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Association between retinal nerve fiber layer thickness and psychiatric disorders: a mendelian randomization study

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Abstract

Background Retinal nerve fiber layer thickness, as a new visual indicator that may help diagnose mental disorders, is gaining attention from researchers. However, the causal relationship between retinal nerve fiber layer thickness and mental disorders is still to be effectively proved.

Methods A bidirectional Two-sample Mendelian randomization analysis was utilized to analyse aggregated data from large-scale genome-wide association studies, we selected genetic loci for retinal nerve fiber layer thickness in independent retinal abnormalities and three prevalent psychiatric disorders (schizophrenia, depression, bipolar disorder) as instrumental variables. The Two-sample Mendelian randomization analysis was mainly performed by inverse variance weighting and weighted median method. The Cochran Q test and leave-one-out sensitivity were used to ensure the robustness of the results. The Mendelian random polymorphism residuals and outliers were used to detect single nucleotide polymorphism outliers, and MR-Egger intercept test was used to test single nucleotide polymorphism horizontal pleiotropy.

Results IVW showed that retinal nerve fiber layer thickness was positively associated with schizophrenia (OR = 1.057, 95%CI: 1.000-1.117, $P < 0.05$), in the study of bipolar disorder, MR analysis also suggested a positive causal relationship between retinal nerve fiber layer thickness and bipolar disorder (OR = 1.025, 95%CI: 1.005–1.046, $P < 0.05$), which indicated possible causal relationships between retinal nerve fiber layer thickness and these two diseases. Depression (OR = 1.000143, 95%CI: 0.9992631–1.001024, $P = 0.74$) indicated no significant causal association. No reverse causal effects of psychiatric disorders on retinal nerve fiber layer thickness were found.

Conclusions A statistically significant causal relationship between retinal nerve fiber layer thickness and schizophrenia and bipolar disorder has been supported by genetic means, indicating RNFL has potential to aid in the diagnosis of schizophrenia and bipolar disorder.

Keywords Retinal nerve fiber layer thickness, Schizophrenia, Bipolar disorder, Depression, Mendelian randomization

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Introduction

The retina is a transparent membrane located in the wall of the eye. It senses light stimuli and converts them into electrical activity on nerve fibers, which are transmitted through the optic nerve to the occipital visual center of the brain, thus forming vision. Previous studies have pointed out that the retina and the central nervous system have the same embryonic origin, and the structure is related to the cerebral cortex, which is regarded as an extension of the central nervous system [1–3]. With the rapid development of retinal imaging technology, we can obtain different structural and functional information through different imaging techniques, including changes in the thickness of retinal structure, the condition of peri-retinal micro-vessels, and the state of cells and inflammation in retinal tissue [4, 5]. Because of the relationship between the retina and the central nervous system, some researchers have linked it to the study of neuropsychiatric diseases.

Mental disorders, such as schizophrenia, depression and bipolar disorder, have been an urgent public health problem in the world due to their high prevalence and disability rate. In the course of actual clinical work, these three mental disorders are intersecting as well as similar in etiology, and co-symptomatic in clinical manifestations, making them easy to miss and misdiagnose in clinical diagnostic evaluations. Besides, on the one hand, mental disorders are often hidden in the early stage, when the symptoms are clear, it usually develops seriously. On the other hand, the diagnosis is based on clinical assessment, and there are currently no biological tools to help diagnose mental illness, which leads to some subjectivity. Therefore, we need a trait biomarker that can help us recognize and diagnose disease. Current research has admittedly pointed out that the pathological basis for the development of schizophrenia is related to a series of biochemical microenvironmental changes in the brain, such as neurodevelopment and neuroinflammation, and that the carriers of these changes are the various cells that make up the brain tissue; at the same time, the fact that the retina has been proved to be homologous to the development of the central nervous system also implies that there exists a similarity between the two, and that the state of the retina may, in a certain degree, parallel the state of the brain [3]. Although the correlation between retinal changes and the clinical manifestations of psychiatric illnesses has not yet been investigated, retinal changes may be considered a potential biomarker for the study of schizophrenia and bipolar disorder. Previous studies in the literature have pointed to a correlation between visual hallucinations and the structural function of the retina [6, 7].

At present, the retina is the only part of the central nervous system that can be imaged optically at a high resolution. At the same time, the information acquired by retinal imaging technology is fast and noninvasive. In recent years, researchers have continued to find correlations between the retina and its associated structures and neurological disorders, and a study of Australian twins found that adults with psychotic symptoms and those diagnosed with schizophrenia had wide retinal micro-vessels [8]. In additional, there have been extensive studies investigating biomarkers at the retinal level using imaging and retinal function assessments (e.g., ERG measurements) that have revealed abnormalities in photoreceptor function. For example, from previous studies of ERG in relation to psychiatric disorders, we can find that both a-wave and b-wave amplitudes in the ERG of patients with schizophrenia and bipolar disorder have undergone significant changes compared to normal subjects, specifically in terms of decreased a-wave amplitude and prolonged b-wave latency, while decreased cone b-wave amplitude has been found only in patients with schizophrenia [9]. In a study of ERGs in patients with major depression compared to normal subjects, patients with MDD showed reduced a-wave amplitudes and reduced patten ERG (pERG) ratios [10]. Accordingly, in recent years, many researchers have tried to use the optical accessibility of the retina to better understand and diagnose the occurrence and development of neuropsychiatric diseases. In this paper we have chosen the metric of retinal nerve fiber layer thickness to explore its relationship with psychiatric disorders.

Mendelian randomization is a genetic statistical method. In scientific research, it is easy for us to find that there may be a correlation between two or more variables, but whether there is a causal relationship is not clear and difficult to prove. MR can help us to solve this problem. According to the rule that genetic variation is randomized in children from the same parents, MR uses genetic variation as instrumental variable to infer whether there is a causal relationship between exposure factors and outcomes, which can effectively overcome the bias caused by confounding and reverse causality [11, 12].

Methods

Study design

Firstly, we selected the target exposure factors and outcomes from several common database. Then, we used Two-Sample Mendelian randomization package installed in the R language to analyse the datas. The two-sample MR method was used to screen the instrumental variables of genetic variation in MR from the database. As an instrumental variable, three conditions should be met: (1) The genetic variant is associated with exposure; (2) The genetic variants were not associated with any of the confounders of the exposure-outcome association; (3) The selected genetic variants as instrumental variables

are conditionally independent of exposure and outcome [13, 14].

Acquisition of study data

Exposure factors in the study of data from the latest database of genome-wide association studies, IEU Open GWAS project (https://gwas.mrcieu.ac.uk/) is an open source data infrastructure, represents a series of different in the different groups of human phenotype and disease outcome [15]. RNFL data were extracted from GWAS (n=31,434). The schizophrenia data for the outcome factors in the study came from the FinnGen database (https://www.finngen.fi/), which is a large public-private partnership. The genome and health data of 500,000 Finnish biobank participants were collected in the database [16]. The schizophrenia data in this study included 5562 affected individuals and 208,674 controls. Data on major depression were from GWAS data on 27,568 affected persons and 457,030 controls, data on bipolar disorder were from GWAS data on 41,917 affected persons and 371,549 controls, and data on anxiety or panic attacks were from GWAS data. Including 6514 affected persons and 478,084 controls. See supplementary information of Table 1 for details.

Statistical treatment

For the selected exposure factor RNFL, in order to obtain independent and effective instrumental variables of genetic variation, we used the extraction instrumental variable function in "Two-Sample MR" to set the data in RNFL to be used only if the following conditions are met: p1=5e-08, clump=TRUE, p2=5e-08, r^2=0.001, kb=10,000 [17, 18]. The above conditions well ensure the independence of the selected instrumental variables, and then extract the instrumental variables in the outcome according to the single nucleotide polymorphism (SNP) of the previous exposure data. The extracted outcome working variable should meet the requirement of having the same SNP as the exposure data but having no relationship with the exposure factor, that is, P>0.05. Since the exposures and outcomes were read by the package "Two-Sample MR" in R language, we took advantage of the function of the package that can automatically find surrogate SNPs, which can be used to solve some cases in which the exposure SNPs cannot be found in the outcomes. In addition, in order to avoid the influence of instrumental variables as much as possible, the data results with F>10 were selected for inclusion in the study (F=(n-k-1/k)(R^2/1-R^2)), n indicates the sample size, k is the number of instrumental variables used in this study, R^2 reflects the extent to which instrumental variables are exposed to interpretation [19, 20]. We also combined the SNP of exposure data with the SNP allele direction of outcome data, and excluded palindromic SNPs that could not determine the direction according to the size of EAF. The heterogeneity of each SNP estimate was evaluated by Cochran Q test [21]. The Mendelian random polymorphism residuals and outliers were used to set instructions for automatically finding and replacing unqualified SNPs to correct the influence of outliers [22]. Finally, we calculated the MR Estimates of RNFL for the three mental disorders according to IVW and weighted median method [23–25]. Reverse MR also obey the above principle, except that the outcome exposure is swapped separately. All statistical processing was performed with the use of the "Two-Sample MR" package in R software, version 4.3.1.

Pleiotropic and sensitivity analyses

Horizontal pleiotropy was evaluated by MR-Egger intercept test. If the intercept term in the MR-Egger intercept test analysis was statistically significant, it indicated that the MR Analysis had horizontal pleiotropy [26, 27]. Sensitivity analyses were performed using the "leave-one-out method" to assess the significance of causal associations between exposures and outcomes [28].

Results

After excluding SNPs with linkage disequilibrium in RNFL, 22, 25, and 21 SNPs associated with schizophrenia, depression and bipolar disorder were included as instrumental variables, and the study was not affected by weak instrumental variables (F>10). After matching the RNFL data with the data of schizophrenia, depression and bipolar disorder, 22, 25, and 21 SNPS were finally included in the study as instrumental variables, respectively. There are respectively 1, 1and 43SNPs in the reverse MR analysis between schizophrenia, depression, bipolar disorder and RNFL.

IVW showed a positive relationship of RNFL on schizophrenia (OR=1.057, 95%CI: 1.000-1.117, P<0.05), and weighted median method also showed a positive relationship of RNFL on schizophrenia (OR=1.048, 95%CI: 1.000-1.117, P<0.05). Sensitivity analysis of RNFL and

Table 1 Instrumental variables in MR analyse

Traits	Consortium	Sample size(cases/controls)	Year	Number of SNPs	Pubmed ID
RNFL		31,434	2021	9,121,075	ebi-a-GCST90014266
schizophrenia			2021	16,380,456	finn-b-F5_SCHZPHR
depression		484,598	2021	9,587,836	ebi-a-GCST90038650
bipolr disorder	PGC	413,466	2021		ieu-b-5110

Table 2 Relevant data for mendelian randomization

Exposure	outcome	SNP	Cochran Q	Method	beta	95%CI	pval
RNFL (ebi-a-GCST90014266)	Schizophrenia (finn-b-F5_SCHZPHR)	22	0.261	IVW	0.055	1.000-1.117	0.049
				Weighted median	0.047	0.973–1.130	0.182
				MR Egger	0.004	0.858–1.174	0.959
RNFL (ebi-a-GCST90014266)	Depression (ebi-a-GCST90038650)	25	0.038	IVW	0.0001	0.999–1.001	0.749
				Weighted median	0.0001	0.999–1.001	0.831
				MR Egger	0.0008	0.998–1.003	0.495
RNFL (ebi-a-GCST90014266)	Bipolar disorder (ieu-b-5110)	21	0.035	IVW	0.025	1.005–1.046	0.011
				Weighted median	0.036	1.012–1.063	0.003
				MR Egger	-0.004	0.938–1.057	0.896
Schizophrenia (finn-b-F5_SCHZPHR)	RNFL (ebi-a-GCST90014266)	1		IVW			
				Weighted median			
				MR Egger			
Depression (ebi-a-GCST90038650)	RNFL (ebi-a-GCST90014266)	1		IVW			
				Weighted median			
				MR Egger			
Bipolar disorder (ieu-b-5110)	RNFL (ebi-a-GCST90014266)	43	0.135	IVW	0.112	0.911–1.375	0.281
				Weighted median	0.213	0.944–1.620	0.121
				MR Egger	-0.116	0.269–2.937	0.849

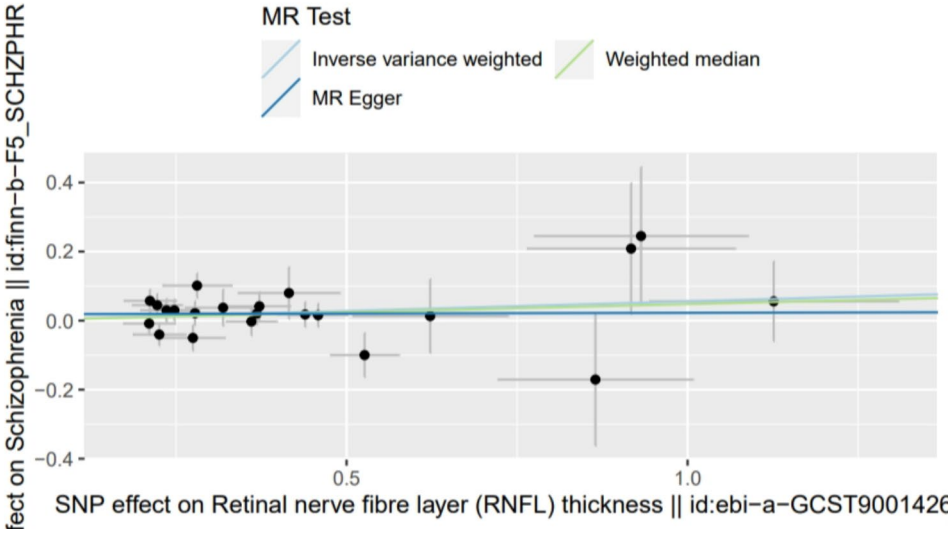

Fig. 1 RNFL & schizophrenia

schizophrenia showed no heterogeneity between SNPs (Cochran Q test, $P=0.28$), and MR-PRESSO results showed that no abnormal SNPs were detected ($P=0.331$). In the study of RNFL and depression, IVW showed that there was no causal relationship between RNFL and depression ($P=0.749$). In the study of RNFL and bipolar disorder, MR Analysis showed a positive relationship of RNFL on bipolar disorder (OR=1.025, 95%CI: 1.005–1.046, $P<0.05$). Weighted median analysis also showed the same results. Sensitivity analysis of RNFL on bipolar disorder showed heterogeneity among SNPs (Cochran Q test, $P=0.031$), which did not affect the validity of the results. MR-PRESSO results showed that no abnormal SNPs were detected. No reverse causal relationship of psychiatric disorders on retinal nerve fiber layer thickness were found. See supplementary information of Table 2 and the following figures(Figs. 1, 2, 3, 4, 5, 6, 7, 8 and 9)for details.

Discussion

In this study, we found that there is a relationship between RNFL thickness and schizophrenia and bipolar disorder, which has also been observed in previous observational studies [29, 30], and this study further indicates that this relationship is a positive causal relationship, whereas RNFL thickness is not related to depressive disorder. There is no reverse causal effects of psychiatric disorders on RNFL in this study. Accordingly, we can regard the RNFL as a promising biomarker to aid in the diagnosis of schizophrenia and bipolar disorder

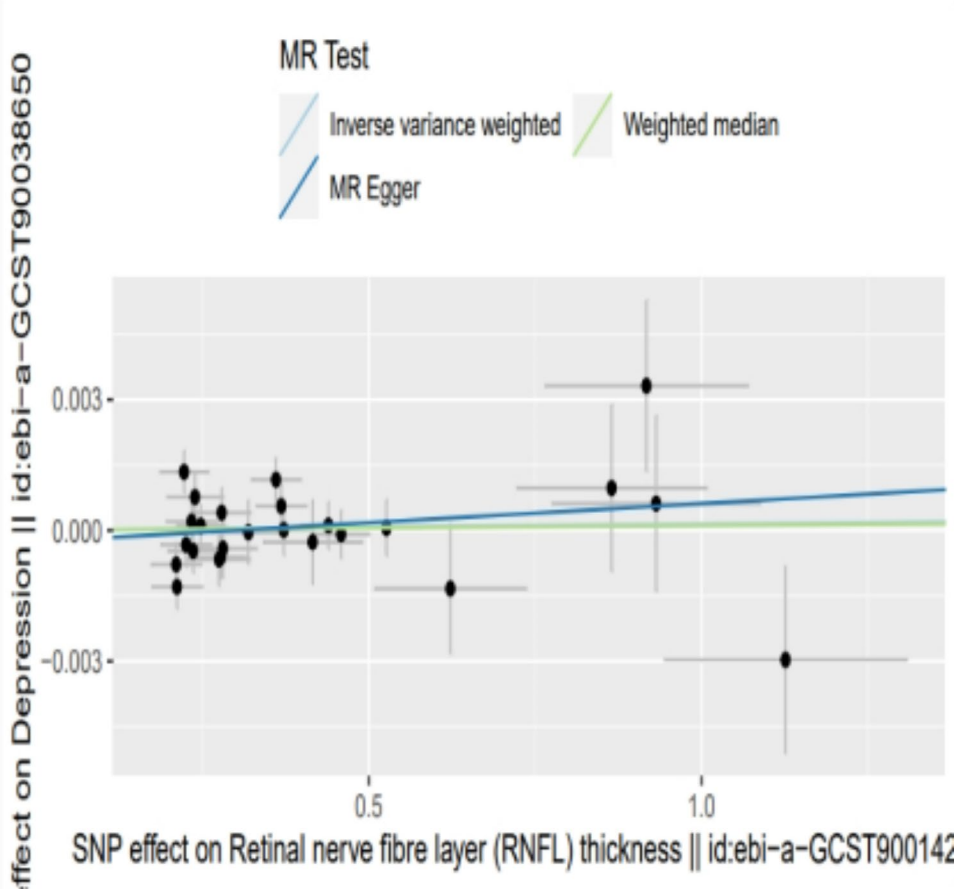

Fig. 2 RNFL & Depression

disorders, and although we cannot discriminate between the two disorders by relying on the RNFL alone, a combination of imaging and assessment of retinal function (e.g., ERG measurements) reveals that reduced b-wave amplitude can be observed in schizophrenia only. This difference may be important in distinguishing between the two diseases [8, 9].

Although the MR analysis led us to the above results, it is important to recognize that the mechanisms linking the state of RNFL to the onset of psychiatric disorders are not yet clear. Therefore, caution should be exercised in drawing conclusions from our findings. Previous studies have pointed out that schizophrenia is a refractory severe mental disorder, and its clinical symptoms such as visual hallucinations is closely related to RNFL [6, 7, 31], and this study also supports this relationship, that is, there is a positive causal relationship between retinal fiber layer thickness and schizophrenia. However, previous studies have shown that there is no significant difference in retinal nerve fiber layer thickness between schizophrenia and healthy controls [32]. The two different results in observational studies on the same issue. We analyzed that this may have potential influence factors, for example, the different duration of disease in the recruited subjects of the disease group when they were enrolled for observation, whether they had taken antipsychotic drugs, and the type of drugs they had taken may be potential factors affecting the final results. This question has been considered and studied in observational studies, but the number of studies is limited. Bipolar disorder is a chronic disabling mental disorder. In this study, a positive causal relationship between RNFL and bipolar disorder was found. Similar to previous observational studies on schizophrenia and RNFL, previous observational studies showed two different results on the relationship between RNFL and bipolar disorder [33]. We analyzed that this may be due to the inconsistent and small number of subjects in the clinical observational studies, and the inconsistent duration of onset may be the potential factors causing the completely opposite results of the clinical observational studies. In addition, the GWAS data on bipolar disorder included in this paper do not clearly reflect the clinical subtypes of bipolar disorder, so we were unable to clarify the correlation of retinal changes with bipolar disorder I and bipolar disorder II, respectively, as well as the differentiation of these two subtypes by retinal changes. The absence of a causal relationship between depression and RNFL in the present study, but the association

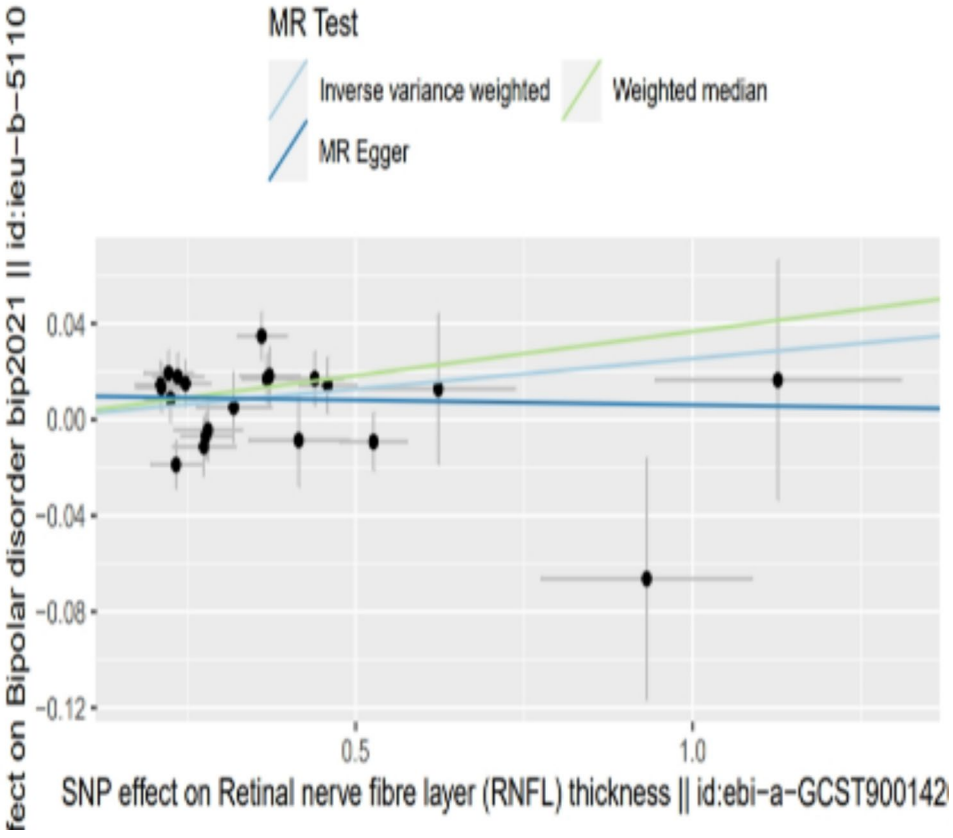

Fig. 3 RNFL & BP MR-Scatter plot

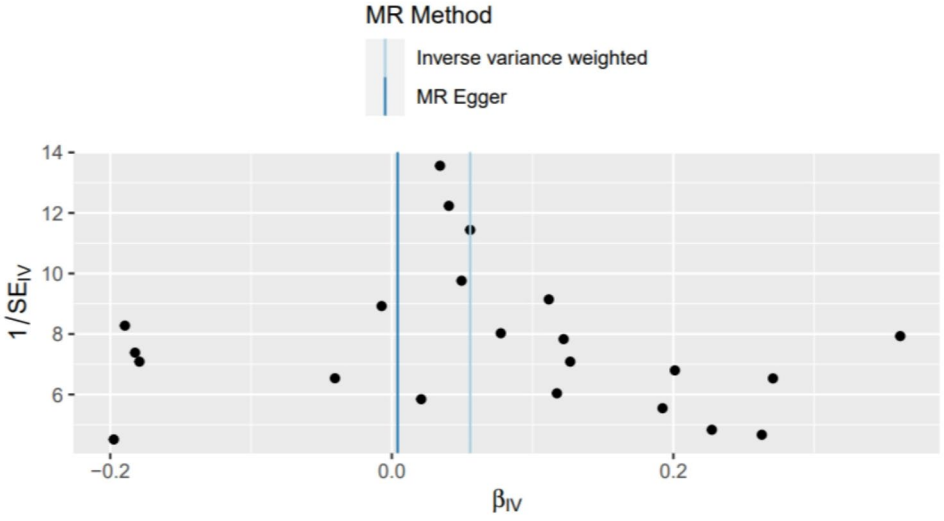

Fig. 4 RNFL & schizophrenia

between depression and RNFL in previous studies, led us to speculate that other factors may be responsible for the association between depression and RNFL in the clinical observational studies.

Our study also has strengths, firstly, reviewing the previous literature, we can find that most of the studies on the relationship between retinal nerve fiber layer thickness and mental disorders are observational studies, and exploring the causal relationship between the two

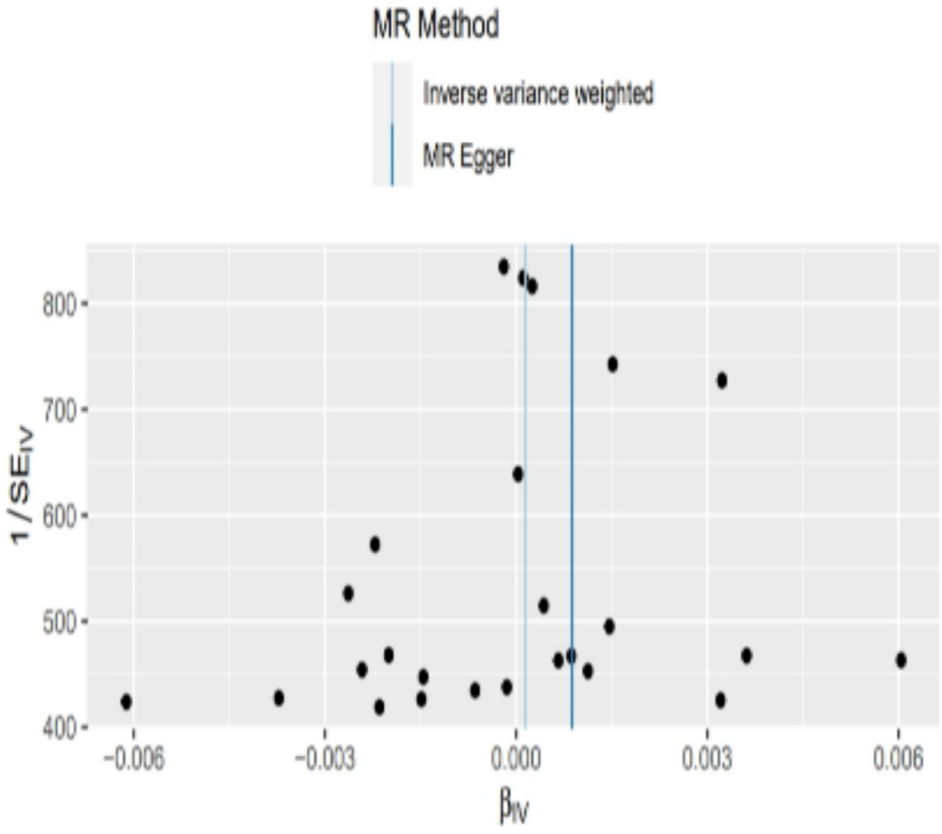

Fig. 5 RNFL & Depression

is novel in this study. Second, our research methodology also offers advantages. Although the development of psychiatric disorder series is the result of multifactorial interactions, and these disorders are not only inherited but also heavily influenced by early life adversities such as perinatal infections, maltreatment or bullying, and substance-related factors such as drugs and alcohol [34–36], one of the major strengths of the Mendelian randomization approach, as opposed to observational studies where it is difficult to accurately control for all confounders, lies in the fact that it utilizes genetic variations as an instrumental variable that can be used to study potential health risks reflecting susceptibility by avoiding confounding factors [11, 12]. Therefore, we can explain that patients with lesions in the RNFL have a higher genetic predisposition to develop schizophrenia and bipolar disorder compared to normal. Indicance threshold of each instrumental variable to $P<5\times10^{-8}$ according to the principle of Bonferroni Correction, which minimizes the possibility of Type I error due to multiple test comparisons, and used various methods to reduce the bias of instrumental variables, such as MR Presso, to further confirm the robustness of our results.

Finally, this study has several limitations. First, the source of exposure and outcome data in our study was selected from a single database, which may have caused some selection bias. Second, although we tested and adjusted for sensitivity in the data we analyzed, we could not fully assess horizontal pleiotropy. Third, limited by the lack of sample introduction in the database, we could not accurately grasp the information of the samples in the data, and could not exclude the confounding factors affecting the analysis results. Fourth, the population samples in our database were mostly from Europe, so the results of this study cannot be replicated among Asians.

Conclusion

We explored that there is a potential positive causal relationship of retinal nerve fiber layer thickness on schizophrenia and bipolar disorder by Mendelian randomization method, which provides another visualization tool for clinicians to diagnose the disease, predict and evaluate the progression of the disease in the future, and has important reference significance for further exploring and revealing the occurrence and development of these two diseases.

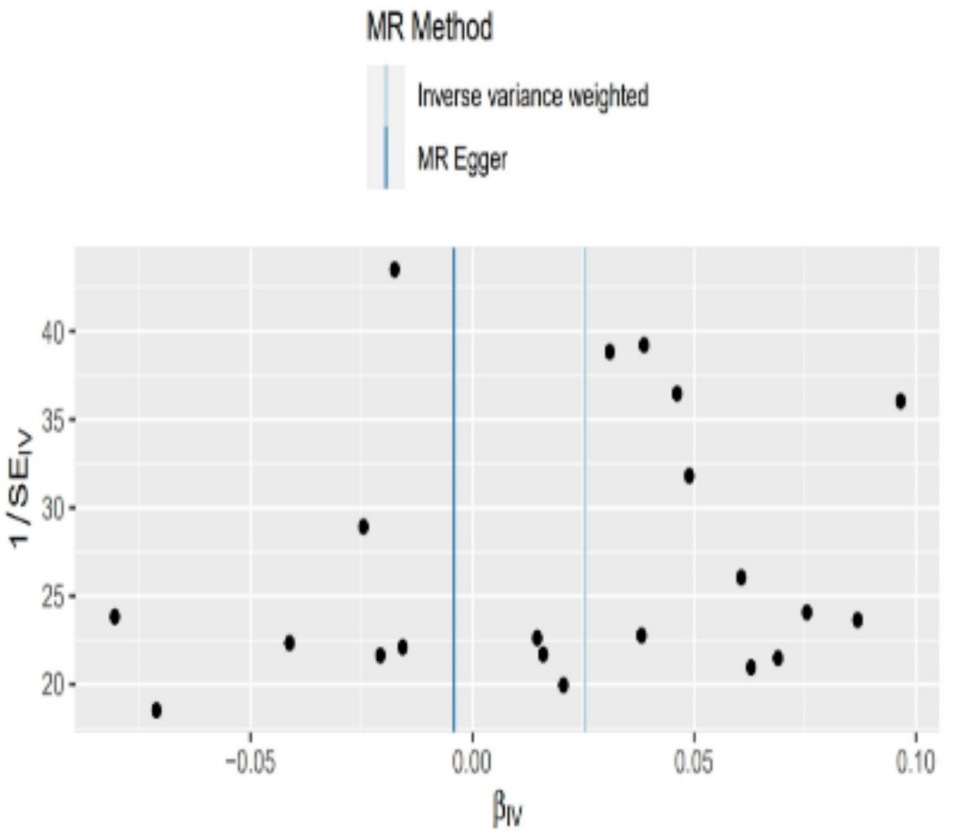

Fig. 6 RNFL & BP MR-Funnel plot

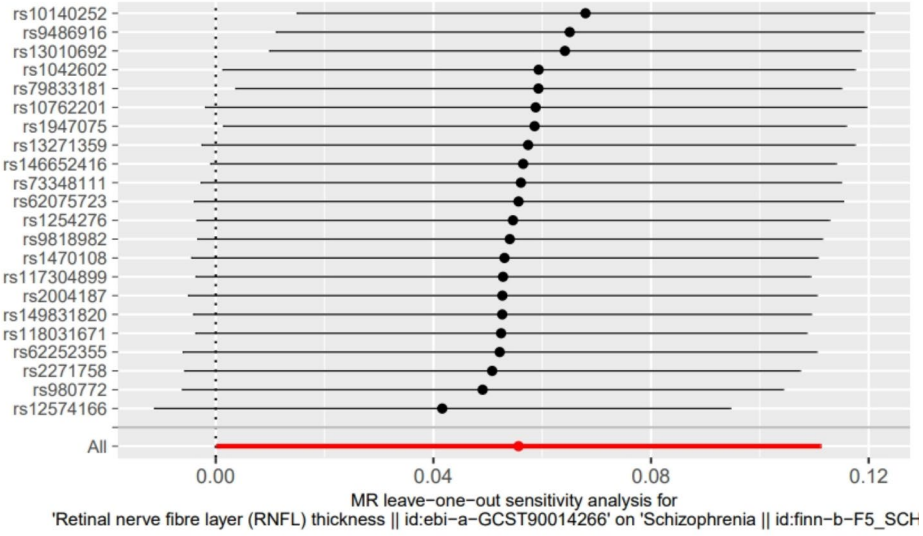

Fig. 7 RNFL & schizophrenia

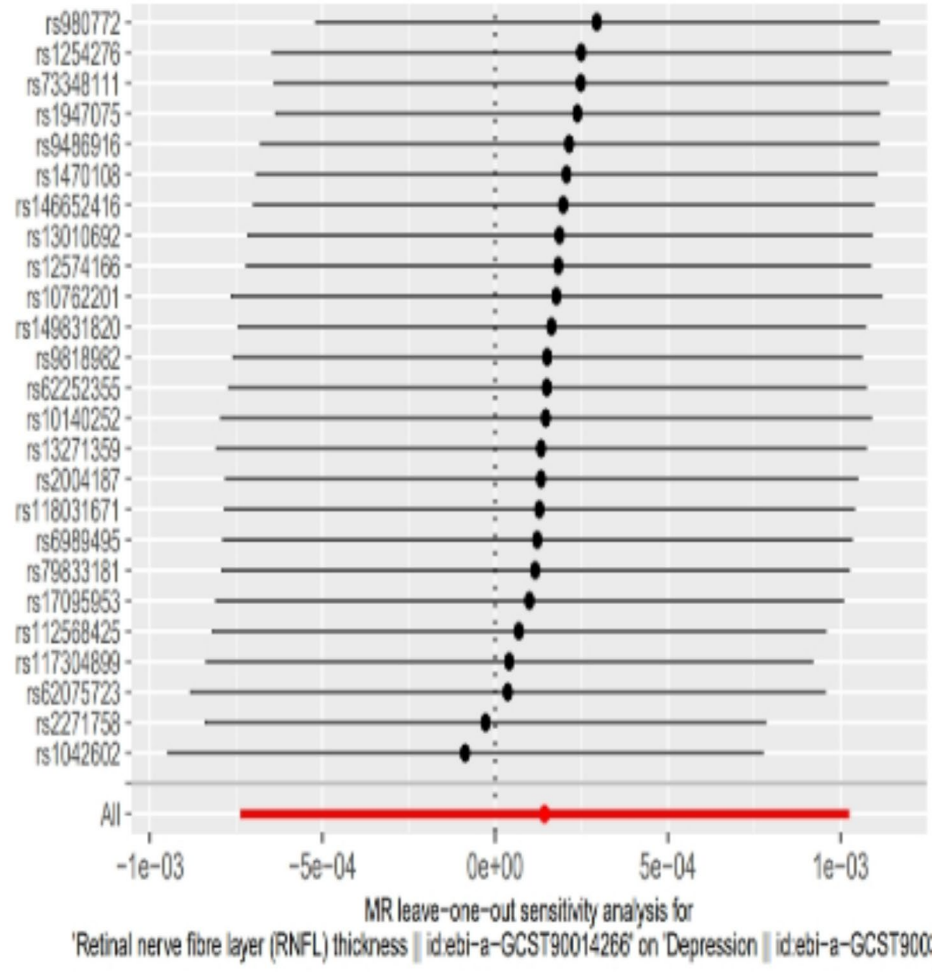

Fig. 8 RNFL & Depression

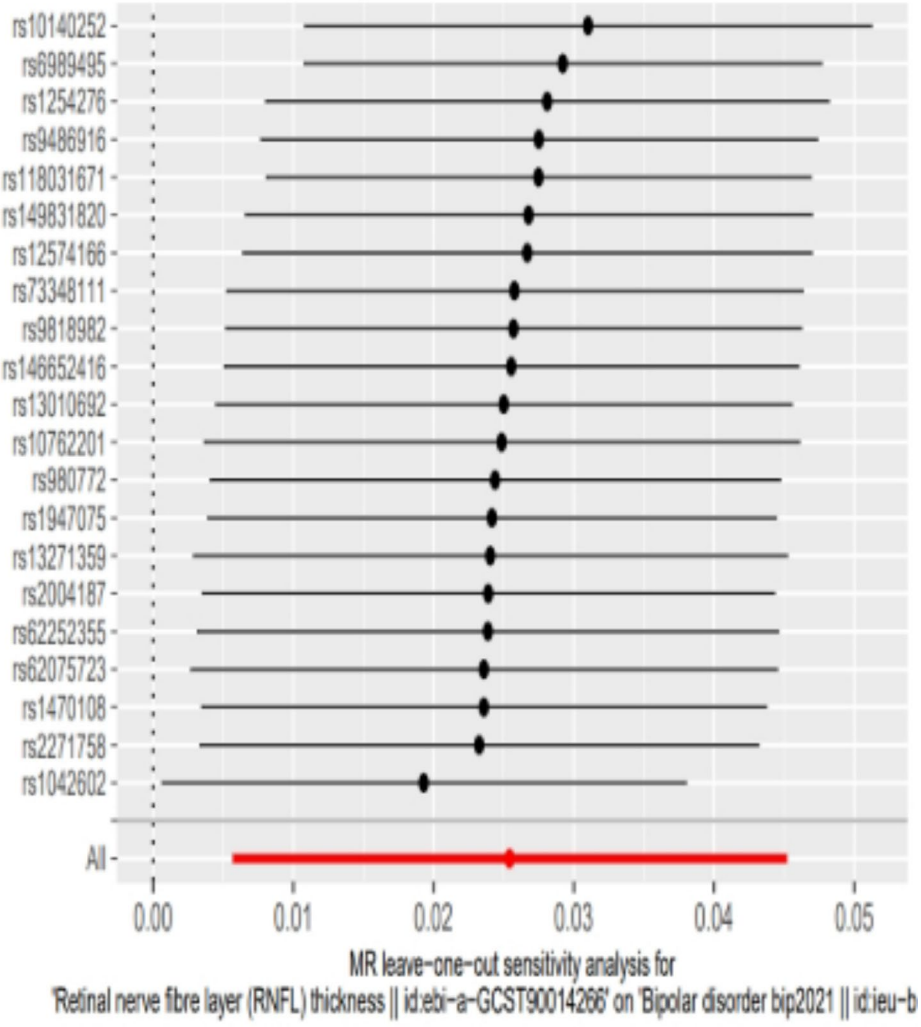

Fig. 9 RNFL & BP MR-Leave one out plot

Abbreviations

MR	Mendelian randomization
RNFL	Retinal nerve fiber layer thickness
GWAS	Genome-wide association studies
SNP	Single nucleotide polymorphism
IVW	Instrumental variable weighted
OR	Odds ratio
CI	Confidence interval
MR-PRESSO	Mendelian randomization pleiotropy residual sum and outlier
BP	Bipolar disorder

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Author contributions
Qfy peimarily chose the theme and wrote the text, Cx and Zxl mainly proofread and correct the article, Gzy , Lyl, Wj and Lq participated in drawing and theme selection, Tzw and Zy made a final review of the article and provided fund support.

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Data availability
All the GWAS summary data are publicly available. GWAS summary data for Retinal nerve fiber layer thickness can be download at IEU Open GWAS (https://gwas.mrcieu.ac.uk). GWAS summary data for psychiatric disorders can be download at IEU Open GWAS(https://gwas.mrcieu.ac.uk).

Declarations

Ethics approval and consent to participate
All the data sources used in this study are summarized data from relevant GWAS studies and the IEU OpenGWAS project database, which are publicly available for free download and do not require approval from the review agency.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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