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ORIGINAL RESEARCH

Gastroesophageal Reflux Disease and Preterm Birth: Univariate and Multivariate Mendelian Randomization

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Background: Observational studies have established a connection between Gastroesophageal reflux disease (GERD) and preterm birth (PTB). Nevertheless, these correlations can be affected by residual confounding or reverse causality, resulting in ambiguity regarding the connection. The objective of this study was to assess the relationship between genetically predicted GERD and PTB.

Methods: Initially, we performed bidirectional univariate Mendelian randomization (UVMR) analysis utilizing publicly accessible genome-wide association studies (GWAS) data. The primary analytical approach employed to determine the causal impact between GERD and PTB is the inverse variance weighted technique (IVW). Subsequently, we utilized multivariate Mendelian randomization (MVMR) to adjust for potential factors that could influence the results, such as body mass index (BMI), maternal smoking around birth, educational attainment, household income, and Townsend deprivation index (TDI). Furthermore, we performed a sequence of comprehensive sensitivity analyses to assess the reliability of our MR findings.

Results: The UVMR analysis results showed a significant correlation between GERD and PTB (odds ratio [OR]: 1.810; 95% confidence interval [CI]: 1.344–2.439; *P*=9.60E-05) in the IVW model, and the Weighted median method (OR=1.591, 95% CI=1.094–2.315, *P*=0.015) revealed consistent results. The inverse MR findings suggest no causal link between PTB and the incidence of GERD. In addition, the sensitivity analysis did not detect heterogeneity or horizontal pleiotropy, and the "leave-one-out" examination confirmed that the causal estimation is unlikely to be influenced by the single nucleotide polymorphisms (SNPs) effect. The MVMR analysis demonstrated that the causal association between GERD and PTB still existed after considering BMI, maternal smoking around birth, educational attainment, household income, and TDI (OR=1.921, 95% CI=1.401–2.634, *P*=5.08E-05).

Conclusion: This study presents evidence indicating that genetically predicted GERD can heighten the risk of PTB. Therefore, it is advisable to perform focused screening for pregnant women with GERD in order to find the initial signs of PTB and promptly apply intervention strategies to extend the duration of pregnancy.

Keywords: Mendelian randomization, gastroesophageal reflux disease, preterm birth, causality

Introduction

PTB is the delivery of a baby between 28 weeks and 37 weeks of gestation. Roughly 15 million infants are delivered preterm year on a global scale, with an incidence rate of around 11%. This number has been steadily growing over the years.[1] PTB, a frequently occurring perinatal problem, is the primary factor leading to mortality in children below the age of 5. It also has detrimental impacts on the growth, development, and long-term well-being of babies,[2] resulting in significant financial strain on both families and society. Therefore, it is imperative to explore potential risk factors and actively prevent high-risk populations for PTB. GERD is a common gastrointestinal disease associated with upper gastrointestinal motility disorders. Due to the reflux of gastric contents into the esophagus, it presents with a series of typical or atypical symptoms such as heartburn, acid reflux, bloating, cough, asthma, and dysphagia.[3] Global epidemiological surveys indicate that the prevalence of GERD is 13.3% based on at least one episode of reflux or heartburn per

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week.[4] The occurrence of gastroesophageal reflux in pregnant women has considerably increased to 38.5% owing to factors such as pregnancy-induced vomiting, heightened intra-abdominal pressure, and alterations in endocrine hormone levels.[5] These factors not only affect the quality of life of pregnant women but also lead to fetal nutrition deficiency and potentially increase the likelihood of adverse pregnancy outcomes. For example, a retrospective cohort study conducted in South Korea revealed that between 2002 and 2014, the prevalence of GERD in the preterm birth group consistently surpassed that in the control group. The occurrence of PTB is significantly correlated with the medical history of GERD, making it a reliable predictive factor for developing PTB.[6] Another machine learning study involving 731 obstetric patients also showed that GERD is a determining factor in PTB.[7] Nevertheless, observational studies are constrained by residual confounding variables and biases stemming from reverse causality, impeding the ability to establish robust causal inferences. Further substantiating evidence is needed to confirm the correlation between GERD and PTB.

Mendelian randomization (MR) is an epidemiological technique designed to address the constraints of observational research and has been extensively utilized in various investigations. The fundamental concept of MR is to utilize genetic variation as an instrumental variable for deducing the causal association between exposure and outcome. Genetic variation, determined by parents during conception and largely unaffected by social environment and personal lifestyle, can effectively mitigate the impact of common confounding factors or reverse causal relationships in observational studies, thus yielding more dependable research outcomes.[8] Multivariate Mendelian randomization (MVMR) is an emerging technology that integrates the genetic variation of several risk factors into a single model, thereby reducing the influence of mixed variables and assessing the associated exposure.[9] Thus, this study employed univariate and multivariate MR analyses to investigate the causal association between GERD and PTB.

Materials and Methods

Study Design

This study conducted univariate and multivariate MR analyses to infer whether there is a causal relationship between GERD and PTB by using genetic variations related to exposure and outcome as instrumental variables (IVs). Figure 1 demonstrates that the efficacy of causal estimation in MR investigations is contingent upon fulfilling three crucial assumptions:[10] firstly, the genetic variants must exhibit a strong association with the exposure; secondly, they should not be linked to any potential confounding factors that could affect the relationship between the exposure and outcome; and thirdly, the variants should not have an independent effect on the outcome, aside from their correlation with the exposure. Prior observational clinical trial data[11–13] indicates that BMI, maternal smoking around birth, educational attainment, household income, and TDI are factors that increase the likelihood of PTB. Thus, we proceeded to do multivariate MR

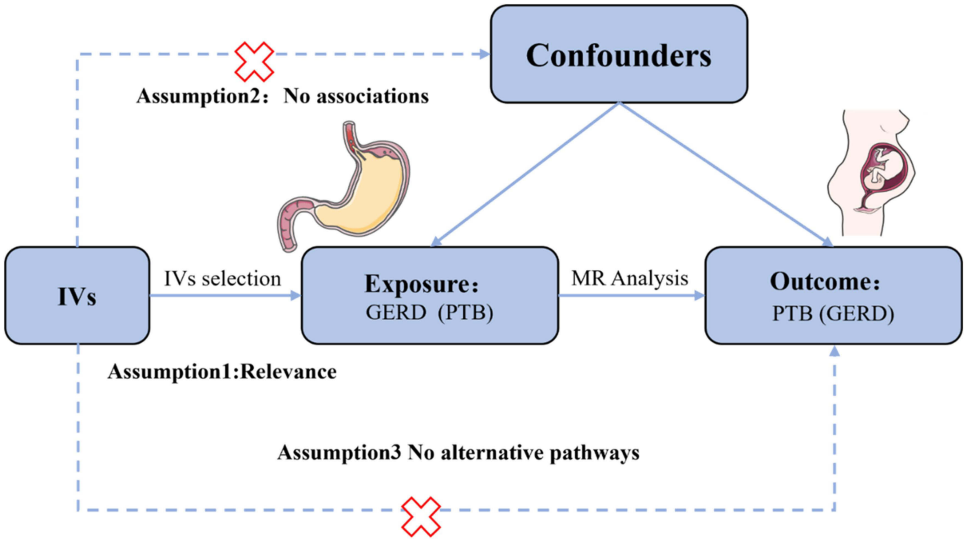

Figure 1 Assumption of the MR analysis for GERD and the risk of PTB.

analysis to account for the genetic predisposition of the confounding factors indicated above. Given that the data we utilize is sourced from publicly accessible GWAS summary databases, ethical assessment is unnecessary.

Data Sources

The genetic summary data pertaining to GERD in this investigation were obtained from a comprehensive GWAS on GERD published by ONG et al[14] in Gut in 2022. The study encompassed a total of 602,604 individuals in the European population, including 129,080 individuals in the case group and 473,524 individuals in the control group. It covered a total of 2,320,781 SNPs. The genetic data concerning PTB is sourced from the FinnGenes database at https://gwas.mrcieu.ac.uk/datasets/finn-b-O15_PRETERM.The dataset consists of 5480 patients in the case group and 98626 cases in the control group, all from the European population, with a total of 16379340 SNPs. We collected summary data on BMI, maternal smoking around birth, educational attainment, household income, and TDI like GIANT and MRC-IEU. The GWAS data samples are exclusively from the European population. Table 1 contains extensive details on all datasets used in this study.

Selection and Evaluation of Instrumental Variable

We followed a certain procedure to pick the IVs in order to meet the three essential assumptions of MR analysis. We identified SNPs highly associated with GERD at a significance level of $P < 5\times10^{-8}$. A cutoff criterion of $P < 1\times10^{-5}$ was used to identify SNPs predictive of PTB due to the small number of accessible SNPs. We set a strict threshold ($r2 < 0.001$ and a clumping distance of 10,000 kb) to address the impact of linkage disequilibrium (LD) among the SNPs, guaranteeing that the chosen IVs were conditionally independent. Only SNPs with the most significant p-values were kept.[15] Additionally, the potential pleiotropic effects were managed by retrieving the secondary phenotype of each SNP from PhenoScan V2 (http://www.phenoscanner.medschl.cam.ac.uk/).[16] SNPs corresponding to BMI, diabetes, drinking, smoking, and other confounding factors or outcomes were excluded from further investigation. We identified exposure IVs from the outcome data and performed data harmonization to exclude SNPs with inconsistent alleles in both exposure and result data.

The strength of IVs was assessed using variance (R^2) and *F*-statistic to reduce the impact of weak instrument bias. The *F*-statistic for each SNP can be calculated using the formula $F = R2/(1-R2)[(N-K-1)/K]$, where N is the sample size, K is the total number of SNPs chosen for MR analysis, and R^2 is the fraction of phenotypic differences explained by all SNPs in the MR model.[17] Determine the R2 for each SNP using the provided formula: $R^2=\Sigma[2\times(1-MAF)\times MAF\times\beta^2/(SE^2\times N)]$, where MAF represents the minor allele frequency, β is the allele effect value, and SE is the standard error.[18] An F-statistic greater than 10 was deemed significant for the relationship between IVs and exposure, guaranteeing that results were not influenced by weak instrument bias.[19] Statistical power for each outcome was calculated employing the online tool accessible at https://shiny.cnsgenomics.com/mRnd/.[20] An 80% or higher power is recommended to provide robust and dependable outcomes.

Table 1 Details of Studies Included in Mendelian Randomization (MR) Analyses

Traits	GWAS ID	Sample Size (cases/controls)	Number of SNPs	Ancestry	Year	PMID
Exposure						
GERD	ebi-a-GCST90000514	129,080/473,524	2,320,781	European	2021	34187846
BMI	ieu-b-40	681,275	2,336,260	European	2018	30124842
Maternal smoking around birth	ukb-b-17685	121,634/276,098	9,851,867	European	2018	NA
Educational attainment	ebi-a-GCST90029013	461,457	11,972,619	European	2018	29892013
Average total household income before tax	ukb-b-7408	397,751	9,851,867	European	2018	NA
TDI	ukb-b-10011	462,464	9,851,867	European	2018	NA
Outcomes						
PTB	finn-b-O15_PRETERM	5,480/98,626	16,379,340	European	2021	NA

Abbreviations: GERD, gastroesophageal reflux disease; PTB, preterm birth; BMI, body mass index; TDI, Townsend deprivation index.

Statistical Analysis

To evaluate the genetic causal effects, multiple methods such as IVW, MR-Egger, weighted median, weighted mode, and simple mode were applied. The techniques provided proof in many situations, with IVW being the primary outcome.[21] The IVW approach extends the Wald ratio estimator that incorporates meta-analytic ideas. It seeks to offer an unbiased calculation, assuming all included SNPs are trustworthy IVs without any horizontal pleiotropy or heterogeneity.[22] The MR Egger approach can identify probable pleiotropy and account for intercept terms in regression analysis.[23] Even with 50% of the data containing invalid independent variables, the weighted median technique can produce reliable estimates of the causal effects. The weighted model method requires a smaller sample size than other methods and may ensure less bias and a lower Type I error rate.[23] The simple model method is less effective than IVW but adds robustness for pleiotropy.[24] Building upon prior research,[11–13] we included BMI, maternal smoking around birth, educational attainment, household income, and TDI in an MVMR analysis. This enabled us to determine the direct influence of GERD on PTB without being influenced by other risk factors. We adopted IVW in our MVMR analysis.

In order to verify the stability and reliability of MR results, this study applied multiple sensitivity analyses for quality control. The Cochran's Q test was utilized to assess heterogeneity among SNPs, where a p-value greater than 0.05 indicates no significant heterogeneity. The MR Egger intercept test was employed to detect horizontal pleiotropy in SNPs, where a p-value less than 0.05 suggests the presence of significant pleiotropy in the analysis results. The MR-PRESSO method was implemented to detect outlier SNPs in the findings. A leave-one-out analysis was conducted to determine if any particular SNP influenced the MR findings. By systematically eliminating SNPs and estimating the cumulative effects of the remaining SNPs, it is possible to assess the influence of an individual SNP on the relationship between exposure and outcome variables. MR analyses were carried out using the TwoSampleMR (version 0.5.6) and MVMR (version 0.3) packages in R (version 4.3.1), with a significance level set at $\alpha = 0.05$.

Result

Genetic Instruments

We discovered 29 SNPs as IVs for GERD to assess its connections with PTB, as outlined in Table 2. All the genetic variations had *F*-statistics above the crucial value of 10, indicating a low likelihood of weak instrumental bias. The statistical power was 100%, confirming the dependability of the data. In the MR analysis of PTB on GERD, we selected 5 SNPs linked to PTB, as shown in Table 3. Most IVs had an *F* value below 10, indicating a potential presence of modest instrumental bias.

Table 2 Detailed Information on the SNPs Associated with GERD

chr	pos	SNPID	EA	OA	β	SE	R2	F
4	159839313	rs10010963	T	C	−0.027	0.005	4.94E-05	29.75
10	106610839	rs1021363	G	A	−0.031	0.005	6.41E-05	38.64
11	38565727	rs10837002	G	C	0.028	0.005	5.00E-05	30.14
5	120144025	rs11953061	T	C	0.028	0.005	5.09E-05	30.64
6	152235339	rs12204714	T	C	−0.029	0.005	5.52E-05	33.29
17	50316131	rs12453010	T	C	0.030	0.005	6.01E-05	36.24
16	60658751	rs12598916	G	C	−0.033	0.005	6.31E-05	38.06
18	35138245	rs12967855	G	A	−0.037	0.005	8.41E-05	50.68
2	144257639	rs13409451	G	A	−0.028	0.005	5.24E-05	31.56
12	15387519	rs1479405	T	C	0.031	0.005	6.20E-05	37.35
20	41223062	rs1883842	G	T	0.031	0.005	5.47E-05	32.99
3	65653157	rs2016933	G	C	−0.031	0.005	5.44E-05	32.76
7	12253880	rs2043539	A	G	0.027	0.005	5.19E-05	31.27
11	113286490	rs2734839	T	C	−0.028	0.005	5.49E-05	33.09
1	44013355	rs2782641	A	G	0.027	0.005	4.98E-05	30.00
21	34291708	rs2834005	C	T	0.030	0.005	5.47E-05	32.96

(*Continued*)

Table 2 (Continued).

chr	pos	SNPID	EA	OA	β	SE	R2	F
12	83969240	rs324769	T	C	−0.027	0.005	5.09E-05	30.68
9	23737627	rs3793577	G	A	0.027	0.005	5.15E-05	31.07
8	73890335	rs3863241	T	C	0.032	0.005	7.56E-05	45.55
2	22549441	rs4300861	T	C	0.031	0.005	6.39E-05	38.52
9	134870755	rs4382592	G	T	−0.030	0.005	5.51E-05	33.23
1	29136686	rs569356	G	A	−0.038	0.007	5.00E-05	30.12
9	122672771	rs7032155	A	C	0.028	0.005	5.29E-05	31.90
18	77580712	rs7241572	A	G	0.037	0.006	6.21E-05	37.43
1	189172684	rs7527682	G	A	−0.027	0.005	5.08E-05	30.63
2	212622818	rs7600261	T	C	0.034	0.005	6.96E-05	41.93
6	17023108	rs9396740	A	G	−0.031	0.006	5.33E-05	32.10
13	66957533	rs9529055	A	G	0.027	0.005	5.08E-05	30.64
13	31833578	rs9542729	G	C	−0.036	0.006	6.08E-05	36.65

Abbreviations: Chr, Chromosome; POS, Gene locus; EA, effector allele; OA, Other alleles; β, Regression coefficient; SE, Standard error.

Table 3 Detailed Information on the SNPs Associated with PTB

chr	pos	SNPID	EA	OA	β	SE	R2	F
8	22118817	rs12542503	C	T	0.1139	0.0248	6.69E-05	6.96
22	33010757	rs2858226	T	C	0.0921	0.02	0.000102	10.58
2	22125367	rs4666291	C	T	0.204	0.0418	2.68E-05	2.79
11	1.29E+08	rs4937381	A	G	0.1014	0.0223	7.94E-05	8.27
7	20689495	rs916738	T	C	0.1195	0.0269	5.18E-05	5.39

Abbreviations: Chr, Chromosome; POS, Gene locus; EA, effector allele; OA, Other alleles; β, Regression coefficient; SE, Standard error.

Estimated Causal Effect of GERD on PTB

We observed a significant association between genetically predicted GERD and an increased likelihood of PTB (OR: 1.810; 95% CI: 1.344–2.439; *P*=9.60E-05) in the IVW model. The result aligned with those from the Weighted median model (OR: 1.591; 95% CI: 1.094–2.315; *P*=0.015). The other three statistical approaches did not demonstrate any association between GERD and PTB. However, based on the OR values in Table 4 and the scatter plot in Figure 2, all methods consistently reflect the same direction of the overall effect. The forest plot illustrates the causal link between genetic predictors of GERD and the risk of PTB, as shown in Figure 3. The Cochran's Q test did not detect heterogeneity, and the MR Egger intercept test did not reveal any signs of horizontal pleiotropy in the MR studies. The MR-PRESSO analysis found no abnormalities among the SNPs. Table 5 presents comprehensive findings from the sensitivity analyses. The leave-one-out plots in our analysis demonstrate the strength of our results, indicating a minimal effect of any single SNP on the causal estimations, as depicted

Table 4 The Results of the Five MR Methods

Method	nSNP	Beta	SE	OR (95% CI)	Pvalue
MR Egger	29	0.501119	1.496399	1.651(0.088~31.002)	0.740
Weighted median	29	0.464557	0.191322	1.591(1.094~2.315)	0.015
Inverse variance weighted	29	0.593569	0.152175	1.810(1.344~2.439)	9.60E-05
Simple mode	29	0.360091	0.367318	1.433(0.698~2.945)	0.335
Weighted mode	29	0.371867	0.333011	1.450(0.755~2.786)	0.274

Abbreviations: GERD, gastroesophageal reflux disease; PTB, preterm birth; SE, standard error.

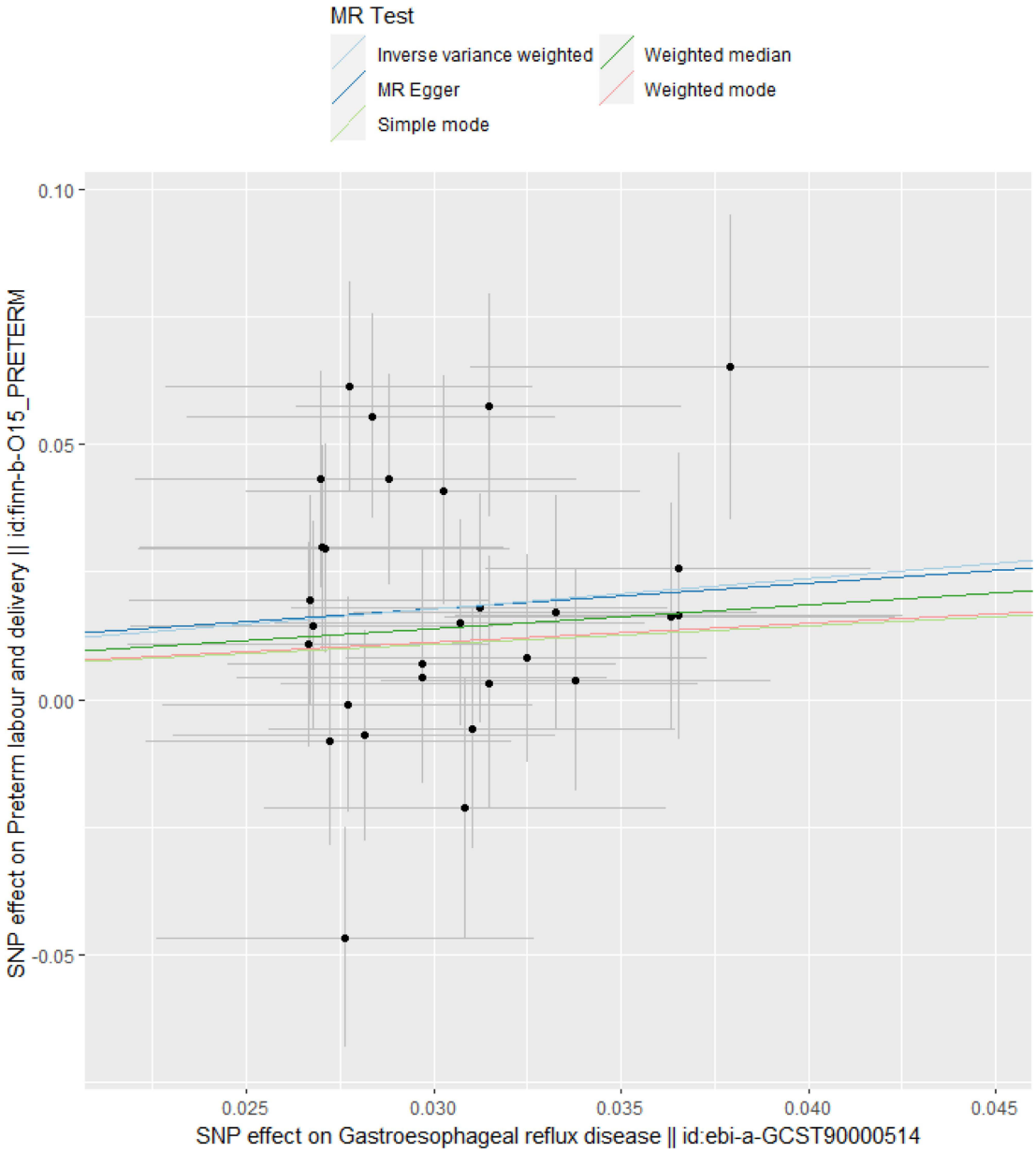

Figure 2 Scatter plot of the two-samples MR analysis.

in Supplementary Figure 1. After accounting for confounding variables such as BMI, maternal smoking around birth, educational attainment, household income, and TDI, a robust causal relationship between GERD and PTB remained evident in the MVMR analysis (OR: 1.921; 95% CI: 1.401–2.634; P = 5.08E-05). Table 6 offers a detailed description of the MVMR findings.

Estimated Causal Effect of PTB and GERD

In the IVW model, there was no evidence of a causative association between the genetic susceptibility to PTB and GERD (OR: 0.992; 95% CI: 0.950–1.036, P = 0.716). The identical findings were derived from the remaining four statistical models. The Cochran's Q-test shows no heterogeneity among SNPs. The MR Egger intercept test reveals no horizontal pleiotropy in the MR analysis results. The MR-PRESSO analysis could not identify any outlier SNP. The detailed outcomes of the sensitivity analyses are displayed in Table 5. The sensitivity analysis in Supplementary Figure 2 demonstrates that a single SNP does not influence the IVW estimation via the "leave one method".

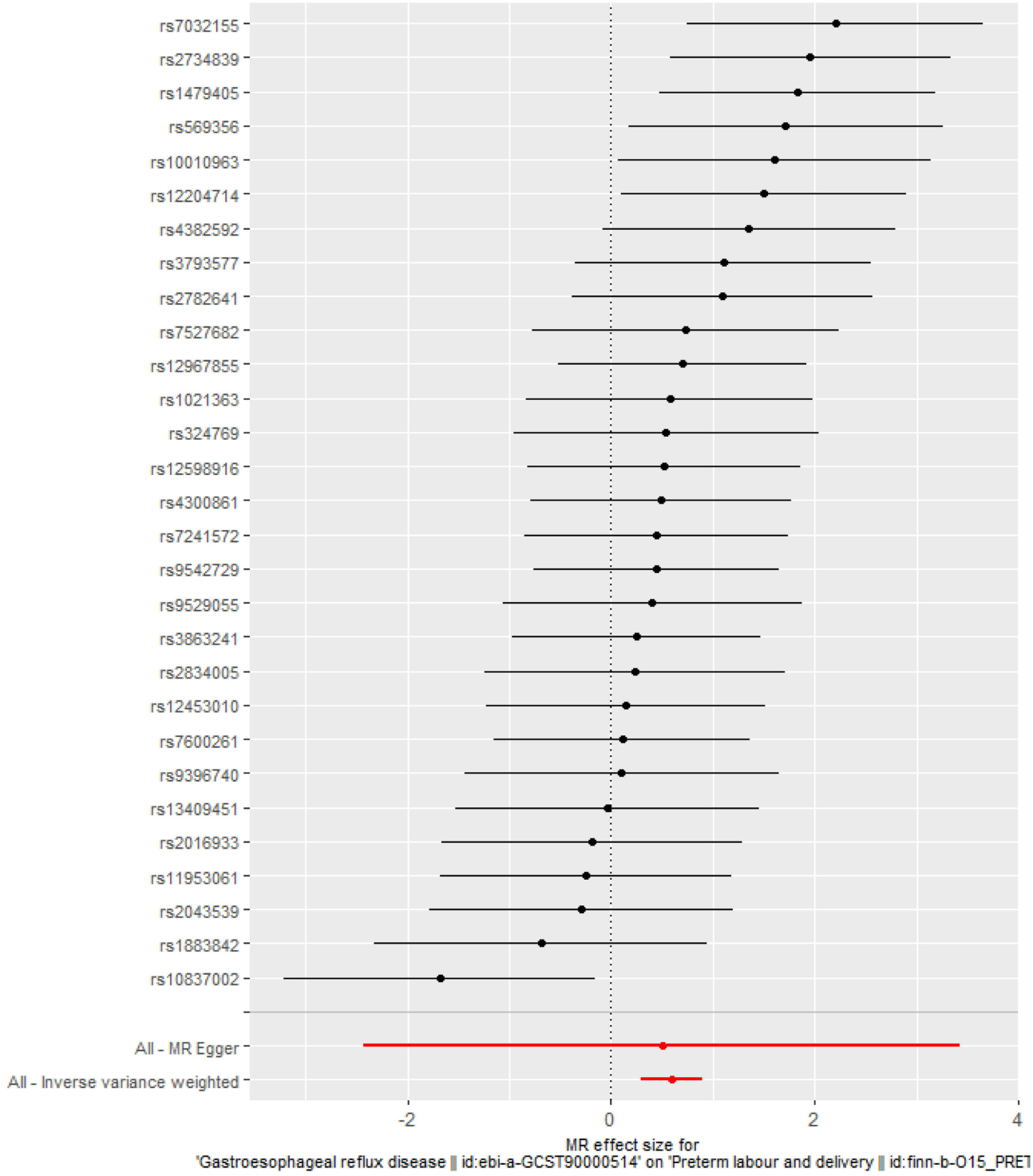

Figure 3 Forest plot of the two-samples MR analysis.

Discussion

This study utilized GWAS aggregated data to conduct univariate and multivariate Mendelian randomization analysis, investigating the potential bidirectional causal link between GERD and PTB from a genetic standpoint. Both the IVW and weighted median methods indicate that GERD is a risk factor for the beginning of PTB, and those with GERD have an increased likelihood of acquiring PTB. Furthermore, after accounting for traits including BMI, smoking during

Table 5 Heterogeneity, Horizontal Pleiotropy, and MR-PRESSO Tests of the Bi-Directional Associations Between GERD and PTB

Model	Pleiotropy Test			Heterogeneity test						MR-PRESSO
	MR-Egger			MR-Egger			Inverse-variance weighted			Global Test
	Intercept	SE	*P*	Q-value	Q-*df*	Q-pval	Q-value	Q-*df*	Q-pval	Pvalue
GERD-PTB	0.002	0.045	0.951	36.445	27	0.106	36.450	28	0.131	0.140
PTB-GERD	−0.0009	0.012	0.940	4.117	3	0.249	4.126	4	0.389	0.429

Abbreviations: GERD, gastroesophageal reflux disease; PTB, preterm birth; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; Q-value, the statistics of Cochran's Q test; SE, standard error.

Table 6 Multivariate MR Study Results

Exposure	nSNP	Beta	SE	OR (95% CI)	P value
GERD	31	0.653	0.161	1.921(1.401~2.634)	5.08E-05
BMI	420	−0.589	0.127	0.555(0.433~0.712)	3.36E-06
Maternal smoking around birth	1	1.288	0.716	3.625(0.890~14.758)	0.072
Educational attainment	54	0.041	0.062	1.042(0.923~1.177)	0.504
Average total household income before tax	13	0.018	0.323	1.018 (0.540~1.918)	0.956
TDI	1	−0.217	0.384	0.805 (0.379~1.708)	0.572

Abbreviations: GERD, gastroesophageal reflux disease; PTB, preterm birth; BMI, body mass index; TDI, Townsend deprivation index.

pregnancy, education level, family income, and social standing, the causal link between GERD and PTB remains present. The findings from the reverse MR analysis did not provide evidence for a causal link between PTB and GERD.

Our MR research findings demonstrate that GERD can elevate the probability of PTB, aligning with earlier epidemiological evidence. A retrospective cohort study of 405,586 pregnant women published in 2022 found a strong association between PTB with a past medical history of GERD and the usage of proton pump inhibitors.[24] This conclusion is similar to the research presented in 2024. Another study established an effective PTB prediction model based on a massive dataset of 124,606 individuals from South Korea and machine learning techniques. The model findings indicated that GERD was one of the top 10 predictors of the relevance of random forest factors in PTB. From 2011 to 2016, there was a notable increase in PTB among GERD patients compared to full-term deliveries, with a statistically significant difference.[25]

GERD may contribute to PTB through specific pathways, though these mechanisms are not fully understood. Some existing studies provide insights that can help clarify these connections. Figure 4 summarizes all the hypotheses and mechanisms discussed regarding the relationship between GERD and PTB. For example, the theory that GERD can

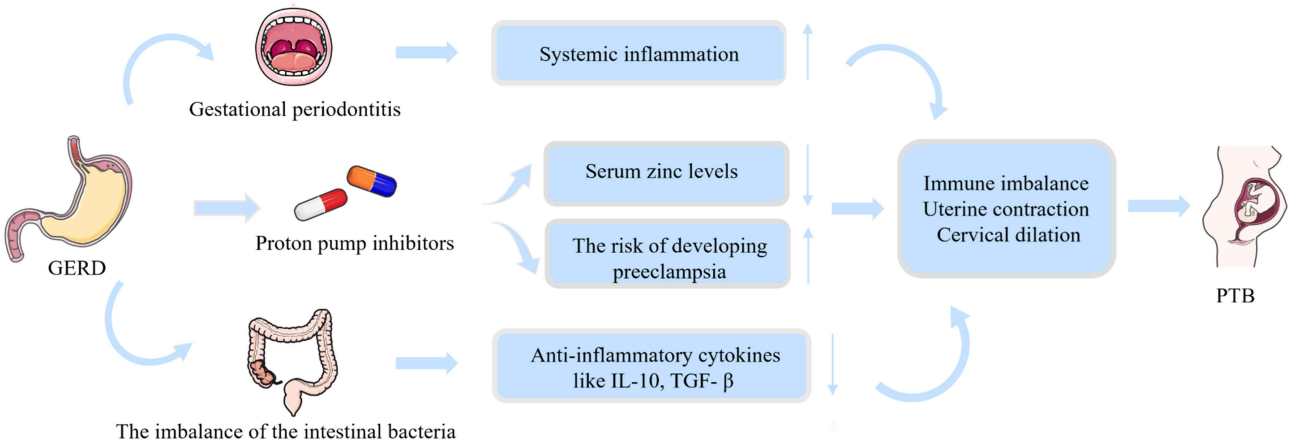

Figure 4 The hypotheses and mechanisms regarding the relationship between GERD and PTB.

significantly elevate the incidence of periodontitis has been confirmed by observational and MR investigations, possibly due to aberrant systemic inflammatory response, inadequate saliva output, and imbalanced dental hygiene in GERD patients. A recent queue study has indicated that compared to healthy pregnant women, gestational periodontitis can significantly increase the risk of PTB (relative risk [RR]: 1.93; 95% CI: 1.09–3.43).[26] Clinical research conducted by Lee et al also showed that GERD is closely related to the risk of gestational periodontitis and systemic inflammation associated with PTB.[7] So we speculate that GERD may increase the risk of periodontitis in pregnant women, resulting in abnormal oral microbiota and systemic inflammatory status, thereby facilitating the entry of microorganisms or inflammatory agents into the fetal placental circulation, triggering uterine contractions and cervical dilation, potentially leading to PTB.

Additionally, proton pump inhibitors (PPIs) are the primary medicines given to treat GERD and may reveal an extra mechanism connecting GERD with PTB. A current cohort analysis found that consuming PPIs corresponds to an elevated probability of preterm birth (OR=1.23, 95% CI:1.14–1.32). Utilizing PPIs may considerably alter the PH level in the gastroduodenal cavity, disrupting the absorption and retention of essential elements like zinc in the body.[27] Simultaneously, case-control research pointed out premature-delivery pregnant women had notably lower serum zinc levels than full-term-delivery pregnant women.[28] The lack of trace elements due to PPI usage among GERD patients may contribute to the higher risk of PTB. Furthermore, a recent study has discovered that the utilization of PPIs during 17–33 weeks of pregnancy can elevate the likelihood of delayed onset preeclampsia (RR=1.6, 95% CI:1.0–2.8). Preeclampsia is a well-known risk factor for PTB[29] and may contribute to the increased likelihood of PTB in patients with GERD.

Finally, the gut flora may play a role in the pathophysiology of GERD-induced PTB. Research has demonstrated that the gut microbiota of preterm pregnant women exhibits significantly lower α diversity than that of full-term pregnant women, with notably reduced levels of Bifidobacterium, Streptococcus, Clostridium, and Bacteroidetes.[30] These beneficial bacteria can produce transforming growth factors- β (TGF- β) and anti-inflammatory cytokines like IL-10, which can inhibit the expression of enzymes related to uterine myometrial remodelling and fetal membrane degradation by producing short-chain fatty acids (SCFAs)., thereby preventing uterine myometrial contraction, amniotic membrane rupture, and PTB. Shi and et al have discovered that the diversity of gastrointestinal communities and bacterial levels in individuals with GERD were notably lower than those in the healthy control group.[31] We hypothesize that GERD could give rise to PTB by disrupting gut microbial homeostasis.

The prospective cohort study from the Netherlands revealed that using calcium-based antacids and PPIs during pregnancy did not reduce the risk of late-onset preeclampsia.[32] This finding indicates that better treatment of GERD during pregnancy does not alter the risk of preeclampsia and subsequent PTB. However, our results underscore the necessity of targeted screening for pregnant women with GERD to detect early signs of PTB and implement timely interventions to prolong pregnancy and improve maternal-fetal outcomes. To our knowledge, this study is the first to employ an MR methodology to determine the genetic causal connection between GERD and PTB. This MR research has multiple strengths. First, it eliminates genetic variations commonly observed in epidemiological research due to potential confounding factors and instead focuses on SNPs closely linked to GERD. Second, the large sample size improves the statistical strength of our study, offering compelling evidence for the found correlations. Third, we performed thorough sensitivity analyses to confirm the accuracy of our findings. Finally, we adopted MVMR to investigate the specific influence of GERD and PTB while accounting for variables including BMI, maternal smoking around birth, educational attainment, household income, and TDI.

Nevertheless, there are constraints. Since we only had access to summary-level data from the GWAS database, we could not assess the non-linear relationship between GERD and PTB. The overrepresentation of individuals of European descent reduces the risk of population stratification bias but restricts the applicability of our results to other ethnicities. Lastly, due to the absence of pertinent GWAS data, subsequent stratified analysis based on gender and age cannot be conducted.

Conclusion

This study indicates that genetically determined GERD is linked to a higher likelihood of PTB. Our research emphasizes the significance of focusing on pregnant women with GERD to identify early indicators of PTB and implement prompt

therapies to extend pregnancy and improve maternal-fetal outcomes. More investigation is required to explore the underlying mechanism.

Data Sharing Statement

The datasets for this study can be found in the IEU open GWAS project, at https://gwas.mrcieu.ac.uk/.

Ethics Statement

This study uses publicly available anonymized data obtained from the UK Biobank, the FinnGen consortium, the GIANT consortium, and the MRC-IEU consortium. According to the Health Insurance Portability and Accountability Act (HIPAA) in the United States and the General Data Protection Regulation (GDPR) in the European Union, the use of such anonymized data does not require Institutional Review Board (IRB) approval. The specific reasons for the exemption are as follows: The data have been de-identified and cannot be traced back to individual subjects. The data are publicly available and do not involve personal identifiable information.

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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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Disclosure

The authors declared no competing interests in this work.

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