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Bidirectional associations between mental disorders, antidepressants and cardiovascular disease

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ABSTRACT

Background Mental disorders have a high comorbidity with cardiovascular disease (CVD), but the causality between them has not been fully appreciated.

Objective This study aimed to systematically explore the bidirectional causality between the two broad categories of diseases.

Methods We conducted Mendelian randomisation (MR) and multivariable MR (MVMR) analyses to evaluate potential causal links between 10 mental disorders, the use of antidepressants and 7 CVDs.

Findings We discovered that major depressive disorder (MDD), attention-deficit/hyperactivity disorder (ADHD) and insomnia exhibit connections with elevated risks of two or more CVDs. Moreover, the use of antidepressants is linked to heightened risks of each CVD. Each distinct CVD is correlated with a greater probability of taking antidepressants. Our MVMR analysis demonstrated that the use of antidepressants is correlated with the elevation of respective risks across all cardiovascular conditions. This includes arrhythmias (OR: 1.28), atrial fibrillation (OR: 1.44), coronary artery disease (OR: 1.16), hypertension (OR: 1.16), heart failure (OR: 1.16), stroke (OR: 1.44) and entire CVD group (OR: 1.35). However, MDD itself was not linked to a heightened risk of any CVD.

Conclusions The findings of our study indicate that MDD, insomnia and ADHD may increase the risk of CVD. Our findings highlight the utilisation of antidepressants as an independent risk factor for CVD, thus explaining the influence of MDD on CVD through the mediating effects of antidepressants.

Clinical implications When treating patients with antidepressants, it is necessary to take into consideration the potential beneficial and detrimental effects of antidepressants.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardiovascular disease (CVD) and mental disorders are highly comorbid, yet the mutual causality between the two broad categories of diseases has yet to be systematically explored.

WHAT THIS STUDY ADDS

⇒ The Mendelian randomisation analysis indicates that several mental disorders could strongly increase the risk of CVD, while CVD has little causal effects on mental disorders. Both major depressive disorder (MDD) and antidepressants have overall influences on CVD. When considered individually, antidepressant use, but not MDD, may confer risk of various cardiovascular outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ When treating patients with antidepressants, it is necessary to take into consideration the potential beneficial and detrimental effects of antidepressants.

INTRODUCTION

Cardiovascular diseases (CVDs) and mental disorders stand as two major classes of leading causes of death and disability globally, with CVD and depression demonstrating a high degree of comorbidity and collectively ranking as the top two contributors to worldwide disability.[1] Both mental illnesses and CVD stem from a blend of genetic and environmental risk elements. The primary manifestations of CVD encompass hypertension, coronary artery disease (CAD), heart failure (HF), stroke and atrial fibrillation (AF). Elevated levels of blood lipids, high arterial pressure, increased blood glucose levels, excess weight, poor dietary patterns, smoking and insufficient physical activity are all significant contributory elements to the development of CVD.[2]

Mental illnesses are widespread and profoundly incapacitating conditions that result in substantial burdens for individuals, families and the community.[3 4] Psychiatric conditions present in various forms, encompassing disorders like major depressive disorder (MDD), bipolar disorder (BD), schizophrenia, anxiety disorder, insomnia, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and others. MDD or depression is marked by a continual state of reduced mood. It stands as one of the prevalent psychological conditions, ranking second worldwide in the context of disease impact. MDD is acknowledged as a distinct contributing factor to the advancement of CVD towards more complex stages, encompassing conditions like ischaemic heart disease, acute myocardial infarction, stroke and CAD. MDD has also demonstrated an association with CVD-attributed morbidity and mortality.[5]

While the significant co-occurrence and interplay between MDD and CVD have been acknowledged, the underlying biological mechanisms linking these two conditions remain predominantly enigmatic. Mental stress can lead to systemic inflammation.

Additional data suggest that inflammation can link mental stress to CVD.[6] Previous studies have indicated that an inflammation process fuelled by irregularities in the immune system could potentially explain the connection between CAD and depression. This is evident in the heightened concentrations of interleukin-6, C reactive protein (CRP), fibrinogen and triglycerides.[7] Alternative research indicates that heightened activity in the sympathetic nervous system, overactivity of the hypothalamic–pituitary–adrenal (HPA) axis and raised inflammation serve as mechanistic links between depression and HF.[5] At the genetic level, it was reported that the sets of variations underlying MDD and common types of CVD substantially overlap. Additionally, Mendelian randomisation (MR) studies show that genetic liability to MDD exerts a causal effect on stroke and CAD.[8]

MDD is commonly managed pharmacologically with various antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors, bupropion and others. Many of these antidepressants have also been linked to an elevated risk of acquiring cardiovascular conditions. For instance, TCAs have been associated with a higher likelihood of stroke and other cardiovascular adverse events, such as myocardial infarction, arrhythmia, HF and cardiovascular death. Fluoxetine has been connected to hypertension and AF, mirtazapine to an increased risk of hypertension and tachycardia, venlafaxine, in a dose-dependent manner, to hypertension, and duloxetine to high blood pressure.[9]

When examining the causal relationship between MDD and CVD, it is crucial to consider the concurrent effects of antidepressant medications administered to patients. However, few studies have yet evaluated the potential impact of the confounding influence of antidepressant use on CVD. Therefore, it is largely unknown whether the increased risk of CVD in patients with MDD can be attributed to MDD itself, antidepressant usage or the combination of the two. The conundrum could hardly be settled by traditional studies for the following reasons: (1) conducting randomised controlled trials that compare patients with depression with and without antidepressant use cannot be accepted from an ethics standpoint; (2) traditional observational studies are susceptible to bias due to variations in disease severity between depressed patients using antidepressants and those who do not. Therefore, it is necessary to examine the direct impacts of MDD and antidepressants on CVD by isolating these effects from each other.

In this study, we used MR to evaluate mutual causal associations between mental disorders and CVD. MR analysis has been increasingly adopted to explore causal relationships between an exposure and an outcome.[10–13] Furthermore, we employed multivariable MR (MVMR) analyses to assess the independent causal effects of MDD and antidepressants on 7 cardiovascular conditions, namely, arrhythmias, AF, CAD, HF, hypertension, stroke, and overall CVD as a group.

MATERIALS AND METHODS

Data and code availability

Publicly available summary datasets from Psychiatric Genomics Consortium (PGC) and other consortia were used in this study. The code script in the study is available on reasonable request to the corresponding author.

Study design and data sources

An overview of the study design is presented in figure 1. Publicly available genome-wide association studies (GWAS) datasets on 10 mental disorders, antidepressant use and 7 cardiovascular conditions were employed in this study table 1. The 10 mental disorders include MDD (N=807 553), BD (N=413 466), schizophrenia (N=130 644), insomnia (N=386 533), ADHD (N=292 548), ASD (N=46 350), obsessive-compulsive disorder (N=10 640), post-traumatic stress disorder (N=174 659), alcohol dependence (N=46 568) and anxiety disorder (N=17 310). The antidepressant dataset included 93 238 cases and 81 923 controls. The cardiovascular conditions included arrhythmias (N=263 611), AF (N=208 594), CAD (N=332 477), HF (N=977 323), hypertension (N=455 303), stroke (N=284 040) and overall CVD as a group (N=342 499). The participants in the CAD dataset were mostly of European origin. Other datasets exclusively included patients of European origin.

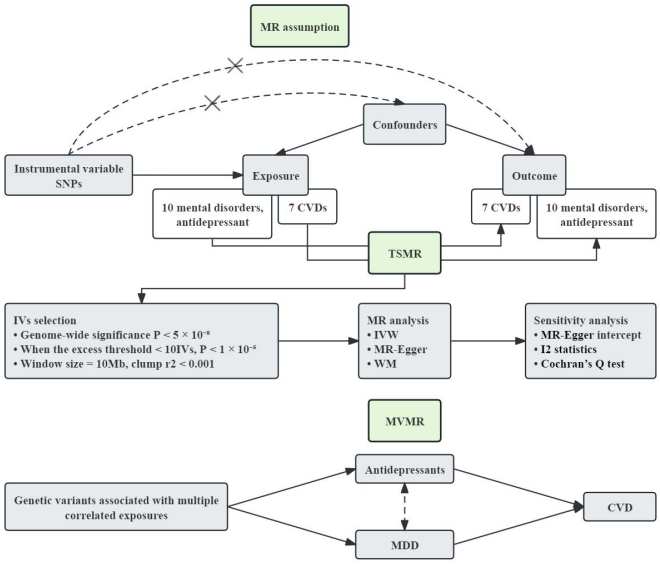

Figure 1 Overview of study design. CVDs, cardiovascular diseases; IVs, instrumental variables; IVW, inverse-variance weighted; MDD, major depressive disorder; MR, Mendelian randomisation; MVMR, multivariable Mendelian randomisation; SNPs, single-nucleotide polymorphisms; TSMR, two-sample Mendelian randomisation; WM, weighted median.

MR analysis

The MR analyses were conducted using three models within the framework of TwoSampleMR (V.0.5.6).[14] The primary method used was the inverse-variance weighted (IVW) model, accompanied by the MR-Egger and weighted median models as complementary approaches. The intercept obtained from the MR-Egger regression analysis was used to assess the presence of average directional pleiotropy.[15] The heterogeneities were gauged by both I^2 statistics and Cochran's Q test (both $I^2>0.25$ and $p<0.05$).[16] The identification of significant associations was based on the false discovery rate calculated from p values obtained in the IVW model. Single-nucleotide polymorphisms that reached genome-wide significance ($p<5\times10^{-8}$) in the exposure datasets were selected to generate independent instrumental variables (IVs), ensuring low linkage disequilibrium ($r^2<0.001$) within a 10 Mb window. When the threshold is exceeded by less than 10 IVs, the p value threshold is used (1×10^{-5}).

MVMR analysis

The MVMR analysis was performed using the TwoSampleMR package (V.0.5.6)[17] to enable the estimation of the direct effects

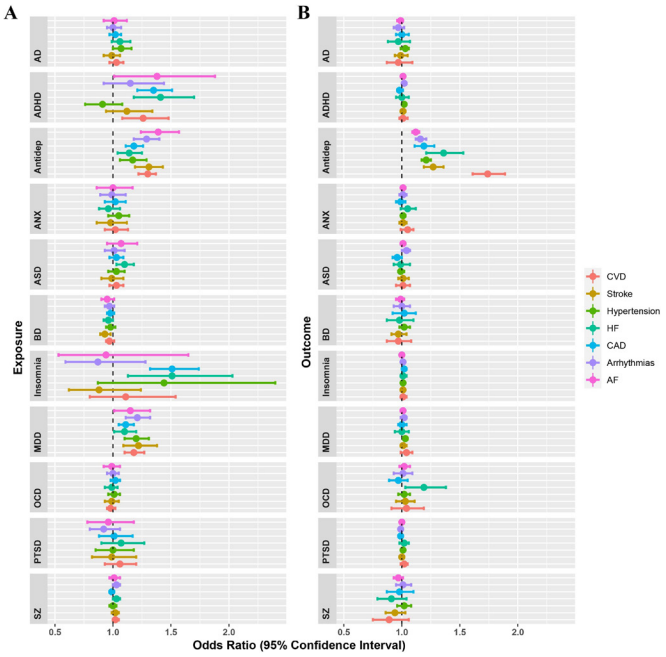

Figure 2 Bidirectional causal associations between mental disorders, antidepressant use and various CVDs. AD, alcohol dependence; ADHD, attention-deficit/hyperactivity disorder; AF, atrial fibrillation; Antidep, antidepressants; ANX, anxiety disorder; ASD, autism spectrum disorder; BD, bipolar disorder; CAD, coronary artery disease; CVD, cardiovascular disease; HF, heart failure; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; SZ, schizophrenia.

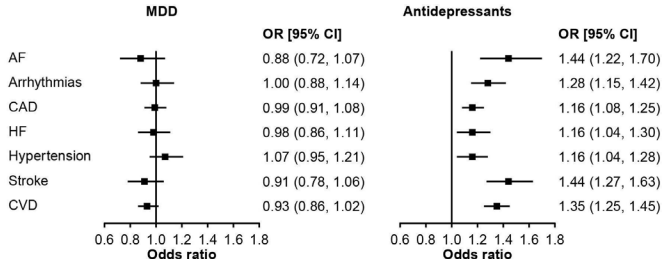

Figure 3 Causal effects of MDD and antidepressant use on CVDs. AF, atrial fibrillation; CAD, coronary artery disease; CVD, cardiovascular disease; HF, heart failure; MDD, major depressive disorder.

of MDD and antidepressant use on the seven specific cardiovascular conditions. IVs corresponding to each exposure were extracted and consolidated into a collection of genetic instruments, which were subsequently inputted into the analytical pipeline.

RESULTS

MR analysis

The causal effects of mental disorders and antidepressants on CVD are presented in online supplemental table 1 and figure 2A. Among the mental disorders, MDD, ADHD and insomnia are major contributors to the risks of CVD. ADHD is associated with an increased risk of CAD (OR: 1.35), HF (OR: 1.41) and CVD (OR: 1.26). Insomnia is associated with an increased risk of CAD (OR: 1.51) and HF (OR: 1.51). The genetic liability to MDD is associated with an increased risk of arrhythmias (OR: 1.21), CVD (OR: 1.18), stroke (OR: 1.22), hypertension (OR: 1.20) and CAD (OR: 1.11). Antidepressant use is associated with an increased risk of each CVD, including stroke (OR: 1.31), arrhythmias (OR: 1.29), AF (OR: 1.39), CAD (OR: 1.18), hypertension (OR: 1.17), HF (OR: 1.14) and all CVD as a group (OR: 1.30).

MDD had an average causal effect of 1.16±0.05 (ranging from 1.10 to 1.22) on the six individualised types of CVD. Antidepressant use had an average causal effect of 1.25±0.10 (ranging from 1.14 to 1.39) on the six individualised types of CVD. Notably, antidepressant use had a higher causal effect on overall CVD (OR: 1.30) compared with MDD (OR: 1.18).

In addition, ASD is associated with an increased risk of HF (OR: 1.10), while BD is associated with a decreased risk of stroke (OR: 0.93).

The causal effects of CVD on mental disorders and antidepressants are presented in online supplemental table 2 and figure 2B. Our analysis detected minimal evidence to support the causal effects of CVD on mental disorders. Only hypertension is associated with a slightly increased risk of ADHD (OR: 1.02) and MDD (OR: 1.03). However, each CVD is associated with an increased risk of antidepressant use, including hypertension (OR: 1.21), AF (OR: 1.12), arrhythmias (OR: 1.16), CAD (OR: 1.19), HF (OR: 1.36), stroke (OR: 1.27) and overall CVD (OR: 1.74).

MR sensitivity analysis showed that the directions of causal effects across the set of applied techniques were largely the same (online supplemental tables 3 and 4). The tests of MR-Egger regression did not detect directional pleiotropy in the analyses (P_pleiotropy ≥0.05 and MR-Egger intercept <0.03). Nevertheless, Cochran's Q test and I^2 statistics support the existence of heterogeneity in most MR analyses.

MVMR analysis

Further exploration of the direct causal effects of MDD and antidepressant use on CVD was conducted with the aid of MVMR, which is capable of separating the influences of the intertwined factors, known to act synergistically. Therefore, each association revealed by MVMR was regarded as a 'direct' or 'independent' causal effect.

The results of the MVMR analysis are shown in figure 3 and online supplemental table 5. We found that the use of antidepressants was associated with higher risks of arrhythmias (OR: 1.28), AF (OR: 1.44), CAD (OR: 1.16), hypertension (OR: 1.16), HF (OR: 1.16), stroke (OR: 1.44) and overall CVD as a group (OR: 1.35). At the same time, MDD was not associated with an increase in the risk of any CVD.

DISCUSSION

Our results suggest that MDD, insomnia and ADHD were robustly associated with an increased risk of CVD, with MDD being the leading contributor to higher risks of CVD. It has been demonstrated that depression poses a significant threat to cardiovascular health and increases the likelihood of unfavourable cardiovascular outcomes among individuals with existing cardiovascular conditions.[5] In the present study, we found that MDD may causally increase the risk of most types of CVD, including arrhythmias, stroke, hypertension, CAD and overall CVD.

We found that ADHD confers risk of several cardiovascular conditions and the effect sizes were relatively large, including a 35% increased risk of CAD, a 41% increased risk of HF (OR: 1.41) and a 26% increased risk of overall CVD. A recent study reported the association between ADHD and an increased risk

Table 1 Summary information of the datasets

Trait	Authors	Year	PMID	N case	N control	N
Attention-deficit/hyperactivity disorder	Demontis *et al*	2023	36702997	38 691	275 986	292 548
Alcohol dependence	Walters *et al*	2018	30482948	11 569	34 999	46 568
Anxiety disorder	Otowa *et al*	2016	26857599	7016	14 745	17 310
Autism spectrum disorder	Grove *et al*	2019	30804558	18 381	27 969	46 350
Bipolar disorder	Mullins *et al*	2021	34002096	41 917	371 549	413 466
Insomnia	Jansen *et al*	2019	30804565	109 402	277 131	386 533
Major depressive disorder	Howard *et al*	2019	30718901	246 363	561 190	807 553
Obsessive-compulsive disorder	Arnold *et al*	2017	28761083	2688	7952	10 640
Post-traumatic stress disorder	Nievergelt *et al*	2019	31594949	23 212	151 447	174 659
Schizophrenia	Trubetskoy *et al*	2022	35396580	53 386	77 258	130 644
Antidepressants	Kurki *et al*	2023	36653562	93 238	81 923	175 161
Coronary artery disease	Nelson *et al*	2017	28714975	71 602	260 875	332 477
Hypertension	Jiang *et al*	2019	31768069	122 620	332 683	455 303
Heart failure	Shah *et al*	2020	31919418	47 309	930 014	977 323
Atrial fibrillation	Kurki *et al*	2023	36653562	40 594	168 000	208 594
Arrhythmias	Kurki *et al*	2023	36653562	59 182	204 429	263 611
Stroke	Kurki *et al*	2023	36653562	34 560	249 480	284 040
Cardiovascular disease	Kurki *et al*	2023	36653562	174 499	168 000	342 499

of coronary heart disease in adulthood.[18] In addition to our results, there are also studies supporting a significant association of genetic predisposition to ADHD with an increased risk of any ischaemic stroke.[19]

Our study suggests that insomnia increases the risk of CAD and HF at the genetic level. Epidemiological studies have shown that individuals with insomnia symptoms have a 41–55% higher risk of myocardial infarction, stroke, CAD and cerebrovascular disease.[20] Results of a meta-analysis of a prospective cohort study showed that insomnia was associated with an increased risk of hypertension and may increase the risk of hypertension by up to 21%.[21]

The use of antidepressants has also been recognised as a contributor to the deterioration of cardiovascular health. Although newer classes of antidepressants, including SSRIs and SNRIs, have been suggested to have safer cardiovascular profiles when compared with TCAs, clinical studies have uncovered an increase in the occurrence of arrhythmias, prolongation of QT interval, hypertension and orthostatic hypotension in the users of newer antidepressants.[22]

Our MR analysis revealed that the overall impact of the use of antidepressants on CVD is greater than that of MDD itself (OR: 1.30 for antidepressants vs 1.18 for MDD). Notably, our MVMR analysis established the use of antidepressants as an independent risk factor for CVD, with a 28% increase in the risk of arrhythmias, a 44% increased risk of AF, a 16% increased risk of CAD, a 16% increased risk of hypertension, a 16% increased risk of HF, a 44% increased risk of stroke and a 35% increased risk of overall CVD. Notably, after subtracting the effects of antidepressants, the causal influences of MDD on each of the examined CVD were diminished to insignificance, indicating that the effect of MDD on these diseases is primarily accounted for by the concomitant use of antidepressants.

Hypertension stands as the most prevalent form of CVD and significantly contributes to various other types of CVD. It is widely recognised that individuals experiencing MDD exhibit a greater occurrence of hypertension compared with the general populace.[23] The rise in blood pressure noticed in people with depression might rely on underlying endothelial dysfunction, a condition often linked to mild inflammation and excessive blood clotting, altered signalling along the HPA axis and sympathetic overactivity. Yet, our research cautiously associates the occurrence of hypertension often seen in people with depression with the usage of antidepressants. Research has demonstrated that antidepressants can impact blood pressure through various mechanisms, encompassing the stimulation of adrenergic, dopaminergic and serotoninergic pathways, along with histamine and choline-dependent systems.[24] It should be noted that for some recent-generation antidepressants, their associated cardiovascular morbidity and mortality were reported as reduced.[25] Notably, among stroke survivors, sertraline has demonstrated the ability to facilitate the restoration of physiological function and elevate the overall quality of health-related experiences.[26] Nevertheless, in randomised controlled trials, antidepressant therapies in patients with both depression and CVD have shown no significant benefits in terms of cardiovascular outcomes. It is worthwhile to note that alleviation of depressive symptoms, regardless of the approach used, should promote a decrease in the occurrence of subsequent cardiovascular events rather than an increase.[27]

Arrhythmia can be life-threatening and have a significant economic impact, with AF being the prevailing form of arrhythmia. A recent meta-analysis showed that the use of antidepressants is significantly associated with an increased risk of AF (relative risk (RR): 1.37), while the risks of ventricular arrhythmias or sudden cardiac death remained unchanged.[28] In our study, higher risks were observed in antidepressant users for either all types of arrhythmias as a group (OR: 1.28) or AF alone (OR: 1.44). Notably, in patients without structural heart disease, idiopathic arrhythmias and AF events may be observed after exposure to certain environmental factors, including medications, which may induce an increase in the QT interval by modifying channel function. A long QT interval may be either genetically determined (congenital long QT syndrome), drug induced or both. In particular, some genetically predisposed individuals may show excessive QT prolongation when taking non-cardiac drugs, including antidepressants that block potassium currents.[29] Specifically, paroxetine, an SSRI, significantly diminishes the rapid sodium flow in cardiomyocytes located in the human left ventricle. This results in the deceleration of

conduction and a decrease in excitability, particularly when a loss-of-function mutation in the SCN5A gene is present.[30]

In MVMR analysis, the largest increase in cardiovascular risks attributed to the use of antidepressants (44%) was for stroke. These risks are well acknowledged in the literature. For example, in a large Medicare-based study of individuals who suffered from traumatic brain injury, the use of SSRIs was associated with an increased risk of haemorrhagic stroke (RR: 1.26), with particular emphasis on escitalopram (RR: 1.33) and sertraline (RR: 1.46).[31] Meta-analyses of the association between the use of any antidepressant and the risk of any stroke also revealed an independent increase in odds of acquiring disease (RR: 1.41), pointing at SSRIs and TCAs as culprits of risk increase, even after adjusting for depression.[32] In a recent study involving older individuals, the likelihood of not responding well to antidepressants was associated with a score related to cardioembolic stroke.[33]

Regarding individuals with CAD, earlier investigations have revealed the impact of antidepressants on cardiovascular results. This impact was most notable in subjects using tricyclics and atypical antidepressants, where there was a notable rise in major adverse cardiovascular incidents within these categories. This association may be, at least in part, mediated by the kynurenine/tryptophan (KYN/TRP) athway, which is known as a key participant and biomarker of both adverse cardiovascular outcomes and antidepressant treatment. In particular, patients using TCAs were shown to have a significantly higher KYN/TRP ratio than non-antidepressant users, which remained significant even after correction for CRP levels.[34] Some studies even suggest that in CAD, an increase in the KYN/TRP ratio could serve as a measure of interferon-γ-mediated immune activation[35] and may predict future coronary events years ahead of the acute episode. Naturally, the connections between the utilisation of antidepressants and CAD might be significantly intricate. This intricacy hinges on the specific kind of antidepressant employed and the inclusion of alternate mechanisms. As an illustration, a prior investigation demonstrated that administering citalopram to individuals with both depression and CAD led to enhanced endothelial functionality, even in conjunction with commonly recommended antiplatelet drugs such as aspirin and clopidogrel.[36]

Our investigation revealed limited evidence in support of the causal influences of CVD on mental disorders. The only noteworthy exceptions were the minor effects of hypertension on ADHD and MDD. In addition, some studies have used cumulative risk models to clarify that many CVD risk factors have certain effects on depression.[37] However, each CVD was robustly associated with antidepressant use, including a 74% increased likelihood of antidepressant use associated with overall CVD. The reason behind the increased probability of using antidepressants due to CVD, without a corresponding increase in MDD, can be attributed to two factors. First, CVD might provoke depressive symptoms that do not meet the criteria for an MDD diagnosis. Second, CVD may increase the risk of depression through the unfavourable socioeconomic consequences that are due to the disease itself, but not through genetic liability to this condition.

We acknowledge the limitations of the GWAS datasets used in this study. First, some patients in the MDD dataset used antidepressants. Second, not all patients in the antidepressant dataset fulfilled the diagnostic criteria for MDD, with some patients having depressive symptoms of a secondary nature. These elements could potentially reduce the differentiation between MDD and antidepressant use, consequently weakening the separation between the distinct impacts of MDD and the use of antidepressants. Other limitations of our study include the reliance of our analyses solely on the genetic predisposition to each of these traits, with no regard to socioeconomic and environmental factors. Depression often leads to an unhealthy lifestyle, lack of physical activity, alcoholism, obesity and poor adherence to any treatment, with a lack of social and family support directly and independently contributing to a poor cardiovascular prognosis.[38] There was no specific categorisation of antidepressants in our study. Certain SSRIs with a high-to-moderate affinity for the sigma-1 receptor may have beneficial effects on CVD.[39] Therefore, the conclusions of our study should be seen as generalisations about the use of antidepressants rather than an indicator of the specific effect of any particular pharmacological compound. Finally, the datasets on antidepressant use, arrhythmias, stroke and CVD came from the FinnGen consortium. Therefore, the dataset of antidepressant use had shared samples with those of arrhythmias, stroke and CVD. The MR estimates between antidepressant use and the three cardiovascular conditions should be interpreted with caution. On the other hand, some aspects of our study are strong. Through the utilisation of MVMR analyses on large-scale GWAS data, our investigation unveiled the independent effects of MDD and antidepressants on common forms of CVD. This methodology offers a distinct advantage compared with conventional epidemiological studies, which are susceptible to reverse causation and confounder bias. Hence, our findings significantly enhance the understanding of the intricate association between MDD, antidepressants and CVD.

CONCLUSION

Our results suggest that MDD, insomnia and ADHD play significant roles in elevating the chances of CVD; while patients with CVD have a higher likelihood of antidepressant use. Our findings highlight the utilisation of antidepressants as an independent risk factor for CVD, thus explaining the influence of MDD on CVD through the mediating effects of antidepressants.

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Contributors FZ—conceptualisation, data curation, methodology, project administration, supervision, visualisation, writing (original draft) and writing (review and editing). HC—investigation, methodology, validation, visualisation, writing (original draft) and writing (review and editing). AB—investigation, methodology, validation, visualisation, writing (original draft) and writing (review and editing). QZ—investigation, methodology, validation, visualisation, writing (original draft) and writing (review and editing). FZ was responsible for the overall content as the guarantor. All authors commented on drafts of the manuscript. All authors approved the final version.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Since all analyses were conducted using publicly available summary statistics rather than individual data, no institutional review board approval was necessary. Ethical approval was obtained in all original studies.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

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