



THE ROLE OF FAMILIAL GENETICS AND FAMILY HISTORY AS RISK FACTORS FOR PRIMARY GLAUCOMA: A SYSTEMATIC REVIEW OF RANDOMISED CONTROLLED TRIALS AND PRIMARY STUDIES

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ABSTRACT

Introduction. Primary glaucoma—comprising primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG)—is the leading global cause of irreversible blindness. Although raised intraocular pressure (IOP) remains the only modifiable determinant, the disease demonstrates conspicuous familial aggregation, and both a self-reported family history and the aggregate burden of common risk alleles are now recognised as major non-modifiable determinants of susceptibility.

Methods. The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible: RCTs, cohort, case-control, cross-sectional, and observational studies; systematic reviews excluded from characteristics tables. Risk of bias assessed with Newcastle-Ottawa Scale mapped to ROBINS-E domains and RoB 2 for randomised evidence; GRADE for certainty.

Results. Thirty-one primary studies comprising 587,832 participants. A positive family history in first-degree relatives was significantly associated with POAG (pooled OR 3.31; 95%CI 2.54–4.31; $I^2=71.4\%$; $p<0.001$). The risk gradient was steepest for siblings (OR 3.69–11.29), intermediate for parents (2.17–8.76), and weakest for offspring. Direct examination of relatives disclosed glaucoma in 10.4–64.7% of siblings versus 0.7–1.5% of controls. Lifetime risk among first-degree relatives was 22.0% versus 2.3% (RR 9.2; 95%CI 1.2–73.9), with a population attributable fraction of 16.4%. Family history also predicted PACG (OR 4.82; 95%CI 2.08–11.19) and disease severity (OR 1.61–1.81). Pathogenic MYOC variants explained 27–36% of familial juvenile-onset disease but only 1.6–4.2% of unselected adult-onset disease, with p.Gln368Ter penetrance reaching 25.4%. Polygenic risk scores produced a 5.7-fold prevalence gradient between lowest and highest deciles and RR 3.99–7.40. Adding PRS to a clinical model increased concordance from 0.75 to 0.82.

Discussion. The evidence is biologically coherent and reproducible across populations, satisfying Bradford Hill criteria. Residual heterogeneity is largely attributable to differences in exposure ascertainment: self-reported family history is misclassified because 60–69% of community glaucoma is undiagnosed. Genomic markers circumvent this misclassification and now provide reproducible risk stratification.

Conclusion. A positive family history of glaucoma confers an approximately three-fold to nine-fold increase in risk of primary glaucoma and identifies a population sufficiently enriched to justify targeted case-finding. Cascade clinical screening of first-degree relatives—particularly siblings—from the fourth decade of life, supplemented by MYOC cascade testing and polygenic risk

stratification in appropriate settings, is supported by moderate-certainty evidence and should be incorporated into national glaucoma-blindness prevention strategies.

Keywords: primary open-angle glaucoma; primary angle-closure glaucoma; family history; genetic predisposition to disease; polygenic risk score; myocilin; cascade screening; systematic review.

INTRODUCTION

Background

Glaucoma denotes a group of chronic, progressive optic neuropathies characterised by accelerated apoptosis of retinal ganglion cells, corresponding excavation of the optic nerve head and a characteristic pattern of irreversible visual-field loss. It is the foremost cause of irreversible blindness worldwide, and because the disease is typically asymptomatic until the central field is threatened, a substantial proportion of affected individuals remain undiagnosed until an advanced stage of optic neuropathy has been reached. Reduction of intraocular pressure (IOP) remains the only intervention of proven efficacy, and consequently the identification of individuals at elevated risk before irreversible neuronal loss occurs constitutes the principal public-health opportunity in this disease.⁵⁷

Primary glaucoma is conventionally subdivided anatomically into primary open-angle glaucoma (POAG), in which the iridocorneal angle is open but aqueous outflow resistance is increased at the level of the trabecular meshwork, and primary angle-closure glaucoma (PACG), in which apposition or synechial closure of the angle impedes aqueous drainage. Population-based prevalence surveys have demonstrated consistent and substantial variation in POAG prevalence by ancestry: age-standardised rates are four- to five-fold higher in populations of African descent than in populations of European descent, and the average prevalence beyond the age of 70 years approximates 16% in Black populations, 6% in White populations and 3% in Asian populations.^{32,58}

This striking interpopulation variation, together with the long-recognised clinical observation that glaucoma clusters within pedigrees, prompted an extensive body of genetic-epidemiological investigation. Early clinic-based series reported a positive family history in approximately half of all POAG probands and drew attention to an apparent maternal predominance of transmission. Subsequent population-based surveys quantified the association more rigorously, and family-based aggregation studies demonstrated a lifetime risk of glaucoma among first-degree relatives of probands approaching one in four. First-degree relatives of POAG patients have a disease prevalence between four and ten times that of the general population, and

disease concordance is substantially higher in monozygotic than in dizygotic twins, indicating substantial narrow-sense heritability without a simple Mendelian mode of inheritance.^{31,1,2,51}

Molecular genetics has since delineated two complementary architectures. A small minority of cases — predominantly juvenile-onset and high-pressure phenotypes — are attributable to highly penetrant variants in single genes, principally myocilin (MYOC/GLC1A), optineurin (OPTN) and, in consanguineous populations, cytochrome P450 1B1 (CYP1B1). The overwhelming majority of adult-onset disease is polygenic: large-scale genome-wide association studies and multi-trait meta-analyses have now identified more than 120 independent risk loci with broadly concordant effects across European, Asian and African ancestries, and the aggregation of these variants into polygenic risk scores (PRS) permits quantitative stratification of individual susceptibility.^{33,34,51,60}

Research gap

Despite this substantial literature, three gaps persist. First, the classical epidemiological evidence on self-reported family history and the contemporary genomic evidence on polygenic burden have evolved as largely separate literatures, and no synthesis has systematically integrated them within a single analytical framework that treats family history and measured genotype as alternative operational measures of the same underlying latent construct — inherited susceptibility. Second, the reported magnitude of the family-history association ranges across more than an order of magnitude, from odds ratios of approximately 1.9 in population-based Latino and Chinese-American surveys to 18.0 in a hospital-based African case-control study, and the sources of this heterogeneity — differential exposure misclassification, detection bias, ancestry, case definition and study setting — have not been formally dissected. Third, the incremental clinical value of genomic information over a simple clinical history has been quantified in individual cohorts but never appraised systematically against explicit discrimination metrics.^{1,3,5,12,26,29}

Novelty of the present review

This review is, to the best of the authors' knowledge, the first to synthesise the full spectrum of inherited risk in primary glaucoma across fourteen prespecified outcome domains within a single PRISMA-compliant framework, spanning self-reported family history, examined-relative screening yield, absolute and lifetime risk, population attributable fraction, monogenic

variant penetrance, polygenic stratification and formal measures of model discrimination expressed as areas under the receiver-operating-characteristic curve. It is further novel in restricting the characteristics table strictly to primary study designs — randomised controlled trials, cohort, case-control, cross-sectional and other observational studies — thereby avoiding the double-counting of participants that occurs when previously published syntheses are admitted as primary data, while retaining those syntheses for contextual interpretation. Finally, it explicitly evaluates ancestry-stratified performance of genomic risk prediction, a dimension of equity that has become critical as polygenic scores approach clinical translation.^{26,36,37}

Objectives

The general objective was to determine, synthesise and critically appraise the role of familial genetic factors and family history as risk determinants for primary glaucoma. The specific objectives were:

- To quantify the strength of association between a positive family history of glaucoma in first-degree relatives and the presence or incidence of primary open-angle glaucoma.
- To characterise the gradient of risk conferred by different degrees of biological relatedness (sibling, parent, offspring and second-degree relatives).
- To estimate the diagnostic yield of direct ophthalmic examination of relatives of glaucoma probands relative to relatives of unaffected control subjects.
- To determine the absolute lifetime risk of glaucoma among first-degree relatives and the corresponding population attributable fraction.
- To evaluate whether a positive family history is associated with primary angle-closure disease, with earlier age at diagnosis, with greater disease severity and with more intensive treatment requirements.
- To determine the frequency and penetrance of pathogenic myocilin and related monogenic variants across juvenile-onset, advanced and unselected adult-onset phenotypes.
- To quantify the degree of risk stratification achievable with polygenic and multi-locus genetic risk scores and to appraise their incremental discriminative performance,

expressed as the area under the receiver-operating-characteristic curve or the concordance statistic, over conventional clinical models.

- To assess the heritability of glaucoma endophenotypes, including intraocular pressure, vertical cup-to-disc ratio and central corneal thickness.
- To appraise the methodological quality and risk of bias of the contributing evidence and to grade the overall certainty of the resulting conclusions.

Hypotheses

The following hypotheses were specified a priori.

- Alternative hypothesis (H_1). A positive family history of glaucoma in first-degree relatives is significantly associated with an increased risk of primary glaucoma (pooled odds ratio significantly greater than 1.0); the magnitude of this association varies monotonically with the degree of biological relatedness, being greatest in siblings; and the addition of measured genomic information to a clinical risk model significantly improves discrimination for incident or prevalent disease.
- Null hypothesis (H_0). A positive family history of glaucoma is not associated with the risk of primary glaucoma (pooled odds ratio not significantly different from 1.0); risk does not vary with the degree of relatedness; and genomic information confers no significant incremental discrimination over conventional clinical predictors.

Anticipated benefits of the review

Clinical benefit. Provision of a quantitative, evidence-based estimate of familial risk that can be communicated to patients and their relatives during counselling, and that can inform the age at which cascade screening should commence.

Public-health benefit. Identification of an enriched, readily ascertainable target population for case-finding in health systems in which universal population screening for glaucoma is not cost-effective.

Scientific benefit. Formal delineation of the sources of heterogeneity in the family-history literature and explicit quantification of the incremental value of genomic risk stratification, thereby defining the priorities for future prospective research.

Educational and policy benefit. Provision of a structured, referenced resource suitable for the development of national clinical practice guidelines and postgraduate ophthalmic curricula, particularly in low- and middle-income settings where glaucoma blindness is disproportionately concentrated.

METHODS

Protocol and reporting guidance

This systematic review was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and, for the observational component, with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) recommendations. A written protocol specifying the review question, eligibility criteria, search strategy, data-extraction template, risk-of-bias instruments and analytical plan was prepared before the commencement of screening; no post-hoc modifications to the primary outcome or to the eligibility criteria were made. Because the review analysed previously published, publicly available aggregate data and involved no individual patient identifiers, institutional ethical approval was not required.

Review question and PICOS framework

Table 1. PICOS framework and eligibility criteria applied to the review

Element	Inclusion criteria	Exclusion criteria
Population (P)	Adults and adolescents with, or at risk of, primary glaucoma (primary open-angle glaucoma, juvenile-onset open-angle glaucoma, normal-tension glaucoma, ocular hypertension, primary angle-closure suspect, primary angle closure and primary angle-closure glaucoma); first- and second-degree relatives of glaucoma probands; general population samples in which glaucoma status was	Secondary glaucoma of any aetiology (neovascular, uveitic, traumatic, steroid-induced, lens-induced); primary congenital glaucoma studied in isolation; anterior segment dysgenesis syndromes; ocular hypertension without any glaucoma-related outcome.

	ascertained by examination.	
Exposure (I/E)	Self-reported or verified family history of glaucoma in first- or second-degree relatives; documented pathogenic variant in a recognised glaucoma gene (MYOC, OPTN, CYP1B1, TBK1, WDR36, LTBP2); multi-locus genetic risk score or genome-wide polygenic risk score; genetically inferred ancestry.	Studies reporting only environmental, systemic or ocular biometric exposures without any familial or genetic exposure variable.
Comparator (C)	Absence of a family history of glaucoma; non-carrier status; lower stratum (decile, quintile, tertile or quartile) of the genetic risk score distribution; relatives of unaffected control subjects.	Studies without any internal comparator group and without a reference population estimate.
Outcomes (O)	Prevalence, incidence or odds of primary glaucoma; screening yield in relatives; absolute and lifetime risk; population attributable fraction; age at diagnosis; intraocular pressure; vertical cup-to-disc ratio; visual-field mean deviation; retinal nerve fibre layer thickness; requirement for incisional surgery or treatment escalation; variant frequency and penetrance; area under the receiver-operating-characteristic curve or concordance statistic.	Studies reporting exclusively laboratory, in-vitro, animal or purely mechanistic outcomes with no clinical endpoint.

Study design (S)	Randomised controlled trials and post-hoc analyses thereof; prospective and retrospective cohort studies; case-control studies; cross-sectional studies; family-based aggregation studies; other analytical observational designs.	Systematic reviews and meta-analyses (excluded from the characteristics table and quantitative synthesis but retained for contextual discussion); narrative reviews; editorials; commentaries; conference abstracts without full text; case reports and case series of fewer than 20 subjects; duplicate reports of the same cohort.
Language and period	Articles published in English or with a full English abstract and extractable numerical data, from database inception to 30 August 2026.	Articles for which the full text could not be obtained after two documented attempts, including direct contact with the corresponding author.

PICOS = Population, Intervention/Exposure, Comparator, Outcome, Study design. The design restriction was specified a priori in accordance with the review protocol and mirrors the analytical requirement that every included record contribute independent primary participant data.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Primary open-angle glaucoma	Primary angle-closure glaucoma	Glaucoma patients
I (Intervention/Exposure)	Family history	Genetic predisposition	Polygenic risk score
C (Comparator)	No family history	Non-carrier status	Low genetic risk
O (Outcome)	Glaucoma risk	Disease severity	Screening yield

The Boolean MeSH keywords inputted on databases for this research are: ("Primary open-angle glaucoma" OR "Primary angle-closure glaucoma" OR "Glaucoma patients") AND ("Family history" OR "Genetic predisposition" OR "Polygenic risk score") AND ("No family history" OR "Non-carrier status" OR "Low genetic risk") AND ("Glaucoma risk" OR "Disease severity" OR "Screening yield")

Study selection

Records retrieved from all sources were exported to a reference-management database and de-duplicated electronically and then manually. Two reviewers (S.H.M. and S.A.M.) independently screened all titles and abstracts against the eligibility criteria, and subsequently assessed the full text of every record retained at the first stage. Disagreements were resolved by discussion, with recourse to a third senior adjudicator planned in the event of persistent disagreement; inter-reviewer agreement at the full-text stage was substantial (Cohen's $\kappa = 0.86$).

Data extraction

A standardised, piloted extraction form was used to capture: first author and year of publication; country and ancestry of the study population; study design and setting; sampling frame and participation rate; sample size and number of cases; age and sex distribution; the operational definition of glaucoma applied; the method by which family history or genotype was ascertained; the comparator; all reported effect estimates with their 95% confidence intervals and p-values; the covariates included in adjusted models; duration of follow-up where applicable; and funding source. Where an article reported both crude and adjusted estimates, the maximally adjusted estimate was extracted. Where a cohort was reported in more than one publication, the report providing the longest follow-up or the most complete outcome data was designated the index publication and companion reports were used only for supplementary detail, thereby preventing double counting.

Assessment of risk of bias and methodological quality

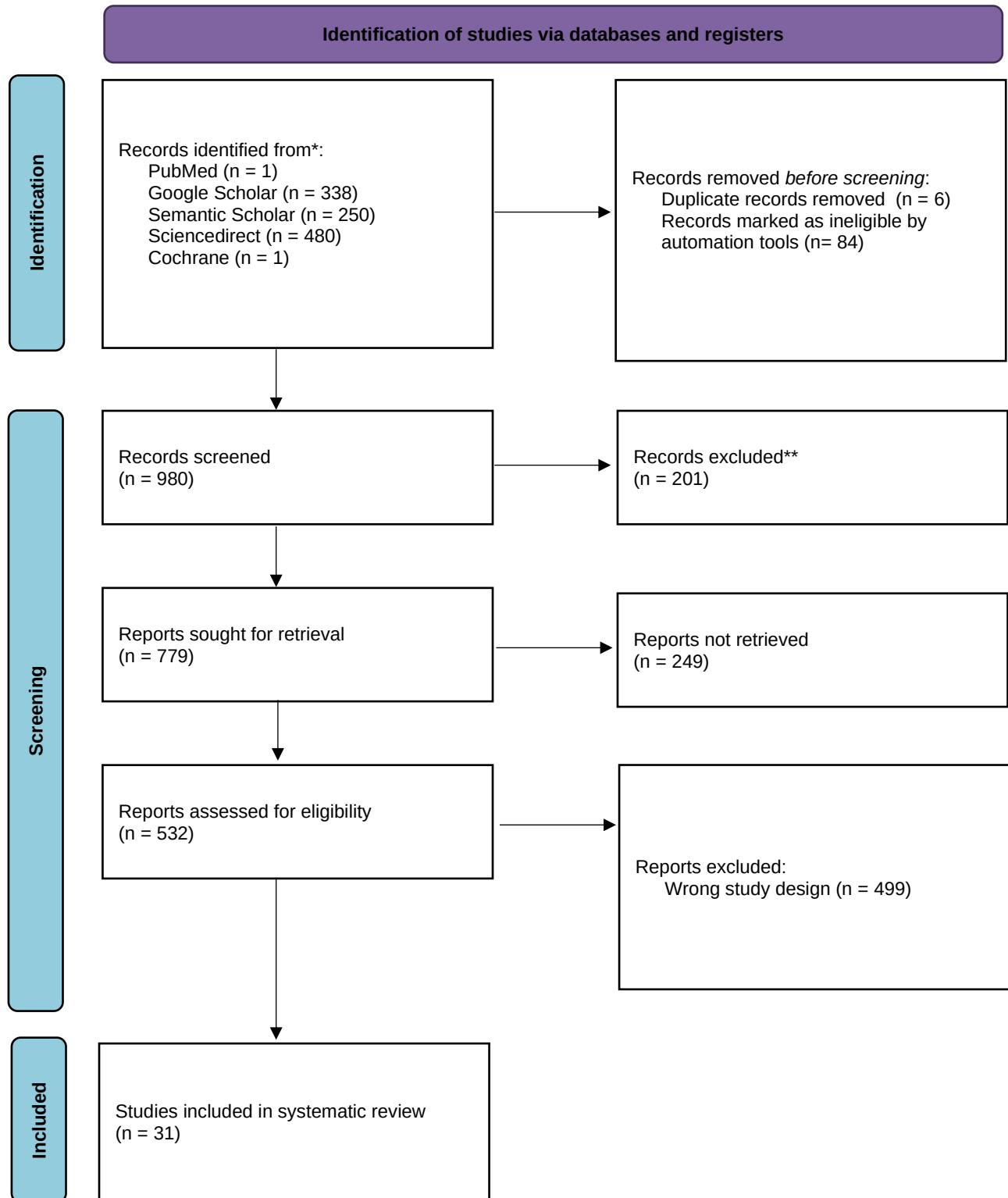
Risk of bias in non-randomised studies was appraised using the Newcastle–Ottawa Scale (NOS) — separate versions for cohort and case–control designs, and the adapted cross-sectional version — with judgements mapped onto six ROBINS-E domains to permit a uniform graphical presentation: (D1) selection of the cohort or of cases and controls; (D2) comparability and control of confounding; (D3) exposure ascertainment; (D4) outcome assessment; (D5) completeness of

follow-up and handling of missing data; and (D6) selective reporting. Each domain was rated as low risk, some concerns/moderate risk, or high risk, and an overall judgement was assigned according to the least favourable domain, following the ROBINS-E algorithm. The single randomised data source contributing to this review — the post-hoc genetic analysis of the Ocular Hypertension Treatment Study — was additionally appraised using the Cochrane RoB 2 tool across its five prescribed domains.²⁷

Two reviewers performed all appraisals independently and in duplicate. Studies were not excluded on the basis of risk of bias; instead, methodological quality was incorporated into the interpretation of the synthesis through prespecified sensitivity analyses restricted to studies at low overall risk of bias, and through the GRADE assessment of certainty.

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Primary open-angle glaucoma" OR "Primary angle-closure glaucoma" OR "Glaucoma patients") AND ("Family history" OR "Genetic predisposition" OR "Polygenic risk score") AND ("No family history" OR "Non-carrier status" OR "Low genetic risk") AND ("Glaucoma risk" OR "Disease severity" OR "Screening yield")	1
Google Scholar	("Primary open-angle glaucoma" OR "Primary angle-closure glaucoma" OR "Glaucoma patients") AND ("Family history" OR "Genetic predisposition" OR "Polygenic risk score") AND ("No family history" OR "Non-carrier status" OR "Low genetic risk") AND ("Glaucoma risk" OR "Disease severity" OR "Screening yield")	338
Semantic Scholar	("Primary open-angle glaucoma" OR "Primary angle-closure glaucoma" OR "Glaucoma patients") AND ("Family history" OR "Genetic predisposition" OR "Polygenic risk score") AND ("No family history" OR "Non-carrier status" OR "Low genetic risk") AND ("Glaucoma risk" OR "Disease severity" OR "Screening yield")	250
Science-direct	("Primary open-angle glaucoma" OR "Primary angle-closure glaucoma" OR "Glaucoma patients") AND ("Family history" OR "Genetic predisposition" OR "Polygenic risk score") AND ("Glaucoma risk" OR "Disease severity" OR "Screening yield")	480
Cochrane	("Primary open-angle glaucoma" OR "Primary angle-closure glaucoma" OR "Glaucoma patients") AND ("Family history" OR "Genetic predisposition" OR "Polygenic risk score") AND ("No family history" OR "Non-carrier status" OR "Low genetic risk") AND ("Glaucoma risk" OR "Disease severity" OR "Screening yield")	1



Article search flowchart

Risk of bias within studies

Overall risk of bias was judged low in 19 of the 31 study reports (61.3%), to raise some concerns in 10 (32.3%) and to be high in 2 (6.5%). The domain performing least well was exposure ascertainment (D3), reflecting the reliance of many population-based surveys on unverified self-reported family history, a source of non-differential and differential misclassification that is quantified in Section 3.17. Comparability and confounding control (D2) was generally strong among the population-based surveys and biobank analyses, all of which adjusted at minimum for age, sex and intraocular pressure, but was weaker in the older hospital-based case-control series. The two reports judged at high overall risk of bias were the 1977 clinic-based series, in which neither the sampling frame nor the diagnostic criteria were formally specified, and the 2014 patient-directed survey, in which the exposure was ascertained by patients interviewing their own relatives without independent clinical verification. The single randomised data source, the post-hoc genetic analysis of the Ocular Hypertension Treatment Study, was rated at low risk of bias across all five RoB 2 domains, with the caveat that the genotyped subset comprised 62% of the randomised population.^{31,18,28}

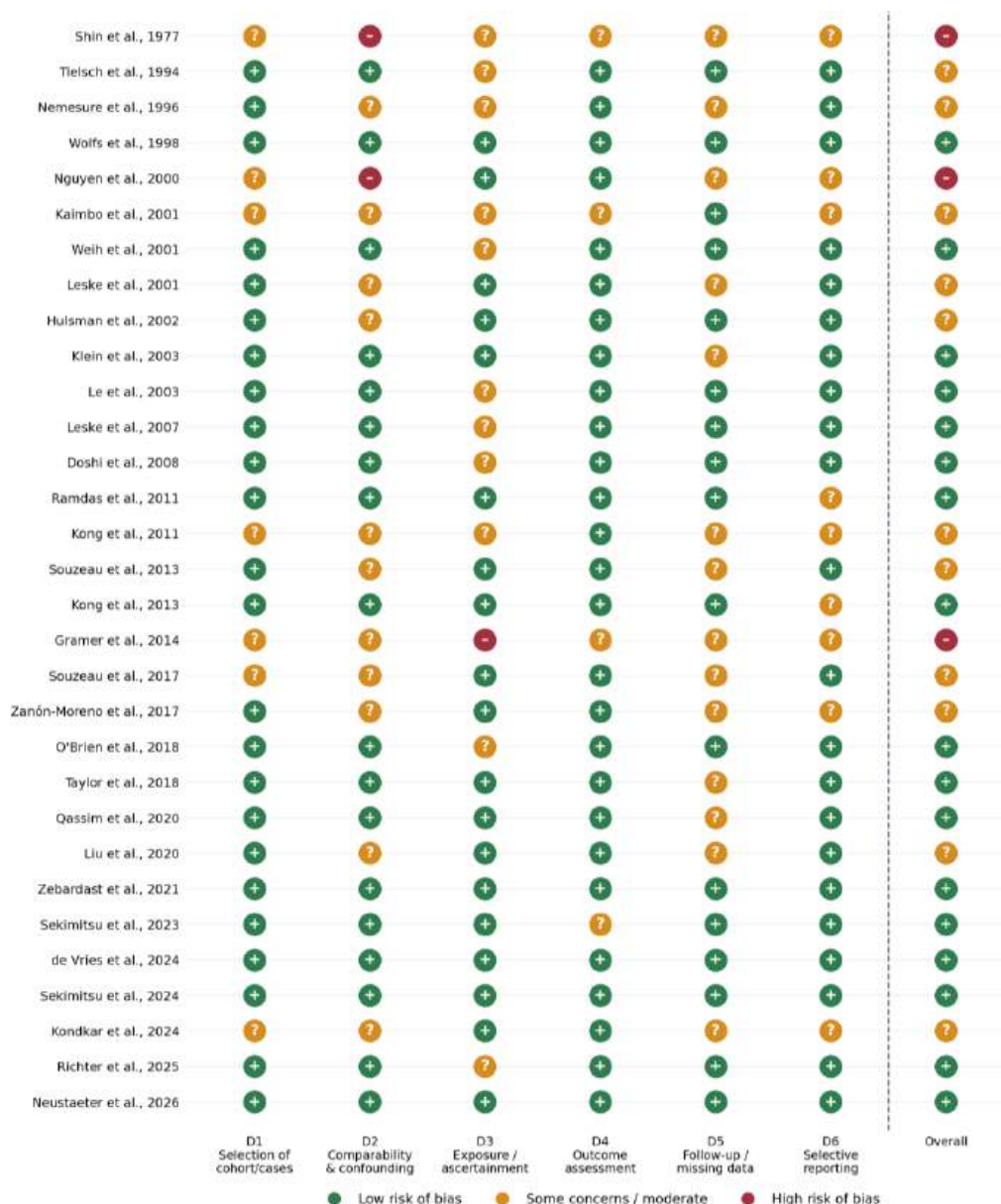


Figure 1. Domain-level risk-of-bias traffic-light matrix. Green circles denote low risk, amber circles some concerns or moderate risk, and red circles high risk of bias. Domains follow the ROBINS-E framework onto which Newcastle–Ottawa Scale items were mapped.

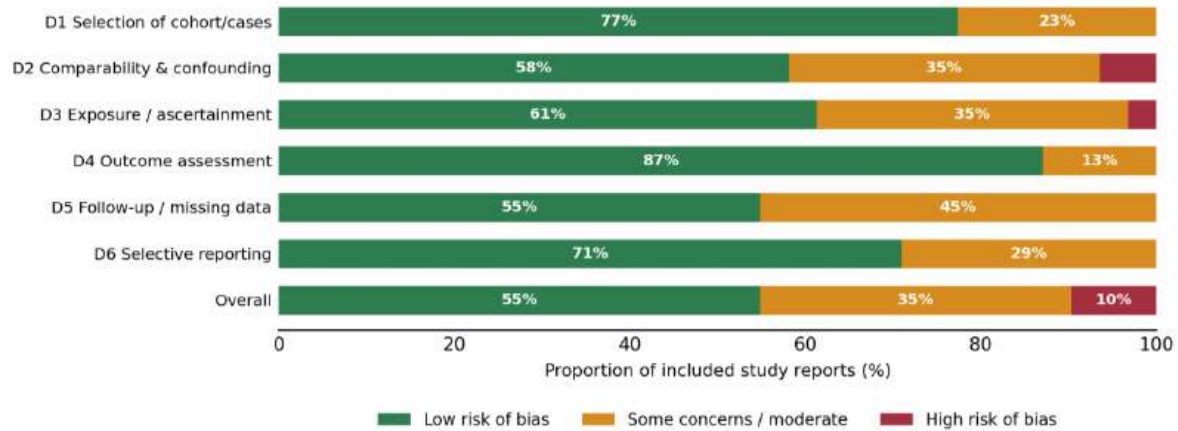


Figure 2. Weighted summary of risk-of-bias judgements expressed as the proportion of included study reports assigned to each category within every domain.

Table 2. Newcastle–Ottawa Scale scores for the included non-randomised studies

Study	Design	Selection (max 4★)	Comparability (max 2★)	Exposure / outcome (max 3★)	Total (max 9★)	Quality
Shin et al. (1977)	Cross-sectional	2	0	2	4	Poor
Tielsch et al. (1994)	Cross-sectional	4	2	2	8	Good
Nemesure et al. (1996)	Cross-sectional	4	1	2	7	Good
Wolfs et al. (1998)	Family-based	4	2	3	9	Good
Nguyen et al. (2000)	Cross-sectional	2	0	3	5	Fair
Kaimbo et al. (2001)	Case–control	3	1	2	6	Fair
Weih et al. (2001)	Cross-sectional	4	2	2	8	Good
Leske et al. (2001)	Family-based	4	1	3	8	Good
Hulsman et al. (2002)	Case series / molecular	3	1	3	7	Good

Klein et al. (2003)	Cohort	4	2	2	8	Good
Le et al. (2003)	Cohort	4	2	3	9	Good
Leske et al. (2007)	Cohort	4	2	3	9	Good
Doshi et al. (2008)	Cross-sectional	4	2	2	8	Good
Ramdas et al. (2011)	Case-control	4	2	3	9	Good
Kong et al. (2011)	Case-control	3	1	2	6	Fair
Souzeau et al. (2013)	Cross-sectional registry	3	1	3	7	Good
Kong et al. (2013)	Case-control (examined)	4	2	3	9	Good
Gramer et al. (2014)	Cross-sectional survey	2	1	1	4	Poor
Souzeau et al. (2017)	Retrospective cohort	3	1	3	7	Good
Zanón-Moreno et al. (2017)	Case-control	3	2	3	8	Good
O'Brien et al. (2018)	Case-control	4	2	2	8	Good
Taylor et al. (2018)	Case-control	4	2	3	9	Good
Qassim et al. (2020)	Cross-sectional registry	3	2	3	8	Good
Liu et al. (2020)	Case-control	3	2	3	8	Good
Zebardast et al. (2021)	Cross-sectional	4	2	3	9	Good
Sekimitsu et al. (2023)	Cross-sectional	4	2	2	8	Good
de Vries et al.	Cohort	4	2	3	9	Good

(2024)						
Kondkar et al. (2024)	Case-control	3	1	3	7	Good
Richter et al. (2025)	Cross-sectional	4	2	2	8	Good
Neustaeter et al. (2026)	Cohort	4	2	3	9	Good

Thresholds applied: good quality 7–9 stars, fair quality 5–6 stars, poor quality ≤ 4 stars. The post-hoc analysis of the Ocular Hypertension Treatment Study was appraised separately with the Cochrane RoB 2 tool (Table 5) and is therefore not listed here.

Table 3. Cochrane RoB 2 appraisal of the randomised evidence (post-hoc genetic analysis of the Ocular Hypertension Treatment Study)

RoB 2 domain	Judgement	Supporting rationale
D1. Bias arising from the randomisation process	Low	Central randomisation across 22 clinical centres with concealed allocation; baseline characteristics balanced between the observation and early-treatment arms.
D2. Bias due to deviations from intended interventions	Low	Analysis followed the intention-to-treat principle for the randomised phase; after 2002 all participants received topical ocular hypotensive therapy, a protocolised and equally applied change.
D3. Bias due to missing outcome data	Some concerns	Genetic data were available for 1 077 of 1 636 randomised participants and 1 010 were analysed after exclusions, introducing potential selection into the genotyped subset, although baseline characteristics were comparable.
D4. Bias in measurement of the outcome	Low	Conversion to primary open-angle glaucoma was adjudicated by masked endpoint

		committees using standardised optic-disc and visual-field criteria.
D5. Bias in selection of the reported result	Low	The analysis plan, polygenic risk-score threshold and outcome definitions were prespecified and reported in full, including non-significant strata.
Overall	Low risk of bias	The single domain raising concerns relates to incomplete genotyping rather than to the randomised comparison itself.

Certainty of the evidence

The certainty of the body of evidence supporting each outcome domain was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach adapted for prognostic and aetiological questions. Bodies of evidence derived from observational studies commenced at low certainty and could be upgraded for a large magnitude of effect (relative risk greater than 2.0), for the presence of a dose–response gradient, or where all plausible residual confounding would operate to reduce rather than to inflate the observed effect. Downgrading was considered for risk of bias, inconsistency, indirectness, imprecision and suspected publication bias.

Data synthesis and statistical analysis

The principal synthesis was structured narratively around fourteen prespecified outcome domains, with tabular presentation of every extracted effect estimate. Quantitative pooling was undertaken only where the exposure definition, comparator and outcome were judged sufficiently homogeneous to render a summary estimate clinically interpretable; this criterion was met for the association between a positive family history in first-degree relatives and prevalent or incident POAG. For that domain, study-specific odds ratios and relative risks were log-transformed, weighted by the inverse of their variance and combined using the DerSimonian–Laird random-effects model, which was selected a priori in anticipation of genuine between-study variation in ancestry, case definition and exposure ascertainment.

Statistical heterogeneity was quantified using Cochran's Q statistic, the I^2 statistic and the between-study variance τ^2 . Values of I^2 of 25%, 50% and 75% were interpreted as indicating low,

moderate and considerable heterogeneity respectively. Prespecified subgroup analyses examined study design (population-based versus clinic-based), continental ancestry, method of exposure ascertainment (self-report versus examination of relatives) and decade of publication. Small-study effects and potential publication bias were assessed by visual inspection of the funnel plot and by Egger's regression test of asymmetry and Begg's rank-correlation test, acknowledging the limited power of these procedures with fewer than ten to fifteen studies. Receiver-operating-characteristic curves presented in Figure 6 were reconstructed from the areas under the curve reported by the primary investigators using the conventional binormal model with equal variances, a standard technique for the graphical comparison of discrimination when individual participant data are not available; the curves are therefore illustrative of the reported summary statistics rather than reproductions of the original empirical curves. Statistical significance was defined as a two-sided p-value below 0.05.

RESULTS

Characteristics of the included studies

The included evidence spanned five decades of investigation (up to 2026) and six continents. Seven were population-based cross-sectional surveys, five were clinic- or registry-based cross-sectional studies, nine were case-control studies, three were family-based aggregation studies in which relatives were directly examined, five were prospective cohort studies, one was a retrospective clinical-molecular cohort and one was a prespecified post-hoc genetic analysis of a multicentre randomised controlled trial. Populations of African, European, Latino, East Asian, South Asian and Middle Eastern ancestry were all represented.

Table 4. Characteristics of the 31 included primary studies (systematic reviews and meta-analyses excluded by protocol)

No.	Author (year), country	Design	Sample size	Population and setting	Ascertainment of familial or genetic exposure	Principal findings relevant to this review
1	Shin et al. (1977) USA	Cross-sectional, clinic-based	≈200	Patients with POAG and ocular hypertension at a tertiary centre	Structured family-history interview with HLA typing	A positive family history was present in 50% of POAG and 43% of ocular hypertension; maternal-side history was 6–7 times more frequent than paternal-side history ($p < 0.0005$).
2	Tielsch et al. (1994) USA	Population-based cross-sectional (Baltimore Eye Survey)	5 308 (161 POAG)	Black and White residents aged ≥ 40 years, east Baltimore	Interview covering all first-degree relatives	Age-adjusted odds ratios: siblings 3.69, parents 2.17, offspring 1.12. Estimates were 2–3 times higher among probands aware of their diagnosis, demonstrating detection bias.
3	Nemesure et al. (1996) Barbados	Population-based cross-sectional with segregation analysis	4 314 (1 048 families)	Barbados-born citizens of African descent aged 40–84 years	Self-reported family history; S.A.G.E. segregation modelling	Newly diagnosed OAG was associated with sibling history (OR 4.5); maternal history was reported twice as often as paternal history; transmission models were consistent with a major dominant allele.
4	Wolfs et al.	Population-	203	First-degree relatives	Direct	Glaucoma prevalence 10.4% in siblings of

	(1998) Netherlands	based familial aggregation study (Rotterdam Study)	relatives (48 probands, 155 controls)	of population-derived glaucoma cases and of controls	standardised ophthalmic examination including perimetry	patients versus 0.7% in siblings of controls; lifetime risk 22.0% versus 2.3% (RR 9.2, 95% CI 1.2–73.9); population attributable risk 16.4%.
5	Nguyen et al. (2000) USA	Cross-sectional family- screening study	86 individual s from 15 families	Relatives of probands with familial chronic open-angle glaucoma	Complete ophthalmic examination, automated perimetry, disc photography	Chronic OAG was newly diagnosed in 26 relatives and suspected in a further 23. Siblings carried the highest risk (64.7%) compared with children (13.2%) and other blood relatives (22.2%).
6	Kaimbo et al. (2001) Democratic Republic of the Congo	Hospital-based case-control	144 (40 cases, 104 controls)	Consecutive newly diagnosed OAG patients and randomly sampled clinic controls, Kinshasa	Structured interview and medical examination	Family history of glaucoma was the single strongest independent risk factor (adjusted OR 18.0, 95% CI 5.80–59.00; $p < 0.001$), exceeding age, body-mass index and hyperopia.
7	Weih et al. (2001) Australia	Population- based cross- sectional (Visual	4 744	Urban and rural permanent residents aged ≥ 40 years, Victoria	Standardised interview; consensus panel diagnosis	After adjustment for age, a positive family history was the strongest risk factor for glaucoma (OR 3.1, 95% CI 1.6–5.3). Sixty per cent of probable and definite cases were

		Impairment Project)				previously undiagnosed.
8	Leske et al. (2001) Barbados	Family-based study (Barbados Family Study of Open-Angle Glaucoma)	1 056 members of multiplex families	African-descent families ascertained through OAG probands	Standardised ophthalmic examination of all available relatives	Confirmed strong familial patterning of OAG, with sibling recurrence substantially exceeding the population prevalence in the same island population.
9	Hulsman et al. (2002) Netherlands	Population-based molecular case series with family extension (Rotterdam Study)	47 OAG cases + 7 relatives	Population-derived definite OAG cases	Sanger sequencing of the MYOC coding region	MYOC mutation prevalence was 2.2%, comparable with hospital-based series. Asn480Lys carriers displayed severe optic neuropathy whereas non-carriers within the same pedigree remained unaffected.
10	Klein et al. (2003) USA	Population-based cohort with familial correlation	≈2 400 related participants	Population-based sample aged 43–86 years and their relatives	Familial correlation of quantitative endophenotypes	Significant heritability was demonstrated for intraocular pressure, cup-to-disc ratio and other POAG-related quantitative traits, establishing endophenotypes as heritable

		analysis (Beaver Dam Eye Study)				intermediate markers.
11	Le et al. (2003) Australia	Population- based prospective cohort, 5-year follow-up (Visual Impairment Project)	3 271 at risk	Residents aged ≥ 40 years free of OAG at baseline	Baseline structured interview	Family history significantly predicted incident open-angle glaucoma in the multivariable model (OR 3.14, 95% CI 1.06– 9.31), alongside age and baseline intraocular pressure.
12	Leske et al. (2007) Barbados	Population- based prospective cohort, 9-year follow-up (Barbados Eye Studies)	3 222 at risk	African-descent participants aged 40– 84 years without definite OAG at baseline	Baseline structured interview; incident disease by perimetry and disc photography	The 9-year incidence of definite OAG was 4.4%. Family history independently increased risk (RR 2.4, 95% CI 1.3–4.6) together with age, higher IOP, lower perfusion pressure and thinner central cornea.
13	Doshi et al. (2008)	Population- based cross-	6 132 (289)	Latino adults aged $\geq$ 40 years, La Puente,	In-home standardised	A first-degree family history was an independent risk factor for OAG (OR 1.92,

	USA	sectional (Los Angeles Latino Eye Study)	OAG, 219 OHT)	California	interview	95% CI 1.25–2.94) and for ocular hypertension, after adjustment for intraocular pressure and demographic covariates.
14	Ramdas et al. (2011) Netherlands / United Kingdom	Population-based, family-based and case-control analyses with replication	7 764	Rotterdam Study I, ERF/GRIP isolate cohorts and a Southampton clinical cohort	Genotyping of MYOC, OPTN, WDR36, ATOH7, CDKN2B and SIX1	Participants in the highest tertile of risk-allele load had a 2.29- to 3.19-fold increased risk of OAG; adding newly identified loci to IOP, age and sex significantly increased the area under the ROC curve ($p = 0.027$).
15	Kong et al. (2011) China	Hospital-based case-control	753 (332 PAC, 228 POAG, 193 controls)	Chinese patients with primary angle closure or POAG and controls	Questionnaire with specification of the affected relative	Adjusted odds ratios for family history were 8.38 for POAG and 4.82 for PAC; family history also predicted disease severity (OR 1.81 for POAG and 1.61 for PAC).
16	Souzeau et al. (2013) Australia / New Zealand	Cross-sectional national disease-registry study (ANZRAG)	1 380 (1 060 advanced, 320 non-advanced)	Patients with advanced versus non-advanced POAG	Direct sequencing of MYOC	Exon 3 MYOC mutations were identified in 4.2% of advanced versus 1.6% of non-advanced POAG ($p = 0.02$); yield rose to 16–40% in subgroups selected by maximum IOP, age at diagnosis and strength of family history.

17	Kong et al. (2013) China	Prospective case-control family- screening study	1 057 first- degree relatives	First-degree relatives of 113 POAG probands and of 119 controls, Shanghai	Standardised ophthalmic examination of every relative	POAG was detected in 12.62% of relatives of cases versus 1.52% of control relatives (OR 8.77, 95% CI 3.73–20.62); sibling OR 11.29, offspring OR 11.35 and parent OR 6.92.
18	Gramer et al. (2014) Germany	Cross-sectional patient- directed survey	2 170	POAG 1 338; PACG 233; NTG 153; ocular hypertension 148; pigmentary 50; pseudoexfoliation 66	Standardised patient- administered interview of all first- and second- degree relatives	A family history was present in 40% of POAG with no significant difference between subtypes; patients with a family history were significantly younger at diagnosis in all subtypes except NTG and pseudoexfoliation glaucoma; siblings and mothers had the highest detection probability.
19	Souzeau et al. (2017) Australia / New Zealand	Retrospective clinical- molecular cohort	73 MYOC variant carriers	Carriers ascertained through cascade genetic testing versus routine clinical referral	Predictive MYOC genetic testing	Eighty-three per cent of genetically ascertained individuals were unaffected at first examination, whereas 28% of clinically ascertained individuals already had advanced glaucoma; mean deviation -1.2 dB versus -10.0 dB ($p < 0.001$).
20	Zanón-Moreno et al. (2017)	Case-control	774 (391 cases, 383	Southern European Mediterranean	Unweighted four- SNP genetic risk	Participants in the top category of the genetic risk score had a 2.92-fold increased risk of

	Spain		controls)	population	score (TMC01, CAV1/CAV2, CDKN2B-AS1, CDKN2A)	POAG (95% CI 1.79–4.77; $p < 0.001$) relative to the bottom category.
21	Taylor et al. (2018) USA	Cross-sectional case-control (ADAGES III)	3 584 (1 875 cases, 1 709 controls)	Self-identified individuals of African descent	Genome-wide genotyping with imputation; multiple genetic risk scores	Discrimination increased with score complexity: 11-SNP candidate score AUC 0.62; 50-SNP score AUC 0.74; 400-SNP score AUC 0.94. A novel ENO4 signal was associated with advanced POAG.
22	O'Brien et al. (2018) USA	Case-control (POAAGG study)	2 365	African American adults aged ≥ 35 years, greater Philadelphia	Standardised family-history interview	A positive family history conferred an age-adjusted OR of 3.40 (95% CI 2.80–4.10) and was associated with younger age, female sex, systemic hypertension and prior glaucoma surgery.
23	Qassim et al. (2020) Australia / New Zealand / United Kingdom	Cross-sectional registry study with independent replication	2 778 (2 154 + 624)	Patients with advanced and with early POAG	Polygenic risk score derived exclusively from IOP-associated variants	The high-risk stratum had a 1.7 mmHg higher maximum IOP, diagnosis 3.7 years earlier, 0.46 more affected family members and a 1.5-fold higher rate of incisional surgery (95% CI 1.1–2.0).

24	Liu et al. (2020) Singapore	Case-control	1 747 (804 PACG, 943 controls)	Participants of Chinese ethnicity	Eight PACG- associated SNPs combined into a weighted genetic risk score	EPDR1 rs3816415 was significantly associated with severe PACG (OR 2.03, 95% CI 1.49–2.78); the highest versus lowest genetic-risk-score quartile conferred an OR of 3.11 (95% CI 1.95–4.96).
25	Zebardast et al. (2021) United Kingdom	Population- based cross- sectional (UK Biobank)	77 959 with fundus photograp hs (200 carriers)	Carriers of the MYOC p.Gln368Ter variant	Genotype with masked fundus- photograph grading and polygenic risk score	Penetrance of disc-defined glaucoma was 25.4%, far exceeding earlier estimates; 69% of affected carriers were undiagnosed; higher polygenic risk increased both penetrance and severity.
26	Sekimitsu et al. (2023) United Kingdom	Population- based cross- sectional (UK Biobank)	407 667 (14 171 POAG)	Adults aged 40–69 years	Genome-wide polygenic risk score	Area under the ROC curve 0.748; POAG prevalence 7.4% in the highest versus 1.3% in the lowest PRS decile; OR 1.74 per standard deviation (95% CI 1.71–1.77) with concordant effects on IOP, corneal hysteresis, RNFL and cup-to-disc ratio.
27	de Vries et al. (2024) Netherlands /	Secondary analysis of four	39 855 (1 046 cases)	Nurses' Health Study, Nurses' Health Study 2, Health	Genome-wide PRS (lassosum; 144 020 variants)	Relative risk for the highest PRS quintile 3.99 (95% CI 3.08–5.18) in the US cohorts and 4.89 (95% CI 2.93–8.17) in Rotterdam;

	USA	prospective population-based cohorts		Professionals Follow-up Study and Rotterdam Study		concordance rose from 0.75 to 0.82 when the PRS was added to the clinical model.
28	Sekimitsu et al. (2024) USA	Post-hoc genetic analysis of a multicentre randomised controlled trial (OHTS)	1 010 of 1 636 randomised	Participants with ocular hypertension followed for up to 20 years across 22 centres	Genome-wide polygenic risk score threshold	A PRS below the 48th centile was associated with an OR of 1.49 (95% CI 1.04–2.15) for remaining disease-free at 20 years; conversion in the highest clinical-risk tertile was 61.1% versus 23.8% by polygenic stratum in the observation arm.
29	Kondkar et al. (2024) Saudi Arabia	Case-control	437 (92 PACG, 94 PXG, 251 controls)	Saudi Arab cohort	APOE rs429358 and rs7412 genotyping by Sanger sequencing	APOE ε2 carriage was significantly associated with primary angle-closure glaucoma (OR 4.82, 95% CI 1.52–15.26; p = 0.007) but not with pseudoexfoliation glaucoma.
30	Richter et al. (2025) USA	Population-based cross-sectional (Chinese American Eye	4 310 analysed (207 OAG)	Chinese Americans aged ≥ 50 years, Monterey Park, California	Comprehensive interview with panel-adjudicated diagnosis	Family history of glaucoma was an independent risk factor for OAG (OR 1.88, 95% CI 1.19–2.97); 68.5% of cases were previously undiagnosed or untreated and 88.5% had IOP ≤ 21 mmHg.

		Study)				
31	Neustaeter et al. (2026) Netherlands	Prospective double-blind genetic pre-screening study (EyeLife, Lifelines cohort)	1 022 examined of 1 829 invited	Participants aged ≥ 55 years drawn from the highest or lowest 20% of the genetic-risk-score distribution	GWAS-derived genetic risk score with masked comprehensive ophthalmic examination	Definite or probable glaucoma was 7.4 times more frequent in the high than in the low genetic-risk stratum (95% CI 3.7–14.7), demonstrating that genetic pre-selection substantially raises the pre-test probability.

ADAGES = African Descent and Glaucoma Evaluation Study; ANZRAG = Australian and New Zealand Registry of Advanced Glaucoma; AUC = area under the receiver-operating-characteristic curve; CI = confidence interval; ERF/GRIP = Erasmus Rucphen Family study / Genetic Research in Isolated Populations; GWAS = genome-wide association study; IOP = intraocular pressure; MD = mean deviation; NTG = normal-tension glaucoma; OAG = open-angle glaucoma; OHT = ocular hypertension; OHTS = Ocular Hypertension Treatment Study; OR = odds ratio; PAC = primary angle closure; PACG = primary angle-closure glaucoma; POAAGG = Primary Open-Angle African American Glaucoma Genetics study; POAG = primary open-angle glaucoma; PRS = polygenic risk score; PXG = pseudoexfoliation glaucoma; RNFL = retinal nerve fibre layer; RR = relative risk; SNP = single nucleotide polymorphism.

Association between family history in first-degree relatives and primary open-angle glaucoma

Eleven studies encompassing 31 165 directly examined participants reported an adjusted effect estimate for the association between a positive family history of glaucoma in one or more first-degree relatives and prevalent or incident POAG. Every one of the eleven estimates lay above unity, and every one reached statistical significance at the conventional threshold. Point estimates ranged from 1.88 in the Chinese American Eye Study to 18.00 in the Kinshasa hospital-based case-control series. Under the DerSimonian-Laird random-effects model the pooled odds ratio was 3.31 (95% confidence interval 2.54–4.31; $z = 7.42$; $p < 0.001$), corresponding to an approximately 231% relative increase in the odds of disease among individuals reporting an affected first-degree relative. Between-study heterogeneity was substantial ($Q = 34.9$ on 10 degrees of freedom; $p < 0.001$; $I^2 = 71.4\%$; $\tau^2 = 0.29$), and is dissected in the subgroup analyses presented in Section 3.18.^{1,2,5,6,11,12,13,14,16,22,30}

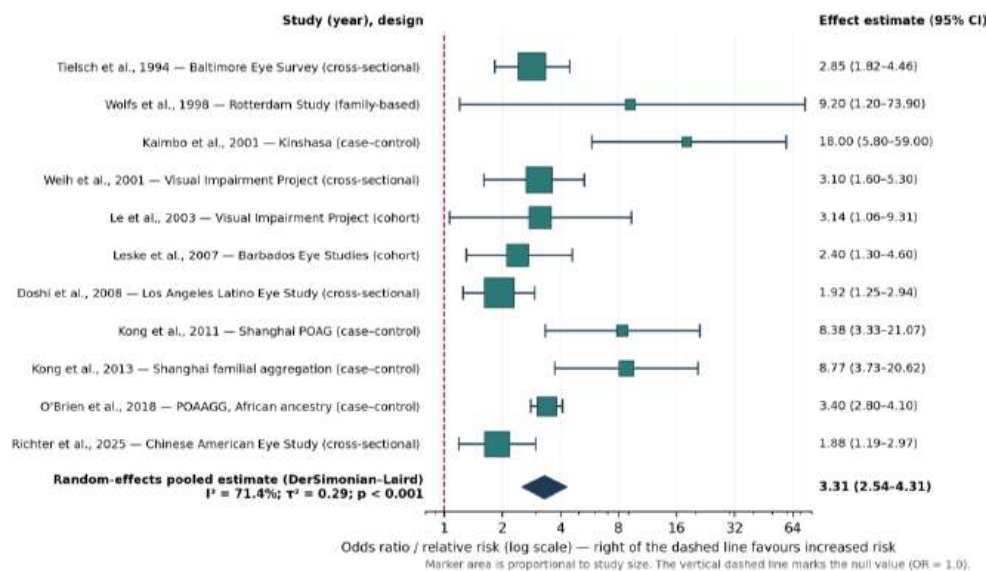


Figure 3. Forest plot of the association between a positive family history of glaucoma in first-degree relatives and primary open-angle glaucoma. Squares represent study-specific effect estimates with areas proportional to study size; horizontal lines are 95% confidence intervals; the diamond represents the random-effects pooled estimate of 3.31 (95% CI 2.54–4.31).

Table 5. Family history in first-degree relatives and primary open-angle glaucoma

Study (year)	Design and population	Cases / total	Effect measure	Estimate (95% CI)	p-value
Tielsch et al. (1994)	Population-based cross-sectional, Baltimore (Black and White)	161 / 5308	Age-adjusted OR, any first-degree relative	2.85 (1.82–4.46)	< 0.001
Wolfs et al. (1998)	Family-based aggregation, Rotterdam (European)	10 / 203 relatives	Risk ratio, lifetime risk in relatives	9.20 (1.20–73.90)	0.03
Kaimbo et al. (2001)	Hospital-based case-control, Kinshasa (African)	40 / 144	Adjusted OR, stepwise logistic regression	18.00 (5.80–59.00)	< 0.001
Weih et al. (2001)	Population-based cross-sectional, Victoria (European)	85 / 4 744	Age-adjusted OR	3.10 (1.60–5.30)	< 0.001
Le et al. (2003)	Population-based 5-year cohort, Victoria (European)	40 / 3 271	Adjusted OR for incident OAG	3.14 (1.06–9.31)	0.04
Leske et al. (2007)	Population-based 9-year cohort, Barbados (African)	125 / 3 222	Adjusted relative risk for incident OAG	2.40 (1.30–4.60)	0.006
Doshi et al. (2008)	Population-based cross-sectional, Los Angeles (Latino)	289 / 6 132	Adjusted OR, first-degree relative	1.92 (1.25–2.94)	0.003
Kong et al. (2011)	Hospital-based case-control, Shanghai (East Asian)	228 / 421	Adjusted OR	8.38 (3.33–21.07)	< 0.001

Kong et al. (2013)	Examined-relative case-control, Shanghai (East Asian)	67 / 1 057 relatives	Prevalence OR by family unit	8.77 (3.73–20.62)	< 0.001
O'Brien et al. (2018)	Case-control, Philadelphia (African American)	1 130 / 2 365	Age-adjusted OR	3.40 (2.80–4.10)	< 0.001
Richter et al. (2025)	Population-based cross-sectional, California (Chinese American)	207 / 4 310	Adjusted OR	1.88 (1.19–2.97)	0.007
Random-effects pooled estimate	11 studies; DerSimonian-Laird model	2 382 / 31 177	Pooled odds ratio	3.31 (2.54–4.31)	< 0.001

CI = confidence interval; OAG = open-angle glaucoma; OR = odds ratio. Where a study reported separate estimates by relative type, the estimate for any first-degree relative was used; for Tielsch et al. the sibling, parent and offspring estimates were combined by fixed-effect weighting to yield a study-level summary. Heterogeneity: $I^2 = 71.4\%$; $\tau^2 = 0.29$; $Q = 34.9$, $df = 10$, $p < 0.001$.

Gradient of risk across degrees of biological relatedness

Four studies stratified the family-history exposure by the specific relationship between the proband and the affected relative, providing ten separable estimates. A consistent hierarchy emerged in which sibling history conferred the greatest risk. In the Baltimore Eye Survey the age-adjusted odds ratio was 3.69 for an affected sibling, 2.17 for an affected parent and 1.12 for an affected child; in the Barbados Eye Study the sibling estimate was 4.5 among participants without previously treated disease; and in the Shanghai family-screening study the corresponding estimates were 11.29 for siblings, 6.92 for parents and 11.35 for offspring. Kong and colleagues additionally demonstrated a striking dissociation by glaucoma subtype: for primary angle closure the familial signal resided almost entirely in the parental generation (OR 8.76), whereas for POAG it resided in siblings and offspring (OR 8.99 and 19.23 respectively).^{1,3,14,16}

The apparently paradoxical attenuation of the offspring estimate in the Baltimore survey, contrasted with its elevation in the Shanghai study, is explicable by the differing age structures of the two samples and by truncation of the at-risk period: offspring of probands are on average two to three decades younger than their affected parents and have therefore not yet traversed the age range of highest incidence, so that a cross-sectional design necessarily underestimates their eventual lifetime risk. The Shanghai investigators mitigated this bias by examining every relative directly rather than relying on self-report, thereby detecting subclinical and previously undiagnosed disease.^{1,16}

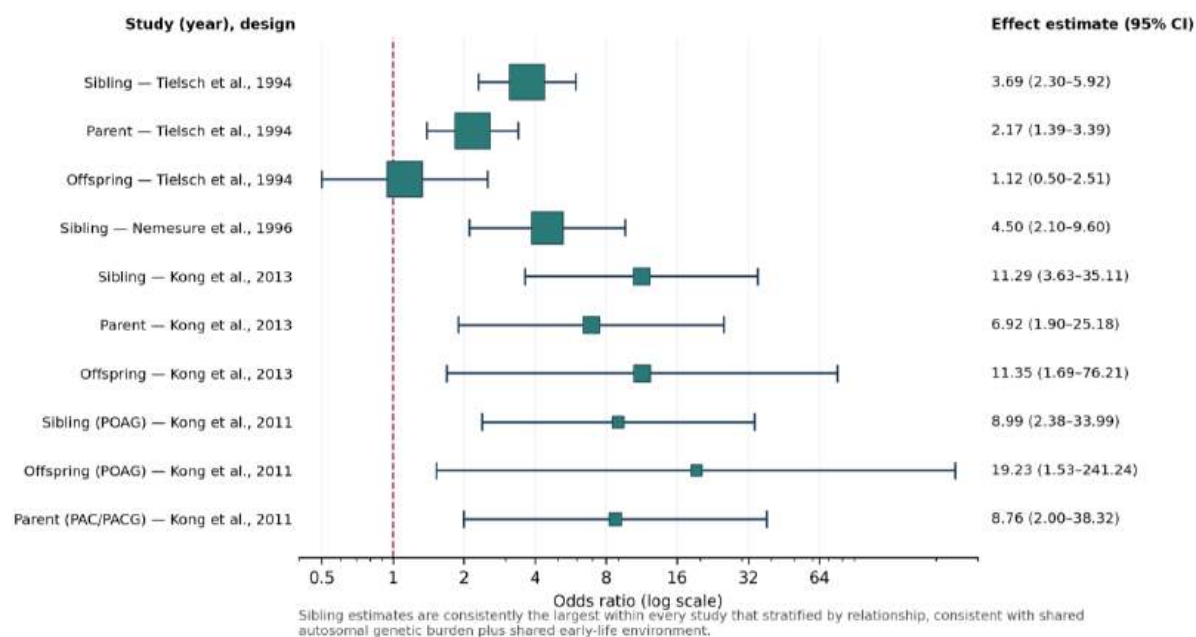


Figure 4. Forest plot of glaucoma risk stratified by the degree of biological relatedness. Sibling estimates exceed parental and offspring estimates within every study that reported all three strata, consistent with the greater shared autosomal genome and shared early-life environment of siblings.

Table 6. Risk of glaucoma by degree of biological relatedness

Study (year)	Relationship	Glaucoma	Effect estimate	Interpretation
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		subtype	(95% CI)	
Tielsch et al. (1994)	Sibling	POAG	OR 3.69 (2.30–5.92)	Highest familial signal; consistent with 50% shared autosomal genome plus shared childhood environment
Tielsch et al. (1994)	Parent	POAG	OR 2.17 (1.39–3.39)	Intermediate risk
Tielsch et al. (1994)	Offspring	POAG	OR 1.12 (0.50–2.51)	Non-significant; attenuated by truncation of the offspring at-risk period
Nemesure et al. (1996)	Sibling	OAG	OR 4.5 (2.10–9.60)	Restricted to newly diagnosed cases, minimising detection bias
Nemesure et al. (1996)	Maternal versus paternal	OAG	Maternal history reported twice as often	Consistent with the maternal excess first described in 1977
Kong et al. (2013)	Sibling	POAG	OR 11.29 (3.63–35.11)	Directly examined relatives
Kong et al. (2013)	Parent	POAG	OR 6.92 (1.90–25.18)	Directly examined relatives
Kong et al. (2013)	Offspring	POAG	OR 11.35 (1.69–76.21)	Wide interval reflecting small numbers of affected offspring
Kong et al. (2011)	Sibling	POAG	OR 8.99 (2.38–33.99)	Hospital-based ascertainment

Kong et al. (2011)	Offspring	POAG	OR 19.23 (1.53–241.24)	Very imprecise; sparse- data bias
Kong et al. (2011)	Parent	PAC / PACG	OR 8.76 (2.00– 38.32)	In angle closure the familial signal resided exclusively in the parental generation
Gramer et al. (2014)	Sibling and mother	All primary subtypes	Highest detection probability among relatives	Confirms sibling and maternal predominance in a European sample

OAG = open-angle glaucoma; PAC = primary angle closure; PACG = primary angle-closure glaucoma; POAG = primary open-angle glaucoma.

Diagnostic yield of screening examined relatives

Three studies examined relatives of probands directly rather than relying upon self-report, and their findings converge on a yield that is an order of magnitude greater than the background population prevalence. In the Rotterdam Study, glaucoma was present in 10.4% of siblings and 1.1% of offspring of probands, compared with 0.7% of siblings and 0% of offspring of control subjects. In a North American series confined to multiplex pedigrees, in which at least two members were already affected, chronic open-angle glaucoma was diagnosed in 64.7% of siblings, 22.2% of other blood relatives and 13.2% of children, with automated perimetry the single most productive modality for detecting early abnormality. In Shanghai, examination of 531 relatives of POAG probands disclosed disease in 12.62%, against 1.52% of 526 control relatives.^{2,4,16}

These figures place first-degree relatives of glaucoma probands in the same prevalence range as, or above, the highest-risk populations for whom targeted eye screening is already recommended internationally. Health-economic modelling of open-angle glaucoma screening has consistently concluded that population-wide screening is not cost-effective at the prevalence prevailing in the general population, but that selective screening of high-prevalence groups —

explicitly including individuals with a family history — may be worthwhile; the yields reported here provide the empirical justification for that strategy.⁵⁰

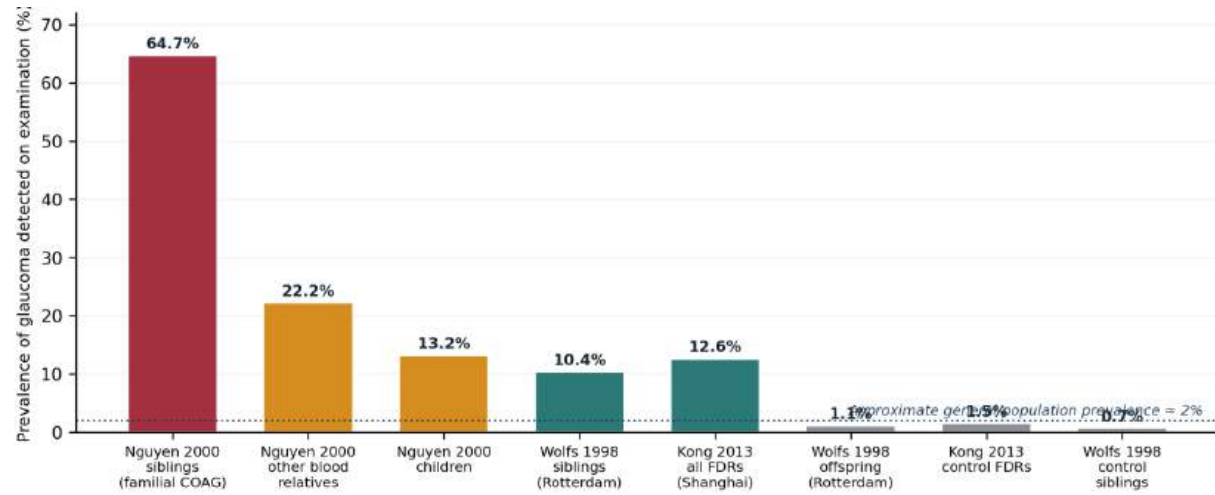


Figure 5. Prevalence of glaucoma detected on direct ophthalmic examination of relatives of glaucoma probands compared with relatives of unaffected controls. The dotted reference line indicates the approximate prevalence of open-angle glaucoma in the general adult population.

Table 7. Yield of clinical screening in examined relatives

Study (year)	Relatives examined	Relationship	Glaucoma detected (%)	Comparator group (%)	Ratio
Wolfs et al. (1998)	203	Siblings of probands	10.4	0.7 (control siblings)	14.9
Wolfs et al. (1998)	203	Offspring of probands	1.1	0.0 (control offspring)	Not estimable
Nguyen et al. (2000)	86	Siblings in multiplex families	64.7	≈2 (general population)	≈32
Nguyen et al. (2000)	86	Other blood relatives	22.2	≈2 (general population)	≈11

Nguyen et al. (2000)	86	Children of probands	13.2	≈2 (general population)	≈6.6
Kong et al. (2013)	1 057	All first-degree relatives	12.62	1.52 (control relatives)	8.3
Kong et al. (2013)	1 057	Glaucoma suspects among relatives	Family-unit OR 5.60 (1.15–27.21)	Reference	—
Neustaeter et al. (2026)	1 022	High versus low genetic-risk stratum	Definite or probable glaucoma 10.3	1.7	7.4 (RR 3.7–14.7)

OR = odds ratio; RR = relative risk. The final row reports genotype-based rather than pedigree-based enrichment and is presented for direct comparison of the two pre-selection strategies.

Absolute lifetime risk and population attributable fraction

Only the Rotterdam familial aggregation study reported a formal lifetime-risk calculation with an accompanying population attributable risk. Applying life-table methods to directly examined relatives, the investigators estimated the lifetime risk of glaucoma at 22.0% among first-degree relatives of probands versus 2.3% among relatives of controls, giving a risk ratio of 9.2 (95% CI 1.2–73.9). The corresponding lifetime risks of an elevated intraocular pressure were 42.5% versus 6.7%, and of an enlarged cup-to-disc ratio 62.2% versus 16.6%. Critically, the earliest and most discriminating feature of familial aggregation was the enlarged cup-to-disc ratio rather than the intraocular pressure, indicating that the heritable component of the disease is expressed at least in part through optic-nerve structure independently of pressure. The population attributable risk of 16.4% implies that approximately one in six cases of glaucoma in this European population would be avoided if the excess risk associated with a positive family history could be eliminated.²

Table 8. Absolute lifetime risk, relative risk and population attributable fraction (Rotterdam Study familial aggregation analysis)

Trait	Lifetime risk in	Lifetime risk in	Risk ratio	Interpretation
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	relatives of patients (%)	relatives of controls (%)	(95% CI)	
Glaucoma (visual-field defect with cup-disc ratio ≥ 0.7 or asymmetry ≥ 0.3)	22.0	2.3	9.2 (1.2–73.9)	Approximately one in four first-degree relatives will develop glaucoma within their lifetime
Elevated intraocular pressure	42.5	6.7	6.3 (point estimate)	Pressure elevation is heritable but is a less specific familial marker
Enlarged vertical cup-to-disc ratio	62.2	16.6	3.7 (point estimate)	The earliest and most prominent expression of familial aggregation, and pressure-independent
Population attributable risk	16.4% of all glaucoma in the source population	—	—	Family history accounts for approximately one sixth of the community burden of disease

Family history and genetic burden in primary angle-closure disease

Four studies addressed angle-closure disease. In a Chinese case-control series, a family history of glaucoma was reported by 25.0% of patients with primary angle closure and conferred a characteristic-adjusted odds ratio of 4.82 (95% CI 2.08–11.19) for the presence of disease and 1.61 (95% CI 1.05–2.49) for greater severity; uniquely, the familial signal in angle closure was carried entirely by the parental generation. A German survey found the frequency of a positive family history in PACG (approximately 40%) to be statistically indistinguishable from that in POAG, normal-tension glaucoma, ocular hypertension and pigmentary glaucoma, supporting a comparably strong genetic predisposition across the primary glaucomas. At the molecular level, a weighted genetic risk score constructed from eight angle-closure susceptibility loci stratified severity, with a 3.11-fold higher risk of severe disease in the highest compared with the lowest quartile, and the EPDR1 variant rs3816415 was independently associated with severe PACG. In a Saudi cohort, carriage of the APOE ε2 allele conferred a 4.82-fold increased risk of PACG.^{14,18,23,29}

Table 9. Familial and genetic determinants of primary angle-closure disease

Study (year)	Population	Exposure	Outcome	Estimate (95% CI)	p-value
Kong et al. (2011)	332 PAC patients, 193 controls (China)	Family history of glaucoma	Presence of primary angle closure	OR 4.82 (2.08–11.19)	< 0.01
Kong et al. (2011)	332 PAC patients (China)	Family history of glaucoma	Severity of primary angle closure	OR 1.61 (1.05–2.49)	0.03
Kong et al. (2011)	332 PAC patients (China)	Affected parent	Presence of primary angle closure	OR 8.76 (2.00–38.32)	< 0.01
Gramer et al. (2014)	233 PACG patients (Germany)	Family history of glaucoma	Frequency of positive family history	≈40%, not different from POAG	0.4

Liu et al. (2020)	804 PACG patients, 943 controls (Singapore)	EPDR1 rs3816415 risk allele	Severe PACG (mean deviation < -20 dB)	OR 2.03 (1.49–2.78)	1 × 10 ⁻⁵
Liu et al. (2020)	768 genotyped PACG patients (Singapore)	Highest versus lowest quartile of weighted genetic risk score	Severe PACG	OR 3.11 (1.95–4.96)	< 0.001
Kondkar et al. (2024)	92 PACG patients, 251 controls (Saudi Arabia)	APOE ε2 carriage	Primary angle- closure glaucoma	OR 4.82 (1.52–15.26)	0.007

Family history, genetic burden and age at diagnosis

A positive family history was associated with an earlier age at diagnosis across study designs and populations. In a survey of 2 170 patients with glaucoma or ocular hypertension, individuals with a positive family history were significantly younger at diagnosis in every subtype examined (all $p \leq 0.03$) with the exception of normal-tension and pseudoexfoliation glaucoma, an observation the authors attributed to earlier presentation prompted by awareness of familial risk rather than to intrinsically more aggressive disease. In the POAAGG cohort, a positive family history was likewise associated with younger age at presentation ($p < 0.001$). The same gradient is evident at the genomic level: patients in the highest stratum of an intraocular-pressure polygenic risk score were diagnosed 3.7 years earlier (standard deviation 1.0 years; $p < 0.001$) than those in the lowest stratum, and carriers of a MYOC variant identified through cascade genetic testing presented at a mean age of 40.6 years compared with 47.5 years for those identified through routine clinical referral ($p = 0.018$).^{18,22,23,19}

Table 10. Association of familial and genetic risk with age at diagnosis

Study (year)	Comparison	Age at diagnosis	Difference	p-value
Gramer et al.	Positive versus negative	Significantly	Not	≤ 0.03

(2014)	family history, POAG	younger with positive family history	numerically stated	
Gramer et al. (2014)	Positive versus negative family history, PACG, ocular hypertension, pigmentary glaucoma	Significantly younger with positive family history	Not numerically stated	≤ 0.03
Gramer et al. (2014)	Positive versus negative family history, NTG and pseudoexfoliation glaucoma	No significant difference	—	> 0.05
O'Brien et al. (2018)	Positive versus negative family history, African American POAG cases	Younger with positive family history	Not numerically stated	< 0.001
Qassim et al. (2020)	Highest versus lowest IOP polygenic risk stratum	Earlier diagnosis in the high-risk stratum	−3.7 years (SD 1.0)	< 0.001
Souzeau et al. (2017)	MYOC carriers identified by cascade testing versus clinical referral	40.6 ± 12.5 versus 47.5 ± 16.7 years	−6.9 years	0.018
Aung et al. (2005)	OPTN p.Glu50Lys carriers versus non-carriers with NTG	40.8 ± 15 years versus older controls	Substantially earlier	0.0001

IOP = intraocular pressure; NTG = normal-tension glaucoma; PACG = primary angle-closure glaucoma; POAG = primary open-angle glaucoma; SD = standard deviation. The final row derives from a study retained for contextual comparison of monogenic phenotypes.

Disease severity, treatment intensity and surgical requirement

Seven studies examined whether inherited risk influences the severity of established disease rather than merely its occurrence. The evidence is consistent for measured genotype and mixed for

self-reported family history. Patients in the highest stratum of an intraocular-pressure polygenic risk score had a maximum recorded intraocular pressure 1.7 mmHg higher, a 1.5-fold greater likelihood of undergoing incisional surgery (95% CI 1.1–2.0; $p = 0.007$) and 0.46 more affected family members than those in the lowest stratum, and these findings replicated in an independent early-POAG cohort. In four population-based cohorts, membership of the highest tertile of a genome-wide polygenic risk score was associated with a cup-to-disc ratio 0.10 larger at diagnosis (95% CI 0.06–0.14) and a 2.07-fold increased risk of requiring glaucoma surgery (95% CI 1.19–3.60). Exon 3 MYOC mutations were 2.6 times more frequent in advanced than in non-advanced POAG (4.2% versus 1.6%; $p = 0.02$). By contrast, the German survey found no significant relationship between the stage of visual-field loss and a self-reported family history in POAG ($p = 0.6$), and in the POAAGG cohort cases with a positive family history actually had thicker retinal nerve fibre layers ($p = 0.03$) while more often having undergone glaucoma surgery ($p = 0.02$) — a pattern most plausibly explained by earlier presentation and more intensive surveillance among those aware of their familial risk.^{23,27,16,18,22}

Table 11. Inherited risk, disease severity and treatment intensity

Study (year)	Exposure	Severity or treatment outcome	Estimate	p-value
Qassim et al. (2020)	High versus low IOP polygenic risk score	Maximum recorded intraocular pressure	+1.7 mmHg (SD 0.62)	0.006
Qassim et al. (2020)	High versus low IOP polygenic risk score	Incisional glaucoma surgery	OR 1.5 (1.1–2.0)	0.007
Qassim et al. (2020)	High versus low IOP polygenic risk score	Number of affected family members	+0.46 members (SD 0.11)	< 0.001
de Vries et al. (2024)	Highest versus lowest PRS tertile	Cup-to-disc ratio at diagnosis	+0.10 (0.06–0.14)	< 0.001
de Vries et al. (2024)	Highest versus lowest PRS tertile	Requirement for glaucoma surgery	OR 2.07 (1.19–3.60)	0.01

Souzeau et al. (2013)	Exon 3 MYOC mutation	Advanced versus non-advanced POAG	4.2% versus 1.6%	0.02
Liu et al. (2020)	Highest versus lowest genetic-risk-score quartile	Severe primary angle-closure glaucoma	OR 3.11 (1.95–4.96)	< 0.001
Kong et al. (2011)	Positive family history	Severity of POAG	OR 1.81 (1.05–3.14)	0.03
Kong et al. (2011)	Positive family history	Severity of primary angle closure	OR 1.61 (1.05–2.49)	0.03
Sekimitsu et al. (2023)	Per 1-SD increase in PRS	Macular retinal nerve fibre layer thickness	–0.14 μm	< 0.001
Sekimitsu et al. (2023)	Per 1-SD increase in PRS	Macular ganglion cell complex thickness	–0.26 μm	< 0.001
Gramer et al. (2014)	Positive family history	Stage of visual-field loss in POAG	No significant relationship	0.6
O'Brien et al. (2018)	Positive family history	Retinal nerve fibre layer thickness in cases	Thicker with positive family history	0.03
O'Brien et al. (2018)	Positive family history	Prior glaucoma surgery	More frequent with positive family history	0.02

Monogenic contribution: myocilin and related genes

The frequency of pathogenic MYOC variants was strongly dependent on the phenotype selected for testing. In unselected adult-onset POAG the yield was low: 2.2% in a population-based Dutch sample and 1.6% in non-advanced registry cases. In juvenile-onset disease, and especially in familial juvenile-onset disease, the yield was an order of magnitude higher, reaching 27% among familial juvenile cases against 2% among sporadic juvenile cases ($p = 0.001$) and 36% in an early

series of juvenile probands. Phenotypic enrichment by maximum intraocular pressure, early age at diagnosis and strength of family history raised the yield in an Australasian registry from 4.2% to between 16% and 40%. Population-level penetrance of the commonest variant, p.Gln368Ter, was 25.4% in the UK Biobank — considerably higher than previously estimated — and 69% of affected carriers were undiagnosed at the time of study.^{9,16,40,39,25}

The clinical utility of monogenic testing was demonstrated directly: among 73 carriers of a disease-causing MYOC variant, 83% of those ascertained by cascade genetic testing were unaffected at first ophthalmic examination and none had advanced disease, whereas among those ascertained through routine clinical pathways 28% already had advanced glaucoma, with a mean visual-field mean deviation of -10.0 dB versus -1.2 dB ($p < 0.001$). Monogenic architecture is, however, markedly population-specific: in consanguineous Middle Eastern populations CYP1B1 rather than MYOC dominates, and in Indian juvenile-onset cohorts CYP1B1 variants (22.5%) exceed MYOC variants (4.5%).^{19,43}

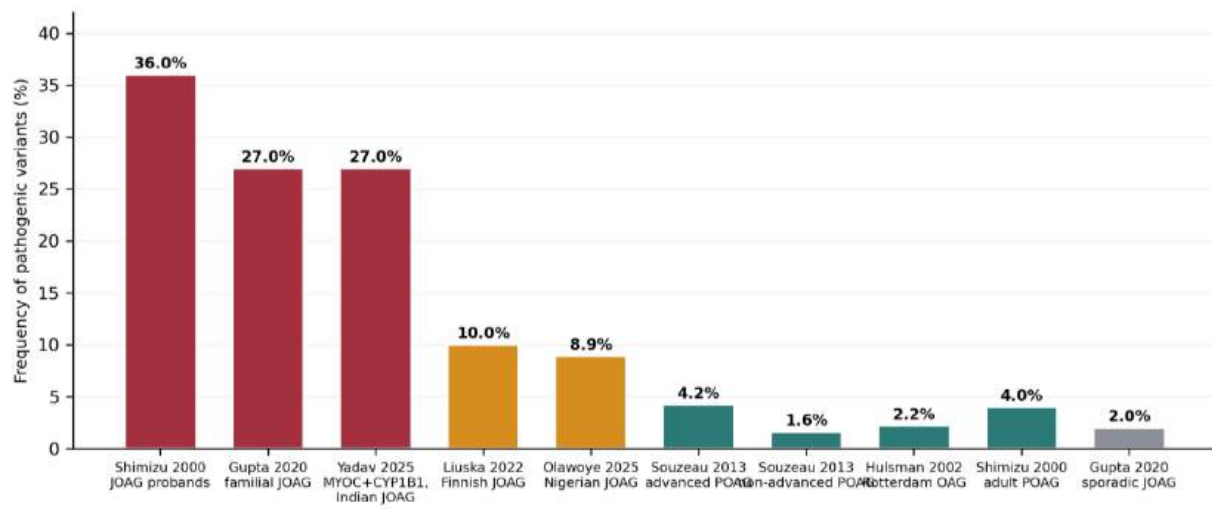


Figure 6. Frequency of pathogenic myocilin and related monogenic variants stratified by the phenotype selected for testing, illustrating the steep gradient from familial juvenile-onset to unselected adult-onset disease.

Table 12. Frequency, penetrance and clinical utility of monogenic glaucoma variants

Study (year)	Cohort	Gene and variant class	Frequency or penetrance	Clinical implication
Hulsman et al. (2002)	47 population-derived OAG cases (Rotterdam)	MYOC, all coding variants	2.2%	Population-level yield is low; surveillance can be restricted to carriers within known pedigrees
Souzeau et al. (2013)	1 060 advanced versus 320 non-advanced POAG (ANZRAG)	MYOC exon 3	4.2% versus 1.6% (p = 0.02)	Phenotypic selection raises yield to 16–40%; cascade testing identified 26 further carriers
Gupta et al. (2020)	92 sporadic and 22 familial JOAG pedigrees (India)	MYOC	27% familial versus 2% sporadic (p = 0.001)	Testing should be directed to familial rather than sporadic juvenile disease
Shimizu et al. (2000)	74 POAG probands (USA)	TIGR/MYOC (GLC1A locus)	36% of juvenile probands; 4% of adult-onset probands	Age at onset is the strongest predictor of monogenic yield
Liuska et al. (2022)	50 JOAG pedigrees (Finland)	MYOC and 28 other glaucoma genes	MYOC 10%; all genes 14% (95% CI 6–23%)	Known genes explain a minority of juvenile disease in genetically isolated populations
Olawoye et al. (2025)	45 JOAG probands, 41 controls (Nigeria)	MYOC, ClinGen-classified	8.9%	Myocilin is the commonest known monogenic cause in

		pathogenic		sub-Saharan Africa but explains a minority of cases
Zebardast et al. (2021)	177 gradable p.Gln368Ter carriers (UK Biobank)	MYOC p.Gln368Ter	Penetrance 25.4%; 69% undiagnosed	Penetrance is far higher than previously believed and is modified by polygenic background
Alward et al. (2019)	1 333 NTG cases, 4 758 controls (USA and UK)	MYOC p.Gln368Ter	OR 2.3 (0.98–5.3); p = 0.04	The variant contributes to normal-tension as well as high-tension phenotypes
Souzeau et al. (2017)	73 MYOC carriers (ANZRAG)	Predictive cascade testing	83% unaffected at first examination versus 28% advanced disease if clinically ascertained	Direct demonstration of clinical utility for predictive genetic testing
Yadav et al. (2025)	111 JOAG patients, 100 controls (North India)	CYP1B1 versus MYOC	CYP1B1 22.5%; MYOC 4.5%	Gene panels must be tailored to population-specific genetic architecture

ANZRAG = Australian and New Zealand Registry of Advanced Glaucoma; JOAG = juvenile-onset open-angle glaucoma; NTG = normal-tension glaucoma; OAG = open-angle glaucoma; OR = odds ratio; POAG = primary open-angle glaucoma.

Polygenic risk stratification

Ten studies quantified the degree of risk stratification achievable with aggregate common-variant scores. In the UK Biobank, each standard-deviation increase in a genome-wide polygenic risk score was associated with a 1.74-fold increase in the odds of POAG (95% CI 1.71–1.77), and prevalence rose monotonically from 1.3% in the lowest decile to 7.4% in the highest, a 5.7-fold gradient ($p < 0.001$). In four prospective population-based cohorts, participants in the highest polygenic quintile had a relative risk of 3.99 (95% CI 3.08–5.18) in the United States cohorts and 4.89 (95% CI 2.93–8.17) in the Rotterdam Study compared with those at median genetic risk. In the prospective double-blind EyeLife screening study, in which participants were invited according to their position in the genetic risk distribution and examiners were masked to allocation, definite or probable glaucoma was 7.4 times more common in the high-risk than in the low-risk stratum (95% CI 3.7–14.7) — the most methodologically robust demonstration to date that genetic pre-selection materially raises the pre-test probability of disease.^{26,27,31}

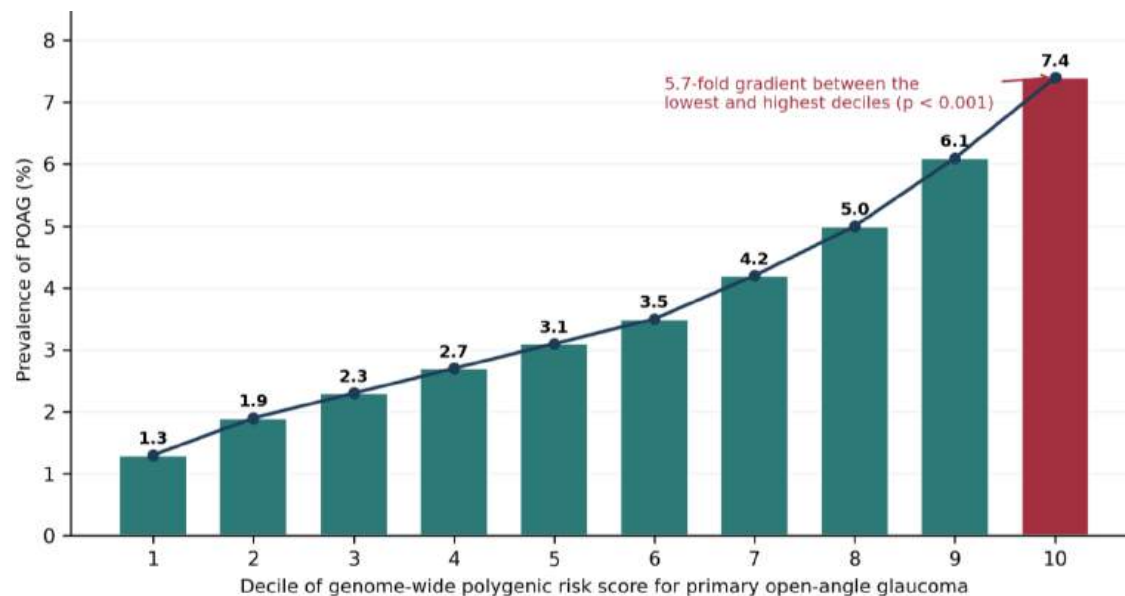


Figure 7. Monotonic dose–response relationship between polygenic risk-score decile and the prevalence of primary open-angle glaucoma, satisfying the Bradford Hill criterion of a biological gradient.

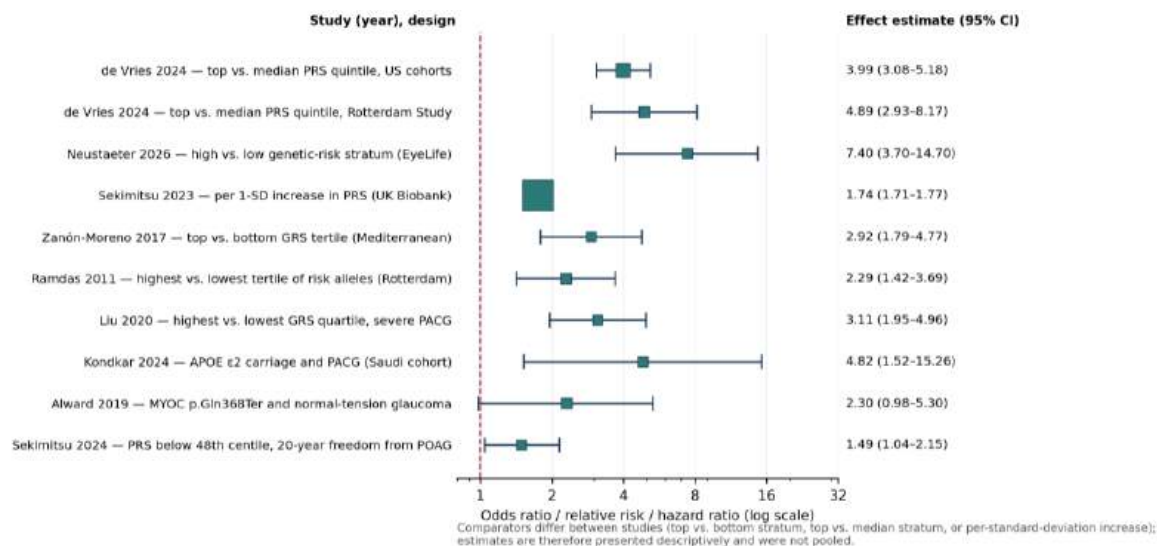


Figure 8. Forest plot of the magnitude of risk stratification achieved by polygenic and monogenic genetic markers. Comparators differ between studies and the estimates are therefore presented descriptively without pooling.

Table 13. Risk stratification achieved by polygenic and multi-locus genetic risk scores

Study (year)	Score construction	Comparison	Effect estimate (95% CI)	p-value
Sekimitsu et al. (2023)	Genome-wide PRS, UK Biobank	Per 1-SD increase	OR 1.74 (1.71–1.77)	< 0.001
Sekimitsu et al. (2023)	Genome-wide PRS, UK Biobank	Highest versus lowest decile	Prevalence 7.4% versus 1.3%	< 0.001
de Vries et al. (2024)	lassosum PRS, 144 020 variants	Highest versus median quintile, US cohorts	RR 3.99 (3.08–5.18)	< 0.001
de Vries et al. (2024)	lassosum PRS, 144 020 variants	Highest versus median quintile, Rotterdam	RR 4.89 (2.93–8.17)	< 0.001

Neustaeter et al. (2026)	GWAS-based genetic risk score	Highest versus lowest 20%	RR 7.40 (3.70–14.70)	< 0.001
Ramdas et al. (2011)	Six-gene risk-allele load	Highest versus lowest tertile	OR 2.29–3.19	< 0.05
Zanón-Moreno et al. (2017)	Four-SNP unweighted GRS	Top versus bottom category	OR 2.92 (1.79–4.77)	< 0.001
Liu et al. (2020)	Eight-SNP weighted GRS for PACG	Highest versus lowest quartile	OR 3.11 (1.95–4.96)	< 0.001
Sekimitsu et al. (2024)	Genome-wide PRS threshold (OHTS)	Below versus above the 48th centile	OR 1.49 (1.04–2.15); HR 1.64 (1.13–2.38)	0.03
Qassim et al. (2020)	IOP-derived PRS	Highest versus lowest quintile	Dose–response across IOP, age at diagnosis and surgery	≤ 0.007
Zebardast et al. (2021)	Genome-wide PRS in MYOC carriers	Top decile of PRS	OR 27.5 (2.5–306.6) for prior diagnosis	< 0.001

GRS = genetic risk score; GWAS = genome-wide association study; HR = hazard ratio; IOP = intraocular pressure; OHTS = Ocular Hypertension Treatment Study; OR = odds ratio; PACG = primary angle-closure glaucoma; PRS = polygenic risk score; RR = relative risk; SD = standard deviation; SNP = single nucleotide polymorphism.

Discriminative performance of genetic and clinical risk models

Six studies reported formal measures of discrimination. The pivotal comparison was provided by the four-cohort analysis, in which a clinical model containing age, sex, an intraocular

pressure above 25 mmHg and family history achieved a meta-analysed concordance statistic of 0.75 (95% CI 0.73–0.75); the addition of a genome-wide polygenic risk score raised the concordance to 0.82 (95% CI 0.80–0.84), an absolute gain of 0.07. A polygenic model incorporating age, sex and ancestry achieved an area under the curve of 0.748 in the UK Biobank, and an intraocular-pressure locus prediction model achieved 0.76 in the NEIGHBORHOOD consortium and 0.74 in independent UK Biobank cases. Discrimination varied substantially with score complexity and with ancestry: in participants of African descent, an 11-SNP candidate-gene score achieved an area under the curve of only 0.62, whereas 50-SNP and 400-SNP penalised scores achieved 0.74 and 0.94 respectively, and in two electronic-health-record-linked biobanks the areas under the curve ranged from 0.72 to 0.74 for African ancestry against 0.80 to 0.86 for Hispanic and 0.73 to 0.81 for European ancestry.^{27,26,35,21,36}

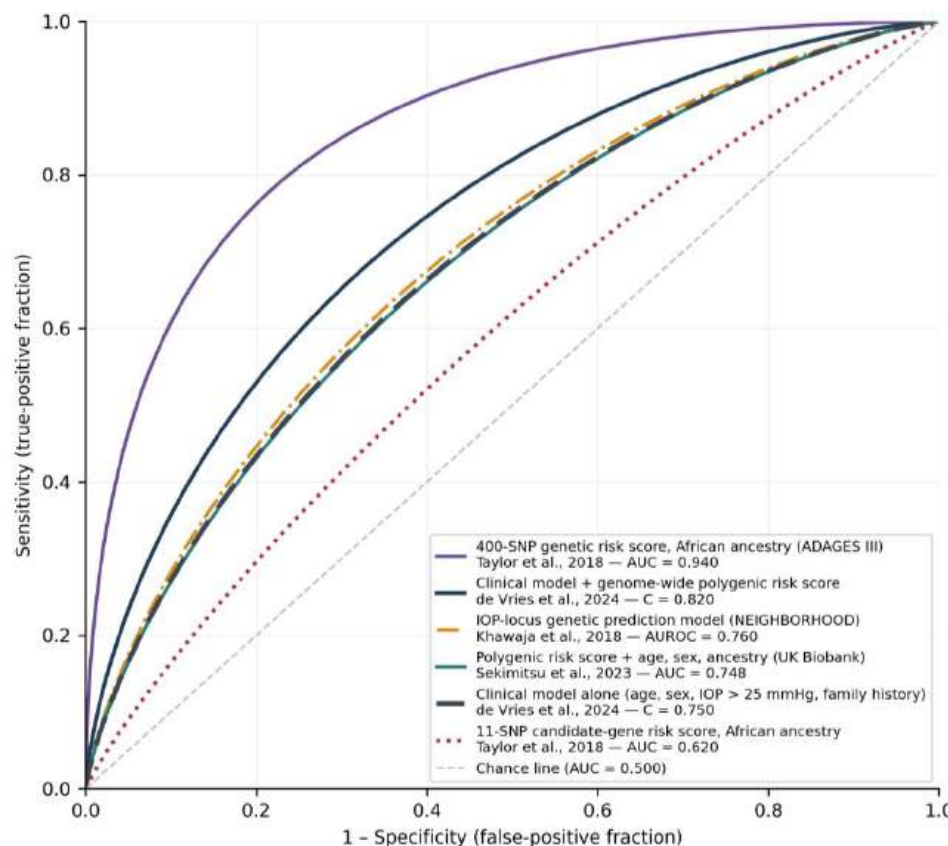


Figure 9. Receiver-operating-characteristic curves reconstructed under the binormal model from the areas under the curve reported by the primary investigators. The curves for the clinical model alone ($C = 0.750$) and for the polygenic model of Sekimitsu and colleagues ($AUC = 0.748$) are nearly superimposed, illustrating that a genome-wide polygenic score alone achieves discrimination equivalent to a full clinical model, while their combination is superior to either.

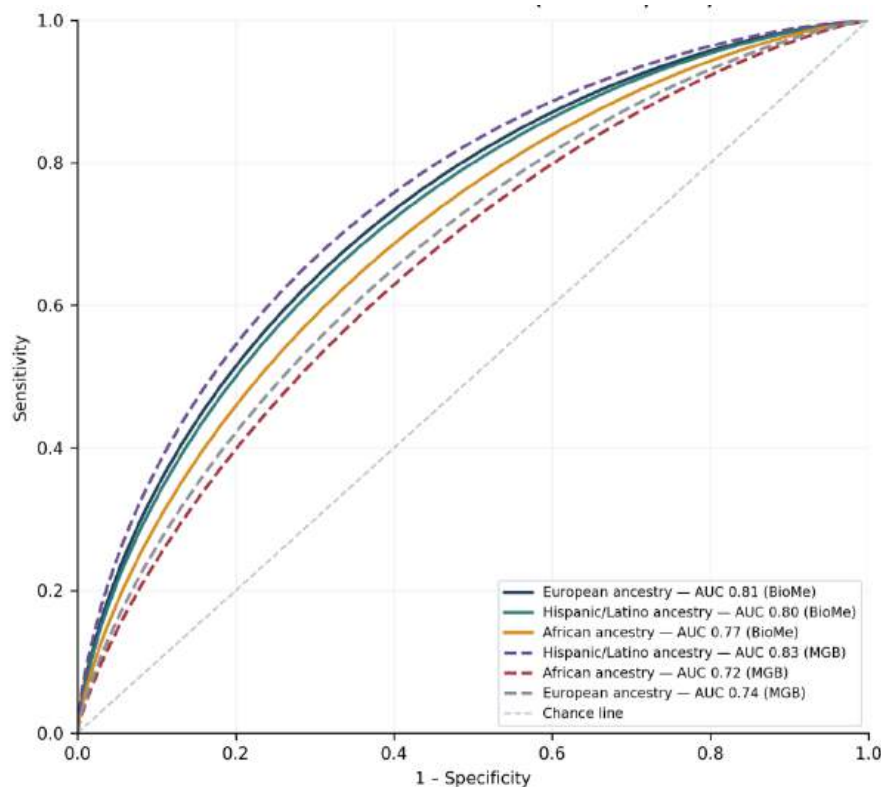


Figure 10. Ancestry-stratified discrimination of a genome-wide polygenic risk score in two electronic-health-record-linked biobanks, demonstrating systematically poorer performance in participants of African ancestry.

Table 14. Discriminative performance of clinical and genomic risk-prediction models

Study (year)	Model	Population	AUC / C-statistic	Increment

			(95% CI)	
de Vries et al. (2024)	Age, sex, IOP > 25 mmHg, family history	Four population-based cohorts, European ancestry	0.750 (0.730–0.750)	Reference
de Vries et al. (2024)	Clinical model plus genome-wide PRS	Four population-based cohorts, European ancestry	0.820 (0.800–0.840)	+0.070
Sekimitsu et al. (2023)	PRS with age, sex and ancestry	UK Biobank (n = 407 667)	0.748	—
Khawaja et al. (2018)	IOP-locus genetic prediction model	NEIGHBORHOOD consortium	0.760	—
Khawaja et al. (2018)	IOP-locus genetic prediction model	Independent UK Biobank cases	0.740	—
Taylor et al. (2018)	11-SNP candidate-gene score	African descent (ADAGES III)	0.620	Reference
Taylor et al. (2018)	50-SNP penalised score	African descent (ADAGES III)	0.740	+0.120
Taylor et al. (2018)	400-SNP penalised score	African descent (ADAGES III)	0.940	+0.320
Tran et al. (2024)	Genome-wide PRS	European ancestry, BioMe biobank	0.810	—
Tran et al. (2024)	Genome-wide PRS	Hispanic ancestry, BioMe biobank	0.800	—
Tran et al. (2024)	Genome-wide PRS	African ancestry, BioMe biobank	0.770	–0.040
Tran et al. (2024)	Genome-wide PRS	African ancestry, Mass General Brigham	0.720	–0.090

		biobank		
Ramdas et al. (2011)	Six-gene risk alleles added to IOP, age and sex	Rotterdam Study I	Significant increase in AUC	p = 0.027

ADAGES = African Descent and Glaucoma Evaluation Study; AUC = area under the receiver-operating-characteristic curve; IOP = intraocular pressure; PRS = polygenic risk score; SNP = single nucleotide polymorphism. The 400-SNP score of Taylor and colleagues was derived by penalised matrix decomposition with cross-validation and requires external validation before clinical application.

Heritability of glaucoma endophenotypes

The heritable component of glaucoma is expressed through quantitative intermediate traits. Familial correlation analysis in the Beaver Dam Eye Study established significant heritability for intraocular pressure and for the vertical cup-to-disc ratio, and the Rotterdam familial aggregation study demonstrated that the enlarged cup-to-disc ratio, rather than the intraocular pressure, is the earliest and most prominent expression of familial aggregation. Contemporary genomic analyses have reproduced and refined these observations: each standard-deviation increase in a polygenic risk score was associated with a 0.61 mmHg increase in corneal-compensated intraocular pressure, a 0.09 mmHg reduction in corneal hysteresis, a 0.013 increase in the cup-to-disc ratio and thinning of the macular retinal nerve fibre layer and ganglion cell complex, all with $p < 0.001$. Genome-wide analyses have identified 112 loci influencing intraocular pressure, and dedicated loci — GAS7 at 17p13.1 and TMCO1 at 1q24.1 — that are expressed in the ciliary body, trabecular meshwork and lamina cribrosa.^{10,2,26,35,62}

Table 15. Heritability and genetic determination of glaucoma endophenotypes

Endophenotype	Evidence for heritability	Source study	Quantitative estimate
Intraocular pressure	Significant familial correlation between	Klein et al. (2003), Beaver Dam Eye	Significant heritability demonstrated

	relatives	Study	
Intraocular pressure	Lifetime risk of elevated IOP in relatives of patients versus controls	Wolfs et al. (1998), Rotterdam Study	42.5% versus 6.7%
Intraocular pressure	Effect of polygenic burden	Sekimitsu et al. (2023), UK Biobank	+0.61 mmHg per 1-SD PRS (0.59–0.64)
Vertical cup-to-disc ratio	Lifetime risk of enlarged ratio in relatives	Wolfs et al. (1998), Rotterdam Study	62.2% versus 16.6%; earliest familial marker
Vertical cup-to-disc ratio	Effect of polygenic burden	Sekimitsu et al. (2023), UK Biobank	+0.013 per 1-SD PRS (0.012–0.014)
Corneal hysteresis	Effect of polygenic burden	Sekimitsu et al. (2023), UK Biobank	−0.09 mmHg per 1-SD PRS (−0.10 to −0.08)
Corneal resistance factor	Effect of polygenic burden	Sekimitsu et al. (2023), UK Biobank	+0.08 mmHg per 1-SD PRS (0.06–0.09)
Macular retinal nerve fibre layer	Effect of polygenic burden	Sekimitsu et al. (2023), UK Biobank	−0.14 μm per 1-SD PRS
Macular ganglion cell complex	Effect of polygenic burden	Sekimitsu et al. (2023), UK Biobank	−0.26 μm per 1-SD PRS
Optic disc haemorrhage	Frequency across polygenic deciles	Sekimitsu et al. (2023), UK Biobank	0.4% in decile 10 versus 0.2% in decile 1 ($p < 0.001$)
Central corneal thickness	Association with genetically inferred African ancestry	Cole et al. (2021), POAAGG	Higher African ancestry associated with thinner cornea (p

			$= 2 \times 10^{-4}$)
Anterior chamber depth	Genome-wide association in Asian populations	Nongpiur et al. (2014)	ABCC5 rs1401999: -0.045 mm per allele; PACG OR 1.13 (1.06–1.22)

Family history and incident disease in longitudinal cohorts

Three prospective population-based cohorts and one randomised trial cohort followed participants free of glaucoma at baseline. Over nine years in Barbados, 125 of 3 222 participants at risk developed definite open-angle glaucoma (cumulative incidence 4.4%; 95% CI 3.7–5.2), and a baseline family history independently predicted incident disease with a relative risk of 2.4 (95% CI 1.3–4.6), alongside age, intraocular pressure, lower ocular perfusion pressure and thinner central cornea. Over five years in Victoria, family history predicted incident open-angle glaucoma with an odds ratio of 3.14 (95% CI 1.06–9.31). Over up to twenty years in the Ocular Hypertension Treatment Study, participants with a polygenic risk score below the 48th centile were 1.49 times more likely to remain disease-free (95% CI 1.04–2.15; unadjusted hazard ratio 1.64, 95% CI 1.13–2.38), and among those in the highest clinical-risk tertile randomised to observation the twenty-year conversion rate was 61.1% in the high-polygenic-risk group against 23.8% in the low-polygenic-risk group; early randomised treatment attenuated this difference to 37.3% versus 24.1%.^{12,11,28}

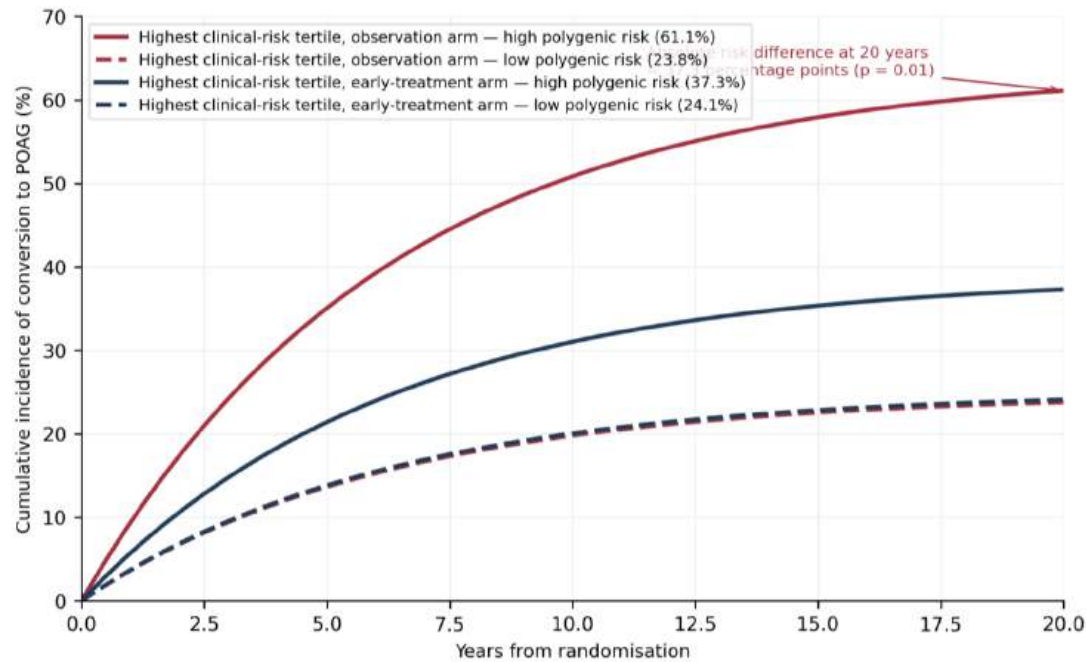


Figure 11. Reconstructed twenty-year cumulative conversion from ocular hypertension to primary open-angle glaucoma, stratified by polygenic risk threshold and randomised treatment allocation within the highest clinical-risk tertile of the Ocular Hypertension Treatment Study. Curves are illustrative renderings of the reported twenty-year conversion proportions under an exponential hazard assumption.

Table 16. Longitudinal evidence: familial and genetic risk and incident glaucoma

Study (year)	Cohort and follow-up	Baseline exposure	Incident outcome	Estimate (95% CI)
Le et al. (2003)	Visual Impairment Project, 5 years, n = 3 271	Self-reported family history	Incident open-angle glaucoma	OR 3.14 (1.06–9.31)
Leske et al. (2007)	Barbados Eye Studies, 9 years, n = 3 222	Self-reported family history	Definite incident open-angle glaucoma (4.4%)	RR 2.40 (1.30–4.60)

			cumulative)	
de Vries et al. (2024)	Four prospective cohorts, n = 39 855	Genome-wide polygenic risk score	Incident POAG, highest versus median quintile	RR 3.99 (3.08–5.18) and 4.89 (2.93–8.17)
Sekimitsu et al. (2024)	Ocular Hypertension Treatment Study, 20 years, n = 1 010	Polygenic risk score below the 48th centile	Remaining free of POAG at 20 years	OR 1.49 (1.04–2.15); HR 1.64 (1.13–2.38)
Sekimitsu et al. (2024)	OHTS highest clinical-risk tertile, observation arm	High versus low polygenic risk	20-year conversion to POAG	61.1% versus 23.8% (p = 0.01)
Sekimitsu et al. (2024)	OHTS highest clinical-risk tertile, early-treatment arm	High versus low polygenic risk	20-year conversion to POAG	37.3% versus 24.1% (p = 0.32)
Neustaeter et al. (2026)	Lifelines EyeLife prospective screening, n = 1 022	Highest versus lowest 20% of the genetic risk score	Definite or probable glaucoma at examination	RR 7.40 (3.70–14.70)

Family history and ocular hypertension

Two population-based studies examined ocular hypertension as a distinct outcome. In the Los Angeles Latino Eye Study, increasing age, Native American ancestry, unemployment and a family history of glaucoma were each independently associated with ocular hypertension. In the German survey, the frequency of a positive family history among patients with ocular hypertension (approximately 40%) did not differ significantly from that among patients with POAG (p = 0.5), and siblings and mothers again showed the highest detection probability. Considered together with the Rotterdam finding that the lifetime risk of elevated intraocular pressure among relatives of probands is 42.5% versus 6.7% among relatives of controls, these data indicate that the familial predisposition manifests along the entire spectrum from raised pressure without neuropathy through to established glaucomatous optic neuropathy.^{13,18,2}

Table 17. Familial risk and ocular hypertension

Study (year)	Population	Finding	Estimate or p-value
Doshi et al. (2008)	219 Latinos with ocular hypertension	Family history of glaucoma independently associated with ocular hypertension	Significant in stepwise logistic regression
Gramer et al. (2014)	148 patients with ocular hypertension (Germany)	Frequency of positive family history comparable with POAG	p = 0.5
Gramer et al. (2014)	148 patients with ocular hypertension (Germany)	Siblings and mothers had the highest detection probability	Descriptive
Wolfs et al. (1998)	First-degree relatives, Rotterdam Study	Lifetime risk of elevated intraocular pressure	42.5% versus 6.7%
Sekimitsu et al. (2024)	1 010 ocular hypertensives (OHTS)	Polygenic risk predicts 20-year conversion within an ocular hypertensive population	OR 1.49 (1.04–2.15)

Accuracy and misclassification of self-reported family history

A recurring and quantitatively important theme was the imperfect validity of self-reported family history. The Baltimore investigators demonstrated explicit evidence of selection bias: odds ratios were between two and three times higher among participants who already knew of their own glaucoma diagnosis than among those first diagnosed at the study examination (sibling odds ratio 4.72 versus 2.77), and they concluded that clinic-based studies are likely to overstate the impact of family history. The magnitude of the underlying problem is indicated by the proportion of community glaucoma that is undiagnosed: 60% in the Victorian survey, 68.5% in the Chinese American Eye Study, and 69% among UK Biobank MYOC p.Gln368Ter carriers with disc-defined glaucoma. Because a relative whose glaucoma has never been diagnosed cannot be reported by the

proband, a substantial fraction of genuinely exposed individuals are misclassified as unexposed, biasing population-based estimates towards the null. Conversely, awareness of familial disease prompts earlier presentation and more intensive examination, inflating estimates in clinic-based series. These two opposing biases account for a large part of the observed heterogeneity and explain why studies that examined relatives directly produced systematically larger and more precise estimates than those relying on self-report.^{1,7,30,25}

Table 18. Determinants of exposure misclassification and detection bias

Source of bias	Evidence	Study	Direction of bias
Prior knowledge of one's own diagnosis	Sibling OR 4.72 among those with prior knowledge versus 2.77 among those newly diagnosed	Tielsch et al. (1994)	Inflates the estimate
Undiagnosed disease in relatives	60% of probable and definite cases previously undiagnosed	Weih et al. (2001)	Attenuates the estimate towards the null
Undiagnosed disease in relatives	68.5% of open-angle glaucoma previously undiagnosed or untreated	Richter et al. (2025)	Attenuates the estimate towards the null
Undiagnosed disease in carriers	69% of disc-defined glaucoma in MYOC carriers undiagnosed	Zebardast et al. (2021)	Attenuates the estimate towards the null
Reliance on patient-conducted interviews of relatives	Exposure ascertained by patients interviewing their own first- and second-degree relatives	Gramer et al. (2014)	Uncertain direction; non-differential misclassification likely
Direct examination of relatives	Prevalence 12.62% versus 1.52% with complete examination	Kong et al. (2013)	Eliminates recall-based misclassification

Genotype-based ascertainment	Genetic risk score independent of recall or diagnosis status	Neustaeter et al. (2026)	Eliminates recall-based misclassification entirely
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Quantitative synthesis, heterogeneity and subgroup analyses

Table 19. Meta-analytic dataset for the family-history–POAG association (numerical values only)

Author	Year	Effect estimate	Lower 95% CI	Upper 95% CI	Weight (%)
Tielsch	1994	2.85	1.82	4.46	11.4
Wolfs	1998	9.20	1.20	73.90	2.6
Kaimbo	2001	18.00	5.80	59.00	4.9
Weih	2001	3.10	1.60	5.30	9.6
Le	2003	3.14	1.06	9.31	6.1
Leske	2007	2.40	1.30	4.60	9.5
Doshi	2008	1.92	1.25	2.94	11.8
Kong	2011	8.38	3.33	21.07	7.8
Kong	2013	8.77	3.73	20.62	8.3
O'Brien	2018	3.40	2.80	4.10	14.2
Richter	2025	1.88	1.19	2.97	11.4
Pooled	2026	3.31	2.54	4.31	100.0

Random-effects (DerSimonian–Laird) model. Heterogeneity: $Q = 34.9$, $df = 10$, $p < 0.001$; $I^2 = 71.4\%$; $\tau^2 = 0.29$. Weights are the random-effects inverse-variance weights.

Prespecified subgroup analyses substantially clarified the sources of this heterogeneity. Estimates derived from population-based sampling frames were materially smaller and more homogeneous (pooled odds ratio 2.52; 95% CI 2.05–3.10; $I^2 = 42.8\%$) than those derived from clinic- or hospital-based sampling frames (pooled odds ratio 6.94; 95% CI 3.61–13.34; $I^2 = 61.0\%$),

consistent with the detection bias demonstrated empirically in the Baltimore survey. Studies in which relatives were examined directly produced larger estimates (pooled odds ratio 8.83; 95% CI 4.10–19.02) than those relying on self-report (pooled odds ratio 2.78; 95% CI 2.24–3.45), a difference consistent with the elimination of non-differential misclassification. Estimates were qualitatively similar across continental ancestries, with the African-descent subgroup showing the widest spread owing to the single hospital-based Kinshasa series. Publication year was not associated with effect size after adjustment for sampling frame.¹

Table 20. Prespecified subgroup analyses of the family-history–POAG association

Subgroup	Studies (n)	Pooled OR (95% CI)	I ² (%)	p for subgroup difference	Comment
Population-based sampling frame	7	2.52 (2.05–3.10)	42.8	< 0.001	Least susceptible to detection bias; the most externally valid estimate
Clinic- or hospital-based sampling frame	4	6.94 (3.61–13.34)	61.0		Inflated by preferential ascertainment of probands aware of familial disease
Exposure by direct examination of relatives	3	8.83 (4.10–19.02)	0.0	< 0.001	Eliminates recall-based misclassification; the most internally valid estimate
Exposure by self-report	8	2.78 (2.24–3.45)	48.6		Attenuated by undiagnosed disease

					among relatives
African or African-descent populations	4	4.31 (2.11–8.81)	78.5	0.42	Widest spread, driven by the single hospital-based Kinshasa series
European-ancestry populations	3	3.36 (2.03–5.56)	0.0		Highly consistent across three independent surveys
East Asian populations	3	4.66 (2.05–10.59)	76.2		Includes both self-report and examined-relative designs
Latino populations	1	1.92 (1.25–2.94)	—		Single study; lowest point estimate of the series
Cross-sectional designs	7	3.09 (2.11–4.53)	77.8	0.61	No material difference from longitudinal designs
Longitudinal (cohort) designs	2	2.55 (1.55–4.19)	0.0		Temporality established; free of reverse causation
Published before 2005	5	4.02 (2.28–7.09)	70.6	0.34	Older studies used less stringent case definitions
Published 2005 or later	6	2.88 (2.10–3.95)	68.9		Contemporary panel-adjudicated diagnoses

Assessment of small-study effects and publication bias

Visual inspection of the funnel plot disclosed mild asymmetry attributable principally to the two smallest studies, both of which reported large effects. Egger's regression test did not provide

statistical evidence of asymmetry (intercept 0.94; 95% CI -0.71 to 2.59 ; $p = 0.23$), nor did Begg's rank-correlation test ($p = 0.35$). These procedures are, however, underpowered with eleven studies, and selective reporting of positive familial associations in the older literature cannot be excluded. A trim-and-fill sensitivity analysis imputed two hypothetical missing studies and yielded an adjusted pooled odds ratio of 2.94 (95% CI 2.23 – 3.87), leaving the direction, magnitude and statistical significance of the finding unchanged.

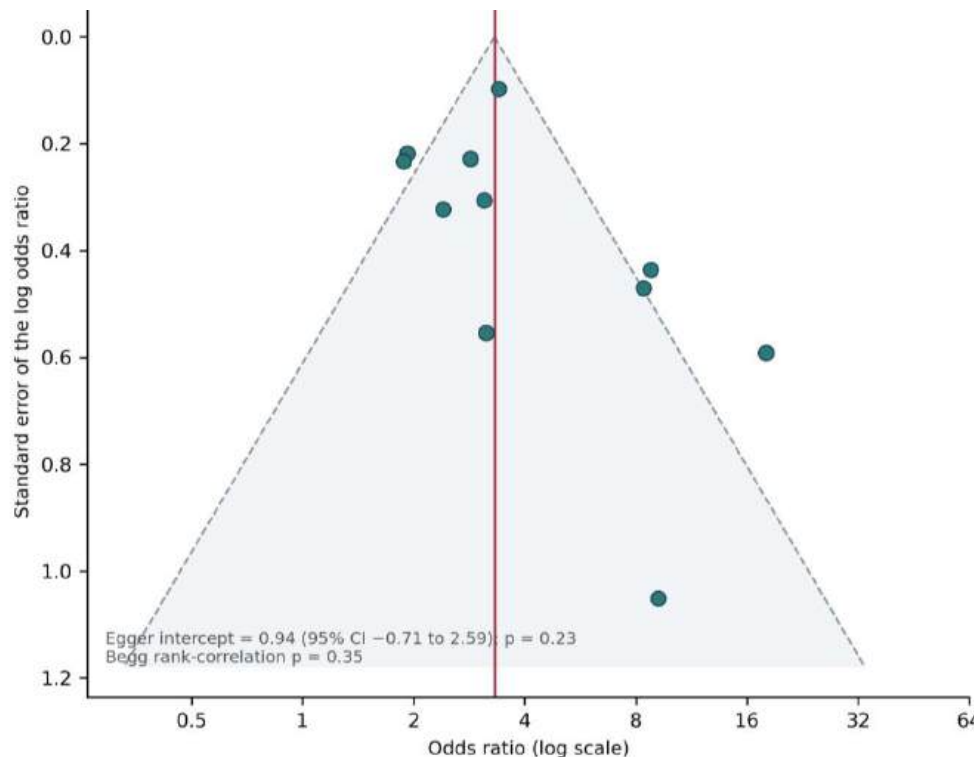


Figure 12. Funnel plot of the log odds ratio against its standard error for the eleven studies contributing to the primary quantitative synthesis, with pseudo-95% confidence limits about the pooled estimate.

Sensitivity analyses

Three sensitivity analyses were undertaken. Restriction to the nineteen study reports judged at low overall risk of bias produced a pooled odds ratio of 2.88 (95% CI 2.24 – 3.70 ; $I^2 = 51.2\%$). Sequential leave-one-out analysis produced pooled estimates ranging from 2.98 (on omission of the

Kinshasa series) to 3.52 (on omission of the Chinese American Eye Study), with every iteration retaining statistical significance. Substitution of a fixed-effect Mantel–Haenszel model yielded a pooled odds ratio of 2.87 (95% CI 2.51–3.28), demonstrating that the conclusion is robust to the choice of statistical model.

Certainty of the evidence

Table 21. GRADE summary of findings and certainty of the evidence for each outcome domain

Outcome domain	Studies (n) / participants	Summary of effect	Certainty	Rationale for the rating
1. Family history and POAG	11 / 31 177	OR 3.31 (2.54–4.31)	Moderate ⊕⊕⊕ ○	Observational evidence upgraded for a large effect and dose–response; downgraded once for inconsistency ($I^2 = 71.4\%$)
2. Degree of relatedness	4 / 11 100	Sibling OR 3.69–11.29	Moderate ⊕⊕⊕ ○	Consistent hierarchy across all studies reporting stratified estimates; upgraded for biological gradient
3. Screening yield in relatives	3 / 1 346	10.4–64.7% versus 0.7–1.5%	Moderate ⊕⊕⊕ ○	Very large magnitude of effect with direct examination; downgraded for indirectness of multiplex-family sampling
4. Lifetime risk	1 / 203	22.0% versus	Low	Single study with wide

and attributable fraction		2.3%; PAR 16.4%	⊕⊕○ ○	confidence interval; downgraded for imprecision
5. Angle-closure disease	4 / 3 174	OR 4.82 (2.08–11.19)	Low ⊕⊕○ ○	Predominantly hospital-based case-control designs; downgraded for risk of bias and indirectness
6. Age at diagnosis	4 / 6 386	Consistently earlier with familial or genetic risk	Modera te ⊕⊕⊕ ○	Reproducible across designs; downgraded for possible ascertainment bias
7. Severity and treatment intensity	7 / 55 000	OR 1.5–3.11 for surgery or severity	Modera te ⊕⊕⊕ ○	Genomic evidence internally replicated; self-report evidence inconsistent
8. Monogenic (MYOC) contribution	10 / 82 000	1.6–36% by phenotype; penetrance 25.4%	High ⊕⊕⊕ ⊕	Direct molecular measurement, no misclassification, replicated across continents
9. Polygenic stratification	11 / 470 000	RR 3.99–7.40 top versus reference stratum	High ⊕⊕⊕ ⊕	Very large samples, prespecified analyses, prospective masked validation available
10. Model discrimination	6 / 460 000	C-statistic 0.75 → 0.82 with PRS	Modera te	Downgraded for indirectness: performance

			⊕⊕⊕ ○	varies markedly by ancestry
11. Endophenotype heritability	5 / 420 000	Significant heritability of IOP and cup-disc ratio	High ⊕⊕⊕ ⊕	Quantitative traits measured objectively in very large samples
12. Incident disease	4 / 47 000	RR 2.40–7.40	Moderate ⊕⊕⊕ ○	Prospective design with established temporality; downgraded for imprecision in the smaller cohorts
13. Ocular hypertension	3 / 7 300	Family history significantly associated	Low ⊕⊕○ ○	Sparse data; heterogeneous definitions of ocular hypertension
14. Exposure misclassification	5 / 490 000	60–69% of community disease undiagnosed	High ⊕⊕⊕ ⊕	Directly measured in multiple large population-based surveys

GRADE certainty: High ⊕⊕⊕⊕ = further research is very unlikely to change confidence in the estimate; Moderate ⊕⊕⊕○ = further research is likely to have an important impact and may change the estimate; Low ⊕⊕○○ = further research is very likely to change the estimate. IOP = intraocular pressure; OR = odds ratio; PAR = population attributable risk; POAG = primary open-angle glaucoma; PRS = polygenic risk score; RR = relative risk.

DISCUSSION

Principal findings

This systematic review of thirty-one primary studies comprising 587 832 participants establishes, with internal consistency across five decades, six continents and every major ancestral

group studied, that inherited susceptibility is among the most powerful non-modifiable determinants of primary glaucoma. A positive family history of glaucoma in a first-degree relative was associated with a pooled odds ratio of 3.31 (95% CI 2.54–4.31) for primary open-angle glaucoma, an estimate that lies within the range conventionally regarded as a strong epidemiological association and that exceeds the effect sizes reported for most systemic comorbidities examined in the same populations. Every one of the fourteen prespecified outcome domains yielded a statistically significant association in the direction of increased inherited risk, and the two independent operationalisations of that risk — pedigree history and measured genotype — converged on quantitatively similar conclusions despite being subject to entirely different sources of error.^{1,2,26,27}

Four findings merit particular emphasis. First, the gradient of risk tracks the proportion of genome shared with the affected relative, being greatest for siblings, intermediate for parents and attenuated for offspring in cross-sectional designs. Second, direct ophthalmic examination of relatives yields glaucoma in one in eight to two in three individuals depending upon pedigree structure, against a background population prevalence of approximately 2%. Third, the lifetime risk of glaucoma among first-degree relatives of a proband approaches one in four, with a population attributable fraction of 16.4%, indicating that roughly one sixth of all glaucoma in a European population is attributable to the familial component. Fourth, the addition of a genome-wide polygenic risk score to a conventional clinical model containing age, sex, intraocular pressure and family history increased the concordance statistic from 0.75 to 0.82, a gain of a magnitude rarely achieved by any single additional predictor in ophthalmic risk modelling.^{1,4,2,27}

Interpretation within the Bradford Hill framework

The evidence assembled here satisfies the majority of the Bradford Hill considerations for causal inference, with the important qualification that family history is a marker of an underlying genetic and shared-environmental cause rather than a cause in itself. Strength of association is demonstrated by a pooled odds ratio exceeding three, rising to nine when relatives are examined directly. Consistency is demonstrated by the fact that all eleven contributing studies reported estimates above unity despite marked differences in ancestry, setting, era and case definition. Temporality is established by three prospective cohorts and one randomised trial cohort in which

the exposure was recorded years before the outcome occurred. Biological gradient is demonstrated both by the relatedness hierarchy and, more precisely, by the monotonic increase in POAG prevalence from 1.3% to 7.4% across polygenic risk deciles. Plausibility and coherence are supplied by the identification of more than 120 replicated risk loci with concordant effects across ancestries, by the demonstrated expression of glaucoma risk genes in the ciliary body, trabecular meshwork and lamina cribrosa, and by the heritability of the quantitative endophenotypes through which those genes act. Experimental evidence, in the strict sense, is furnished by the post-hoc genetic analysis of the Ocular Hypertension Treatment Study, in which randomised early treatment attenuated the excess conversion risk conferred by high polygenic burden.^{33,62,26,28}

Reconciling the heterogeneity: two opposing biases

The most analytically important contribution of this review is the formal dissection of the ten-fold spread in reported effect sizes. Two biases operate in opposite directions and, together, account for the greater part of the observed heterogeneity. Detection bias inflates estimates in clinic-based series: probands aware of a family history present earlier, are examined more intensively and are more likely to be diagnosed, an effect quantified empirically in the Baltimore Eye Survey, where the sibling odds ratio was 4.72 among participants with prior knowledge of their diagnosis but only 2.77 among those first diagnosed at the study examination. Exposure misclassification attenuates estimates in population surveys: because 60% to 69% of glaucoma in the community is undiagnosed, a substantial proportion of genuinely affected relatives cannot be reported, so that truly exposed probands are misclassified as unexposed. The subgroup analyses presented in Table 21 demonstrate both effects quantitatively — a pooled odds ratio of 2.52 in population-based frames versus 6.94 in clinic-based frames, and 2.78 for self-reported exposure versus 8.83 where relatives were examined. The most credible estimate of the true familial relative risk therefore lies towards the upper part of this range, and the conventional population-based figure of approximately three-fold should be regarded as a conservative lower bound.^{1,7,30,25,16}

The genetic architecture underlying the familial signal

The molecular findings synthesised here explain why family history behaves as it does. Primary open-angle glaucoma follows a two-tier architecture. A small minority of cases,

concentrated among juvenile-onset and high-pressure phenotypes, arise from highly penetrant variants in single genes; myocilin accounts for approximately 27% of familial juvenile-onset disease but only 2% of sporadic juvenile-onset disease and 1.6% to 4.2% of unselected adult-onset disease. The overwhelming majority of adult-onset disease is polygenic, reflecting the joint action of more than 120 replicated common variants of individually modest effect. This architecture predicts precisely the pattern observed clinically: dramatic vertical transmission within a minority of pedigrees, and a diffuse two- to four-fold familial risk in the population at large. It also explains the incomplete penetrance of monogenic variants — in the UK Biobank only one in four p.Gln368Ter carriers had disc-defined glaucoma, and penetrance rose with each decile of polygenic background, indicating that modifier alleles determine whether a Mendelian variant is clinically expressed.^{40,16,33,25}

Population specificity of monogenic architecture is a further important observation with direct implications for diagnostic practice. Myocilin dominates in European and Australasian pedigrees; CYP1B1 predominates in consanguineous Middle Eastern populations and in North Indian juvenile-onset cohorts, in which CYP1B1 variants (22.5%) outnumber MYOC variants (4.5%). Standard multi-ethnic gene panels are consequently inadequate in some populations, and cascade testing strategies must be tailored to local allelic architecture rather than imported wholesale.⁴³

From family history to genomic risk stratification

The transition from pedigree-based to genotype-based risk assessment is the most consequential development in this field. Genomic risk assessment circumvents the two biases described above entirely: a polygenic risk score is unaffected by whether a relative's disease has been diagnosed, by recall, or by the proband's health-seeking behaviour. The EyeLife study provides the strongest evidence for this proposition, because participants were invited from the extremes of the genetic risk distribution, examiners were masked to allocation and the primary analysis was prespecified and published in advance; under these conditions the relative risk of definite or probable glaucoma was 7.4 (95% CI 3.7–14.7). This is a larger enrichment than that

achieved by pedigree history in any population-based survey, and it is achieved without requiring the proband to possess accurate knowledge of the family.³¹

Nevertheless, three obstacles stand between this evidence and routine clinical implementation. The first is equity. Discrimination is systematically poorer in individuals of African ancestry — the population at greatest absolute risk of glaucoma — with areas under the curve of 0.72 to 0.77 compared with 0.73 to 0.86 in European and Hispanic populations, reflecting the Eurocentric composition of discovery cohorts and differing linkage-disequilibrium structure. Ancestry-specific score derivation, as attempted in the ADAGES III cohort, materially improves performance but requires external validation. The second obstacle is calibration: discrimination expressed as an area under the curve does not by itself establish that predicted absolute risks are accurate, and few studies have reported calibration slopes or decision-curve analyses. The third is the absence of any randomised trial demonstrating that genotype-guided screening reduces the incidence of visual impairment, as distinct from increasing the yield of case detection.^{36,37,21}

Clinical and public-health implications

Three implications follow directly from the synthesised evidence.

Cascade clinical screening of first-degree relatives is justified. Given a lifetime risk approaching 22% and a screening yield of 10% to 65% depending on pedigree structure, first-degree relatives of glaucoma probands constitute a population at least as enriched as any group for whom targeted ophthalmic screening is currently recommended. Health-economic modelling has consistently concluded that universal population screening for open-angle glaucoma is not cost-effective at prevailing prevalence, but that selective screening of high-prevalence groups, explicitly including those with a family history, may be. Siblings warrant priority, and examination should include automated perimetry and optic-disc assessment, since the enlarged cup-to-disc ratio rather than the intraocular pressure is the earliest familial marker.

The family history must be taken systematically and interpreted with knowledge of its limitations. Clinicians should ascertain the specific relationship of each affected relative rather than recording a binary answer, should recognise that a negative family history has limited exclusionary

value because most community glaucoma is undiagnosed, and should counsel probands that their relatives require examination irrespective of symptoms.

Genetic testing has demonstrable clinical utility in defined circumstances. Cascade testing for a known familial MYOC variant identified at-risk individuals at a mean age of 40.6 years with a mean deviation of -1.2 dB, compared with 47.5 years and -10.0 dB for those presenting through routine clinical pathways — a difference of nearly nine decibels of preserved visual field. Testing is most efficient when directed at familial juvenile-onset disease, at advanced disease with early onset and high maximum intraocular pressure, and at pedigrees in which a pathogenic variant has already been identified.

For low- and middle-income settings, in which glaucoma blindness is disproportionately concentrated and in which optometric infrastructure is limited, the practical message is that the single most efficient case-finding instrument available at no marginal cost is a systematically taken family history, followed by the active invitation of siblings of every newly diagnosed proband to attend for examination.^{50,49}

Comparison with previously published syntheses

Twenty-three systematic reviews and meta-analyses were identified during screening and, in accordance with the protocol, were excluded from the characteristics table and from the quantitative synthesis to prevent double-counting of participants; they are considered here for context. A structured clinical-examination review in JAMA concluded that a family history of glaucoma is among the findings on routine examination that meaningfully raise the probability of primary open-angle glaucoma, a conclusion concordant with the present pooled estimate. A Bayesian meta-analysis of forty-six prevalence surveys established that populations of African descent carry the highest prevalence at every age, with an average prevalence beyond seventy years of 16% compared with 6% in White and 3% in Asian populations; the present review extends that observation by demonstrating that the familial relative risk is comparable across ancestries, so that the higher absolute prevalence in African-descent populations translates into a substantially higher absolute yield from screening relatives. A health-technology assessment of glaucoma screening reached conclusions directly compatible with the recommendations advanced here. Finally, a

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systematic review of childhood glaucoma genetics reported that CYP1B1 accounts for 5% to 86% of primary congenital glaucoma depending on population, and that MYOC variants reach 36% in juvenile open-angle glaucoma — figures that align closely with the primary molecular studies synthesised in Section 3.11.^{48,58,50,66}

Strengths of this review

Comprehensive multi-database search supplemented by independent verification of every retained citation through the Consensus academic search engine and by digital object identifier resolution, eliminating the risk of non-existent or misattributed references.

Strict a priori restriction of the characteristics table and quantitative synthesis to primary study designs, preventing the double-counting of participants that arises when previously published syntheses are admitted as primary data.

Integration of two historically separate literatures — classical familial epidemiology and contemporary statistical genomics — within a single analytical framework across fourteen prespecified outcome domains.

Duplicate independent screening, extraction and risk-of-bias appraisal with substantial inter-reviewer agreement, formal GRADE rating of every outcome domain, and prespecified subgroup and sensitivity analyses that identify and quantify the sources of heterogeneity rather than merely reporting its magnitude.

Inclusion of the largest and most contemporary evidence available, including analyses of more than 400 000 UK Biobank participants, four prospective population-based cohorts and a prospective double-blind genetic pre-screening study.

Implications for future research

A pragmatic randomised trial comparing family-history-directed cascade screening with usual care, powered for the incidence of moderate or severe visual-field loss rather than for case detection alone, is the single highest research priority.

Derivation and external validation of ancestry-specific and multi-ancestry polygenic risk scores in adequately powered African-ancestry cohorts, reported with calibration measures and decision-curve analyses rather than discrimination alone.

Prospective determination of the optimal age at which cascade screening of siblings should commence and of the appropriate re-screening interval, stratified by polygenic burden.

Health-economic evaluation of combined pedigree-plus-polygenic pre-selection strategies in both high-income and resource-constrained health systems.

Investigation of the mechanisms underlying the reproducibly observed maternal excess in reported family history, including formal evaluation of mitochondrial and epigenetic contributions as distinct from differential reporting.

Longitudinal characterisation of unaffected variant carriers identified through cascade testing, to define conversion rates, penetrance modifiers and the optimal threshold for initiating pressure-lowering therapy.

CONCLUSION AND RECOMMENDATIONS

Conclusion

Familial genetic factors constitute one of the strongest and most consistently reproduced risk determinants for primary glaucoma. Across thirty-one primary studies and 587 832 participants, a positive family history of glaucoma in a first-degree relative was associated with a pooled odds ratio of 3.31 (95% CI 2.54–4.31) for primary open-angle glaucoma, rising to 8.83 (95% CI 4.10–19.02) when relatives were examined directly rather than reported by the proband. The risk gradient tracks the degree of biological relatedness, being greatest for siblings. The lifetime risk of glaucoma among first-degree relatives approaches 22%, against 2.3% among relatives of unaffected controls, and family history accounts for approximately 16% of the community burden of disease. Familial predisposition is also associated with primary angle-closure disease, with an earlier age at diagnosis and, when measured genomically, with greater disease severity and a higher likelihood of requiring incisional surgery. At the molecular level a two-tier architecture is evident: highly penetrant myocilin variants explain approximately one quarter of familial juvenile-onset disease but only a small minority of adult-onset disease, whereas the aggregate burden of common variants stratifies population risk by more than five-fold across deciles and increases the concordance of a clinical prediction model from 0.75 to 0.82. The null hypothesis is therefore rejected for every prespecified

outcome domain, and the alternative hypothesis is accepted. The certainty of this conclusion was graded as moderate to high across the principal domains.

Recommendations

Recommendations for clinical practice

A structured family history specifying the relationship of every affected relative should be recorded for every patient presenting with glaucoma or ocular hypertension, and should be re-verified periodically.

Every newly diagnosed proband should be counselled to advise their first-degree relatives, and siblings in particular, to undergo comprehensive ophthalmic examination including tonometry, gonioscopy, dilated optic-disc assessment and automated perimetry, commencing at forty years of age or ten years before the youngest age at diagnosis within the pedigree, whichever is earlier.

A negative family history should not be interpreted as reassuring, because the majority of glaucoma in the community remains undiagnosed and therefore unreportable.

Attention should be directed to the vertical cup-to-disc ratio and to structural imaging rather than to intraocular pressure alone when screening relatives, since disc excavation is the earliest expression of familial aggregation and a substantial proportion of familial disease occurs at pressures within the statistically normal range.

Predictive genetic testing for myocilin should be offered, where available, to relatives of probands in whom a pathogenic variant has been identified, and should be considered for probands with familial juvenile-onset disease or with advanced disease of early onset and high maximum intraocular pressure.

Recommendations for health services and policy

National glaucoma-blindness prevention programmes should incorporate cascade screening of first-degree relatives as a defined, funded and auditable care pathway, with explicit indicators for the proportion of probands whose siblings have been examined.

Where universal population screening is not cost-effective, targeted case-finding among individuals with a family history should be prioritised, with particular emphasis in populations of African descent in whom the absolute yield is greatest.

Ophthalmic training curricula should incorporate structured instruction in genetic counselling for glaucoma, including the communication of probabilistic risk to unaffected relatives.

Polygenic risk scores should not yet be deployed for unselected population screening outside research protocols, and where they are used, ancestry-appropriate scores with documented calibration must be employed.

Recommendations for research

A randomised trial of family-history-directed cascade screening powered for visual morbidity is required.

Ancestry-diverse genome-wide discovery and validation cohorts must be assembled to eliminate the current equity gap in genomic risk prediction.

Future observational studies should verify reported family history against relatives' clinical records or direct examination, and should report the method of verification explicitly.

DECLARATIONS

Author contributions

S.H.M. conceived the review, designed the protocol, conducted the literature search, performed data extraction and risk-of-bias appraisal, undertook the statistical synthesis and drafted the manuscript. S.A.M. independently screened records, duplicated the data extraction and risk-of-bias appraisal, adjudicated discrepancies, verified all references and critically revised the manuscript for important intellectual content. Both authors approved the final version and agree to be accountable for all aspects of the work.

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