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ORIGINAL RESEARCH

Causal Effects of Endometriosis Stages on Adverse Pregnancy and Perinatal Outcomes: A Mendelian Randomization Study

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Purpose: This mendelian randomization (MR) study aimed to investigate whether endometriosis, overall and stratified by stage (I/II vs III/IV), confers causal effects on adverse pregnancy and perinatal outcomes.

Methods: Exposure data came from FinnGen for ASRM-staged endometriosis (stage I/II and III/IV) and the largest cross-ancestry GWAS meta-analysis of endometriosis, while 12 adverse pregnancy outcomes from FinnGen or GWAS catalog were defined by ICD codes. The inverse variance weighted (IVW) method was used for primary estimates, and sensitivity analyses including heterogeneity tests, horizontal pleiotropy tests, and leave-one-out analyses were performed using R packages.

Results: The IVW analysis revealed that endometriosis was causally associated with an increased risk of intrahepatic cholestasis of pregnancy (ICP) [odds ratio (OR) 1.29, 95% confidence interval (CI) 1.01–1.64, p = 0.045] and premature rupture of membranes [OR 1.14, 95% CI 1.01–1.29, p = 0.028]. The advanced stages of endometriosis (III–IV) (OR 1.24, 95% CI 1.06–1.44, p = 0.006) play a more prominent role in increasing the risk of ICP compared to early stages (I–II) (OR 1.16, 95% CI 0.94–1.43, p = 0.159). However, no significant causal relationships were found between endometriosis and other adverse pregnancy outcomes. Sensitivity analyses indicated most results were robust without pleiotropy (p>0.05), except for significant heterogeneity in premature separation of placenta across stages and potential horizontal pleiotropy in gestational hypertension.

Conclusion: Our findings suggest stage III/IV endometriosis as an independent causal factor for ICP, necessitating intensified hepatobiliary function monitoring in these patients. The lack of causal association between endometriosis and other obstetric complications highlights the multifactorial nature of adverse pregnancy outcomes. Future multicenter studies should explore biomarkers reflecting endometriosis-associated hepatobiliary dysfunction to guide targeted interventions.

Keywords: endometriosis, endometriosis stages, pregnancy complications, perinatal outcomes, Mendelian randomization

Introduction

Endometriosis is a prevalent gynecological disorder affecting approximately 10% of reproductive-aged women worldwide, characterized by the growth of endometrial tissue outside the uterine cavity.[1] This condition not only leads to severe pelvic pain and discomfort but is also associated with reproductive challenges, including infertility, miscarriage, and other pregnancy-related complications.[2–5] The burden of endometriosis extends beyond physical symptoms, incurring psychosocial well-being and imposing significant economic costs on affected individuals and healthcare systems.[4] Current treatment options, including pharmacological interventions, surgical management, and assisted reproductive technologies, have limitations regarding efficacy, side effects, and suitability for patients at different disease stages.[6] Therefore, there is a pressing need for more comprehensive research to identify effective intervention strategies and management practices.[7]

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While the association between endometriosis and infertility is well-established, its potential impact on pregnancy outcomes remains controversial.[8] Observational studies and meta-analyses have reported associations between endometriosis and adverse pregnancy and perinatal outcomes.[9] However, the conclusions of these studies have not been consistent. Some meta-analyses report significant associations with miscarriage, preterm birth (PTB), placenta previa, small for gestational age (SGA) infants, and gestational diabetes mellitus (GDM),[10–12] while others find no statistically significant relationships after adjusting for confounders.[13] Despite these findings, there is still no consensus on these effects due to potential confounding biases and methodological flaws in previous studies. Notably, the potential differential effects across endometriosis stages (I–IV) remain poorly characterized. Understanding these relationships is critical for developing targeted clinical management strategies and informing patients about potential risks during pregnancy. This research gap underscores the importance of elucidating the impact of endometriosis on pregnancy outcomes across different disease stages.

Mendelian randomization (MR) provides a robust solution to these limitations by leveraging genetic variants as IVs to establish causal inferences while minimizing confounding.[14,15] In our MR study, a two-sample MR approach was used to elucidate the causal relationship between endometriosis and adverse pregnancy and perinatal outcomes. This study aims to test the following causal hypotheses: (1) Overall endometriosis is causally associated with increased risk of adverse pregnancy and perinatal outcomes; (2) Endometriosis stages exert differential causal effects on these outcomes, with advanced stages (III/IV) having stronger associations with adverse outcomes than early stages (I/II). It is acknowledged that Mendelian randomization estimates of causal effects are valid only under the specific assumptions that the genetic instruments are robustly associated with endometriosis, and not associated with confounders or any pathways to the outcome independent of the exposure. Our study aims to clarify the impact of endometriosis on reproductive health and outcomes, ultimately aiming to improve clinical practices and patient care in managing this complex condition. The outcomes of this research may inform the development of more personalized and targeted treatment strategies, significantly improving the quality of life for women affected by endometriosis.

Methods

To investigate the relationship between endometriosis and adverse pregnancy outcomes, we conducted a stage-stratified two-sample Mendelian randomization analysis. To ensure robust evidence for associations, we selected the FinnGen biobank as the outcome database, as it hosts the most comprehensive GWAS dataset for these outcomes, including 12 adverse pregnancy outcomes. Subsequently, exposure GWAS data were obtained via the IEU Open GWAS database (https://gwas.mrcieu.ac.uk/). Furthermore, as the FinnGen biobank is the only accessible GWAS database classifying endometriosis into the ASRM (American Society for Reproductive Medicine) stages I–II and ASRM stages III–IV, we used its stage-stratified endometriosis GWAS data as the exposure variable in the second part of the study and selected genetic variants that were strongly associated with the aforementioned 12 adverse pregnancy outcomes on the GWAS Catalog (https://www.ebi.ac.uk/gwas/). An overview of the research design is presented in Figure 1.

MR Assumptions

MR estimates causal effects only when three core assumptions are satisfied: (1) the genetic instruments are strongly associated with the exposure; (2) the genetic instruments are not associated with confounding factors that affect both endometriosis and adverse pregnancy outcomes; (3) the genetic instruments influence adverse pregnancy outcomes only through endometriosis.

Data Source

Saori et al conducted the largest cross-ancestry GWAS meta-analysis of endometriosis, involving 4511 cases and 227,260 controls.[16] We selected this GWAS dataset as the exposure data for endometriosis to support further analyses. Additionally, we collected GWAS data of endometriosis ASRM stages I–II (with 7061 cases and 247,557 controls) and endometriosis ASRM stages III–IV (with 9150 cases and 245,468 controls) from the FinnGen database. The details are presented in Table 1.

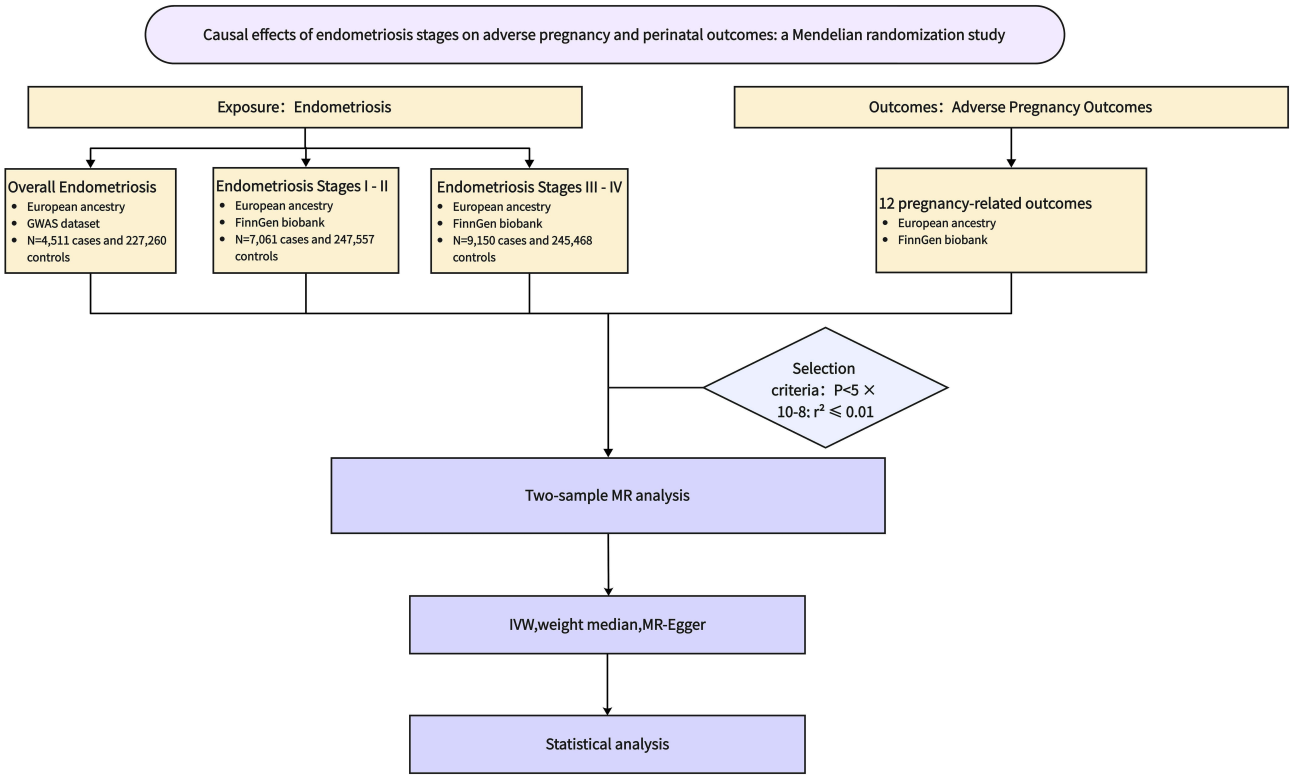

Figure 1 Study design of Mendelian randomization between endometriosis and adverse pregnancy outcomes. The number of SNPs remaining after each filtering step is indicated in the boxes. Arrows (→) indicate the flow to the next step. The cross symbol indicates the exclusion of SNPs.
Abbreviations: IVW, inverse variance weighted; MR, Mendelian randomization.

We investigated 12 pregnancy-related outcomes, including spontaneous abortion, gestational diabetes, hypertensive disorders, and postpartum depression, using data from FinnGen. These outcomes were defined based on International Classification of Diseases (ICD) codes. These datasets are presented in Table 1, which includes gestational hypertension (with 4255 cases and 114,735 controls), gestational diabetes (5687 cases and 117,892 controls), intrahepatic cholestasis of pregnancy (940 cases and 122,639 controls), placenta praevia (596 cases and 104,247 controls), polyhydramnios (547 cases and 104,247 controls), postpartum depression (7604 cases and 59,601 controls), postpartum haemorrhage (3670 cases and 98,626 controls), premature rupture of membranes (3011 cases and 104,247 controls), premature separation of placenta (294 cases and 104,247 controls), pre-eclampsia or eclampsia (3903 cases and 114,735 controls), placental disorders (102 cases and 104,247 controls), and spontaneous abortion (9113 cases and 89,340 controls). Additionally, after acquiring exposure data (FinnGen's stage-stratified endometriosis data), we retrieved outcome data for the 12 adverse pregnancy outcomes from the GWAS Catalog (https://www.ebi.ac.uk/gwas/). However, only 6 GWAS data contained enough details for further MR analysis (Table 1). The data used in this study were derived from the FinnGen database and publicly available data in the GWAS Catalog. For the Ethics approval MR analysis in this study, we ensured no overlap between the populations of the exposure dataset and the outcome dataset. All information regarding the population sources is presented in Table 1, and details related to the study setting and population context can be accessed via the FinnGen database and the GWAS Catalog website.

Instrument Variable Selection

In this study, we used LD-based methods to identify SNP characteristics for valid instrument variables (IVs). For MR analysis, IVs must meet three criteria: (1) SNPs significantly associated with endometriosis at genome-wide significance ($p < 5 \times 10^{-8}$); (2) pairwise linkage disequilibrium (LD) $< r^2 \leq 0.01$ to exclude correlated variants; (3) F-statistic > 10 per SNP to minimize weak instrument bias. F-statistic was calculated by $R^2 \times (N - k - 1)/[(1 - R^2) \times k]$, where N was the GWAS sample size, k was the number of SNPs, and R^2 showed the variability of endometriosis explained by each SNP.[17] The detailed

Table 1 Summary Information on Data Used in MR Studies

Finn ID/GWAS ID	Exposure/Outcome	Source	Case	Control	Number of SNPs	Population
ebi-a-GCST90018839	Endometriosis	https://gwas.mrcieu.ac.uk/	4511	227,260	24,089,752	European
N14_ENDOMETRIOSIS_ASRM_STAGE1_2	Endometriosis ASRM stage I/II	https://r11.finngen.fi/	7061	247,557	21,300,352	European
N14_ENDOMETRIOSIS_ASRM_STAGE3_4	Endometriosis ASRM stage III/IV	https://r11.finngen.fi/	9150	245,468	21,300,352	European
finn-b-GEST_DIABETES	Gestational diabetes	https://gwas.mrcieu.ac.uk/	5687	117,892	16,379,784	European
finn-b-O15_GESTAT_HYPERT	Gestational hypertension	https://gwas.mrcieu.ac.uk/	4255	114,735	16,379,648	European
finn-b-O15_ICP	Intrahepatic Cholestasis of Pregnancy	https://gwas.mrcieu.ac.uk/	940	122,639	16,379,784	European
finn-b-O15_PLAC_DISORD	Placental disorders	https://gwas.mrcieu.ac.uk/	102	104,247	16,379,357	European
finn-b-O15_PLAC_PRAEVIA	Placenta praevia	https://gwas.mrcieu.ac.uk/	596	104,247	16,379,382	European
finn-b-O15_PRE_OR_ECLAMPSIA	Pre-eclampsia or eclampsia	https://gwas.mrcieu.ac.uk/	3903	114,735	16,379,723	European
finn-b-O15_MEMBR_PREMAT_RUPT	Premature rupture of membranes	https://gwas.mrcieu.ac.uk/	3011	104,247	16,379,429	European
finn-b-O15_PLAC_PREMAT_SEPAR	Premature separation of placenta	https://gwas.mrcieu.ac.uk/	294	104,247	16,379,367	European
finn-b-O15_POLYHYDR	Polyhydramnios	https://gwas.mrcieu.ac.uk/	547	104,247	16,379,375	European
finn-b-O15_POSTPART_DEPR	Postpartum depression	https://gwas.mrcieu.ac.uk/	7604	59,601	16,376,275	European
finn-b-O15_POSTPART_HEAMORRH	Postpartum haemorrhage	https://gwas.mrcieu.ac.uk/	3670	98,626	16,379,289	European
finn-b-O15_ABORT_SPONTAN	Spontaneous abortion	https://gwas.mrcieu.ac.uk/	9113	89,340	16,379,138	European
GCST90043951	Gestational diabetes	https://www.ebi.ac.uk/gwas/	864	6977	11,831,065	European
GCST90454232	Gestational hypertension	https://www.ebi.ac.uk/gwas/	9071	284,968	18,300,146	European
GCST90095084	Intrahepatic cholestasis of pregnancy	https://www.ebi.ac.uk/gwas/	1138	153,642	7,591,169	European
GCST90301704	Preeclampsia	https://www.ebi.ac.uk/gwas/	1728	192,399	8,481,769	European
GCST90454238	Premature rupture of membranes	https://www.ebi.ac.uk/gwas/	13,342	261,265	18,300,032	European
GCST90454240	Premature separation of placenta	https://www.ebi.ac.uk/gwas/	1065	268,941	18,300,019	European

information of all selected instrumental variables is provided in Supplementary Table 1. SNPs linked to exposure were retrieved from outcome data (adverse pregnancy and perinatal outcomes). To reduce the possible bias from population heterogeneity, all the GWAS consortia employed in our MR study were restricted to those of European ancestry.

MR Analysis

Analyses were performed using the "TwoSampleMR" package (version 0.6.7) in R software (version 4.4.1). The "TwoSampleMR" package offered five useful methods. The Inverse-Variance Weighted (IVW) method was favored as the primary one due to its variance-handling ability. The simple mode provided basic insights, the weighted mode enhanced precision by considering SNP weights, the weighted median balanced extreme values, and the MR-Egger regression accounted for confounding factors. For IVW analysis, heterogeneity was assessed using Cochran's Q test: If $p > 0.05$ (homogeneous data), a fixed-effects model was used; If $p \leq 0.05$ (heterogeneous data), a random-effects model was applied. A two-tailed $p < 0.05$ was considered statistically significant for causal associations. Multiple testing correction was not applied in this study, as we used a stringent genome-wide significance threshold ($P < 5\times10^{-8}$) to select genetic instruments—this threshold inherently reduces the risk of false-positive results from multiple outcome analyses, and over-correction may increase the risk of false-negative findings for clinically meaningful associations.

Sensitivity Analyses

The MR design was based on three assumptions, including correlation with exposure, independence from confounders, and exclusion of restrictions unrelated to outcome. To test them, we did sensitivity analyses, including: (1) Heterogeneity tests (Cochran's Q test) to assess consistency across SNPs; (2) Horizontal pleiotropy tests (MR-Egger intercept) to detect variants affecting outcomes via non-exposure pathways (significant when $p < 0.05$); (3) Leave-one-out analysis to evaluate the influence of individual SNPs by recalculating estimates after removing each SNP sequentially.

Results

In this study, we employed a two-sample MR approach to investigate the causal effects of endometriosis on various adverse pregnancy and perinatal outcomes. The instrumental variables (IVs) for endometriosis were selected based on GWAS summary statistics, ensuring that the SNPs used were strongly associated with endometriosis ($p < 5\times10^{-8}$) and

satisfied the criteria for linkage equilibrium ($r^2 < 0.01$). The F-statistics for all IVs were above 10, indicating that the instruments were sufficiently strong to avoid weak instrument bias. However, due to the limited number of SNPs significantly associated with endometriosis (ebi-a-GCST90018839), we relaxed the significance threshold to $p < 5\times10^{-6}$ for IVs selection. Detailed genetic information on selected GWAS datasets were showed in Table 1, while detailed genetic information on selected SNPs were showed in Supplemental Table 1.

Impact of Endometriosis on Adverse Pregnancy Outcomes

Using the IVW method as the primary analysis approach, we investigated the causal relationship between endometriosis and 12 adverse pregnancy outcomes. The results indicated that endometriosis, as a whole, was causally associated with an increased risk of intrahepatic cholestasis of pregnancy (ICP) [odds ratio (OR) 1.29, 95% confidence interval (CI) 1.01–1.64, p = 0.045] and premature rupture of membranes [OR 1.14, 95% CI 1.01–1.29, p = 0.028]. However, no significant causal relationships were found between endometriosis and other adverse pregnancy outcomes, such as postpartum haemorrhage (OR 1.02, 95% CI 0.91–1.15, p = 0.693), placenta praevia (OR 1.12, 95% CI 0.87–1.45, p = 0.381), gestational hypertension (OR 1.04, 95% CI 0.93–1.16, p = 0.506), gestational diabetes (OR 1.03, 95% CI 0.95–1.13, p = 0.480), premature separation of placenta (OR 1.15, 95% CI 0.80–1.66, p = 0.455), pre-eclampsia or eclampsia (OR 0.94, 95% CI 0.84–1.05, p = 0.280), polyhydramnios (OR 1.09, 95% CI 0.83–1.42, p = 0.527), postpartum depression (OR 0.99, 95% CI 0.91–1.08, p = 0.834), spontaneous abortion (OR 1.04, 95% CI 0.96–1.12, p = 0.321), placental disorders (OR 0.76, 95% CI 0.41–1.40, p = 0.375). (Figure 2, detailed MR estimates are provided in Supplementary Table 2).

To address potential confounding factors, for the MR analysis of endometriosis and ICP, we removed rs144241592 due to its close relation to weight and BMI, which could confound the causal relationship. When exploring endometriosis and premature rupture of membranes, we removed rs11202704, as it was closely associated with smoking initiation according to https://ldlink.nih.gov, to minimize smoking-related confounding. To evaluate the impact of exclusion, we compared the effect sizes and p-values before and after removal, and no qualitative changes in significance ($p < 0.05$) were observed for any exposure-outcome pair. This indicates that the excluded SNPs had minimal impact on the overall results, confirming the robustness of our instrument selection. Sensitivity analyses, including leave-one-out (Supplementary Figure 1), scatter (Supplementary Figure 2), and funnel plots (Supplementary Figure 3), supported these findings. The forest plots for all outcomes are shown in Supplementary Figure 4.

Impact of Endometriosis Stages I–II and III–IV on Adverse Pregnancy Outcomes

When analyzing the impact of different endometriosis stages on adverse pregnancy outcomes, we found distinct results. For endometriosis stages I–II, there was no significant causal relationship with any of the 12 adverse pregnancy outcomes (Figure 3, detailed MR estimates are provided in Supplementary Table 3).

In contrast, endometriosis stages III/IV were causally associated with an increased risk of ICP (OR 1.24, 95% CI 1.06–1.44, p = 0.006). Sensitivity analyses in stage-stratified analyses showed no significant heterogeneity for most outcomes, consistent with the overall findings. These results suggested that advanced endometriosis (III–IV) plays a more prominent role in increasing the risk of ICP compared to early stages (I–II) (Figure 4, detailed MR estimates are provided in Supplementary Table 4). When investigating the relationship between stage III/IV endometriosis and adverse pregnancy outcomes, we removed SNPs associated with ICP pathogenesis from https://ldlink.nih.gov to minimize confounding, including rs1209731, which was associated with a hypercoagulable state; rs11031005, which was linked to sex hormone levels and spontaneous dizygotic twinning; and rs4849124, which was related to allergic diseases such as asthma, hay fever, or eczema. The removal of these SNPs helped prevent the distortion of the true causal relationship, especially in relation to ICP. While stage III/IV endometriosis is associated with ICP, preterm premature rupture of membranes (PROM) is only associated with endometriosis as an overall exposure (regardless of disease stage).

Sensitivity Analyses

A series of sensitivity analyses were conducted to assess the robustness of our MR findings. Cochran's Q test was used to evaluate the heterogeneity of IVs. For most of the causal effects, no significant heterogeneity was observed ($p > 0.05$).

Exposure	Outcome	No.of SNP	Method	P	OR(95% CI)
Endometriosis	Gestational diabetes	19	MR Egger	0.306	0.87 (0.68 to 1.12)
			Weighted median	0.205	1.08 (0.96 to 1.23)
			Inverse variance weighted	0.480	1.03 (0.94 to 1.13)
			Simple mode	0.202	1.17 (0.93 to 1.49)
			Weighted mode	0.203	1.17 (0.93 to 1.47)
Endometriosis	Gestational hypertension	19	MR Egger	0.022	1.45 (1.09 to 1.95)
			Weighted median	0.554	1.05 (0.90 to 1.21)
			Inverse variance weighted	0.506	1.04 (0.93 to 1.16)
			Simple mode	0.950	1.01 (0.75 to 1.36)
			Weighted mode	0.709	1.05 (0.81 to 1.36)
Endometriosis	Intrahepatic Cholestasis of Pregnancy	18	MR Egger	0.018	2.46 (1.26 to 4.81)
			Weighted median	0.062	1.33 (0.99 to 1.81)
			Inverse variance weighted	0.045	1.28 (1.01 to 1.64)
			Simple mode	0.348	1.30 (0.77 to 2.19)
			Weighted mode	0.184	1.34 (0.89 to 2.02)
Endometriosis	Placental disorders	19	MR Egger	0.848	0.84 (0.14 to 4.97)
			Weighted median	0.787	0.89 (0.39 to 2.03)
			Inverse variance weighted	0.375	0.76 (0.41 to 1.40)
			Simple mode	0.681	1.40 (0.29 to 6.82)
			Weighted mode	0.723	1.30 (0.32 to 5.32)
Endometriosis	Placenta praevia	19	MR Egger	0.332	0.68 (0.32 to 1.44)
			Weighted median	0.655	0.92 (0.64 to 1.33)
			Inverse variance weighted	0.381	1.12 (0.87 to 1.45)
			Simple mode	0.338	0.70 (0.35 to 1.41)
			Weighted mode	0.364	0.73 (0.37 to 1.42)
Endometriosis	Preeclampsia or eclampsia	19	MR Egger	0.201	1.24 (0.90 to 1.70)
			Weighted median	0.348	0.93 (0.80 to 1.08)
			Inverse variance weighted	0.280	0.94 (0.84 to 1.05)
			Simple mode	0.220	0.84 (0.65 to 1.10)
			Weighted mode	0.449	0.91 (0.71 to 1.16)
Endometriosis	Premature rupture of membranes	18	MR Egger	0.676	0.93 (0.66 to 1.31)
			Weighted median	0.175	1.12 (0.95 to 1.32)
			Inverse variance weighted	0.028	1.14 (1.01 to 1.29)
			Simple mode	0.408	1.12 (0.86 to 1.46)
			Weighted mode	0.502	1.09 (0.85 to 1.39)
Endometriosis	Premature separation of placenta	19	MR Egger	0.398	0.63 (0.22 to 1.80)
			Weighted median	0.305	1.32 (0.78 to 2.23)
			Inverse variance weighted	0.455	1.15 (0.80 to 1.66)
			Simple mode	0.388	1.57 (0.58 to 4.27)
			Weighted mode	0.406	1.57 (0.56 to 4.44)
Endometriosis	Polyhydramnios	19	MR Egger	0.446	0.73 (0.34 to 1.60)
			Weighted median	0.836	0.96 (0.67 to 1.39)
			Inverse variance weighted	0.527	1.09 (0.83 to 1.42)
			Simple mode	0.676	0.87 (0.44 to 1.68)
			Weighted mode	0.670	0.87 (0.47 to 1.61)
Endometriosis	Postpartum depression	19	MR Egger	0.392	1.12 (0.87 to 1.43)
			Weighted median	0.696	0.98 (0.88 to 1.09)
			Inverse variance weighted	0.834	0.99 (0.91 to 1.08)
			Simple mode	0.814	1.02 (0.83 to 1.26)
			Weighted mode	0.900	0.99 (0.81 to 1.21)
Endometriosis	Postpartum haemorrhage	19	MR Egger	0.693	1.07 (0.76 to 1.50)
			Weighted median	0.993	1.00 (0.85 to 1.17)
			Inverse variance weighted	0.693	1.02 (0.91 to 1.14)
			Simple mode	0.678	1.06 (0.80 to 1.42)
			Weighted mode	0.598	1.08 (0.82 to 1.40)
Endometriosis	Spontaneous abortion	19	MR Egger	0.540	1.07 (0.86 to 1.34)
			Weighted median	0.964	1.00 (0.91 to 1.11)
			Inverse variance weighted	0.321	1.04 (0.96 to 1.12)
			Simple mode	0.945	1.01 (0.84 to 1.21)
			Weighted mode	0.842	0.98 (0.84 to 1.16)

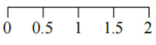

Figure 2 Forest plot for the impact of endometriosis on adverse pregnancy and perinatal outcomes.
Abbreviations: OR, odds ratio; SNP, single-nucleotide polymorphism; IVW, inverse-variance weighted.

Exposure	Outcome	No.of SNP	Method	P	OR(95% CI)
Endometriosis ASRM STAGE I/II	Gestational diabetes	15	MR Egger	0.968	1.02 (0.36 to 2.92)
			Weighted median	0.942	1.01 (0.73 to 1.40)
			Inverse variance weighted	0.861	1.02 (0.81 to 1.29)
			Simple mode	0.987	1.00 (0.59 to 1.72)
			Weighted mode	0.976	0.99 (0.60 to 1.63)
Endometriosis ASRM STAGE I/II	Gestational hypertension	15	MR Egger	0.347	0.83 (0.58 to 1.20)
			Weighted median	0.623	0.98 (0.89 to 1.07)
			Inverse variance weighted	0.922	1.00 (0.91 to 1.08)
			Simple mode	0.964	1.00 (0.84 to 1.18)
			Weighted mode	0.851	0.99 (0.86 to 1.14)
Endometriosis ASRM STAGE I/II	Intrahepatic cholestasis of pregnancy	14	MR Egger	0.314	0.64 (0.28 to 1.47)
			Weighted median	0.288	1.15 (0.89 to 1.49)
			Inverse variance weighted	0.159	1.16 (0.94 to 1.43)
			Simple mode	0.806	0.94 (0.56 to 1.57)
			Weighted mode	0.829	0.96 (0.64 to 1.43)
Endometriosis ASRM STAGE I/II	Preeclampsia	15	MR Egger	0.252	0.68 (0.35 to 1.28)
			Weighted median	0.908	0.99 (0.80 to 1.22)
			Inverse variance weighted	0.716	0.97 (0.84 to 1.13)
			Simple mode	0.493	1.15 (0.78 to 1.69)
			Weighted mode	0.743	0.94 (0.65 to 1.35)
Endometriosis ASRM STAGE I/II	Premature rupture of membranes	15	MR Egger	0.062	1.31 (1.01 to 1.71)
			Weighted median	0.650	1.02 (0.94 to 1.11)
			Inverse variance weighted	0.579	1.02 (0.95 to 1.09)
			Simple mode	0.718	0.97 (0.82 to 1.14)
			Weighted mode	0.271	1.08 (0.95 to 1.23)
Endometriosis ASRM STAGE I/II	Premature separation of placenta	15	MR Egger	0.084	2.67 (0.95 to 7.49)
			Weighted median	0.197	1.20 (0.91 to 1.59)
			Inverse variance weighted	0.280	1.15 (0.89 to 1.48)
			Simple mode	0.445	1.19 (0.78 to 1.82)
			Weighted mode	0.391	1.19 (0.81 to 1.76)

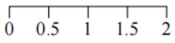

Figure 3 Forest plot for the impact of endometriosis Stages I–II on adverse pregnancy and perinatal outcomes.
Abbreviations: OR, odds ratio; SNP, single-nucleotide polymorphism; IVW, inverse-variance weighted.

However, when it came to the associations between different stage of endometriosis and premature separation of placenta, significant heterogeneity was observed. Specifically, for endometriosis stage I/II and premature separation of placenta, the p-value was 0.037. Similarly, for endometriosis stage III/IV and premature separation of placenta, the p-value was also less than 0.05. These results indicated significant heterogeneity in these two stage-stratified associations (Table 2).

MR-Egger regression detected horizontal pleiotropy. Most relationships showed non-significant intercept terms ($p > 0.05$), suggesting no pleiotropic bias. Notably, the association between endometriosis and gestational hypertension had a significant MR-Egger intercept (p-value = 0.027), indicating potential horizontal pleiotropy (Table 2).

Leave-one-out analysis was performed by stepwise elimination of each IV. No single SNP was found to have a dominant influence on the overall MR estimates for most outcomes. However, for the association between endometriosis and premature rupture of membranes, one SNP slightly affected the result, but the overall causal relationship remained significant. For stage-stratified analyses, the sensitivity plots—including leave-one-out, scatter, forest, and funnel plots—are provided in Supplementary Figures 5–8 for stage I/II and Supplementary Figures 9–12 for stage III/IV. The complete lists of instrumental variables used in the Mendelian randomization analyses for each specific adverse pregnancy outcome are provided in Supplementary Tables 5–16.

Discussion

Endometriosis is a prevalent gynecological disorder characterized by the growth of endometrial-like tissue outside the uterine cavity, affecting approximately 10% of women of reproductive age.[18] Previous studies have established

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Exposure	Outcome	No.of SNP	Method	P	OR(95% CI)
Endometriosis ASRM STAGE III/IV	Gestational diabetes	27	MR Egger	0.399	1.26 (0.74 to 2.13)
			Weighted median	0.409	1.11 (0.87 to 1.42)
			Inverse variance weighted	0.737	1.03 (0.86 to 1.23)
			Simple mode	0.717	1.10 (0.67 to 1.79)
			Weighted mode	0.548	1.12 (0.77 to 1.65)
Endometriosis ASRM STAGE III/IV	Gestational hypertension	27	MR Egger	0.216	0.91 (0.78 to 1.05)
			Weighted median	0.491	0.98 (0.91 to 1.05)
			Inverse variance weighted	0.579	1.01 (0.96 to 1.07)
			Simple mode	0.573	0.96 (0.84 to 1.10)
			Weighted mode	0.438	0.96 (0.87 to 1.06)
Endometriosis ASRM STAGE III/IV	Intrahepatic cholestasis of pregnancy	22	MR Egger	0.632	0.88 (0.54 to 1.46)
			Weighted median	0.176	1.16 (0.93 to 1.45)
			Inverse variance weighted	0.006	1.24 (1.06 to 1.44)
			Simple mode	0.675	1.10 (0.70 to 1.74)
			Weighted mode	0.988	1.00 (0.66 to 1.53)
Endometriosis ASRM STAGE III/IV	Preeclampsia	26	MR Egger	0.339	0.85 (0.61 to 1.18)
			Weighted median	0.093	0.88 (0.75 to 1.02)
			Inverse variance weighted	0.785	0.98 (0.88 to 1.10)
			Simple mode	0.262	0.83 (0.61 to 1.14)
			Weighted mode	0.167	0.85 (0.67 to 1.06)
Endometriosis ASRM STAGE III/IV	Premature rupture of membranes	27	MR Egger	0.472	1.06 (0.91 to 1.24)
			Weighted median	0.356	1.03 (0.96 to 1.10)
			Inverse variance weighted	0.670	1.01 (0.96 to 1.07)
			Simple mode	0.724	1.03 (0.89 to 1.19)
			Weighted mode	0.481	1.05 (0.92 to 1.20)
Endometriosis ASRM STAGE III/IV	Premature separation of placenta	27	MR Egger	0.585	1.18 (0.65 to 2.15)
			Weighted median	0.480	1.08 (0.87 to 1.34)
			Inverse variance weighted	0.524	1.07 (0.87 to 1.30)
			Simple mode	0.734	1.07 (0.74 to 1.54)
			Weighted mode	0.615	1.07 (0.82 to 1.41)

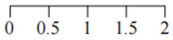

Figure 4 Forest plot for the impact of endometriosis Stages III–IV on adverse pregnancy and perinatal outcomes.
Abbreviations: OR, odds ratio; SNP, single-nucleotide polymorphism; IVW, inverse-variance weighted.

a correlation between endometriosis and adverse pregnancy outcomes, but the exact nature of these relationships remains unclear. Understanding the intricate relationship between endometriosis and pregnancy outcomes is essential for developing effective management strategies and improving patient care. The present Mendelian randomization study provides novel genetic evidence supporting stage-specific causal relationships between endometriosis and pregnancy-related complications. Our findings demonstrate that advanced-stage endometriosis (III/IV) exhibits a causal effect on ICP, while no significant associations were observed for other adverse pregnancy/perinatal outcomes across all stages. These results refine our understanding of endometriosis-related reproductive risks and emphasize the importance of disease progression in mediating specific pathological pathways.

This study revealed a significant causal association between advanced-stage (III–IV) endometriosis and the development of ICP, whereas no significant association was observed for early-stage (I–II) disease. Previous retrospective studies have reported elevated ICP risk in endometriosis patients, yet the stage-specific risk profile remained unexplored.[19] The association may be explained by estrogen hypersensitivity and impaired hepatobiliary function in women with endometriosis. Endometriosis has been linked to altered estrogen metabolism and liver enzyme dysfunction, which may predispose to abnormal bile acid accumulation during pregnancy. Endometriosis patients often present with elevated estrogen levels and progesterone resistance,[2] and the hyperestrogenic state during pregnancy may suppress hepatic membrane transporter functions,[20] thereby inducing cholestasis. The amplified inflammatory milieu and estrogen-driven metabolic perturbations characteristic of stage III/IV endometriosis appear to potentiate bile acid homeostasis disruption, thereby elevating susceptibility to ICP, particularly dysregulated cyclooxygenase-2 (COX-2) and estrogen receptor α (ERα) pathway activation.[21] The findings demonstrate a stage-dependent association between endometriosis severity and gestational hepatic dysfunction, with advanced-stage disease (III/IV) showing progressive deterioration that

Table 2 MR Results of Heterogeneity and Directional Pleiotropy

id.exposure	id.outcome	Outcome	Heterogeneity			Pleiotropy		
			Q	Q *df*	Q p-value	Intercept	SE	p-value
ebi-a-GCST90018839	finn-b-GEST_DIABETES	Gestational diabetes	12.961	18	0.794	0.025	0.018	0.184
ebi-a-GCST90018839	finn-b-O15_GESTAT_HYPERT	Gestational hypertension	21.646	18	0.248	−0.050	0.021	0.027
ebi-a-GCST90018839	finn-b-O15_ICP	Intrahepatic Cholestasis of Pregnancy	23.213	17	0.142	−0.098	0.049	0.061
ebi-a-GCST90018839	finn-b-O15_PLAC_DISORD	Placental disorders	10.900	18	0.899	−0.015	0.126	0.908
ebi-a-GCST90018839	finn-b-O15_PLAC_PRAEVIA	Placenta praevia	16.743	18	0.541	0.073	0.053	0.184
ebi-a-GCST90018839	finn-b-O15_PRE_OR_ECLAMPSIA	Pre-eclampsia or eclampsia	22.380	18	0.216	−0.041	0.022	0.084
ebi-a-GCST90018839	finn-b-O15_MEMBR_PREMAT_RUPT	Premature rupture of membranes	11.971	17	0.802	0.031	0.025	0.226
ebi-a-GCST90018839	finn-b-O15_PLAC_PREMAT_SEPAR	Premature separation of placenta	18.387	18	0.430	0.089	0.074	0.247
ebi-a-GCST90018839	finn-b-O15_POLYHYDR	Polyhydramnios	17.915	18	0.461	0.058	0.055	0.303
ebi-a-GCST90018839	finn-b-O15_POSTPART_DEPR	Postpartum depression	20.596	18	0.300	−0.018	0.017	0.326
ebi-a-GCST90018839	finn-b-O15_POSTPART_HEAMORRH	Postpartum haemorrhage	20.454	18	0.308	−0.007	0.024	0.777
ebi-a-GCST90018839	finn-b-O15_ABORT_SPONTAN	Spontaneous abortion	20.786	18	0.290	−0.005	0.016	0.760
N14_ENDOMETRIOSIS_ASRM_STAGE1_2	GCST90043951	Gestational diabetes	14.108	14	0.442	0.000	0.074	0.998
N14_ENDOMETRIOSIS_ASRM_STAGE1_2	GCST90454232	Gestational hypertension	23.547	14.000	0.052	0.026	0.026	0.345
N14_ENDOMETRIOSIS_ASRM_STAGE1_2	GCST90095084	Intrahepatic cholestasis of pregnancy	16.376	13.000	0.229	0.087	0.060	0.175
N14_ENDOMETRIOSIS_ASRM_STAGE1_2	GCST90301704	Preeclampsia	14.344	14.000	0.424	0.052	0.046	0.273
N14_ENDOMETRIOSIS_ASRM_STAGE1_2	GCST90044479	Preeclampsia and eclampsia	12.860	14.000	0.538	−0.122	0.118	0.320
N14_ENDOMETRIOSIS_ASRM_STAGE1_2	GCST90436545	Preeclampsia and eclampsia	10.520	13.000	0.651	0.019	0.111	0.869
N14_ENDOMETRIOSIS_ASRM_STAGE1_2	GCST90454238	Premature rupture of membranes	18.495	14.000	0.185	−0.036	0.018	0.072
N14_ENDOMETRIOSIS_ASRM_STAGE1_2	GCST90454240	Premature separation of placenta	24.738	14.000	0.037	−0.120	0.073	0.122
N14_ENDOMETRIOSIS_ASRM_STAGE3_4	GCST90296696	Gestational diabetes	29.557	26.000	0.286	−0.010	0.010	0.345
N14_ENDOMETRIOSIS_ASRM_STAGE3_4	GCST90043951	Gestational diabetes	20.545	26.000	0.765	−0.029	0.037	0.437
N14_ENDOMETRIOSIS_ASRM_STAGE3_4	GCST90454232	Gestational hypertension	25.350	26.000	0.499	0.016	0.010	0.133
N14_ENDOMETRIOSIS_ASRM_STAGE3_4	GCST90095084	Intrahepatic cholestasis of pregnancy	20.541	21.000	0.487	0.049	0.035	0.180
N14_ENDOMETRIOSIS_ASRM_STAGE3_4	GCST90301704	Preeclampsia	22.241	25.000	0.622	0.022	0.023	0.357
N14_ENDOMETRIOSIS_ASRM_STAGE3_4	GCST90454238	Premature rupture of membranes	39.253	26.000	0.046	−0.007	0.011	0.538
N14_ENDOMETRIOSIS_ASRM_STAGE3_4	GCST90454240	Premature separation of placenta	51.812	26.000	0.002	−0.015	0.042	0.720

correlates with elevated maternal-fetal morbidity risks. This biological gradient underscores the necessity for stage-stratified clinical surveillance to mitigate adverse outcomes in severe endometriosis pregnancies. Additionally, the relationship between endometriosis and ICP should be further explored to elucidate the specific pathways involved, potentially opening avenues for targeted therapeutic interventions.

Observational studies have yielded conflicting evidence regarding endometriosis and adverse pregnancy outcomes, with reported associations ranging from elevated risks of placenta previa, preterm delivery, and hypertensive disorders to null findings.[8,22] These inconsistencies likely arise from inherent limitations in observational designs, particularly residual confounding by ART utilization, conception delays, and endometriosis-associated comorbidities. The inherent fertility disparity across endometriosis subtypes introduces selection bias, particularly as stage III/IV cases exhibit 2.3-fold elevated infertility rates relative to early-stage disease, thereby systematically modifying the clinical population attaining pregnancy.[23] This study employs Mendelian randomization to elucidate the causal effects of different stages and locations of endometriosis on adverse pregnancy and perinatal outcomes. By leveraging genetic variants as instrumental variables, we aim to mitigate confounding factors and enhance the reliability of our findings.[24] This methodological approach bolsters the causative inference regarding the impact of endometriosis on adverse pregnancy outcomes while minimizing the influence of unmeasured confounders, thereby providing a more robust framework for understanding the disease's implications during pregnancy.

Our Mendelian randomization study provides novel genetic evidence supporting the causal effect of endometriosis on PROM. The primary analysis demonstrated a 14% increased risk of PROM per genetic predisposition to endometriosis (OR 1.14, 95% CI 1.01–1.29). Evidence from a large-scale cohort encompassing 2,854,149 women, including 4006 cases with endometriosis, demonstrated a statistically significant correlation between PROM and endometriosis.[25] Specifically, for women with histologically confirmed endometriosis, an elevated risk of preterm premature rupture of membranes (PPROM) prior to 32 gestational weeks was reported.[26] A meta-analysis further indicated that endometriosis is associated with a 2.3-fold increased risk of PROM.[27] While no MR studies have directly investigated the endometriosis-PROM relationship, a prior MR analysis revealed no significant causal link between endometriosis and preterm birth.[28] However, no significant causal relationships were observed in MR analyses when stratified by disease stage (ASRM - stage I–II or ASRM-stage III/IV endometriosis). This is likely due to the The American Fertility Society (rAFS) staging system focusing on surgical observations such as lesion size and adhesions, where genetic heterogeneity across stages may be weaker than clinical phenotypic differences.[29] Despite the null stage-specific findings, the robust genetic evidence for an overall causal association between endometriosis and PROM highlights that endometriosis should be recognized as a risk factor for PROM irrespective of clinical stage. Endometriosis is characterized by a systemic inflammatory environment and altered immune response, which may predispose to PROM through matrix degradation and fetal membrane weakening, irrespective of anatomical stage. Although a significant association with PROM was observed in the "overall endometriosis" analysis, this association sometimes failed to reach statistical significance in subgroup analyses stratified by disease stage (eg, stages III/IV). This likely does not indicate that advanced-stage disease is unrelated, but rather reflects diminished statistical power due to reduced sample size after stratification, thereby limiting the ability to detect existing associations. Results of the present MR analyses did not detect stage-specific causal effects, the established overall genetic link supports a generalized risk profile; however, the nuanced mechanisms underlying stage-independent vs stage-dependent associations warrant further clarification through large-scale prospective studies with detailed phenotypic stratification.

Furthermore, the presented results revealed no causal associations between endometriosis and the 10 investigated adverse pregnancy outcomes (including gestational hypertension, medication-induced abortion, spontaneous abortion, pre-eclampsia, eclampsia, placenta previa, postpartum hemorrhage, etc), aligning with Yan Huang et al's MR findings of no significant causal links between endometriosis and abortion subtypes.[30] Sensitivity analyses indicated potential horizontal pleiotropy in gestational hypertension. Notably, gestational hypertension, preeclampsia, and eclampsia all fall under the category of Hypertensive Disorders of Pregnancy (HDP), representing distinct sequential stages in the progression of this disease spectrum. Conflicting evidence exists regarding endometriosis and HDP. Yizheng Zu et al identified a significant association between advanced-stage endometriosis (ASRM stage III/IV) and pre-eclampsia.[31] However, the study did not explicitly disclose the GWAS datasets utilized in their analysis. To address this discrepancy,

we systematically queried three pre-eclampsia/eclampsia GWAS datasets (GCST90301704, GCST90044479, GCST90436545) from the GWAS Catalog (https://www.ebi.ac.uk/gwas/) as outcome to establish a MR analysis, but found no significant causal links between endometriosis (unstaged or stage-stratified) and pre-eclampsia or eclampsia. Notably, clinical studies investigating this relationship have yielded conflicting conclusions.[10,32] Given these discrepancies and the absence of robust evidence from our MR analyses, we cannot conclude a significant causal relationship between endometriosis and HDP. Consequently, the issue of pleiotropy associated with gestational hypertension does not exert a significant impact on our study conclusions.

Although significant heterogeneity was observed in the analyses of endometriosis and premature separation of placenta, which weakened the reliability of the conclusion of negative association, the results from Supplementary Tables 2–4 revealed that no association between endometriosis and placental abruption indicated by analytical methods other than the IVW approach—including simple mode, weighted mode, MR-Egger, and weighted median. Therefore, based on the data included in this study, we cannot conclude a significant causal relationship between endometriosis and premature separation of placenta. Further studies integrating well-phenotyped cohorts and standardized disease staging are warranted to resolve these inconsistencies.

The strength of our study lies in the stratification of MR analyses by disease stage of endometriosis. Our results demonstrated a meaningful causal relationship between advanced-stage endometriosis (ASRM stage III–IV) and ICP, whereas early-stage endometriosis (ASRM stage I–II) failed to reveal significant associations. This stratified approach offers critical insights into the etiological contributions of severe endometriosis to adverse pregnancy outcomes, highlighting the necessity of incorporating disease severity and lesion distribution into future causal inference frameworks. In conclusion, our study underscores the importance of recognizing the stage-dependent impacts of endometriosis on pregnancy, particularly regarding the risk of ICP. These insights not only inform clinical management strategies for women with endometriosis but also highlight the necessity for ongoing research into the pathophysiological mechanisms underlying these relationships. Addressing the gaps in knowledge regarding the effects of endometriosis on a broader spectrum of pregnancy outcomes will ultimately contribute to improved care for affected individuals and their families.[33]

The limitations of this study include a relatively small sample size, which may impact the generalizability of the results. Notably, for rare outcomes (eg, placental abruption, n = 102), the statistical power may be insufficient to detect small effect sizes, which should be considered when interpreting the non-significant results for these outcomes. Additionally, the lack of clinical validation analyses raises concerns about the robustness of the findings, as the diversity of the dataset could introduce inter-study variability. Furthermore, potential confounding factors that were not accounted for may still influence the observed relationships between endometriosis stages and adverse pregnancy outcomes. Moreover, the significance threshold to $p < 5\times10^{-6}$ for IVs selection for endometriosis (ebi-a-GCST90018839) due to the limited number of SNPs, which may increase the risk of including weak instruments and false-positive associations. However, sensitivity analyses to verify the robustness of results, and no weak instruments were identified. In addition, we acknowledge that analyzing multiple outcomes increases the risk of false positives. Given the exploratory nature of our study and the fact that a stringent instrument selection threshold ($p < 5\times10^{-6}$) was already applied to minimize false associations at the IV selection stage, we prioritized avoiding over-correction that might mask potentially true biological relationships. The findings should therefore be interpreted as hypothesis-generating and require validation in independent cohorts. These limitations suggest the need for cautious interpretation of the results and highlight the importance of conducting larger, multi-center studies to enhance the reliability of the conclusions drawn from this research.

Conclusions

In conclusion, this study provides valuable insights into the causal relationship between different stages of endometriosis and the risk of intrahepatic cholestasis of pregnancy, while failing to establish significant associations with other adverse pregnancy outcomes. These findings underscore the necessity for tailored clinical management strategies for patients with advanced endometriosis during pregnancy. Notably, the findings of this study are based on GWAS data from populations of European ancestry, and thus may not be directly generalizable to non-European populations due to potential differences in genetic background, environmental factors, and clinical practice patterns across ancestries. Future research

should aim to expand upon these results, exploring additional biomarkers and mechanistic pathways that may further elucidate the complexities of endometriosis and its impact on reproductive health, ultimately improving patient care.

Data Sharing Statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics Approval

All participating studies involved in the GWAS obtained informed consent from the study populations. As we utilized publicly available datasets to conduct MR, no additional ethics approval was required. A certification of ethics approval waiver was consented to by the ethics committee of the third Affiliated hospital of Sun Yat-sen University.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors state that they have no conflict of interest.

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