examines the analytical approach, we judged most studies to have at least some concerns about the analyses and reporting. We assessed nine (41%) studies as having low risk of bias with appropriate approaches to analyses and model building and nothing to suggest selective reporting. We assessed six studies (27%) each as having moderate risk of bias (Founti 2020; Greenfield 2007; Krug 1995; Medeiros 2009; Sullivan-Mee 2023; Zhang 2016) and seven studies

(32%) as having high risk of bias (Dascalu 2021; Fursova 2022; Jonas 2004; Leung 2009; Wilson 2002; Wright 2020; Yoshikawa 2018) because they used univariable estimates or stepwise approaches to build their models.

Synthesis of results

Across the included studies, we found 331 estimates for 40 prognostic factors under the main domains of demographic, systemic, lifestyle, ocular, and other factors. We synthesized most prognostic factors qualitatively as there was substantial heterogeneity in the definitions of the prognostic factors (e.g. continuous and binary or categorical with different cut-offs); the measures used (e.g. hazard ratios, odds ratios, risk ratios, rates, etc.); the analyses (i.e. univariable or multivariable); the definition of progression; and the timing of follow-up (from 2 years to 8 years). All extracted study estimates can be found on OSF (available at: <https://osf.io/q2tz7/>). The supplemental file on OSF gives the specific ways in which all prognostic factors were assessed and how we classified them for our synthesis. Both Table 1 and the following synthesis of results section use the higher-level groupings of prognostic factors to permit synthesis in situations where the same kind of prognostic factor was assessed but in a slightly different way. For our synthesis, we also break down some larger categories (e.g. baseline visual field) into their more specific subcategories (i.e. mean deviation and visual field index), although the table may present only the higher level categories.

In general, while the studies that we included reported the estimates for associations between prognostic factors and progression as univariable or multivariable analyses, they were not designed as studies of prognostic models (i.e. they did not try to derive the best prediction models for progression). Only three studies reported the development/validation of models (Lee 2022; Medeiros 2009; Wright 2020) and only one of those was designed with the purpose of creating the model using data from an existing cohort study (Lee 2022).

We planned to stratify our synthesis by three time periods, but the inclusion of time as a stratification factor drastically limited our ability to conduct any meta-analyses. Similarly, we accepted multiple definitions for progression as long as it was the same outcome domain (e.g. visual field deterioration through different assessments). Consequently, we considered only the definition of the prognostic factor, the measure of association, and type of analysis in determining which factors' estimates could be quantitatively synthesized (Supplementary material 6).

We conducted 12 meta-analyses for 11 prognostic factors across the five domains. Wherever relevant, we stratified analyses for univariable and multivariable estimates while focusing primarily on multivariable estimates. Our summary of findings tables were stratified by domain and include the prognostic factors for which we have quantitative syntheses. We did not discuss the risk of bias for each prognostic factor because only one study (Leske 2007) had a low risk of bias overall. Therefore, we have low confidence in most evidence due to the potential risk of bias, inconsistency, and indirectness in the evidence. Most of the studies referred to POAG, except for Leske and colleagues (Leske 2007) who evaluated a PXFG population.

Prognostic factors for visual field progression

Demographic prognostic factors

Many studies examined at least one demographic characteristic as a prognostic factor for glaucoma progression. These include age, sex, and race/ethnicity. We were able to conduct meta-analyses of age and sex. [Summary of findings 1](#) presents our GRADE assessments of the demographic factors for which we were able to conduct meta-analysis. [Table 2](#) presents an overview of the numbers and directions of associations for each demographic prognostic factor, including any meta-analytic estimates.

Age

Thirteen studies ($n = 20$ estimates) explored age as a prognostic factor in progression of visual field amongst the participants diagnosed with POAG (Biswas 2020; Chauhan 2008; Founti 2020; Greenfield 2007; Jonas 2004; Lee 2022; Lee 2023; Leung 2009; Medeiros 2009; Pappelis 2019; Sullivan-Mee 2023; Wilson 2002; Yu 2016). Of the 20 estimates, 14 were positive associations between increased age and progression, five were negative associations, and one was null. The consistency of estimates suggests that older age, either as a continuous measure at baseline or by some categorization, was often associated with an increased risk of progression. One study investigated age as a prognostic factor for change in RNFL thickness and reported that younger age was found to be associated with a faster rate of RNFL thickness reduction ($P < 0.001$) (Biswas 2020). It was possible to undertake a meta-analysis of multivariable HRs of four studies reporting visual field outcomes across two time periods (3 to 4 years and 5+ years) (Chauhan 2008; Lee 2023; Sullivan-Mee 2023; Yu 2016). The pooled HR was 1.01 (95% CI 0.97 to 1.05), with a high degree of heterogeneity ($\text{Tau}^2 = 0.00$, $I^2 = 89\%$), which was consistent with the other estimates that could not be combined (Analysis 1.1). The evidence is very uncertain about the association between age and glaucoma progression (very low certainty).

Sex

Eight studies ($n = 9$ estimates) investigated sex as a prognostic factor for visual field progression amongst participants diagnosed with POAG (Chauhan 2008; Founti 2020; Greenfield 2007; Jonas 2004; Lee 2022; Leske 2007; Pappelis 2019; Wilson 2002). The studies presented a mix of multivariable and univariable estimates and measures of effect (i.e. hazard ratio, P value, rate of progression) over two to six years of follow-up. Only two of the eight studies reported sufficient evidence for an association between female sex and increased progression (Chauhan 2008; Pappelis 2019). Of the nine estimates, five indicated a positive association between female sex and glaucoma progression, two were negative, and two did not provide a direction of effect. Four studies reported hazard ratios which we were able to combine in meta-analyses stratified by multivariable and univariable estimates. The combined multivariable analyses of two studies (Chauhan 2008; Founti 2020) suggest females may have a 64% greater hazard of progression than males (HR 1.64, 95% CI 1.15 to 2.34; $\text{Tau}^2 = 0.00$, $I^2 = 0\%$), whereas the combined univariable estimates from three studies (Founti 2020; Greenfield 2007; Leske 2007) indicated insufficient evidence of an effect (Analysis 1.2). The evidence suggests that female sex may be associated with increased glaucoma progression (low certainty).

Race/ethnicity

Only two studies ($n = 3$ estimates) reported race or ethnicity as a prognostic factor of visual field deterioration amongst participants with POAG (Founti 2020; Medeiros 2009). Neither of these studies found that ethnicity or race had an effect on visual field progression in univariable or multivariable analyses. Two of the three estimates found that being an African American was associated with progression compared to a non-African American, and one found being white was associated with progression compared to non-white.

Systemic prognostic factors

Many studies assessed systemic diseases or phenomena related to systemic conditions as prognostic factors of POAG visual field progression. These systemic diseases or conditions include: hypertension, cardiac or cerebral vascular diseases, migraine, Raynaud's phenomenon, diabetes, sleep apnea and cold hands and feet/extremities. We were able to combine data in meta-analyses for hypertension, cardiovascular disease, migraine, and Raynaud's syndrome. [Summary of findings 2](#) presents our GRADE assessments of the systemic factors for which we were able to conduct meta-analysis. [Table 3](#) presents an overview of the numbers and directions of associations for each systemic prognostic factor, including any meta-analytic estimates.

Systemic hypertension

Six studies ($n = 12$ estimates) assessed the relationship of systemic hypertension as a prognostic factor for visual field progression amongst patients with POAG (Dascalu 2021; Founti 2020; Greenfield 2007; Leske 2007; Leung 2009; Medeiros 2009). The estimates were evenly split in the direction of association, with three studies reporting null, negative associations (Founti 2020; Leske 2007; Medeiros 2009), and three studies (Dascalu 2021; Greenfield 2007; Leung 2009) finding evidence of positive associations between hypertension and progression with effects ranging from an HR of 1.48 (95% CI 1.04 to 2.10) to an OR of 5.44 ($P = 0.027$). Four studies (Founti 2020; Greenfield 2007; Leske 2007; Leung 2009) presented hazard ratios which we were able to combine in random-effects meta-analyses, stratified by adjustment status. Neither of the meta-analyses had sufficient evidence to suggest hypertension as a prognostic factor for progression (Analysis 2.1). The evidence is very uncertain about the effect of hypertension on glaucoma progression (very low certainty).

Cardiac/cerebral vascular comorbidities

Six studies ($n = 17$ estimates) evaluated cardiac or vascular comorbidities as prognostic factors in predicting progression of POAG (Chauhan 2008; Dascalu 2021; Founti 2020; Greenfield 2007; Leske 2007; Leung 2009). We combined the estimates from two studies that presented univariable estimates for cardiovascular disease (Founti 2020; Leske 2007) and found insufficient evidence of an association (HR 1.06, 95% CI 0.75 to 1.49; $\text{Tau}^2 = 0.00$, $I^2 = 0\%$) (Analysis 2.2). All other estimates were too heterogeneous to combine, reporting different measures of cardiovascular comorbidities.

Ten of the estimates were positive and had enough precision to suggest associations between the presence of these comorbidities and progression of glaucoma. Chauhan 2008 reported an increased hazard of progression with abnormal baseline antidiolipin (HR 3.86, 95% CI 1.60 to 9.31); Dascalu 2021 reported five times higher

odds (OR 5.83, $P < 0.01$) of visual field loss and optic nerve damage amongst those who had ischemic heart disease; and Leung 2009 reported that both silent cerebral infarcts (HR 1.61, 95% CI 1.09 to 2.36) and history of cerebrovascular accident (CVA) (RR 2.28, 95% CI 1.03 to 5.06) were associated with progression in a backward and forward stepwise model.

In addition to the presence of cardiovascular disease which we included in the meta-analysis, Founti 2020 evaluated six other potential cardiac prognostic factors, such as history of heart attack, angina, claudication, and found no consistent evidence of associations. Similarly, Greenfield 2007 reported the associations between heart rate measures and the use of beta-blockers on visual field progression and found no consistent evidence of associations. Considering our meta-analyses as well as the individual study estimates that could not be combined, evidence suggests cardiovascular disease may be associated with progression of glaucoma (low certainty).

Migraine

Three studies ($n = 3$ estimates) presented univariable effects of migraine on the progression of POAG, over a range of two to six years (Founti 2020; Greenfield 2007; Leske 2007). Two of the three estimates were negative and one was positive, although none found evidence of an association between migraine and visual field or optic disc progression amongst the people with POAG. Our meta-analysis also did not find evidence of a positive association (HR 1.06, 95% CI 0.67 to 1.67; $\text{Tau}^2 = 0.04$, $I^2 = 22\%$) (Analysis 2.3). The evidence is very uncertain about the effect of migraines on glaucoma progression (very low certainty).

Raynaud's phenomenon

Three studies ($n = 3$ estimates) evaluated the univariable prognostic effect of Raynaud's phenomenon on visual field progression from two to six years (Founti 2020; Greenfield 2007; Leske 2007). Two of the three estimates were positive and one negative, although none found evidence of an association between Raynaud's and visual field progression. Our meta-analysis of the three studies also did not find evidence of a positive association (HR 1.21, 95% CI 0.85 to 1.73; $\text{Tau}^2 = 0.00$, $I^2 = 0\%$) (Analysis 2.4). The evidence is very uncertain about the effect of Raynaud's syndrome on glaucoma progression (very low certainty).

Diabetes

Two studies ($n = 2$ estimates) reported diabetes mellitus as a predictor of visual field loss amongst POAG (Dascalu 2021; Greenfield 2007). We were unable to conduct a meta-analysis of the estimates (one positive and one negative) and neither Greenfield 2007 (HR 0.79, 95% CI 0.31 to 2.02) nor Dascalu 2021 (OR 1.46, 95% CI not reported, $P = 0.322$) found evidence of associations between having type 2 diabetes (or being treated for diabetes mellitus) and visual field progression in POAG.

Sleep apnea

Founti 2020 ($n = 1$ estimate) assessed whether sleep apnea could be a prognostic factor in univariable analyses and found a negative association with progression of glaucoma (HR 0.96, 95% CI 0.24 to 3.91).

Cold extremities

Founti 2020 ($n = 1$ estimate) also assessed whether having cold hands or feet may be a prognostic factor in univariable analyses and found a positive association with progression of glaucoma over two years (HR 1.13, 95% CI 0.73 to 1.74).

Lifestyle prognostic factors

Lifestyle prognostic factors were less commonly studied and were reported from only three studies. These included smoking and body mass index. We could not combine the data across any of these studies for these two prognostic factors. As we were unable to conduct any meta-analyses of these factors, we did not judge their certainty of evidence and have no associated summary of findings table. Table 4 presents an overview of the numbers and directions of associations for each lifestyle prognostic factor, including any meta-analytic estimates.

Smoking

Two studies ($n = 4$ estimates) assessed smoking as a prognostic factor for visual field deterioration and all estimates were negative, suggesting smoking may be a protective factor against progression (Founti 2020; Leske 2007). Founti 2020 used univariable proportional hazards regression to derive hazard ratios for progression over two years amongst ever-smokers and present smokers as compared with never-smokers. In univariable analyses, ever smoking was found to reduce the hazard of progression by 40% (HR 0.60, 95% CI 0.40 to 0.92). After inclusion in the multivariable model which controlled for several other covariates, it maintained a protective effect of similar magnitude (HR 0.59, 95% CI 0.37 to 0.93). Being a current smoker was also protective of progression, but with no evidence of an association in both studies (Founti 2020; Leske 2007).

Body mass index (BMI)

Two studies ($n = 2$ estimates) assessed BMI as a prognostic factor for progression assessed through visual field deterioration (Founti 2020; Pappelis 2019). Whereas Founti 2020 found no association with the hazard over a two-year time period in univariable analyses (HR 0.98, 95% CI 0.93 to 1.02), Pappelis 2019 controlled for several important confounders and found that each unit increase in BMI was associated with a 0.01 dB per year slower change in the rate of progression over more than five years of follow-up ($P = 0.032$).

Ocular prognostic factors

Twenty-one studies reported 233 associations between 23 ocular factors and the progression of glaucoma. The most commonly assessed factors included IOP (14 studies, 30 estimates), visual field parameters (11 studies, 30 estimates), central corneal thickness (9 studies, 14 estimates), refractive errors/myopia (8 studies, 14 estimates), and disc hemorrhage (6 studies, 9 estimates).

Most estimates within prognostic factors were not combinable in meta-analyses due to heterogeneity in the measures (e.g. continuous, dichotomized, categorized), the analysis approach (e.g. multivariable or univariable measures of association like rates, hazard ratios, odds ratios), and the definition of the progression. We were able to conduct five meta-analyses for intraocular pressure, central corneal thickness, disc hemorrhage, and bilateral disease. Summary of findings 3 presents our GRADE assessments of the ocular factors for which we were able to conduct meta-analysis.

Table 5 presents an overview of the numbers and directions of associations for each ocular prognostic factor, including any meta-analytic estimates.

Intraocular pressure

Intraocular pressure was the most frequently evaluated prognostic factor for the progression of POAG. Fourteen studies ($n = 30$ estimates) studied how change in IOP affects visual field progression, rate of change in nerve fiber layer thickness and change in optic disc assessment amongst diagnosed people with POAG and the effect estimates were heterogenous. IOP was assessed as a continuous variable (per mmHg change) or dichotomized, and at different time points including: baseline, pretreatment, highest during initial six months, mean, peak, and undefined. The evidence for an effect was mixed, as nineteen of the associations were positive, nine were negative, and two did not have a direction specified. Eight studies (Krug 1995; Medeiros 2009; Pappelis 2019; Wilson 2002; Wright 2020; Yoshikawa 2018; Yu 2016; Zhang 2016) found no evidence of association across the different measures whereas six (Biswas 2020; Chauhan 2008; Founti 2020; Lee 2022; Leske 2007; Sullivan-Mee 2023) found evidence of an association.

Five studies presented meta-analyzable estimates of the effect of continuous IOP on visual field deterioration: three multivariable hazard ratios (Chauhan 2008; Founti 2020; Yu 2016) and two multivariable odds ratios (Medeiros 2009; Yoshikawa 2018). The evidence from these both was also mixed as the HR had sufficient evidence for an association (HR 1.08, 95% CI 1.03 to 1.13; $\text{Tau}^2 = 0.00$, $I^2 = 16\%$) (Analysis 3.1) but the OR did not (OR 0.96, 95% CI 0.84 to 1.10; $\text{Tau}^2 = 0.01$, $I^2 = 50\%$) (Analysis 3.2). The evidence suggests increased intraocular pressure may be associated with the progression of glaucoma, but this is uncertain (low certainty).

Baseline visual field

Baseline visual field severity (measured with mean deviation [MDev] or Visual Field Index [VFI]) was the next most commonly studied ocular prognostic factor, with 11 studies presenting 30 estimates across two subcategories for visual field: MDev, and visual field index. The evidence was mixed, with 14 estimates having a positive association, 13 having a negative association, and three having null or undefined directions.

Mean deviation

Eight studies ($n = 26$ estimates) assessed mean deviation across many measures, including continuous (e.g. 1 dB higher, 1 dB worse, dB with 10-2 MDev, dB with 24-2 MDev, consecutive deterioration) and dichotomized severity of visual field (VF) defects (e.g. ≤ -4.0 dB vs. > -4.0 dB, presence of 10-2 VF defect) (Founti 2020; Lee 2022; Leske 2007; Medeiros 2009; Sullivan-Mee 2023; Yoshikawa 2018; Yu 2016; Zhang 2016). The measures and outcomes were too heterogenous to permit meta-analysis but, in general, mean deviation did not appear to be an important prognostic factor as only 11 estimates from three of the studies (Leske 2007; Sullivan-Mee 2023; Yoshikawa 2018) found evidence of associations. Of note, Sullivan-Mee 2023 found that the presence of a visual field defect was associated with 22 times increased hazard of progression in multivariable analysis (HR 22.22, 95% CI 7.52 to 66.00).

Visual field index

The evidence for the severity of disease measured with visual field index was more heterogeneous and less frequently reported than mean deviation. Three studies provided four estimates for the association with progression: one study found evidence of a positive association with visual field index (Biswas 2020), one found no association with visual field index (Zhang 2016), and one found a positive association with baseline CIGTS score, but not with baseline AGIS score and progression (Wilson 2002).

Central corneal thickness

Nine studies ($n = 14$ estimates) reported the association of CCT and visual field deterioration amongst people with POAG, finding mixed evidence: six estimates were null or of undefined direction, five negative (thinner CCT associated with faster progression), and three positive (Founti 2020; Greenfield 2007; Lee 2022; Leske 2007; Leung 2009; Pappelis 2019; Yoshikawa 2018; Yu 2016; Zhang 2016). Only three studies found evidence of the associations (Lee 2022; Leung 2009; Zhang 2016) but the effect sizes were small. Leung 2009 found the largest effect but assessed a per 30 μm decrease in thickness, whereas other studies assessed a per 1 μm increase in thickness. Two studies each presented multivariable (Leung 2009; Yu 2016) and univariable (Founti 2020; Greenfield 2007) hazard ratios that we were able to combine with meta-analyses. Neither the multivariable nor univariable analysis had sufficient evidence to discern an association (Analysis 3.3). The evidence is very uncertain about the effect of central corneal thickness on glaucoma progression (very low certainty).

Refractive errors and myopia

Eight studies ($n = 14$ estimates) reported associations of refractive errors and visual field progression, none of which were combinable due to differences in the measures used (Biswas 2020; Founti 2020; Greenfield 2007; Jonas 2004; Lee 2022; Leske 2007; Yoshikawa 2018; Yu 2016). Six of the associations were null or did not indicate the direction, five were negative, and three were positive. Four studies (Founti 2020; Jonas 2004; Leske 2007; Yoshikawa 2018) described the association between refractive error in the progression of visual fields of people with POAG. None of these four studies found evidence of associations between refractive errors and visual field progression with a follow-up duration of two to five years. Four studies (Biswas 2020; Founti 2020; Lee 2022; Yu 2016) assessed the relationship between axial length and the rate of progression through visual field index and rate of change in nerve fiber layer thickness. The only association that had sufficient evidence of an effect from 14 estimates was categorized as high myopia (axial length ≥ 26 mm), which was negatively associated with the rate of change of RNFL thickness (-0.21% per year, $P = 0.02$) (Biswas 2020). Greenfield 2007 assessed the relationship between spherical equivalent and progression in univariable Cox proportional hazard regression and found no effect (HR 1.00, 95% CI 0.89 to 1.11).

Disc hemorrhage

Six studies ($n = 9$ estimates) assessed the relationship between disc hemorrhage and progression (Founti 2020; Greenfield 2007; Lee 2023; Leske 2007; Leung 2009; Yoshikawa 2018). Eight of the estimates were positive and one was null, suggesting the presence of disc hemorrhage increased the likelihood of progression. We were able to include five studies in meta-analyses of multivariable (Founti 2020; Lee 2023; Leung 2009) and univariable (Founti 2020; Greenfield 2007; Leske 2007) hazard ratios. We found the presence

of disc hemorrhage to be a clinically important prognostic factor in both multivariable (HR 2.03, 95% CI 1.55 to 2.67; $\text{Tau}^2 = 0.00$, $I^2 = 0\%$) and univariable (HR 1.51, 95% CI 1.12 to 2.02; $\text{Tau}^2 = 0.00$, $I^2 = 0\%$) analyses (Analysis 3.4). The evidence suggests the presence of disc hemorrhage may be associated with the progression of glaucoma (low certainty).

Retinal nerve fiber layer (RNFL) thickness

Five studies ($n = 9$ estimates) explored RNFL thickness (change over time or at baseline) as a prognostic factor in visual field progression (Biswas 2020; Lee 2023; Medeiros 2009; Sullivan-Mee 2023; Yu 2016). The association was usually assessed as the thinning rate and only two found positive associations, whereas seven associations were negative. Four of the studies (Biswas 2020; Lee 2022; Sullivan-Mee 2023; Yu 2016) found that eyes with RNFL thinning were associated with an increased risk of progression, either dichotomized or per $1\ \mu\text{m}$. Medeiros 2009 found each $1\ \mu\text{m}$ decrease in thickness was associated with a 5% increase in the odds of progression in multivariable logistic regression (OR 1.05, 95% CI 0.98 to 1.12).

Optic disc

Size

Four studies ($n = 10$ estimates) assessed the association between optic disc size measures (e.g. cup-to-disc ratio, optic disc area, minimal and maximal disc diameter, and OCT rim area) and progression (Greenfield 2007; Jonas 2004; Krug 1995; Zhang 2016). None of the studies found sufficient evidence to suggest optic disc size as a predictor of glaucoma progression and seven of the estimates did not have a reported direction (3 were positive).

Vessel density

In contrast to other studies of optic disc characteristics, Lee 2023 assessed optic disc vessel density (1 estimate) and parapapillary choroidal vessel density (1 estimate), finding sufficient evidence that both are protective of progression in multivariable analyses.

Ocular perfusion pressure

Of the three studies assessing perfusion pressure as a prognostic factor, two found evidence of large negative (i.e. protective) effects as both a continuous (i.e. per mmHg lower) (HR 1.21, 95% CI 1.12 to 1.31; Greenfield 2007) and dichotomized (≤ 125 mmHg) (Leske 2007) predictor in univariable (HR 1.39, 95% CI 1.03 to 1.87) and multivariable (HR 1.42, 95% CI 1.04 to 1.94) analyses. Founti 2020 found no association between each mmHg increase and progression defined through visual field deterioration.

Bilateral disease of POAG

Two studies (Founti 2020; Leske 2007) reported five positive estimates of bilateral disease as a prognostic factor for glaucoma. Although the follow-up times were very different between these studies — respectively two years and eight years — we combined the multivariable estimates and found bilateral disease to increase the hazard of progression by 77% over unilateral disease (HR 1.77, 95% CI 1.35 to 2.32; $\text{Tau}^2 = 0.00$, $I^2 = 0\%$) (Analysis 3.5). The evidence suggests the presence of bilateral disease is likely to be associated with increased glaucoma progression (moderate certainty).

Choroidal microvascular dropout

Two studies ($n = 3$ estimates) assessed the presence of choroidal microvascular dropout as a prognostic factor and found only

positive associations (Lee 2023; Fursova 2022). Lee 2023 reported an increased hazard of progression in eyes with cMvD (HR 1.7, 95% CI 1.03 to 2.95) and disc microvascular dropout (HR 1.99, 95% CI 1.11 to 3.56). Fursova 2022 did not provide specific estimates but reported cMvD was more often detected in eyes with POAG with a lower MDef index, lower RNFL thickness, and optic disc perfusion and vessel density.

Optic nerve

Structural

Two studies ($n = 13$ estimates) assessed the association between optic nerve structural measures and progression of glaucoma (Jonas 2004; Lee 2022). Jonas 2004 reported estimates of six multivariable and six univariable probabilities for associations between neuroretinal rim area overall and for specific zones, but only the overall rim area had sufficient evidence of an effect (no direction reported for any associations). Lee 2022 found that each 1-unit increase in the lamina cribrosa curvature index was associated with a lower rate of progression in both multivariable and univariable estimates.

Peripapillary nerve fiber layer indices

The study conducted by Zhang 2016 assessed structural parameters ascertained through OCT as potential prognostic factors of visual field progression. Concerning the peripapillary nerve fiber layer (NFL) indices (13 measures), most estimates did not have sufficient evidence of effect and seven did not report a direction. In general, the parameters that appeared to have associations with progression were inferior nerve fiber layer thickness and abnormal focal loss volume (6 estimates, 4 of which had sufficient evidence of a positive association). Other factors and indices for the nerve fiber layer (e.g. OCT cup-to-disc ratio, OCT NFL overall, OCT NFL superior quadrant, OCT NFL global loss volume, OCT ganglion cell complex (GCC) overall, and OCT GCC superior hemisphere) did not have any association with progression.

Macular ganglion cell parameters

Zhang 2016 also explored 13 different macular ganglion cell (GCC) parameters as prognostic factors of VF progression and found all to be positively associated with an increased likelihood of progression. In contrast to the peripapillary nerve fiber layer indices, abnormal macular ganglion cell parameters were nearly all associated with progression as compared to normal GCC parameters. Indices included GCC overall, GCC inferior hemisphere, GCC global loss volume, and GCC fluid loss volume as continuous and categorical (normal, borderline, and abnormal) measures. All factors except for the borderline categorical indices (compared with their respective normal categories) were found to be associated, with hazard ratios ranging from 1.18 to 3.07.

Retinal vessel calibers

One study (Lin 2023) assessed the effect of narrowing retinal vessel calibers (both arterial and venular) by quartile on progressive RNFL thinning and visual field deterioration. This study presented 12 multivariable and 12 univariable estimates across these outcomes: 20 of the associations were positive and four negative. Focusing on the multivariable analyses, neither arterial nor venular narrowing was associated with progressive RNFL thinning. However, arterial narrowing of retinal vessel calibers was associated with VF deterioration, with all three quartiles having hazard ratios ranging

from 3.93 (95% CI 1.03 to 14.98) to 7.57 (95% CI 1.56 to 36.73), while venular narrowing had no association with VF deterioration.

Peripapillary region vascular matrices

Wang 2022 assessed different peripapillary region vascular matrices, including cpVD of the temporal, superotemporal, inferotemporal, superonasal, inferonasal, nasal, and global regions, and the vessel diameter index and fractal dimension with multivariable and univariable hazard ratios (18 estimates). The superotemporal region was the only estimate that had sufficient evidence of a positive association and all evidence was mixed: 11 positive associations and seven negative.

Vitreo-retinal degeneration

Medeiros 2009 reported on the association between vitreo-retinal degeneration and visual field progression and found a 28% increase in the odds of progression over five years per 1% lower SVD (multivariable OR 1.28, 95% CI 1.02 to 1.59).

Macular region vascular matrices

Wang 2022 presented 16 estimates (8 each for multivariable and univariable) of the association between different macular superficial capillary plexus zones and progression over three to four years. None of the multivariable analyses had sufficient evidence to show an association, although 13 were positive, two negative, and one null.

Corneal hysteresis

The study conducted by Founti 2020 found that those who had higher corneal hysteresis had slower progression of POAG (HR 0.86, 95% CI 0.77 to 0.96).

Exfoliation glaucoma

Leske 2007 reported three strong associations, suggesting having PXFG rather than POAG is a strong predictor of perimetric or optic disc progression by eight years in both univariable (HR 3.21, 95% CI 2.04 to 5.07) and multivariable (HR 2.12, 95% CI 1.30 to 3.46) analyses.

Pseudophakia

Greenfield 2007 did not find sufficient evidence of a large protective effect against visual field progression amongst those with a pseudophakic lens compared to those without (univariable HR at 3 to 4 years; 0.41, 95% CI 0.10 to 1.70).

Other prognostic factors

Several studies assessed the association between the progression of glaucoma and other potential factors such as receiving treatment, family history, and signal strength from imaging. We were able to conduct one meta-analysis for this domain by considering the receipt of a treatment in a randomized trial to be its own "prognostic" factor as all showed an association with a protective effect. [Summary of findings 4](#) presents our GRADE assessments of the other factors for which we were able to conduct meta-analysis. [Table 6](#) presents an overview of the numbers and directions of associations for each other prognostic factor, including any meta-analytic estimates.

Pharmacological factors or treatment for glaucoma

Five studies ($n = 10$ estimates) assessed whether there was an association between progression of open-angle glaucoma and past or current treatment for glaucoma or other comorbidities (Founti 2020; Greenfield 2007; Leung 2009; Leske 2007; Pappelis 2019). Three studies examined treatments with interventions including latanoprost 0.005% (Founti 2020), brimonidine 0.2% (Greenfield 2007), argon-laser trabeculoplasty plus betaxolol (Leske 2007) and found all were protective, reducing the hazard of progression between 40% to 74% over different time periods (2 years, 3 to 4 years, and 5+ (8) years) in both univariable and multivariable analyses. Meta-analysis of these three studies, to obtain a general effect of "treatment" showed a reduction in the risk of progression for both multivariable (HR 0.44, 95% CI 0.31 to 0.61; $\text{Tau}^2 = 0.03$, $I^2 = 37\%$) and univariable (HR 0.56, 95% CI 0.44 to 0.72; $\text{Tau}^2 = 0.00$, $I^2 = 0\%$) estimates (Analysis 4.1). Two studies assessed the association between other drugs and glaucoma progression. Leung 2009 found simvastatin use was protective for glaucoma progression with a risk ratio of 0.36 (95% CI 0.14 to 0.91). Pappelis 2019 observed no relationship between the rate of progression and the number of glaucoma medications ($P = 0.056$), statin use ($P = 0.086$), or angiotensin receptor blocker use ($P = 0.097$). The evidence suggests treatment for glaucoma with pharmacologics may be associated with large decreases in glaucoma progression (low certainty).

Family history of glaucoma

Three studies ($n = 3$ estimates) included family history of glaucoma as a prognostic factor for the progression of glaucoma and the evidence was mixed (Founti 2020; Greenfield 2007; Leske 2007). Although all three assessed progression across different time periods – from two years, three to four years, and over five years – the hazard ratios were all close to one (two positive, one negative) with wide confidence intervals.

Glaucoma surgery

Although we excluded studies in which participants either previously or as part of the intervention received surgeries to treat their glaucoma, one prospective, observational study (Lee 2022) allowed participants to undergo glaucoma surgery during their follow-up. One hundred and twenty-five of 712 (17.5%) of participants in Lee 2022 underwent some form of glaucoma surgery in the first six months of follow-up. As a prognostic factor included in the analyses, they found it was associated with a reduction in the rate of progression in univariable analyses (Beta -0.445, 95% CI -0.626 to -0.265), but had no effect after adjusting for other important confounders (Beta -0.005, 95% CI -0.198 to 0.188) (Lee 2022).

Signal strength

Biswas 2020 included the signal strength from the OCT imaging as a factor that may be related to the rate of change in RNFL thickness. Although they included only images with a signal strength greater than or equal to six in their analysis, they found a higher signal strength was associated with a faster rate of RNFL thinning ($P < 0.001$).

GRADE summary of findings

We judged the certainty of evidence for the 11 prognostic factors for which we were able to conduct 12 quantitative syntheses. [Summary of findings 1](#); [Summary of findings 2](#); [Summary of](#)

findings 3; and Summary of findings 4 present the assessments and accompanying plain text summaries of the associations between these prognostic factors and glaucoma progression. Where both multivariable (adjusted) and univariable estimates were meta-analyzed, we assessed the strength of the multivariable estimates.

There is moderate-certainty evidence to support the finding that the bilateral disease presence of disc hemorrhage is a prognostic factor associated with VF progression in people with glaucomas (including POAG, PXFG, NTG). There is low-certainty evidence that female sex and the presence of disc hemorrhage are associated with progression, and low-certainty evidence that treatment with pharmacologics is protective of progression. The evidence is inconsistent and uncertain about the associations between progression and age at baseline (very low), the presence of hypertension (very low), cardiovascular disease (low), migraine history (very low), Raynaud's syndrome (very low), increased IOP (low), and increased central corneal thickness (very low).

The overall certainty of evidence for our prognostic factors was generally very low ($n = 5$), low ($n = 6$), or moderate ($n = 1$). The most common reason for downgrading was indirectness because most studies had different time periods of follow-up and no meta-analysis included only studies from a single time period (i.e. 2 years, 3 to 4 years, or 5+ years). The risk of bias was the next most common reason for downgrading because eight of 10 studies contributing to the 12 meta-analyses were at high risk of bias. We did not consider different sets of adjustment factors in multivariable analyses as contributing to greater uncertainty, as no models across all studies were exactly the same.

DISCUSSION

Overview of results

This prognostic factor review included 22 studies with over 110 reports that presented over 330 prognostic estimates for 40 different characteristics of glaucoma patients and their eyes at baseline and their associations with progression of open-angle glaucoma. Of the 40 prognostic factors reported in the studies, we found that eight demographic, ocular, and other characteristics were positive or negative predictors of glaucoma progression (see below). Other prognostic factors had either heterogenous evidence of an association with progression or observed no associations, suggesting they may not be important for predicting progression of glaucoma. The prognostic factors we identified as having potential associations with glaucoma progression could be used to inform further primary research (e.g. confirmatory prognostic studies) as they identify individuals or communities at high risk of disease progression. Additionally, our findings may be useful in developing clinical prediction models as some factors that would otherwise be included in models may be considered less important for prediction and possibly removed, thereby reducing noise and increasing parsimony.

In general, we encountered some methodological challenges with our review and the evidence. There was a major gap in the evidence base for assessing the prognostic factors for functional and structural progression of primary open-angle glaucoma (POAG) and there was a lack of clarity in primary studies in defining the prognostic factors for development of POAG versus defining the prognostic factors to assess the progression of POAG. We also had a major gap in the number of studies that

assessed prediction models: all studies reported some measure of prognostic association with progression, but only three reported creating or validating prediction models. Prediction models are multivariable models developed to estimate the likelihood of an outcome, based on a set of factors, whether the factors are causally related to the outcome or not [15]. Conversely, causal prognostic research can also be done with multivariable models, but the aim and approach are different as investigators try to determine the exact strength of associations by adjusting for the most appropriate set of confounders [15]. Our finding that these types of studies were uncommon highlights the need for more confirmatory prognostic studies for glaucoma progression. We observed a high level of uncertainty around the associations and the outcomes in the included studies, which aligns with the uncertainty that has also been identified for the effectiveness of interventions for glaucoma [185].

Considerable levels of statistical heterogeneity, lack of reporting on evaluated prognostic factors, methods of measurement of prognostic factors, lack of including multiple variables in analyses, reliance on univariable models, and poor quality of reporting hindered our ability to undertake meta-analyses on some important prognostic factors. Despite the limitations of the evidence, this review lays a strong foundation for further exploring the prognostic factors for progression of POAG, since this has not been done before. We propose that future prognostic factor studies should be properly planned, using rigorous methods and current standards for prognostic research [14], thereby building a more valid evidence base and capacity for conducting prognostic factor research.

Prognostic factors found to be associated with progression of glaucoma

We found that eight of 40 (20%) factors that had been reported were associated with glaucomatous visual field progression amongst people with POAG, as evident through meta-analyses or from evidence from multiple studies or estimates that could not be statistically combined. Presence of disc hemorrhage, decreased retinal nerve fiber layer thickness, abnormal macular ganglion cell parameters, increased optic disc vessel density, presence of choroidal microvascular dropout, presence of bilateral disease, presence of exfoliation glaucoma, and treatment for glaucoma could be used as predictors of visual field progression of the POAG. The evidence for most of these was assessed as low or very low certainty, and we considered only presence of bilateral disease as having moderate-certainty evidence. Treatment for glaucoma is started or escalated when there is disease progression. Thus, it is not surprising that we found this association in our review.

The finding that thinning of retinal nerve fiber layer thickness and macular ganglion cell parameters are prognostic factors for visual field deterioration is not surprising as they are manifestations of disease progression. It is well known that there is some divergence between structural and functional changes in glaucoma. Relatedly, our review found low to very low-certainty evidence of associations with factors pertaining to blood flow to the retina and optic nerve, such as disc hemorrhages, optic disc vessel density, choroidal microvascular dropout, and systemic vascular comorbidities. These factors may be under-recognized in clinical practice as factors for progression. Conversely, we found one study which showed higher optic disc vessel density to have a protective effect on VF progression. A review conducted by Chan and

colleagues reported the proof of concept that changes in the retinal vasculature are associated with glaucoma. However, this review did not provide temporal associations [186]. We observed that having bilateral disease increases the risk of progression of POAG, as observed in other primary studies [187]. Other factors such as choroidal micro-vasculature dropout increase the hazard of progression.

Several prognostic factors had mixed evidence overall for an association, but some studies observed associations worth investigating further in confirmatory studies. Some specific prognostic factors had a single large association with progression from individual studies: baseline anti-cardiolipin level, cerebral and cardiac vascular comorbidities, history of silent cerebral infarcts, and presence of severe baseline VF defects. Although these specific factors could be considered important for prognosis, when grouped with other related estimates for higher-level classification of prognostic factors (i.e. cardiac/cerebral vascular comorbidities and visual field mean deviation, respectively), the evidence for these types of prognostic factors was mixed. Relatedly, although a high level of intraocular pressure (IOP) at baseline was expected to be a prognostic factor and was highly studied, the evidence from our included studies was mixed, and it was not clearly a factor with a strong association, despite one of the two meta-analyses showing an association. This could possibly be due to the influence of effective IOP-lowering treatments used in patients with perceived high or uncontrolled IOP: five studies included some kind of treatment as a factor for progression and found that it was effective in slowing progression with moderate certainty. It may also be that the association between treatment and progression is confounded by clinicians' perception of high risk of glaucoma and prescribing patterns (particularly in observational studies). Additionally, older age, either as a continuous measure at baseline or by some categorization, was often associated with an increased risk of progression in studies, although seven of 20 (35%) estimates were not.

Prognostic factors not found to be associated with progression of glaucoma

We did not find any statistically significant summary estimates through meta-analyses for age, presence of hypertension or cardiac/cerebral disorders, migraine, Raynaud's phenomenon, and central corneal thickness (CCT), which is a relatively novel finding compared to the conventional evidence based on prognostic factors for POAG. Vascular factors associated with disease progression are possibly more relevant for people with diagnosis of POAG and relatively low IOP, commonly described as normal-tension glaucoma (NTG).

A sufficient number of homogeneous effect estimates were not available to allow us to conduct a meta-analysis on race/ethnicity, smoking, BMI, refractive error including myopia, RNFL thickness, optic disc size and ocular perfusion pressure. Instead, we summarized the effect estimates narratively. Though optic disc size is routinely measured and used in clinical practice, we did not find sufficient homogeneous results to conduct a meta-analysis and, interestingly, none of the primary studies found optic disc size to be a significant predictor of visual field progression of POAG. Similarly, though there is strong body of evidence showing race/ethnicity as a strong prognostic factor for POAG, we did not find sufficient evidence to report ethnicity/race as a predictor of visual field progression in POAG.

There were several other factors where some meta-analysis was possible, but the evidence was not consistent with the qualitative syntheses of other estimates. We found varying evidence for female sex as a predictor of progression: the combined adjusted analyses of two studies suggest females may have a 64% greater hazard of progression than males, whereas the combined unadjusted estimates from three studies indicated no association. We did not find strong evidence supportive of systemic hypertension as a predictor of glaucoma progression. A recent review conducted by Eijgen and colleagues reported a bi-modal pattern of association between systemic blood pressure and glaucoma [188]. However, the conclusions are not clear with regard to prognostic factors for glaucoma development versus prognostic factors for glaucoma progression. Another meta-analysis by Leung and colleagues on systematic antihypertensive medication, IOP, and glaucoma reported that systemic antihypertensive medications have a heterogenous effect on glaucoma, which is compatible with our review findings [189]. Additionally, we found the evidence for cardiac or cerebrovascular abnormalities and POAG progression was highly heterogeneous, which is in contrast to a review which found many primary studies which have reported that cardiovascular disease is an important prognostic factor [190]. This may also derive from incorrect assumptions about the effects of prognostic factors in primary study designs. Most of the cardiac prognostic factors such as angina and claudication were found to have no or uncertain associations with progression of open-angle glaucoma.

The cup-to-disc (C/D) ratio is not commonly used in clinical practice for assessing the progression of POAG, though there have been a few publications of the utility of the C/D ratio in the detection of glaucoma [191]. The C/D ratio depends mainly on the size of the optic disc, and it increases with glaucomatous damage, but it is a subjective measurement. We found that family history was not a predictor of POAG progression. Perhaps family history is more related to developing glaucoma and not a prognostic factor for progression as reported in the review, due to uncertainties around ascertaining a positive or negative family history [22]. It is also possible that people with a family history of glaucoma may be treated more aggressively because of that assumed risk, thereby obscuring the relationship when not properly controlled.

Strengths and weaknesses of the review

We developed a prognostic review protocol and developed a comprehensive search strategy under the guidance of an information specialist. We conducted a comprehensive and systematic search of several relevant electronic databases without any language restriction to improve the sensitivity of our search yield. We followed Cochrane and standard international guidelines on prognostic factor reviews in developing the methods, conducting the review, and reporting results. Another strength of our review is that we have included studies with a sufficient sample size for estimating prognostic associations with a restriction to more than 200 participants or eyes.

The main limitation of this review is the lack of reporting of prognostic factors in primary studies and poor methodological rigor, since many were not proper "prognostic factor" primary studies. Prognostic factor research seeks to understand the relationships between characteristics and future outcomes in people with a given disease [16]. While we found studies that reported estimates of association with progression, the

studies were not designed and powered to assess the strength of the relationships between prognostic factors and glaucoma progression. Reporting of the results through meta-analyses was limited due to clinical and statistical heterogeneity in study outcomes, variations in follow-up duration, different effect estimates chosen by primary study authors in reporting results, and different types of analyses (i.e. adjusted and unadjusted and different sets of confounding factors considered). Although we attempted to minimize the variations in study participants, there were different definitions for including participants with POAG in different study settings. In addition, there was a lack of clarity in the definition of assessing or developing the prognostic factors for developing POAG versus the progression of POAG. Another limitation related to the evidence and our purpose is the correlations amongst many of the factors that we assessed individually, ignoring their relationships and potential for interaction in progression. For example, disc hemorrhages are more frequent in female patients, so these two prognostic factors may be found in the same patient. Our purpose was exploratory, and thus we were not assessing prognostic models, and we did not evaluate the performance of multiple predictors together, which may limit the direct clinical applicability of this review. Following our purpose, another limitation was our selection of factors to include in the summary of finding tables, which we prespecified to be the factors for which we could conduct meta-analyses, assuming that these would have the most evidence and likely be "important". This approach could potentially bias the summary to factors that are assumed important and therefore studied more in the literature, even if they are not actually clinically meaningful.

Quality of the evidence

We found a high risk of bias amongst the included studies in their adjustment for other prognostic factors, study attrition, and statistical analysis and reporting (Figure 3). These challenges are well known in prognostic research and the recommendations are clear that prognostic factor studies must be of suitable sample size, prospective, registered, have appropriate statistical analyses, and have more transparency in the reporting of all factors and outcomes considered [16]. We encountered high heterogeneity in the definitions of predictors or prognostic factors and in the outcomes for progression. This heterogeneity led to practical difficulties for synthesis in terms of what data can be meta-analyzed and how to summarize our results in an appropriate way that would be useful for clinicians, researchers, and policymakers.

With regard to the characteristics of the participants, we encountered a limitation in evaluating prespecified subgroups of interest, such as the types of treatments and the relationships that may not be linear. The heterogeneity of the outcomes unfortunately meant that even if we could separate the studies and participants into subgroups, the sample sizes and numbers of studies would have been too few to permit us to draw valid or reasonable conclusions about differences in associations.

With regard to the applicability of the time periods that we prespecified, we chose to synthesize estimates for prognostic factors without dividing the evidence into different time periods, and instead downgraded it for indirectness in the summary of the findings. We have also noted that for some prognostic factors, the timing may be more or less relevant (e.g. pharmacologic treatment versus demographics/lifestyle), but we applied this approach over all prognostic factors consistently. There were insufficient data to

explore the effects of primary studies with high risk of bias and, for the same reasons, we were not able to further assess the sources of high heterogeneity.

Agreements and disagreements with other studies or reviews

A systematic review conducted by Ernest and colleagues reported that age, disc hemorrhage, baseline visual field loss, baseline IOP, and exfoliation syndrome are clearly associated prognostic factors of visual field progression [34]. Their review also found that a family history of glaucoma, atherosclerosis, systemic hypertension, visual acuity, sex, systolic blood pressure, myopic refractive error, and Raynaud's phenomenon were unlikely to be associated with glaucoma progression [34]. In general, our review reached similar conclusions regarding most factors and their likely associations with the notable exceptions of age and IOP, for which we found mixed evidence. One other key difference between our reviews is that we were able to conduct several meta-analyses, whereas Ernest and colleagues' review involved only qualitative syntheses.

To our knowledge, this is the first prognostic factor review to explore predictors of visual field progression of POAG and identify potential candidate prognostic factors by their associations. Consequently, there is limited evidence from other reviews to compare with our findings. One practical difficulty in comparing our findings with other reviews is the lack of a clear separation between assessing the prognostic factors for the development/pathogenesis of POAG and exploring the prognostic factors for disease progression ascertained through standard investigations such as perimetry. Most of the reviews on this topic are a mix of "risk factors" and prognostic factors. As an example, a review of population-based studies from 1990 to 2019 conducted by Grzybowski and colleagues concluded the importance of vascular risk factors in pathogenesis as well as progression of glaucomatous optic neuropathy using the same effect estimates [192]. The systematic review and meta-analysis conducted by Aldarrab and colleagues found that diabetes duration, elevated IOP, and fasting glucose levels are major risk factors for glaucoma [193]. The authors defined these "exposures" as risk factors for developing glaucoma, as opposed to prognostic factors for the progression of glaucoma, which may explain why we found there was less evidence of an association for these characteristics. The meta-analysis published by Lungowel and colleagues reported an association between thinner CCT and glaucomatous eyes. However, we did not find that CCT was a consistent predictor of POAG progression [194].

Some reviews have also reported estimates for other prognostic factors, such as levels of trace elements (i.e. lead [Pb] exposure and glaucoma) [195]; oxidative/anti-oxidative stress markers (i.e. increased oxidative stress in glaucoma) [196]; nocturnal blood pressure drop fall and visual field progression (OR 3.32, 95% CI 1.84 to 6.00 in > 10% systolic and OR 2.09, 95% CI 1.20 to 3.64 in > 10% diastolic) [32]; obstructive sleep apnea and glaucoma (pooled OR 1.49 95% CI 1.16 to 1.91) [197] and vitamin D and glaucoma (variable level of evidence) [198]. Other reviews have also identified vascular endothelial growth factors [199], *Helicobacter pylori* infection [200], and air-pollution [201] as potential risk factors for glaucoma. We did not find any primary studies that presented evidence of these as prognostic factors for glaucoma progression.

AUTHORS' CONCLUSIONS

There is evidence to support the finding that the presence of disc hemorrhage, thinning of retinal nerve fiber layer thickness, increased optic disc vessel density, presence of bilateral disease, presence of choroidal microvascular dropout, abnormal macular ganglion cell parameters, presence of exfoliation glaucoma, and treatment for glaucoma could be used as prognostic factors to assess visual field progression in people with POAG, although the evidence is mostly uncertain. Evidence for other reported and accepted prognostic factors is less compelling based on our review findings and many are inconclusive. Though we identified numerous longitudinal studies with a sufficient number of years of follow-up to assess visual field progression, the substantial/considerable level of heterogeneity in study design, definitions used for prognostic factors evaluated, measurement of prognostic factors and clinical outcomes, and frequent univariable analyses, limited our ability to synthesize and report on some of the results we extracted from primary studies.

Implications for practice

The evidence generated in the current prognostic factor review suggests that there are several prognostic factors with very low to moderate certainty of an association with progression of glaucoma and thus with uncertain clinical implications. Clinicians should be aware of the increased risk of progression in people with pseudoexfoliation, disc hemorrhages, and bilateral disease. Imaging tests of ocular blood flow associated with glaucoma progression, baseline cardiopulmonary level and silent cerebral infarct would need confirmation before recommending their use in clinical practice.

Implications for research

Methodologically rigorous prognostic factor studies are required to determine prognostic factors associated with structural and functional progression of POAG. The high heterogeneity in study design features, the definition of POAG, different time periods of follow-up, different definitions used in classifying the prognostic factors and variations in measurement tools/equipment should be standardized based on international guidelines in future studies. In addition, there should be a clear definition to demarcate prognostic factors for disease development versus the prognostic factors for disease progression. Nevertheless, we believe our findings may be relevant to future efforts to develop prognostic models for the progression of glaucoma and consider important factors. There may also be some benefit for future research in global consensus in defining and assessing the prognostic factors to be assessed in glaucoma studies, similar to a core outcome set for studies of interventions. Additionally, it may be helpful for future studies of prognostic factors to focus on a small set of possible factors within a category, rather than all identified, to narrow the scope and increase the possibility for analyses.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: [10.1002/14651858.CD015436.pub2](https://doi.org/10.1002/14651858.CD015436.pub2).

Supplementary material 1 Search strategies

Supplementary material 2 Characteristics of included studies

Supplementary material 3 Characteristics of excluded studies

Supplementary material 4 Characteristics of studies awaiting classification

Supplementary material 5 Characteristics of ongoing studies

Supplementary material 6 Analyses

Supplementary material 7 Data package

Supplementary material 8 Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS-PF) - list of data extraction items

Supplementary material 9 Quality in Prognostic Studies (QUIPS) tool

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

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The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Barbara S. Hawkins, Johns Hopkins University School of Medicine;
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Anupa Shah, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Andrew Savage, Cochrane Central Editorial Service;
- Copy Editor (copy editing and production): Anne Lethaby, Cochrane Central Production Service;
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Contributions of authors

MPP developed the initial draft of the prognostic review protocol under the guidance of AAB and GV as a fulfillment of Evidence

Synthesis Ireland (ESI) Fellowships. MPP wrote the first draft of the review protocol. AAB, GV, RQ, TL, YT, MPP, and QD contributed to developing and revising the protocol. All protocol authors provided input into the planned methodological aspects of the review, and approved the final draft for publication.

MPP, QD, RQ and SL conducted the titles and abstracts, and full-text screening. MPP, QD, RQ and SL conducted the full-text data extraction and methodological quality assessment, with contributions from GR and MM. RQ and MPP prepared the final dataset of outcomes for synthesis. RQ conducted the statistical analysis. RQ and MPP interpreted the findings and wrote the narrative descriptions of the synthesis under the guidance of GV. RQ and MPP wrote the first draft of the manuscript results under the guidance of GV, with contributions from QD, MM and GR. All authors reviewed, edited, and approved the final draft of the manuscript for submission.

Declarations of interest

- Riaz Qureshi, Su-Hsun Liu, and Tianjing Li reported a grant from the National Eye Institute, National Institutes of Health, USA; payment to the institution. Riaz Qureshi, Su-Hsun Liu, and Tianjing Li are part of Cochrane Eyes and Vision (CEV). Tianjing Li is Coordinating Editor for Cochrane Eyes and Vision (CEV) and Su-Hsun Liu is the Managing Editor for CEV. Su-Hsun Liu and Tianjing Li have no role in the editorial process for this review.
- Manuele Michelessi received payment from SIFI to attend meetings. Gloria Roberti received payment from NTC Pharma to participate in an Advisory Board; received payment from Zeiss to prepare a presentation at the World Glaucoma Congress; received payment from Omikron SRL to organise three meetings.
- Mapa Piyasena, Qëndresë Daka, Yemisi Takwoingi, Augusto Azuara-Blanco, and Gianni Virgili declared no conflicts of interest.

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Data, code and other materials

As part of the published Cochrane Review, the following are made available for download by users of the Cochrane Library: full search strategies for each database ([Supplementary material 1](#)); full citations of each unique report for all studies included, ongoing or awaiting classification, or excluded at the full-text stage, in the final review ([Supplementary material 2](#); [Supplementary material 3](#); [Supplementary material 4](#); [Supplementary material 5](#)); analysis data ([Supplementary material 6](#)); and data packages ([Supplementary material 7](#)). Appropriate permissions have been obtained for such use. Analyses and data management were conducted within Cochrane's authoring tool, Review Manager Web (55), using the inbuilt computation methods. All extracted study estimates and detailed risk of bias assessments are publicly available in the Open Science Framework (OSF): <https://osf.io/q2tz7/>

Date	Event	Description
3 November 2022	Amended	Correction of author byline

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ADDITIONAL TABLES

Table 1. Overview of synthesis and included studies

Study	Study design, follow-up period	Sample size, country, setting	Baseline characteristics	Specific prognostic factors assessed					Definition of glaucoma progression
				Demo-graphic	Systemic	Lifestyle	Ocular	Other	
Biswas 2020	Cohort study, 5.5 years or more	135 participants (245 eyes) India, secondary care	Age, mean $\pm$ SD years: 56.6 $\pm$ 13.8, Female sex, n (%): NR	Age			IOP, Myopia/refractive error, RNFL, Signal strength, and VF (VFI)		VFI changes and retinal nerve fiber layer thickness changes were measured by a linear mixed model analysis.
Chauhan 2008	Cohort study, 5 years $\pm$ 6 months	258 participants (258 eyes) Canada, secondary care	Age, mean $\pm$ SD years: 62.7 (11.1) Female sex, n (%): 128 (50%) Ethnicity, category (n, %): • White: (234, 91%) • Black (15, 6%) • Latinx: (1, 0%) • Other: 8 (3%)	Age, sex/gender	Vascular (cardiac or cerebral)		IOP		VF deterioration is determined using glaucoma change probability analyses.
Dascalu 2021	Cohort study, 4 years $\pm$ 6 months	204 participants (204 eyes) Romania, secondary care	Age, mean $\pm$ SD years: 51.0 $\pm$ 2.1, Female sex, n (%): 139 (68.1%)		Diabetes, hypertension/hypotension, and vascular (cardiac or cerebral)				Perimetric progression and/or progression documented by imaging. No further details
Founti 2020	RCT, 2 years $\pm$ 6 months	516 participants (NR eyes) United Kingdom, secondary care	Age, mean $\pm$ SD years: 65.2 to 65.7 $\pm$ 10.2 to 11.3 Female sex, n (%): 222 (48.1%) Ethnicity, n (%):	Age, race/ethnicity, sex/gender	Cold hands and feet, hypertension/hypotension, hysteresis, migraine,	Body mass index, smoking	Bilateral glaucoma, CCT, disc hemorrhage, IOP, myopia/refractive error, perfusion	Family history of glaucoma, treatment	VF deterioration was assessed by GPA, with at least 3 VF locations worse than baseline at the 5% levels for 2 consecutive reliable VF and at least 3 VF locations worse than baseline at the

Table 1. Overview of synthesis and included studies *(Continued)*

			White: 417 (90.4%)		Ray-naud's, sleep apnea, vascular (cardiac or cerebral)	pressure, VF (MDev)	5% levels for the 2 subsequent consecutive VFs.
Fursova 2022	Cohort study, 24 months	258 participants (258 eyes) Russia, secondary care	Age, mean $\pm$ SD years: NR Female sex, n (%): 114 (55%)			Choroidal microvascular dropout	Not specified, only that a subgroup of participants experienced a higher rate of progression
Greenfield 2007	RCT, follow-up period NR	190 participants (380 eyes) United States, secondary care	Age, mean $\pm$ SD years: 64.9 $\pm$ 10.7 Female sex, n (%): 113 (59.4%)	Age, sex/gender	Diabetes, hypertension/hypotension, migraine, Raynaud's, vascular (cardiac or cerebral)	CCT, disc hemorrhage, myopia/refractive error, optic disc size, perfusion pressure, Raynaud's, vascular (cardiac or cerebral), pseudophakic lens	Family history of glaucoma, pharmacologic VF progression as determined by pointwise linear regression. Linear regression of the sensitivity (in dB) was performed at each test location to obtain the rate of change at that location.
Jonas 2004	Cohort study, 5.5 years or more	416 participants (763 eyes) Germany, secondary care	Non-progressing eyes Age, mean $\pm$ SD years: 48.0 $\pm$ 12.3 Female sex, n (%): 311 (47.3%) Progressing eyes Age, mean $\pm$ SD years: 56.0 $\pm$ 11.0 Female sex, n (%): 56 (52.8%)	Age, sex/gender		Myopia/refractive error, optic disc size, optic nerve (structural)	Pointwise regression analysis for each of the 59 locations in the VF. Progression was assumed if a difference of larger than 1 dB per year was observed for the local defect.

Table 1. Overview of synthesis and included studies (Continued)

Krug 1995	RCT, 5 years ± 6 months	271 participants (542 eyes) United States, primary care	Age, mean ± SD years: 60 Female sex, n (%): NR (44%) Ethnicity, n (%): - White: NR (45%) - Black: NR (43%) - Latinx: NR - Other: NR (12%)				IOP, optic disc size		VF deterioration consists of the detection of localized change based on a comparison of the threshold values from two consecutive, regularly scheduled examinations to the corresponding values from the baseline VF.
Lee 2022	Cohort study, 5 years ± 6 months	712 participants (712 eyes) Republic of Korea, secondary care	Age, mean ± SD years: 54.1 ± 14.5 Female sex, n (%): 361 (50.1%)	Age, sex/gender			CCT, IOP, myopia/refractive error, optic nerve (structural), VF (MDev), VF (pattern SD)	Past glaucoma surgery	OCT RNFL thinning calculates the rate of change of RNFL thickness relative to the baseline thickness per year.
Lee 2023	Cohort study, 5 years ± 6 months	266 participants (266 eyes) Republic of Korea, secondary care	VF progressor Age, mean ± SD years: 56.2 ± 13.9 Female sex, n (%): 33 (41.3%) VF non-progressor Age, mean ± SD years: 59.9 ± 11.4 Female sex, n (%): 72 (38.7%)	Age			Choroidal microvascular dropout, disc hemorrhage, optic disc vessel density, RNFL		VF progression determined by a “likely progression” results in GPA or a significant negative rate (P < 0.05) of change in VF MDev trend-based analysis
Leske 2007	RCT, 4 years	255 participants (255 eyes)* Sweden, secondary care	Age, mean ± SD years: 68.1 ± 4.9 Female sex, n (%): 169 (66%)	Age, sex/gender	Hypertension/hypotension, migraine, Raynaud's, vascular (cardiac or cerebral)	Smoking	Bilateral, CCT, disc hemorrhage, CCT, disc hemorrhage, exfoliation glaucoma*, IOP, myopia/refrac-	Family history of glaucoma	Perimetric progression is defined as significant changes from baseline in at least 3 of the same progression points in 3 consecutive visual fields, as assessed by pattern deviation-based Glaucoma Change Probability Maps and optic disc

Table 1. Overview of synthesis and included studies (Continued)

						tive error, perfusion pressure, VF (MDev)		progression requires clear change on an optic disc fol- low-up photograph.
Leung 2009	Cohort study, 3 years ± 6 months	286 partici- pants (286 eyes) Hong Kong, secondary care	SCI+ Age, mean ± SD years: 72.4 ± 10.7 Female sex, n (%): NR SCI- Age, mean ± SD years: 63.2 ± 14.2 Female sex, n (%): NR	Age	Hyperten- sion/hy- potension, vascular (cardiac or cerebral)	CCT, disc he- morrhage	Pharma- cologic	VF progression based on CNTGS criteria
Lin 2023	Cohort study, 3 years ± 6 months	197 partici- pants (390 eyes) Hong Kong, tertiary re- ferral center	Progressive RNFL thin- ning Age, mean ± SD years: 58.2 ± 12.3 Female sex, n (%): 33 (47.8%) Without progressive RNFL thinning Age, mean ± SD years: 59.8 ± 11.4 Female sex, n (%): 166 (51.7%) VF deterioration Age, mean ± SD years: 55.6 ± 11.5 Female sex, n (%): 9 (40.9%) Without VF deteriora- tion			Retinal-ves- sel calibers		VF deterioration deter- mined by GPA or progres- sive RNFL thinning mea- sured by OCT GPA

Table 1. Overview of synthesis and included studies (Continued)

			Age, mean ± SD years: 59.8 ± 11.5					
			Female sex, n (%): 190 (51.6%)					
Medeiros 2009	Cohort study, 5 years ± 6 months	253 partici- pants (253 eyes) United States, ter- tiary care	Progressors Age, mean ± SD years: 59.5 ± 11.3 Female sex, n (%): 16 (52%) Ethnicity, n (%): • White: 29 (94%) • Black: 2 (6%) • Latinx: 0 (0%) • Other: 0 (0%) Non-progressors Age, mean ± SD years: 55.2 ± 13.6 Female sex, n (%): 57 (60%) Ethnicity, n (%): • White: 89 (94%) • Black: 2 (2%) • Latinx: 2 (2%) • Other: 2 (2%)	Age, race/ ethnicity	Hyperten- sion/hy- potension	IOP, RNFL, VF (MDev), and vit- reo-retinal degenera- tion	VF progression using GPA based on the EMGT crite- ria and structural progres- sion over time, assessed by stereophotograph compari- son	
Pappelis 2019	Cohort study, 5 years ± 6 months	362 partici- pants (362 eyes) Nether- lands, sec- ondary care	Glaucoma patients Age, mean ± SD years: 61.8 ± 9.9 Female sex, n (%): 46.0% Glaucoma suspects (converted) Age, mean ± SD years: 58.3 ± 10.0	Age, sex/ gender	BMI	CCT, IOP	Pharma- cologic	For glaucoma patients, the rate of progression is cal- culated as the slope of the MDev over time. For glauco- ma suspects, progression is the conversion to a glauco- ma diagnosis.

Table 1. Overview of synthesis and included studies (Continued)

Female sex, n (%): 56.6% Glaucoma suspects (not converted) Age, mean $\pm$ SD years: 55.4 $\pm$ 11.3 Female sex, n (%): 54.2%						
Sulli-van-Mee 2023	Cohort study, 3 years $\pm$ 6 months	202 participants (394 eyes) United States, sec-ondary care	Age, mean $\pm$ SD years: 69.4 (POAG), 65.0 (glau-coma suspects) Female sex, n (%): NR	Age	IOP, RNFL, VF (MDev), VF (pattern SD)	Rate of 24-2 MDev change (dB/year) over time, cal-culated using the least squares linear regression for each eye and GPA VF pro-gression events
Wang 2022	Cohort study, 4 years $\pm$ 6 months	164 partici-pants (270 eyes) Hong Kong, secondary care	Progressed NTG Age, mean $\pm$ SD years: 59.7 $\pm$ 11.1 Female sex, n (%): 14 (53.8%) Non-progressed NTG Age, mean $\pm$ SD years: 60.5 $\pm$ 11.7 Female sex, n (%): 71 (51.4%)		Macular re-gional vas-cular ma-trices, peri-papillary re-gion vascu-lar matrices	Glaucoma progression was identified by the presence of VF deterioration, which was determined with refer-ence to the GPA, which con-tains both event-based and trend-based analyses.
Wilson 2002	Cohort study, 10 years	155 partici-pants (287 eyes) West Indies, secondary care	Age, mean $\pm$ SD years: 52.3 (NR) Female sex, n (%): 108 (70%)	Age, sex/ gender	IOP, VF (VFI)	Progression is defined by worsening of the score from the baseline value by $\geq$ 4 points in the AGIS system and by $\geq$ 3 points in the CIGTS system.
Wright 2020	RCT, 4 years $\pm$ 6 months	344 partici-pants (588 eyes)	SLT Age, mean $\pm$ SD years: 63.4 $\pm$ 12.0		IOP, VF (MDev)	VF rate of progression over time is estimated by using a trend-based method to evaluate change at each of the 52 measured locations.

Table 1. Overview of synthesis and included studies (Continued)

		United Kingdom, primary care	Female sex, n (%): 151 (43.9%)			
			Medical therapy			
			Age, mean $\pm$ SD years: 62.9 $\pm$ 11.6			
			Female sex, n (%): 164 (47.7%)			
Yoshikawa 2018	Cohort study, 5 years $\pm$ 6 months	311 participants (622 eyes) Japan, secondary care	Age, mean $\pm$ SD years: 57.7 $\pm$ 11.3 Female sex, n (%): 82 (61.2%)		CCT, disc hemorrhage, IOP, myopia/refractive error, VF (MDev)	Deterioration of MDev slope is defined if the MDev slope showed a significantly (P > 0.05) negative value calculated by the least-square method in the final VF test and consecutive decreases in MDev value are defined as a successive decrease in MDev values (> 0.05 dB) between two consecutive tests.
Yu 2016	Cohort study, 5.5 years $\pm$ 6 months	139 participants (240 eyes) Hong Kong, secondary care	Age, mean $\pm$ SD years: NR Female sex: 85 (61.1%)	Age	CCT, IOP, myopia/refractive error, RNFL, VF (MDev)	VF progression is evaluated with two methods separately: an event-based analysis, with reference to the EMGT criteria, and a trend-based analysis, using pointwise linear regression criteria.
Zhang 2016	Cohort study, 2 years $\pm$ 6 months	188 participants (277 eyes) United States, secondary care	Progression Age, mean $\pm$ SD years: 63.8 $\pm$ 8.27 Female sex: 49 (59%) Ethnicity, n (%): • White: NR • Black: 8 (9.6%) • Latinx: NR • Other: NR		CCT, IOP, macular ganglion cell complex parameters, optic disc size, prepapillary nerve fiber layer indices, VF (MDev), VF (pattern SD), and VFI	VF deterioration is defined by both event-based and trend-based GPA.

Table 1. Overview of synthesis and included studies *(Continued)*

Non-progression

Age, mean $\pm$ SD: 62.2 $\pm$ 10.1

Female sex, n (%): 116 (59.8%)

Ethnicity, n (%):

- White: NR
- Black: 20 (10.3%)
- Latinx: NR
- Other: NR

AGIS: Advanced Glaucoma Intervention Study

BMI: body mass index

CCT: central corneal thickness

CIGTS: Collaborative Initial Glaucoma Treatment Study

CNTGS: Collaborative Normal-Tension Glaucoma Study

dB: decibel

DM: diabetes mellitus

EMGT: Early Manifest Glaucoma Trial

GPA: guided progression analysis

IOP: intraocular pressure

MDev: mean deviation

NR: not reported

NTG: normal tension glaucoma

OCT: optical coherence tomography

POAG: primary open angle glaucoma

RCT: randomized controlled trial

RNFL: retinal nerve fiber layer

SCI+: silent cerebral infarct positive

SCI-: silent cerebral infarct negative

SD: standard deviation

SLT: selective laser trabeculoplasty

VF: visual field

VFI: visual field index

*Leske 2007 includes both POAG and exfoliation glaucoma participants.

Table 2. Summary of demographic prognostic factor estimates/associations

Type of prognostic factor	Number of studies (number of estimates)	Meta-analysis result (number of studies) adjusted or univariable	Direction of associations*		
			+	-	∅
Age	13 studies (20 estimates)	HR _{adj} = 1.01 [0.97, 1.05]; I ² = 89% (4 studies)	14	5	1
Female sex	8 studies (9 estimates)	HR _{adj} = 1.64 [1.15, 2.34]; I ² = 0% (2 studies) HR _{uni} = 1.16 [0.91, 1.49]; I ² = 0% (3 studies)	5	2	2
Minority race/ethnicity	2 studies (3 estimates)	Not applicable	2	1	0

HR: hazard ratio

* Direction determined by standardizing the effects such that more of an exposure (e.g. older age, presence of comorbidities, greater visual field deviation, greater central corneal thickness, etc.) or a chosen reference (e.g. female vs. male, minority vs. majority race) was positive if it increased the likelihood of progression and negative if it decreased the likelihood of progression, irrespective of statistical significance. Direction was null if the effect estimate was exactly null (e.g. relative effect = 1.0) or if the direction of effect was not reported.

Table 3. Summary of systemic prognostic factor estimates/associations

Type of prognostic factor	Number of studies (number of estimates)	Meta-analysis result (number of studies) adjusted or univariable	Direction of associations*		
			+	-	∅
Systemic hypertension	6 studies (12 estimates)	HR _{adj} = 1.33 [0.68, 2.60]; I ² = 84% (3 studies) HR _{uni} = 0.89 [0.67, 1.17]; I ² = 0% (2 studies)	6	6	0
Cardiac/cerebral vascular comorbidities	6 studies (17 estimates)	HR _{uni} = 1.06 [0.75, 1.49]; I ² = 0% (2 studies)	10	7	0
Migraine	3 studies (3 estimates)	HR _{uni} = 1.06 [0.67, 1.67]; I ² = 22% (3 studies)	1	2	0
Raynaud's phenomenon	3 studies (3 estimates)	HR _{uni} = 1.21 [0.85, 1.73]; I ² = 0% (3 studies)	2	1	0
Diabetes	2 studies (2 estimates)	Not applicable	1	1	0

Table 3. Summary of systemic prognostic factor estimates/associations (Continued)

Sleep apnea	1 study (1 estimate)	Not applicable	0	1	0
Cold extremities	1 study (1 estimate)	Not applicable	1	0	0

HR: hazard ratio

*Direction determined by standardizing the effects such that more of an exposure (e.g. older age, presence of comorbidities, greater visual field deviation, greater central corneal thickness, etc.) or a chosen reference (e.g. female vs. male, minority vs. majority race) was positive if it increased the likelihood of progression and negative if it decreased the likelihood of progression, irrespective of statistical significance. Direction was null if the effect estimate was exactly null (e.g. relative effect = 1.0) or if the direction of effect was not reported.

Table 4. Summary of lifestyle prognostic factor estimates/associations

Type of prognostic factor	Number of studies (number of estimates)	Meta-analysis result (number of studies) adjusted or univariable	Direction of associations*		
			+	-	∅
Smoking	2 studies (4 estimates)	Not applicable	0	4	0
Body mass index	2 studies (2 estimates)	Not applicable	1	1	0

*Direction determined by standardizing the effects such that more of an exposure (e.g. older age, presence of comorbidities, greater visual field deviation, greater central corneal thickness, etc.) or a chosen reference (e.g. female vs. male, minority vs. majority race) was positive if it increased the likelihood of progression and negative if it decreased the likelihood of progression, irrespective of statistical significance. Direction was null if the effect estimate was exactly null (e.g. relative effect = 1.0) or if the direction of effect was not reported.

Table 5. Summary of ocular prognostic factor estimates/associations

Type of prognostic factor	Number of studies (number of estimates)	Meta-analysis result (number of studies) adjusted or univariable	Direction of associations*		
			+	-	∅
Intraocular pressure	14 studies (30 estimates)	HR _{adj} = 1.08 [1.03, 1.13]; I ² = 16% (3 studies) OR _{adj} = 0.96 [0.84, 1.10]; I ² = 50% (2 studies)	19	9	2
Baseline visual field (mean deviation and visual field index)	11 studies (30 estimates)	Not applicable	14	13	3
Central corneal thickness	9 studies (14 estimates)	HR _{adj} = 1.13 [0.85, 1.51]; I ² = 80% (2 studies – per 30um thinner) HR _{uni} = 1.00 [1.00, 1.00]; I ² = 0%	3	5	6

Table 5. Summary of ocular prognostic factor estimates/associations (Continued)
(2 studies – per 1 um thicker)

Refractive errors and myopia	8 studies (14 estimates)	Not applicable	3	5	6
Disc hemorrhage	6 studies (9 estimates)	HR _{adj} = 2.03 [1.55, 2.67]; I ² = 0% (3 studies) HR _{uni} = 1.51 [1.13, 2.02]; I ² = 0% (3 studies)	8	0	1
Retinal nerve fiber layer thickness	5 studies (9 estimates)	Not applicable	2	7	0
Optic disc size and vessel density	5 studies (12 estimates)	Not applicable	3	2	7
Ocular perfusion pressure	3 studies (4 estimates)	Not applicable	0	3	1
Bilateral disease of POAG	2 studies (5 estimates)	HR _{adj} = 1.77 [1.35, 2.32]; I ² = 0% (2 studies)	5	0	0
Choroidal microvascular dropout	2 studies (3 estimates)	Not applicable	3	0	0
Other ocular factors (n = 10)**	9 studies (102 estimates)	Not applicable	64	17	19

HR: hazard ratio

POAG: primary open-angle glaucoma

*Direction determined by standardizing the effects such that more of an exposure (e.g. older age, presence of comorbidities, greater visual field deviation, greater central corneal thickness, etc.) or a chosen reference (e.g. female vs. male, minority vs. majority race) was positive if it increased the likelihood of progression and negative if it decreased the likelihood of progression, irrespective of statistical significance. Direction was null if the effect estimate was exactly null (e.g. relative effect = 1.0) or if the direction of effect was not reported.

**Other ocular factors include 10 factors: *structural optic nerve* (2 studies, 13 estimates); *peripapillary nerve fiber layer indices* (1 study, 13 estimates); *macular ganglion cell parameters* (1 study, 13 estimates); *narrowing retinal vessel calibers* (1 study, 24 estimates); *peripapillary region vascular matrices* (1 study, 18 estimates); *vitreo-retinal degeneration* (1 study, 1 estimate); *macular region vascular matrices* (1 study; 16 estimates); *corneal hysteresis* (1 study, 1 estimate); *exfoliation glaucoma* (1 study, 2 estimates); *pseudophakia* (1 study, 1 estimate)

Table 6. Summary of other prognostic factor estimates/associations

Type of prognostic factor	Number of studies (number of estimates)	Meta-analysis result (number of studies) adjusted or univariable	Direction of associations*		
			+	-	∅
Pharmacologic factors or treatment for glaucoma	5 studies (10 estimates)	HR _{adj} = 0.44 [0.31, 0.61]; I ² = 37% (3 studies)	0	10	0

Table 6. Summary of other prognostic factor estimates/associations (Continued)

 $HR_{uni} = 0.56 [0.44, 0.72]; I^2 =$

0%

(2 studies)

Family history of glaucoma	3 studies (3 estimates)	Not applicable	2	1	0
Glaucoma surgery	1 study (2 estimates)	Not applicable	0	2	0
Signal strength	1 study (1 estimate)	Not applicable	1	0	0

HR: hazard ratio

*Direction determined by standardizing the effects such that more of an exposure (e.g. older age, presence of comorbidities, greater visual field deviation, greater central corneal thickness, etc.) or a chosen reference (e.g. female vs. male, minority vs. majority race) was positive if it increased the likelihood of progression and negative if it decreased the likelihood of progression, irrespective of statistical significance. Direction was null if the effect estimate was exactly null (e.g. relative effect = 1.0) or if the direction of effect was not reported.