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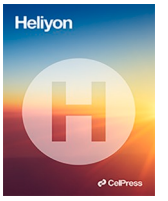

Research article

Causal associations between vitamin D and postpartum depression: A bidirectional mendelian randomization study

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ABSTRACT

Background: Previous epidemiological studies have reported associations between vitamin D and postpartum depression (PPD); however, the findings are inconsistent. This study employs bidirectional Mendelian Randomization (MR) to investigate the causal link between serum 25-hydroxyvitamin D [25(OH)D] levels and PPD. By utilizing genetic data from cohorts, this research aims to provide a more robust understanding of the potential relationship between vitamin D and PPD, addressing a critical gap in the current literature.

Methods: A bidirectional MR analysis was conducted to investigate the genetic association between serum 25(OH)D and PPD using summary statistics extracted from GWAS datasets. The study included data from 15,668 patients with PPD and 376,755 healthy controls of European ancestry. The GWAS data for 25(OH)D were obtained from two studies within the UK Biobank, encompassing 496,946 and 79,366 participants. The primary analysis employed the inverse-variance weighted (IVW) method, while supplementary MR estimates were derived through the MR-Egger and weighted median (WME) methods. Furthermore, sensitivity analyses were implemented to ensure robustness and reliability, including Cochran's Q test, MR-PRESSO, MR-Egger intercept test, and the leave-one-out test.

Results: The MR study revealed no substantial genetic correlation between serum 25(OH)D levels and PPD (OR = 1.065, 95%CI = 0.878–1.293, P = 0.522 for set A; OR = 0.978, 95 % CI = 0.669–1.430, P = 0.910 for set B). Additionally, in the reverse analysis, we did not observe a significant causal impact of PPD on serum 25(OH)D (OR = 1.001, 95%CI = 0.974–1.028, P = 0.951 for set A; OR = 1.011, 95%CI = 0.992–1.031, P = 0.261 for set B). The results obtained from MR-Egger and WME analyses concord with those derived from the IVW method. Conducting leave-one-out tests did not identify any single nucleotide polymorphism that might have influenced the MR results, confirming the robustness and reliability of the findings.

Conclusions: The results suggest the absence of a causal link between vitamin D concentrations and PPD. Inconsistent observations in previous observational studies may be attributed to residual confounding.

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1. Introduction

Postpartum depression (PPD) is a depressive disorder that specifically occurs in the unique physiological period following childbirth, making it one of the most common complications associated with the postpartum period [1]. The incidence of PPD in women without a history of depression ranges from 12 % to 17.7 % [2,3]. Its manifestations include persistent low mood, diminished interest in daily activities, and reduced volitional activity. Notably, approximately 80 % of cases present with somatic symptoms, such as insomnia, headaches, body aches, and dizziness. Furthermore, individuals may even exhibit suicidal tendencies [4]. A study indicates that maternal PPD increases the risk of mental disorders in offspring [5]. Therefore, effective prevention and treatment of PPD are crucial aspects of promoting eugenics.

Vitamin D is an essential microelement and also functions as a steroid hormone. It primarily exists in two biologically active forms: 25-hydroxyvitamin D [25(OH)D] and 1,25-dihydroxyvitamin D3 [6]. The synthesis and metabolism of vitamin D within the body are intricate, and abnormalities in these pathways can lead to decreased levels of serum vitamin D. In recent years, Vitamin D has gained widespread attention, not only for its impact on calcium-phosphorus metabolism but also for its influence on anxiety and depression [7]. An increasing number of researchers are recognizing the importance of vitamin D to pregnancy outcomes or complications. There may be sufficient evidence to suggest that measuring vitamin D levels before pregnancy or during the first three months of pregnancy can serve as a prognostic biomarker for miscarriage. Implementing vitamin D assessment and supplementation into routine obstetric practice may be a future trend [8]. Postpartum women are considered a high-risk population for vitamin D deficiency [9]. Some observational studies suggest a link between vitamin D levels and PPD [10,11], while other research has demonstrated no correlation [12]. The association between vitamin D level, as measured by 25(OH)D, and PPD has been a topic of extensive research for several decades. However, due to confounding factors and reverse causation, the true relationship between PPD and vitamin D remains unclear.

Mendelian randomization (MR) enables causal inference and offers reliable estimates regarding the relationship between exposure and outcome [13]. Unlike observational studies, MR utilizes single nucleotide polymorphisms (SNPs) identified from genome-wide association studies as instrumental variables (IVs), effectively eliminating confounding factors and reverse causation [14]. Thus, we adopt a bidirectional two-sample MR approach to explore potential causal associations between vitamin D and PPD.

2. Materials and methods

2.1. Study design and data sources

MR employs genetic variants as instrumental variables (IVs), which must meet three key assumptions (Lawlor, 2016) [15]: Firstly, the IV should have a strong correlation with the exposure. Secondly, it should not be associated with any known confounding factors. Thirdly, the IV should only affect the outcome through its impact on the exposure. In this particular study, a two-sample MR design was employed, examining the relationship between 25(OH)D and PPD as both exposure and outcome variables. The study's overview is presented in Fig. 1.

The GWAS data for PPD were sourced from the Finn consortium (https://www.finngen.fi/en): finn-b O15_POSTPART_DEPR, comprising 15,668 patients with PPD and 376,755 healthy controls of European ancestry, with a total of 16,380,465 tested SNPs. The GWAS data for 25(OH)D were obtained from two studies within the UK Biobank, including 496,946 and 79,366 participants of European ancestry, with 6,896,093 tested SNPs for set A of 25(OH)D [16] and 2,538,249 tested SNPs for set B of 25(OH)D [17], respectively. Table 1 describes the details regarding the characteristics of the data sources from the years 2018, 2020, and 2021. Our MR study utilized the publicly available GWAS database due to its comprehensive nature and ability to identify genetic variants associated with complex traits or diseases, which have obtained ethical approval and informed consent. This research aligns with the guidelines outlined in the STROBE-MR statement [18], and no additional ethical or informed consent is required.

2.2. Selection criteria for genetic variants

Within the scope of the MR analyses, the incorporated SNPs served as genetic IVs. To ensure the reliability of the MR estimates,

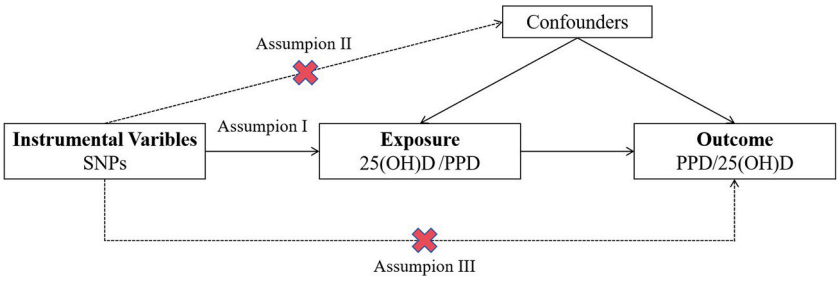

Fig. 1. An overview of the MR study design. Note: SNPs, single nucleotide polymorphisms; 25(OH)D, 25-hydroxyvitamin D; PPD, postpartum depression.

specific criteria were followed for selecting SNPs that were closely associated with vitamin D levels. These criteria include (1) SNPs with genome-wide significance ($P < 5 \times 10^{-8}$) and showing independence as variants ($r^2 \leq 0.001$); (2) Each included SNPs having an F-statistic threshold exceeding 10 to mitigate potential bias from variants with low statistical strength. To evaluate the causal effect of PPD on serum vitamin D levels, PPD was selected as the exposure, and a significance threshold of $P = 5 \times 10^{-6}$ was used for SNP selection.

2.3. Statistical analysis

To assess bidirectional causal associations between vitamin D and PPD, MR Egger, Weighted Median (WME), and Inverse Variance Weighted (IVW) methods were used. The IVW method was the primary reference in this study. It was found that IVW analysis is the most accurate method in MR when both pleiotropy and heterogeneity analyses yield negative results [19]. MR Egger, which considers the intercept, was used to assess pleiotropy [20]. WME assumes that half of the instrumental variables are effective and analyzes the causal relationship between exposure and outcome [21]. However, MR Egger and WME have comparatively limited power compared to IVW, resulting in wider confidence intervals (CI). Therefore, these approaches are used as supplementary methods in this study.

Sensitivity analyses play a pivotal role in MR studies, aiming to detect potential pleiotropy. In this study, a comprehensive set of sensitivity analyses was employed, including leave-one-out, MR-Egger, and MR-PRESSO methods. Heterogeneity was assessed through Egger Cochran's Q statistic and IVW Cochran's Q statistic, with a significance level of $P > 0.05$ indicating low heterogeneity. This suggests that IVs exhibit random fluctuations in estimated values without horizontal pleiotropy. The MR Egger regression intercept served as an indicator of directional pleiotropy. Additionally, the MR-PRESSO analysis identified potential outlier SNPs, providing adjusted results after excluding anomalies to correct for horizontal pleiotropy. The leave-one-out method systematically excluded each SNP, computing results with the remaining SNPs to evaluate whether individual SNPs disproportionately influenced the association.

MR analysis was performed utilizing R software (version 4.2.2) with the "TwoSampleMR" R package. Statistical significance was defined as a two-sided P-value less than 0.05.

3. Results

3.1. Characteristics of IVs

Significant SNPs highly associated with 25(OH)D were selected as IVs in the GWAS. A total of 118 and 8 SNPs for set A and set B significantly associated with 25(OH)D ($p < 5 \times 10^{-8}$) were identified, respectively, ensuring the removal of chain imbalance (r2<0.001, 10,000 kb). Eliminating SNPs with an intermediate allele frequency, 102 SNPs of set A and 7 SNPs of set B were ultimately included for subsequent analysis (Supplementary Table S1). All F-statistics for the instrumental variables of 25(OH)D exceeded 10, indicating a low likelihood of weak instrument bias.

For the IVs related to PPD, a more lenient threshold ($P < 5 \times 10^{-6}$) was employed in this study to encompass a broader range of SNPs associated with PPD. This approach was adopted to ensure the inclusion of a more comprehensive set of genetic markers relevant to PPD. In the reverse MR analysis, 8 SNPs for set A and 7 for set B significantly correlated with PPD were used after linkage disequilibrium removal, with no evidence of weak instrumental variable bias (Supplementary Table S2).

3.2. Causal effects of serum 25(OH)D levels on PPD

As shown in Table 2, the IVW method did not provide evidence of a causal relationship between genetically predicted levels of 25 (OH)D and the risk of PPD. In set A, the odds ratio (OR) was 1.065 with a 95 % confidence interval (CI) of (0.878–1.293), and the p-value was 0.522. Similarly, in set B, the OR was 0.978 with a 95 % CI of (0.669–1.430), and the p-value was 0.910. These results indicated a lack of causation between genetically predicted 25(OH)D levels and PPD risk using the IVW method. The results of MR-Egger and WME analyses aligned with those of the IVW analysis, underscoring the reliability of the MR findings. This concordance across multiple MR methods enhanced the robustness and credibility of the analytical outcomes.

3.3. Causal effects of PPD on serum 25(OH)D levels

In Table 3, reverse MR results were presented. Two-sample Mendelian randomization analyses yielded limited evidence regarding the impact of PPD on serum 25(OH)D levels when utilizing set A (8 SNPs, IVW OR 1.001 [95 % CI 0.974, 1.028]) or set B (7 SNPs, IVW

Table 1
Description of GWAS used for each phenotype.

Phenotype	Data sources	Year	Sample size	SNPs (n)	Ancestry
PPD	FinnGen	2021	392,423 (15,668 cases; 376,755 controls)	16,380,465	European
25(OH)D (set A)	UK Biobank	2020	496,946	6,896,093	European
25(OH)D (set B)	UK Biobank	2018	79,366	2,538,249	European

Notes: GWAS, genome-wide association studies; 25(OH)D, 25-hydroxyvitamin D; PPD, postpartum depression; SNPs, single nucleotide polymorphisms.

Table 2
MR analysis of 25(OH)D levels and the risk of PPD.

Exposure	Outcome	Method	OR (95%CI)	P
25(OH)D (set A)	PPD	MR Egger	0.898 (0.685–1.176)	0.2140
		Weighted median	1.131 (0.869–1.472)	0.3610
		IVW (Random effects)	1.065 (0.878–1.293)	0.5215
		IVW (Fixed effects)	1.065 (0.902–1.258)	0.4563
25(OH)D (set B)		MR Egger	0.564 (0.255–1.249)	0.0840
		Weighted median	0.883 (0.554–1.405)	0.5985
		IVW (Random effects)	0.978 (0.626–1.529)	0.9232
		IVW (Fixed effects)	0.978 (0.669–1.430)	0.9098

Note: MR, mendelian randomization; 25(OH)D, 25-hydroxyvitamin D; PPD, postpartum depression; OR, odds ratio; CI, confidence intervals; WME, weighted median; IVW, Inverse-variance weighted.

OR 1.011 [95 % CI 0.992, 1.031]) (Table 3). The β coefficients of PPD associated with serum 25(OH)D for MR-Egger and WME were 1.031 (95 % CI: 0.886 to 1.199; P = 0.309) and 0.990 (95 % CI: 0.966 to 1.015; P = 0.420) for set A, respectively. Moreover, both MR-Egger (OR = 0.999, 95 % CI = 0.942–1.059, P = 0.482) and WME (OR = 1.019, 95 % CI = 0.992–1.047, P = 0.161) methods reached a consistent conclusion in set B. The outcomes from all three methods (IVW, WME, and MR-Egger) collectively indicated that genetically predicted PPD was not significantly associated with serum 25(OH)D levels.

3.4. Sensitivity analysis

The heterogeneity and horizontal pleiotropy results for 25(OH)D and PPD as exposures are presented in Table 4. The tests for horizontal pleiotropy demonstrated P-values>0.05, consistent with assumptions 2 and 3. In set A, when 25(OH)D was the exposure, MR Egger Q = 132.532, P = 0.016; IVW Q = 136.445, P = 0.011. Conversely, when PPD was the exposure, MR Egger Q = 15.460, P = 0.017; IVW Q = 18.973, P = 0.008. Both bidirectional heterogeneity tests for set B and PPD showed P > 0.05, indicating the absence of heterogeneity.

The robustness of our results was affirmed through a leave-one-out analysis, highlighting the stability of our findings (Fig. 2A–D). This analysis revealed that the outcomes were not markedly influenced by individual SNPs. Funnel plots are shown in Fig. 3 (A-D).

4. Discussion

This study represents the first application of bidirectional two-sample MR analysis to investigate the relationship between 25(OH)D levels and PPD. The results reveal the absence of a causal relationship between genetically determined variations in 25(OH)D levels and the risk of PPD. While a majority of available observational studies, often employing cross-sectional or case-control designs, have reported there exists an inverse correlation between the levels of 25(OH)D and postpartum depression [22,23], some studies have failed to establish a significant association between 25(OH)D levels and the occurrence or development of PPD [24,25]. Indeed, the true nature of the relationship between PPD and 25(OH)D remains unclear due to confounding factors and potential reverse causation. The results of the MR analysis align closely with the conclusions of the latter set of studies.

Depression is a pervasive emotional disorder that can manifest at any stage of life, with PPD being a specific emotional challenge faced by women following childbirth [26]. Since the seminal report by Berk et al. [27] in 2007, highlighting the potential link between vitamin D deficiency and mental disorders, medical researchers have embarked on investigations into the relationship between vitamin D levels during the perinatal period and the occurrence of perinatal depression. Vitamin D deficiency is highly prevalent among pregnant women, which is associated with a higher rate of miscarriage [28,29]. During pregnancy, women not only require vitamin D for their own metabolic needs, but also need to provide nutritional support for the growth and development of the fetus [30]. The process of childbirth involves significant physical exertion, leading to increased energy expenditure and a weakened digestive capacity. Furthermore, postpartum women often experience reduced outdoor activities, resulting in decreased vitamin D obtained

Table 3
MR analysis of the risk of PPD and 25(OH)D levels.

Exposure	Outcome	Method	OR (95%CI)	P
PPD	25(OH)D (set A)	MR Egger	1.031 (0.886–1.199)	0.3090
		Weighted median	0.990 (0.966–1.015)	0.4202
		IVW (Random effects)	1.001 (0.974–1.028)	0.9505
		IVW (Fixed effects)	1.001 (0.985–1.017)	0.9186
	25(OH)D (set B)	MR Egger	0.999 (0.942–1.059)	0.4820
		Weighted median	1.019 (0.992–1.047)	0.1614
		IVW (Random effects)	1.011 (0.988–1.035)	0.3489
		IVW (Fixed effects)	1.011 (0.992–1.031)	0.2608

Note: MR, mendelian randomization; 25(OH)D, 25-hydroxyvitamin D; PPD, postpartum depression; OR, odds ratio; CI, confidence intervals; WME, weighted median; IVW, Inverse-variance weighted.

Table 4
Sensitivity analysis of the causal association between 25(OH)D and the risk of PPD.

		Strength test		MR-Egger		Cochran Q test			
Exposure	Outcome	F	R2(%)	Egger intercept	P	Q (Egger)	P	Q (IVW)	P
25(OH)D (set A)	PPD	113.028	0.023	0.007	0.089	132.532	0.016	136.445	0.011
25(OH)D (set B)		309.528	0.385	0.016	0.344	6.806	0.235	8.290	0.218
PPD	25(OH)D (set A)	22.558	0.034	0.010	0.287	15.460	0.017	18.973	0.008
	25(OH)D (set B)	23.332	0.035	0.001	0.943	8.640	0.124	8.650	0.194

Note: MR, mendelian randomization; 25(OH)D, 25-hydroxyvitamin D; PPD, postpartum depression; IVW, Inverse-variance weighted.

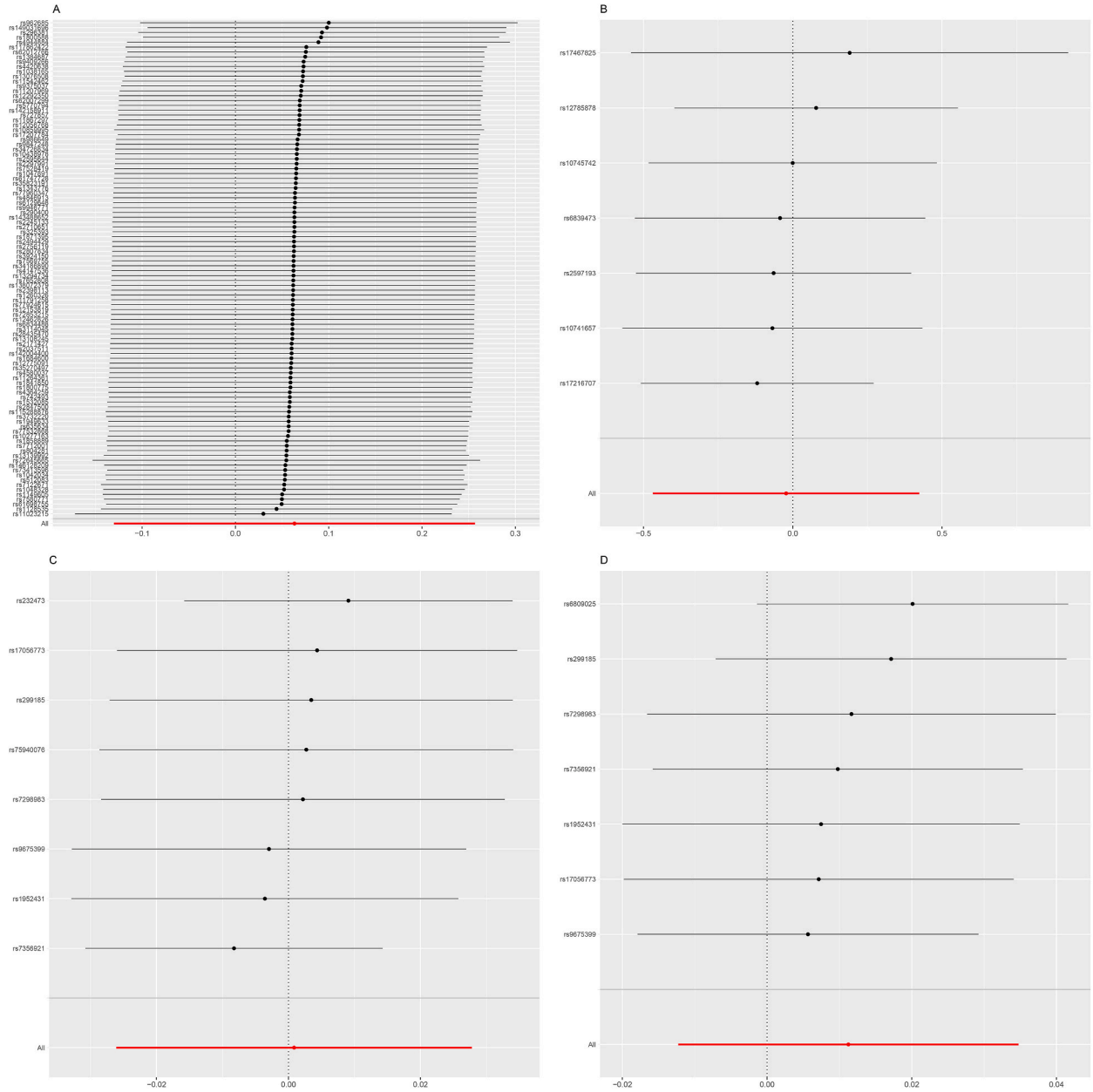

Fig. 2. Leave-one-out analysis of the effect of 25(OH)D on PPD and PPD on 25(OH)D. (A–B) The effect of serum 25(OH)D levels in set A (A) and set B (B) on PPD. (C–D) The effect of PPD on serum 25(OH)D levels in set A (C) and set B (D). Note: 25(OH)D, 25-hydroxyvitamin D; PPD, postpartum depression.

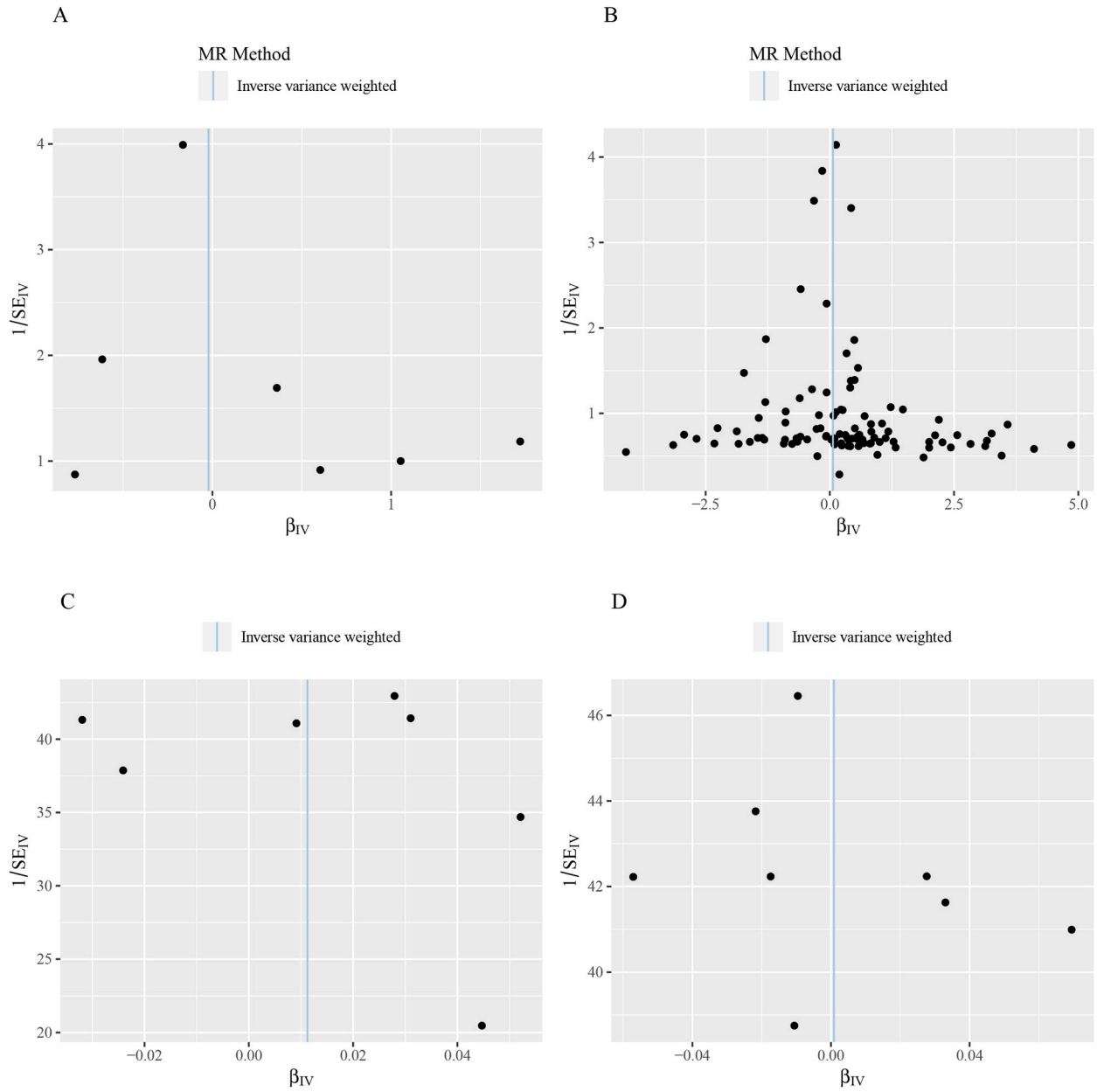

Fig. 3. Funnel plots of the effect of 25(OH)D on PPD and PPD on 25(OH)D. (A–B) The effect of serum 25(OH)D levels in set A (A) and set B (B) on PPD. (C–D) The effect of PPD on serum 25(OH)D levels in set A (C) and set B (D). Note: 25(OH)D, 25-hydroxyvitamin D; PPD, postpartum depression.

through sunlight exposure [31]. Consequently, postpartum women constitute a high-risk group for vitamin D deficiency. Current research suggests that vitamin D may influence the occurrence of PPD through various mechanisms, including immune modulation, alterations in calcium concentration, impact on hippocampal cell differentiation and apoptosis, and modulation of the hypothalamic-pituitary-gonadal axis function [32–34].

It is crucial to delve into the implications of the observed absence of a causal relationship between genetically determined variations in 25(OH)D levels and the risk of PPD. This outcome challenges the prevailing notion derived from numerous observational studies. One potential explanation for the non-causal relationship observed in the MR analysis is the avoidance of reverse causation and the reduction of confounding factors inherent in the study design. The use of genetic instruments as proxies for vitamin D levels minimizes the likelihood of reverse causation, where PPD could influence 25(OH)D levels. This strengthens the causal inference drawn from the study, providing a more reliable assessment of the true nature of the relationship.

Additionally, the lack of a causal link might stem from the multi-factorial nature of PPD. While observational studies have hinted at

an association between lower 25(OH)D levels and increased PPD risk, the MR analysis, by design, allows for a more controlled examination, isolating the genetic component of vitamin D levels from other potential confounding variables [35]. The absence of a causal relationship in this context suggests that other factors, beyond vitamin D levels, may contribute more substantially to the development of PPD. It is essential to acknowledge the limitations and complexities inherent in studying mental health outcomes. PPD is a multifaceted condition influenced by various genetic, environmental, and lifestyle factors [36]. The MR results, while providing valuable insights, do not negate the potential relevance of vitamin D in the broader context of maternal mental health.

This study possesses several strengths within the context of investigating causal associations between vitamin D and PPD through a bidirectional MR study. The use of a bidirectional MR design in this research is a notable advantage. This design mitigates reverse causation and minimizes residual confounding, as genetic variations serve as upstream determinants of both vitamin D levels and other lifestyle factors. By incorporating genetic instruments, the study achieves a more nuanced understanding of the causal relationships involved. Furthermore, the study contributes to the limited existing literature on the effectiveness of vitamin D supplementation in treating PPD. The findings offer valuable insights, supplementing current observational research and supporting causal relationships between vitamin D and the development of PPD. This contribution adds depth to the field of nutritional prevention of PPD.

Nevertheless, the study had several limitations. Firstly, the study population was restricted to a specific ethnic group, which might compromise the reliability and generalizability of the findings. Secondly, the use of genetic variants as instrumental variables assumed a robust association with vitamin D levels and a lack of pleiotropy. However, genetic variants might not perfectly capture the effect of vitamin D on PPD, and the assumption of no pleiotropy might not always hold [37]. Furthermore, the study did not account for clinical variables that might interact with vitamin D levels or PPD, such as age, parity, lifestyle factors, or concurrent illnesses [38]. The assessment of depression levels was limited by the aggregated nature of the data from the GWAS, which restricted the exploration of the association between vitamin D levels and the severity of depression. Further investigation and prospective studies are warranted to confirm and strengthen the validity of this finding within the realm of scientific research.

The conclusion drawn from the bidirectional MR study indicated a lack of causal association between vitamin D levels and PPD. This study, employing a robust methodology, did not find evidence supporting a causal link in either direction. These findings contribute to the growing body of literature on risk factors of PPD and suggest that the observed correlation between vitamin D and PPD may be attributed to confounding factors rather than a direct causal relationship. Further research is warranted to explore additional factors that may influence PPD providing a more comprehensive understanding of its etiology.

Data availability

The data from this study are available in online repositories, which can be found here: https://gwas.mrcieu.ac.uk/.

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CRediT authorship contribution statement

Tongtong Lin: Writing – original draft. **Linling Zhu:** Writing – original draft. **Yifei Dai:** Methodology, Data curation. **Zhiyin Zhang:** Methodology, Data curation. **Dingheng Li:** Writing – review & editing, Project administration. **Xinyun Yang:** Project administration.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33349.

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