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Investigating causal associations between the genetic liability to primary open-angle glaucoma and psychiatric disorders

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Abstract

Current observational evidence on psychiatric diseases and primary open-angle glaucoma (POAG) is controversial. Our study aims to evaluate the putative causal associations between the genetic liability to psychiatric disorders and POAG, and add updated evidence to their linkage. Summary statistics of genome-wide association studies (GWASs) involving 192,702 participants (15,229 cases and 177,473 controls) were used for POAG. Large-scale GWAS summary datasets for psychiatric disorders of interest were also collected. Bi-directional two-sample Mendelian randomization analyses were performed, and sensitivity analyses were conducted to evaluate the robustness of our results. Genetically predicted POAG was causally associated with a slightly increased risk of schizophrenia (odds ratio [OR] = 1.035, 95% confidence interval [CI]: 1.009–1.062, $p = 0.008$). No evidence of causality was found for POAG and other selected psychiatric disorders (OR = 1.022, 95% CI: 0.988–1.056, $p = 0.214$ for attention deficit hyperactivity disorder; OR = 1.016, 95% CI: 0.984–1.049, $p = 0.325$ for anxiety disorder; OR = 1.040, 95% CI: 0.987–1.097, $p = 0.143$ for bipolar disorder; OR = 0.992, 95% CI: 0.967–1.017, $p = 0.526$ for depressive disorder) and vice versa. Our findings indicate the mild causal effect of a genetic predisposition to POAG on schizophrenia, and the effects on other psychiatric disorders are not significant. Optimized strategies for their observed comorbidity should be further developed in clinical practice.

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Introduction

Psychiatric disorders have become highly important health issues for society and people worldwide[1,2]. According to the Global Burden of Disease Study, psychiatric disorders are reported to be strongly associated with premature mortality and serve as the consistent leading causes of lifelong disability[1,3,4]. Glaucoma, as a typical neurodegenerative disease, is a leading cause of irreversible blindness, with a sharply increasing global prevalence, which is projected to affect over 110 million people in 2040[5,6]. Primary open-angle glaucoma (POAG), which is largely influenced by genetic factors, is known to be the most common subtype of glaucoma and threatens the visual health of over 44 million individuals worldwide[7–9]. Both of the diseases impede the independence of individuals, which are gradually considered serious public health problems.

Emerging studies have demonstrated the comorbidity of psychiatric disorders and glaucoma. As a chronic and progressive disease characterized by vision impairment, glaucoma, especially POAG, is reported to impose negative emotional impacts on patients and even force them into psychological disturbances[10–13]. Patients with POAG are found to have different personality profiles and temperaments compared with healthy people[13]. Plenty of studies have reported that patients with glaucoma are prone to suffer from various types of psychiatric disorders. A high prevalence of glaucoma is found in severely mentally ill patients, especially those with schizophrenia[14,15]. The results are also supported by another population-based study, which shows that glaucoma, especially POAG, is associated with an increased risk of schizophrenia, bipolar disorder, and depressive disorder[16]. Furthermore, previous studies also indicate that the frequency of having anxiety and depression episodes is higher in patients with POAG and other subtypes of glaucoma[17–20]. A recent meta-analysis verifies that patients with glaucoma experience a higher prevalence and severity of depression, anxiety, and other psychological conditions[21]. Another meta-analysis also finds that the prevalence of depression is 25% among patients with glaucoma[22]. In reverse, a history of psychiatric disorders will exacerbate the development of glaucoma, suggesting that psychological disturbances would worsen glaucoma progression[23].

These interesting findings of observational studies have brought the potential role of glaucoma in the development of psychiatric disorders into the spotlight. Although some of them indicate a certain amount of pathophysiological and psychosocial risk factors, the insidious development of psychiatric disorders and glaucoma makes it difficult to recognize and prevent them in a timely manner. In addition, the previous observational findings might be biased by potential confounders. A positive clinical association means only an epidemiological comorbidity, while whether there is a causal relationship remains unexplored. As we already noted, there remain considerable limitations of the explanatory power of the observational results; therefore, a major breakthrough for current research will be to investigate the relevance of the potential risk exposures to the causation of these diseases using an innovative approach[24].

Through recent advances in genetics, psychiatric disorders and POAG were found to be highly polygenic and with an extensive biological pleiotropy[24–31]. The polygenic bases and the advances of genetic technologies provide an opportunity to explore their potential causal relationship at a number of both genetic and epidemiological levels. In the absence of convincing randomized controlled trials, Mendelian randomization is considered an alternative to estimate the causal association between two

traits[32–36]. Based on the principle that genetic variants are randomly assigned, Mendelian randomization analysis can minimize the influences of confounding factors and reverse causality, which are considered to be limitations of observational epidemiological studies[37,38]. Therefore, a Mendelian randomization study estimating the potential causal relationship between psychiatric disorders and POAG is warranted.

In this study, we performed bi-directional two-sample Mendelian randomization analyses to evaluate the potential causal associations between a genetic liability to psychiatric disorders and glaucoma. By investigating the genetic causality, we aimed to provide new insights into the observed comorbidity in previous studies, serving as new evidence for early-stage prevention and diagnosis of psychiatric disorders and glaucoma.

Materials and methods

Genome-wide association study datasets for psychiatric disorders and POAG

Summary statistics of genome-wide association studies (GWASs) of the selected psychiatric disorders (i.e., schizophrenia, attention deficit/hyperactivity disorder [ADHD], anxiety disorder, bipolar disorder, and depressive disorder) and POAG were collected (Supplementary Table S1)[29,39–42]. Genetic information on schizophrenia was obtained from the GWAS summary statistics released by the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC), which consisted of 15,358,497 single-nucleotide polymorphisms (SNPs) from 33,640 cases and 43,456 controls[40]. The GWAS summary-level dataset of ADHD was also obtained from the PGC, which contained 8,047,420 SNPs derived from 20,183 cases and 35,191 controls[41]. For anxiety disorder, summary statistics were acquired from FinnGen, including 12,513 cases and 198,110 controls[42]. The GWAS summary statistics for bipolar disorder were derived from a GWAS meta-analysis, which contained 9,483,147 SNPs, 7,647 cases, and 27,303 controls[39] The GWAS dataset for depressive disorder was sourced from FinnGen, which was based on 16,380,457 SNPs and consisted of 23,424 cases and 192,220 controls[42]. The summary statistics of the POAG discovery dataset were obtained from a GWAS meta-analysis, which included 15,229 cases and 177,473 controls[29]. Furthermore, an independent replication cohort (FinnGen, including 3,412 cases and 210,201 controls) was accessed and analyzed to confirm the findings in the discovery dataset when there was a positive result[42].

Detailed information about the study designs, including sample collection, quality control, and method imputation, was reported in each publication and was manually checked to avoid sample overlap[29,39–42]. All analyses in our study were conducted using publicly accessible, de-identified, and summary-level data; therefore, no additional ethical approval or informed consent was required.

Selection of genetic instrumental variables

A workflow of the general Mendelian randomization analysis process of this study is shown in Fig. 1. After collecting the above-mentioned GWAS datasets for POAG and the five selected psychiatric disorders, we then selected SNPs as independent genetic instrumental variables (IVs) of exposure from them.

The IVs for the five psychiatric disorders and POAG were selected using the same criteria. The IVs were extracted on the basis of the arbitrary *p*-value cut-off. All relevant SNPs at the GWAS significance threshold ($p < 5 \times 10^{-6}$) were selected from each trait with the aim of obtaining more IVs. Thereafter, all the selected SNPs were clumped by linkage disequilibrium with an r^2 threshold of < 0.001 and a 10-Mb window to ensure that the IVs for the exposure datasets were independent. PhenoScanner V2 database (http://phenoscanner.medschl.cam.ac.uk) was applied to avoid potential confounding by calculating each IV and its proxies ($r^2 > 0.8$)[43]. SNPs with indirect linkage disequilibrium effects ($r^2 > 0.8$) were excluded to prevent association with the outcome. All the IVs selected needed to meet the following assumptions: (1) SNPs, as IVs, are strongly associated with the exposure. The F-statistic for each SNP was calculated as $F = (\text{beta\_exposure/se\_exposure})^2$, and the instrument strength > 10 was considered sufficient for analysis; (2) IVs are not associated with any confounding factors; (3) IVs are not directly associated with outcome (no horizontal pleiotropy)[44].

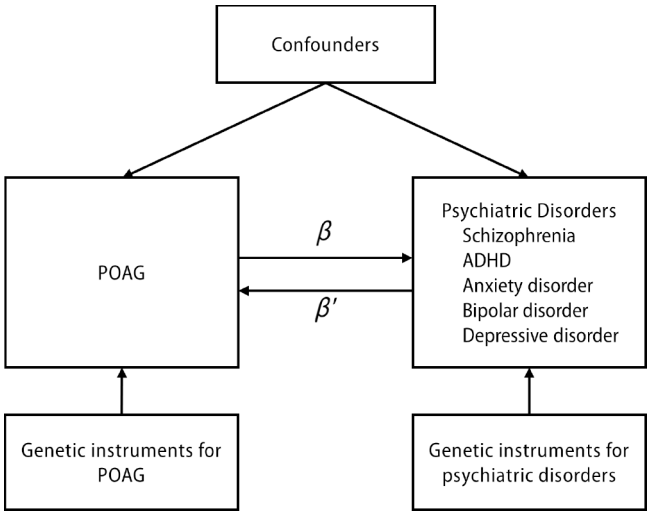

Fig. 1 Workflow figure of the bi-directional two-sample Mendelian randomization analysis process of this study. β and β' are the beta coefficients for the corresponding estimated causal effects.

Two-sample Mendelian randomization analysis

For the analysis of the causal relationship between POAG and the five common psychiatric disorders, bi-directional two-sample Mendelian randomization analysis was employed in our study. Mendelian randomization analysis was conducted first in one direction to investigate whether POAG has a genetically causal association with five common psychiatric disorders (schizophrenia, ADHD, anxiety disorder, bipolar disorder, and depressive disorder). Thereafter, Mendelian randomization analysis in the opposite direction was conducted to assess the reverse causality of these five common psychiatric disorders on POAG.

Inverse variance weighted (IVW) regression with multiplicative random effects method was adopted as the primary causal inference, since the IVW method provides robust causal estimations of the two traits and is most widely used in Mendelian randomization analyses[44]. Meanwhile, three alternative Mendelian randomization methods, including the Mendelian randomization–Egger (MR-Egger), the weighted median, and the weighted mode methods, were additionally performed in our analyses to complement and improve the reliability of the IVW results. The MR-Egger method uses the slope coefficient of the Egger regression to show the causal effect, which could provide a more robust estimation when there are no invalid IVs[45]. The weighted median method can even identify a positive causal estimation when up to 50% of IVs are invalid[46]. The weighted mode method estimates the evidence of causality by classifying the IVs into groups, which relaxes the assumptions of Mendelian randomization and is able to identify the causality even with a majority of invalid IVs[47]. The Mendelian

randomization results aRE all reported as odds ratios (OR) with 95% confidence intervals (CIs), which were interpreted as the estimated causal effect per standard deviation (1 SD) of change in exposure on the outcome risk.

Sensitivity analysis

For validation of our putative causal association between POAG and the five common psychiatric disorders, sensitivity analyses were performed for IV quality control based on the results of Mendelian randomization.

Although the IVW method is generally recognized as a better method of causal inference, the validity of these Mendelian randomization results would be reliable only when all of the IVs are without heterogeneity and horizontal pleiotropy[47]. Therefore, for the traits with an IVW with $p < 0.05$ and IVs > 2, we performed heterogeneity tests using Cochran's Q test and the I^2 index to detect the outlier IVs and adjust them[48]. The presence of heterogeneity was considered when $p < 0.05$ in Cochran's Q test and I^2 index > 50%. The detected outliers were then discarded from the analyses.

Meanwhile, the Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) global test and the MR-Egger regression test were performed to detect the presence of any horizontal and directional pleiotropy, respectively[45,49]. The MR-PRESSO method indicates the potential pleiotropic outliers through a correction test. Therefore, to reduce the effect of horizontal pleiotropy, potential pleiotropic outlier IVs detected by the MR-PRESSO outlier test would undergo stepwise removal. While in MR-Egger regression test results, the intercept was used to show the mean pleiotropic effects. The presence of pleiotropy was indicated by the MR-Egger regression method, and the IVW results were invalid at $p < 0.05$. In addition, leave-one-out analysis was also executed for traits with multiple IVs to check whether the reported causality was obviously driven by a single IV. Similarly, the indicated outlier IVs were detected to improve the results of Mendelian randomization. A value with $p < 0.05$ was considered as an outlier and removed from the analyses.

Bi-directional Mendelian randomization analysis

After investigating the causal association between POAG and the five common psychiatric disorders separately, we explored the reverse causality by extending the MR analysis above to bi-directional causal inference. As mentioned above, forward Mendelian randomization analyses were conducted by using POAG as the exposure and the psychiatric disorders as the outcomes. Conversely, the reverse Mendelian randomization analyses used individual psychiatric disorders as the exposure and POAG as the outcome to explore the potential causal association between POAG and psychiatric disorders. The standards of the parameters and the Mendelian randomization methods were set the same for the forward and reverse analyses, as well as the discovery and replication datasets.

A causality between the exposure and the outcome was accepted when the IVW result was significant and one of the following conditions was satisfied: (1) no heterogeneity was detected when the causal effects of the MR-Egger, weighted median, and weighted mode methods were in the same direction; (2) heterogeneity was detected but corrected by the MR-PRESSO global test (< 50% of IVs were considered as outliers); or (3) heterogeneity was detected and > 50% of the outliers were detected by MR-PRESSO global test, but the causal effects of the MR-Egger, weighted median, and weighted mode methods were significant and in the same direction[49–51].

A p-value of < 0.01 after Bonferroni correction was considered statistically significant, and a p-value between 0.01 and 0.05 was considered suggestively significant in our Mendelian randomization analyses. All two-sample Mendelian randomization analyses were performed using the TwoSampleMR R package in the R software (version 4.1.1)[52].

Results

GWAS datasets and instrumental variable selection

The GWAS summary statistics on the selected psychiatric disorders and POAG used in our study were carefully compared for database quality control. We manually checked the sample description of every GWAS summary dataset to make sure that the samples of the exposure were different from those of the outcome. Therefore, our Mendelian randomization results were unlikely to be influenced by sample overlap between each exposure–outcome pair. The list of IVs used for the Mendelian randomization analyses of POAG on psychiatric disorders of interest in this study is provided in Table 1.

The putative causal effect of POAG on psychiatric disorders

According to the current epidemiological findings on glaucoma and psychiatric disorders, glaucoma patients are prone to developing psychiatric disorders during disease progression. As such, we first performed the forward Mendelian randomization analysis of POAG on each psychiatric disorder of interest to investigate the causality. The summarized results of all forward Mendelian randomization analyses are shown in Table 2, Fig. 2, and Supplementary Fig. S1. More detailed information on the forward Mendelian randomization analyses, such as the results of the assessment of heterogeneity, as well as the MR-Egger regression test and the MR-PRESSO outlier test, is provided in Table 2 and Table 3.

Our results showed that genetically predicted POAG was significantly and positively associated with schizophrenia when considering the best causal estimation (IVW OR = 1.035, 95% CI: 1.009–1.062, $p = 0.008$; all results from four different methods were directionally consistent) (Table 2, Fig. 2). A p-value of 0.008 < 0.01 (adjusted p-value with Bonferroni correction for multiple testing) was considered significant. A forest plot visually displayed the positive association between genetic liability to POAG and schizophrenia risk (Supplementary Fig. S1a). Cochran's Q test revealed no heterogeneity across the recruited IVs ($Q = 101.545$, $p = 0.330$) (Table 2). The MR-PRESSO global test and MR-Egger regression test detected no presence of any horizontal pleiotropy or directional pleiotropy (MR-Egger intercept = -1.406×10^{-3}, SE = 3.620×10^{-3}, $p = 0.699$; MR-PRESSO global test, $p = 0.357$) (Table 3). The leave-one-out test detected no outliers, and the result was stable and would not be significantly altered by any individual SNP (Supplementary Fig. S2a). This is also presented in the funnel plot (Supplementary Fig. S3a). The scatter plot of genetic association with POAG versus genetic association with schizophrenia showed a significantly positive causality between the two diseases (Fig. 3a).

As for the other psychiatric disorders, the estimated causality consistently suggested that genetic predisposition to POAG was not related to any of them. Our results showed no evidence of the causal associations of POAG with ADHD (IVW OR = 1.022, 95% CI: 0.988–1.056, $p = 0.214$) (Table 2, Fig. 2). All four models suggested consistent results of no causality, even though no heterogeneity and pleiotropy were detected ($Q = 113.915$, $p = 0.090$; MR-Egger intercept = 2.562×10^{-4}, SE = 4.768×10^{-3}, $p = 0.957$; MR-PRESSO global test, $p = 0.095$) (Table 2, Table 3). This estimated effect was stable with no outliers, as detected by the leave-one-out test (Supplementary Fig. S2b) and shown in the funnel plot (Supplementary Fig. S3b). The scatter plot and forest plot also show a lack of association between

Table 1. Detailed information of SNPs in the Mendelian randomization analysis of POAG and the psychiatric disorders of interest.

SNP	Chr	Location	Association with SCZ			Association with ADHD			Association with AD			Association with BD			Association with DD		
			β	SE	*p*	*β*	SE	*p*	*β*	SE	*p*	*β*	SE	*p*	*β*	SE	*p*
rs10151220	14	34715465	/	/	/	−0.204	0.182	0.262	/	/	/	0.198	0.295	0.501	/	/	/
rs10160502	11	45376816	−0.030	0.146	0.838	−0.368	0.169	0.029	/	/	/	−0.405	0.301	0.179	/	/	/
rs10248136	7	39077397	−0.146	0.123	0.236	−0.120	0.152	0.430	−0.074	0.162	0.647	−0.283	0.255	0.266	−0.137	0.124	0.271
rs10268299	7	48105158	−0.261	0.171	0.126	−0.386	0.212	0.068	0.295	0.238	0.216	−0.542	0.343	0.114	0.079	0.183	0.667
rs10448285	9	129397014	0.064	0.096	0.505	−0.231	0.121	0.056	−0.197	0.124	0.110	−0.087	0.201	0.666	0.018	0.095	0.853
rs10517281	4	54027595	−0.062	0.139	0.653	−0.010	0.165	0.951	0.163	0.164	0.320	−0.067	0.288	0.817	−0.144	0.126	0.253
rs10800155	1	165723770	0.058	0.057	0.309	0.097	0.073	0.180	−0.025	0.063	0.684	−0.118	0.117	0.313	0.003	0.048	0.954
rs10906230	10	12851181	−0.030	0.169	0.861	−0.101	0.208	0.627	0.021	0.223	0.926	0.001	0.346	0.997	−0.284	0.171	0.097
rs109467	7	83278893	0.125	0.136	0.357	0.024	0.167	0.885	0.130	0.173	0.453	−0.800	0.277	0.004	0.188	0.134	0.160
rs1139795	22	19867771	0.074	0.106	0.487	0.130	0.133	0.330	−0.080	0.171	0.639	−0.011	0.213	0.961	/	/	/
rs113985657	6	597203	−0.053	0.146	0.718	−0.152	0.168	0.367	0.020	0.171	0.905	−0.096	0.285	0.736	0.153	0.131	0.245
rs114367221	16	51601948	−0.155	0.138	0.262	/	/	/	/	/	/	−0.279	0.271	0.304	/	/	/
rs11606709	11	46730522	0.566	0.169	0.001	0.034	0.201	0.867	0.017	0.222	0.939	0.310	0.341	0.363	−0.277	0.171	0.106
rs11658334	17	58830188	0.229	0.148	0.121	−0.336	0.183	0.067	0.032	0.193	0.868	0.094	0.304	0.757	−0.159	0.148	0.283
rs11694522	2	228085471	−0.068	0.168	0.683	0.003	0.205	0.990	−0.070	0.201	0.729	−0.083	0.351	0.813	0.039	0.155	0.803
rs117907084	8	8094540	−0.268	0.196	0.173	/	/	/	0.219	0.154	0.157	−0.359	0.426	0.400	0.069	0.118	0.561
rs11968883	6	158971411	0.053	0.152	0.730	0.000	0.191	1.000	−0.482	0.197	0.014	−0.337	0.316	0.287	−0.159	0.151	0.291
rs12133258	1	247990141	−0.098	0.159	0.537	0.012	0.196	0.950	/	/	/	0.069	0.321	0.831	/	/	/
rs12208086	6	36586070	0.181	0.120	0.132	0.003	0.151	0.985	0.274	0.145	0.059	0.015	0.246	0.952	0.030	0.112	0.785
rs12238998	1	92052303	0.003	0.159	0.986	−0.108	0.198	0.587	−0.258	0.218	0.237	0.255	0.322	0.428	0.126	0.169	0.455
rs12421242	11	102066240	−0.022	0.155	0.889	0.069	0.188	0.716	0.089	0.199	0.656	0.170	0.314	0.589	0.043	0.153	0.779
rs12540035	7	116159526	−0.085	0.113	0.449	0.151	0.139	0.280	−0.028	0.183	0.877	0.068	0.227	0.764	−0.075	0.141	0.594
rs12548263	8	124498734	0.247	0.174	0.156	/	/	/	−0.219	0.230	0.341	1.046	0.357	0.003	−0.001	0.177	0.994
rs12969002	18	11724979	0.411	0.161	0.011	0.060	0.197	0.761	−0.116	0.216	0.591	0.027	0.336	0.937	0.029	0.165	0.859
rs13022278	2	35862610	0.169	0.181	0.351	0.041	0.177	0.816	−0.329	0.225	0.143	0.184	0.299	0.539	−0.232	0.172	0.179
rs13085037	3	124312984	−0.005	0.163	0.977	0.299	0.200	0.135	0.060	0.186	0.749	0.182	0.337	0.589	−0.050	0.143	0.726
rs1385069	6	134374204	0.194	0.154	0.210	0.076	0.195	0.698	0.032	0.201	0.872	−0.020	0.314	0.950	0.365	0.154	0.018
rs1422174	5	92194417	−0.019	0.171	0.909	/	/	/	−0.093	0.289	0.748	−0.579	0.386	0.133	0.065	0.221	0.770
rs145556337	2	200444431	0.118	0.133	0.372	/	/	/	0.030	0.171	0.862	0.092	0.362	0.800	0.217	0.131	0.097
rs150372522	18	65972342	0.179	0.168	0.285	−0.077	0.204	0.705	−0.201	0.251	0.425	−0.060	0.335	0.859	−0.235	0.194	0.227
rs1577488	1	101078400	−0.044	0.129	0.733	−0.025	0.163	0.879	0.259	0.150	0.085	0.096	0.265	0.718	−0.018	0.116	0.878
rs1649068	10	60304864	0.158	0.103	0.123	0.289	0.125	0.021	0.072	0.135	0.595	0.089	0.208	0.671	0.048	0.104	0.643
rs17125973	14	53415359	0.114	0.168	0.498	0.283	0.204	0.164	0.192	0.231	0.405	0.293	0.345	0.395	0.034	0.177	0.847
rs1743080	14	92020604	0.061	0.151	0.684	−0.008	0.184	0.967	−0.242	0.216	0.261	0.814	0.304	0.007	0.029	0.166	0.860
rs17527016	4	111963719	−0.133	0.125	0.287	/	/	/	0.123	0.147	0.404	0.113	0.237	0.633	−0.076	0.113	0.500
rs190835765	4	38483655	0.019	0.133	0.889	/	/	/	0.323	0.133	0.015	0.311	0.259	0.230	0.076	0.102	0.453
rs2027312	9	129920463	−0.094	0.132	0.474	0.077	0.161	0.630	0.082	0.178	0.644	−0.038	0.266	0.888	0.153	0.137	0.265
rs2113818	2	12890860	0.255	0.155	0.101	−0.172	0.189	0.363	0.236	0.205	0.249	0.124	0.317	0.696	0.054	0.158	0.732
rs2207441	6	164325217	−0.127	0.154	0.410	0.305	0.189	0.107	0.023	0.193	0.905	−0.200	0.322	0.535	−0.246	0.148	0.097
rs2439386	15	67025403	−0.072	0.164	0.662	0.340	0.200	0.090	0.035	0.224	0.877	−0.101	0.345	0.770	−0.010	0.171	0.955
rs2472494	9	107695539	0.104	0.059	0.076	−0.026	0.074	0.724	0.031	0.078	0.695	−0.019	0.118	0.872	−0.044	0.060	0.463
rs2514879	8	108273318	−0.172	0.135	0.203	−0.014	0.162	0.929	−0.236	0.176	0.178	0.352	0.273	0.197	0.089	0.135	0.508
rs2526100	7	11677778	−0.010	0.159	0.952	−0.091	0.190	0.631	−0.147	0.212	0.489	0.190	0.324	0.558	−0.223	0.163	0.171
rs257336	16	65055840	−0.210	0.132	0.112	0.115	0.161	0.476	/	/	/	0.656	0.270	0.015	/	/	/
rs2579998	6	51477322	0.021	0.084	0.803	0.157	0.101	0.121	0.143	0.104	0.172	0.087	0.173	0.616	0.189	0.080	0.018
rs2667477	12	84023388	0.120	0.101	0.234	−0.137	0.123	0.266	−0.008	0.140	0.953	0.393	0.204	0.054	−0.111	0.108	0.305
rs2735114	6	29910034	0.568	0.196	0.004	−0.006	0.166	0.970	−0.075	0.181	0.679	0.422	0.278	0.128	0.227	0.138	0.101
rs28497695	15	57023951	0.284	0.126	0.025	/	/	/	−0.157	0.164	0.337	0.481	0.254	0.058	−0.273	0.125	0.030
rs286487	10	90030119	−0.082	0.165	0.620	0.284	0.198	0.151	0.001	0.224	0.995	−0.091	0.338	0.787	−0.136	0.172	0.427
rs2875238	11	130282078	−0.033	0.158	0.832	−0.057	0.211	0.785	−0.107	0.203	0.599	0.206	0.319	0.519	−0.151	0.156	0.334
rs31916	5	14814883	0.150	0.171	0.381	0.064	0.208	0.758	−0.021	0.227	0.925	−0.422	0.355	0.235	0.013	0.174	0.941
rs33155	12	30985442	/	/	/	−0.245	0.179	0.170	0.280	0.182	0.125	−0.132	0.304	0.663	0.249	0.140	0.077
rs33912345	14	60976537	/	/	/	/	/	/	0.145	0.088	0.099	0.016	0.127	0.901	−0.007	0.067	0.920
rs34163217	1	178586984	0.080	0.173	0.643	−0.001	0.205	0.995	−0.275	0.233	0.238	−0.591	0.350	0.092	0.239	0.180	0.182
rs34508066	3	66837509	0.126	0.157	0.423	0.130	0.196	0.506	0.104	0.215	0.630	−0.128	0.322	0.691	−0.091	0.165	0.580
rs35592623	8	120702717	0.048	0.177	0.788	0.042	0.225	0.850	0.313	0.222	0.159	0.069	0.374	0.854	0.253	0.171	0.138
rs35666652	11	86491772	−0.141	0.163	0.385	−0.050	0.199	0.802	0.416	0.227	0.068	0.379	0.336	0.259	/	/	/
rs3825942	15	74219582	/	/	/	−0.275	0.150	0.066	0.114	0.153	0.455	0.075	0.251	0.766	0.183	0.117	0.120
rs3909355	5	120654808	−0.148	0.176	0.399	−0.056	0.215	0.794	−0.502	0.203	0.014	−0.151	0.362	0.676	−0.346	0.156	0.026
rs4076000	1	68837169	/	/	/	0.058	0.188	0.757	0.003	0.197	0.989	0.348	0.310	0.263	0.112	0.152	0.462
rs41283694	10	60156574	0.218	0.171	0.202	0.055	0.226	0.807	−0.127	0.450	0.777	0.836	0.327	0.011	0.329	0.350	0.347
rs4142696	12	26800201	−0.153	0.172	0.374	0.107	0.210	0.611	−0.271	0.203	0.181	0.049	0.352	0.890	−0.158	0.155	0.310
rs41543317	17	44087500	/	/	/	0.142	0.167	0.395	0.039	0.169	0.817	−0.142	0.275	0.605	0.001	0.130	0.993

(to be continued)

Table 1. (continued)

SNP	Chr	Location	Association with SCZ			Association with ADHD			Association with AD			Association with BD			Association with DD		
			β	SE	*p*	*β*	SE	*p*	*β*	SE	*p*	*β*	SE	*p*	*β*	SE	*p*
rs4307771	2	213723819	−0.067	0.154	0.666	/	/	/	0.323	0.238	0.175	−0.380	0.325	0.242	0.305	0.183	0.096
rs4414666	2	66537344	0.098	0.152	0.518	0.097	0.187	0.605	−0.057	0.202	0.779	0.425	0.319	0.182	−0.188	0.155	0.223
rs4441044	11	69500363	−0.016	0.158	0.918	−0.158	0.194	0.416	−0.152	0.220	0.488	0.229	0.319	0.473	−0.205	0.168	0.224
rs4612174	6	136462744	−0.020	0.097	0.837	−0.142	0.121	0.241	−0.051	0.124	0.680	0.144	0.200	0.472	−0.103	0.095	0.279
rs4652964	1	38078300	−0.226	0.157	0.150	−0.300	0.190	0.113	−0.203	0.208	0.331	0.270	0.319	0.397	−0.322	0.159	0.044
rs4653159	1	36579215	/	/	/	0.298	0.156	0.056	−0.057	0.167	0.733	0.102	0.270	0.707	−0.004	0.128	0.977
rs4775427	15	61951235	0.126	0.145	0.383	0.148	0.176	0.400	−0.214	0.189	0.257	0.088	0.297	0.767	0.125	0.145	0.388
rs4842316	12	79974565	−0.180	0.157	0.252	−0.251	0.192	0.191	−0.007	0.220	0.976	0.602	0.318	0.058	−0.129	0.169	0.446
rs55882252	2	153361700	0.131	0.110	0.237	0.159	0.136	0.241	0.033	0.144	0.816	0.067	0.224	0.765	−0.079	0.110	0.474
rs56233426	3	186128816	0.089	0.109	0.416	0.116	0.157	0.462	−0.061	0.138	0.660	0.284	0.224	0.204	/	/	/
rs565066	11	56871325	−0.218	0.160	0.172	0.123	0.195	0.528	−0.057	0.228	0.803	0.269	0.324	0.405	−0.230	0.176	0.191
rs5750494	22	38176979	0.072	0.156	0.646	0.474	0.191	0.013	0.072	0.199	0.718	0.236	0.312	0.449	0.007	0.153	0.964
rs58073046	11	120248493	0.202	0.103	0.050	0.245	0.121	0.043	0.186	0.131	0.155	0.374	0.207	0.071	−0.061	0.101	0.543
rs58265464	5	149408929	0.065	0.147	0.658	0.243	0.188	0.197	/	/	/	0.288	0.298	0.334	/	/	/
rs6117318	20	6507717	−0.115	0.127	0.363	0.144	0.151	0.343	/	/	/	0.134	0.253	0.595	/	/	/
rs62283811	3	171820890	0.168	0.143	0.239	−0.201	0.181	0.265	0.043	0.167	0.797	−0.012	0.370	0.975	0.026	0.128	0.842
rs6475604	9	22052734	−0.005	0.042	0.913	0.008	0.051	0.882	−0.012	0.054	0.824	0.115	0.085	0.177	0.019	0.042	0.656
rs6490697	13	22679011	−0.003	0.119	0.978	0.007	0.144	0.963	0.083	0.144	0.563	−0.096	0.248	0.699	−0.154	0.111	0.167
rs6519133	22	39096602	0.099	0.154	0.523	−0.308	0.205	0.134	0.112	0.193	0.562	0.312	0.310	0.315	−0.189	0.148	0.201
rs6602453	10	10840849	0.246	0.145	0.089	0.242	0.177	0.172	−0.067	0.196	0.731	−0.026	0.293	0.929	−0.140	0.150	0.351
rs6729430	2	11934756	−0.096	0.210	0.649	/	/	/	/	/	/	0.388	0.314	0.217	/	/	/
rs6845653	4	7899379	0.027	0.067	0.688	0.130	0.084	0.122	−0.046	0.085	0.589	0.040	0.138	0.771	−0.055	0.065	0.400
rs686768	11	86361508	0.173	0.129	0.180	−0.259	0.157	0.099	0.195	0.163	0.231	−0.041	0.268	0.879	0.120	0.126	0.338
rs687914	2	45878760	/	/	/	−0.090	0.212	0.672	−0.061	0.241	0.802	−0.426	0.338	0.207	0.156	0.185	0.399
rs6920127	6	92582660	−0.047	0.172	0.785	−0.063	0.210	0.765	−0.024	0.223	0.916	−0.375	0.353	0.288	−0.108	0.171	0.527
rs6951875	7	103632175	/	/	/	−0.280	0.223	0.209	−0.029	0.227	0.900	−0.341	0.360	0.344	0.038	0.174	0.827
rs7099316	10	126469005	0.017	0.152	0.912	0.402	0.184	0.029	0.120	0.201	0.550	0.474	0.309	0.126	−0.153	0.155	0.322
rs7137828	12	111932800	−0.006	0.116	0.957	0.136	0.144	0.346	0.009	0.150	0.950	0.203	0.234	0.386	−0.050	0.116	0.665
rs72637444	13	97876689	0.149	0.192	0.436	−0.159	0.222	0.472	0.080	0.232	0.729	−0.413	0.372	0.268	−0.021	0.179	0.909
rs7275118	20	18010447	0.155	0.155	0.317	−0.214	0.197	0.276	−0.028	0.197	0.886	−0.407	0.321	0.204	−0.111	0.151	0.464
rs73071655	20	1121939	−0.082	0.173	0.636	0.027	0.217	0.901	0.685	0.243	0.005	0.154	0.354	0.663	0.105	0.187	0.574
rs735379	2	34257592	−0.213	0.173	0.219	−0.192	0.214	0.369	0.089	0.228	0.697	0.337	0.361	0.350	0.011	0.175	0.948
rs754634	14	75097431	0.070	0.174	0.686	0.053	0.214	0.805	0.233	0.226	0.304	−0.016	0.354	0.964	0.144	0.174	0.409
rs7739648	6	1540483	0.167	0.091	0.067	−0.174	0.110	0.116	0.054	0.116	0.639	−0.242	0.186	0.193	−0.092	0.089	0.300
rs782610	2	55935395	−0.142	0.155	0.359	0.330	0.189	0.080	−0.353	0.231	0.126	−0.254	0.315	0.420	−0.082	0.177	0.645
rs78914827	5	133415082	−0.023	0.153	0.880	−0.066	0.183	0.718	0.026	0.226	0.907	−0.321	0.317	0.312	−0.104	0.173	0.549
rs7946009	11	128387422	0.083	0.155	0.593	0.086	0.192	0.655	0.061	0.200	0.760	−0.393	0.315	0.213	0.102	0.154	0.507
rs7969703	12	18218609	0.097	0.176	0.581	0.298	0.210	0.155	0.163	0.192	0.396	−0.191	0.368	0.604	0.154	0.148	0.297
rs929218	7	117653665	−0.186	0.151	0.218	0.156	0.186	0.401	−0.538	0.194	0.005	−0.802	0.304	0.008	−0.120	0.150	0.424
rs9470997	6	39166247	0.165	0.157	0.294	0.235	0.193	0.224	0.124	0.205	0.544	0.769	0.330	0.020	−0.048	0.157	0.762
rs9544017	13	76247179	−0.099	0.135	0.463	−0.296	0.166	0.074	0.309	0.176	0.078	0.104	0.272	0.703	0.163	0.135	0.226
rs9819278	3	85144350	0.033	0.121	0.785	0.260	0.150	0.083	0.065	0.156	0.676	−0.363	0.249	0.145	0.029	0.120	0.811
rs9913911	17	10031183	0.024	0.074	0.745	−0.024	0.094	0.799	0.025	0.096	0.791	−0.064	0.159	0.689	0.117	0.074	0.111
rs993471	1	103385373	/	/	/	0.059	0.158	0.711	−0.449	0.176	0.011	−0.537	0.265	0.043	−0.277	0.135	0.040
All - Inverse variance weighted			0.035	0.013	0.008	0.021	0.017	0.214	0.016	0.016	0.325	0.040	0.027	0.143	−0.008	0.013	0.526
All - MR Egger			0.047	0.034	0.172	0.019	0.047	0.686	0.077	0.042	0.069	0.054	0.072	0.458	0.046	0.033	0.165

ADHD, attention deficit/hyperactivity disorder; AD, anxiety disorder; BD, bipolar disorder; Chr, chromosome; DD, depressive disorder; POAG, primary open-angle glaucoma; SCZ, schizophrenia; SE, standard error; SNP, single-nucleotide polymorphism.

POAG and ADHD (Fig. 3b, Supplementary Fig. S1b). Similarly, other causal association estimations suggested that genetic predisposition to POAG was not related to anxiety disorder (IVW OR = 1.016, 95% CI: 0.984–1.049, p = 0.325), bipolar disorder (IVW OR = 1.040, 95% CI: 0.987–1.097, p = 0.143), or depressive disorder (IVW OR = 0.992, 95% CI: 0.967–1.017, p = 0.526) (Table 2, Fig. 2), and were not disturbed by any heterogeneity or pleiotropy (Tables 2, 3). In addition, no outliers were found by the leave-one-out test (Supplementary Fig. S2c–e), and the corresponding results were demonstrated individually by funnel plots (Supplementary Fig. S3c–e). The scatter plots and forest plots presented no evidence of the causal effect of POAG on anxiety disorder, bipolar disorder, and depressive disorder (Fig. 3c–e and Supplementary Fig. S1c–e).

The putative causality of psychiatric disorders on POAG

After conducting the forward analyses, we found that only schizophrenia was genetically caused by POAG, while the other disorders were not. Nevertheless, whether this was a unidirectional causality remained inconclusive. Therefore, we performed the reverse analyses by extending the forward ones to the corresponding bi-directional causal inferences. Through using individual psychiatric disorders as the exposure and POAG as the outcome, we further explored whether there was any reverse causality from a genetic liability to psychiatric disorders to POAG. A summary of the reverse causality results is shown in Table 4 and Supplementary Fig. S4. Other results, such as the assessment of heterogeneity,

Table 2. Mendelian randomization analysis for the causal effects of POAG on psychiatric disorders of interest.

Exposure	Outcome	Method	SNPs	Mendelian randomization				Heterogeneity	
				OR	LL	UL	*p*	Q	Q_*p*
POAG	SCZ	IVW	97	1.035	1.009	1.062	0.008	101.545	0.330
		MR-Egger	97	1.048	0.980	1.121	0.172	101.383	0.308
		Weighted median	97	1.026	0.986	1.067	0.214		
		Weighted mode	97	1.028	0.973	1.087	0.328		
		MR PRESSO	97	1.035	1.009	1.062	0.008		
	ADHD	IVW	96	1.022	0.988	1.056	0.214	113.915	0.090
		MR-Egger	96	1.019	0.930	1.117	0.686	113.911	0.079
		Weighted median	96	1.009	0.957	1.065	0.732		
		Weighted mode	96	1.028	0.948	1.115	0.505		
		MRPRESSO	96	1.022	0.988	1.056	0.214		
	AD	IVW	99	1.016	0.984	1.049	0.325	103.610	0.330
		MR-Egger	99	1.080	0.995	1.171	0.069	101.019	0.370
		Weighted median	99	1.020	0.970	1.073	0.443		
		Weighted mode	99	1.000	0.935	1.070	0.994		
		MR-PRESSO	99	1.016	0.984	1.049	0.325		
	BD	IVW	107	1.040	0.987	1.097	0.143	128.276	0.070
		MR-Egger	107	1.055	0.916	1.215	0.458	128.222	0.061
		Weighted median	107	1.048	0.972	1.129	0.222		
		Weighted mode	107	1.048	0.938	1.171	0.407		
		MR-PRESSO	107	1.040	0.987	1.097	0.143		
	DD	IVW	96	0.992	0.967	1.017	0.526	104.871	0.229
		MR-Egger	96	1.047	0.982	1.116	0.165	101.382	0.283
		Weighted median	96	1.002	0.964	1.042	0.914		
		Weighted mode	96	0.996	0.946	1.049	0.883		
		MR-PRESSO	96	0.992	0.967	1.017	0.526		

ADHD, attention deficit/hyperactivity disorder; AD, anxiety disorder; BD, bipolar disorder; DD, depressive disorder; IVW, inverse variance weighted; LL, lower limits of odds ratio; OR, odds ratio; POAG, primary open-angle glaucoma; SCZ, schizophrenia; SNP, single-nucleotide polymorphism; UL, upper limits of odds ratio.

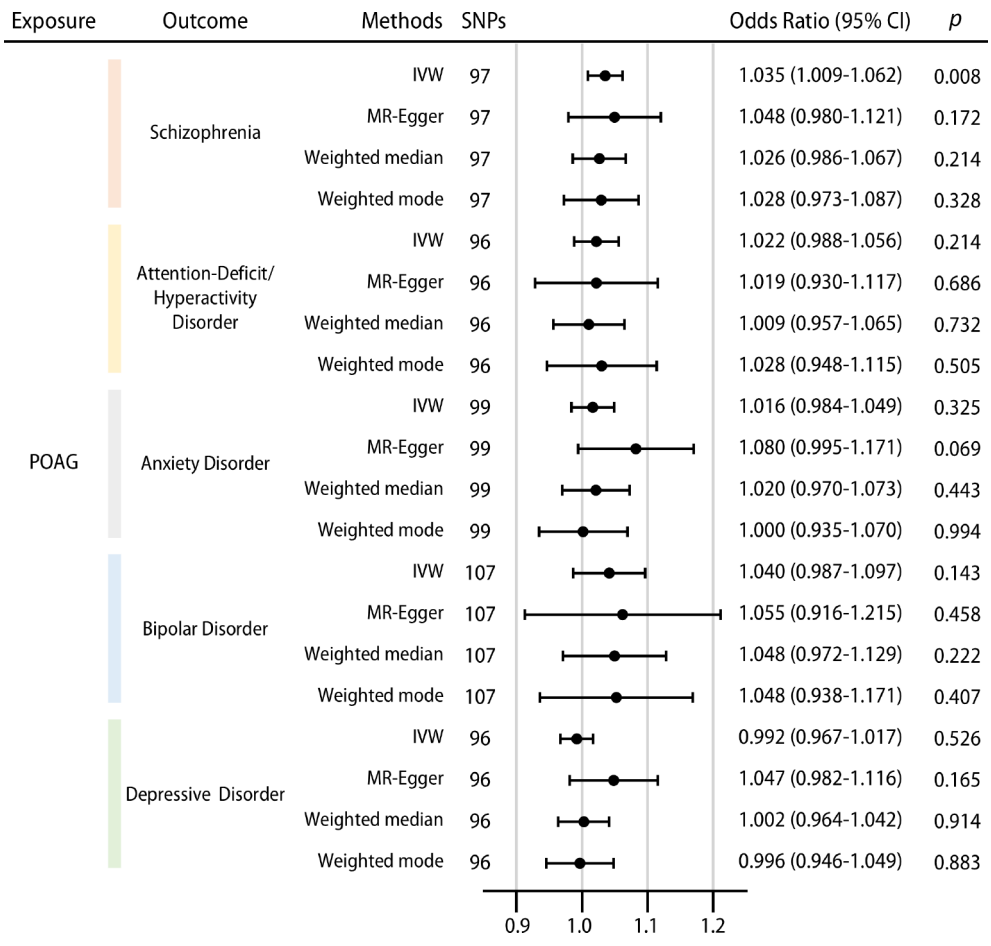

Fig. 2 The causal effects of POAG on schizophrenia (SCZ), ADHD, anxiety disorder (AD), bipolar disorder (BD), and depressive disorder (DD). Error bars represent the 95% confidence intervals[39] for the estimated effects. IVW, inverse variance weighting.

Table 3. Assessment of the pleiotropy of the Mendelian randomization analysis for the causality of POAG on the psychiatric disorders of interest.

Exposure	Outcome	MR-Egger intercept			MR-PRESSO global test	
		Intercept	SE	*p*	RSSobs	*p*
POAG	SCZ	−1.406E-03	3.620E-03	0.699	103.453	0.357
	ADHD	2.562E-04	4.768E-03	0.957	116.353	0.095
	AD	−6.995E-03	4.435E-03	0.118	105.523	0.349
	BD	−1.589E-03	7.535E-03	0.833	130.448	0.079
	DD	−6.239E-03	3.469E-03	0.075	106.935	0.252

ADHD, attention deficit/hyperactivity disorder; AD, anxiety disorder; BD, bipolar disorder; DD, depressive disorder; POAG, primary open-angle glaucoma; SCZ, schizophrenia; SE, standard error.

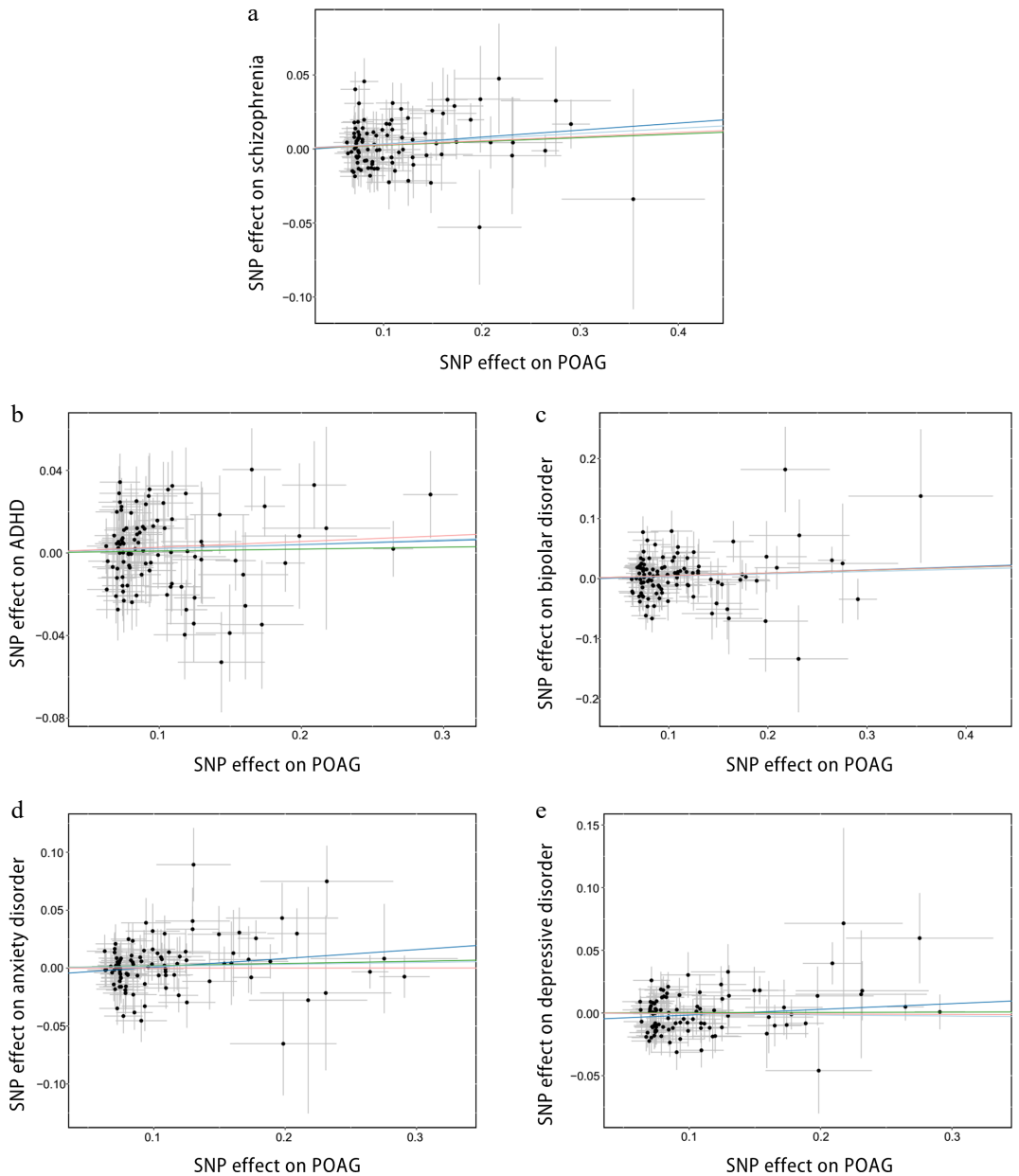

Fig. 3 Scatter plots of the causal effects of POAG on the psychiatric disorders of interest. (a) Effects of POAG on schizophrenia (SCZ); (b) effects of POAG on ADHD; (c) effects of POAG on anxiety disorder (AD); (d) effects of POAG on bipolar disorder (BD); (e) effects of POAG on depressive disorder (DD). The slope of each line indicates the causal effects estimated by each method. Light blue, inverse variance weighted (IVW) method; dark blue, MR-Egger method; green, weighted median method; pink, weighted mode method. SNP, single nucleotide polymorphism.

as well as the MR-Egger regression test and the MR-PRESSO outlier test, are demonstrated in Table 4 and Supplementary Table S2 .

Our results reported that genetic susceptibility to schizophrenia failed to be associated with POAG (IVW OR = 1.034, 95% CI: 0.983–1.088, p = 0.192) (Table 4). All four models consistently demonstrated the same. The forest plot did not display any causal associations (Supplementary Fig. S4a). After performing Cochran's Q test, no heterogeneity was detected (Q = 67.835, p = 0.256)

Table 4. Mendelian randomization analysis for the causal effect of the psychiatric disorders of interest on POAG.

Exposure	Outcome	Method	SNPs	Mendelian randomization				Heterogeneity	
				OR	LL	UL	*p*	Q	Q_*p*
SCZ	POAG	IVW	62	1.034	0.983	1.088	0.192	67.835	0.256
		MR-Egger	62	1.022	0.847	1.232	0.823	67.815	0.228
		Weighted median	62	1.042	0.971	1.118	0.250		
		Weighted mode	62	1.068	0.923	1.235	0.381		
		MR PERSSO	62	1.034	0.983	1.088	0.192		
ADHD	POAG	IVW	41	0.941	0.880	1.006	0.074	47.089	0.205
		MR Egger	41	0.824	0.615	1.104	0.202	46.107	0.202
		Weighted median	41	0.951	0.869	1.042	0.282		
		Weighted mode	41	0.976	0.811	1.176	0.803		
		MR-PRESSO	41	0.941	0.880	1.006	0.074	47.089	0.205
AD	POAG	IVW	14	1.085	0.970	1.213	0.153	7.889	0.851
		MR-Egger	14	1.039	0.798	1.354	0.779	7.767	0.803
		Weighted median	14	1.109	0.960	1.281	0.159		
		Weighted mode	14	1.113	0.902	1.372	0.337		
		MR-PRESSO	14	1.085	0.970	1.213	0.153		
BD	POAG	IVW	28	1.039	0.997	1.083	0.068	13.929	0.982
		MR-Egger	28	1.037	0.945	1.139	0.450	13.927	0.974
		Weighted median	28	1.041	0.979	1.107	0.198		
		Weighted mode	28	1.034	0.951	1.123	0.441		
		MR-PRESSO	28	1.039	0.997	1.083	0.068		
DD	POAG	IVW	25	1.084	0.977	1.202	0.129	25.029	0.404
		MR-Egger	25	0.995	0.795	1.245	0.967	24.280	0.388
		Weighted median	25	1.132	0.970	1.321	0.115		
		Weighted mode	25	1.208	0.911	1.602	0.202		
		MR-PRESSO	25	1.084	0.977	1.202	0.129		

ADHD, attention deficit/hyperactivity disorder; AD, anxiety disorder; BD, bipolar disorder; DD, depressive disorder; IVW, inverse variance weighted; LL, lower limits of odds ratio; OR, odds ratio; POAG, primary open-angle glaucoma; SCZ, schizophrenia; SNP, single-nucleotide polymorphism; UL, upper limits of odds ratio.

(Table 4). No horizontal and directional pleiotropy was indicated by the MR-PRESSO global test (MR-PRESSO global test $p = 0.278$) and the MR-Egger regression test (MR-Egger intercept = 1.042×10^{-3}, SE = 7.863×10^{-3}, $p = 0.895$), respectively (Supplementary Table S2). The leave-one-out test and funnel plot showed no outliers; therefore, the estimated causal effect of schizophrenia on POAG was stable and would not be significantly influenced by any SNP (Supplementary Figs S5a and S6a). The invalid causal effect was also demonstrated in the scatter plot (Supplementary Fig. S7a).

As for the other psychiatric disorders, including ADHD (IVW OR = 0.941, 95% CI: 0.880–1.006, $p = 0.074$), anxiety disorder (IVW OR = 1.085, 95% CI: 0.970–1.213, $p = 0.153$), bipolar disorder (IVW OR = 1.039, 95% CI: 0.997–1.083, $p = 0.068$), and depressive disorder (IVW OR = 1.084, 95% CI: 0.977–1.202, $p = 0.129$), our results indicated that there was a lack of a causal effect of these psychiatric disorders on POAG (Table 4 and Supplementary Fig. S4b–e). No evidence of heterogeneity and pleiotropy was found among them (Table 4 and Supplementary Table S2). Other results, such as those of the leave-one-out tests, funnel plots, and scatter plots, are presented in Supplementary Figs S5b–e, S6b–e, and S7b–e.

Validation of the putative causality between POAG and schizophrenia

Since a genetic predisposition to POAG was positively associated with the incidence of schizophrenia, a validation dataset was introduced to further validate the putative causal relationship. Repeatedly, as the discovery dataset, we performed both a bi-directional two-sample Mendelian randomization analysis to investigate the existence and direction of the putative causality. The summarized results of the validation dataset are shown in Supplementary Tables S3 and S4.

A significantly and positively causal effect of the genetic predisposition to POAG on the risk of schizophrenia was reported and validated when considering the best causal estimation in the validation dataset (IVW OR = 1.062, 95% CI: 1.016–1.109, $p = 0.007$; all results from four different methods were directionally consistent) (Supplementary Table S3). A p-value of 0.007 < 0.01 (adjusted p-value after Bonferroni correction) was considered to be significant. The forest plot and scatter plot presented the positive association between POAG and the risk of schizophrenia visually (Supplementary Fig. S8a, b). No evidence of heterogeneity and pleiotropy was revealed by the Cochran's Q test (Q = 2.009, $p = 0.919$) (Supplementary Table S3), or the MR-PRESSO global test (MR-PRESSO global test $p = 0.916$) and MR-Egger regression test (MR-Egger intercept = 1.125×10^{-3}, SE = 2.382×10^{-2}, $p = 0.964$) (Supplementary Table S5). The leave-one-out plot and funnel plots are presented in Supplementary Fig. S8c, d.

In contrast, no causal effect of schizophrenia on POAG was found in the reverse analysis of the validation dataset (IVW OR = 0.970, 95% CI: 0.887–1.061, $p = 0.510$) (Supplementary Table S4). Detailed information is shown in the corresponding tables and figures (Supplementary Table S6 and Supplementary Fig. S9a–d). This result served as a good validation of our discovery dataset.

Discussion

Psychiatric diseases and glaucoma are increasingly prevalent, accounting for continual rises in healthcare costs, which are becoming a substantial share of disability cases in the general population worldwide[1–5,53,54]. Currently, increasing studies remind us of the comorbidity between psychiatric diseases and glaucoma[10–13]. A significantly higher prevalence of psychiatric disorders was observed in patients with glaucoma, and vice versa[14–20,23,55]. These epidemiological findings suggested that psychiatric disorders and glaucoma may be closely correlated. However, given the limitations of the observational studies, simply and superficially relying on the

observational studies will never be satisfactory. Current understandings have been restricted to observing their comorbidity rather than extending to a causality study.

To the best of our knowledge, our study comprehensively explored the causal associations between psychiatric disorders and glaucoma. We suggest that genetically predicted POAG is mildly associated with the risk of schizophrenia, whereas schizophrenia was not causally associated with POAG. No evidence of a causal association between POAG and other psychiatric disorders, including ADHD, anxiety disorder, bipolar disorder, and depressive disorder, was found.

Our findings add updated knowledge to the observational findings for POAG and schizophrenia. This is consistent with the recent studies demonstrating that a diagnosis of glaucoma preceded a diagnosis of schizophrenia[16,56]. Several studies also found that patients with glaucoma have a higher prevalence of schizophrenia[14–16]. The retinal vascular trajectory, which was related to retinal nerve fiber layer thinning and retinal vasculature, was closely related to schizophrenia and might explain the causal association[57]. In addition, microvascular dysfunction in the retinal arterioles was also observed in both glaucoma and schizophrenia, indicating their connections[58–60]. More importantly, CAV1 and CAV2, which are significantly associated with POAG, were also indicated to be involved in the development of schizophrenia[61–65]. The involvement of neurodegenerative disease-related factors should also be given careful consideration. Higher polygenic risk for schizophrenia was reported to be associated with a thinner ganglion cell inner plexiform layer (GC-IPL) thickness[66]. Patients with schizophrenia were also found to show measurable differences in retinal neural integrity, such as reduced macular GC-IPL and retinal nerve fiber layer (RNFL) thicknesses, which are hallmarks of glaucoma's development and progression[67]. One of the neurotrophic factors, called brain-derived neurotrophic factor (BDNF), was found to be associated with schizophrenia[68]. BDNF supports the survival and functional maintenance of retinal ganglion cells, whose degeneration is a hallmark of glaucoma[69]. However, the causal association is mild in our study, and larger-scale datasets are required to further validate the findings. The latest literature has also reported that sleep-related factors, such as getting up easily in the morning and sleep duration, are associated with a higher risk of POAG[70]. We believe that future analyses using more comprehensive datasets will provide valuable evidence of the potential mediators in the complex mechanisms between POAG and psychiatric disorders.

Intriguingly, our findings are in contrast to other studies that reported the associations between other psychiatric disorders and glaucoma[17–20]. Nevertheless, those observed associations might be due to unmeasured confounding factors and biases of the observational research, and the current evidence is not adequate to support the existence of a causal association. Furthermore, psychiatric disorders are among the comorbid conditions that are often present among patients with chronic diseases[71,72]. Since patients with glaucoma often suffer from a chronic disease process and are continuously afraid of blindness, they are prone to developing psychiatric disorders, such as anxiety and depression[12,73,74]. In addition, there are several clinical studies implying that the anticholinergic effects of antipsychotics used among patients with psychiatric diseases could increase the intraocular pressure and contribute to the development of glaucoma[75,76]. All of these serve as confounders that reduce the explanatory power of the observational results.

One of the strengths of our study lies in the bi-directional two-sample Mendelian randomization design. Mendelian randomization is thought to offer a 'natural' randomized trial for large-scale populations, and is considered to be Mother Nature's randomized controlled trial, ranking at the top in the hierarchy of the scientific evidence pyramid[37]. This approach makes our study less susceptible to confounders, reverse causality, and error measurement. Additionally, we are able to estimate the bi-directional causal associations with a validation dataset to prevent the possibility of false positive results. We also performed a series of sensitivity analyses to ensure the consistency of our causal estimation and the absence of any heterogeneity or pleiotropy, making our findings more credible. Investigating the genetic causal association could help to further understand how genetic variants contribute to the disease's development and progression. Besides the delivery of high-quality interventions, our identification and quantification of causality are also vital for the implementation of effective prevention strategies. Our study also has limitations. A less stringent threshold ($p < 5 \times 10^{-6}$) was adopted as the trade-off between IV quality and quantity. Although we made efforts to ensure the robustness of the results by implementing rigorous sensitivity approaches, such as the MR-Egger, weighted median, and MR-PRESSO methods, larger-scale datasets are required for further validation in the future. The population only involved individuals of European ancestry, and exploration of ethnic discrepancies could be conducted if data are available. Additionally, while the FinnGen dataset is geographically distinct, residual population stratification still cannot be entirely ruled out to avoid sample overlap issues. Subgroup analyses, including stratifications based on age and sex, could not be performed due to the limitations of the currently available GWAS summary statistics. The current controversy on epidemiological evidence is mainly focused on POAG, and further exploration of other subtypes of glaucoma could be performed.

Conclusions

In conclusion, our study suggests a potential causal association of a genetic liability to POAG with schizophrenia, while no evidence of causality for a genetic predisposition to schizophrenia on POAG was identified. The causal associations of a genetic liability to POAG and other psychiatric disorders, including ADHD, anxiety disorder, bipolar disorder, and depressive disorder, were unfounded, indicating that the previously observed correlations might be affected by potential confounding factors. Optimized strategies for their observed comorbidity should be further developed in clinical practice.

Ethical statements

No ethical approval was required, as this study has been conducted using publicly available and open-access summary statistics, and no human subjects or animals were enrolled.

Author contributions

The authors confirm their contributions to the paper as follows: study conception and design: Zheng C, Zeng R, Wu G, Hu Y, Yu H; data collection: Zheng C; analysis and interpretation of results: Zheng C, Zeng R; draft manuscript preparation: Zheng C, Zeng R, Wu G; critical revision of the manuscript for important intellectual content: Hu Y, Yu H; manuscript revision: Zheng C, Zeng R, Wu G; funding acquisition: Yu H; administrative, technical, or material support: Hu Y, Yu H. All authors reviewed the results and approved the final version of the manuscript.

Data availability

GWAS summary statistics are available from the original manuscript of each study in Supplementary Table S1 and the GWAS catalog (www.ebi.ac.uk/gwas). All of the codes used in the study are available upon reasonable request from the corresponding author.

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Conflict of interest

The authors declare that they have no conflict of interest.

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