Observational Study

Medicine

OPEN

Role of lifestyle factors in mediating the effect of mood swings on cardiovascular diseases

A mediation Mendelian randomization study

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Abstract

It has been found that individuals with psychiatric illnesses are predisposed to an elevated risk of cardiovascular diseases (CVDs). Mood swing is a clinically relevant characteristic linked to psychiatric disorders. This study examined the possible relationship between genetically predicted mood swings and CVDs risk. In this mediation Mendelian randomization (MR) study, we compiled data from genome-wide association studies examining mood swings (n = 451,619) and 5 CVDs among Europeans, including coronary artery disease (CAD) (n = 547,261), major coronary heart disease events (MCEs) (n = 361,194), all-cause heart failure (AHF) (n = 218,208), atrial fibrillation (n = 1030,836), and stroke (n = 446,696). The inverse variance weighting method was considered the primary assessment approach in MR analysis, and several sensitivity analyses were performed to evaluate the reliability of the results. Furthermore, the mediating effect of lifestyle factors including smoking, alcohol intake, walking, and waist–hip ratio was explored by using a two-step MR. According to our MR analysis, mood swings were genetically associated with a higher risk of CAD (OR, 2.101; 95% CI, 1.200–3.679; $P = .009$), AHF (OR, 2.761; 95% CI, 1.312–5.810; $P = .007$), and MCE (OR, 1.048; 95% CI, 1.022–1.076; $P < .001$). In the two-step MR analysis, smoking may mediate the causal pathways from mood swings to CAD (27%), MCE (18%), and AHF (26%). Our MR study revealed a potential causal relationship between mood swings and CVDs, smoking may play an important role in it, highlighting the need for regulating mood stability and build a healthy lifestyle to prevent the onset of CVDs. However, due to the limitations of MR, further research is needed to confirm these associations and clarify the underlying mechanisms.

Abbreviations: AF = atrial fibrillation, AHF = all-cause heart failure, AIF = alcohol intake frequency, CAD = coronary artery disease, CAR = cortisol awakening response, CVDs = cardiovascular diseases, GWAS = genome-wide association studies, IVs = instrumental variables, IVW = inverse variance weighted, MCE = major coronary heart disease events, MR = Mendelian randomization, SARS-CoV-2 = syndrome-coronavirus 2, SI = smoking initiation, SNPs = single nucleotide polymorphisms, WFP = walking for pleasure, WHR = waist–hip ratio.

Keywords: cardiovascular disease, mediation Mendelian randomization, mood swings, smoking

1. Introduction

Cardiovascular diseases (CVDs) have become one of the biggest public health challenges worldwide over the past 30 years. The prevalence of chronic diseases such as CVDs has significantly increased over the past 2 decades. From 1990 to 2019, the number of CVD fatalities has increased from

This work was supported by National Key Research and Development Program of China (2022YFC3602400, 2022YFC3602404), and National Natural Science Foundation of China (grant no. 82270474), and Henan Cardiovascular Disease Center (Central China Subcenter of National Center for Cardiovascular Diseases) (2023-FZX18).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The utilization of publicly available data obviated the necessity for ethics approval and consent to participate.

All authors gave final approval for this version to be published. All authors read and approved the final manuscript.

Supplemental Digital Content is available for this article.

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How to cite this article: Shi Z, Gao Y, Shi Q, Zhang Z, Yu H, Lv M, Zhang T, Chen D, Gu Y, Ma C, Guo Q, Li M. Role of lifestyle factors in mediating the effect of mood swings on cardiovascular diseases: A mediation Mendelian randomization study. Medicine 2025;104:20(e42444).

Received: 19 January 2025 / Received in final form: 23 April 2025 / Accepted: 25 April 2025

http://dx.doi.org/10.1097/MD.0000000000042444

12.1 million to 18.6 million.[1] The development of CVDs has been shown to be influenced by a complex interplay of various modifiable risk factors, including socioeconomic status, physical environment, individual lifestyle choices, and genetic predispositions.[2]

In the post-COVID era, 6.2% of individuals with symptomatic severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection experienced long COVID symptoms, apart from respiratory symptoms, mood swings is also one of the common symptoms.[3,4] Individuals suffering from mental disorders such as depression or anxiety are prone to experiencing mood swings. These are characterized by sudden and unpredictable changes in their behavior.[5,6] There were a lot of increasing evidences that mental disorders were causally related to biological processes and behaviors that contribute to and cause CVDs, and interventions to improve psychological health might confer beneficial impacts on cardiovascular health.[7–9] However, there had been limited research on the causal relationship between mood swings and CVDs.

Mendelian randomization (MR) has emerged as a valuable tool in epidemiology for understanding causal relationships. By using genetic variations as instrumental variables (IVs), MR helps to minimize the biases typically present in observational studies.[10] In this mediation MR analysis, we utilized single nucleotide polymorphisms (SNPs) identified in genome-wide association studies (GWAS) of mood swings as IVs to explore the causal links between 5 prevalent CVDs. Additionally, we employed a two-step MR approach to examine the potential mediating role of lifestyle factors.

2. Methods

2.1. Data sources

This MR study data derived from the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/). To minimize potential bias arising from population stratification, MR analyses were restricted to individuals of European descent. A summary of the research design is illustrated in Figure 1. For the dataset of mood swings, we used summary statistics from a GWAS of UK Biobank with a sample size of 451,619 (204,412 cases and 247,207 controls). We chose 5 CVDs, including coronary artery disease (CAD), major coronary heart disease events (MCE), atrial fibrillation (AF), all-cause heart failure, and stroke as outcomes. Four lifestyles such as smoking initiation (SI), alcohol intake frequency (AIF), walking for pleasure (WFP), and waist–hip ratio (WHR) were obtained as mediators.

All studies contributed to this research received ethical approval from the ethics committees responsible for them, and obtained informed consent from everyone participating in the studies. Table 1 summarized the demographic characteristics of the participants involved in this study.

2.2. Selection of IVs

This study met the 3 key assumptions of classical MR analysis: (1) the IVs directly influenced the exposure; (2) the IVs were not linked to any confounders; and (3) the IVs affected the outcome risk solely through the exposure, without acting through alternative pathways.[11] To meet these conditions, we selected SNPs associated with exposure factors ($P < 5 \times 10^{-8}$) as candidate IVs firstly. Independent IVs were obtained by excluding SNPs in linkage disequilibrium with a threshold of $r^2 = 0.001$ and kb = 10,000 secondly. To excluded potential pleiotropic effects, "Phenoscanner V2" was used to remove SNPs that corresponding to the phenotype related to the outcomes thirdly.[12] Finally, we used F-statistics to evaluate the strength of the IVs and avoid weak instrument bias.[13] We selected SNPs with F > 10, considered a valid threshold, as instrumental variables. The F-statistic was calculated using the formula $F = \beta^2/SE^2$, where β represents the effect on the risk of exposure and SE is the standard error.

2.3. Statistical and sensitivity analyses

Five different MR analysis methods were employed: MR-Egger, weighted median, inverse variance weighted (IVW), simple mode, and weighted mode. The IVW method was chosen as the primary analytic approach to evaluate the associations between mood swings and the risk of CVDs. All statistical analyses were conducted using R software (version 4.2.3), with the TwoSampleMR R package, which supports the IVW, MR-Egger, weighted median, simple mode, and weighted mode methods. A two-sided *P*-value of <.01 (Bonferroni correction: 0.05/5) was considered statistically significant.

We applied the IVW (Q) and MR-Egger regression (Q) methods to assess heterogeneity, and the MR-Egger intercept test to examine horizontal pleiotropy, with statistical significance set at $P < .05$. A leave-one-out analysis was conducted to evaluate the potential influence of individual SNPs on the overall results.[14] Furthermore, the Mendelian Randomization Pleiotropy Residual Sum and Outlier test was utilized to detect and remove horizontal pleiotropic outliers.[15]

2.4. Mediation MR analysis

Some risk factors of CVD are significantly associated with mood swings, such as SI, AIF, WFP, and WHR. Therefore, a two-step MR was used to estimate to what extent the causal relationship

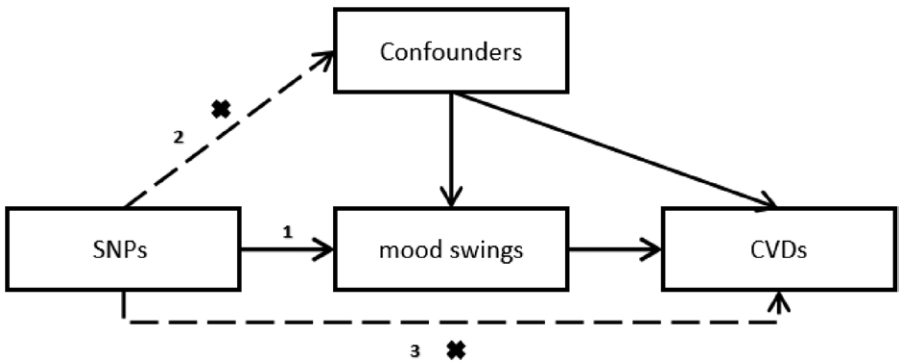

Figure 1. Study design flowchart of the Mendelian randomization analysis. The Mendelian randomization approach relies on 3 key assumptions: (1) the instrumental variables are robustly associated with the exposure; (2) the instrumental variables are independent of any confounding factors; (3) the instrumental variables influence the outcomes solely through the exposure and not through any other pathways.

was mediated by these risk factors. In the first step, the causality of irritability on these potential mediators was confirmed. In the second step, we used the IVs that were significantly associated with the mediators to assess the causal association between the mediators and the risk of CVDs causally associated with mood swings (Fig. 2).

3. Results

We extracted IVs that were significantly associated with mood swings from the GWAS ($P < 5 \times 10^{-8}$) and removed those in linkage disequilibrium with an r^2 threshold of < 0.001 within a 10,000-kb window. SNPs associated with CVDs were subsequently retrieved from the PhenoScanner V2 database. SNPs linked to confounding factors, as well as those with palindromic or incompatible alleles, were excluded. As a result, 57 independent SNPs associated with mood swings were selected, 26 SNPs were deleted due to related to the outcomes (hypertension, diabetes, smoking, drinking), 31 SNPs were included as IVs finally (Data S5, Supplemental Digital Content, https://links.lww.com/MD/O892). These screened SNPs were then used in subsequent analyses. The IV strength test (F-statistic > 10) showed no evidence of weak instrument bias. In mood swings to CAD, we excluded 1 SNP due to the presence of palindromic sequences.

Using the IVW method, we found that genetically mood swings might have potential relationship with higher odds of CAD (IVW: OR, 2.101; 95% CI, 1.200–3.679; $P = .009$), all-cause HF (IVW: OR, 2.761; 95% CI, 1.312–5.810; $P = .007$), and MCE (IVW: OR, 1.048; 95% CI, 1.022–1.076; $P < .001$). However, we did not find enough evidence for the relationships between mood swings with AF (IVW: OR, 0.978; 95% CI, 0.664–1.442; $P = .912$), and stroke (IVW: OR, 1.275; 95% CI, 0.722–2.250; $P = .402$), (Figure S1, Supplemental Digital Content, https://links.lww.com/MD/O893). The two-sample MR estimates for the associations between mood swings and the risk of CVDs were displayed in Figure 3.

Sensitivity analyses, including the IVW (Q), MR-Egger (Q), and MR-Egger intercept tests, were conducted to evaluate potential heterogeneity and horizontal pleiotropy (Table 2). The MR-Egger intercept test indicated no evidence of pleiotropy, while the IVW (Q) and MR-Egger (Q) tests suggested varying degrees of heterogeneity in the associations with CAD and major coronary heart disease events (Table 2). Additionally, the leave-one-out analysis confirmed that the observed causal relationship between mood swings and CVD risk was not driven by any single SNP (Figure S2, Supplemental Digital Content, https://links.lww.com/MD/O894). Funnel and forest plots, which provide a more intuitive view of heterogeneity, are shown in (Figures S3 and S4, Supplemental Digital Content, https://links.lww.com/MD/O895).

In the mediation MR analysis, we selected 3 outcomes CAD, MCE, and all-cause HF whose P-value <.05 in the two-sample MR analysis. Firstly, we assessed the causal effect of mood swings on SI (IVW, OR: 2.553 (1.761, 3.701), $P < .001$), mood swings on AIF (IVW, OR: 1.941 (1.406, 2.678), $P < .001$), mood swings on WFP (IVW, OR: 0.870 (0.796, 0.951), $P = .002$), and mood swings on WHR (IVW, OR: 1.349 (1.139, 1.599)), $P < .001$). In the second step, we confirmed the causal effect association of mediators on CAD, MCE, and all-cause HF (Table 3). Finally, we assessed the causal effect of

Table 1

Data sources and instrumental variables strength assessment.

Traits	Sample size (cases/controls)	Population	GWAS ID
Exposure		European	
Mood swings	204,412/247,207	European	ukb-b-14180
Outcomes		European	
Coronary artery disease	122,733/424,528	European	ebi-a-GCST005195
Major coronary heart disease event	10,157/351,037	European	ukb-d-I9_CHD
All-cause heart failure	23,397/194,811	European	finn-b-I9_HEARTFAIL_ALLCAUSE
Atrial fibrillation	60,620/970,216	European	ebi-a-GCST006414
Stroke	40,585/406,111	European	ebi-a-GCST005838
Mediator			
Smoking initiation	311,629/321,173	European	ieu-b-4877
Alcohol intake frequency	336,965 (all)	European	ukb-a-25
Types of physical activity in last 4 weeks: walking for pleasure	328,755/130,621	European	ukb-b-7337
Waist–hip ratio	502,773 (all)	European	ebi-a-GCST90029009

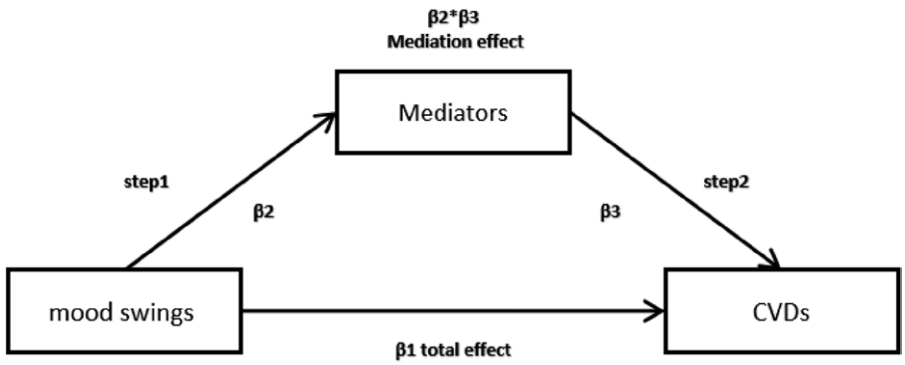

Figure 2. The overview of two-step mediation analysis. In the first step, the causality of mood swings on potential mediators was confirmed. In the second step, IVs significantly associated with the mediators are used to assess the causal effect between mediators and the risk of CVDs causally associated with mood swings. Total effect = β1; mediation effect = β2*β3; proportion mediated = (β2*β3)/β1. IVs = instrumental variables.

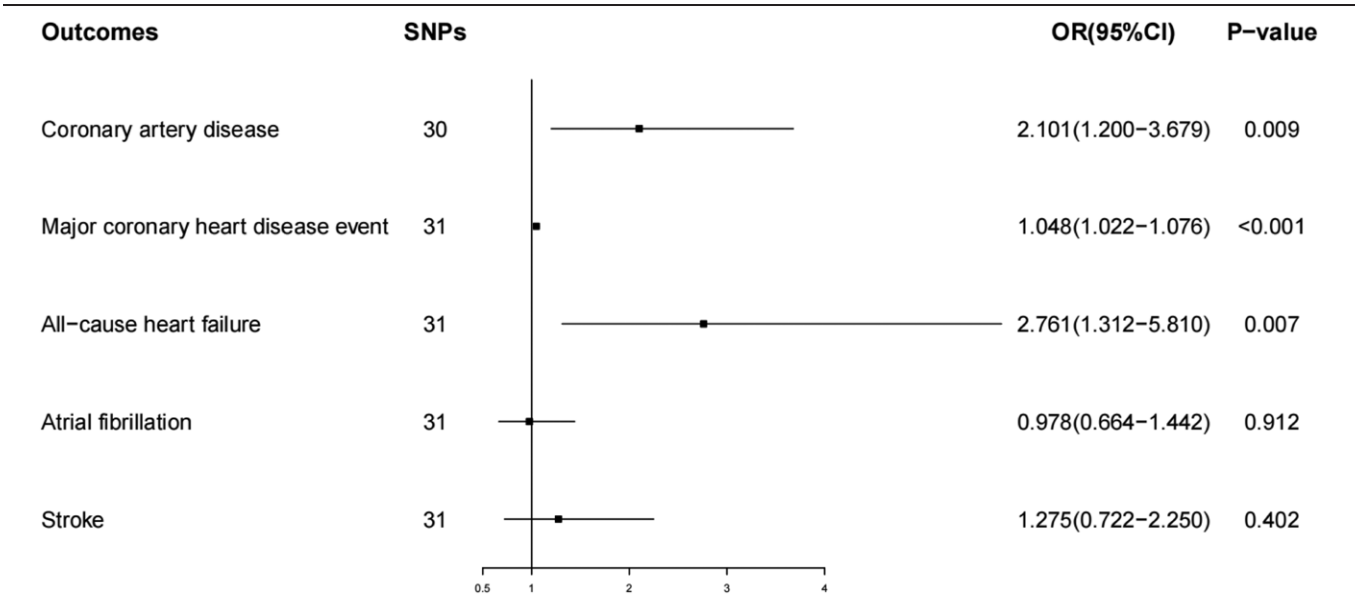

Figure 3. Associations of mood swings and the risk of CVDs. Results derived from IVW analyses. CI = confidence interval; CVDs = cardiovascular diseases; IVW = inverse variance weighted; OR = odds ratio; SNPs = single nucleotide polymorphisms.

Table 2

Pleiotropy and heterogeneity test of the mood swings IVs from CVD GWAS.

	Pleiotropy test			Heterogeneity test					
	MR-Egger			MR-Egger			Inver-variance weighted		
Outcomes	Intercept	SE	*P*	Q	Q_df	Q_*p*val	Q	Q_df	Q_*p*val
Coronary artery disease	-0.015	0.013	.281	55.123	28	0.002	57.500	29	0.001
Major coronary heart disease event	-2.83E-04	0.001	.660	42.754	29	0.048	43.046	30	0.058
All-cause heart failure	0.025	0.018	.177	39.482	29	0.093	42.092	30	0.070
Atrial fibrillation	-0.013	0.010	.172	29.743	29	0.427	31.759	30	0.379
Stroke	-0.019	0.014	.178	42.792	29	0.048	45.608	30	0.034

CVDs = cardiovascular diseases, df = degree of freedom, GWAS = genome-wide association studies, IVs = instrumental variables, MR = Mendelian randomization, Q = heterogeneity statistic Q.

mood swings on several CVDs through the mediating effect, we found that 4 mediators play a certain role between mood swings and CAD (Table 4).

4. Discussion

This study utilized two-sample MR analyses with GWAS summary data to explore the causal association between mood swings and 5 CVDs traits. The results hinted at a potential causal relationship that genetically heightened mood swings may contribute to an elevated risk of certain CVDs. To be specific, experiencing mood swings predict a higher risk of CAD, MCE, and all-cause HF. However, we did not obtain sufficient evidence to substantiate associations between mood swings with AF and stroke. And 4 lifestyle mediators play a certain role between mood swings and some CVDs.

Mood swings played a central role in the clinical manifestations of mental disorders. According to the statistics, although mood swings occurred most frequently in individuals with bipolar disorder (22.6%), it was likewise prevalent among those with personality disorder (17.8%) and schizophrenia (15.5%).[16] A survey conducted in England found that mood swings is a common experience, with a population rate of 13.9%. The survey found that mood swings was more common among women compared to men, with the peak prevalence occurring in the 16 to 24 years old age group, and the rate gradually declining with increasing age, such that only 7% of individuals aged 65 to 74 years old reported experiencing mood swings.[17] The meta-analysis revealed that people who have serious mental illnesses may cause an elevated risk of cardiovascular mortality and morbidity compared to the general population. For instance, the estimated risks for schizophrenia ranged from a hazard ratio of 1.25 (95% CI: 1.04–1.51, $P = .016$) for total CVD events, to a rate ratio of 3.82 (95% CI: 3.10–4.71, $P < .001$) for HF.[18] A study of over 80,000 postmenopausal women without prior CVDs found that mood swings was significantly associated with total CVDs and increased all-cause mortality.[19] In addition, a recent MR analysis suggested that mood swings genetically increased the risk of CAD (OR = 1.67, $P < .001$).[20] Our findings align with prior research, with the innovation of revealing this phenomenon from a genetic perspective, particularly the correlation between mood swings and increased risk of major coronary heart disease event.

Despite the association between mood swings and CAD or HF development, the precise pathophysiological mechanisms underlying this linkage remained poorly defined. The involved reasons could be related to the following aspects.

4.1. Hypothalamic–pituitary–adrenal axis dysregulation

The cortisol awakening response (CAR), characterized by a transient spike in cortisol secretion upon morning awakening, and mood swings appeared to be associated with elevated CAR

Table 3

The mediation analysis results of mood swings on CVDs via smoking, alcohol intake, walking, and waist–hip ratio.

Mood swings on mediators			
	Number of SNPs	**OR (95% CI)**	***P***
Smoking initiation (SI)	30	2.553 (1.761, 3.701)	<.001
Alcohol intake frequency (AIF)	31	1.941 (1.406, 2.678)	<.001
Walking for pleasure (WFP)	31	0.870 (0.796, 0.951)	.002
Waist–hip ratio (WHR)	31	1.349 (1.139, 1.599)	<.001
Smoking initiation on CVDs			
	Number of SNPs	**OR (95% CI)**	***P***
Coronary artery disease	72	1.241 (1.127, 1.368)	<.001
Major coronary heart disease event	85	1.009 (1.005, 1.013)	<.001
All-cause heart failure	85	1.329 (1.175, 1.502)	<.001
Alcohol intake frequency on CVDs			
	Number of SNPs	**OR (95% CI)**	***P***
Coronary artery disease	39	1.186 (1.028, 1.367)	.019
Major coronary heart disease event	43	1.002 (0.996, 1.008)	.455
All-cause heart failure	42	1.135 (0.932, 1.383)	.208
Walking for pleasure on CVDs			
	Number of SNPs	**OR (95% CI)**	***P***
Coronary artery disease	17	0.250 (0.118, 0.533)	<.001
Major coronary heart disease event	20	0.935 (0.898, 0.973)	<.001
All-cause heart failure	20	0.516 (0.157, 1.689)	.274
Waist–hip ratio on CVDs			
	Number of SNPs	**OR (95% CI)**	***P***
Coronary artery disease	280	1.322 (1.220, 1.432)	<.001
Major coronary heart disease event	312	1.007 (1.004, 1.010)	<.001
All-cause heart failure	308	0.997 (0.919, 1.081)	.941

Table 4

The mediation effect of mood swings on CVDs via smoking, alcohol intake, walking, and waist–hip ratio.

Trait	**Total effect**	**Mediation effect**	**Direct effect**	**Proportion mediated**
SI (mood swings on CAD)	0.742	0.203	0.539	27%
SI (mood swings on MCE)	0.047	0.008	0.039	18%
SI (mood swings on AHF)	1.016	0.266	0.749	26%
AIF (mood swings on CAD)	0.742	0.113	0.629	15%
AIF (mood swings on MCE)	0.047	0.001	0.046	3%
AIF (mood swings on AHF)	1.016	0.084	0.932	8%
WFP (mood swings on CAD)	0.742	0.193	0.549	26%
WFP (mood swings on MCE)	0.047	0.009	0.038	20%
WFP (mood swings on AHF)	1.016	0.093	0.923	9%
WHR (mood swings on CAD)	0.742	0.084	0.659	11%
WHR (mood swings on MCE)	0.047	0.002	0.045	5%
WHR (mood swings on AHF)	1.016	-0.001	1.017	0%

AHF = all-cause heart failure, AIF = alcohol intake frequency, CAD = coronary artery disease, direct effect = $\beta1–\beta2*\beta3$, MCE = major coronary heart disease event, mediation effect = $\beta2*\beta3$, proportion mediated = $(\beta2*\beta3)/\beta1$; SI = smoking initiation, total effect = $\beta1$, WFP = walking for pleasure, WHR = waist–hip ratio.

levels.[21] Prospective nested case–control studies and MR analyses had demonstrated a positive association between morning plasma cortisol levels and the incidence of CVDs.[22] As one of the potential pathways, elevated CAR levels were likely to mediate the association between mood swings and CVDs.

4.2. Sleep disturbance and circadian rhythm dysfunction

A meta-analysis found a positive association between disturbances in circadian patterns as well as delayed sleep timing and mood swings.[23] Humans exhibited circadian rhythms in key cardiovascular functions, including higher daytime and lower nighttime blood pressure, and higher morning platelet aggregability. Disrupting these rhythms was possible to increase cardiovascular risk, for example, circadian misalignment had been shown to increase waking blood pressure and 24-hour average systolic and diastolic blood pressure. Moreover, circadian misalignment decreased cardiac vagal modulation during wake periods and increased levels of inflammatory markers.[24] Therefore, mood swings could lead to CVDs by affecting circadian rhythms.

4.3. Dysbiosis of microbiota–gut–brain axis

The gut–brain axis played a crucial role in maintaining homeostasis, and with the microbiome having emerged as an important modulator of gut–brain signaling, this led to the establishment of the concept of a microbiota–gut–brain axis. Recent evidence suggests that the composition of the gut microbial community could play a role in mood changes among mentally and physically healthy adults.[25,26] A causal role of gut microbiota in CVDs has been further supported by abundant direct experimental evidence. Gut microbiota transplantation studies, microbiota-dependent pathways, and microbial metabolites had been demonstrated to influence host metabolism and CVDs.[27] But the gut microbiota was highly diverse, and the specific intrinsic connections remained to be further studied.

4.4. COVID-19 infection

The COVID-19 infection emerged in 2019 and caused hundreds of millions of infections globally thus far. Although the worldwide pandemic had largely subsided, numerous studies revealed that SARS-CoV-2 invasion was not confined to the respiratory system only, but also inflicted damages across multiple organ systems throughout the body.[28] As aforementioned, mood swings was a common symptom following COVID-19 infection. Meanwhile, meta-analyses showed increased incidence of depression and anxiety disorders resulting from SARS-CoV-2 infection.[29,30] A large-scale cohort study revealed that COVID-19 infection led to heightened susceptibility across a spectrum of CVDs.[31] Several potential mechanisms underlying the increased CVDs risk following COVID-19 had been proposed, such as direct myocardial injury, endothelial dysfunction, and sustained inflammation.[32,33] Besides, SARS-CoV-2 infection was associated with a higher risk of diabetes and might cause 3% to 5% excess burden of diabetes at a population level.[34] These could explain the increased incidence of CVDs induced by COVID-19. However, the precise mechanisms of COVID-19–mood swings–CVDs remained to be elucidated.

4.5. Behavioral factors

In addition, some evidence indicates that behavioral mechanisms play a certain role in mediating the association between mood swings and CVDs, as individuals with mood swings frequently engage in adverse health behaviors, including binge eating, excessive alcohol, which represent established risk factors predisposing to CVDs.[35–38] Our mediating MR results further supported this conclusion.

This MR study has several meaningful strengths. First, we carefully excluded genetic variants associated with potential confounders commonly observed in epidemiological research, focusing only on SNPs with a strong association with mood swings. Second, the large sample size improved statistical power, providing robust evidence for the observed associations. Additionally, the Mendelian Randomization Pleiotropy Residual Sum and Outlier test was used to identify and remove horizontal pleiotropic outliers, ensuring the reliability of our results. Finally, a series of sensitivity analyses, including IVW, MR-Egger, and leave-one-out tests, were conducted to confirm the robustness of our findings.

Nevertheless, this study has some limitations. First, our analysis was confined to individuals of European descent, which, while minimizing demographic bias, restricts the generalizability of the results to non-European populations. Further research is needed to confirm these findings in more diverse ethnic groups. Second, heterogeneity was detected to varying extents using the IVW (Q) and MR-Egger (Q) methods, which may affect the precision of the causal estimates.

5. Conclusion

Our MR study revealed a potential causal relationship between mood swings and CVDs, smoking may play an important role in it, highlighting the need for regulating mood stability and build a healthy lifestyle to prevent the onset of CVDs. However, due to the limitations of MR, further research is needed to confirm these associations and clarify the underlying mechanisms.

Author contributions

Conceptualization: Zhuocheng Shi, Yang Gao, Qingbo Shi, Zhiwen Zhang, Cao Ma, Quan Guo.
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