Original Article

Causal association between pregnancy disorders and neonatal jaundice: a two-sample Mendelian randomization study

Yingying Wang[1,2], Shanshan Li[1,2], Jiajin Lu[1,2], Tianming Yuan[1]

[1]Department of Neonatology, Children's Hospital, Zhejiang University School of Medicine, Hangzhou, China; [2]Department of Neonatology, Shaoxing Keqiao Women & Children's Hospital, Shaoxing, China

Contributions: (I) Conception and design: Y Wang, T Yuan; (II) Administrative support: Y Wang, T Yuan; (III) Provision of study materials or patients: S Li, J Lu; (IV) Collection and assembly of data: S Li, J Lu; (V) Data analysis and interpretation: Y Wang, T Yuan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Tianming Yuan, PhD. Department of Neonatology, Children's Hospital, Zhejiang University School of Medicine, Hangzhou 310052, China. Email: yuantianming@zju.edu.cn.

Background: Some studies have suggested that complications during pregnancy, such as preeclampsia, leiomyoma during pregnancy, oxytocin induction, and mode of delivery, may be risk factors for neonatal jaundice. Herein, we applied Mendelian randomization (MR) analysis to investigate a causal association between pregnancy disorders and neonatal jaundice.

Methods: Data related to neonatal jaundice and pregnancy disorders (including pre-eclampsia or eclampsia, gestational diabetes, and gestational edema) were sourced from the FinnGen Consortium and Integrated Epidemiology Unit (IEU) databases. Inverse-variance weighted (IVW) was used as a main approach for data analysis, while MR-Egger, weighted median (WM), and weighted mode methods were used to validate the robustness of the results. MR-Egger regression method was applied to explore the presence of horizontal pleiotropy. MR pleiotropy residual sum and outlier (MR-PRESSO) method was used to detect potential outliers. Cochran's Q test was used to assess heterogeneity among instrumental variables (IVs); leave-one-out (LOO) analyses were used to evaluate the presence of predominant IVs.

Results: The IVW approach showed that pre-eclampsia or eclampsia {odds ratio (OR) [95% confidence interval (CI)]: 0.86 (0.36–2.07), P=0.73}, gestational edema and proteinuria [OR (95% CI): 1.04 (0.62–1.74), P=0.87], and gestational diabetes mellitus [OR (95% CI): 0.95 (0.60–1.49), P=0.81] were not associated with neonatal jaundice. The MR-Egger regression results showed that horizontal pleiotropy did not affect the relationship between exposure factors and outcomes. Also, no heterogeneity was observed. The MR-PRESSO analysis showed no outliers, confirming that these data were robust.

Conclusions: Our data suggested no genetic causal association between pre-eclampsia or eclampsia, gestational edema, proteinuria, gestational diabetes mellitus, and neonatal jaundice. However, further research is needed to determine if these results apply to other races.

Keywords: Preeclampsia; gestational edema; proteinuria neonatal jaundice; gestational diabetes mellitus; Mendelian randomization (MR)

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Introduction

Neonatal jaundice, which results from the accumulation of unconjugated bilirubin, is a common condition that occurs during the transitional period after birth (1). Neonatal jaundice is a common cause of readmission to the hospital after birth (2). It occurs in approximately 80% of preterm and 60% of term neonates worldwide (3). In most cases, it is a mild, transient, and self-limiting condition that

resolves without treatment (3). However, severe cases may lead to neuropathological changes in the cerebellum and hippocampus (4,5). Thus, the presence of neonatal jaundice often results in diagnostic evaluation.

Gestational diabetes, hypertension, infections, preeclampsia, preterm labor, pregnancy loss/miscarriage, and depression are the most common complications during pregnancy (6), some of which may lead to serious health problems. For example, a cross-sectional study that included 630 Iranian women reported a significant relationship between maternal preeclampsia and neonatal jaundice indices (7). Another study investigated maternal disease factors associated with neonatal jaundice and discovered that syphilis, leiomyoma during pregnancy, and salpingo-oophoritis before pregnancy are major risk factors for neonatal jaundice (8). Moreover, Garosi *et al.* (9) suggested that the mode of delivery and oxytocin induction may also contribute to jaundice. In addition, Jiang *et al.* (10) investigated the association between the risk of neonatal pathological jaundice and maternal blood parameters in 1,309 newborns and their mothers from 2019 to 2020 and discovered a potential link between neonatal pathological jaundice and maternal blood parameter levels. Although these observational studies have suggested that some pregnancy disorders and complications may be associated with an increased risk of neonatal jaundice, these studies did not take into consideration confounding factors, which may further explain a causal relationship between the two.

Mendelian randomization (MR) is a method that uses genetic variants as instrumental variables (IVs), effectively reducing the impact of confounding factors and providing more reliable causal inferences (11). So far, MR has been increasingly applied to examine causal inference in patients with neonatal jaundice (12). Yet, the relationship between pregnancy features and neonatal jaundice is still not fully understood.

In this study, we used MR analysis to investigate a causal association between pregnancy disorders (including pre-eclampsia or eclampsia, gestational diabetes, and gestational edema) and neonatal jaundice. This data may further explain the causal association between pregnancy disorders and neonatal jaundice. We present this article in accordance with the STROBE-MR reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-335/rc).

Highlight box

Key findings

- The study found no causal association between pregnancy disorders—specifically pre-eclampsia or eclampsia, gestational edema, proteinuria, and gestational diabetes mellitus—and neonatal jaundice. Multiple analytical methods confirmed these results, including Mendelian randomization (MR)-Egger regression, which ruled out horizontal pleiotropy. MR pleiotropy residual sum and outlier showed no outliers. Additionally, there was no heterogeneity among the instrumental variables.

What is known and what is new?

- Prior studies have suggested associations between pregnancy complications and an increased risk of neonatal jaundice.
- This study employed Mendelian randomization to evaluate these associations, proving that no genetic causal link exists between the examined pregnancy disorders and neonatal jaundice.

What is the implication, and what should change now?

- These findings indicate that the direct impact of specific pregnancy disorders on neonatal jaundice may be overstated, suggesting a need for healthcare providers to reconsider their monitoring strategies. Further research should focus on diverse populations and explore additional maternal and neonatal factors influencing jaundice, particularly in various racial and ethnic groups.

Methods

Study design

The analysis adhered to three assumptions of MR studies (*Figure 1*) (13): (I) it was not associated with the outcomes due to confounding pathways; (II) it did not affect the outcome; (III) it was associated with the exposure. This study used single nucleotide polymorphisms (SNPs) from genome-wide association studies (GWAS) available data as IVs for MR analysis. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Our analyses did not require approval from the ethics committee.

Data source

The GWAS summary statistics for neonatal jaundice (GWAS ID: finn-b-P16_NEONTAL_JAUND_OTH_UNSP_CAUSES, which included 218,608 European cases) from other and unspecified causes were sourced from the FinnGen Consortium. The outcome data for pregnancy disorders were also sourced from the FinnGen project: (I) pre-eclampsia or eclampsia (GWAS ID: finn-b-O15_

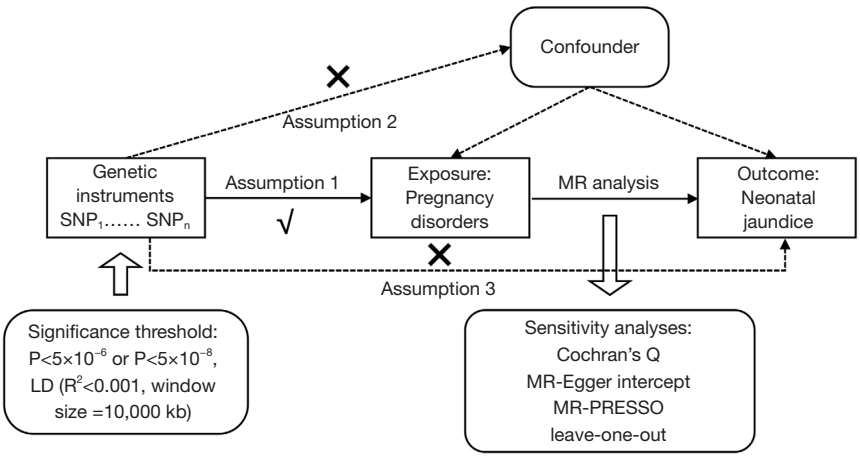

Figure 1 Study design for MR analysis. This figure illustrates the three key components of the MR study: (I) the instrumental variables exhibit an association with the pregnancy disorders; (II) the instrumental variables are not associated with confounding factors; (III) the instrumental variables do not possess a direct connection with the neonatal jaundice. SNP, single nucleotide polymorphism; MR, Mendelian randomization; LD, linkage disequilibrium; MR-PRESSO, MR pleiotropy residual sum and outlier.

PRE_OR_ECLAMPSIA, including 182,549 European cases); (II) gestational [pregnancy-induced] edema and proteinuria without hypertension (GWAS ID: finn-b-O15_GESTAT_OEDEM_PREINUR, including 114,735 European cases); (III) gestational diabetes (GWAS ID: finn-b-GEST_DIABETES including 5,687 European cases). All participants in this study were of European (Finnish) ancestry (14). The summary-level data were harmonized and archived in the Medical Research Council Integrative Epidemiology Unit (MRC-IEU) OpenGWAS (https://gwas.mrcieu.ac.uk/).

IVs selection

The IVs included in this study met the following criteria (15): first, SNPs related to preeclampsia or eclampsia, gestational edema proteinuria, and gestational diabetes mellitus were screened separately based on $P<5\times10^{-8}$. When the number of SNPs screened was small, the P value was adjusted to 5×10^{-6}. Then, SNPs with a minimum minor allele frequency (MAF) >0.01 were screened (16) and linkage disequilibrium (LD) between SNPs was removed based on the following criteria (17): window size =10,000 kb, $R^2<0.001$. When the selected IVs were not present in the summary data of the outcome, we searched for SNPs with high LD ($R^2>0.8$) with the IVs as proxy SNPs and replaced them. F value was calculated for each SNP to evaluate the strength of the IV (18), excluding the possibility of weak instrument bias between the IV and the exposure factor; the following formula was applied: $F = R^2 * (N-2)/(1-R^2)$, where R^2 was the proportion of exposure variance explained by the SNP in the IV, and the requirement for the F value was >10.

Statistical analysis

This analysis primarily employed the inverse-variance weighted (IVW) method to assess the causal association between outcome risks and exposure by calculating the odds ratio (OR) and 95% confidence interval (CI). IVW is the primary method for interpreting MR results, which calculates the weighted average of effect sizes by considering the inverse variance of each SNP as weights (19). Next, the MR-Egger, WM, and weighted mode methods were used to validate the robustness of the results. The MR-Egger method accounts for the presence of intercept and provides accurate causal effect estimates in the presence of pleiotropic bias (20); the weighted median (WM) method assumes that half of the IVs are valid, analyzing the causal association between exposure and outcome (21). Due to the presence of four outcome factors in this study, the false discovery rate (FDR) correction method was used to correct the P values for multiple testing, with P_{FDR} <0.05 considered statistically significant (22).

Subsequently, a series of sensitivity analyses were conducted to detect potential heterogeneity in MR studies. Cochran's *Q* test (23) was used to assess heterogeneity

Table 1 The causal relationship between pregnancy disorders and neonatal jaundice

Exposure	Outcome	No. SNPs	Methods	OR (95% CI)	P
Pre-eclampsia or eclampsia	NJ	9	MR Egger	3.53 (0.43–29.06)	0.28
			WM	0.62 (0.22–1.75)	0.36
			IVW	0.86 (0.36–2.07)	0.73
			Simple mode	0.51 (0.10–2.68)	0.45
			Weighted mode	0.51 (0.10–2.63)	0.45
Gestational (pregnancy-induced) edema and proteinuria without hypertension	NJ	8	MR Egger	0.93 (0.17–5.07)	0.93
			WM	0.86 (0.44–1.68)	0.66
			IVW	1.04 (0.62–1.74)	0.87
			Simple mode	0.82 (0.30–2.24)	0.71
			Weighted mode	0.80 (0.30–2.09)	0.66
Gestational diabetes (for exclusion	NJ	19	MR Egger	0.94 (0.32–2.73)	0.91
			WM	0.81 (0.42–1.58)	0.54
			IVW	0.95 (0.60–1.49)	0.81
			Simple mode	0.54 (0.17–1.70)	0.31
			Weighted mode	0.79 (0.42–1.49)	0.47

NJ, neonatal jaundice from other and unspecified causes; SNPs, single nucleotide polymorphisms; MR, Mendelian randomization; WM, weighted median; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval.

among IVs, with P>0.05 indicating low heterogeneity, meaning the estimates among IVs were randomly distributed and had little impact on IVW results. Considering the potential impact of genetic variation on the estimation of association effects, this study used the MR-Egger regression method to explore the presence of horizontal pleiotropy; when the intercept of MR-Egger regression approached zero or was not statistically significant, this suggested the absence of pleiotropy (24). Additionally, the MR pleiotropy residual sum and outlier (MR-PRESSO) method was used to detect potential outliers (i.e., SNPs with P<0.05) and re-estimate causal associations after their removal to correct for horizontal pleiotropy (25). A leave-one-out (LOO) analysis was employed to assess the robustness and consistency of the results (26).

All statistical analyses in this study were executed using R software version 4.3.0, leveraging the "TwoSampleMR" package. The results were reported as ORs with corresponding 95% CIs.

Results

In this study, we assessed a causal effect of pregnancy disorders (including pre-eclampsia or eclampsia, gestational diabetes, and gestational edema) as exposure factors on neonatal jaundice as an outcome. Nine IVs related to preeclampsia or eclampsia were screened, along with 8 IVs related to gestational edema and proteinuria, and 19 IVs related to gestational diabetes. There were no deletions and no need to search for proxy SNPs. More information regarding IV selection is shown in Tables S1-S3. F-statistical values, used to evaluate the strength of the IVs, are shown in Table S4.

The IVW approach showed that pre-eclampsia or eclampsia [OR (95% CI): 0.86 (0.36–2.07), P=0.73], gestational edema and proteinuria [OR (95% CI): 1.04 (0.62–1.74), P=0.87], and gestational diabetes mellitus [OR (95% CI): 0.95 (0.60–1.49), P=0.81] were not associated with neonatal jaundice (*Table 1*). Secondary analysis methods, including the MR–Egger regression, weight-median, simple mode and weighted mode, further confirmed this data (*Table 1*, *Figure 2*). No heterogeneity between independent SNPs when applied to the IVW estimates was shown when Cochran's Q test was applied (*Table 2*, *Figure 3*). Also, the LOO sensitivity analysis showed that our results were not biased by SNPs (*Figure 4*).

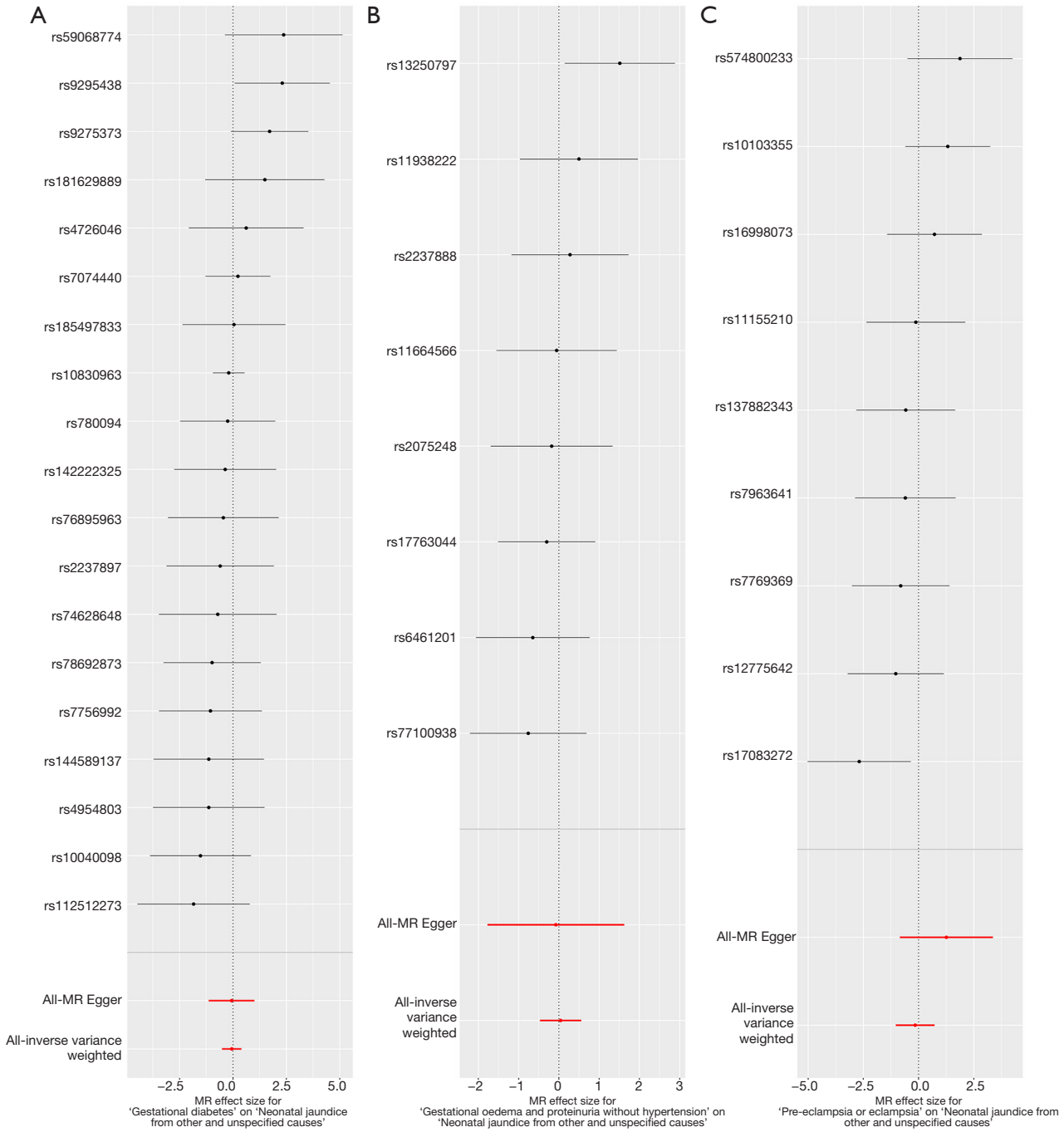

Figure 2 Forest plot showing no association between the risk of pregnancy disorders and neonatal jaundice. (A) Gestational diabetes; (B) gestational oedema and proteinuria without hypertension; (C) pre-eclampsia or eclampsia. MR, Mendelian randomization.

The MR-Egger regression method further confirmed that horizontal pleiotropy did not influence our results (*Table 2*, *Figure 5*). The MR-PRESSO analysis showed no outliers, suggesting robust results (*Table 3*).

Discussion

Hyperbilirubinemia is often encountered in term newborns. It is usually defined as an elevated bilirubin level >5 mg/dL within the first 24 hours of life (27). If not resolved in

Table 2 Results of heterogeneity and multifunctionality tests for IVs

Exposure	Outcome	Heterogeneity		Pleiotropy	
		Q statistic (IVW)	P value	MR-Egger intercept	P value
Pre-eclampsia or eclampsia	NJ	11.46	0.18	–0.251	0.196
Gestational (pregnancy-induced) edema and proteinuria without hypertension	NJ	7.43	0.39	0.03	0.99
Gestational diabetes (for exclusion)	NJ	19.12	0.38	0.002	0.985

IVs, instrumental variables; NJ, neonatal jaundice; IVW, inverse-variance weighted; MR, Mendelian randomization.

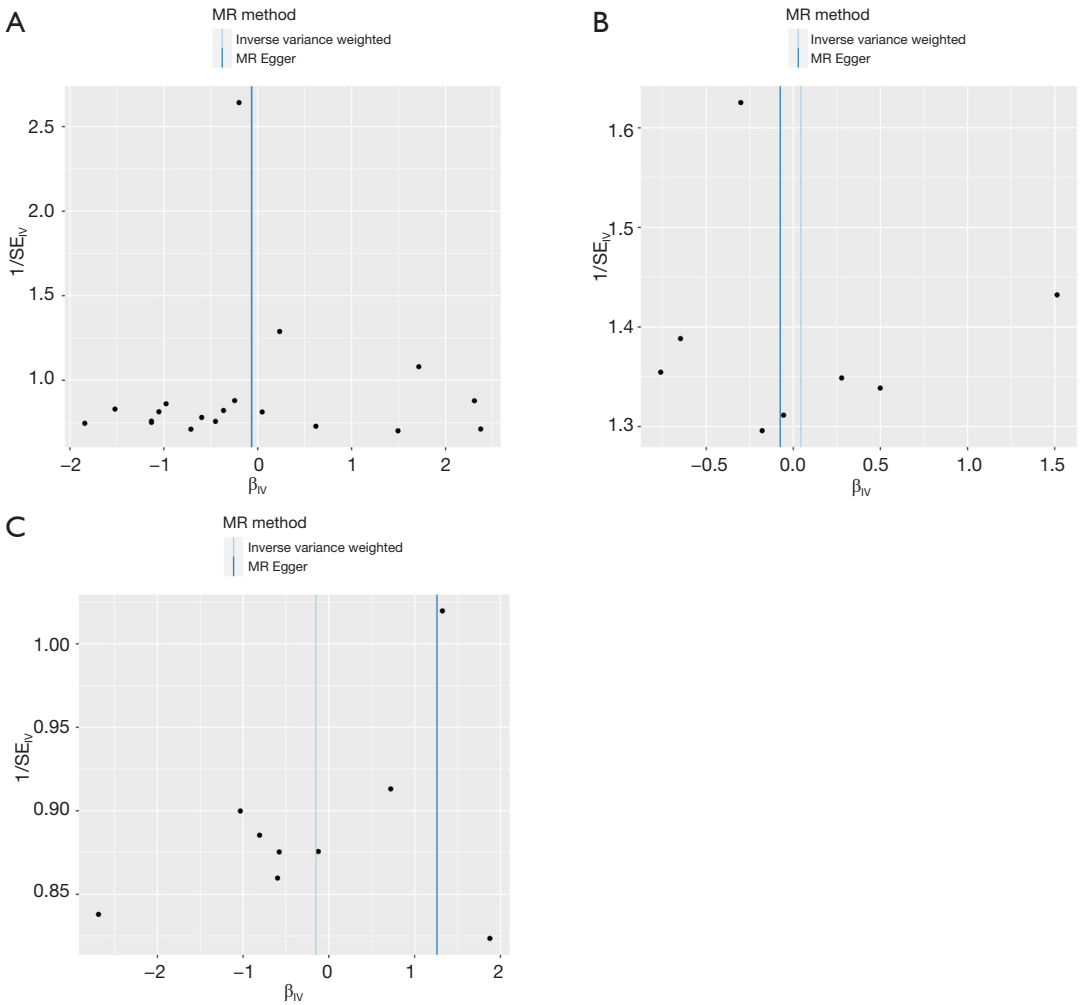

Figure 3 Funnel plot showing no association between the risk of pregnancy disorders and neonatal jaundice. (A) Gestational diabetes; (B) gestational oedema and proteinuria without hypertension; (C) pre-eclampsia or eclampsia. IV, instrumental variable; MR, Mendelian randomization.

time, it may have severe consequences for newborns. Fetal-maternal blood group incompatibility, prematurity, hemolytic causes, and a previously affected sibling are the common risk factors for hyperbilirubinemia (28,29). Moreover, an increasing number of studies have reported an association between certain pregnancy complications,

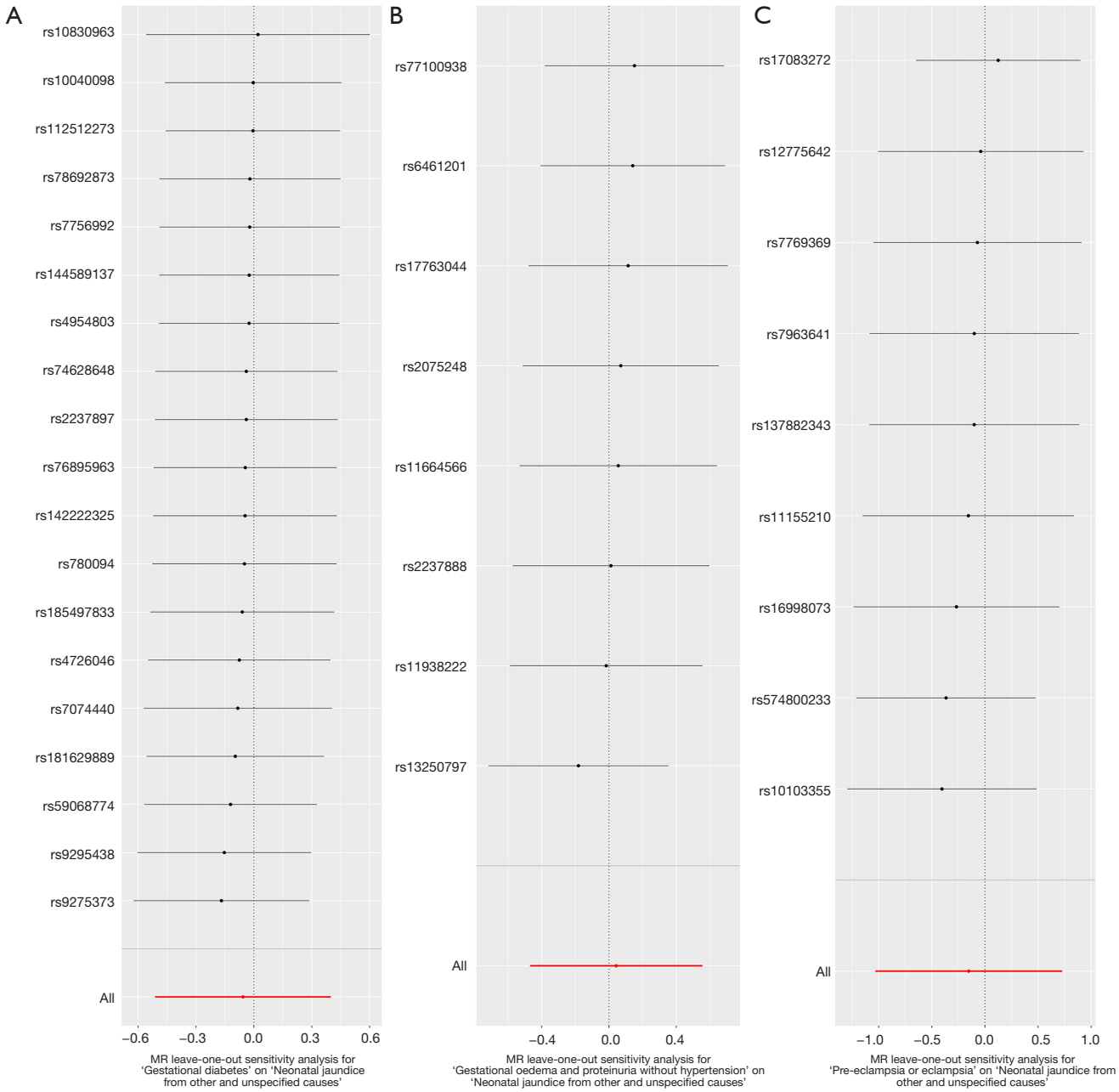

Figure 4 LOO plot showing no association between the risk of pregnancy disorders and neonatal jaundice. (A) Gestational diabetes; (B) gestational oedema and proteinuria without hypertension; (C) pre-eclampsia or eclampsia. MR, Mendelian randomization; LOO, leave-one-out.

such as gestational diabetes and pre-eclampsia in mothers, and hyperbilirubinemia. However, data are still debatable. For example, He *et al.* (30) investigated the correlation between neonatal hyperbilirubinemia and hypoglycemia in pregnant Chinese women with diabetes and found that gestational diabetes has an increased risk of neonatal hyperbilirubinemia. On the contrary, Jährig and colleagues (31) reported that the stage of maternal diabetes did not influence the course of neonatal bilirubin levels. Still, in his study, prolonged and higher bilirubinaemia was

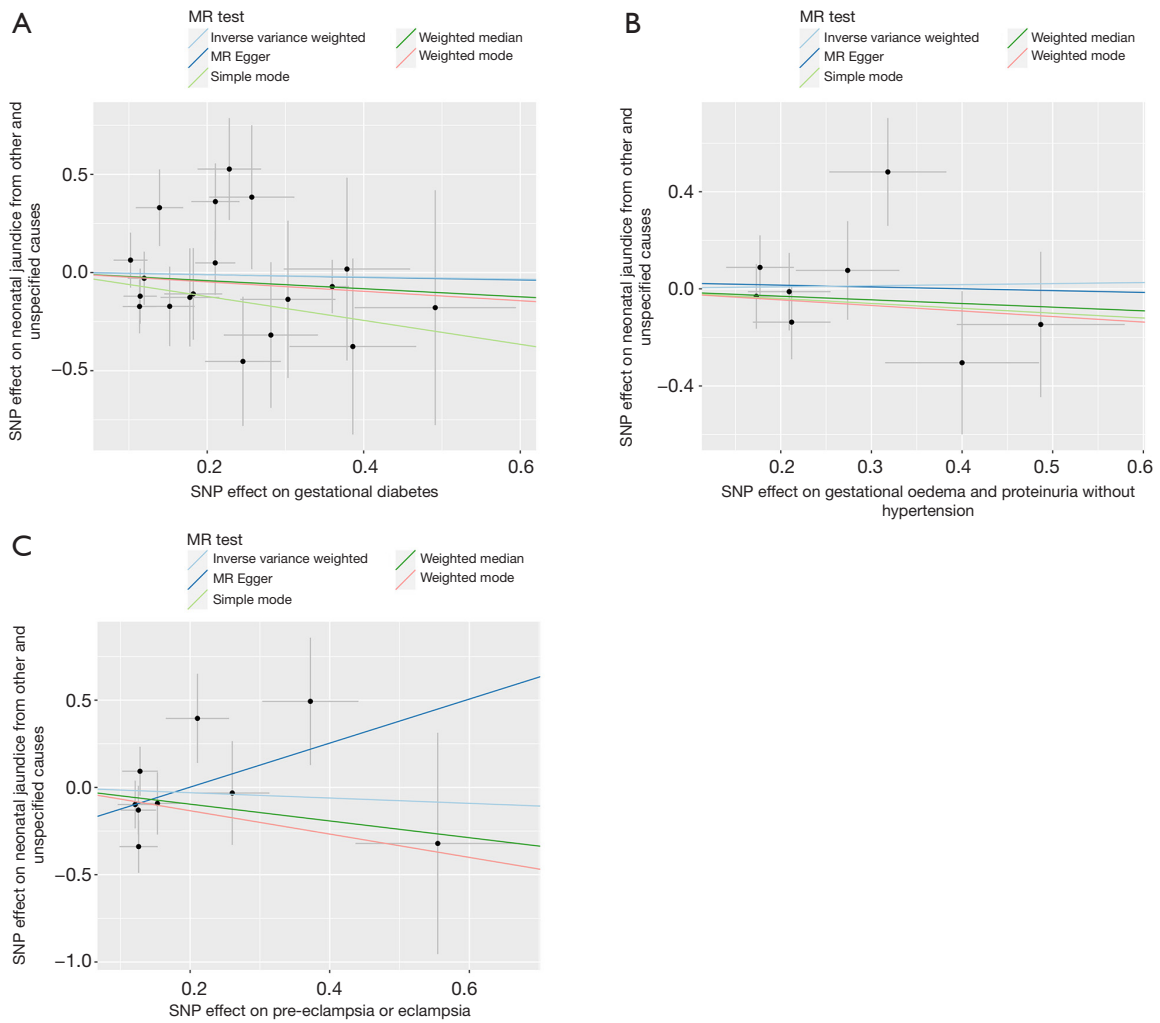

Figure 5 Scatter plot showing no association between the risk of pregnancy disorders and neonatal jaundice. (A) Gestational diabetes; (B) gestational oedema and proteinuria without hypertension; (C) pre-eclampsia or eclampsia. MR, Mendelian randomization; SNP, single nucleotide polymorphism.

Table 3 MR-PRESSO results

Exposure	Outcome	Raw		Outlier corrected		Global P	No. of outliers	Distortion P
		OR (95% CI)	P	OR (95% CI)	P			
Pre-eclampsia or eclampsia	NJ	0.86 (0.36–2.07)	0.74	–	–	0.193	–	–
Gestational (pregnancy-induced) edema and proteinuria without hypertension	NJ	1.04 (0.62–1.74)	0.87	–	–	0.401	–	–
Gestational diabetes (for exclusion)	NJ	0.95 (0.60–1.49)	0.81	–	–	0.412	–	–

MR-PRESSO, MR pleiotropy residual sum and outlier; NJ, neonatal jaundice; OR, odds ratio; CI, confidence interval; MR, Mendelian randomization.

observed in some neonates compared to controls. Also, hyperbilirubinemia was most prominent in cases with an increased birthweight/length ratio. Another retrospective cross-sectional study (32) observed no increase in peak neonatal transcutaneous bilirubin in term (≥37 weeks) infants of mothers with pre-gestational diabetes after undergoing thirty seconds of delayed cord clamping. Furthermore, a systematic review (33), which included 17 articles (1 prospective article, 2 retrospective papers, 12 cross-sectional papers, and 2 historical cohort articles), revealed that preeclampsia is among the risk of the maternal risk factors of neonatal hyperbilirubinemia. However, most of these studies were observational. Also, most did not consider confounding factors (e.g., genetic influence on disease development).

The role of genetic factors in neonatal jaundice has been gradually recognized. For example, Lin *et al.* assessed 5 neonates with severe hyperbilirubinemia and found 8 variations (HBA2 c.C369G, ABCC2 c.C3825G, G6PD c.G1388A, UGT1A1 c.G211A, EPB41 c.G520A, c.1213-4T>G, c.A1474G, and SPTB c.A1729G) related to the disease progression (34). Moreover, Yang *et al.* (35) explored the clinical value of newborn genomic screening for neonatal intensive care unit infants (taking neonatal hyperbilirubinemia as an example). A total of 33 out of 60 variants reported for carrier status were pathogenic, 3 variants were of uncertain significance, and 24 were likely pathogenic. We speculate that adverse pregnancy disorders may also increase susceptibility to neonatal hyperbilirubinemia/neonatal jaundice through genetic effects. Thus, a two-sample MR study was applied to explore the relationship between neonatal jaundice and multiple adverse pregnancy disorders (including pre-eclampsia or eclampsia, gestational edema and proteinuria, gestational diabetes mellitus) at the genetic level, with potential value for further research on the etiology of neonatal jaundice. In observational data, MR analysis is a common tool for investigating the causal relations between potentially modifiable risk factors and health outcomes (11). In this study, nine IVs related to preeclampsia or eclampsia were screened, along with 8 IVs related to gestational edema and proteinuria, and 19 IVs related to gestational diabetes. We found no causal genetic correlation between pre-eclampsia or eclampsia, gestational edema and proteinuria, or gestational diabetes and neonatal hyperbilirubinemia, which suggests that genetic variation related to these pregnancy complications does not affect hyperbilirubinemia. Nevertheless, only patients with European ancestry were considered in this study. It is well-known that neonatal jaundice may vary among races. For example, some studies have shown a higher rate of neonatal jaundice occurrence among East Asian and mixed Asian/white infants than among white infants (36). Thus, further research is needed to determine if these results apply to other races.

There are also some limitations in this study. First, this study focused on maternal SNPs and their association with pregnancy disorders; yet, it is also important to acknowledge the potential role of neonatal genetic factors in the development of jaundice. For example, neonatal SNPs associated with bilirubin metabolism and red blood cell turnover can influence the risk of neonatal jaundice (37). In addition, the possible interaction between maternal genetic predispositions (e.g., gestational diabetes) and neonatal genetic factors that could jointly influence the risk of neonatal jaundice was not adequately considered in the present study. Thus, future research should incorporate maternal and neonatal genetic data. This would provide a more complete understanding of the genetic influences on neonatal jaundice and help differentiate between maternal environmental influences and direct neonatal genetic risk factors.

Conclusions

This study provides a detailed MR analysis of pregnancy disorders and neonatal jaundice. Although our results suggested no causal association between pregnancy complications and neonatal jaundice, we acknowledge that several observational cohort findings point to a possible causal relationship, highlighting the need for further well-designed prospective studies to minimize the biases of observational studies and provide more GWAS data for future MR analyses. Future research could benefit from more diverse ethnic samples and functional validation of genetic variants. Also, further studies and clinical trials are warranted to prove a clear association between pregnancy disorders and neonatal jaundice, which could improve quality of life in the future.

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Footnote

Reporting Checklist: The authors have completed the

STROBE-MR reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-335/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-335/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-335/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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