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ORIGINAL RESEARCH ARTICLE

Causal relationships between mitochondrial DNA copy number and hypertensive disorders in pregnancy: A Mendelian randomization study

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Abstract

Introduction: The association between mitochondrial DNA (mtDNA) copy number and hypertensive disorders in pregnancy has been explored in several observational studies; however, due to methodological limitations and confounding factors, consistent conclusions have not been reached.

Objectives: This study aimed to determine whether genetically predicted mtDNA copy number has a causal effect on the risk of hypertensive disorders in pregnancy using Mendelian randomization (MR) analysis.

Methods: MR analyses were performed to assess genetic relationships and potential causal associations among four hypertensive pregnancy outcomes: Pre-existing hypertension complicating pregnancy, gestational hypertension, pre-eclampsia or eclampsia (POE), and pre-eclampsia (PE). The mtDNA copy number for each outcome was obtained from genome-wide association study datasets. The primary MR method was inverse variance weighting (IVW), supported by four complementary approaches (MR-Egger, weighted median, simple mode, and weighted mode) to ensure robust inference.

Results: IVW analysis revealed a significant inverse correlation between mtDNA copy number and both POE (odds ratio [OR] 95% confidence interval [CI] = 0.738 [0.578 – 0.943]; p=0.015) and PE (OR [95% CI] = 0.735 [0.563 – 0.960]; p=0.024), suggesting a protective effect of higher mtDNA copy number.

Conclusion: This MR investigation demonstrates a positive causal relationship between higher mtDNA copy number and reduced risk of PE and related hypertensive disorders in pregnancy.

Keywords: Hypertensive disorders in pregnancy; Mitochondrial DNA copy number; Mendelian randomization, Single nucleotide polymorphism; Instrumental variable

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1. Introduction

Pre-eclampsia (PE) is a hypertensive disorder of pregnancy characterized by a series of syndromes marked by high blood pressure, which can have a profound impact on maternal and fetal health.[1,2] It is a multisystem disorder defined by a new onset of hypertension and proteinuria, or hypertension with significant end-organ dysfunction, with or without proteinuria.[3] Epidemiologically, hypertensive disorders in pregnancy, including PE, affect

approximately 2 – 8% of pregnancies globally.[4,5] Notably, there is an increasing trend in these disorders; for example, in the United States, the incidence of hypertensive disorders in pregnancy rose from 13.3% in 2017 to 15.9% in 2019.[6] The implications of hypertensive pregnancy disorders extend beyond immediate maternal health risks—such as eclampsia and HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count)—to include long-term cardiovascular morbidity.[7-9] In addition, these conditions are associated with adverse fetal outcomes, including intrauterine growth restriction (IUGR), prematurity, and increased perinatal mortality.[10,11] The pathophysiology of PE is complex, involving factors such as placental ischemia and maternal endothelial dysfunction, which underscores the necessity for early detection and management to mitigate health risks for both mother and child.[3,12,13]

Mitochondrial DNA (mtDNA), which is distinct from nuclear DNA, is maternally inherited and forms a compact genome essential for mitochondrial function, particularly energy production.[14,15] This genome encodes 13 proteins that are essential for the electron transport chain and oxidative phosphorylation, which are key processes in adenosine triphosphate synthesis.[16] Regulation of mtDNA copy number is adaptive, modulating according to cellular energy requirements and stress responses, highlighting the role in cellular metabolism and adaptability.[17,18]

Recent studies have identified a correlation between mtDNA copy number and hypertensive disorders in pregnancy, particularly PE.[19,20] Mechanistic investigations suggest that changes in mtDNA copy number may affect mitochondrial function, leading to increased oxidative stress and endothelial dysfunction – both central to the development of PE.[21,22] Further studies propose that these mtDNA copy number variations could potentially influence placental angiogenesis and immune responses, contributing to the pathological landscape of PE.[23,24]

Williams *et al.* identified a link between increased mtDNA copy numbers and placental abruption risk in women with PE, suggesting a potential link between elevated mtDNA copy numbers and adverse pregnancy outcomes.[25] Vishnyakova *et al.* documented enhanced mitochondrial activity in early-onset pre-eclamptic placentas, indicating adaptive mitochondrial responses to pre-eclamptic.[26] Conversely, Cushen *et al.* reported lower concentrations of circulating cell-free mtDNA in women with PE compared to healthy controls,[27] which contrasts with the findings of increased mtDNA copy number in other studies. These differences underscore the complexity of mtDNA copy number dynamics in pregnancy-related hypertensive disorders, emphasizing the need for further research.

Existing literature examining the correlation between mtDNA copy number and hypertensive illnesses in pregnancy faces significant constraints. Most studies are observational and offer preliminary evidence of an association but do not establish causality.[25-28] These limitations stem from potential biases and confounding variables inherent in observational study designs.

The aim of this study is to bridge this gap using Mendelian randomization (MR), a method that utilizes genetic variants as proxies for risk factors to infer causal relationships.[29] The strength of MR lies in its ability to approximate the conditions of randomized controlled trials, thereby overcoming the limitations of observational studies. By leveraging genetic data, MR analysis is able to provide more definitive evidence to support a direct causal role of mtDNA copy number in the development of hypertensive disorders in pregnancy. This approach holds promise for advancing understanding of the etiological significance of mtDNA in these conditions and could potentially guide future therapeutic interventions.

2. Materials and methods

2.1. Study design

A two-sample MR analysis was conducted to determine the causal correlation between mtDNA copy number and hypertensive disorders in pregnancy. Single nucleotide polymorphisms (SNPs) served as instrumental variables (IVs).[30] To ensure the validity of the MR analysis, three key assumptions were tested.[31] First, the selected IVs had to be significantly associated with mtDNA copy number. Second, the IVs needed to be independent of potential confounders that could affect both the exposure and the outcome. Third, the IVs were required to influence hypertensive disorders in pregnancy solely through their effect on mtDNA copy number. The study design is illustrated in Figure 1.

Genetic instruments for mtDNA copy numbers were extracted from the INTERVAL study, which included 395,718 participants, the majority of whom were European.[32] This study accounted for multiple covariates, including age, gender, genotyping chip model, and 20 genetic principal components. Data for hypertensive disorders in pregnancy were obtained from the FinnGen database (Round 10, https://r10.risteys.finngen.fi/). Outcomes from the FinnGen database included four traits: pre-existing hypertension complicating pregnancy (EH), gestational hypertension (GH), PE or eclampsia (POE), and PE. Details of these outcomes and their web sources are provided in Table 1. All original studies obtained informed consent and received ethical approval. Independent SNPs associated with mtDNA copy number were selected using a window size of 10 megabase and a linkage disequilibrium clumping threshold of $r^2 = 0.001$. Only genome-wide

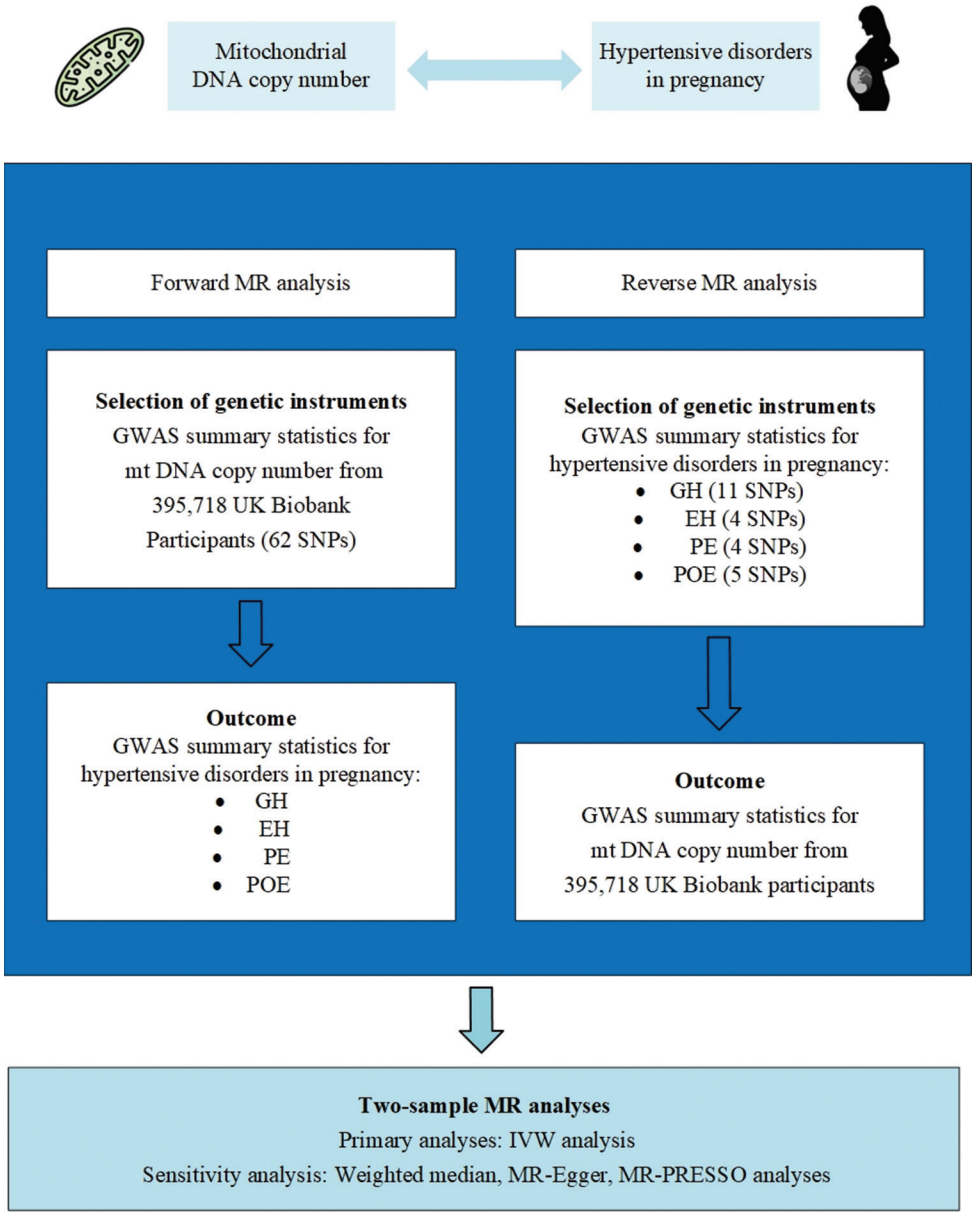

Figure 1. Overview of the bidirectional MR framework used to investigate the causal effect relationship between mtDNA copy number and hypertensive disorders in pregnancy
Abbreviations: EH: Pre-existing hypertension complicating pregnancy; GH: Gestational hypertension; GWAS: Genome-wide association study; IVW: Inverse variance weighting; MR: Mendelian randomisation; mtDNA: mitochondrial DNA; PE: Pre-eclampsia; POE: Pre-eclampsia or eclampsia; SNPs: Single nucleotide polymorphisms.

significant SNPs ($p<5 \times 10^{-8}$) were included to ensure strong instrument strength and reduce redundancy.

2.2. Statistical analyses

The random-effects inverse variance weighted (IVW) approach was employed as the main strategy for MR analysis.[33] To provide a comprehensive assessment, four additional MR methods were also used: weighted median, MR-Egger, simple mode, and weighted mode. Although these techniques provide an extensive assessment, their statistical power may be lower than that of the IVW test. Odds ratio (OR) and 95% confidence interval (95% CI) were used to evaluate the association between mtDNA copy numbers and hypertensive disorders in pregnancy.

2.3. Sensitivity analyses

To ensure the robustness of the findings, a series of sensitivity analyses was conducted. Cochran's Q statistic

Table 1. Description of GWAS datasets used in MR analyses investigating the relationship between mtDNA copy number and hypertensive disorders in pregnancy

Phenotypes	Consortium	Cases/ controls	Adjusted variables	PubMed ID/web source
mtDNA copy number	UK Biobank	395,718	Age, sex, chip type, 20 genetic principal components, and blood cell counts	35023831
GH	FinnGen consortium	9,535/211,957	Age, genotyping batch, 10 principal components	https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_O15_GESTAT_HYPERT.gz
EH	FinnGen consortium	2,527/211,957	Age, genotyping batch, 10 principal components	https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_O15_EXIST_HYPERT _COMPLIC.gz
PE	FinnGen consortium	7,377/211,957	Age, genotyping batch, 10 principal components	https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_O15_PREECLAMPS.gz
POE	FinnGen consortium	7,965/211,957	Age, genotyping batch, 10 principal components	https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_O15_PRE_OR_ECLAMPSIA.gz

Abbreviations: EH: Pre-existing hypertension complicating pregnancy; GH: Gestational hypertension; GWAS: Genome-wide association study; MR: Mendelian randomisation; mtDNA: mitochondrial DNA; PE: Pre-eclampsia; POE: Pre-eclampsia or eclampsia.

was applied to assess heterogeneity in the data.[33] The MR-Egger intercept analysis was employed to investigate horizontal pleiotropy.[34] To determine whether any single SNP disproportionately affected the outcomes, a leave-one-out analysis was employed. Furthermore, reverse MR analyses were conducted to assess the potential reverse causal relationship between mtDNA copy number and hypertensive disorders in pregnancy, complementing the findings from the forward MR analysis. All analyses employed R (version 4.2.0) and RStudio (version 2022.02.2, Inc., USA), utilizing the R packages "TwoSampleMR" and "MR-PRESSO."

3. Results

3.1. Genetic IVs for mtDNA copy number

A total of 6,694 SNPs associated with genome-wide significance ($p<5 \times 10^{-8}$) were initially identified. After excluding 6,628 SNPs due to high linkage disequilibrium ($r^2 > 0.001$) based on a reference panel, 66 independent SNPs were retained for the primary analysis (Table S1). Following the removal of SNPs associated with potential confounders, 51 IVs were used for EH, 50 for GH, 51 for PE, and 51 for POE. Using the IVW method, mtDNA copy number was found to be significantly correlated with POE (OR [95% CI] = 0.738 [0.578 – 0.943], p=0.015) and PE (OR [95% CI] = 0.735 [0.563 – 0.960]; p=0.024) (Table 2).

3.2. Sensitivity analysis

Instrumental heterogeneity was observed in the analysis of mtDNA copy number effects on GH, as indicated by Cochran's Q test ($p<0.05$; Table 2). The MR-PRESSO method was employed to identify and eliminate outlier SNPs with significant heterogeneity, thereby enhancing the robustness of the results. The MR-Egger intercept analysis revealed no evidence of horizontal pleiotropy. Scatter plots showed the causal effects of mtDNA copy number on hypertensive disorders in pregnancy across the five MR approaches, with a positive or negative relationship indicated by the direction of the slope (Figure 2). The leave-one-out analysis suggested that no specific SNPs exerted a disproportionate influence on the overall causal estimates (Figure S1). Leave-one-out analyses for the reverse MR are presented in Figure S2.

3.3. Reverse MR analysis

In the reverse MR study examining the link between hypertensive disorders in pregnancy and mtDNA copy number, 11 SNPs were utilized for GH, 4 for EH, 4 for PE, and 5 for POE (Table S2). The results provided no evidence of a reverse causal link between hypertensive disorders in pregnancy and mtDNA copy number (Table 3).

4. Discussion

This study provides evidence of a significant causal relationship between mtDNA copy number and hypertensive disorders in pregnancy, particularly PE and its related phenotypes. Through rigorous MR analysis, this study demonstrated that a higher mtDNA copy number considerably lowers the probability of developing these disorders. This discovery highlights mtDNA copy number as a useful biomarker for identifying women at higher risk, offering new insights into the prevention and management of these prevalent pregnancy complications.

The observed protective association may be explained by the essential role of mitochondria in energy metabolism and oxidative stress regulation during pregnancy. Elevated

Table 2. MR estimates assessing the relationship between genetically predicted mtDNA copy number and the risk of hypertensive disorders in pregnancy

Outcome	No. of SNPs	Methods	ORa	95% CI	*p*-value	MR-Egger intercept (p)	Cochran's Q-test		Outliers (MR-PRESSO) b
							Q	*p*-value	
GH	50	IVW	0.753	0.565 – 1.003	0.052	0.239	99.947	<0.001*	rs77261872
		Weighted median	0.667	0.400 – 1.113	0.127				
		MR-Egger	1.099	0.554 – 2.180	0.789				
		Weighted mode	0.733	0.525 – 1.024	0.069				
EH	51	IVW	0.827	0.535 – 1.280	0.395	0.850	63.474	0.095	NA
		Weighted median	0.731	0.323 – 1.652	0.454				
		MR-Egger	0.908	0.315 – 2.617	0.859				
		Weighted mode	0.793	0.440 – 1.429	0.441				
PE	51	IVW	0.735	0.563 – 0.960	0.024*	0.245	66.160	0.052	NA
		Weighted median	0.754	0.363 – 1.568	0.454				
		MR-Egger	1.041	0.551 – 1.966	0.902				
		Weighted mode	0.797	0.553 – 1.150	0.225				
POE	51	IVW	0.738	0.578 – 0.943	0.015*	0.210	61.905	0.120	NA
		Weighted median	0.839	0.594 – 1.185	0.320				
		MR-Egger	1.041	0.581 – 1.865	0.894				
		Weighted mode	0.859	0.452 – 1.634	0.645				

Notes: [a]The ORs represent the odds ratios per 1-standardized unit increase in the mtDNA copy number. [b]MR-PRESSO was employed to detect and correct potential outlier variants. The detected outlier, if any, is presented. *$p<0.05$.
Abbreviations: CI: Confidence interval; EH: Pre-existing hypertension complicating pregnancy; GH: Gestational hypertension; IVW: Inverse variance weighting; MR: Mendelian randomization; mtDNA: mitochondrial DNA; NA: Not applicable; OR: Odds ratio; PE: Pre-eclampsia; POE: Pre-eclampsia or eclampsia; SNPs: Single nucleotide polymorphisms.

mtDNA copy number is typically a cellular response to increased metabolic demands or oxidative stress, suggesting enhanced mitochondrial activity to support placental development. In contrast, lower mtDNA copy numbers may reflect mitochondrial dysfunction or insufficient adaptation to oxidative stress, potentially contributing to the pathogenesis of hypertensive disorders in pregnancy.

Recent studies have also suggested that infections, such as COVID-19 and the Zika virus, may exacerbate the risk of hypertensive disorders during pregnancy.[35] Research has shown that these viral infections can lead to inflammatory responses that impact mitochondrial function, potentially influencing the development of preeclampsia and other hypertensive disorders in pregnancy.[34] In particular, maternal COVID-19 has been linked to increased oxidative stress, which could affect placental function and contribute to endothelial dysfunction.[36] Similarly, the Zika virus has raised concerns regarding its indirect effects on placental health and maternal vascular adaptation.[37]

Nutritional and therapeutic interventions, such as betaine and inositol supplementation, have emerged as potential therapeutic strategies for improving pregnancy outcomes, including reducing the risk of hypertensive disorders. Betaine is involved in key methylation processes crucial for placental development and fetal health. Inositol, particularly myoinositol, has been associated with improved metabolic regulation during pregnancy, lung maturation, and breast tissue development—factors contributing to favorable pregnancy outcomes.[38]

Previous studies have demonstrated that impaired mitochondrial function can lead to endothelial dysfunction, inflammation, and increased vascular resistance, all of which are characteristic features of PE. Barron *et al.* demonstrated that maternal serum from PE patients alters mitochondrial dynamics and promotes inflammation through interleukin-6 modulation, indicating that compromised mitochondrial integrity is a direct contributor to the vascular and inflammatory pathology of PE.[39] McCarthy and Kenny demonstrated that mitochondrial metabolism in endothelial cells can be significantly disrupted by PE plasma mediators, resulting in increased mitochondrial reactive oxygen species production—a trigger for endothelial dysfunction and inflammation.[40] Correia *et al.* further explored the role of placental mitochondrial function in angiogenesis and endothelial regulation, emphasizing that mitochondrial

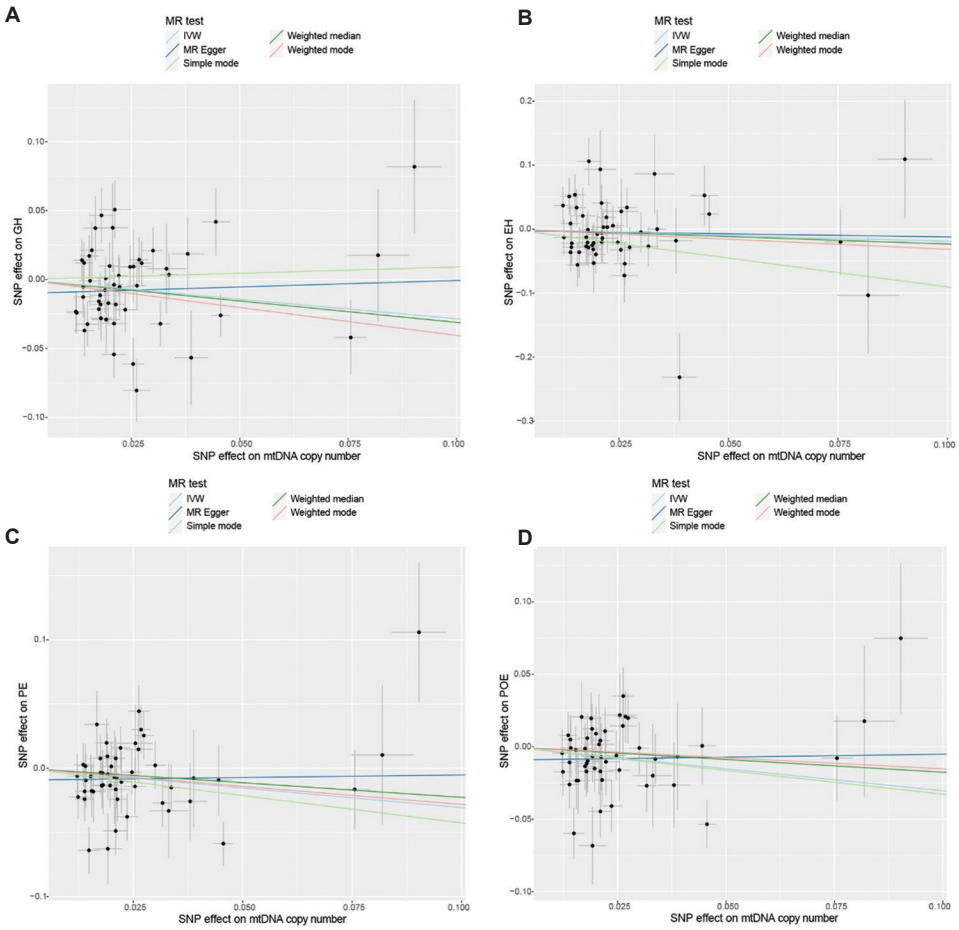

Figure 2. The forward MR analyses showing scatter plots of the association between mtDNA copy number and hypertensive disorders in pregnancy. Plots for GH (A), EH (B), PE (C), and POE (D) were derived using five MR approaches.
Abbreviations: EH: Pre-existing hypertension complicating pregnancy; GH: Gestational hypertension; IVW: Inverse variance weighting; MR: Mendelian randomisation; mtDNA: mitochondrial DNA; PE: Pre-eclampsia; POE: Pre-eclampsia or eclampsia; SNPs: Single nucleotide polymorphisms.

adaptations or dysfunctions can impact vascular health and contribute to PE development by increasing anti-angiogenic factors such as sFlt-1.[41] In addition, mitochondrial dysfunction has been implicated in insufficient trophoblast invasion and abnormal spiral artery remodeling – two processes critical to the pathogenesis of PE.[42,43] These findings reinforce the plausibility of the causal link identified in our MR study.

The MR analysis in this study demonstrates that higher mtDNA copy numbers are significantly associated with a reduced risk of PE. This is consistent with the findings of Busnelli *et al.*, who observed higher mtDNA copy numbers in controls compared to PE-IUGR cases.[44] Both studies suggest that increased mtDNA copy number may mitigate oxidative stress and inflammation early in pregnancy, promoting healthier placental development. These converging findings highlight the potential of mtDNA copy number as a predictive biomarker and point to the importance of mitochondrial-targeted interventions in reducing PE risk.

Conversely, the findings of Pandey *et al.* present an apparent contradiction, as they found an association between higher mtDNA copy and early-onset PE, suggesting an adaptive response of mitochondria to higher oxidative stress.[45] This discrepancy could be attributed to differences in study design. While Pandey *et al.* employed an observational approach, our study used MR analysis to establish causality. Furthermore, the differences in sample type (placental tissue vs. peripheral blood) and timing of sample collection could contribute to the observed variations in results.

Taken together, the alignment with Busnelli *et al.* and contrast with Pandey *et al.* underscore the complexity of mtDNA dynamics in the pathophysiology of PE. These variations highlight the need for further investigation to

Table 3. Reverse MR estimates assessing the associations of hypertensive disorders in pregnancy and genetically predicted mtDNA copy number

Exposure	No. of SNPs	Methods	ORa	95% CI	*p*-value	MR-Egger intercept (p)	Cochran's Q test		Outliers (MR-PRESSO) b
							Q	*p*-value	
GH	11	IVW	1.005	0.992 – 1.018	0.476	0.864	6.897	0.735	NA
		Weighted median	1.011	0.991 – 1.033	0.311				
		MR-Egger	1.001	0.957 – 1.047	0.969				
		Weighted mode	1.011	0.993 – 1.029	0.244				
EH	4	IVW	1.002	0.991 – 1.014	0.673	0.764	0.632	0.889	NA
		Weighted median	1.005	0.989 – 1.021	0.602				
		MR-Egger	1.011	0.961 – 1.064	0.710				
		Weighted mode	1.004	0.991 – 1.017	0.554				
PE	4	IVW	0.986	0.945 – 1.029	0.525	0.331	5.956	0.051	NA
		Weighted median	1.010	0.979 – 1.043	0.569				
		MR-Egger	0.814	0.605 – 1.096	0.308				
		Weighted mode	1.010	0.979 – 1.042	0.524				
POE	5	IVW	0.987	0.951 – 1.025	0.491	0.878	15.167	0.004*	rs12567119
		Weighted median	1.013	0.982 – 1.045	0.461				
		MR-Egger	0.964	0.726 – 1.279	0.814				
		Weighted mode	1.010	0.981 – 1.039	0.508				

Notes: [a]The ORs represent the odds ratios per 1-standardised unit increase in the mtDNA copy number. [b]MR-PRESSO was employed to detect and correct for potential outlier variants. The detected outlier, if any, is presented. *$p<0.05$.
Abbreviations: CI: Confidence interval; EH: Pre-existing hypertension complicating pregnancy; IVW: Inverse variance weighting; GH: Gestational hypertension; MR: Mendelian randomization; mtDNA: mitochondrial DNA; NA: Not applicable; OR: Odds ratio; PE: Pre-eclampsia; POE: Pre-eclampsia or eclampsia; SNPs: Single nucleotide polymorphisms.

elucidate how mtDNA copy number modulates disease risk, particularly with respect to onset timing, severity, and placental versus systemic mitochondrial profiles. A deeper understanding of these mechanisms will be critical to developing targeted diagnostic and therapeutic approaches.

Several limitations of this investigation must be acknowledged. First, the validity of causal inference in MR studies depends on specific assumptions, including the absence of horizontal pleiotropy. Although we employed various strategies (e.g., MR-Egger, MR-PRESSO) to test and account for pleiotropy, the complete elimination of residual confounding cannot be guaranteed. Second, this study focused solely on genetic determinants of mtDNA copy number; non-genetic influences, such as environmental exposures, lifestyle factors, and coexisting conditions, were not considered. Future research should integrate these components into their analyses in order to provide a more comprehensive understanding of the multifactorial nature of hypertensive disorders in pregnancy.

5. Conclusion

This research provides strong evidence for a potential causal link between higher mtDNA copy number and a reduced risk of PE. Additional investigation is warranted to elucidate the underlying biological mechanisms and validate these results in diverse populations. Ultimately, this work lays the foundation for the development of personalized prevention and intervention strategies aimed at PE.

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Conflict of interest

The authors declare there are no competing interests, including potential ones, to disclose in relation to the publication of this paper.

Author contribution

Conceptualization: Lunzhi Liu, Ke Yi
Data curation: Lunzhi Liu, Ao Wang
Formal analysis: Lunzhi Liu
Methodology: Lunzhi Liu, Ke Yi

Writing – original draft: Lunzhi Liu, Ao Wang
Writing – review & editing: Lunzhi Liu, Ke Yi

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Data is available from the corresponding author upon reasonable request.

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