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Psychiatric disorders and cardiovascular diseases: A mendelian randomization study

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ABSTRACT

Background: Previous researches have demonstrated a connection between psychiatric disorders and cardiovascular diseases (CVDs), but the cause-and-effect relationship is still unclear. To that goal, the mendelian randomization (MR) method was used to study the causal link between psychiatric disorders and CVDs.

Methods: Genome-wide association studies (GWAS) data were collected for four CVDs, including coronary artery disease (n = 547,261), atrial fibrillation (n = 537,409), heart failure (n = 977,323) and ischemic stroke (n = 440,328). Summary data for four psychiatric disorders, including bipolar disorder (n = 51,710), major depressive disorder (n = 480,359), schizophrenia (n = 127,906) and attention deficit hyperactivity disorder (n = 55,374), came from the Psychiatric Genomics Consortium (PGC). All participants were European. The IVW method was mainly used, and the reliability of the results was increased using sensitivity analyses such as MR-Egger, Cochrane's Q test, MR-PRESSO and leave-one-out.

Results: MR revealed that the attention deficit hyperactivity disorder was linked to an increased risk of atrial fibrillation (OR, 1.085; 95% CI, 1.021–1.153; P = 0.008), heart failure (OR, 1.117; 95% CI, 1.044–1.195; P = 0.001), and ischemic stroke (OR, 1.146; 95% CI, 1.052–1.248; P = 0.002). The schizophrenia was linked to an increased risk of heart failure (OR, 1.035; 95% CI, 1.006–1.066; P = 0.017), but was found to be suggestively inverse associated with coronary artery disease (OR, 0.969; 95% CI, 0.941–0.997; P = 0.03). The major depressive disorder was associated with higher odds of coronary artery disease (OR, 1.109; 95% CI, 1.018–1.208; P = 0.018), while the bipolar disorder was linked to a reduced incidence of coronary artery disease (OR, 0.894; 95% CI, 0.831–0.961; P = 0.002) and heart failure (OR, 0.889; 95% CI, 0.829–0.955; P = 0.001). There were no clear relationships between other psychiatric disorders and CVDs.

Conclusion: The results provide genetic proof of a possible causal relationship between psychiatric disorders and CVDs. These results imply that psychiatric disorders may be the cause of some CVDs, and that some abnormal mental states may increase or reduce the likelihood of CVDs, providing guidance for the CVDs prevention.

1. Introduction

Cardiovascular diseases (CVDs), including coronary artery disease (CAD), atrial fibrillation (AF), heart failure (HF), ischemic stroke

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(IS) and thrombotic diseases, are still the main cause of the global disease burden due to their high morbidity and mortality, posing a huge threat to human life and health [1–4]. The potential link between psychiatric disorders and CVDs has attracted considerable attention from scholars in recent times. According to reports, persons diagnosed with serious psychiatric diseases (e.g., schizophrenia, bipolar disorder) have a life expectancy 15–20 years lower than the general population, with CVD considered an important cause of death in patients suffering from severe psychiatric disorders [5–7]. Meanwhile, previous observational studies have shown that compared to the general population, those with psychiatric disorders, such as bipolar disorder (BPD) [8], depression [9,10], schizophrenia [11], and attention deficit hyperactivity disorder (ADHD) [12], are at a higher risk of CVD. Furthermore, in a study published by the American Heart Association (AHA), depression is recommended to be elevated as an early warning sign for patients with acute coronary syndrome [13], suggesting a significant relationship between psychiatric disorders and CVDs, which could lead to new guidance for the prevention of CVDs [14]. Although the causal relationship between the two has not been proven, this problem can still be solved by using Mendelian randomization (MR).

MR is a method of analysis that investigates the cause-and-effect relationship between sources of exposure and outcome following the idea of random allelic assignment [15]. Similar to randomization in randomized controlled trials, this approach evaluates whether there is an impact of exposure on outcome, with genetic variants taken as instrumental variables (IVs) [16]. Genetic variations are randomly passed to offspring and do not change after pregnancy, which means that they are not disturbed by external factors, and that they can effectively mitigate the likelihood for bias and reverse causality, overcoming the limitations of observational studies [17].

Herein, a two-sample MR analysis was carried out to investigate the causal link between psychiatric disorders (ADHD, schizophrenia, Major depressive disorder MDD, BPD) and CVDs (CAD, AF, IS, HF). The findings will offer fresh perspectives on the pathogenesis and treatment of CVDs.

2. Methods

2.1. Study design

With a two-sample MR method, the potential causal link between psychiatric illnesses and CVDs was assessed. The reliability of the results was ensured by sensitivity analysis. MR is based on three key tenets: (1) IVs need to be closely connected to exposure factors, including ADHD, schizophrenia, MDD, and BPD; (2) IVs do not have any confounding variables; (3) IVs only influences the result through exposure factors. This study followed the recommendations of the STROBE-MR [18]. Since all the data used have already been made available to the public, no additional ethical approval was necessary. The specific study design is shown in Fig. 1.

2.2. Psychiatric disorders GWAS sources

Herein, IVs of four psychiatric disorders were selected from GWAS, including ADHD, schizophrenia, MDD, and BPD. Their statistics came from the PGC [19]. These included 20,183 and 35,191 controls for ADHD disorders, 52,017 and 75,889 controls for schizophrenia, 135,458 and 344,901 controls for MDD and 20,352 and 31,358 controls for BPD. The study cohort was exclusively of European heritage descent to avoid bias related to race-related confounding factors. Table 1 presents more details about the GWAS data set included in this analysis.

2.3. CVD GWAS sources

Genetic association data for CAD were derived from the research of Van der Harst et al. [20], involving 122,733 cases and 424,528

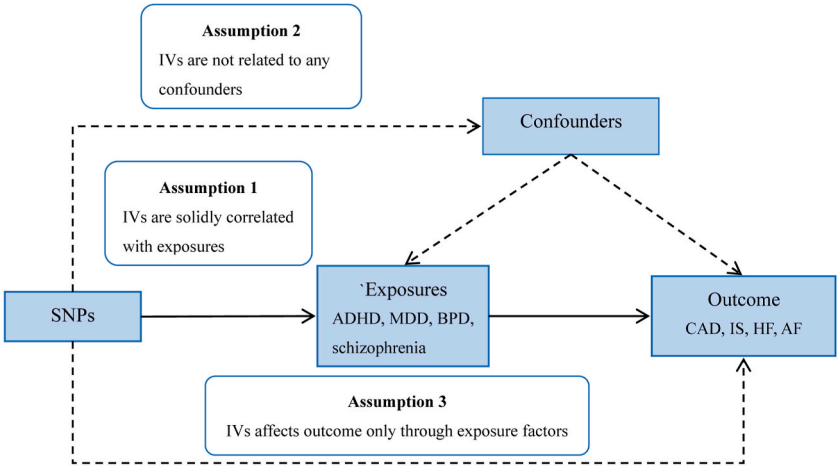

Fig. 1. The Mendelian randomization study design.

Table 1
Detailed information of the GWAS datasets used in the present study. CAD coronary artery disease, AF atrial fibrillation, HF heart failure, IS ischemic stroke, PGC Psychiatric Genomics Consortium, ADHD attention deficit hyperactivity disorder, BPD bipolar disorder, MDD major depressive disorder.

Phenotype	Study or Consortium	Sample size	Cases,n	Controls,n	Ancestry
Exposures					
ADHD	PGC	55,374	20,183	35,191	European
Schizophrenia	PGC	127,906	52,017	75,889	European
MDD	PGC	480,359	135,458	344,901	European
BPD	BPD-PGC	51,710	20,352	31,358	European
Outcomes					
CAD	Van der Harst et al.	547,261	122,733	424,528	European
AF	Roselli et al.	537,409	55,114	482,295	European
HF	Shah et al.	977,323	47,309	930,014	European

controls. The genetic association data for AF were derived from the study of Roselli et al. [21], involving 55,114 cases and 482,295 controls. Genetic association data on HF came from Shah et al. [22] who studied 47,309 cases and 930,014 controls, and Malik et al. [23] who collected data from 34,217 patients and 406,111 controls. The majority of the study population was of European descent, and

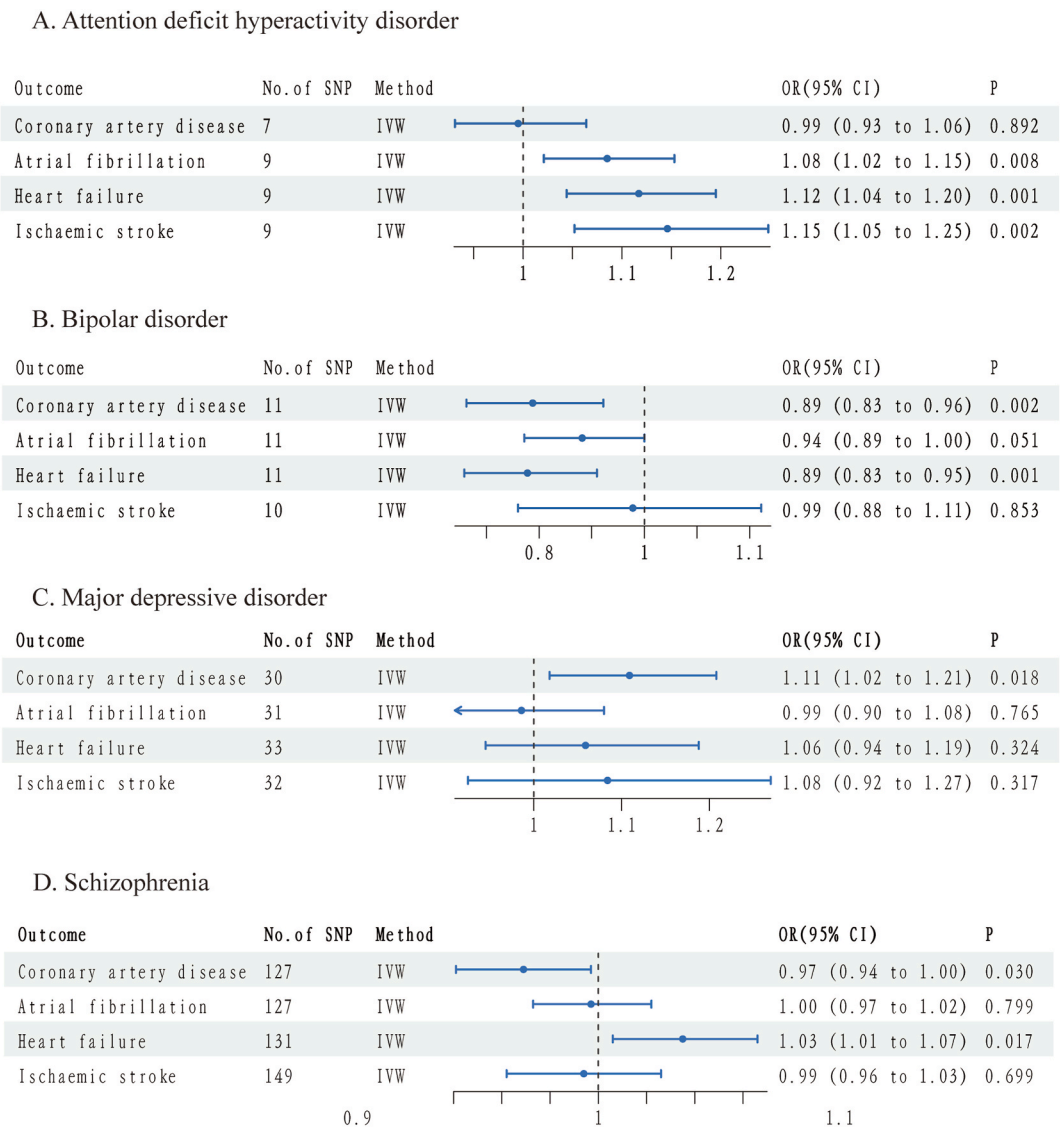

Fig. 2. A forest plot showing associations between psychiatric disorders and cardiovascular diseases based on the IVW method.
OR odds ratio, CI confidence interval, SNP single nucleotide polymorphism, IVW inverse-variance weighted.

estimates of genetic associations were gender-adjusted. Table 1 presents comprehensive information regarding the sources of GWAS used in this work.

2.4. Selection of IVs

First, IVs closely associated with psychiatric disorders ($P < 5 \times 10^{-8}$) were screened as SNPs ($r^2 < 0.001$ and distance >5000 kb), making it possible to ensure independence of SNPs [24]. At the same time, a query was conducted in the Phenosanner database to determine whether the included SNPs were not related to known confounding factors. An evaluation was conducted to figure out whether the selected SNPs had instrument bias by evaluating the F value, and the following is the calculating formula: $F=R^2 \times (N-2)/(1-R^2)$ [25]. All of the SNPs considered in this analysis have F values greater than 10, indicating the existence of no weak instrument bias. Finally, 9 SNPs for ADHD, 16 SNPs for BPD, 157 SNPs for schizophrenia, and 36 SNPs for MDD were selected. Details of

Table 2
IVW method and sensitivity analyses using WMA and MR-Egger method for the mendelian randomization analyses of psychiatric disorders and cardiovascular diseases. OR odds ratio, CI confidence interval, SNP single nucleotide polymorphism, IVW inverse-variance weighted, CAD coronary artery disease, AF atrial fibrillation, HF heart failure, IS ischemic stroke.

Exposure and outcome	N SNPs	Method	OR	95%CI	Pval
Attention deficit hyperactivity disorder					
CAD	7	IVW	0.995	0.931–1.064	0.892
	7	MR Egger	1.044	0.798–1.366	0.765
	7	Weighted median	0.963	0.883–1.051	0.401
AF	9	IVW	1.085	1.021–1.153	0.008
	9	MR Egger	1.049	0.803–1.370	0.737
	9	Weighted median	1.088	1.007–1.175	0.033
HF	9	IVW	1.117	1.044–1.195	0.001
	9	MR Egger	1.026	0.778–1.354	0.860
	9	Weighted median	1.125	1.032–1.226	0.007
IS	9	IVW	1.146	1.052–1.248	0.002
	9	MR Egger	0.960	0.670–1.375	0.830
	9	Weighted median	1.139	1.019–1.272	0.022
Schizophrenia					
CAD	127	IVW	0.969	0.941–0.997	0.03
	127	MR Egger	1.014	0.903–1.138	0.814
	127	Weighted median	0.982	0.950–1.016	0.299
AF	127	IVW	0.997	0.973–1.022	0.799
	127	MR Egger	1.015	0.922–1.118	0.759
	127	Weighted median	1.005	0.971–1.040	0.774
HF	131	IVW	1.035	1.006–1.066	0.017
	131	MR Egger	1.117	0.995–1.253	0.062
	131	Weighted median	1.029	0.992–1.068	0.121
IS	149	IVW	0.994	0.962–1.026	0.699
	149	MR Egger	0.999	0.876–1.139	0.991
	149	Weighted median	0.994	0.952–1.037	0.776
Major depressive disorder					
CAD	30	IVW	1.109	1.018–1.208	0.018
	30	MR Egger	1.097	0.722–1.668	0.667
	30	Weighted median	1.104	0.978–1.246	0.111
AF	31	IVW	0.986	0.900–1.080	0.765
	31	MR Egger	1.108	0.687–1.786	0.678
	31	Weighted median	0.994	0.878–1.125	0.922
HF	33	IVW	1.059	0.945–1.188	0.324
	33	MR Egger	1.028	0.581–1.821	0.925
	33	Weighted median	1.158	1.005–1.334	0.042
IS	32	IVW	1.084	0.925–1.270	0.317
	32	MR Egger	0.768	0.331–1.783	0.544
	32	Weighted median	1.072	0.892–1.289	0.460
Bipolar disorder					
CAD	11	IVW	0.894	0.831–0.961	0.002
	11	MR Egger	0.796	0.492–1.288	0.377
	11	Weighted median	0.897	0.832–0.967	0.005
AF	11	IVW	0.941	0.886–1.000	0.051
	11	MR Egger	1.325	0.939–1.869	0.144
	11	Weighted median	0.974	0.905–1.048	0.475
HF	11	IVW	0.889	0.829–0.955	0.001
	11	MR Egger	1.049	0.664–1.658	0.843
	11	Weighted median	0.870	0.796–0.950	0.002
IS	10	IVW	0.989	0.880–1.111	0.853
	10	MR Egger	1.003	0.466–2.162	0.993
	10	Weighted median	1.028	0.912–1.159	0.649

these SNPs are shown in Supplementary Table S1, Table S2, Table S3, and Table S4.

2.5. Statistical analysis

In this investigation, the primary method used to examine the relationship between psychiatric disorders and CVDs was inverse-variance weighted (IVW). The data were then translated into odds ratio (OR) and 95% confidence interval (CI) [26]. When only one SNP was available, the Wald ratio method was used [27]. The subsequent sensitivity analysis was carried out to ensure the robustness of the research findings: First, Cochrane's Q test was used to evaluate the heterogeneity of each SNP estimate. If there was heterogeneity ($P < 0.05$), the IVW random effects model was used to analyze the association; otherwise, the IVW fixed effects model would be used. Secondly, the bias caused by horizontal pleiotropy was identified and reduced through the intercept of MR-Egger regression [28]. Thirdly, MR-PRESSO test [29] was used to detect abnormal SNPs affecting the results and re-calibrating the results after removing the outliers. Finally, the leave-one-out sensitivity analysis was conducted to eliminate each SNP in turn, so as to detect whether the SNP had an impact on the results. All statistical analyses were performed in R 4.1.2 software using Mendelian Randomization [30] and MR-PRESSO packages, $\alpha = 0.05$.

3. Results

3.1. Attention deficit hyperactivity disorder

The genetic prediction results showed that the ADHD was linked to an increased risk of AF (OR, 1.085; 95% CI, 1.021–1.153; P = 0.008), HF (OR, 1.117; 95% CI, 1.044–1.195; P = 0.001), and IS (OR, 1.146; 95% CI, 1.052–1.248; P = 0.002) in IVW analysis. However, genetically predicted CAD (OR, 0.995; 95% CI, 0.931–1.064; P = 0.892) did not show any association with ADHD, as seen in Fig. 2 and Table 2. Sensitivity tests demonstrated that the MR-Egger intercept did not demonstrate imbalanced horizontal pleiotropy for CAD (P = 0.732), AF (P = 0.805), HF (P = 0.556) or IS (P = 0.354). According to Cochrane's Q test, the results were not impacted by heterogeneity in any of the studies (CAD Q statistic = 5.118; P = 0.529; HF Q statistic = 4.276; P = 0.831; AF Q statistic = 2.2; P = 0.974; and IS Q statistic = 5.549; P = 0.698). By using the MR-PRESSO test, two outlier SNPs of CAD (rs1222063, rs28411770) were detected, which were corrected for possible outliers. All sensitivity analysis results are included in Supplemental Tables S5 and S6, while Fig. S1 and Fig. S5 show the forest plots and scatter plots.

3.2. Schizophrenia

Fig. 2 and Table 2 demonstrate the results that the schizophrenia was linked to an increased risk of HF (OR, 1.035; 95% CI, 1.006–1.066; P = 0.017), but the schizophrenia was found to be suggestively inversely related to CAD (OR, 0.969; 95% CI, 0.941–0.997; P = 0.03). However, neither subgroups of AF (OR, 0.997; 95% CI, 0.973–1.022; P = 0.799) nor IS (OR, 0.994; 95% CI, 0.962–1.026; P = 0.699) showed any association with schizophrenia. Besides, sensitivity analyses revealed that the MR-Egger intercept did not demonstrate imbalanced horizontal pleiotropy for CAD (P = 0.423), AF (P = 0.700), HF (P = 0.187) or IS (P = 0.931), although some heterogeneity was observed (CAD Q statistic = 237.605; P = 7.22E-09; AF Q statistic = 162.594; P = 0.016; HF Q statistic = 193.494; P = 0.0002; and IS Q statistic = 196.042; P = 0.005). Three outlier SNPs of CAD (rs11191580, rs4702, rs61937595), four outlier SNPs of AF (rs11191580, rs12151767, rs12833624, rs3739118), one outlier SNP of HF (rs13107325), and one outlier SNP of IS (rs13107325) were detected through the MR-PRESSO test. After correcting for possible outliers, the results of all these associations were proven valid. All sensitivity analysis results are included in Supplemental Tables S5 and S6, while Fig. S2 and Fig. S6 show the forest plots and scatter plots.

3.3. Major depressive disorder

The genetic prediction results showed that the MDD was associated with higher odds of CAD (OR, 1.109; 95% CI, 1.018–1.208; P = 0.018). However, other CVDs such as AF (OR, 0.986; 95% CI, 0.900–1.080; P = 0.765), HF (OR, 1.059; 95% CI, 0.945–1.188; P = 0.324), and IS (OR, 1.084; 95% CI, 0.925–1.270; P = 0.317) did not significantly present associations with MDD (Fig. 2, Table 2). Sensitivity analyses revealed that the MR-Egger intercept did not demonstrate imbalanced horizontal pleiotropy for CAD (P = 0.961), AF (P = 0.631), HF (P = 0.918) or IS (P = 0.421). Meanwhile, some heterogeneity was observed for HF (Q statistic = 47.391; P = 0.039) and IS (Q statistic = 55.436; P = 0.004) but not for CAD (Q statistic = 30.374; P = 0.396) and AF (Q statistic = 33.926; P = 0.284). Two outlier SNPs of CAD (rs10950398, rs2005864), one outlier SNP of AF (rs915057), and one outlier SNP of IS (rs159963) were detected through the MR-PRESSO test, which were corrected for possible outliers. All sensitivity analysis results are included in Supplemental Tables S5 and S6, while Fig. S3 and Fig. S7 show the forest plots and scatter plots.

3.4. Bipolar disorder

The BPD was linked to lower risk of CAD (OR, 0.894; 95% CI, 0.831–0.961; P = 0.002) and HF (OR, 0.889; 95% CI, 0.829–0.955; P = 0.001). However, neither subgroups of AF (OR, 0.941; 95% CI, 0.886–1.000; P = 0.051) nor IS (OR, 0.989; 95% CI, 0.880–1.111; P = 0.853) showed any association with BPD (Fig. 2 and Table 2). Meanwhile, sensitivity analyses revealed MR-Egger intercept did not demonstrate imbalanced horizontal pleiotropy for CAD (P = 0.644), AF (P = 0.08), HF (P = 0.494) or IS (P = 0.971). Some

heterogeneity was observed for CAD (Q statistic = 19.366; P = 0.036) and IS (Q statistic = 20.193; P = 0.017) but not for AF (Q statistic = 12.769; P = 0.237) and HF (Q statistic = 13.628; P = 0.191). One outlier SNP of IS (rs71395455) was detected through the MR-PRESSO test. All sensitivity analysis results are included in Supplemental Tables S5 and S6, while Fig. S4 and Fig. S8 show the forest plots and scatter plots.

4. Discussion

Herein, the aggregated GWAS data were used to research the causal connection between psychiatric disorders (ADHD, schizophrenia, MDD, BPD) and CVD (CAD, AF, IS, HF) via a two-sample MR study. Results have revealed a link between ADHD and higher risk of AF, HF, and IS; schizophrenia is linked to a higher rate of HF and a negative association with CAD; MDD is linked to a higher risk of CAD, while BPD is linked to both CAD and HF adversely. However, no significant association was found between other psychiatric disorders and CVDs.

Recently, numerous observational studies have demonstrated the close association between psychiatric disorders and the occurrence and prognosis of CVDs. In addition, ADHD medications may raise blood pressure and heart rate, raising questions regarding cardiovascular safety [31,32]. The present results are consistent with a cohort study [33] demonstrating that depression causes Chinese adults' cardiovascular mortality to increase, especially males, and with three other studies [34–36] showing a high risk association between depression and CAD. Unlike the three studies, the effect of MDD on other CVD (HF, AF, and ischemic stroke) was also explored in this study. At the same time, the meta-analysis of Gan Y et al. [37] indicated that CAD and myocardial infarction were more common in persons with depression, which is supported by the present study. A research of schizophrenia and CVD conducted by Hennekens CH et al. [11] demonstrated CAD as the leading factor of early death in schizophrenia patients. Furthermore, genetic prediction of schizophrenia was hereby found to increase the susceptibility to HF, which is partially consistent with a bidirectional MR study conducted by Veeneman, Rada R et al. [38]. Veeneman, Rada R et al. ever confirmed a potential causal relationship between schizophrenia and HF, but found no significant association with CAD. In this research, a new potential causal relationship between schizophrenia and CAD was identified. In addition, contrary to evidence that adults with BPD develop CVD excessively and prematurely [39,40], this study found that BPD was negatively associated with the risk of CAD (OR = 0.894, P = 0.002) and HF (OR = 0.889, P = 0.001). However, the results of this study are not completely consistent with the results of previous observational studies, which may be attributed to the following reasons: First, most of the previous studies came from observational studies and cohort studies, and the results might be influenced by confounding factors and reverse causation. Second, the previous researches have the problem of small research scale and sample size. In addition, heterogeneity exhibited by the Cochrane's Q test may have reduced the potency of the present study [41].

Thus, the causal relationship between psychiatric disorders and CVDs has been extensively confirmed, but the pathophysiological mechanism linking the development of the two is still unclear, which has inspired considerable studies. For example, it has been shown that constant mental stress can lead to the development of a pro-inflammatory state and indirectly cause endothelial dysfunction, which both a precursor to atherosclerosis and a major factor in the etiology of several CVDs [42,43]. Endothelial dysfunction has also been shown to be a characteristic marker of depression, and vascular endothelial growth factor matters considerable in developing depression by making the blood-brain barrier more permeable [44]. In addition, in terms of oxidative stress, the total bilirubin levels drop due to mood swings, and a decrease in this antioxidant is generally associated with an increase in blood pressure [45]. Additionally, the discovered link between psychiatric disorders and cardiovascular diseases can be explained at the genetic level. Immune-related genes are involved in part of the etiology, which has been confirmed by AdrianiW et al. [46]. Overall, the present findings provide new insights into the association between psychiatric disorders and CVDs, but considering its key role in helping clinical management and drug development, additional research is still needed to clarify the complicated mechanisms between the two.

The advantages of this study lie in the following aspects: First, the MR study reduced the bias of confounding factors and reverse causality in observational studies. Secondly, the data came from GWAS datasets with a large sample size, which had strong statistical power and reduced weak IVs bias. Finally, a variety of sensitivity analyses were performed to evaluate the results' reliability.

This study, however, still has some limitations. European ancestry was the source of the pooled data used in this investigation., terribly limiting its applicability to non-European populations. And Cochrane's Q test showed that some SNPs in this study had pleiotropy, but the SNPS with pleiotropy was adopted the IVW random effects model, and whether pleiotropic SNPSs were associated with other secondary traits was evaluated to minimize their influence on the results. Finally, although exposure factors were extracted from the sex-specific GWAS database, the relevant data on outcomes did not distinguish between genders. Additionally, although gender adjustments were made, the effect of sex specificity on outcomes could still not be fully explored [47].

5. Conclusions

Overall, the findings show that psychiatric illnesses and CVDs are related in a causal way. According to studies, HF, AF, and IS are more likely to occur in people with ADHD, schizophrenia increases the risk of HF and has an adverse effect on the development of CAD, MDD increases the risk of CAD, and BPD has a negative correlation with both CAD and HF. In order to lower cardiovascular morbidity and mortality and enhance long-term outcomes in mental patients, additional research should concentrate on the processes underlying the link between psychiatric disorders and CVDs.

Data

The original data used in this study are included in the Table 1.

Data availability statement

The datasets presented in this study come from IEU OpenGWAS (https://gwas.mrcieu.ac.uk/) and PGC (https://www.med.unc.edu/pgc/) are available for free download. Further inquiries can be directed to the corresponding authors.

CRediT authorship contribution statement

Xiaohui Sui: Conceptualization, Data curation, Investigation, Software, Validation, Visualization. **Tingting Liu:** Data curation, Investigation, Writing – original draft. **Yi Liang:** Data curation, Investigation, Software, Writing – original draft. **Baoqing Zhang:** Conceptualization, Software, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20754.

Abbreviations

CVD	cardiovascular disease
MR	mendelian randomization
OR	odds ratio
CIs	confidence intervals
CAD	coronary artery disease
AF	atrial fibrillation
HF	heart failure
BPD	bipolar disorder
ADHD	attention deficit hyperactivity disorder
AHA	American Heart Association
IVs	instrumental variables
MDD	major depressive disorder
IS	ischemic stroke
PGC	Psychiatric Genomics Consortium
GWAS	genome-wide association studies
SNPs	single nucleotide polymorphisms
IVW	inverse-variance weighted

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