Evaluation of the Observational Associations and Shared Genetics Between Glaucoma With Depression and Anxiety

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Purpose. Glaucoma, a leading cause of blindness worldwide, is suspected to exhibit a notable association with psychological disturbances. This study aimed to investigate epidemiological associations and explore shared genetic architecture between glaucoma and mental traits, including depression and anxiety.

Methods. Multivariable logistic regression and Cox proportional hazards regression models were employed to investigate longitudinal associations based on UK Biobank. A stepwise approach was used to explore the shared genetic architecture. First, linkage disequilibrium score regression inferred global genetic correlations. Second, MiXeR analysis quantified the number of shared causal variants. Third, specific shared loci were detected through conditional/conjunctional false discovery rate (condFDR/conjFDR) analysis and characterized for biological insights. Finally, two-sample Mendelian randomization (MR) was conducted to investigate bidirectional causal associations.

Results. Glaucoma was significantly associated with elevated risks of hospitalized depression (hazard ratio [HR] = 1.54; 95% confidence interval [CI], 1.01–2.34) and anxiety (HR = 2.61; 95% CI, 1.70–4.01) compared to healthy controls. Despite the absence of global genetic correlations, MiXeR analysis revealed 300 variants shared between glaucoma and depression, and 500 variants shared between glaucoma and anxiety. Subsequent condFDR/conjFDR analysis discovered 906 single-nucleotide polymorphisms (SNPs) jointly associated with glaucoma and depression and two associated with glaucoma and anxiety. The MR analysis did not support robust causal associations but indicated the existence of pleiotropic genetic variants influencing both glaucoma and depression.

Conclusions. Our study enhances the existing epidemiological evidence and underscores the polygenic overlap between glaucoma and mental traits. This observation suggests a correlation shaped by pleiotropic genetic variants rather than being indicative of direct causal relationships.

Keywords: glaucoma, intraocular pressure, depression, anxiety, genetic overlap

Glaucoma is one of the most prevalent chronic eye diseases, progressively leading to blindness and significantly impacting overall quality of life.[1–3] In the United Kingdom, it ranks as the second most common cause of visual impairment, constituting 23% of all follow-up attendances to the UK hospital eye service.[4] As we previously demonstrated, the prevalence of depressive symptoms is higher in patients with glaucoma than in the general public.[5] Consequently, individuals with glaucoma may be particularly vulnerable to psychological disturbances, including depression and anxiety, the two most common forms of psychiatric consultations.[6] Given the general increase in their incidence, addressing the management of both glaucoma and depression or anxiety becomes crucial as a public health concern.

Recent epidemiological studies have reported potential associations between glaucoma and mental disorders.[6–10] However, most existing studies employed cross-sectional designs and did not comprehensively address essential confounders, including intraocular pressure (IOP).[11–13] Despite this, genetic correlations between glaucoma and mental disorders have not been previously reported. Investigating the relationships between glaucoma and mental disorders from a genetic standpoint can furnish biological evidence substantiating the connection between these conditions and offering valuable biological insights.

Like most complex conditions, glaucoma, depression, and anxiety each exhibit strong genetic etiologies. The heritability of glaucoma has been estimated to be up to 70% in Caucasian family-based studies,[14] indicating a prominent genetic component in its causation. Among individuals of European ancestry, the most prevalent type of glaucoma, primary open-angle glaucoma (POAG), has an estimated heritability of 81% in Caucasian families.[15] Irrespective of the glaucoma classification, it is well established that IOP, with a high heritability of up to 60% in twin studies, stands as one of the most critical risk factors for glaucoma.[16,17] On the other hand, with regard to depression and anxiety, the estimated heritabilities have ranged from 30% to 50% in twin and family studies conducted by the Psychiatric Genomics Consortium (PGC).[18,19] For these polygenic diseases, it is imperative to clarify whether there is a shared genetic etiology. Furthermore, identifying their genetic overlap at the individual locus level is essential to highlight putative genes and provide evidence for therapeutic targets.

The current study aims to characterize longitudinal associations and further elucidate the genetic underpinnings between glaucoma and comorbid depression and anxiety. Specifically, we conducted genome-wide association studies (GWASs) of glaucoma and IOP with phenotypes consistent with the epidemiological analysis, and we employed a stepwise approach to characterize the potential shared genetic architecture using established techniques. First, we applied linkage disequilibrium score regression (LDSR)[20,21] to calculate the overall genetic correlation. Second, we utilized MiXeR to infer the shared polygenic architecture, considering both concordant and opposite effect directions.[22,23] Third, we employed the conditional false discovery rate/conjunctional false discovery rate (condFDR/conjFDR) method to detect specific shared single-nucleotide polymorphisms (SNPs).[24–27] Finally, two-sample Mendelian randomization (MR)[28] analysis was utilized to test

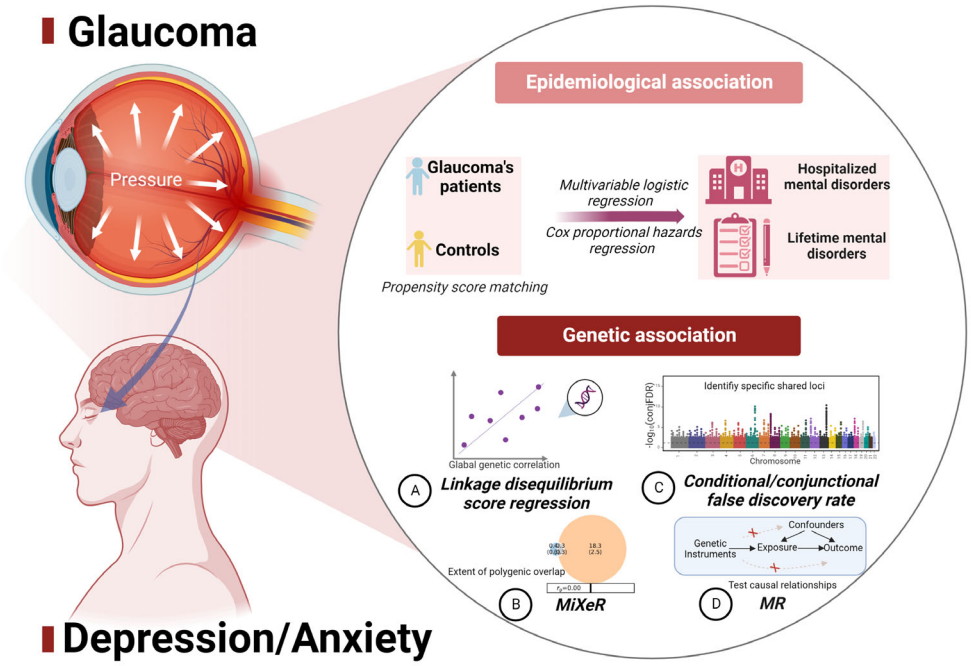

Figure 1. Guideline of this study. The epidemiological analysis utilized UK Biobank data, encompassing information on glaucoma, intraocular pressure, and mental health. Depression and anxiety outcomes were characterized as lifetime and incident hospitalized disorders. The genetic analysis focused on exploring shared genetic architecture between glaucoma and mental health, employing techniques such as LDSR, MiXeR, and condFDR/conjFDR methods based on GWAS summary-level data. Additionally, an MR study was conducted to examine bidirectional causal relationships.

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bidirectional associations. The flowchart outlining our study is presented in Figure 1.

Methods

Study Population

The UK Biobank recruited 502,505 participants between 2006 and 2010. These participants attended assessment centers located throughout the United Kingdom where a comprehensive set of phenotypic information and biological samples was collected.[29] The overall study protocol (http://www.ukbiobank.ac.uk/resources/) and specific test procedures (http://biobank.ctsu.ox.ac.uk/crystal/docs.cgi) can be accessed online. All participants provided consent for the follow-up of their health.

Ethical approval of the UK Biobank study was granted by the North West Multi-centre Research Ethics Committee (11/NW/0382). Our access to data from the UK Biobank cohort was approved by the UK Biobank Ethics Advisory Committee (application ID: 86091). We followed the Strengthening the Reporting of Observational Studies in Epidemiology Statement reporting guideline of cohort studies.

Ascertainment of Glaucoma and IOP

In the UK Biobank, glaucoma cases were identified in the baseline questionnaire (2006–2010) as patients who responded "glaucoma" to the following questions: (1) "Has a doctor told you that you have any of the following problems with your eyes?", or (2) "In the touch screen, you selected that you have been told by a doctor that you have other serious illnesses or disabilities; could you now tell me what they are?"

Controls for the glaucoma cases were selected based on a reply of "none" to the following two questions: (1) "Has a doctor told you that you have any of the following problems with your eyes?", and (2) "In the touch screen, you selected that you have been told by a doctor that you have other serious illnesses or disabilities; could you now tell me what they are?" The controls also had corneal-compensated intraocular pressure (IOPcc) of both eyes less than 21 mmHg assessed at baseline. The ascertainment of glaucoma cases and controls was in accordance with previous GWAS research on glaucoma.[30] For sensitivity analysis, we restricted POAG cases based on the International Classification of Diseases (ICD) codes criteria, in alignment with previous GWAS research on POAG.[31]

A subset of participants (n = 113,285) underwent ocular examination in 2009 that included IOP measurements using an Ocular Response Analyzer non-contact tonometer (Reichert Corporation, Depew, NY, USA). In this study, we utilized IOPcc, which is expected to be less influenced by corneal factors compared to Goldmann-correlated IOP measures. IOPcc has also been employed in previously reported GWASs for IOP.[30,32] Considering the potential impact of glaucoma treatment on IOP, we excluded participants with a history of glaucoma or corneal surgery. To address missing data for participants using glaucoma medication, we imputed pretreatment IOPcc by dividing the measured IOPcc by 0.7. IOPcc values of <6 mmHg or >50 mmHg were set to "missing." Participant-level IOPcc values were calculated by averaging the values from both the right and left eyes.

Measurements of Depression and Anxiety

The depression cases were divided into lifetime depression and incident hospitalized depression (see eMethods section in the Supplementary Materials). Controls for depression were individuals who did not meet the above criteria and did not score higher than five on the Patient Health Questionnaire during the online assessment conducted in 2016 to 2017.[33] Individuals diagnosed by a professional with "mania, hypomania, bipolar, or manic depression"; "schizophrenia"; "autism, Asperger's, or autistic spectrum disorder"; or "personality disorder" were excluded from the study.[18]

Similarly, cases of anxiety cases were categorized into lifetime anxiety and incident hospitalized anxiety (see eMethods section in Supplementary Materials). Controls were defined as individuals who did not meet the above criteria and did not score five or greater on the General Anxiety Disorder seven-item questionnaire (GAD-7).[34] Individuals diagnosed by a professional with conditions such as "mania, hypomania, bipolar, or manic-depression"; "schizophrenia"; "autism, Asperger's, or autistic spectrum disorder"; or "personality disorder" were also excluded.

Covariables of the UK Biobank

Demographic information included age, sex, and Townsend deprivation index. Ethnicity was self-reported and confirmed through genotyping analysis and was categorized as Caucasian or non-Caucasian. Additional covariates, such as educational qualifications (college/university degree or others), smoking status (never or former/current), alcohol consumption status (never or former/current), physical activity (meeting or not meeting moderate/vigorous/walking recommendation), and family history of severe depression (no or yes), were obtained through standardized questionnaires. Obesity was defined as body mass index over 30 kg/m^2. Diabetes mellitus, hypertension, and hyperlipidemia were determined by self-report, doctor diagnoses, medications, and physical measurements (refer to the eMethods section in Supplementary Materials).

Genotype Data

Genotype data were accessible for 488,377 participants in the UK Biobank. Individuals with a genotyping call rate of <95%, who were one of each pair of related individuals (detected within third-degree relatives), or those with ancestry other than Caucasian (detected through principal component analysis involving study participants and reference samples of known ancestry) were excluded. For the glaucoma GWAS (n_{case} = 5909, $n_{control}$ = 90,551) and IOPcc GWAS (n_{total} = 82,373), we conducted association analyses using PLINK software.[35] Genotype quality control has been described previously.[36] Age, sex, genotyping array, and the first five principal components calculated by Bycroft et al.[37] were included as covariates in the analysis. In addition, two summary statistics from previously published glaucoma-related GWASs were obtained for sensitivity analyses, including a multitrait analysis of glaucoma[30] and a meta-analysis of the POAG GWAS in Europeans.[31]

For depression[18] and anxiety,[19] we utilized previous published summary statistics from the PGC derived from analyses conducted among diverse European cohorts, with

exclusions of data from the UK Biobank. The depression meta-analysis GWAS was comprised of five population-based studies ($n_{case} = 45{,}591$, $n_{control} = 97{,}674$). Similarly, the anxiety meta-analysis GWAS was conducted across seven independent studies ($n_{case} = 7016$, $n_{control} = 14{,}745$).

The GWAS datasets were collected from December 2021 to February 2022, and data analysis was performed from February 2022 to August 2022. Comprehensive details regarding phenotypic definitions and cohort information for each individual study can be found in the eMethods section of the Supplementary Materials. Ethics approvals of all GWAS datasets included in this study were obtained from the relevant ethics committees, and informed consent was obtained from all participants.

Statistical Analysis

Phenotypic Analysis. Continuous variables were presented as mean differences with standard deviations (SDs) and compared using unpaired *t*-tests. Categorical variables were reported as numbers and percentages and compared using Pearson's χ^2 tests. Propensity score matching was employed, taking into account age, sex, ethnicity, and the Townsend index to select controls for each glaucoma or POAG participant. Cox proportional hazard regression models were utilized to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident mental disorders, and logistic regression models were employed to estimate odds ratios (ORs) and 95% CIs for lifetime disorders. The multivariable analysis was adjusted for age, sex, ethnicity, Townsend index, educational attainment, smoking, alcohol consumption, obesity, physical activity, history of hypertension, diabetes, hyperlipidemia, visual acuity, and family history of depression. Additionally, the associations between glaucoma with incident diabetic retinopathy and dementia were also assessed as negative controls. All P values were two-sided, and $P < 0.05$ was considered significant.

LDSR Analysis. We employed LDSR (https://github.com/bulik/ldsc) to calculate the overall genetic correlation between glaucoma/IOPcc and mental disorders. To ensure population ancestry matching, linkage disequilibrium (LD) scores from individuals of European ancestry were utilized for estimating genetic correlation.[20,22]

MiXeR Analysis. Polygenic overlaps, irrespective of the overall genetic correlation, were assessed using MiXeR.[22] Unlike LDSR, which assumes that each SNP has an infinitesimally small effect on every trait (infinitesimal model), MiXeR relies on a prior distribution of genetic effect sizes that align more closely with biologically plausible (causal mixture model). The results from MiXeR are depicted in Venn diagrams. A Dice coefficient (a measure of polygenic overlap on a 0%–100% scale) is computed to assess the overlap.

Conditional Quantile–Quantile Plots. We constructed conditional quantile–quantile (QQ) plots to visualize the cross-phenotype polygenic enrichment. Enrichment exists when the proportion of SNPs associated with a primary phenotype (e.g., glaucoma) increases as a function of the strength of the association with a secondary phenotype (e.g., depression).[22] Each QQ plot reveals the distribution of P values for the primary phenotype conditioning on the significance of association with the secondary phenotype at $P < 0.10$, $P < 0.01$, $P < 0.001$, and $P < 0.0001$. All QQ plots and MiXeR analyses were performed in Python 3.5 using the precimed/mixer package (https://github.com/precimed/mixer).

CondFDR/ConjFDR Analysis. The condFDR/conj FDR approach was applied to enhance genetic discovery power and pinpoint specific shared loci that may not surpass the significance threshold in traditional GWAS analyses.[24] Similar to standard GWAS analysis, the condFDR/conjFDR method does not operate on a causal level but instead identifies LD proxies of the underlying causal variants. In pleiotropy analysis, the FDR reflects the possibility of non-pleiotropy for an SNP. The condFDR approach, grounded in Bayesian statistics, amplifies the ability to identify loci associated with a primary phenotype by leveraging associations with a secondary phenotype.[38] This approach re-ranks test statistics by utilizing the associations between variants and the secondary phenotype, subsequently recalculating the associations between these variants and the primary phenotype. Inverting the roles of primary and secondary phenotypes yields the inverse condFDR values. Following the repetition of condFDR for both traits, we applied conjFDR analysis to pinpoint shared genetic loci. Defined as the maximum of the two condFDR values, conjFDR can detect loci jointly associated with two phenotypes.[39] Consistent with previous publications, the FDR significance cutoff was 0.05 for conjFDR.[26,40]

Functional Annotation. To delineate the LD-independent genomic regions proximal to the identified signals, we employed the functional mapping and annotation (FUMA) protocol (https://fuma.ctglab.nl/).[41] SNPs with a conjFDR < 0.05 and at $r^2 < 0.6$ with each other were deemed to be independent significant SNPs; among these, those approximating linkage equilibrium at $r^2 < 0.1$ were considered lead SNPs.[26,27] Additionally, these independent significant SNPs were cross-referenced with the GWAS catalog (https://www.ebi.ac.uk/gwas/) to provide insights into previously reported associations with diverse phenotypes. Gene-based analyses were conducted in MAGMA as implemented in FUMA.[42] Independent significant SNPs and SNPs that were in LD with the independent significant SNPs were then annotated for functional consequences on gene functions based on Ensembl genes (build 85) using ANNOVAR[43] and deleteriousness (Combined Annotation-Dependent Depletion [CADD]) score.[44] Gene-set (pathway)–based tests were performed using Gene Ontology (GO) through the clusterProfiler package in R (R Foundation for Statistical Computing, Vienna, Austria). Bonferroni correction was applied for multiple comparisons.

MR Analyses. To evaluate potential causal effects between glaucoma/IOP and mental disorders, we conducted a bidirectional two-sample MR analysis. The primary method for estimating the causal effect was the multiplicative random-effect inverse variance-weighted (IVW) estimate.[45] Sensitivity analyses were conducted using MR–Egger, weighted median, weighted mode, simple mode, and MR pleiotropy residual sum and outlier (PRESSO) tests. All MR analyses were performed in R using the TwoSampleMR R package (https://mrcieu.github.io/TwoSampleMR/) and MR–PRESSO R package (https://github.com/rondolab/MR-PRESSO). Statistical power for the MR analysis was contingent on several parameters, including a type I error of 1.25% after multiple testing corrections, the proportion of variance in the exposure explained by genetic instruments, and the "true" causal effect of exposures on outcomes. Further details are provided in the eMethods section of the Supplementary Materials.

Results

Observational Findings

Among 502,505 UK Biobank participants, 7522 individuals diagnosed with glaucoma (40 to 72 years old and 47% female) were included (Supplementary Fig. S1). The baseline characteristics, stratified by glaucoma status, are detailed in Supplementary Table S1. After generating 6426 pairs (n = 12,852) through 1:1 matching on the propensity score, involving individuals with documented glaucoma and those without eye disorders or elevated IOP (Table 1), 350 individuals with glaucoma were identified as having baseline depression (5.45%). During the 11.3-year follow-up period (interquartile range, 11.0–12.4 years), incident hospitalized depression was diagnosed in 3.11% (n = 187) of glaucoma patients and 2.09% (n = 127) of controls, after excluding individuals with baseline depression. Notably, individuals with glaucoma at baseline exhibited a 54% higher risk of incident hospitalized depression (95% CI, 1.01–2.34) compared with controls. Similar results were observed in the association between glaucoma and anxiety. After excluding participants with baseline anxiety, 2.87% (n = 182) of glaucoma patients and 1.83% (n = 116) of controls experienced incident hospitalized anxiety. Individuals with glaucoma demonstrated a significantly higher risk of incident hospitalized anxiety (HR = 2.61; 95% CI, 1.70–4.01) than controls (Table 1). However, no significant association was observed between glaucoma and lifetime depression or anxiety after adjusting for all covariables.

In sensitivity analyses, we additionally adjusted for IOPcc and observed that glaucoma patients were still more likely to suffer from incident hospitalized depression and anxiety (HR = 1.65; 95% CI, 1.13–2.41) compared with controls (HR = 2.06; 95% CI, 1.47–2.90). When specifically classified as POAG based on ICD codes, individuals with POAG exhibited an increased risk of incident hospitalized anxiety (HR = 2.51; 95% CI, 1.19–5.27) compared to healthy controls. Considering elevated IOP as a well-established risk factor for the development and progression of glaucoma, we also conducted sensitivity analyses using elevated IOPcc as the exposure (Supplementary Fig. S1). No significant association was observed between elevated IOPcc and mental disorders (Table 1). Utilizing incident diabetic retinopathy (as ocular disorder) and dementia (as neurodegenerative disease) as outcomes, we found that the associations between glaucoma and incident diabetic retinopathy (HR = 2.31; 95% CI, 0.75–7.09, P = 0.14), as well as dementia (HR = 1.02; 95% CI, 0.51–2.07; P = 0.95), were not significant. These sensitivity analyses underscore the robustness and interpretability of our results.

Quantification of Genetic Overlap

We performed GWASs of glaucoma and IOPcc within European ancestry from the UK Biobank, phenotypes of which are consistent with the epidemiological analysis. Manhattan plots and independent significant loci ($P < 5 \times 10^{-8}$) are depicted in Supplementary Figure S2 and Supplementary Tables S2 and S3, respectively. For depression and anxiety, we utilized recent large GWAS data from the PGC, excluding UK Biobank data.[18,19]

Using LDSR, we estimated the European-based liability-scale h^2 for glaucoma and IOPcc identified in the UK Biobank to be 6.25% (SE = 0.71%) and 17.91% (SE = 1.27%), respectively, with a significant genetic correlation (r_g = 0.72, SE = 0.06, P = 8.97e-33) between glaucoma and IOPcc. However, cross-trait LDSR revealed no significant whole-genome level correlation between glaucoma and depression (r_g = 0.02, SE = 0.04, P = 0.64), glaucoma and anxiety (r_g = 0.0017, SE = 0.10, P = 0.99), IOP and depression (r_g = −0.03, SE = 0.03, P = 0.41), or IOP and anxiety (r_g = −0.03, SE = 0.07, P = 0.65; Supplementary Table S4).

Although no global genetic correlation was identified, MiXeR analysis revealed that out of the 800 causal variants linked to glaucoma, 300 (SE = 0.3) were shared with depression and 500 (SE = 0.3) were shared with anxiety (Figs. 2A, 2B). The overall polygenic overlaps between glaucoma with depression and glaucoma with anxiety were 3.27% and 8.10%, respectively (Supplementary Table S5). However, suboptimal model fit was indicated by differences between the model-predicted plots and the observed plots (Figs. 2A, 2B). In the sensitivity analysis utilizing results from

Table 1. Multivariable Regression for Incident Depression and Anxiety Disorders Associated With Glaucoma and IOPcc

	Hospitalized Depression			Lifetime Depression		
Participants	Cases, n (%)	Model 1 HR (95% CI); P	Model 2 HR (95% CI); P	Cases, n (%)	Model 1 HR (95% CI); P	Model 2 HR (95% CI); P
Glaucoma	187 (3.11)	**1.51 (1.20–1.89); <0.001**	**1.54 (1.01–2.34); 0.044**	516 (38.62)	1.12 (0.96–1.30); 0.16	1.12 (0.86–1.46); 0.40
IOPcc						
<21	116 (1.81)	1 [Ref]	1 [Ref]	570 (36.35)	1 [Ref]	1 [Ref]
≥21	105 (1.63)	0.96 (0.78–1.20); 0.71	0.91 (0.70–1.17); 0.45	536 (35.10)	0.93 (0.81–1.08); 0.34	1.00 (0.85–1.18); 0.98
	Hospitalized Anxiety			**Lifetime Anxiety**		
Glaucoma	182 (2.87)	**1.59 (1.26–2.01); <0.001**	**2.61 (1.70–4.01); <0.001**	329 (19.65)	**1.24 (1.02–1.51); 0.028**	1.07 (0.76–1.50); 0.71
IOPcc						
<21	111 (1.66)	1 [Ref]	1 [Ref]	373 (18.55)	1 [Ref]	1 [Ref]
≥21	121 (1.81)	1.05 (0.81–1.35); 0.72	1.03 (0.76–1.39); 0.84	343 (17.40)	0.91 (0.78–1.07); 0.27	0.91 (0.76–1.10); 0.33

Model 1 has been adjusted for age and sex, and Model 2 has been adjusted for age, sex, ethnicity, Townsend index, educational attainment, smoking, alcohol consumption, obesity, physical activity, history of hypertension, diabetes, hyperlipidemia, visual acuity, and family history of depression. Bold values denote statistical significance at the $P < 0.05$ level.

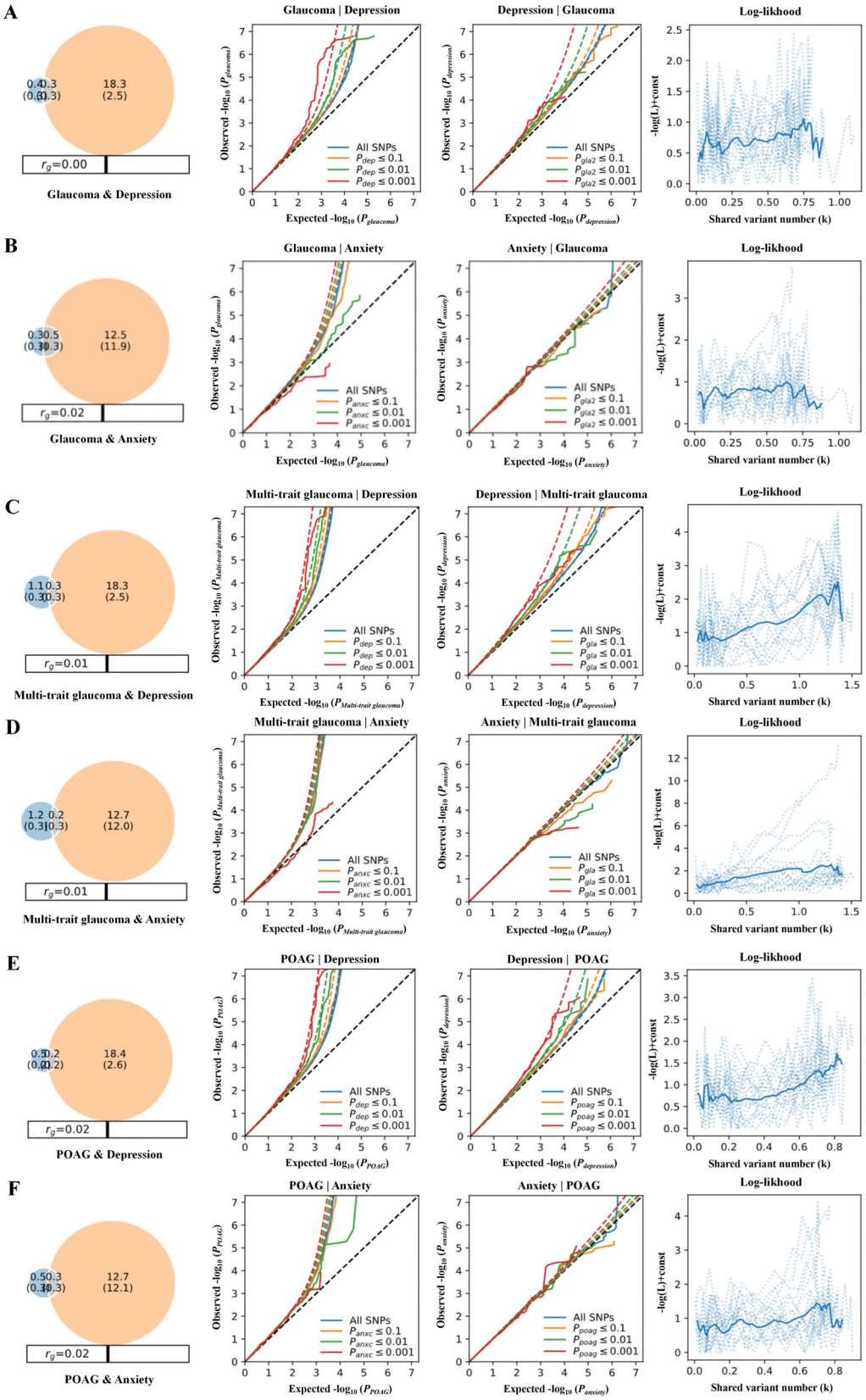

Figure 2. Venn diagram, conditional QQ plots, and log-likelihood plots depicting the genetic overlaps shared between glaucoma and mental disorders. The Venn diagram provides an estimate of the number of causal variants (*gray*) shared between glaucoma and depression/anxiety, with numbers in thousands and standard errors in parentheses. Conditional QQ plots depict the observed versus expected $-\log_{10} P$ values in the primary trait, relative to the significance of association with the secondary trait at $P \le 0.1$ (*orange lines*), $P \le 0.01$ (*green lines*), and $P \le 0.001$ (*red lines*). Log-likelihood plots of the MiXeR models are presented, showcasing the negative log-likelihood of the bivariate fit as a function of the π parameter, with the remaining parameters of the model constrained to their fitted values.

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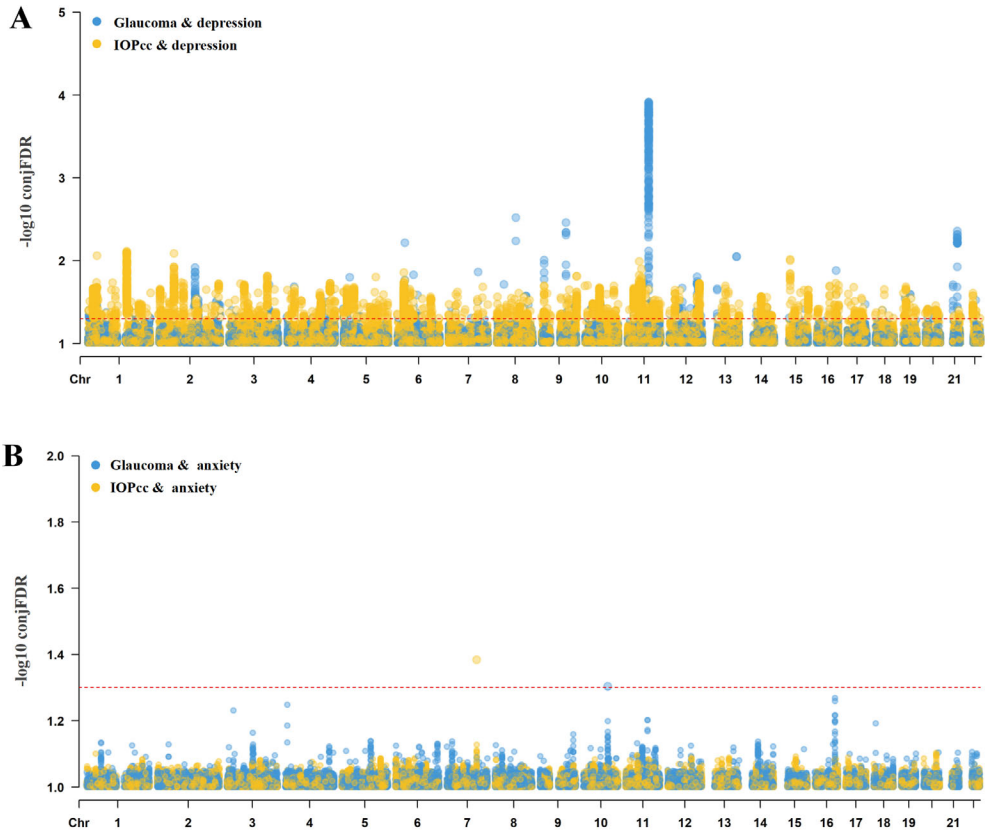

Figure 3. Manhattan plots for common genetic variants jointly associated between glaucoma-related traits and depression (**A**) and between glaucoma-related traits and anxiety (**B**). The Manhattan plots illustrate the $-\log_{10}$-transformed conjFDR values for each SNP on the *y*-axis, and the chromosomal positions are depicted along the *x*-axis. The *red line* signifies the conjFDR threshold for significant association (<0.05).

previous multitrait glaucoma and POAG GWASs, consistent polygenic overlap was observed. Specifically, 300 (SE = 0.3) variants were associated with both multitrait glaucoma and depression (Dice coefficient = 3.08%) (Fig. 2C), and 200 (SE = 0.3) variants were associated both multitrait glaucoma and anxiety (Dice coefficient = 4.29%) (Fig. 2D). Similarly, 200 (SE = 0.2) variants were associated both POAG and depression (Dice coefficient = 2.62%) and 300 (SE = 0.3) variants were associated both POAG and anxiety (Dice coefficient = 5.39%), as shown in Figures 2E and 2F and detailed in Supplementary Table S5. To visually illustrate the pleiotropic enrichment pattern between each pair of phenotypes, we generated conditional QQ plots by conditioning one phenotype on the other and vice versa (Fig. 2).

To pinpoint specific shared loci, independent of the genetic correlation, we employed the condFDR/conjFDR methodology to enhance genetic discovery power, revealing 906 SNPs jointly associated with glaucoma and depression (Supplementary Table S6). Upon comparing the effect directions of the shared SNPs, we observed that 515 SNPs exhibited consistent effect directions in glaucoma and depression, whereas 391 had opposite effect directions. Meanwhile, two SNPs (rs61198698 and rs61861119) on chromosome 10 were found to be associated with both glaucoma and anxiety, exhibiting consistent effect directions (Supplementary Table S7). This finding aligns with the absence of significant genetic correlation and lends support to the hypothesis of mixed effect directions between glaucoma and mental disorders. The Manhattan plot depicting the chromosomal positions of independent SNPs and their corresponding negative $\log_{10}$ condFDR/conjFDR values is shown in Figure 3 and Supplementary Figure S3.

Moreover, we identified 3224 shared SNPs associated with both IOP and depression (Supplementary Table S8), and one shared SNP (rs76444092) between IOP and anxiety. Within the shared SNPs between IOP and depression, 41 were consistent with the identified shared loci between glaucoma and depression (Supplementary Table S9).

Functional Annotations

The functional annotation of the 906 shared SNPs between glaucoma and depression across 108 risk loci reveals a predominant intergenic (44.3%) and intronic (40.1%) distribution, with 0.7% located in exonic regions. These SNPs are linked to 170 protein-coding genes, and their functional consequences on gene functions and deleteriousness were annotated by MAGMA (Supplementary Table S11). Six loci shared between glaucoma and depression have been previously identified in GWASs as being related to both glaucoma and mental traits and mapped to genes such as *LTBP3*, *LTBP2*, *RERE*, *TRAPPC3*, *CTTNBP2*, *MAP7D1*, and *CTTNBP2* (Supplementary Table S10). GO analysis for the 170 protein-coding genes unveiled significantly associated molecular functions, including enzyme binding and kinase binding (Supplementary Fig. S4A). For the intergenic SNPs jointly associated with glaucoma and anxiety disorder, the proximal target genes are *NIP7P1* and *XRCC6P1*.

Table 2. Two-Sample MR Results for the Bidirectional Relationships Between Glaucoma/IOPcc and Mental Disorders

		Depression Outcome		*P**			Anxiety Outcome		*P**		
MR Methods	**SNPs, *n***	**OR (95% CI)**	***P***	**Intercept**	**Heterogeneity**	**Global**	**OR (95%CI)**	***P***	**Intercept**	**Heterogeneity**	**Global**
Glaucoma											
IVW	16	1.01 (0.96–1.07)	0.62	—	**1.27e-04**	—	1.07 (0.97–1.19)	0.17	—	0.41	—
MR–Egger	16	0.97 (0.81–1.16)	0.73	0.60	**9.46e-05**	—	0.84 (0.61–1.16)	0.31	0.14	0.53	—
Weighted median	16	1.00 (0.95–1.05)	0.89	—	—	—	1.03 (0.90–1.18)	0.69	—	—	—
Weighted mode	16	0.99 (0.92–1.06)	0.78	—	—	—	1.01 (0.85–1.19)	0.92	—	—	—
MR–PRESSO	16	1.01 (0.96–1.07)	0.71	—	—	**0.001**	1.08 (0.97–1.20)	0.14	—	—	0.54
IOP											
IVW	36	1.02 (0.99–1.04)	0.14	—	0.49	—	0.99 (0.92–1.06)	0.82	—	0.35	—
MR–Egger	36	1.00 (0.93–1.07)	0.93	0.58	0.45	—	1.04 (0.83–1.31)	0.71	0.65	0.31	—
Weighted median	36	1.02 (0.99–1.05)	0.28	—	—	—	1.03 (0.93–1.14)	0.53	—	—	—
Weighted mode	36	1.00 (0.94–1.07)	0.96	—	—	—	1.06 (0.92–1.21)	0.43	—	—	—
MR–PRESSO	36	1.01 (0.99–1.04)	0.19	—	—	0.46	1.00 (0.93–1.07)	0.95	—	—	0.45
		Glaucoma Outcome		***P***			**IOP Outcome**		***P***		
MR Methods	**SNPs, *n***	**OR (95% CI)**	***P***	**Intercept**	**Heterogeneity**	**Global**	**OR (95% CI)**	***P***	**Intercept**	**Heterogeneity**	**Global**
Depression											
IVW	38	0.09 (3.67e-04–2.20e+01)	0.39	—	0	—	1.02 (0.90–1.16)	0.74	—	0.80	—
MR–Egger	38	9.51 (2.734e-06–3.30e+07)	0.77	0.52	0	—	1.11 (0.79–1.57)	0.55	0.60	0.77	—
Weighted median	38	6.16 (1.45–26.20)	**0.01**	—	—	—	1.04 (0.88–1.24)	0.63	—	—	—
Weighted mode	38	3.66 (0.76–17.50)	0.11	—	—	—	0.97 (0.67–1,42)	0.88	—	—	—
MR–PRESSO	38	0.09 (0.0003–23.46)	0.40	—	—	**<0.001**	1.02 (0.91–1.14)	0.72	—	—	0.79
Anxiety											
IVW	12	0.96 (0.89–1.03)	0.26	—	0.52	—	0.99 (0.92–1.05)	0.68	—	0.52	—
MR–Egger	12	0.87 (0.72–1.05)	0.17	0.29	0.54	—	0.89 (0.75–1.06)	0.22	0.24	0.57	—
Weighted median	12	0.96 (0.86–1.07)	0.44	—	—	—	0.98 (0.89–1.07)	0.65	—	—	—
Weighted mode	12	0.98 (0.83–1.16)	0.82	—	—	—	0.91 (0.78–1.05)	0.22	—	—	—
MR–PRESSO	12	0.96 (0.89–1.03)	0.26	—	—	0.52	0.99 (0.92–1.05)	0.68	—	—	0.51

* *P* Intercept is the *P* value for the MR–Egger intercept; *P* Heterogeneity is the *P* value for heterogeneity using Cochran's *Q* test; and *P* Global is the *P* value for the MR–PRESSO global test.

Furthermore, the functional annotation of 3224 shared SNPs associated with IOP and depression identified 444 lead SNPs enriched in 667 protein-coding genes (Supplementary Table S12). Enriched GO terms of these protein-coding genes are presented in Supplementary Figure S4B. Notably, 48 shared genes between IOP and depression overlapped with the shared protein-coding genes between glaucoma and depression.

Two-Sample MR Analyses

We employed a two-sample MR approach to investigate bidirectional causal relationships between glaucoma and mental traits, including depression and anxiety. The 16 independent SNPs ($P < 5 \times 10^{-8}$) (Supplementary Table S2) were used as proxies for genetically predicted glaucoma. No statistically significant causal effects of genetically predicted glaucoma on depression and anxiety were found, as indicated in Table 2. The heterogeneity analysis found that there was heterogeneity in the analysis for causal relationships between glaucoma and depression (the P values for heterogeneity of IVW and MR–Egger were both less than 0.05). MR–PRESSO test outcomes demonstrated that there were horizontal pleiotropic outliers. After removing these SNP outliers, no causal relationship between glaucoma and depression was found.

MR analyses assessing causality in the opposite direction were also performed. A total of 38 and 12 independent SNPs were used as proxies for genetically predicted depression and anxiety, respectively. Similarly, insufficient causal evidence could be found for the causal effects of mental disorders on glaucoma (all $P > 0.1$ for IVW method). The MR–PRESSO test outcomes also detected horizontal pleiotropic outliers, and MR estimates remained null after removal of outliers (Table 2).

The statistical power of the bidirectional MR results between glaucoma and mental traits was sufficient (>80%, Supplementary Table S13). Therefore, low statistical power and weak instruments are unlikely to explain our results. Analyses assessing bidirectional causality between IOPcc and mental traits were also performed, but no apparent evidence was discovered (all $P \geq 0.1$) (Table 2).

Discussion

This study investigated the epidemiological association between glaucoma and mental disorder and uncovered a shared underlying genetic architecture in individuals of European descent. Several observations can be made from the present study. First, we found evidence that glaucoma is associated with hospitalized depression and anxiety over a long-term follow-up. Second, we revealed that a subset of genetic variants influencing glaucoma also impacts depression and anxiety. Third, multiple shared SNPs were identified with a mixture of allelic effect directions through condFDR/conjFDR analysis. Fourth, no genetic evidence supports causal relationships between glaucoma and mental disorders. Collectively, these results suggest that genetic associations between glaucoma and mental health primarily stem from divergent effect distributions of pleiotropic genetic variants rather than causal effects.

In this cohort study from the UK biobank, we validated the heightened risks of hospitalized depression and anxiety disorders among glaucoma patients. This confirmation was established through propensity score matching and adjustment for essential demographic, medical, and lifestyle covariates. Our results are in line with the majority of the current literature on comorbidity among glaucoma, depression, and anxiety.[9,46,47] In contrast, our study provides a comprehensive prospective analysis with an extended follow-up and incorporates additional adjustments for elevated IOPcc. Our epidemiological findings suggest that the co-occurrence of mental disorders in glaucoma patients may not be attributed to elevated IOPcc, pointing to the possibility of other underlying mechanisms. However, with regard to lifetime mental disorders diagnosed during online mental health follow-up, we did not observe significant positive associations. It is important to note that these results might be constrained by the relatively low proportion of participants who responded to the online follow-up, potentially limiting the generalizability of findings in the context of lifetime depression and lifetime anxiety disorder. Nevertheless, the replication of these research inquiries through meta-analyses or other extensive longitudinal datasets is imperative for further validation and robustness.

The mechanisms that underlie the observed relationships between glaucoma and mental disorders are intricate, but several established pathways can be identified. First, visual field loss and vision disabilities can cause or exacerbate psychiatric disorders due to difficulties with performing daily activities, fear of potential blindness, and a heavy economic burden.[13] Second, shared risk factors, including demographics (advanced age[48] and ethnic backgrounds[4,49]), lifestyle (dynamic exercise[50] and smoking[51,52]), and comorbidities (hypertension, diabetes, and obesity[13]), may also be responsible for the association between glaucoma and psychiatric disorders. Third, some medications used in the treatment of psychiatric disorders may have side effects that impact ocular health.[53] Conversely, medications used for glaucoma management might have neuropsychiatric effects.[54] Furthermore, a deep investigation of the common genetic mechanisms contributes to a better understanding of the phenotypic overlap and might provide new molecular therapeutic targets for patients suffering from both glaucoma and mental disorders. To understand the common genetic basis between glaucoma and mental disorders, it should be noted that our MiXeR results indicate that a substantial part of the polygenic architecture of glaucoma was shared with depression and anxiety. Combined with evidence of similar overlap obtained using previously published results of multitrait glaucoma and POAG GWASs and the two-sample MR results, these findings indicate the presence of a pool of "pleiotropic" genetic variants that affect general vulnerability to glaucoma and mental-related disorders. Nevertheless, additional research encompassing genetic studies and exploration of specific shared mechanisms remains essential to unravel the complexities of the relationship between glaucoma and psychiatric disorders.

We next employed conjFDR/condFDR analysis to identify the 906 SNPs jointly associated with glaucoma and depression and two SNPs shared between glaucoma and anxiety. Among the 906 shared SNPs, 56.8% exhibited a consistent direction of allelic effect, whereas 43.2% showed an opposite direction. In silico analyses of these loci indicate potential effects on protein-coding genes and functional pathways related to enzyme binding and kinase binding. Given the accumulating evidence that enzymes and kinases play crucial roles in diverse cellular processes,

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such as signal transduction, neuronal differentiation, and metabolism, contributing to the overall functioning and development of neurons,[55] it is plausible to speculate that alterations in neuron development related to enzyme and kinase binding may be involved in the shared pathogenesis contributing to the phenotypic comorbidity between glaucoma and psychiatric disorders.[56–58] Furthermore, we identified a total of 3224 distinct shared SNPs between IOPcc and depression, with a small proportion (1.27%) being consistent with the identified shared loci between glaucoma and depression. These findings suggest that the genetic mechanisms contributing to the comorbidity between glaucoma and depression may differ from those between IOP and depression. Few shared loci were identified between glaucoma and anxiety or IOP and anxiety, aligning with the subsequent MR results. Our findings provide biological insights into the genetic basis of the comorbidity between glaucoma and depression, spotlighting several putative glaucoma genes, including *LTBP3*, *LTBP2*, *RERE*, *TRAPPC3*, *CTTNBP2*, *MAP7D1*, and *CTTNBP2*. These genes, previously identified in GWASs related to both glaucoma and mental traits, should be subject to further experimental validation, as they hold the potential for drug discovery and personalized treatment strategies.

As genetic variants are relatively independent of environmental factors and are established well before the onset of diseases, genetic analysis using MR could minimize residual confounding and reverse causation issues.[28] For MR analysis, we use genetic variation to investigate the causal effects of glaucoma or IOPcc on depression and anxiety. The MR analysis results did not reveal a causal relationship between glaucoma and mental traits, including depression and anxiety. Our study possessed ample statistical power to detect the effects of glaucoma on mental disorders, with the exception of IOPcc. Our findings suggest that the observed associations between glaucoma and mental health are predominantly determined by divergent effect distributions of pleiotropic genetic variants rather than casual effects. Nevertheless, we believe that the MR analysis requires replication in future studies when larger GWAS samples are available.

The present study has certain limitations. First, despite employing multivariable regression models and propensity score matching to control for various covariates, the observational nature of the study introduces potential limitations related to behavioral, social, and genetic confounders not accounted for. Second, the identification of glaucoma cases at baseline relied on self-reports, thus introducing potential bias. However, it is worth noting that previous research has demonstrated a high concordance between GWAS results for clinically validated cases and those identified through self-reporting.[31] Third, because GWASs were conducted in individuals of Western European ancestry, the generalizability of the results to non-European populations may be limited.

In conclusion, our study enhances the understanding of the relationship between glaucoma and mental disorders. The findings extend prior epidemiological studies, providing further support for the hypothesis of a shared genetic basis between glaucoma and psychiatric disorders.

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