Causal Association Between Circulating Macrophage Inflammatory Protein 1α (MIP-1α) Levels and Eclampsia: A Two-Sample Mendelian Randomization Study

Keywords
Preeclampsia, Mendelian randomization, Macrophage, White blood cell, Eclampsia

Abstract

Introduction

Preeclampsia-eclampsia (PE) poses serious risks to maternal and fetal health. Inflammatory markers—such as WBC counts, macrophage-related factors (e.g., serum clusters, MIF, CSF proteins, and inflammatory proteins), and procalcitonin—are implicated in PE, but their causal roles remain unclear. This study investigates these potential causal relationships.

Material and methods

Using summary statistics from the FINNGEN R12 cohort database for outcomes and previously published Genome-wide association studies (GWAS) for a comprehensive panel of circulating inflammatory markers, a two-sample Mendelian randomization (MR) analysis was performed. The primary analytical method was inverse-variance weighted (IVW), supplemented by weighted median, weighted mode, and MR-Egger regression. Sensitivity analyses included MR-Egger, MR-PRESSO, Cochran's Q test, and leave-one-out analysis to assess pleiotropy, heterogeneity, and the robustness of the findings.

Results

The IVW method, following rigorous outlier correction and sensitivity analyses, revealed a significant protective causal association between genetically predicted macrophage inflammatory protein-1α (MIP-1α) levels and eclampsia (odds ratio = 0.16, 95% confidence interval 0.05 - 0.46, P<0.001, PFDR=0.024). Conversely, no robust causal associations were observed for other investigated exposures, including circulating white blood cell counts, procalcitonin, other macrophage-related cytokines such as MIP-1β, serum differentiation clusters, MIF, or CSF proteins, with either preeclampsia or eclampsia. After the removal of outliers, no pleiotropic variants were detected. Leave-one-out analysis further confirmed the absence of influential genetic variants, substantiating the robustness of the findings.

Conclusions

This study supports a significant causal link between MIP-1α levels and Eclampsia, highlighting the role of specific inflammatory pathways in its development.

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Running title: Levels of MIP-1α and Eclampsia

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Conclusion: This study supports a significant causal link between MIP-1α levels and Eclampsia, highlighting the role of specific inflammatory pathways in its development.

Keywords: White blood cell, Macrophage, Preeclampsia, Eclampsia, Mendelian randomization

Introduction

Preeclampsia–eclampsia (PE) is a severe pregnancy disorder marked by new-onset hypertension and proteinuria after 20 weeks of gestation[1]. Progression to eclampsia with seizures endangers both mother and fetus[2]. PE causes multi-organ dysfunction, adverse perinatal outcomes, and long-term cardiovascular morbidity[3-5], and is linked to preterm birth, fetal growth restriction, and stillbirth[6]. It affects approximately 6–7% of pregnancies worldwide, especially in low- and middle-income regions[7]. Risk factors include chronic hypertension, primiparity, extreme maternal age, obesity, and multiple gestations[8]. Emerging evidence implicates inflammation and infection in endothelial dysfunction[9]. Because current care is largely supportive and delivery remains the only definitive therapy, identifying inflammatory biomarkers and clarifying causal pathways are critical for early prediction and targeted intervention.

PE features systemic inflammation and immune dysregulation. Circulating white blood cell (WBC) counts serve as general indicators of immune activation in infections and autoimmune diseases[10, 11]. Procalcitonin, a calcitonin precursor released during systemic inflammation, is a well-established indicator of bacterial sepsis[12, 13]. Macrophage-related cytokines, including macrophage inflammatory proteins (MIPs), macrophage migration inhibitory factor (MIF), and colony-stimulating factors (CSFs), have been implicated in PE through their influence on immune balance and endothelial integrity[14]. Furthermore, research has shown that dysregulated macrophage functions lead to exacerbated systemic inflammation, which can significantly affect endothelial function in PE patients[15, 16]. Elevated MIF levels promote inflammatory signaling, whereas CSFs enhance monocyte differentiation, both contributing to disease progression[17, 18]. Clinical studies suggest that altered levels of these markers are

associated with PE severity and onset[19]. However, most evidence is observational and limited by confounding and reverse causation, leaving causal relationships unclear. Mendelian randomization (MR) utilizes genetic variants as instrumental variables to infer causality, effectively minimizing biases typical of observational studies[20]. Previous genetic epidemiology studies have confirmed heritable associations between circulating metabolites and complex diseases, supporting MR as a powerful genomic tool for causal inference[21]. Recent two-sample Mendelian randomization studies published in Archives of Medical Science further illustrate the applicability of this framework in complex diseases[22]. Bidirectional MR has also been adopted to strengthen causal directionality assessment[23]. MR analyses linking circulating metabolites to disease risk provide additional examples of summary-statistics–based causal inference[24]. Similar applications to respiratory outcomes underscore the broad utility of MR in epidemiology[25]. Here, we applied a two-sample MR design to systematically assess the causal effects of circulating WBC subtypes (basophils, eosinophils, lymphocytes, monocytes, neutrophils), procalcitonin, macrophage surface clusters (CD14, CD40, CD44), MIF, CSFs (CSF1, CSF2, CSF3), and macrophage inflammatory proteins (MIP-1α, MIP-1β) on the risk of preeclampsia and eclampsia, aiming to elucidate their pathogenic roles and identify potential therapeutic targets.

Materials and methods

Study Design

The study design is illustrated in **Figure 1**. A two-sample MR study was conducted to investigate the causal relationships between an expanded set of exposures—including circulating WBCs, procalcitonin levels, macrophage serum differentiation clusters, MIF, CSF related factors, and macrophage inflammatory proteins—and the outcomes of PE.

Using genetic data from published studies, variants associated with these immune and inflammatory markers were identified and employed as instrumental variables (IVs). The selection of IVs adhered to three tailored core assumptions, reflecting the specifics of the broader exposure factors and their relation to PE[20]: (A) Each single nucleotide polymorphism (SNP) must be strongly associated with the immune markers, including WBCs, procalcitonin, and macrophage-related factors. (B) SNPs must be independent of known confounders that could influence both the markers and the risk of PE. (C) SNPs should impact the risk of PE solely through their effects on these specified markers, without influencing other pathways.

Data Sources

Summary statistics for preeclampsia and eclampsia were obtained from the large FINNGEN R12 cohort database, where eclampsia included 9,023 cases and 259,313 controls, and preeclampsia consisted of 88 cases and 259,313 controls. Genetic data on WBC counts, including basophil, eosinophil, lymphocyte, monocyte, and neutrophil counts, were sourced from a trans-ethnic meta-analysis of 15 hematological traits involving 519,288, 524,923, 521,594, 474,001, and 474,237 subjects, respectively[26]. Genetic statistics for procalcitonin were derived from the INTERVAL study, which included data from 3,301 subjects within a randomized trial of approximately 50,000 participants examining different blood donation intervals[27]. Genome-wide association studies (GWAS) data for macrophage serum differentiation clusters (including TREM2, CD86, CD44, CD163, CD209, CD40, CD80, CD14) and macrophage-related factors such as MIF, and CSFs (CSF1, CSF2, and CSF3) were collected from previously published studies [28], involving over 5,300 subjects. Data for macrophage inflammatory proteins (levels of MIP-1α and macrophage inflammatory protein 1b)

were sourced from published literature[29], with MIP-1α including 3,522 subjects and macrophage inflammatory protein 1b including 8,243 subjects. Detailed SNP information is provided in **Table S1**. To minimize bias due to population stratification, all SNPs and summary data were sourced exclusively from European ancestry populations.

Selection of IVs

Stringent criteria were applied to identify SNPs strongly associated with each exposure. For Macrophage Inflammatory Protein 1b levels, serum levels of TREM2, CD209, CD163, MIF (macrophage migration inhibitory factor), neutrophil count, lymphocyte count, monocyte count, basophil count, and eosinophil count, only genome-wide significant SNPs ($P < 5 \times 10^{-8}$) were retained. For exposures including MIP-1α levels, procalcitonin levels, serum levels of CSF1, CD80, CSF2, CD86, CSF3, CD14, CD44, and CD40, a relaxed genome-wide significance threshold ($P < 5 \times 10^{-6}$) was used to ensure sufficient instrument strength; Subsequently, SNPs with a minor allele frequency (MAF)≤0.01 were excluded. Linkage disequilibrium (LD) clumping was then performed using a window of 10,000 kb and an R^2 threshold of ≥ 0.001 to ensure the independence of selected instruments[30]. If any exposure-associated SNPs were not available in the outcome GWAS, they were replaced by proxy SNPs in high linkage disequilibrium (LD) ($R^2 > 0.8$). Palindromic SNPs with ambiguous strand orientation were removed to avoid alignment errors. Finally, the strength of each instrumental variable was evaluated using the F-statistic, with values >10 indicating low risk of weak instrument bias and ensuring the validity of causal inference[31].

MR Analysis

Causal relationships between circulating WBC subtypes, procalcitonin levels, and preeclampsia-eclampsia were primarily evaluated using the inverse-variance weighted (IVW) method, which estimates a pooled effect size by weighting each SNP's estimate by the inverse of its variance[32]. To strengthen the robustness of causal inference, additional MR methods were applied, including MR-Egger, weighted median, and weighted mode. MR-Egger accounts for directional pleiotropy by incorporating an intercept term [32] , while the weighted median approach provides consistent estimates even if up to 50% of the instruments are invalid[33]. The weighted mode method identifies the most frequent causal effect across SNPs, weighting by their precision[34]. All analyses were performed using the "TwoSampleMR" package in R (version 4.0.5). To address the issue of multiple testing, P-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) correction method.

Sensitivity Analysis

To assess heterogeneity among IVs, Cochran's Q test was performed based on IVW estimates, with $P<0.05$ indicating significant heterogeneity[35]. Leave-one-out analysis was also conducted to detect influential SNPs by sequentially removing each variant and re-estimating the causal effect[36]. MR-Egger regression was used to evaluate horizontal pleiotropy, with a non-significant intercept suggesting no directional pleiotropic bias[37]. In addition, the Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) method was used to detect and correct for outlier SNPs (defined as $P<0.05$), followed by re-analysis after excluding these variants[38]. Funnel plot symmetry was examined to visually assess heterogeneity and potential asymmetry in the distribution of SNP effects.

Results

Selection of IVs

In the study, the following numbers of SNPs were identified for each exposure factor: Basophil count (197 SNPs), CD14 (16 SNPs), CD163 (6 SNPs), CD209 (6 SNPs), CD40 (14 SNPs), CD44 (10 SNPs), CD80 (9 SNPs), CD86 (13 SNPs), Eosinophil count (440 SNPs), Lymphocyte count (506 SNPs), MIP-1α levels (7 SNPs), Macrophage inflammatory protein 1b levels (7 SNPs), Monocyte count (509 SNPs), Neutrophil count (419 SNPs), Procalcitonin levels (10 SNPs), Serum levels of protein CSF1 (16 SNPs), CSF2 (18 SNPs), CSF3 (15 SNPs), MIF (2 SNPs), and TREM2 (3 SNPs). The number of IVs retained per exposure ranged from 2 to 509. The F-statistics for all identified IVs exceeded 10, confirming their strength as instruments. Detailed SNP information and the final number of IVs for each exposure are provided in **Table S2**, with exclusions summarized in **Table S3**.

MR results

We initially conducted MR analyses to explore the causal effects of circulating WBC subtypes, procalcitonin, and macrophage-related factors on preeclampsia and eclampsia. However, MR-PRESSO identified several outliers **(Table S4–Table S6)**. After removing these variants, we re-ran the complete analysis. All results presented below are based on the outlier-adjusted dataset.

After outlier correction, IVW analysis revealed a robust and statistically significant causal association between MIP-1α levels and eclampsia (odds ratio (OR)= 0.16, 95% confidence interval (CI): 0.05–0.46, $P < 0.001$, PFDR = 0.024; **Table 1**), highlighting MIP-1α as a potential causal factor. In contrast, no significant associations were observed for other exposures—including neutrophil count, lymphocyte count,

procalcitonin, macrophage serum differentiation clusters, MIF, CSF, and other macrophage inflammatory proteins—with either preeclampsia or eclampsia (**Table 1**). Visual summaries of the MIP-1α–eclampsia association are shown in **Figure 2**. Scatter plots and forest plots for null results are available in **Figure S1–Figure S2**; sensitivity results including leave-one-out and funnel plots are presented in **Figure S3–Figure S4**.

Sensitivity Analyses

Sensitivity analyses supported the robustness of the observed association between MIP-1α levels and eclampsia. No significant heterogeneity was found (Cochran's Q P = 0.63), and MR-Egger regression indicated no directional pleiotropy (intercept P = 0.20; **Table 2**). The MR-PRESSO global test also showed no residual pleiotropy (P=0.70; **Table 3**). Leave-one-out analysis confirmed that no single SNP drove the association, and funnel plots showed symmetry, suggesting no heterogeneity.

For exposures showing no significant associations, sensitivity analyses after outlier removal revealed significant heterogeneity in analyses of basophil, eosinophil, lymphocyte, monocyte, and neutrophil counts with preeclampsia (Cochran's Q, P<0.05). However, as the primary IVW method used in this study was based on a random-effects model, a certain degree of heterogeneity is acceptable. MR-PRESSO results suggested potential pleiotropy for these exposures, though no specific outlier SNPs were identified. Importantly, MR-Egger intercept tests revealed no significant evidence of directional pleiotropy. Further exploration through leave-one-out analysis led to the exclusion of rs13511 and rs2713548 for eosinophil count, and rs113142693 for lymphocyte count due to their potential influence; however, the null associations for these counts with preeclampsia remained non-significant even after these exclusions.

Collectively, these comprehensive sensitivity analyses reinforce the robustness of the null findings for these inflammatory markers.

Discussion

This MR study provides novel genetic evidence supporting a potentially protective causal association between higher circulating levels of MIP-1α (also known as CCL3) and a reduced risk of eclampsia. This finding remained robust across multiple sensitivity analyses, with no indication of significant heterogeneity or horizontal pleiotropy after appropriate outlier correction. In contrast, no causal evidence was found for circulating WBC subtypes, procalcitonin, macrophage serum differentiation clusters, MIF, CSF-related factors, or other macrophage inflammatory proteins with either preeclampsia or eclampsia. These results suggest a specific inflammatory pathway involving MIP-1α in the pathogenesis of eclampsia, while broader inflammatory markers appear unlikely to play a direct causal role. Further research is needed to explore the underlying mechanisms and therapeutic implications.

Our MR study identified a significant protective genetic association between higher constitutive MIP-1α levels and a reduced risk of eclampsia (OR=0.16). This finding, while robust in our genetic analysis, presents an interesting contrast to some literature describing MIP-1α primarily as a pro-inflammatory chemokine involved in recruiting immune cells to sites of inflammation [39]. One possible explanation for this protective effect observed in our study could be that genetically determined, chronically higher (but potentially well-regulated) levels of MIP-1α might play a modulatory role in the specific context leading to eclampsia. For instance, higher baseline MIP-1α could precondition the immune response, leading to a more controlled or resolving

inflammatory process rather than an uncontrolled exacerbation that contributes to the severe neuroinflammatory and vascular events in eclampsia. It is also conceivable that MIP-1α, in certain concentrations or contexts, might promote the recruitment of specific monocyte/macrophage subsets with regulatory or tissue-repair functions, or influence other cytokine networks in a manner that ultimately protects against the progression to eclampsia. The specificity of this protective finding for eclampsia, and not preeclampsia (though statistical power for preeclampsia was limited), further suggests that MIP-1α's role might be particularly relevant in the distinct pathophysiological pathways that lead to the severe neurological manifestations of eclampsia.

Previous observational studies examining MIP-1α in preeclampsia/eclampsia have yielded inconsistent findings. Salazar Garcia et al.[40] reported higher early-pregnancy serum MIP-1α concentrations in women with preeclampsia than in controls (median 35.7 vs 17.7; U=120; P=0.029) and lower MCP-1 levels (median 233.8 vs 390.9; U=183; P=0.021). In contrast, another cohort reported no overall cytokine concentration differences but a lower proportion of women with detectable MIP-1α among those who later developed

(14/39 vs 76/117; P=0.003)[41]. Taylor et al.[42] observed no significant mid-pregnancy difference in circulating MIP-1α between preeclamptic and normotensive pregnancies. Overall, while some clinical studies have suggested elevated MIP-1α as a pro-inflammatory feature in preeclampsia, others found decreased or unchanged levels; our MR results differ by indicating a genetically proxied, long-term higher MIP-1α exposure may instead exert a protective effect against eclampsia. Taken together, clinical studies do not converge on a single direction of association and, on balance, are not clearly aligned with our MR-based protective effect for eclampsia. This discordance

may reflect differences in exposure timing, disease definition, measurement methods, or sample characteristics, as well as uncontrolled confounding inherent to observational studies. Our MR approach, by utilizing genetic variants as unconfounded proxies for lifelong exposure, bypasses many of these limitations and suggests a fundamental, potentially protective, influence of higher constitutive MIP-1α levels specifically on the development of eclampsia, rather than merely reflecting a transient state associated with preeclampsia. The specificity of our finding for eclampsia, and not preeclampsia, is noteworthy. This could be attributed to distinct pathophysiological mechanisms differentiating eclampsia (particularly its severe neurological component) from preeclampsia, or a greater statistical power to detect an effect on eclampsia (9,023 cases) compared to preeclampsia (only 88 cases) in our outcome GWAS dataset. Clinically, these findings suggest that circulating MIP-1α may have potential value as an early predictive biomarker for identifying women at lower genetic risk of eclampsia. Integration of MIP-1α into multi-marker screening models alongside established angiogenic and clinical indicators such as the soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF) ratio, maternal age, blood pressure, and body mass index could improve early risk stratification[43, 44]. Moreover, the immunomodulatory properties of the MIP-1α/ CC chemokine receptor 5 (CCR5) axis highlight possible therapeutic relevance. Agents targeting this pathway, or interventions that fine-tune inflammatory responses such as vitamin D supplementation and statin therapy, may merit further evaluation in high-risk pregnancies[45, 46]. Although our MR findings do not directly imply causality for therapeutic modulation, they provide a rationale for future mechanistic and translational studies aimed at harnessing this pathway for maternal vascular protection.

In contrast to the significant association observed for MIP-1α, this study did not find causal evidence linking other widely investigated inflammatory biomarkers to either preeclampsia or eclampsia. This broad set of null findings is equally important, suggesting that general markers of systemic inflammation, such as total WBC counts or levels of procalcitonin (primarily a marker of bacterial infection), or even other macrophage-related cytokines like MIP-1β, are unlikely to be primary causal drivers in the etiology of these hypertensive disorders of pregnancy. These markers may instead represent epiphenomena, reflecting secondary responses to the underlying disease processes (e.g., systemic inflammation, oxidative stress, immune dysregulation, or co-occurring infections) rather than initiating pathogenic factors[47-50]. For example, changes in WBC counts might indicate physiological alterations during pregnancy, infections, or stress conditions, while procalcitonin primarily serves as a marker for bacterial infections. Observational studies have reported associations between certain markers (such as increased neutrophil counts or decreased lymphocytes) and PE[51, 52], but these relationships may reflect confounding factors or merely represent disease activity rather than causal mechanisms. As MR analyses assess genetically predicted lifelong exposure effects, our negative findings suggest these general inflammatory markers are unlikely direct causal contributors to the onset of preeclampsia or eclampsia. This highlights the specific role of the MIP-1α pathway and its potential centrality in eclampsia pathogenesis.

This study has several notable strengths. First, it is the first to systematically explore the causal relationships between an extensive range of circulating white blood cell counts, procalcitonin levels, and macrophage-related factors (including serum differentiation clusters, MIF, CSF-related factors, and macrophage inflammatory proteins) with

preeclampsia and eclampsia using a MR approach. This provides a novel genetic perspective and stronger causal inference compared with traditional observational designs. Second, we utilized large-scale GWAS summary data and performed comprehensive sensitivity analyses using multiple MR methodologies to ensure the robustness of our findings. However, there are also several limitations. First, our GWAS data primarily originated from populations of European descent, limiting the generalizability of the results to other ethnic groups, such as Asian populations. Replication in diverse ancestral cohorts is crucial. Second, a major limitation is the substantially low statistical power for the preeclampsia outcome, with only 88 cases available from the FINNGEN R12 GWAS. This severely restricts our ability to detect any true, possibly more modest, causal associations for any of the investigated markers, including MIP-1α, with preeclampsia. Consequently, the lack of association with preeclampsia should be interpreted with extreme caution and does not necessarily imply no role, but rather insufficient power to detect one. Third, while MR design significantly reduces confounding, it cannot fully exclude biases from unknown or unmeasured confounders, particularly those arising from horizontal pleiotropy. Lastly, we examined circulating biomarkers, which may not fully represent the localized immune conditions in specific tissues such as the placenta.

Conclusion

In conclusion, this MR study provides compelling genetic evidence for a new, potentially protective causal association between higher genetically predicted circulating MIP-1α levels and a reduced risk of eclampsia, a finding that distinguishes MIP-1α from a range of other general inflammatory markers that showed no such causal

link. This suggests that MIP-1α may play a specific, and perhaps unexpectedly modulatory, role in the extreme neurological pathophysiology of eclampsia. While the precise mechanisms underlying this protective association remain to be elucidated and require dedicated functional investigation, our findings highlight the MIP-1α pathway as a priority for future research into the pathogenesis and potential therapeutic targeting of eclampsia. Future studies should aim to replicate these findings in diverse populations, particularly with larger, adequately powered GWAS for preeclampsia outcomes, and integrate MR with functional genomics and experimental models to dissect the molecular basis of MIP-1α's role. Such endeavors could ultimately pave the way for novel strategies to predict, prevent, or treat the devastating consequences of eclampsia.

Declarations

Ethics approval and consent to participate

This article is a two-sample Mendelian randomization study. The data for this study were obtained from publicly available databases and published literature data and does not require ethical approval and written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this article and supplementary information files.

Authors' contributions

Ying Zhang and Yanling Wei carried out the studies and participated in its design. Liangfeng Chen participated in collecting data, and drafted the manuscript. Ziyun Shi and Yanchuan Li participated in acquisition of data and draft the manuscript. Yi Wan and Ying Zhang performed the statistical analysis and interpretation of data. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Figure Legends

Figure 1. Flowchart of the study design.

Figure 2. The causal relationships between MIP-1α levels and Eclampsia: (A)Scatter plot; (B)Forest plot; (C)leave-one-out analysis; (D) Funnel plot.

Supplementary materials

Figure S1. Scatter plot of the causal relationships between circulating white blood cell and macrophage-related factors and preeclampsia-eclampsia. (A) Basophil count and Pre-eclampsia. **(B)** CD40 and Eclampsia. **(C)** Eosinophil count and Pre-eclampsia. **(D)** Lymphocyte count and Pre-eclampsia. **(E)** Macrophage inflammatory protein 1α levels and Eclampsia. **(F)** Monocyte count and Pre-eclampsia. **(G)** Neutrophil count and Pre-eclampsia.

Figure S2. Forest plot of the causal relationships between circulating white blood cell and macrophage-related factors and preeclampsia-eclampsia. (A) Basophil count and Pre-eclampsia. **(B)** CD40 and Eclampsia. **(C)** Eosinophil count and Pre-eclampsia. **(D)** Lymphocyte count and Pre-eclampsia. **(E)** Macrophage inflammatory protein 1α levels and Eclampsia. **(F)** Monocyte count and Pre-eclampsia. **(G)** Neutrophil count and Pre-eclampsia.

Figure S3. The leave-one-out plot of the causal relationships between circulating white blood cell and macrophage-related factors and preeclampsia-eclampsia. (A) Basophil count and Pre-eclampsia. **(B)** CD40 and Eclampsia. **(C)** Eosinophil count and Pre-eclampsia. **(D)** Lymphocyte count and Pre-eclampsia. **(E)** Macrophage inflammatory protein 1α levels and Eclampsia. **(F)** Monocyte count and Pre-eclampsia. **(G)** Neutrophil count and Pre-eclampsia.

Figure S4. Funnel plot of the causal relationships between circulating white blood cell and macrophage-related factors and preeclampsia-eclampsia. (A) Basophil count and Pre-eclampsia. **(B)** CD40 and Eclampsia. **(C)** Eosinophil count and Pre-eclampsia. **(D)** Lymphocyte count and Pre-eclampsia. **(E)** Macrophage inflammatory protein 1a levels and Eclampsia. **(F)** Monocyte count and Pre-eclampsia. **(G)** Neutrophil count and Pre-eclampsia.

Table S1. Overview of the data source.

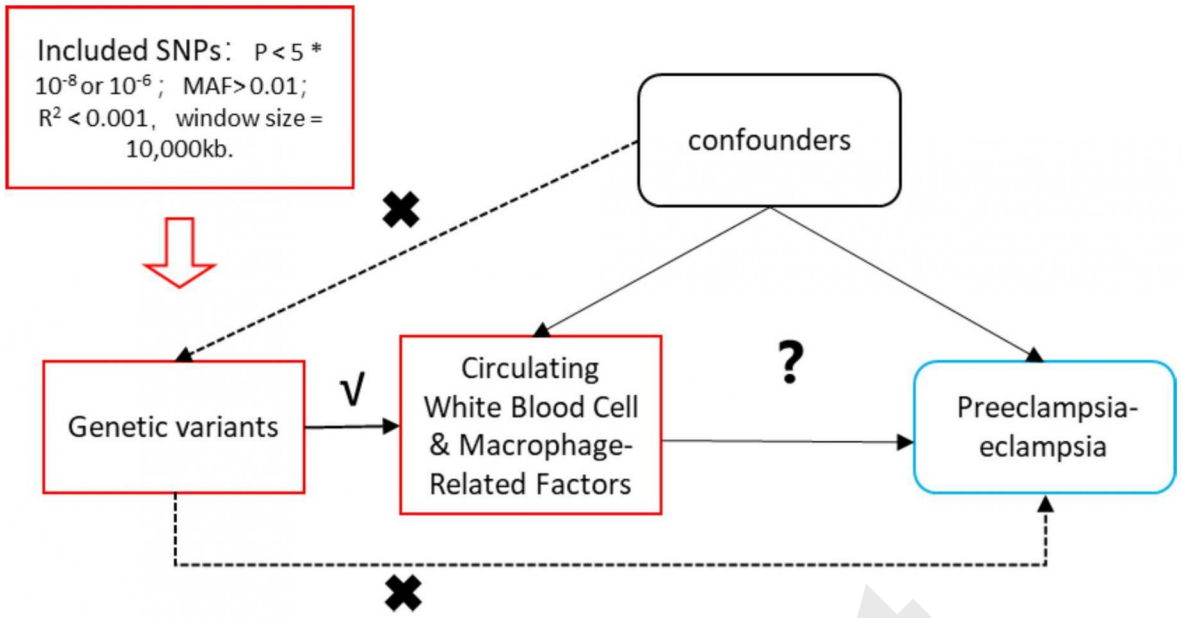
Table S2. Detailed information of SNPs in the MR analysis of circulating white blood cell and macrophage-related factors and procalcitonin levels on preeclampsia.

Table S3. Detailed information of IVs in the MR analysis of circulating white blood cell and macrophage-related factors and procalcitonin levels on preeclampsia.

Table S4. MR estimates of assessing the causal effects of circulating white blood cell and macrophage-related factors on preeclampsia-eclampsia. (before outlier-removal)

Table S5. Assessing the heterogeneity and horizontal pleiotropy between circulating white blood cell and macrophage-related factors with preeclampsia-eclampsia. (before outlier-removal)

Table S6. Detection and correction of horizontal pleiotropy using MR-PRESSO method**.** (before outlier-removal)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confounders
Genetic variants
√
Circulating White Blood Cell & Macrophage-Related Factors
?
Preeclampsia-eclampsia

Table 1. MR estimates of assessing the causal effects of circulating white blood cell and macrophage-related factors on preeclampsia-eclampsia (outlier-corrected).

Exposure	Outcome	Nsnp	Method	OR_CL	P	FDR
CD40	Eclampsia	12	Inverse variance weighted	1.0575 (0.3899 - 2.8686)	0.9125	0.966923
Macrophage inflammatory protein 1α levels	Eclampsia	6	Inverse variance weighted	0.1658 (0.0593 - 0.4634)	0.0006	0.024446
basophil count	Pre-eclampsia	196	Inverse variance weighted	0.9792 (0.8688 - 1.1036)	0.7304	0.946584
eosinophil count	Pre-eclampsia	437	Inverse variance weighted	1.0173 (0.9407 - 1.1001)	0.6675	0.946584
lymphocyte count	Pre-eclampsia	488	Inverse variance weighted	0.9889 (0.9167 - 1.0668)	0.7731	0.946584
monocyte count	Pre-eclampsia	496	Inverse variance weighted	1.0289 (0.9623 - 1.1001)	0.4038	0.918528
neutrophil count	Pre-eclampsia	404	Inverse variance weighted	0.9775 (0.8934 - 1.0695)	0.6195	0.943392

Table 2. Assessing the heterogeneity and horizontal pleiotropy between circulating white blood cell and macrophage-related factors with preeclampsia-eclampsia (outlier-corrected).

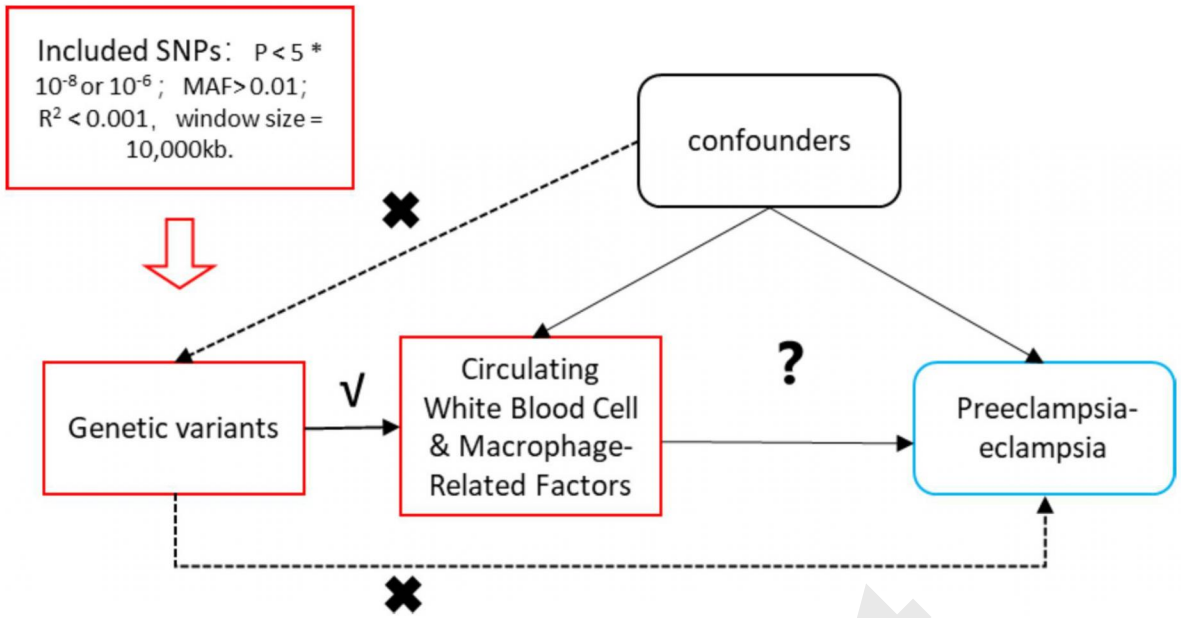
Exposure	Outcome	Heterogeneity		Pleiotropy	
		Q statistic (IVW)	*P* value	MR-Egger Intercept	*P* value
basophil count	Pre-eclampsia	264.1032	0.000717501	6.80E-05	0.981036
eosinophil count	Pre-eclampsia	629.8006	3.20×10^{-9}	0.001575	0.460704
lymphocyte count	Pre-eclampsia	602.2796	0.000272167	0.000441	0.818709
Macrophage inflammatory protein 1α levels	Eclampsia	3.419768	0.635561013	0.373097	0.203426
monocyte count	Pre-eclampsia	773.1157	1.51×10^{-14}	0.000245	0.882045
neutrophil count	Pre-eclampsia	609.6303	1.20×10^{-10}	0.001834	0.396076
CD40	Eclampsia	12.40869	0.33371981	-0.42906	0.068272

Note: Cochran's Q statistic is used for detecting heterogeneity about the IVW estimate.

Table 3. Detection and correction of horizontal pleiotropy using MR-PRESSO method (outlier-corrected).

Exposure	Outcome	Raw		Outlier corrected		Global P	Number of outliers	Distortion P
		OR (CI%)	*P*	OR (CI%)	*P*			
basophil count	Pre-eclampsia	0.988 (0.8767 - 1.1135)	0.843498998	NA (NA - NA)	NA	0.000285714	NA	NA
eosinophil count	Pre-eclampsia	1.01 (0.9344 - 1.0918)	0.801773004	NA (NA - NA)	NA	$<1\times10^{-4}$	NA	NA
lymphocyte count	Pre-eclampsia	0.9862 (0.9145 - 1.0634)	0.717462022	NA (NA - NA)	NA	$<5\times10^{-5}$	NA	NA
Macrophage inflammatory protein 1α levels	Eclampsia	0.1658 (0.0709 - 0.3879)	0.008967771	NA (NA - NA)	NA	0.706	NA	NA
monocyte	Pre-eclampsia	1.021 (0.956	0.536370914	NA (NA -	NA	<0.00014285714285	NA	NA

count		- 1.0904)		NA)		7143		
neutrophil count	Pre-eclampsia	0.9752 (0.8928 - 1.0651)	0.576801626	NA (NA - NA)	NA	<0.00014285714285 7143	NA	NA
CD40	Eclampsia	1.0575 (0.3899 - 2.8686)	0.914512084	NA (NA - NA)	NA	0.396	NA	NA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confounders
Genetic variants
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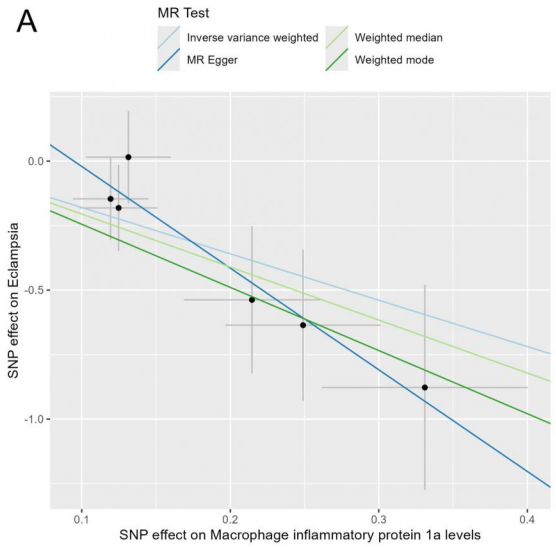
Circulating White Blood Cell & Macrophage-Related Factors
?
Preeclampsia-eclampsia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Inverse variance weighted
MR Egger
Weighted median
Weighted mode
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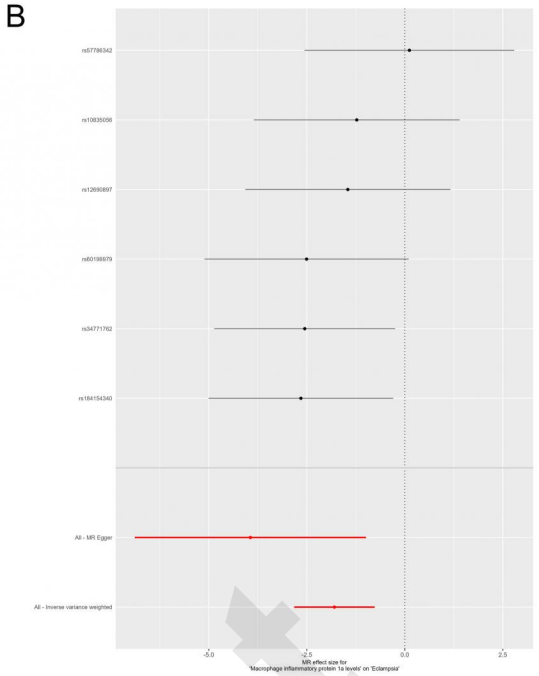
0.2
0.3
0.4
SNP effect on Macrophage inflammatory protein 1a levels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All - MR Egger
All - Inverse variance weighted
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-2.5
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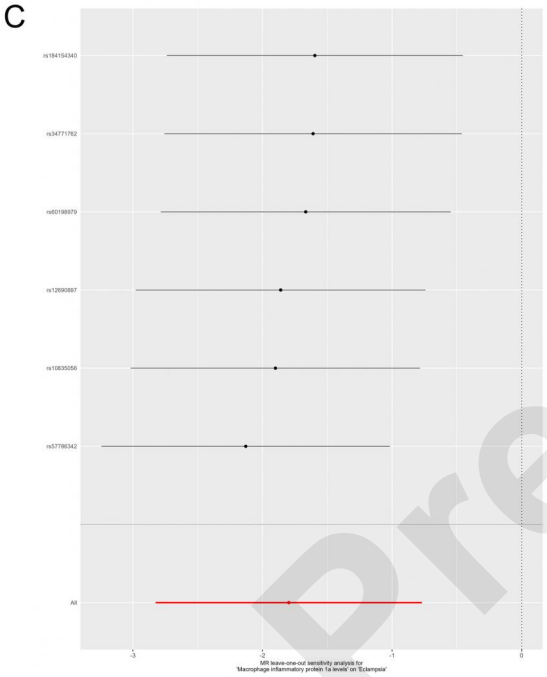
2.5
MR effect size for
'Macrophage inflammatory protein 1a levels' on 'Eclampsia'


C
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rs57786342
All
-3
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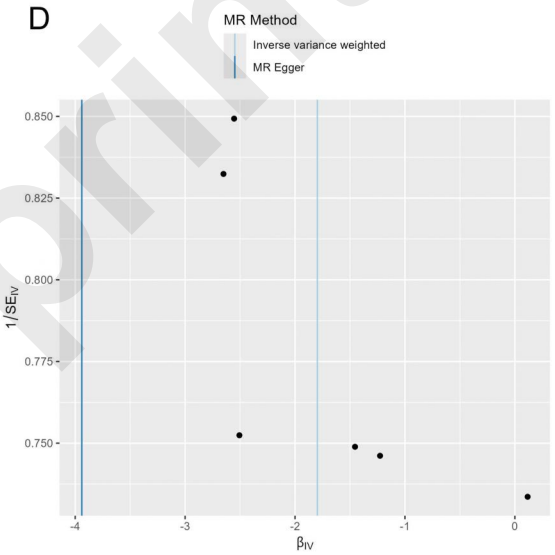
MR leave-one-out sensitivity analysis for
'Macrophage inflammatory protein 1a levels' on 'Eclampsia'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Inverse variance weighted
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-4
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