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ORIGINAL RESEARCH

Bidirectional Mendelian Randomization Analysis of Mood Disorders and Risk of Preeclampsia-Eclampsia

Chenyang Zhao[1,2,*], Fangjun Chen[3,*], Qiong Li[1,2], Lixiu Peng[1], Chaoyan Yue[4]

[1]Department of Obstetrics and Gynecology, The First People's Hospital of Chenzhou, Chenzhou, People's Republic of China; [2]Department of Obstetrics and Gynecology, Jinan University, Guangzhou, People's Republic of China; [3]Department of Laboratory Medicine, Zhongshan Hospital, Fudan University, Shanghai, People's Republic of China; [4]Obstetrics & Gynecology Hospital of Fudan University, Shanghai Key Laboratory of Reproduction and Development, Shanghai Key Laboratory of Female Reproductive Endocrine Related Diseases, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chaoyan Yue, Obstetrics & Gynecology Hospital of Fudan University, Shanghai Key Laboratory of Reproduction and Development, Shanghai Key Laboratory of Female Reproductive Endocrine Related Diseases, Fang Xie Road, No. 419, Shanghai, People's Republic of China, Email 20111250007@fudan.edu.cn

Objective: Mood disorders and preeclampsia-eclampsia (PE) are two major public health problems. The genetic association of the two problems is unclear. We conducted a bidirectional Mendelian randomization (MR) analysis to explore the potential casual relationships between mood disorder subtypes (bipolar disorder, depression, manic/hyper symptoms) and PE.

Methods: Summary statistics for bipolar disorder (7481 cases and 9250 controls), depression (13,559 cases and 435,855 controls), manic/hyper symptoms (3177 cases and 28,140 controls) were derived from IEU open GWAS project. Summary data for PE were obtained from FinnGen consortium (7965 cases and 211,852 controls) and IEU open GWAS project (2355 cases and 264,887 controls). Four methods were applied in our MR analysis, including the inverse variance weighting (IVW), MR-Egger, weighted median and weighted mode. Meta-analysis method was used to assess the combined effect from two independent database. A series of sensitivity analyses were conducted to estimate the robustness of results.

Results: The combined effect from two data sources indicated that there were casual associations between bipolar disorder and PE (OR = 1.15, 95% CI: 1.08–1.22, $P < 0.001$), depression and PE (OR = 1.07, 95% CI: 1.01–1.13, $P = 0.01$). No significant association was observed between manic/hyper symptoms and PE. Reverse MR analysis demonstrated no casual effect of PE on bipolar disorder, depression or manic/hyper symptoms. Sensitivity analysis confirmed the robustness of the bidirectional MR results.

Conclusion: Our findings provided evidence that bipolar disorder and depression are causally associated with PE.

Keywords: mood disorder, preeclampsia-eclampsia, Mendelian randomization analysis

Introduction

Preeclampsia-eclampsia (PE) is a serious pregnancy complication characterized by new-onset hypertension after 20 weeks of gestation, accompanied by features such as proteinuria, acute kidney injury, and liver function abnormalities.[1] PE, as a pregnancy-specific and progressive disorder, has a complex pathogenesis.[2–6] So identifying the relative contributions of different risk factors is crucial for risk stratification and early prediction. Mood disorders during pregnancy often co-occur with PE and other complications, posing a significant threat to maternal and infant health.[7,8]

Mood disorders are a major global public health concern, encompassing a set of complex psychological syndromes that affect cognition, behavior, and emotional regulation.[9] The subtypes of mood disorders include bipolar disorder, severe depression, and manic/hypomanic symptoms.[10] While often grouped under bipolar disorder, manic/hyper symptoms represent a unique clinical phenotype with distinct neurobiological and physiological profiles.[11] Mood disorders may lead to endocrine changes, affecting the secretion of vasoactive hormones, promoting endothelial dysfunction, exacerbating the risk of hypertension, and directly contributing to the occurrence and progression of PE.[12–15] Mood

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disorders may also indirectly increase the risk of PE through unhealthy lifestyles and the avoidance of antenatal care behaviors,[16] while increased stress is a significant trigger for hypertension.[17] Despite variations in the existing research regarding the association between the two,[18–20] the high prevalence of mood disorders and their impact on physiological health cannot be overlooked, as they are the second leading cause of global disability and premature death. Delving deeper into the causal relationship between mental states (such as bipolar disorder and depression) and pregnancy complications can lead to more accurate strategies for the prevention, early identification, and intervention of pregnancy complications, comprehensively protecting the physical and mental health of pregnant women and effectively reducing adverse pregnancy outcomes. However, previous observational studies have inherent limitations that cannot be fully overcome, including susceptibility to confounding, reverse causality, and influence of sample size, which may introduce bias into the results.

To address this issue, Mendelian randomization (MR) can be employed as a method of analysis. MR analysis investigates the cause-and-effect relationship between exposures and outcomes by utilizing genetic variants as instrumental variables (IVs).[21] These genetic variations are randomly inherited and are not influenced by external factors, thus minimizing bias and reverse causality commonly found in observational studies.[22] By using MR, we can gain a better understanding of the causal relationship between psychiatric disorders and PE.

Methods

Study Design

This study aimed to investigate the potential bidirectional causal relationship between three mood disorders, namely bipolar disorder, depression, manic/hyper symptoms, and the development of PE. To achieve this, a two-sample bidirectional MR analysis was conducted. The MR analysis applied the inverse variance weighted (IVW) method as the main statistical approach. Additionally, secondary methods, including MR-Egger, weighted median, and weighted mode, were utilized to assess the robustness of the results. To further validate the findings, a series of sensitivity analysis methods, such as weighted median, MR-Egger, and MR-PRESSO, were performed. It is important to note that all MR analyses relied on three key assumptions. Firstly, the instrumental variables used, representing genetic variants, needed to exhibit strong correlations with the exposures. Secondly, the genetic variants should be independent of any potential confounding factors. Lastly, it was assumed that the genetic variants influenced the outcomes solely through the exposures.[23] The overview of this study design is showed in Figure 1.

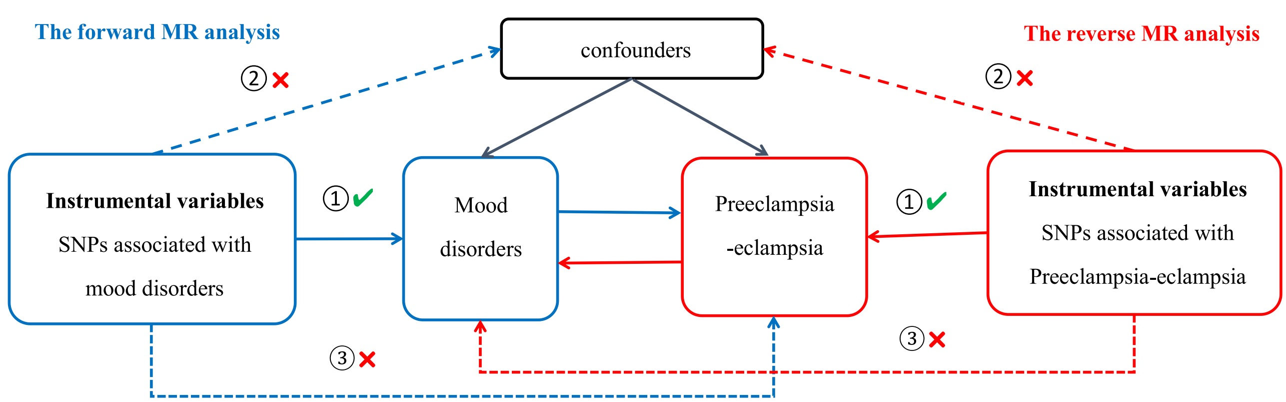

Figure 1 Study design of the bidirectional mendelian randomization between three subtypes of mood disorders and preeclampsia-eclampsia. All MR analyses relied on three key assumptions: ① Genetic instruments are associates with exposures; ② Genetic instruments are not related with any confounders; ③ Genetic instruments affect the outcomes only via exposures. "√" indicates that the assumption is satisfied, while "×" indicates that the assumption is not satisfied. The solid line represents an association between the exposure and the outcome, while the dashed line represents no association between the exposure and the outcome.
Abbreviations: SNP, single-nucleotide polymorphism; MR, Mendelian randomization.

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Data Sources

Summary-level genetic data for bipolar disorder, depression, and manic/hyper symptoms were obtained from the IEU Open GWAS project (https://gwas.mrcieu.ac.uk/datasets/), which provides publicly available genome-wide association study summary statistics. Specifically, genome-wide association summary statistics for bipolar disorder was collected from a large-scale GWAS including 7481 cases and 9250 controls,[24] the association statistics for depression came from a recent study which consisted of 13,559 cases and 435,855 controls,[25] the association statistics for manic/hyper symptoms were derived from 3177 cases and 28,140 controls. All disorders were assessed using standard diagnostic criteria.[26] Genetic predictors of PE were obtained from the most comprehensive GWAS in FinnGen (R10 version) (https://r10.finngen.fi/pheno/O15_PRE_OR_ECLAMPSIA) consortium including 7965 cases and 211,852 controls and IEU open GWAS project (https://gwas.mrcieu.ac.uk/datasets/) consisting of 2355 cases and 264,887 controls.[25] All the PE cases met the criteria for clinical diagnosis. All participant samples in each GWAS were of European ancestry. All the summarized data used in this study are freely accessible and did not require ethical approval. The different traits of the data sources are summarized in Table S1.

Genetic Instrument Selection

First, we selected single-nucleotide polymorphisms (SNPs) associated with bipolar disorder to PE in FinnGen, depression to PE in FinnGen and IEU that reached the genetic-wide significant threshold ($P < 5{\times}10^{-7}$) as the preliminary result. But we obtained SNPs related with manic/hyper symptoms to PE in FinnGen at $P < 5{\times}10^{-5}$ and SNPs assocciated with bipolar disorder to PE in IEU, manic/hyper symptoms to PE in IEU at $P < 5{\times}10^{-7}$. We used SNPs associated with PE from FinnGen to bipolar disorder at $P < 5 \times 10^{-5}$, depression and manic/hyper symptoms at $P < 5{\times}10^{-7}$. But we chosed SNPs related with PE from IEU to bipolar disorder at $P < 5 \times 10^{-7}$, depression and manic/hyper symptoms at $P < 5{\times}10^{-6}$. These adjustments were implemented to ensure an adequate number of IVs for MR analysis, while consisting of the SNPs most significantly associated with the exposures.[27] Then, we excluded SNPs in linkage disequilibrium using the PLINK algorithm (r^2 threshold < 0.001, window size > 10,000kb).[28] Furthermore, we conducted the harmonization of the effect direction to ensure that the effects of the SNPs on exposures and outcomes corresponding to the same effect allele.[29] Lastly, we calculated the F statistic of the SNPs to determine their statistical value. SNPs with an F statistic > 10 were identified as robust enough to overcome weak instrument bias.[30] All the SNPs applied in this MR analysis of each pair of exposure and outcome are presented in Table S2.

Statistical Analysis

We employed the IVW method as the primary statistical model.[31] The IVW random effects method was applied to estimate the association between genetic predisposition for bipolar disorder, depression, manic/hyper symptoms and PE. Other three effective methods including MR-Egger, weighted median and weighted mode were also applied to evaluate the possible relationship comprehensively. To improve the power of statistical tests and refine the estimation of effect sizes, we incorporated outcome data from two distinct data sources (FinnGen and IEU) and conducted a combined meta-analysis using MR method, quantitatively combining the OR values from both data sources. The choice of model was based on prior assumptions about the underlying causal effects, rather than solely on the magnitude of heterogeneity. The random-effects model was selected a priori to account for potential heterogeneity across genetic instruments, as recommended in methodological guidelines.[32]

Three sensitivity analyses were conducted, including weighted median,[33] MR-Egger intercept[34] and MR-PRESSO globlal test[35] approaches to valid the reliability of our results. Assuming that at least 50% of the SNPs are valid, the weighted median method can yield consistent causal estimates and detect potential heterogeneity.[33] The Cochran's Q value was used to assess the heterogeneity among genetic variations, and heterogeneity was considered when $P < 0.05$. The MR-Egger intercept were used to test for potential pleiotropy, and an intercept P-value < 0.05 indicated the presence of pleiotropy.[34] The MR-PRESSO method was employed to detect outliers and provide causal estimate after the removal of corresponding outliers.[35] All analyses were conducting using the TwoSampleMR[36] and MR-PRESSO[35] packages in R software (version 4.3.0).

Results

Mood Disorders on Risk of PE

Bipolar disorder and depression have been found to increase the risk of PE in the FinnGen consortium (bipolar disorder, IVW: OR = 1.16, 1.09–1.24, $P < 0.001$; depression, IVW: OR = 1.06, 1.00–1.13, $P = 0.048$), and the results were similar in the IEU (bipolar disorder, IVW: OR=1.11, 0.95–1.29, $P = 0.207$; depression, IVW: OR = 1.14, 0.98–1.32, $P = 0.101$), although the results were not statistically significant ($P > 0.05$). However, after meta-analysis of the two data sources, the odds ratio of PE was 1.15 (95% CI, 1.08–1.22, $P < 0.001$) for bipolar disorder and 1.07 (95% CI, 1.01–1.13, $P = 0.01$) for depression. Manic/hyper symptoms was not related with risk of PE neither in the FinnGen consortium (IVW: OR = 0.86, 0.51–1.46, $P = 0.572$) nor in the IEU study (IVW: OR = 0.69, 0.24–1.94, $P = 0.479$) (Figures 2, S1 and Table S3). For these causal estimations, sensitivity analyses suggested that mild heterogeneity existed in the analysis of bipolar disorder on the PE in FinGen, depression and manic/hyper symptoms on the PE in IEU by Cochran's Q test and funnel plots (Figure S2). We detected pleiotropy in the analysis of depression and manic/hyper symptoms on PE by using MR-Egger intercept and MR-PRESSO ($P < 0.05$). However, there was no evidence of pleiotropy in the analysis of bipolar disorder and PE from two databases, depression and PE from FinnGen consortium, manic/hyper symptoms and PE from FinnGen consortium both by using MR-Egger intercept and MR-PRESSO ($P > 0.05$) (Table 1). Leave-one-out analyses suggested that none of the single SNP could drive these causal effects (Figure S3).

PE on Risk of Mood Disorders

In reverse MR analysis, our results revealed no significant association between PE with bipolar disorder, depression or manic/hyper symptoms across all MR methods (Figures 3, S4 and Table S4). Cochran's Q test and funnel plots (Figure S5) suggested minimal evidence of heterogeneity in the association between PE and the risk of psychiatric disorders. Moreover, MR-Egger intercept and MR-PRESSO indicated the absence of potential horizontal pleiotropy (Table 2). The leave-one-out analysis also demonstrated the stability of the results (Figure S6).

Discussion

The current MR analysis investigated the causal effect of bipolar disorder, depression and manic/hyper symptoms on the risk of PE in a combined sample of 10,320 cases and 476,739 controls. Our study is the first to explore the causal association between bipolar disorder, depression or manic/hyper symptoms and PE. Bipolar disorder was found to increase the risk of PE, showing a 15% higher likelihood of PE occurrence (OR, 1.15, 95% CI, 1.08–1.22). Similarly, depression was also linked to an increased risk of PE, with a 7% higher chance of PE (OR, 1.07, 95% CI: 1.01–1.13). However, no causal effect was observed between manic/hyper symptoms and PE. Furthermore, reverse MR analysis showed that PE had no significant association with bipolar disorder, depression or manic/hyper symptoms.

The casual relationships between bipolar disorder, depression and PE may be explained by several underlying mechanisms. Firstly, bipolar disorder and depression during pregnancy may alter the excretion of vasoactive hormones or other neuroendocrine transmitters,[12] which in turn increases the risk of hypertension and subsequently PE.[13] It is also possible that depression may cause such vascular changes through dysregulated hormones and eventually lead to preeclampsia. Secondly, bipolar disorder and depression and PE share common risk factors. It is possible that bipolar disorder and depression lead to poor health behaviors such as smoking, poor sleep hygiene, physical inactivity, and unhealthy nutritional patterns, increasing the risk of adverse outcomes and making it less likely for individuals to seek prenatal care.[16] These factors contribute to the occurrence and development of PE. Thirdly, biomarkers of endothelial dysfunction, including circulating endothelial cells, endothelial progenitor cells, and soluble vascular cell adhesion molecules are elevated in patients with depression.[14] Biological markers of endothelial injury, such as urotensin-II and endocan are significantly higher in blood of bipolar disorder patients than in that of controls.[15] Endothelial dysfunction is a major pathomechanism of preeclampsia. Lastly, bipolar disorder and depression may be caused by increased stress, which may in turn increase blood pressure, cause vasoconstriction, decrease uterine blood flow and fetal hypoxia, and increase the risk of PE.[17]

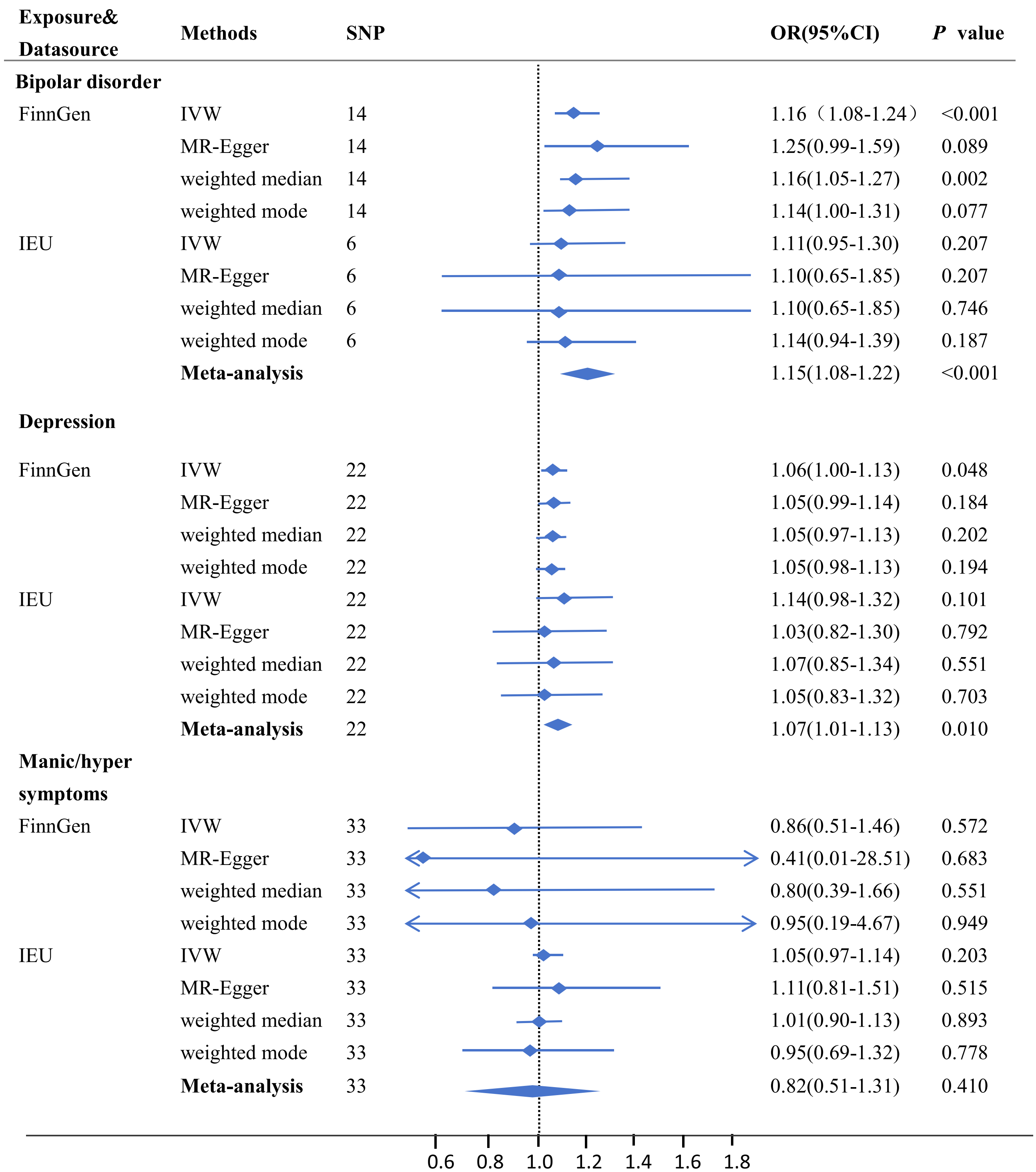

Figure 2 Association of three subtypes of mood disorders with risk of preeclampsia-eclampsia. Estimates were obtained from the IVW methods. The final effects were calculated by meta-analysis of the two data sources.

Abbreviations: PE, preeclampsia-eclampsia; FinnGen, FinnGen Consortium; IEU, IEU open GWAS project; OR, odds ratio; CI, confidence interval; IVW, inverse variance weighting.

Table 1 Sensitivity Analysis of Association of Mood Disorders with Preeclampsia-Eclampsia from Two Databases

Exposure	Data Source of Outcome	Heterogeneity		Pleiotropy	
		Q	*P* value	*P* value of MR-Egger	*P* value of MR-PRESSO
Bipolar disorder	FinnGen	13	0.47	0.52	0.55
Bipolar disorder	IEU	4	0.56	0.98	0.61
Depression	FinnGen	20	0.56	0.72	0.64
Depression	IEU	22	0.38	0.29	0.44
Manic/hyper symptoms	FinnGen	30	0.57	0.73	0.56
Manic/hyper symptoms	IEU	39	0.17	0.08	0.18

Abbreviations: FinnGen, FinnGen Consortium; IEU, IEU open GWAS project; MR, Mendelian randomization.

Our findings about the casual effects of bipolar disorder and depression on PE have clinical significance. Our study may open some discussion and the potential psychology-neurology-immunology-endocrinological approach in PE research. Some practical aspects can be taken on board. For example, assessment of the maternal mental health during pregnancy plays an important role in the management of the preconception stage and can help stratify the risk of PE and identify high-risk individuals. Healthcare professionals should pay more attention to the pregnant women who have bipolar disorder and depression, and take early medical intervention to prevent the development of PE. However, all of this will require further studies to confirm the findings.

This study has several strengths, including the MR design, which strengthens the causal inference in the associations between depression, bipolar disorder and the risk of PE. Additionally, we challenged the conventional view that gestational hypertension disorders increase risk of mood disorders. The study was conducted on two independent populations, and the consistent results confirmed the robustness of the results. However, there are limitations to consider. Firstly, although the studied population was limited to individuals of European ancestry to reduce population bias, this limits the generalizability of the findings to other populations. Secondly, the *p*-value threshold was set at different levels to include sufficient SNPs to maintain study power, but the study had no weak instrumental variables according to the F statistics > 10. Thirdly, to ensure sufficient instrumental variables for analysis, we did use less stringent p-value thresholds (including $p < 5\times10^{-7}$, $p < 5\times10^{-6}$, and $p < 5\times10^{-5}$) for SNP selection in certain exposure datasets where instrument availability was limited. We clarify that while these relaxed thresholds helped improve instrument strength and statistical power, they also carry a trade-off in terms of potential validity, and our results should be interpreted with this consideration in mind. Finally, MR analysis examines the impact of lifetime exposure on outcomes and the effect sizes observed in MR analyses may differ from those of short-term interventions evaluated in randomized controlled trials. Further researches are needed to address the limitations of this study, including larger and more diverse datasets, replication studies, and a multidisciplinary approach involving functional studies, genetic investigations, and clinical trials to investigate the mechanisms underlying the influence of mood disorders on PE. These efforts may provide insights into potential prevention and treatment strategies.

Conclusion

In conclusion, this MR study provides genetic evidence supporting a potential causal link between bipolar disorder, depression, and PE, offering new insights into the pathophysiological mechanisms underlying PE. While MR strengthens causal inference compared to observational studies, it suggests causality. These findings highlight the importance of assessing maternal mental health during pregnancy, which may help identify women at higher risk of PE and inform early preventive strategies. However, further research in more diverse populations is needed to confirm these associations and evaluate their generalizability across different ancestries and clinical settings.

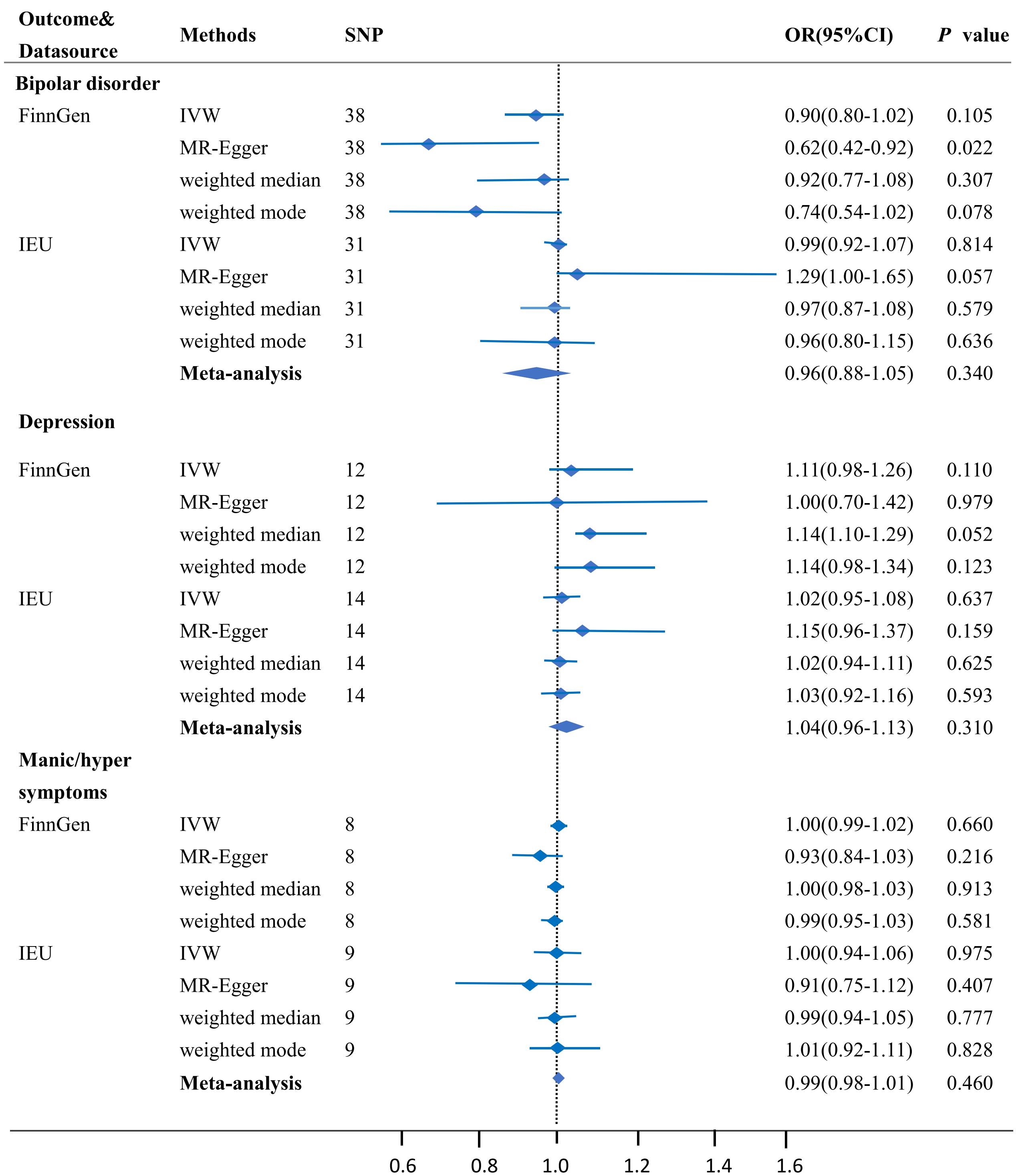

Figure 3 Association of preeclampsia-eclampsia with risk of three subtypes of mood disorders. Estimates were obtained from the IVW methods. The final effects were calculated by meta-analysis of the two data sources.

Abbreviations: PE, preeclampsia-eclampsia; FinnGen, FinnGen Consortium; IEU, IEU open GWAS project; OR, odds ratio; CI, confidence interval; IVW, inverse variance weighting.

Table 2 Sensitivity Analysis of Association of Preeclampsia-Eclampsia from Two Databases with Three Subtypes of Mood Disorders

Outcomes	Data Source of Exposure	Heterogeneity		Pleiotropy	
		Q	*P* value	*P* value of MR-Egger	*P* value of MR-PRESSO
Bipolar disorder	FinnGen	46	0.15	0.06	0.15
Bipolar disorder	IEU	21	0.04	0.53	0.06
Depression	FinnGen	6	0.50	0.19	0.48
Depression	IEU	31	0.40	0.04	0.41
Manic/hyper symptoms	FinnGen	14	0.40	0.18	0.40
Manic/hyper symptoms	IEU	3	0.96	0.68	0.97

Abbreviations: FinnGen, FinnGen Consortium; IEU, IEU open GWAS project; MR, Mendelian randomization.

Ethical Approval and Informed Consent

Our institution (Ethics Committee of Chenzhou First People's Hospital) has determined that this research is exempt from review by the Institutional Review Board (IRB) or ethics committee in accordance with national guidelines, specifically Article 32, Items 1 and 2, of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (February 18, 2023, China), which state that studies using anonymized or publicly available data without personal identifiers are exempt from ethical review.

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Disclosure

The authors declared that they have no conflicts of interest in this work.

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