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ORIGINAL RESEARCH

Causal Relationship Between Migraine and Postpartum Depression: A Two-Sample Bidirectional Mendelian Randomization Study

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Background: The possible causative relationship between migraine and postpartum depression (PPD) is examined in this study. Prior research has shown a strong correlation between the two conditions, but the exact cause is unknown.

Methods: A bidirectional Mendelian randomization (MR) approach was employed to assess causality, utilizing discovery and replication samples from publicly available genome-wide association study (GWAS) datasets. Causal effects were estimated using the inverse-variance weighted (IVW) method, MR-Egger regression, and three additional MR approaches. Sensitivity analyses, including tests for heterogeneity, horizontal pleiotropy, and leave-one-out analysis, were conducted to evaluate the robustness of the findings.

Results: Overall, no significant causal effect of migraine on PPD risk was identified in either the discovery (IVW: OR=1.018; 95% CI=0.928–1.117; P=0.706) or replication analysis (IVW: OR=2.097; 95% CI=0.328–13.409; P=0.434) in forward MR analysis. Similarly, no causal effect of migraine on PPD was observed in female-only analyses. Moreover, reverse MR analysis found no significant causal effect of PPD on migraine risk in discovery (IVW: OR=1.036; 95% CI=0.999–1.075; P=0.057) or replication (IVW: OR=1.001; 95% CI=1.000–1.002; P=0.274) analysis, and no causal effect was observed in female-only analyses. No evidence of heterogeneity or horizontal pleiotropy was detected in sensitivity tests.

Conclusion: The current MR study indicates no significant causal relationship between migraine and PPD.

Keywords: migraine, postpartum depression, Mendelian randomization, causal effect

Introduction

Postpartum depression (PPD) is a global public health concern, presenting as a complex mental health disorder characterized by severe anxiety and various physical, emotional, and behavioral changes.[1] Symptoms of PPD typically arise within the first four weeks after delivery, although they may also occur during pregnancy or up to one year after delivery.[2] These symptoms include low mood, intense mood swings, frequent crying, difficulty bonding with the newborn, severe anxiety, panic attacks, and, in severe cases, thoughts of self-harm or harm to the baby, as well as suicidal ideation.[3] Affecting approximately 10%-15% of women of reproductive age, PPD poses substantial risks to both maternal and child health.[4] Unlike major depressive disorder (MDD), PPD is strongly associated with hormonal fluctuations and the interplay of physical, emotional, and psychological changes during the perinatal period. These abrupt hormonal changes are known to influence brain function, contributing to the variable mental health symptoms observed in affected individuals.[5,6]

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Migraine, one of the most prevalent headaches, is characterized by recurrent, unilateral, and pulsatile pain of moderate to severe intensity and is widely recognized as a debilitating condition. Women are two to three times more likely than men to experience migraines, with around 40% of women affected by the end of their reproductive years.[7] According to the 2021 Global Burden of Disease Study, migraine was the third leading contributor to neurological disability-adjusted life years (DALYs) and the foremost cause of disability among women.[8] Studies have indicated that the onset of migraines is influenced by factors such as environmental triggers, hormonal fluctuations, and lifestyle-related elements, including sleep deprivation, stress, and insufficient rest. Following childbirth, the sharp decline in estrogen and progesterone levels triggers migraine episodes in approximately 25% of women within two weeks postpartum, with nearly half experiencing migraines within the first month.[9–12] In 2021, Gordon-Smith et al reported a potential association between migraine and PPD, consistent with findings from recent large-scale studies, including a Swedish population-based analysis.[13] However, the precise causal link between migraine and PPD remains unclear.

Some studies have shown that abnormal brain activity in migraine and PPD patients is mainly distributed in overlapping areas such as the hippocampus, cingulate gyrus, orbitofrontal cortex, prefrontal cortex, amygdala, and parahippocampal gyrus, based on neuroimaging evaluation.[14,15] Planchuelo-Gomez et al found widespread differences in white matter structure in patients with migraine.[16] Long et al observed significantly increased fractional anisotropy (FA) and axial diffusivity (AD) in the right anterior thalamic radiation (ATR) tract, as well as increased FA and reduced radial diffusivity in the cingulum tract, in women with PPD compared to those without the condition.[17] Dysfunction in glutamate (Glu) metabolism has also been associated with both migraine and PPD. Research by Aimie Laura Peek demonstrated significantly elevated Glu levels in migraine patients.[18] Zhao et al found that Glu levels in the medial prefrontal cortex (MPFC) of PPD patients were significantly higher than those in healthy controls, suggesting a link between Glu dysfunction in the MPFC and PPD.[19]

Mendelian randomization (MR) analysis provides a framework for evaluating causal relationships between exposures and outcomes by using single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) derived from genome-wide association study (GWAS) datasets. This approach leverages genetic variants associated with exposures to minimize confounding, thereby enabling clearer assessments of causality.[20] MR has been broadly applied to investigate causal associations in numerous areas, including cardiovascular disease,[21] rheumatology,[22] and mediation analysis.[23]

Today, increasing research has explored the association between migraine and PPD, the direction of causality remains undetermined. So, it is intriguing and critical to investigate the mutually causative consequences of migraine and PPD. This study addresses this gap by conducting a bidirectional two-sample MR analysis to examine potential causal links between migraine and PPD, providing new insights into their mutual influence.

Methods

Study Design

This MR study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) guidelines. To evaluate the causal relationship between migraine and PPD, we applied a bidirectional two-sample MR approach using SNPs as IVs (Figure 1). All data were obtained from a publicly available genome-wide association study (GWAS); therefore, no additional ethical approval was required.

To ensure the robustness and validity of our conclusions, we performed two separate bidirectional MR analyses following discovery and replication protocols. All selected datasets were derived from the most recent or largest publicly available GWAS. In the discovery analysis, migraine data were obtained from a 2023 GWAS dataset (https://www.decode.com/summarydata/), comprising 4,326,854 participants.[24] This dataset was based on a meta-analysis of clinically diagnosed migraine, including migraine with aura (MA) and without aura (MO), using data from Iceland, Denmark, the United Kingdom, the United States, Norway, and Finland. PPD data were sourced from the FinnGen consortium (finngen_R8_O15_POSTPART_DEPR), which included 249,835 participants. The FinnGen project is a large-scale public-private partnership integrating genomic and health data from 500,000 Finnish biobank donors, with clinical endpoints defined using Finnish health registry data. All datasets were used for both forward and reverse MR analysis. In

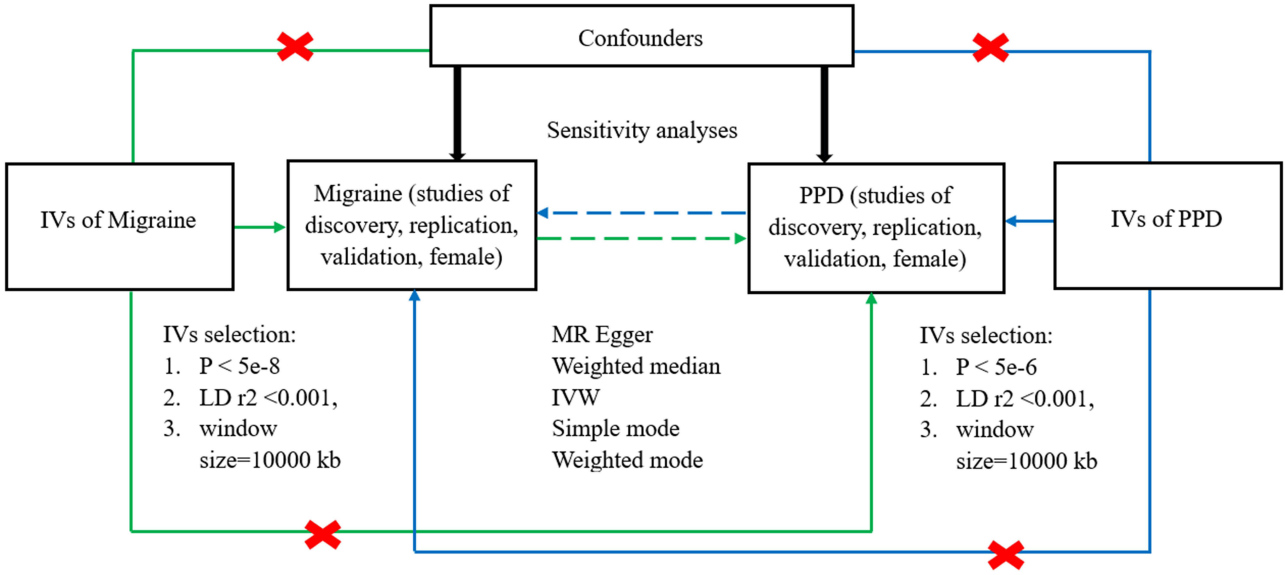

Figure 1 Sketch of the study design. The green represented the forward MR analyses, with migraine as exposure and PPD as the outcome. The blue represented the reverse MR analyses, with PPD as exposure and migraine as the outcome.
Abbreviations: PPD, postpartum depression; MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms.

the replication analysis, migraine data were obtained from the dataset ebi-a-GCST90038646, available through the Integrative Epidemiology Unit (IEU) GWAS database (https://gwas.mrcieu.ac.uk/), which included 484,598 participants. This dataset was based on self-reported disease status and age-at-diagnosis and is considered less biased than International Classification of Diseases, 10th Revision (ICD-10) coding alone.[25] PPD data were derived from a GWAS meta-analysis conducted by Guintivano et al, based on 18 European-ancestry cohorts totaling 70,765 participants (https://doi.org/10.6084/m9.figshare.24204843).[26] These datasets were also applied for both forward and reverse MR analyses.

In addition, we included a 2021 study on migraine in women, comprising 302,262 participants, for forward analysis.[27] For reverse analysis, we used data from the UK Biobank (UKBB GWAS Round 2; http://www.nealelab.is/uk-biobank), which included 194,174 European participants,[28] to investigate the potential causal effect of gender differences on PPD risk. For PPD in these analyses, we again used the finngen_R8_O15_POSTPART_DEPR dataset from the FinnGen consortium, which included 249,835 participants.

To minimize the potential impact of population stratification due to racial heterogeneity, all datasets were restricted to participants of European ancestry. While minor genetic differences may exist between Anglo-Saxon and Mediterranean populations, they are considered negligible in the context of this study (Supplementary Table 1).

Selection of IVs

The chosen IVs conformed to three primary assumptions: (1) IVs must be strongly associated with exposure variables, (2) IVs must not associated with confounding factors, and (3) IVs must affect the outcome exclusively through the exposure variables.[29] We applied stringent criteria for IV selection. First, SNPs were required to meet a significant threshold of $P<5\times10^{-8}$ for migraine in the discovery, replication, and female-specific groups during forward MR analysis. When fewer eligible SNPs were available, a relaxed threshold of $P<5\times10^{-6}$ was adopted to increase the number of valid IVs. For PPD, due to the absence of SNPs meeting the $P<5\times10^{-8}$ threshold, we employed the more lenient $P<5\times10^{-6}$ cutoff in reverse MR analysis to maximize IV inclusion.

Linkage disequilibrium clumping was conducted using the 1000 Genomes Project European reference panel, applying an r2>0.001 and a clumping window of 10,000 kb to ensure SNP independence.[30] To examine potential confounding, the correlation between IVs and known confounders was evaluated using the LDtrait database (https://ldlink.nih.gov/?tab=ldtrait). Weak instrument bias was assessed using F-statistics, calculated as follows: $F=R^2\times(N-2)/(1-R^2)$[31] and $R^2=2\times(1-EAF)\times EAF\times\beta^2$, where N represents the sample size of the exposure GWAS data, β is the effect estimate of the SNP on

the exposure, and EAF is the effect allele frequency.[32] An F-statistic greater than 10 was considered indicative of adequate instrument strength, minimizing the risk of weak instrument bias.

Statistical Analysis

To evaluate the causal relationship between migraine and PPD, the inverse-variance weighted (IVW) method was employed as the primary analytical approach, supported by MR-Egger, weighted median, and weighted mode methods. When heterogeneity was present, a random-effects model was used for IVW, as determined by the Cochrane Q test ($P<0.05$). Leave-one-out analysis was conducted to test the stability of the MR results by sequentially excluding each SNP. Horizontal pleiotropy was assessed using the MR-Egger intercept test,[33] and MR-Pleiotropy Residual Sum and Outliers (MR-PRESSO) test.[34] All statistical analyses were performed using the "TwoSampleMR" (version 0.5.7) and "MRPRESSO" (version 1.0) packages in R (version 4.4.2), with statistical significance defined as a two-tailed $P<0.05$.

Result

Discovery Analysis

IV Selection

For the forward MR analysis, data were extracted from the migraine GWAS by Bjornsdottir et al[24] and the PPD dataset from the FinnGen consortium. A total of 46 SNPs were initially identified from the migraine dataset using a genome-wide significance threshold of $P<5\times10^{-8}$. Following LD pruning and harmonization procedures, 8 SNPs were excluded, resulting in 38 SNPs retained as IVs for migraine. In the reverse MR analysis (PPD as exposure, migraine as outcome), 31 SNPs were selected from the PPD dataset using a relaxed significance threshold of $P<5\times10^{-6}$. After removing 3 SNPs due to LD pruning and harmonization, 28 SNPs remained for use as IVs for PPD. No SNPs were excluded based on LD trait tool screening. All selected IVs demonstrated F-statistics greater than 10, indicating a low risk of weak instrument bias. Full details of all included SNPs are provided in Supplementary Tables 2 and 3.

MR Analyses of Migraine and PPD

No significant heterogeneity was detected using the heterogeneity test (IVW) for either forward MR analysis (PIVW=0.575; Table 1 and Figure 2) or reverse MR analysis (PIVW=0.238; Table 1, Supplementary Figure 1).

In the IVW models, no significant causal effect was observed in either direction: forward MR analysis (IVW: OR=1.018; 95% CI=0.928–1.117; P=0.706) and reverse MR analysis (IVW: OR=1.036; 95% CI=0.999–1.075; P=0.057), as visualized in the forest and scatter plots (Figures 3 and 4; Supplementary Figures 2 and 3). These findings were consistent across four additional MR methods (Table 2).

Mild horizontal pleiotropy was detected in the forward MR analysis using the MR-Egger intercept test (P=0.041), but not in the reverse analysis (P=0.937; Table 1). Subsequent MR-PRESSO analysis and leave-one-out plots identified no

Table 1 Heterogeneity Test and Horizontal Pleiotropy Test of Migraine and PPD

Exposure/Outcome	Heterogeneity Test (MR-Egger)			Heterogeneity Test (IVW)			Horizontal Pleiotropy Test (MR-Egger)			MR-PRESSO Global Test
	Q	df	P-Value	Q	df	P-Value	Intercept	se	P-Value	P-Value
Discovery										
Migraine on PPD	30.26439	36	0.738	34.75760	37	0.575	0.01610737	0.007598827	0.041	0.602
PPD on Migraine	31.82280	26	0.199	31.83061	27	0.238	−0.0002829676	0.003542343	0.937	0.260
Replication										
Migraine on PPD	60.11085	58	0.399	62.41430	59	0.356	−0.0100022	0.006709163	0.141	0.372
PPD on Migraine	32.49885	25	0.144	32.50075	26	0.177	4.738654e-06	0.0001239272	0.970	0.246
Females										
Migraine on PPD	11.90453	14	0.614	15.11804	15	0.443	0.02974174	0.01659115	0.095	0.456
PPD on Migraine	26.21907	24	0.342	27.38807	25	0.337	−0.003586459	0.003467054	0.311	0.421

Abbreviation: PPD, Postpartum depression.

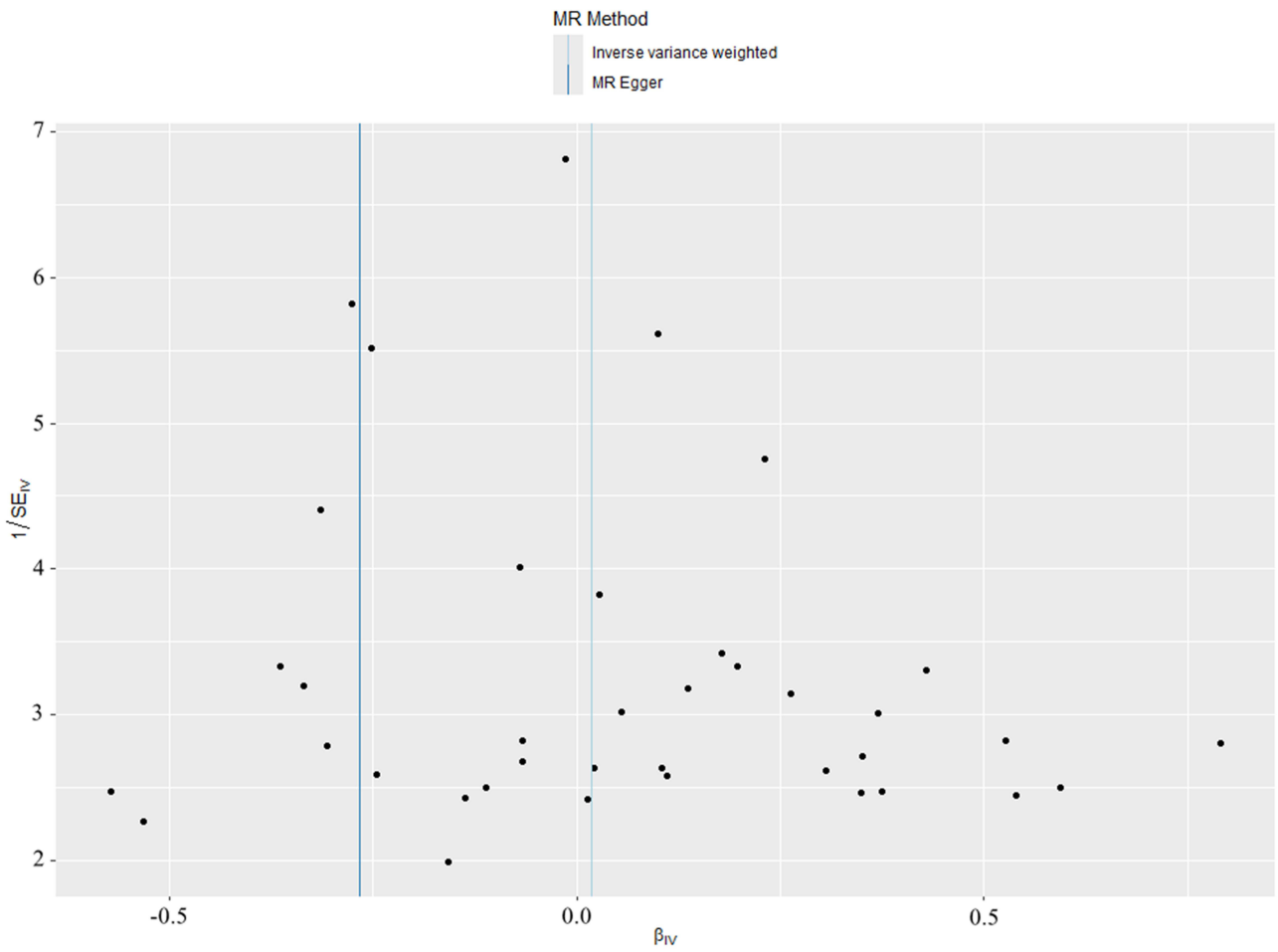

Figure 2 The funnel plot of the heterogeneity of migraine and PPD (discovery).

outliers in either the forward (P=0.372) or reverse MR analyses, supporting the robustness of the results (Table 1; Figure 5 and Supplementary Figure 4).

Replication Analysis

IV Selection

In the forward MR analysis (migraine on PPD), data were obtained from the studies by Dönertaş et al (migraine)[25] and Guintivano et al (PPD)[26] In general, 61 SNPs were initially identified from the migraine dataset using a significance threshold of $P<5\times10^{-6}$. After LD pruning and harmonization, 3 SNPs were excluded, resulting in 58 SNPs retained as IVs for migraine. In the reverse MR analysis (PPD on migraine), 28 SNPs were from the PPD dataset using the same P-value threshold. One SNP was removed through LD pruning and harmonization, yielding 27 SNPs as IVs for PPD. No SNPs were excluded based on LD trait tool screening. All selected IVs had F-statistics >10, indicating low risk of weak instrument bias. Full SNP details are presented in Supplementary Tables 3 and 4.

MR Analyses of Migraine and PPD

No significant heterogeneity was detected with heterogeneity test (IVW) in both forward MR analysis ($P_{IVW}=0.356$) (Table 1, Supplementary Figure 5) and reverse MR analysis ($P_{IVW}=0.177$) (Table 1, Supplementary Figures 6). IVW results showed no significant causal effect in either direction: forward MR analysis: forward MR analysis (IVW: OR=2.097; 95% CI=0.328–13.409; P=0.434) and reverse MR analysis (IVW: OR=1.001; 95% CI=1.000–1.002; P=0.274), as illustrated in forest and scatter plots (Supplementary Figures 7–10). These findings were consistent across

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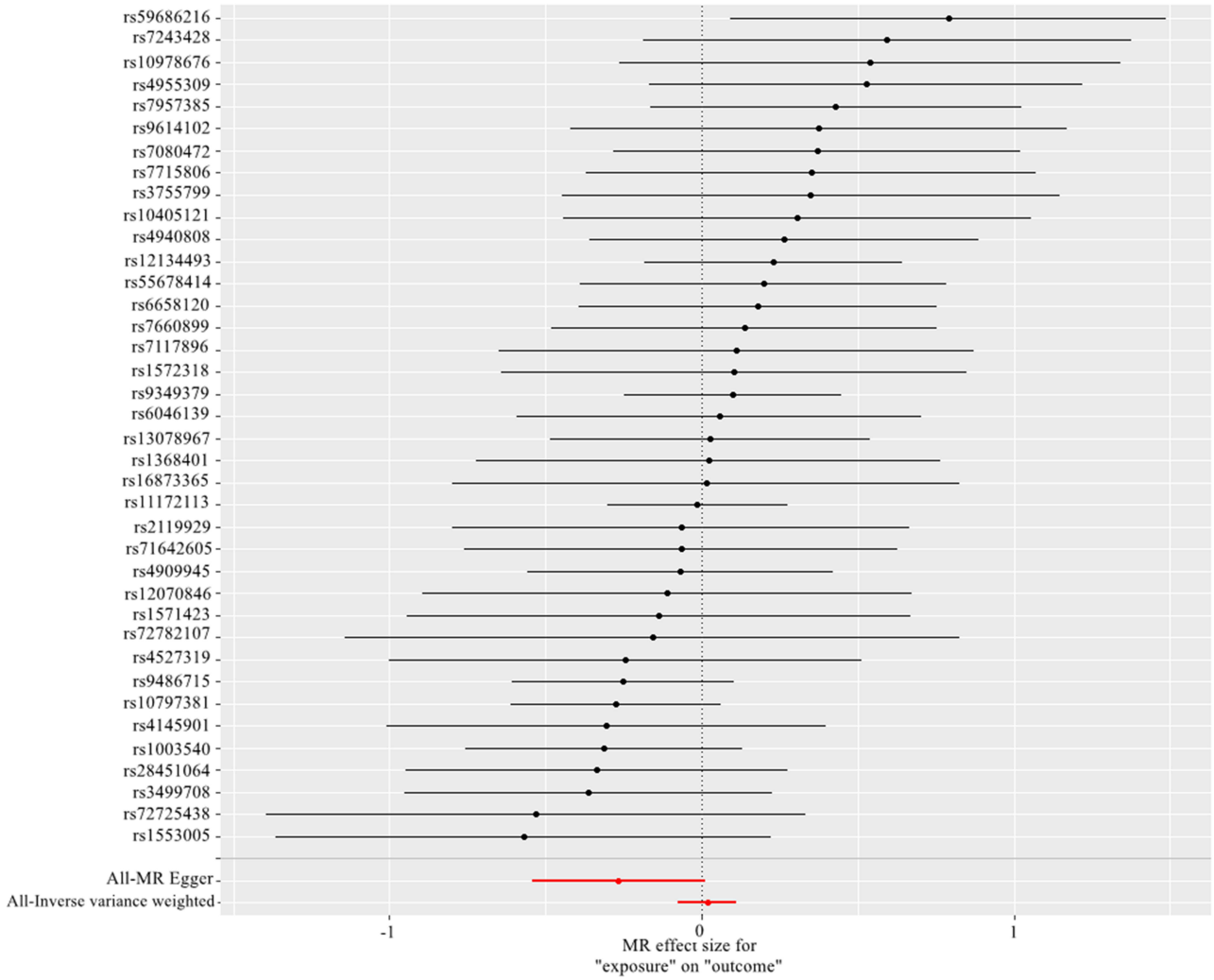

Figure 3 The forest plot of the causal effects of migraine and PPD (discovery).

the four complementary MR methods (Table 2). MR-Egger intercept tests indicated no horizontal pleiotropy in either forward (P=0.141) or reverse (P=0.970) MR analyses (Table 1). Further MR-PRESSO analysis and leave-one-out plots revealed no outliers in either forward (P=0.372) or reverse (P=0.246) MR analyses, supporting the stability of the findings (Table 1; Supplementary Figures 11 and 12).

Subgroup (Female) Analysis

IV Selection

For the forward MR analysis (migraine on PPD), data were sourced from Choquet et al (migraine)[27] and FinnGen consortium (PPD) studies. In general, 19 SNPs were identified using a significance threshold of $P<5\times10^{-8}$ from the migraine dataset. After LD pruning and harmonization, 3 SNPs were excluded, leaving 16 SNPs for use as IVs for migraine. For the reverse MR analysis (PPD on migraine), data were obtained from Bycroft et al (migraine)[28] and FinnGen consortium (PPD). In general, 28 SNPs were identified from the PPD dataset ($P<5\times10^{-6}$); following the removal of 2 SNPs, 26 remained as IVs. All selected IVs had F-statistics >10, indicating no evidence of weak instrument bias. SNP details are provided in Supplementary Tables 6 and 7.

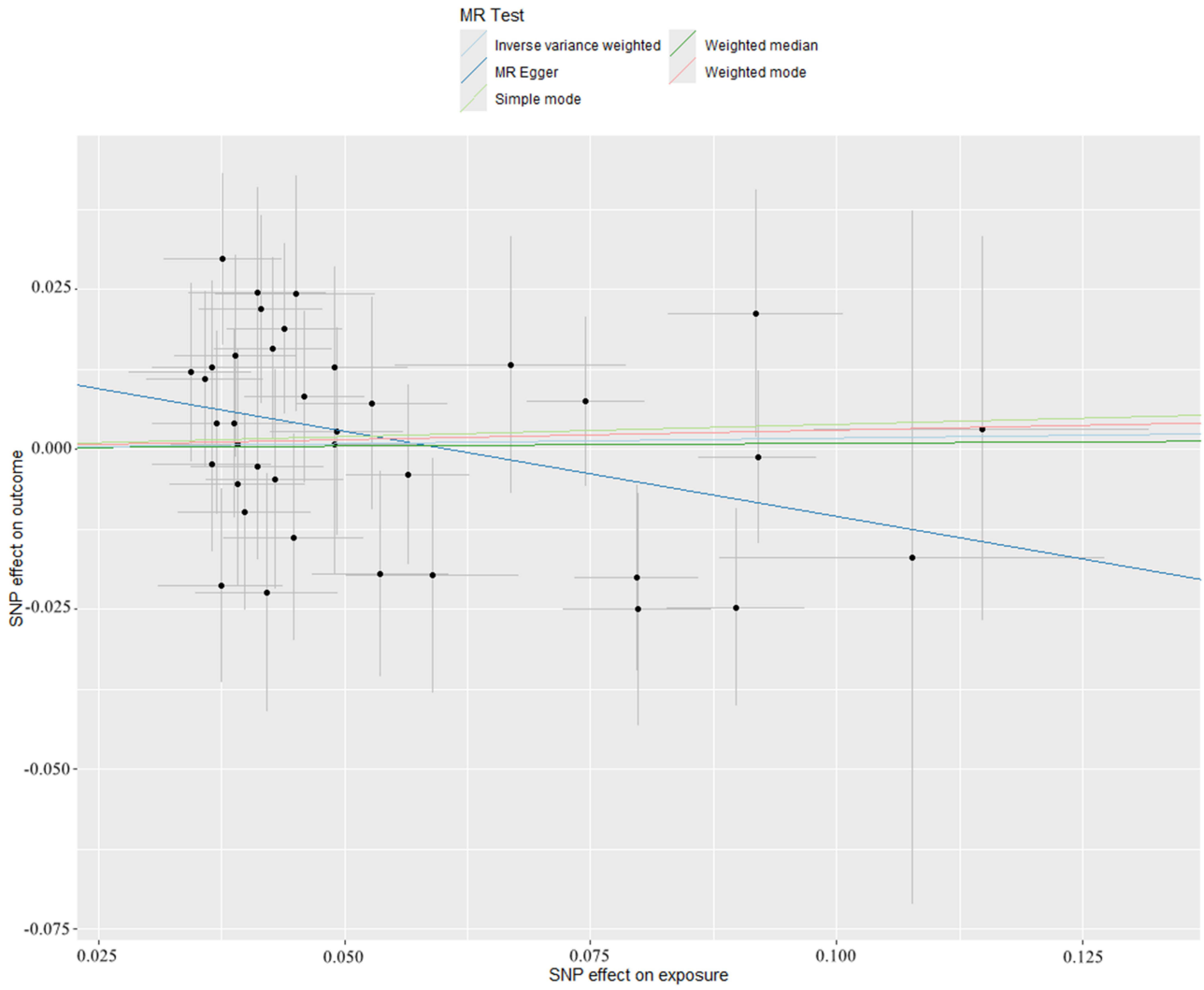

Figure 4 The scatter plot of the causal effect of migraine and PPD (discovery).

MR Analyses of Migraine and PPD

No significant heterogeneity was found with heterogeneity test (IVW) in both forward MR analysis (P_{IVW}=0.443) (Table 1, Supplementary Figure 13) and reverse MR analysis (P_{IVW}=0.337) (Table 1, Supplementary Figures 14). No significant causal effect was observed in both forward MR analysis (IVW: OR=0.952; 95% CI=0.873–1.038; P=0.268) and reverse MR analysis (IVW: OR=0.995; 95% CI=0.959–1.033; P=0.788) with IVW analysis., These results were consistent across all additional MR methods (Table 2), as shown in the forest and scatter plots (Supplementary Figures 15–18). No horizontal pleiotropy was detected by the MR-Egger intercept in either forward (P=0.095) or reverse (P=0.311) analyses (Table 1). MR-PRESSO tests and leave-one-out plots showed no outliers in either the forward (P=0.456) or reverse (P=0.421) analyses, reinforcing the robustness of the findings (Table 1; Supplementary Figures 19 and 20).

Discussion

PPD is a distinct subtype of MDD that significantly affects the psychological and physical well-being of new mothers. Migraine is the most common headache disorder among women and is characterized by moderate to severe unilateral pulsatile pain, frequently accompanied by nausea and vomiting. Both migraine and PPD exhibit genetic predisposition and familial aggregation, suggesting the possibility of shared biological mechanisms. In this study, we conducted a bidirectional MR analysis to examine the causal relationship between migraine and PPD. By utilizing six of the largest

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Table 2 Causal Effects of Migraine and PPD

Exposure/Outcome	P Value	SNP	Methods	OR	95%CI	P-Value
Discovery						
Migraine on PPD	P<5e-8	38	MR Egger	0.767	0.581–1.012	0.069
			Weighted median	1.009	0.879–1.157	0.903
			Inverse variance weighted	1.018	0.928–1.117	0.706
			Simple mode	1.039	0.775–1.394	0.799
			Weighted mode	1.030	0.816–1.301	0.803
PPD on Migraine	P<5e-6	28	MR Egger	1.039	0.965–1.119	0.317
			Weighted median	1.046	0.996–1.098	0.074
			Inverse variance weighted	1.036	0.999–1.075	0.057
			Simple mode	1.044	0.962–1.133	0.314
			Weighted mode	1.042	0.971–1.118	0.259
Replication						
Migraine on PPD	P<5e-6	58	MR Egger	89.861	0.462–17,483.351	0.100
			Weighted median	1.645	0.096–28.130	0.731
			Inverse variance weighted	2.097	0.328–13.409	0.434
			Simple mode	0.054	0.000–11.263	0.288
			Weighted mode	3.665	0.076–175.821	0.513
PPD on Migraine	P<5e-6	27	MR Egger	1.001	0.999–1.002	0.388
			Weighted median	1.001	1.000–1.002	0.198
			Inverse variance weighted	1.001	1.000–1.002	0.274
			Simple mode	1.001	0.998–1.004	0.649
			Weighted mode	1.000	0.999–1.001	0.660
Females						
Migraine on PPD	P<5e-8	16	MR Egger	0.683	0.470–0.992	0.065
			Weighted median	0.939	0.829–1.063	0.317
			Inverse variance weighted	0.952	0.873–1.038	0.268
			Simple mode	0.835	0.652–1.069	0.173
			Weighted mode	0.837	0.686–1.020	0.099
PPD on Migraine	P<5e-6	26	MR Egger	1.028	0.957–1.104	0.463
			Weighted median	1.013	0.961–1.068	0.633
			Inverse variance weighted	0.995	0.959–1.033	0.788
			Simple mode	1.008	0.922–1.102	0.865
			Weighted mode	1.029	0.962–1.100	0.417

Abbreviation: PPD, Postpartum depression.

and most recent GWAS, we ensured robust sample sizes to enhance statistical power and minimize the risk of false-positive findings. To account for potential sex-specific effects, we also performed subgroup analyses focusing on females. However, this MR analysis did not identify any significant causal association between migraine and PPD in either direction.

The relationship between migraine and PPD has garnered increasing attention over the past two decades. The hormonal withdrawal hypothesis suggests that a rapid postpartum decline in hormones such as progesterone, estradiol, and their neuroactive metabolites (eg, allopregnanolone) may increase susceptibility to depressive symptoms.[35] Gordon-Smith et al reported a specific association between the lifetime presence of migraine and PPD within 6 weeks of delivery, suggesting a potential role of sex hormones in aetiology.[13] Furthermore, a higher risk of PPD has been linked to significant acute pain during pregnancy. Victor et al have shown that migraine prevalence reaches nearly 25% among women of reproductive age.[36] A cohort study by Welander et al further indicated a potential link between migraine and peripartum anxiety and depression, suggesting a persistent role of inflammatory and hormonal factors throughout the peripartum period.[37] Moreover, observational research has explored the association of both migraine and PPD with

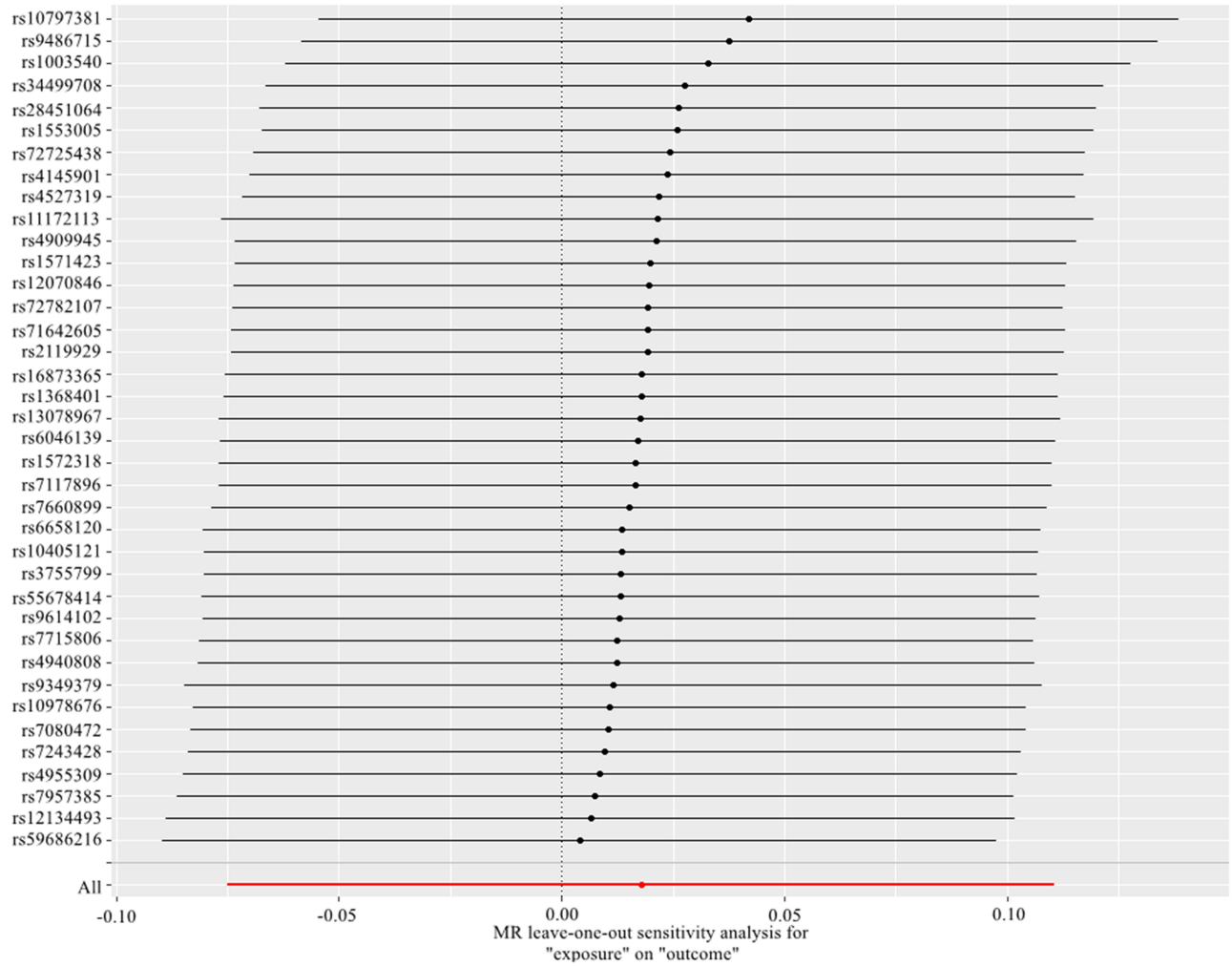

Figure 5 Forest plot of the "leave-one-out" sensitivity analysis method to show the influence of individual SNPs on the results of migraine and PPD (discovery).

dysregulated inflammatory markers, supporting the consideration of anti-inflammatory agents as adjunctive treatments for these conditions.[38,39]

To our knowledge, this is the first study to evaluate the potential causal association between migraine and PPD using genetic variants as IVs. Our findings provide strong evidence against the causal effect of migraine on PPD. Similarly, reverse MR analysis found no causal influence of PPD on migraine risk. While the number of studies examining the direct link between migraine and PPD remains limited; numerous investigations have reported a bidirectional association between migraine and MDD. As a clinical subtype of MDD, PPD shares significant genetic overlap with migraine,[40] implying common and critical genetic risks in the central and peripheral neurological systems.[41,42] Individuals with migraines often experience heightened anxiety, which can precede the onset of depression.[43] Conversely, individuals with depression face an approximately twofold increased risk of developing migraines.[44]

Pharmacological studies have demonstrated that tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors are effective in treating both depression and migraines.[45,46] Clinical trials also indicate that transcranial magnetic stimulation is beneficial for patients with migraines and comorbid depression.[47] Neuroimaging research has revealed structural and functional abnormalities in brain regions implicated in both migraine and depressive disorders, including the anterior cingulate cortex, prefrontal cortex, amygdala, and hippocampus.[48]

Yang et al identified widespread functional changes in migraine patients with and without depression, with specific alterations observed in the right paracentral lobule and spindle-shaped cortical regions among individuals with comorbid

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migraine and depression.[49] Although PPD is a distinct subtype of MDD characterized by pronounced hormonal fluctuations, our bidirectional MR study found no causal association between migraine and PPD, suggesting that neither condition serves as a direct risk factor for the other. While previous studies have reported potential comorbidity between migraine and PPD based on genetic and neuroimaging evidence, the etiology of psychiatric disorders remains multifactorial, involving complex interactions between genetic and environmental components. Based on the current MR findings, it is plausible that the pathogenic signaling pathways of migraine and PPD exhibit only limited overlap and do not constitute direct causal mechanisms for mutual occurrence.

In a 2021 study, Gordon-Smith et al reported a significant association between migraine and PPD within six weeks postpartum in a UK cohort of women with depression, suggesting that early postpartum hormonal changes may exert a specific influence on women with migraine who later develop depressive symptoms.[13] In contrast, the present study did not observe such an association, possibly because the results were primarily based on genetic mutation analysis, which did not account for dynamic hormonal fluctuations. Furthermore, Gordon-Smith's investigation focused on PPD diagnosed within six months postpartum, whereas our study may have encompassed a broader timeframe, further highlighting the time-sensitive nature of the PPD phenotype. Future research should aim to expand sample sizes, standardize PPD assessment timepoints, and incorporate dynamic hormone monitoring to elucidate the mechanisms underlying the migraine–PPD association. Moreover, investigations should explore whether particular subgroups, such as individuals with heightened hormone sensitivity, are more susceptible to comorbid migraine and PPD. These findings, while inconclusive, suggest that the relationship between migraine and PPD may be modulated by various factors and that further phenotypic stratification is necessary to clarify and validate this association.

This study offers several notable strengths. First, MR analysis is a reliable tool for identifying causal relationships between exposures and outcomes, functioning similarly to randomized controlled trials. Second, this is the first study to employ a bidirectional MR approach to assess migraine–PPD causality using the most comprehensive GWAS datasets available. Third, all selected IVs had F-statistics greater than 10, minimizing the likelihood of weak instrument bias. Fourth, sensitivity and leave-one-out analyses revealed no influential SNPs that might distort causal estimates, thereby affirming the stability of our results. Additionally, the use of the LD trait database helped exclude horizontal pleiotropy, further supporting the reliability of our conclusions. Despite these strengths, several limitations should be acknowledged. First, the use of a relaxed P-value threshold ($P<5\times10^{-6}$) to increase the number of SNPs for PPD IVs may have compromised statistical power and affected the reliability of the results. Second, this analysis was limited to GWAS data from individuals of European ancestry, restricting the generalizability of findings to other ethnic or racial groups. Third, the MR analysis lacked stratification by age or other relevant demographic and clinical factors, relying solely on summary-level GWAS data. Finally, although no substantial heterogeneity or horizontal pleiotropy was detected, residual undetected pleiotropy may still exist and potentially bias the findings. Moreover, MR remains methodologically constrained by challenges in instrument selection, sample size demands, stringent assumptions, multifaceted exposures/outcomes, gene-environment interplay, and societal confounders. MR mainly relies on observational data rather than experimental data. This means that we cannot fully control potential confounding factors, which may affect the accuracy of the results. To address these gaps, future studies could employ more direct designs to investigate the migraine-PPD association, such as prospective cohort studies with longitudinal tracking of migraine attack frequency and PPD symptom severity at multiple postpartum timepoints (eg, 1, 3, and 6 months) to establish temporal relationships to adjust time-varying confounders such as sleep disruption or hormonal fluctuations.

Migraine and PPD are both prevalent disorders among women, and their individual and potential joint impacts warrant clinical attention. Given their comorbidity characteristics and potential association, it is essential to establish an early identification and intervention system in clinical practice. For pregnant women with a history of migraine, depression risk screening should be initiated early in pregnancy, followed by regular (eg, monthly) dynamic assessments. Preventive interventions may include both pharmacological treatments for migraine and proactive psychological support to mitigate the risk of PPD. For the common anxiety traits observed in migraine patients, relaxation training can be used to reduce stress responses. In postpartum women, close monitoring of emotional status is recommended, particularly during periods of hormonal fluctuation. A multidimensional early intervention strategy may disrupt the pathological link

between migraine and PPD, thereby reducing comorbidity incidence and improving outcomes for both mothers and infants.

Conclusion

In summary, our bidirectional MR study indicates no significant causal relationship between migraine and PPD. Future research should aim to validate these findings across diverse populations and further explore the underlying etiological mechanisms.

Abbreviations

PPD, Postpartum depression; MDD, Major depressive disorder; DALYs, Disability adjusted life years; MR, Mendelian randomization; GWAS, Genome-wide association study; IVW, Inverse variance weighted; SNPs, Single nucleotide polymorphisms; IVs, Instrumental variables; STROBE-MR, Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization; MR-PRESSO, MR-Pleiotropy Residual Sum and Outliers; LD, linkage disequilibrium; IEU, Integrative Epidemiology Unit.

Data Sharing Statement

The raw data of this study were obtained from open published databases, IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/), FinnGen consortium (https://www.finngen.fi/en) and UK Biobank (http://www.nealelab.is/uk-biobank), and all data were freely downloaded and used. Synthesis and statistics data are provided within the manuscript or Supplementary Information files.

Ethics Approval and Consent to Participate

As per the regulations outlined in People's Republic of China's "Notice on the Implementation of Ethical Review Measures for Life Science and Medical Research", our study falls under the exemption criteria specified in Section 4 of the regulation. Therefore, ethics approval was not required for this research, as it met the following conditions:

a. Exemption Premise: The study exclusively utilized publicly available data, specifically summary-level data from Genome-Wide Association Studies (GWAS), which does not involve sensitive personal information, pose harm to individuals, or compromise their privacy.

b. Exemption Provision: Our research adheres to the exemption circumstances outlined in Section 4 of the regulation: We utilized lawfully obtained publicly available data for our analysis. The data used in this study were fully anonymized, ensuring the privacy and confidentiality of individuals. Our research focuses on analyzing existing data and does not involve interventions, human biological samples, or activities related to reproductive cloning, genetic manipulation, or germ cells.

Due to the nature of our study and its compliance with the exemption criteria, we did not require explicit ethics approval. While informed consent was not obtained from individual participants since the study involved publicly available data, we ensured that all data accessed and analyzed were fully de-identified and complied with the terms of use and guidelines provided by the data source. We affirm that this research was conducted in accordance with the applicable laws, regulations, and ethical standards.

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Disclosure

The authors report no conflicts of interest in this work.

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