Heliyon 10 (2024) e35401

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

# Causal relationship between systemic lupus erythematosus and adverse pregnancy outcomes: A two-sample Mendelian randomized study☆,☆☆

Tao Zhu, Gao Zhan *, Zheng Shang, Zhao Ying

*Department of Gynecology, The Fifth Affiliated Hospital of Zhengzhou University, Zhengzhou, 450000, China*

ARTICLE INFO

*Keywords:*
Systemic lupus erythematosus
Adverse pregnancy outcome
Pre-eclampsia,causality
Mendelian randomization

ABSTRACT

*Background:* Systemic lupus erythematosus (SLE) is associated with adverse pregnancy outcome (APO). However, the genetic causality of this association remains unclear. In this study, Mendelian randomization (MR) was used to explore the potential causal relationship between SLE and APO risk.

*Methods:* We selected 45 single nucleotide polymorphisms (SNPs) associated with SLE from published genome-wide association studies (GWAS). APO's statistics are obtained from the GWAS database. MR estimates were performed using the inverse variance-weighted (IVW) method, the MR-Egger method, and the weighted median (WM) method. Sensitivity analysis was performed using Cochran's Q test, MR-Egger intercept, MR-pleiotropic residual and outlier method, stay-one analysis and funnel plot.

*Results:* The results showed a causal relationship between SLE and pre-eclampsia (OR = 1.036, 95 % confidence interval 1.006 to 1.068, P = 0.019), and no significant causal relationship was found between SLE and other adverse pregnancy outcomes, including postpartum hemorrhage, placental abruption, spontaneous abortion, premature rupture of membranes, fetal distress, gestational diabetes mellitus. These findings were robust in several sensitivity analyses.

*Conclusion:* This MR study demonstrated the causal effect of SLE on preeclampsia. It provides important clues for identifying and early predicting risk factors for preeclampsia.

## 1. Introduction

Systemic Lupus Erythematosus (SLE) is a heterogeneous autoimmune disease characterized by diverse clinical courses and outcomes. The manifestations and symptoms of this disease can range from mild to severe, potentially affecting one or multiple organ systems, and they may vary over time, making diagnosis challenging [1]. The high prevalence of SLE, its chronic nature, and the overreliance on corticosteroid therapy can lead to long-term organ damage, including life-threatening systemic organ involvement. Recent research spanning [2] regions globally estimates the worldwide incidence of SLE at 5.14 cases per 100,000 person-years [3].

Adverse Pregnancy Outcomes (APO) encompass all pathological pregnancies and childbirth-related complications. Despite

☆ In this study, Mendelian randomization (MR) was used to explore the potential causal relationship between SLE and APO risk.☆☆ Studies have found a significant genetic correlation between SLE and the risk of preeclampsia.

* Corresponding author. The Fifth Affiliated Hospital of Zhengzhou University, China.
*E-mail address:* 3595471403@qq.com (G. Zhan).

https://doi.org/10.1016/j.heliyon.2024.e35401
Received 8 December 2023; Received in revised form 27 July 2024; Accepted 29 July 2024
Available online 30 July 2024

multiple public health and medical interventions aimed at reducing APO, its incidence remains relatively high [4]. Considering the short-term and long-term adverse effects of APO on both mothers and infants, it is widely recognized as a significant public health concern. Increasing evidence suggests that SLE may play a pivotal role in the pathogenesis of APO. According to Megan et al. SLE patients face a threefold increased risk of preeclampsia, a twentyfold increase in maternal mortality, and elevated rates of infection and thrombosis [5]. Analyses conducted between 2011 and 2013 revealed lower live birth rates and increased complications among SLE pregnant women compared to non-SLE counterparts [6]. A controlled study found a significantly higher rate of fetal loss and spontaneous abortion among SLE pregnant women [7]. However, the causality of these correlations remains unclear due to potential biases, including residual confounding factors and reverse causation.

Traditional epidemiological studies frequently grapple with issues such as potential confounding factors and reverse causation, which can skew the estimation of causality. Mendelian Randomization (MR), an innovative epidemiological method, addresses these challenges by utilizing genetic variation as an instrumental variable (IV) to examine causal relationships between exposure factors and observed outcomes. This methodology capitalizes on the random allocation of single-nucleotide polymorphisms (SNPs) at conception, effectively serving as a natural randomization mechanism. Since these genetic variations are assigned randomly at conception and are generally independent of the confounding variables that often plague observational studies, MR is inherently protected against reverse causation.

In this study, we utilized a two-sample MR analysis to assess the causal relationship between Systemic Lupus Erythematosus (SLE) and seven common Adverse Pregnancy Outcomes (APOs), namely, postpartum hemorrhage (PPH), placental abruption (AP), spontaneous abortion (SAB), premature rupture of membranes (PROM), fetal distress (FD), gestational diabetes mellitus (GDM), and preeclampsia (PE). To our knowledge, this investigation is pioneering in its exploration of the causal influence of SLE on the development of these pregnancy complications, potentially setting a foundation for targeted interventions and improved management strategies in pregnant women afflicted with SLE.

## 2. Materials and methods

### 2.1. Data sources

We obtained the genome-wide association study (GWAS) dataset for Systemic Lupus Erythematosus from the IEU database (IEU OpenGWAS project, mrcieu.ac.uk) [8]. GWAS summary data for Postpartum Hemorrhage, Placental Abruption, Spontaneous Abortion, Premature Rupture of Membranes, Gestational Diabetes Mellitus, Fetal Distress, and Preeclampsiawere sourced from the FinnGen consortium's GWAS results. Detailed information regarding the cohorts involved, genotyping, endpoint definitions, and association testing can be accessed on the FinnGen website. Specific details are provided in Table 1.

### 2.2. Experimental design

As depicted in Fig. 1, our study aims to investigate the role of Systemic Lupus Erythematosus (SLE) in Adverse Pregnancy Outcomes (APO). To achieve this objective, we conducted Mendelian Randomization (MR) analyses utilizing genome-wide association study (GWAS) data from two separate samples. When applying MR analysis, to mitigate the impact of bias on research outcomes, we ensured the fulfillment of three fundamental assumptions:1. The chosen Instrumental Variable (IV) shows a significant association with SLE. The strength of each genetic instrument is evaluated using the F-statistic: $F=R2 \times (N-2)/(1-R2)$; $R2 = 2 \times EAF \times (1-EAF) \times \beta 2$ [9]. In this formula, R2 refers to the cumulative explained variance of the selected IVs on SLE and EAF denoting the effect allele frequency, β indicating the estimated effect of SNP, and N refers to the sample size of the GWAS. An F-statistic value greater than 10 suggests that the IV robustly predicts the outcome. 2. IV is independent of other confounding factors.3. IV exclusively influences the outcome through the exposure factor [10].

### 2.3. Instrumental variable selection

To identify instrumental variables that satisfy the three core MR assumptions, we conducted a series of screening processes. First, we selected independent single nucleotide polymorphisms (SNPs) that were closely associated with SLE and had p-values less than $5 \times 10\hat{}-8$. Next, we used PLINK clumping to exclude SNPs in linkage disequilibrium ($r\hat{}2 < 0.001$, kb = 10,000) [11]. In cases where the

**Table 1**
Details of the GWAS included in the Mendelian randomization.

| GWAS ID | Trait | Case | Control | Number of SNPs | Population |
|---|---|---|---|---|---|
| ebi-a-GCST003156 | Systemic lupus erythematosus | 5201 | 9066 | 7,071,163 | European |
| finn-b-O15_POSTPART_HEAMORRH | Postpartum hemorrhage | 3670 | 98,626 | 16,379,289 | European |
| finn-b-O15_PLAC_PREMAT_SEPAR | Abruptio placenta | 294 | 104,247 | 16,379,367 | European |
| finn-b-O15_ABORT_SPONTAN | Spontaneous abortion | 9113 | 89,340 | 16,379,138 | European |
| finn-b-O15_MEMBR_PREMAT_RUPT | Premature rupture of membranes | 3011 | 104,247 | 16,379,429 | European |
| finn-b-GEST_DIABETES | Gestational diabetes | 5687 | 117,892 | 16,379,784 | European |
| finn-b-O15_LABOUR_FETAL_STRESS | fetal stress | 3480 | 98,626 | 16,379,258 | European |
| finn-b-O15_PREECLAMPS | Pre-eclampsia | 3556 | 114,735 | 16,379,671 | European |

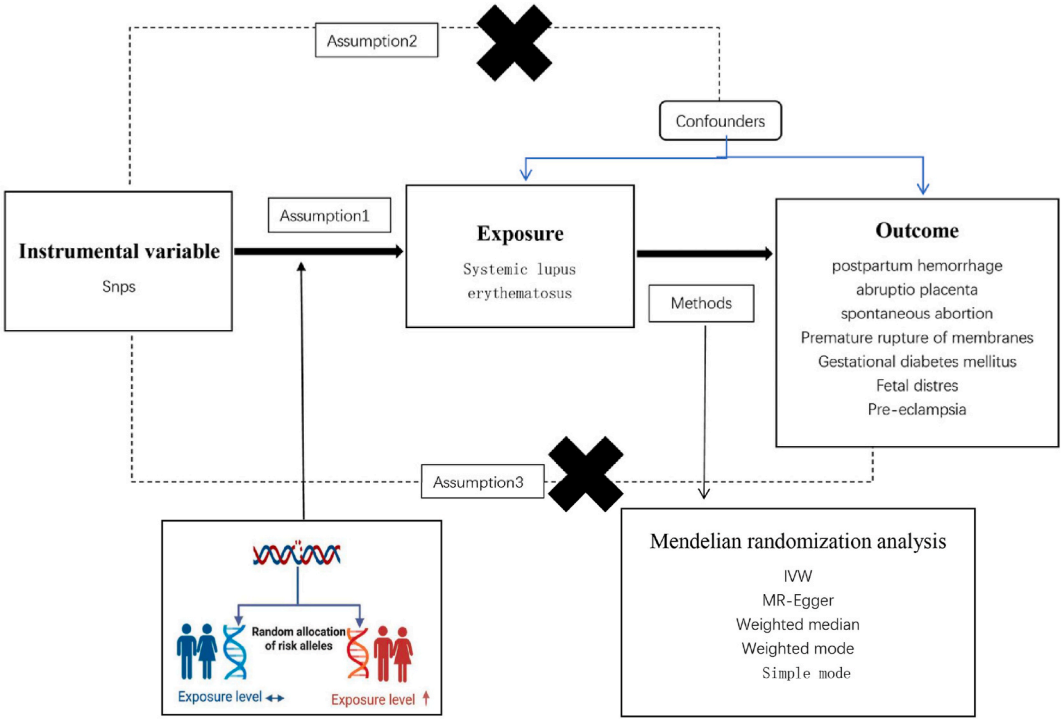


**Fig. 1.** An overview of the study design.

target SNP was not found in the GWAS results, we searched for alternative SNPs with high linkage disequilibrium (R^2 > 0.8). Finally, by harmonizing the exposure and outcome datasets, we excluded ambiguous SNPs with inconsistent allele alleles and SNPs with intermediate allele frequencies.

### *2.4. MR analysis*

In this study, we employed a variety of complementary methods to validate the robustness of our experimental results. These methods included Inverse Variance Weighting (IVW), MR-Egger regression, Weighted Median, Simple Mode, and Weighted Mode. IVW method as the primary analytical approach, was widely utilized [12]. Additionally, we used the Weighted Median and MR-Egger methods as supplementary analyses to investigate biases resulting from invalid instruments and pleiotropy [13]. For ease of interpretation, we converted the beta values of experimental results into Odds Ratios (OR) and calculated 95 % Confidence Intervals (CI).

### *2.5. Sensitivity analysis*

To ensure the reliability of our experimental results, we conducted several sensitivity analyses. Firstly, we assessed horizontal pleiotropy through MR-Egger regression, with the average pleiotropic effect represented by the intercept term in MR-Egger regression [14]. The intercept term of MR–Egger regression is increasingly used to detect the presence of pleiotropy among instrumental variables. If the linear regression intercept Egger–intercept of the MR–Egger model is close to 0 ($P > 0.05$), it suggests that there is no pleiotropy affecting the instrumental variables; In contrast, a significant intercept indicates genetic pleiotropy, thereby invalidating the exclusion restriction hypothesis.Subsequently, we evaluated heterogeneity using Cochran's Q-statistic. This statistically quantifies the degree of variance between the variables of the instrument. In this case, a P-value of less than 0.05 indicates significant heterogeneity, implying significant variation that may affect the validity of the MR analysis results. Additionally, we performed MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) analysis to detect and correct for outliers and moderate pleiotropy [15]. Finally, we employed leave-one-out analysis to examine the robustness and consistency of the results. The "leave-one-out" method refers to the gradual elimination of each SNP, calculating the meta-effect of the remaining SNPs, and observing whether the results change after each SNP is removed. All analyses were conducted using the "TwoSampleMR" and "MRPRESSO" packages in R (version 4.1.3), which are specifically designed for performing sophisticated Mendelian randomization studies and provide tools for addressing pleiotropy and other potential biases in genetic association data.

## 3. Results

### 3.1. Genetic instruments for systemic lupus erythematosus

In our study, we ultimately selected 45 important and independent single nucleotide polymorphisms (SNPs) as genetic instruments for SLE. These SNPs met the criteria for significance ($P < 5 \times 10^{-8}$) and independence (LD $r^2 < 0.001$). The F-statistics for all selected SNPs exceeded 80, indicating the absence of weak instrument bias. For detailed information about these 45 SNPs, please refer to Supplementary Table S1. Additionally, summary information on SNPs related to the association between systemic lupus erythematosus and adverse pregnancy outcomes (APO) can be found in Supplementary Tables S2.1 to S2.7.

### 3.2. Causal effects of systemic lupus erythematosus on adverse pregnancy outcomes

The results of the MR analysis are shown in Fig. 2.

The analysis did not find a significant causal relationship between SLE and the risk of postpartum hemorrhage (OR = 1.003, 95 % CI: 0.973–1.034, P = 0.841). This result was consistent with other testing methods (Fig. 3A), and there was no significant heterogeneity or horizontal pleiotropy detected in the analysis (Tables S3 and S4; Fig. S1A).

There was no evidence to suggest a causal relationship between SLE and the risk of placental abruption (OR = 1.008, 95 % CI: 0.901–1.129, P = 0.884). This result was consistent with other testing methods (Fig. 3B), and no significant heterogeneity or horizontal pleiotropy was observed in the analysis (Tables S3 and S4; Fig. S1B).

The analysis did not find a significant causal relationship between SLE and the risk of spontaneous abortion (OR = 1.001, 95 % CI: 0.980–1.021, P = 0.94), this finding is similar to that of the rest of the test methods (Fig. 3C). There was no significant heterogeneity

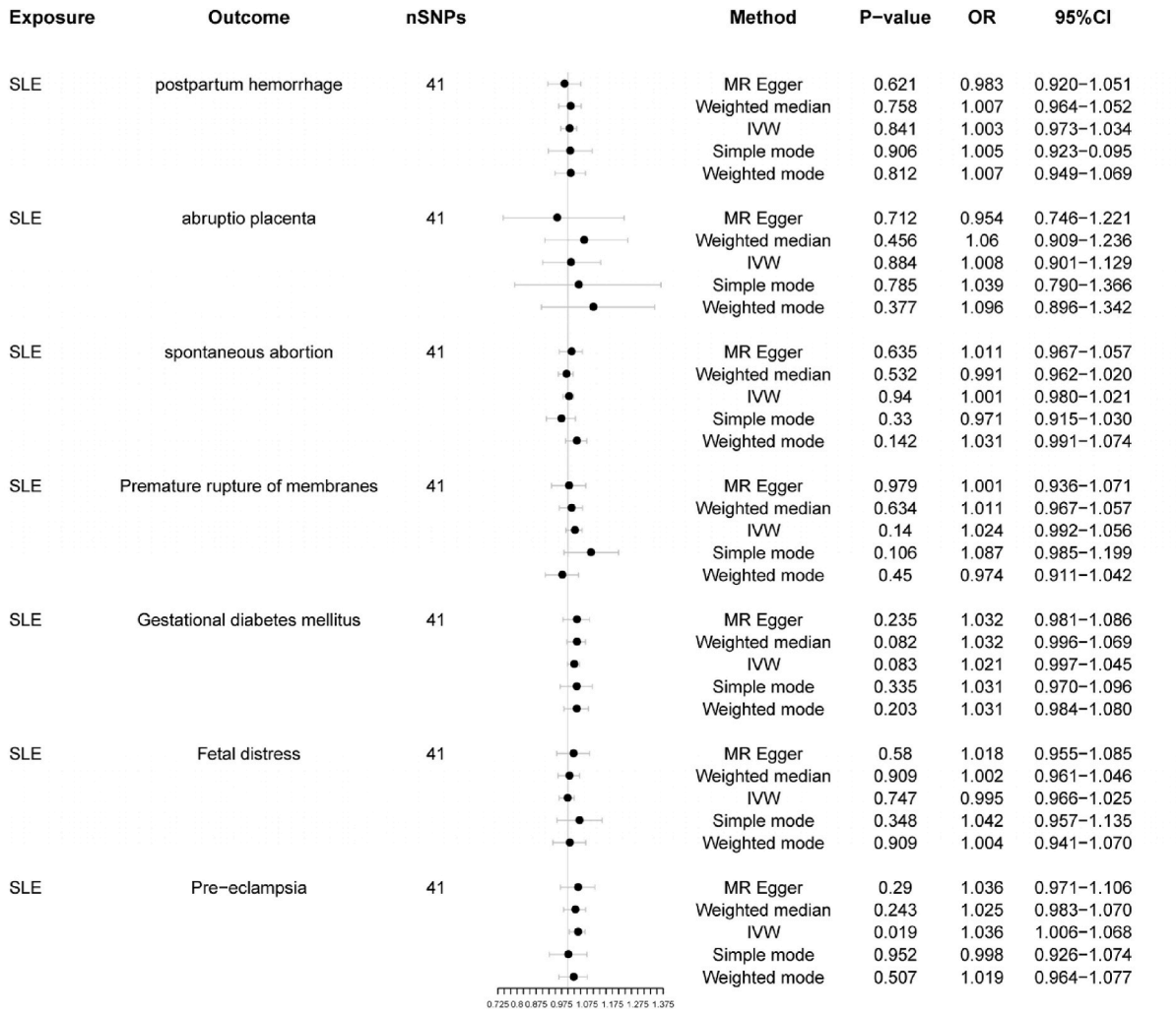


**Fig. 2.** MR results for association of SLE and APO.

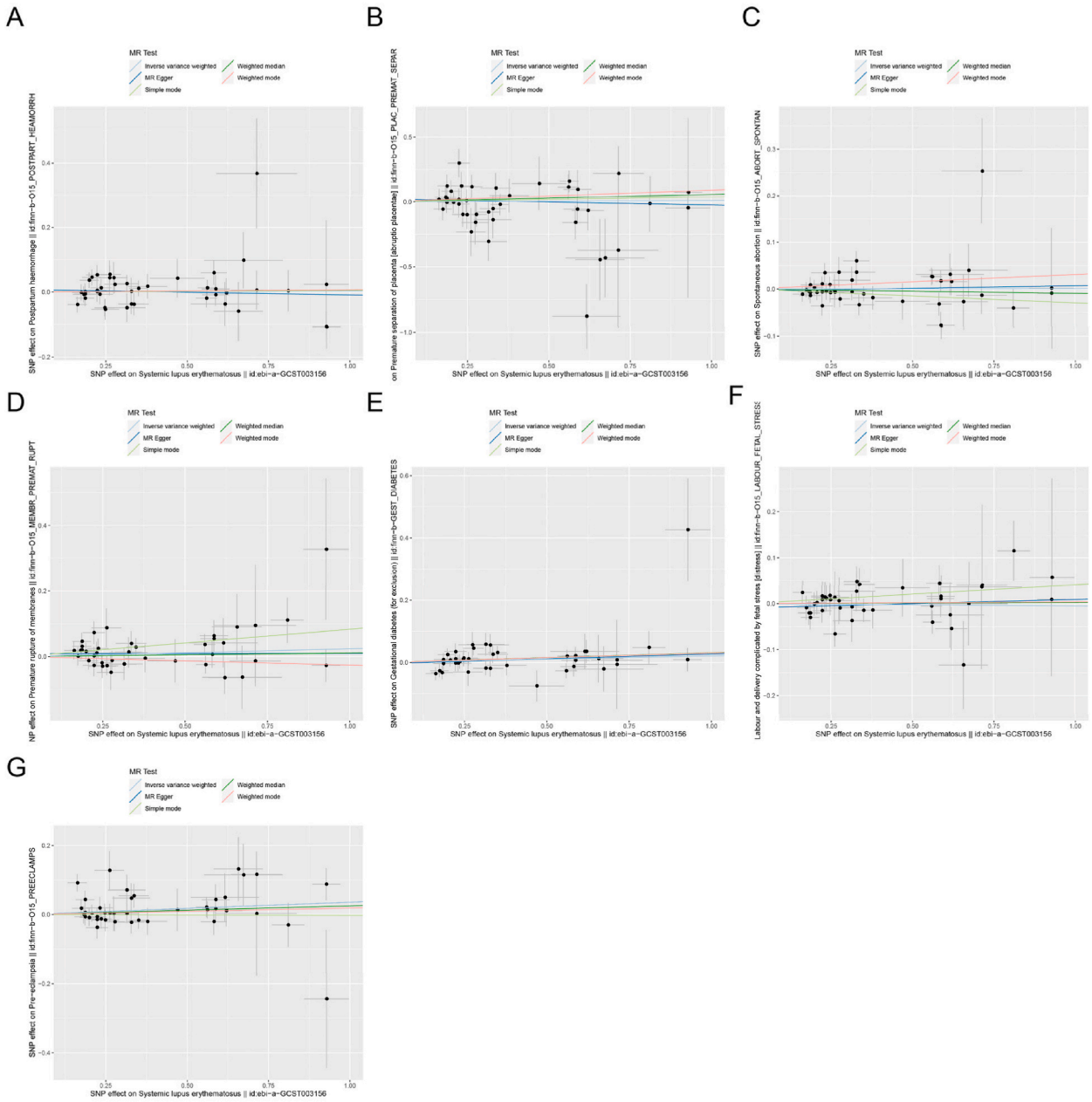


**Fig. 3.** Scatter plot of the association between SLE and Adverse Pregnancy Outcomes Postpartum hemorrhage(A), abruptio placenta (B), spontaneous abortion (C), Premature rupture of membranes (D), Gestational diabetes mellitus (E), Fetal distress (F),Pre-eclampsia(G). Five lines reveal the estimated effect sizes by MR methods.

detected in Cochran's Q test, and MR-Egger regression and MR-PRESSO did not find significant horizontal pleiotropy (Tables S3 and S4; Fig. S1C).

The analysis did not find a genetic association between SLE and premature rupture of membranes (OR = 1.024, 95 % CI: 0.992–1.056, P = 0.14). MR-Egger and Weighted Median methods also showed similar results (Fig. 3D). Various tests, including Cochran's Q test, MR-Egger regression, MR-PRESSO, and leave-one-out analysis, indicated relatively robust MR estimates (Tables S3 and S4; Fig. S1D).

The analysis did not find a significant genetic correlation between SLE and the risk of GDM (OR = 1.021, 95 % CI: 0.997–1.04, P = 0.083). MR-Egger and Weighted Median methods also yielded consistent results (Fig. 3E). Sensitivity analysis did not indicate significant horizontal pleiotropy or heterogeneity (Tables S3 and S4). Leave-one-out analysis confirmed the stability of the MR estimates (Fig. S1E).

There was no evidence to suggest a causal relationship between SLE and the risk of fetal distress (OR = 0.995, 95 % CI: 0.966–1.025, P = 0.747). Other testing methods also suggested no causal relationship (Fig. 3F). Additionally, Cochran's Q test did not detect significant heterogeneity, and MR-Egger regression (intercept P = 0.429) and MR-PRESSO (global test P = 0.926) did not find significant horizontal pleiotropy (Tables S3 and S4).

Different methods yielded different conclusions for the relationship between SLE and preeclampsia. The IVW method found a significant genetic correlation between SLE and the risk of preeclampsia (OR = 1.036, 95 % CI: 1.006–1.068, P = 0.019). However, MR-Egger (OR = 1.036, 95 % CI: 0.971–1.106, P = 0.29) and Weighted Median methods (OR = 1.025, 95 % CI: 0.983–1.070, P = 0.243) did not find a significant genetic correlation between SLE and the risk of preeclampsia (Fig. 3G). Due to the lack of significant heterogeneity (P = 0.352) or horizontal pleiotropy (intercept P = 0.998, global test P = 0.383), the IVW results were considered more reliable (Tables S3 and S4). Leave-one-out analysis also confirmed the stability of the MR estimates (Fig. S1G).Finally, the funnel plot of systemic lupus erythematosus and adverse pregnancy outcomes is shown in Fig. S2.

## 4. Discussion

In this study, we employed Mendelian randomization (MR) analysis for the first time to investigate the causal relationship between systemic lupus erythematosus and adverse pregnancy outcomes. Our research findings indicate a genetic causal relationship between SLE and preeclampsia (PE), while no significant genetic association was observed with other adverse pregnancy outcomes.

The relationship between SLE and adverse pregnancy outcomes (APOs) is an ongoing area of research, and current evidence is not yet sufficient to definitively establish a direct causal link between the two. Julia et al.'s study revealed an increased risk of early-onset preeclampsia in women with SLE, and this elevated risk appeared to be unrelated to traditional risk factors such as pre-pregnancy hypertension, antiphospholipid syndrome (APS), body mass index (BMI), or smoking [16]. A nationwide retrospective study conducted by Nicole et al. found that adolescents and young women with SLE were more prone to experiencing adverse pregnancy-specific outcomes compared to their peers, including preeclampsia/eclampsia, maternal mortality, preterm birth, spontaneous abortion, and induced abortion. Furthermore, hospitalization duration and costs were correspondingly increased [17]. In a seven-year study conducted in Shanghai, China, it was discovered that SLE significantly increased the risk of adverse pregnancy outcomes [18]. A retrospective study at a tertiary hospital in Oman indicated a correlation between pregnancies in SLE patients and a higher rate of miscarriage and gestational diabetes risk [19]. Research targeting Gullah African American women revealed that even after adjusting for age, education, number of pregnancies, and insurance coverage, SLE patients still had an increased likelihood of adverse pregnancy outcomes [20]. Our study's results align with the aforementioned research, demonstrating an increased risk of preeclampsia (PE) in individuals with SLE. MR study also indicates that there is no significant association between SLE and postpartum hemorrhage, placental abruption, spontaneous abortion, premature rupture of membranes, fetal distress, and gestational diabetes mellitus. While some studies (but not all) have observed associations between SLE and these outcomes, the inconsistent results may be attributed to confounding factors commonly present in observational studies [21]. MR analysis did not find evidence of causality between SLE and these adverse pregnancy outcomes, and sensitivity analysis suggests the robustness of these findings. Therefore, SLE may not be a causal factor for these adverse pregnancy outcomes.

Effective management of Systemic Lupus Erythematosus (SLE) during pregnancy necessitates meticulous preconception planning and thorough prenatal care. Women with SLE should ideally achieve disease remission at least six months before conception and modify or cease medications such as methotrexate and mycophenolate mofetil due to their teratogenic risks [22]. A critical component of this management strategy involves screening for anti-Ro and anti-La antibodies (anti-SSA or SSB), which significantly heighten the risk of fetal heart block, necessitating diligent fetal cardiac monitoring and proactive interventions throughout the pregnancy [23]. Regular assessments of maternal health and fetal development are crucial during pregnancy, with a particular focus on kidney function, blood pressure, and signs of disease flare-ups. Medications like prednisone and hydroxychloroquine are generally maintained to control disease activity and reduce the likelihood of flares, as they are considered safe for use during pregnancy. Additionally, prophylactic measures, including vaccinations against influenza and pneumonia, are advocated to avert infections. Postpartum care should be vigilant, with ongoing monitoring for flare-ups and adjustments in medication as necessary. Breastfeeding is encouraged unless contraindicated by specific treatments [24]. Moreover, the management of SLE during pregnancy must also take into account any comorbid gynecological conditions that could influence pregnancy outcomes, such as uterine fibroids, adenomyosis, endometriosis, and uterine malformations. For example, uterine fibroids may expand during pregnancy due to hormonal changes, potentially leading to complications such as fetal growth restriction and preterm labor, which necessitates regular ultrasound examinations [25–28]. Adenomyosis may increase the risk of miscarriage and labor complications, managed by alleviating pain and conducting regular MRI or ultrasound evaluations. While pregnancy may reduce symptoms related to endometriosis, it increases risks such as ectopic pregnancies; hence, management typically involves fertility treatments prior to pregnancy and close surveillance thereafter. Uterine anomalies, such as a bicornuate or septate uterus, elevate the risks of miscarriage and preterm delivery, which are managed through prenatal ultrasound and potentially corrective surgery prior to conception [29–31]. Overall, managing SLE during pregnancy requires a multidisciplinary approach involving rheumatologists, obstetricians specializing in high-risk pregnancies, and other healthcare professionals to ensure the safety and well-being of both mother and child. This strategy not only helps mitigate the risks associated with SLE but also promotes a healthier outcome for the pregnancy and the postpartum period.

During pregnancy, preeclampsia represents a severe pathological condition, often characterized by seizures occurring subsequent to prodromal symptoms. For both the pregnant woman and the fetus, eclampsia poses a life-threatening acute medical scenario [32]. Hence, prompt initiation of emergency therapeutic measures during eclamptic episodes is paramount to safeguarding the lives and well-being of both mother and child. Standard emergency protocols typically encompass oxygen therapy, fetal monitoring, termination

of pregnancy via the safest and least traumatic means, and prevention of complications. Delivery stands out as one of the most effective treatments for both preeclampsia and eclampsia [33]. Induction of labor is a common strategy employed in managing hypertensive disorders during pregnancy. Misoprostol, an orally administered prostaglandin at low doses, finds extensive utility in labor induction. Studies suggest an association between low-dose oral misoprostol and increased incidence of vaginal delivery, alongside a potential reduction in fetal heart rate variability induced by excessive stimulation [34]. Recent research emphasizes differential mRNA expression profiles induced by hypoxia in trophoblast cells, offering potential insights into the pathophysiological mechanisms underlying preeclampsia [35]. The uteroplacental circulation serves as the most metabolically active interface between the mother and the fetus [36], thereby rendering oxygen delivery to the fetus of paramount importance. Near-infrared spectroscopy (NIRS) emerges as a novel and relatively unexplored technique facilitating non-invasive assessment of tissue oxygenation status via continuous measurement of microcirculatory levels of available oxygen. NIRS presents a novel direct approach for measuring intra-placental oxygenation, boasting safety and relatively objective advantages [37,38].

Our study has, for the first time, provided clear evidence of a direct genetic causal relationship between systemic lupus erythematosus (SLE) and preeclampsia (PE), consistent with previous observational research. SLE patients are more prone to developing preeclampsia compared to the general population, and the reasons behind this association may include the following:1. Abnormal/Chronic Inflammation: Abnormal or chronic inflammation is considered a major pathogenic mechanism for PE. In PE, Th1-type immunity and pro-inflammatory cytokines play a dominant role [39]. Furthermore, an increase in Th17 cells, a decrease in Treg cells, and abnormal activation of antigen-presenting cells (such as monocytes, macrophages, and dendritic cells) have been observed [3,40]. SLE, as a severe autoimmune disease characterized by the accumulation of autoantibodies and immune complex deposition, may stimulate immune system activation, thereby triggering PE [41]. 2. Endothelial Dysfunction: SLE patients exhibit reduced functionality of endothelial cells and circulating angiogenic cells (CAC), which is associated with decreased levels of vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF). According to research by Nhek et al. SLE sera can activate platelets and lead to endothelial cell activation and the production of pro-inflammatory mediators in an IL-1-dependent manner [42]. In SLE, there is a significant imbalance between endothelial cell damage and healing [43], which may affect the maintenance of vascular function and the regulation of blood components' transport across the vascular wall, including proteins, fluids, ions, and cells [44]. SLE may contribute to the hypertension observed in preeclampsia by affecting anti-angiogenic factors and causing endothelial dysfunction. Endothelial dysfunction-induced maternal hypertension is one of the characteristic features of PE [45]. 3. Antiphospholipid Syndrome (APS) Complications: APS is a systemic autoimmune disease that can co-occur in as many as one-third of SLE cases [37]. It is characterized by the presence of antiphospholipid antibodies, and studies have shown a significant association between the presence of antiphospholipid antibodies and PE [44,46]. APS may promote obstetric complications through the activation of endothelial cells, platelets, and white blood cells, leading to other autoimmune and inflammatory complications [37].

Our research has several advantages:1. The use of Mendelian randomization design effectively mitigates the influence of confounding factors and reverse causality. 2. Rigorous screening of single nucleotide polymorphisms (SNPs) ensures the independence of instrumental variables. 3. The use of a large sample size and recent data enhances the reliability of the study. However, our study also has some limitations: 1. Certain genetic mechanisms like DNA methylation, RNA editing, and transposon inactivation, which are inherent limitations of MR analysis, may impact the results. 2. Since all the genome-wide association study (GWAS) databases used are based on European populations, the study results may exhibit racial bias. 3. A very small number of sensitive SNPs were found in the leave-one-out analysis, but their small number did not affect the final result. These findings underscore the complexity and necessity of considering both methodological strengths and population-specific limitations when applying Mendelian Randomization in diverse settings.

## 5. Conclusion

This is the inaugural study to investigate the causal relationship between Systemic Lupus Erythematosus and adverse pregnancy outcomes through Mendelian Randomization analysis. We discovered a positive correlation between SLE and an elevated risk of preeclampsia, highlighting the critical need for intensified prenatal care and proactive early interventions for pregnant women diagnosed with SLE to mitigate potential negative obstetric consequences. Additionally, our findings offer valuable insights into identifying and preemptively predicting risk factors for preeclampsia, paving the way for improved clinical strategies and outcomes. This study not only advances our understanding of the impact of autoimmune diseases on pregnancy but also reinforces the importance of tailored healthcare provisions for affected women.

## Consent for publication

Not applicable.

## Date availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

## Ethical statement

Ethical approval was not provided for this study on human participants because we used the publicly available GWAS catalog to conduct a two-sample MR study. No additional ethical approval was required due to the re-analysis of previously summary-level data.

## Funding

No funding

## CRediT authorship contribution statement

**Tao Zhu:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Data curation. **Gao Zhan:** Writing – review & editing, Supervision. **Zheng Shang:** Methodology, Data curation. **Zhao Ying:** Resources, Investigation.

## Declaration of competing interest

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

## Acknowledgments

We thank all the researchers who contributed in this MR study. We also thank all the institutions and researchers who provided data for this MR study.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35401.

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

## References

[1] S. Lazar, J.M. Kahlenberg, Systemic lupus erythematosus: new diagnostic and therapeutic approaches, Annu. Rev. Med. 74 (2023) 339–352.
[2] E.Y. Yen, R.R. Singh, Brief report: lupus-an unrecognized leading cause of death in young females: a population-based study using nationwide death certificates, 2000-2015, Arthritis Rheumatol. 70 (8) (2018) 1251–1255.
[3] J. Tian, et al., Global epidemiology of systemic lupus erythematosus: a comprehensive systematic analysis and modelling study, Ann. Rheum. Dis. 82 (3) (2023) 351–356.
[4] C. Li, C. Liu, N. Li, Causal associations between gut microbiota and adverse pregnancy outcomes: a two-sample Mendelian randomization study, Front. Microbiol. 13 (2022) 1059281.
[5] M.E. Clowse, et al., A national study of the complications of lupus in pregnancy, Am. J. Obstet. Gynecol. 199 (2) (2008) 127 e1–e6.
[6] E. Peart, M.E. Clowse, Systemic lupus erythematosus and pregnancy outcomes: an update and review of the literature, Curr. Opin. Rheumatol. 26 (2) (2014) 118–123.
[7] P.E. Georgiou, et al., Outcome of lupus pregnancy: a controlled study, Rheumatology 39 (9) (2000) 1014–1019.
[8] S. Sakaue, et al., A cross-population atlas of genetic associations for 220 human phenotypes, Nat. Genet. 53 (10) (2021) 1415–1424.
[9] B.L. Pierce, H. Ahsan, T.J. Vanderweele, Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants, Int. J. Epidemiol. 40 (3) (2011) 740–752.
[10] K.J. Mukamal, M.J. Stampfer, E.B. Rimm, Genetic instrumental variable analysis: time to call mendelian randomization what it is. The example of alcohol and cardiovascular disease, Eur. J. Epidemiol. 35 (2) (2020) 93–97.
[11] C. Genomes Project, et al., An integrated map of genetic variation from 1,092 human genomes, Nature 491 (7422) (2012) 56–65.
[12] V. Zuber, et al., Selecting likely causal risk factors from high-throughput experiments using multivariable Mendelian randomization, Nat. Commun. 11 (1) (2020) 29.
[13] S. Burgess, et al., Guidelines for performing Mendelian randomization investigations: update for summer 2023, Wellcome Open Res 4 (2019) 186.
[14] J. Bowden, M.V. Holmes, Meta-analysis and Mendelian randomization: a review, Res. Synth. Methods 10 (4) (2019) 486–496.
[15] J.S. Ong, S. MacGregor, Implementing MR-PRESSO and GCTA-GSMR for pleiotropy assessment in Mendelian randomization studies from a practitioner's perspective, Genet. Epidemiol. 43 (6) (2019) 609–616.
[16] J.F. Simard, et al., Early-onset preeclampsia in lupus pregnancy, Paediatr. Perinat. Epidemiol. 31 (1) (2017) 29–36.
[17] N. Ling, E. Lawson, E. von Scheven, Adverse pregnancy outcomes in adolescents and young women with systemic lupus erythematosus: a national estimate, Pediatr Rheumatol Online J 16 (1) (2018) 26.
[18] J. Wu, et al., Pregnancy outcomes among Chinese women with and without systemic lupus erythematosus: a retrospective cohort study, BMJ Open 8 (4) (2018) e020909.
[19] R. Abdwani, L. Al Shaqsi, I. Al-Zakwani, Neonatal and obstetrical outcomes of pregnancies in systemic lupus erythematosus, Oman Med. J. 33 (1) (2018) 15–21.
[20] A. Barnado, et al., Pregnancy outcomes among African-American patients with systemic lupus erythematosus compared with controls, Lupus Sci Med 1 (1) (2014) e000020.
[21] G. Davey Smith, S. Ebrahim, Epidemiology–is it time to call it a day? Int. J. Epidemiol. 30 (1) (2001) 1–11.
[22] O. Ibarra Barrueta, et al., Biological and immunosuppressive medications in pregnancy, breastfeeding and fertility in immune mediated diseases, Farm. Hosp. 47 (1) (2023) 39–49.
[23] B. Wainwright, et al., Autoimmune-mediated congenital heart block, Best Pract. Res. Clin. Obstet. Gynaecol. 64 (2020) 41–51.

[24] Society for Maternal-Fetal Medicine, Electronic address, p.s.o., et al., Society for Maternal-Fetal Medicine Consult Series #64: Systemic lupus erythematosus in pregnancy, Am. J. Obstet. Gynecol. 228 (3) (2023) B41–B60.
[25] E.L. Babunashvili, et al., Outcomes of laparotomic myomectomy during pregnancy for symptomatic uterine fibroids: a prospective cohort study, J. Clin. Med. 12 (19) (2023).
[26] M.P. Wendel, E.F. Magann, The impact of adenomyosis on pregnancy and pregnancy outcomes: a review, Obstet. Gynecol. Surv. 77 (8) (2022) 495–500.
[27] A. Etrusco, et al., Current medical therapy for adenomyosis: from bench to bedside, Drugs 83 (17) (2023) 1595–1611.
[28] P. Vercellini, et al., Association of endometriosis and adenomyosis with pregnancy and infertility, Fertil. Steril. 119 (5) (2023) 727–740.
[29] S. Delplanque, et al., Fertility, pregnancy, and clinical outcomes after uterine arteriovenous malformation management, J. Minim. Invasive Gynecol. 26 (1) (2019) 153–161.
[30] S.A. Vaz, S.K. Dotters-Katz, J.A. Kuller, Diagnosis and management of congenital uterine anomalies in pregnancy, Obstet. Gynecol. Surv. 72 (3) (2017) 194–201.
[31] E. Feghali, et al., Concurrent diagnosis of adenomyosis and congenital uterine anomalies: a review, J. Personalized Med. 13 (5) (2023).
[32] R. Roberti, et al., Status epilepticus in pregnancy: a literature review and a protocol proposal, Expert Rev. Neurother. 22 (4) (2022) 301–312.
[33] M. Laskowska, Eclampsia: a critical pregnancy complication demanding enhanced maternal care: a review, Med. Sci. Mon. Int. Med. J. Exp. Clin. Res. 29 (2023) e939919.
[34] R.S. Kerr, et al., Low-dose oral misoprostol for induction of labour, Cochrane Database Syst. Rev. 6 (6) (2021) CD014484.
[35] Z. Liu, et al., Transcriptomic profiling in hypoxia-induced trophoblast cells for preeclampsia, Placenta 136 (2023) 8–17.
[36] G.J. Burton, et al., Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy, Placenta 30 (6) (2009) 473–482.
[37] J.S. Knight, D.W. Branch, T.L. Ortel, Antiphospholipid syndrome: advances in diagnosis, pathogenesis, and management, BMJ 380 (2023) e069717.
[38] M.B. Jakovac, et al., Evaluation of placental oxygenation by near-infrared spectroscopy in relation to ultrasound maturation grade in physiological term pregnancies, Open Med. 18 (1) (2023) 20230843.
[39] R. Boij, et al., Biomarkers of coagulation, inflammation, and angiogenesis are independently associated with preeclampsia, Am. J. Reprod. Immunol. 68 (3) (2012) 258–270.
[40] G.P. Sacks, C.W. Redman, I.L. Sargent, Monocytes are primed to produce the Th1 type cytokine IL-12 in normal human pregnancy: an intracellular flow cytometric analysis of peripheral blood mononuclear cells, Clin. Exp. Immunol. 131 (3) (2003) 490–497.
[41] H. Lou, G.S. Ling, X. Cao, Autoantibodies in systemic lupus erythematosus: from immunopathology to therapeutic target, J. Autoimmun. 132 (2022) 102861.
[42] S. Nhek, et al., Activated platelets induce endothelial cell activation via an interleukin-1beta pathway in systemic lupus erythematosus, Arterioscler. Thromb. Vasc. Biol. 37 (4) (2017) 707–716.
[43] S. Rajagopalan, et al., Endothelial cell apoptosis in systemic lupus erythematosus: a common pathway for abnormal vascular function and thrombosis propensity, Blood 103 (10) (2004) 3677–3683.
[44] D.S. Boeldt, I.M. Bird, Vascular adaptation in pregnancy and endothelial dysfunction in preeclampsia, J. Endocrinol. 232 (1) (2017) R27–R44.
[45] A. Ahmed, H. Rezai, S. Broadway-Stringer, Evidence-based revised view of the pathophysiology of preeclampsia, Adv. Exp. Med. Biol. 956 (2017) 355–374.
[46] K. Abou-Nassar, et al., The association between antiphospholipid antibodies and placenta mediated complications: a systematic review and meta-analysis, Thromb. Res. 128 (1) (2011) 77–85.