Heritability of glaucoma and glaucoma-related endophenotypes: Systematic review and meta-analysis protocol, 2017
PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Yes/No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Yes, included under the title: Heritability of glaucoma and glaucoma-related endophenotypes: Systematic review and meta-analysis protocol
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	No, this is a new protocol.
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes, this protocol is registered in PROSPERO, with a registration number: CRD42017064504.
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes; stated on the cover page.
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes, page 15.
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	No, this is a new protocol.
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Yes, page 15.

Sponsor	5b	Provide name for the review funder and/or sponsor	Yes, page 15.
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes, as stated on page 15.
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes, briefly stated from page 1 to 5.
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes. The study will address the following research questions: 1. How much of the variance in glaucoma and glaucoma-related endophenotypes is due to genetic factors? 2. What is the proportion of variance accounted for by additive genetic influences (A), common environment (C), and unique environment (E)? 3. Do heritability estimates vary between different populations and study designs? Page 6.
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes; it is explained under inclusion and exclusion criteria, page 7.
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes. To capture as much literature as possible, systematic search will be undertaken in MEDLINE (PubMed), EMBASE, Web of Science, and ScienceDirect. In addition, Google Scholar will be

			used as a supplementary search database. Only published and full text articles will be used. If additional information is required, authors of the original articles will be contacted by email. Stated on page 7.
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes. Search string and number of articles found from a preliminary PubMed search, is presented under table 1, page 9.
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes. Eligible articles will be exported to RefWorks citation management software and duplicates will be removed. Full text, as well as relevant data, of all selected papers will be retrieved. Details are presented on page 7.
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Yes. To minimize errors, abstract and full paper screening and data extraction will be conducted independently by two reviewers. We will present the process of search and study selection using PRISMA flow process chart. Briefly stated on page 10.
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators.	Yes. The data extraction for eligible articles will be archived in a database and in order to ensure all relevant data are collected per study, a standardized form will be utilized (Supplementary file_2). Briefly stated on page 10.

Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes. Heritability estimates for any type of glaucoma or endophenotypes related to pressure (intraocular pressure), angle (anterior chamber depth, anterior chamber volume, angle opening distance, angle recess area, trabecular iris space area or Bruch's membrane opening), disk morphology (cup area, cup diameter, disk area, disk diameter, rim area, vertical or horizontal cup-to-disk ratio), ganglion cell complex, retinal nerve fiber layer, or central corneal thickness will be considered. Page 7.
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes. Heritability estimation, commonly reported in %, is the outcome measurement that we will synthesize and report from several studies. Articles describing heritability results based on: 1. Family 2. Twin 3. Adoption, and 4. GWAS study designs will be included; described on page 6 and 7.
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis.	Yes. The methodological quality of selected articles will be assessed and rated using the National Health Institute Quality Assessment tool for Observational Cohort and Cross-Sectional Studies.

			Quality score of individual articles will be used in sub-group analysis for exploring the variation in heritability estimates. Page 6 and 11.
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	No. Presuming that heritability estimates are different between populations, heterogeneity between studies is expected; we didn't put an upper threshold for I^2-statistic. However, original studies conducted on any type of glaucoma and glaucoma-related endophenotypes and those which reported heritability outcome data, or that could be estimated from intraclass correlation or linear regression coefficient will be included for quantitative analysis. Possible heterogeneity in heritability estimates will be explored through conducting subgroup/sensitivity analyses. Papers that didn't estimate heritability or estimated heritability from only significant SNP/s or genetic loci will not be considered for quantitative analysis. Page 7 describes about this.
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of	Yes. Heritability estimates are different between populations, we will use a random effects model for meta-analyses. Pooled

		consistency (such as I^2, Kendall's τ)	heritability estimates, including 95% confidence intervals, and summary statistics for quantitative data will be described and presented in tables and figures. Quantitative assessment of heterogeneity in findings between studies and publication bias will be performed and reported. The heterogeneity of heritability estimation between articles will be reported using Cochrane's Q test and I^2-statistic. The presence of publication bias will be visualized with funnel plots, and statistically tested with an Egger's test. Page 10 and 11.
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes. For assessing the possible factors that might explain the variation in heritability, subgroup analysis will be performed based on; ethnicity, study design, data analysis method, number of variables controlled for confounding, mean-age, and methodological quality score. In addition, sensitivity analysis will be carried out by excluding the three most heterogenous articles per endophenotype. To explore the sensitivity of heritability estimates to mean-age and ethnicity, analyses will be conducted on a series of combinations

			of these variables. Page 11.
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes. If search result does not have sufficient studies per glaucoma or endophenotype, or if studies are not eligible for quantitative analysis, findings will be synthesized and narrated, and summary statistics for quantitative data will be described and presented in tables and figures. Page 7 and 11.
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes. The presence of any potential publication bias will be visualized with funnel plots, and any asymmetry of the funnel plots will be statistically tested with an Egger's test; described on page 10.
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes. Two independent reviewers, who will be blinded to each other, will assess the methodological quality of each study using the National Health Institute Quality Assessment tool for Observational Cohort and Cross-Sectional Studies, which contains 14-yes/no checklists. Quality assessment evaluation includes; whether the research question/objective is clearly stated; if inclusion/exclusion criteria is clearly specified and defined; whether method of data analysis and outcome measure was

	clearly defined; and if confounding variables were controlled for their impact on the dependent variable. Page 10 briefly describes about this issue.

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.