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ORIGINAL RESEARCH

Genetic Insights Into Lipid Traits and Lipid-Modifying Drug Targets in Pregnancy Complications: A Two-Sample Mendelian Randomization Study

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Background: Dyslipidemia is linked to pregnancy complications, but its causal role remains uncertain. This two-sample Mendelian Randomization (MR) study investigated the causal relationship between lipid traits and pregnancy complications and evaluated the impact of lipid-modifying drug targets.

Methods: Genetic instruments for lipid traits and targets for lipid-modifying drugs were obtained from the Global Lipids Genetics Consortium. Three pregnancy complications' summary statistics came from the FinnGen R9 database. Significant drug targets underwent further analysis using Expression Quantitative Trait Loci data, and mediation analysis identified potential mediators.

Results: Increased high-density lipoprotein cholesterol (HDL-C) reduced the incidence of preeclampsia (OR: 0.755, 95% CI: 0.639–0.891, p=0.001, FDR=0.012) and gestational diabetes mellitus (GDM) (OR: 0.835, 95% CI: 0.741–0.942, p=0.003, FDR=0.018). Genetic proxies for cholesteryl ester transfer protein (*CETP*) inhibition correlated with a decreased risk of preeclampsia (OR: 0.863, 95% CI: 0.786–0.947, p=0.002, FDR=0.027), while genetic inhibition of HMG-CoA reductase (*HMGCR*) increased preeclampsia risk (OR: 1.700, 95% CI: 1.189–2.431, p=0.004, FDR=0.036). Genetically mimicking the enhancement of lipoprotein lipase (*LPL*) related to a reduced risk of GDM (OR: 0.681, 95% CI: 0.560–0.829, $p=1.29\times10^{-4}$, FDR=0.004). Higher *LPL* expression in subcutaneous adipose tissue also reduced GDM risk (OR: 0.642, 95% CI: 0.454–0.909, p=0.013). Waist circumference (4.2%) and waist-to-hip ratio adjusted by BMI (5.7%) partially mediated *LPL*'s effect on GDM risk.

Conclusion: Elevated HDL-C levels help prevent preeclampsia and GDM. *CETP* and *LPL* could be therapeutic targets for preeclampsia and GDM, respectively. However, caution is advised with *HMGCR*-targeting drugs, as they may increase the preeclampsia risk.

Keywords: lipids, lipid-modifying drugs, preeclampsia, gestational diabetes mellitus, Mendelian randomization

Introduction

Pregnancy complications often pose a significant threat to the maternal and fetal health. Among the various pregnancy complications, preeclampsia, gestational diabetes mellitus (GDM), and intrahepatic cholestasis of pregnancy (ICP) stand out due to their high incidence rate. These conditions also have substantial negative impacts on both the mother and the fetus.[1–3] Currently, substantial research has been conducted on these complications; however, the underlying mechanisms remain poorly understood, and the available treatment options are limited and often ineffective. Therefore, it is imperative to investigate the risk factors and potential mechanisms of these complications to develop appropriate prevention and treatment strategies for them. Recently, there has been a growing focus on the role of dyslipidemia in

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these issues. In a large-scale population study involving 9911 women, Arnon et al observed substantial elevation of total cholesterol (TC) and triglyceride (TG) levels in both preeclampsia and GDM.[4] Enquobahrie et al discovered a correlation between reduced high-density lipoprotein cholesterol (HDL-C) levels and the higher incidence of preeclampsia and GDM.[5] Additionally, a meta-analysis that included nine studies and 786 participants discovered that patients with ICP exhibited elevated TC, TG, and low-density lipoprotein cholesterol (LDL-C) in comparison to healthy pregnant women.[6] Nevertheless, these conventional studies cannot confirm a direct causal link between lipid traits and the three pregnancy complications. Confounding factors and reverse causation may obscure the true relationship.

Moreover, given the strong association between dyslipidemia and these complications, exploring the potential benefits of lipid-modifying drugs for affected individuals has garnered increasing interest. Currently, several lipid-modifying drugs are commonly used in clinical practice, including statins, cholesterol absorption inhibitors, bile acid sequestrants, niacin, fibrates, omega-3 fatty acids, and their derivatives.[7,8] Among these, statins are the most commonly used class of lipid-modifying drugs. Their primary mechanism of action involves reduction of LDL-C levels.[9,10] In addition, statins exhibit anti-inflammatory, antioxidant, endothelial function-enhancing, plaque-stabilizing, and anti-thrombotic properties.[11–13] These multifaceted actions make statins a cornerstone in the treatment of cardiovascular diseases and systemic inflammatory conditions.[14] Preeclampsia is a severe pregnancy complication caused by abnormal placental development, leading to maternal endothelial damage and systemic inflammatory response.[1] Growing evidence suggest that statins hold promise for preventing preeclampsia. For instance, Kumasawaet et al discovered that pravastatin stimulated the production of placental growth factor and improved the symptoms of preeclampsia in a mouse model.[15] In human studies, early reports indicated that the use of pravastatin in women with preeclampsia resulted in improved blood pressure and better pregnancy outcomes.[16] However, a recent larger multicenter randomized controlled trial (RCT) found that pravastatin treatment for preeclampsia failed to show any benefit. It potentially even caused harm.[17] This discrepancy underscores the need for further investigation. Furthermore, research on the efficacy of lipid-modifying drugs for GDM and ICP, remains limited.

To address these research gaps and inconsistencies, our study employed a two-sample Mendelian Randomization (MR) approach. This method uses genetic variants as instrumental variables to provide stronger causal evidence by minimizing confounding and reverse causation. Compared to traditional observational studies, MR offers a more robust way to clarify causal relationships. For drug targets, genetic variations in genes that encode protein targets can affect gene expression or function similarly to how drugs act, potentially predicting outcomes in RCTs.[18,19] Moreover, unlike the gold standard RCTs used to determine drug efficacy, MR analysis does not involve direct interventions on study subjects, making it particularly suitable for studying special populations such as pregnant women and fetuses. Currently, MR studies have been extensively applied to investigate causal links in a variety of diseases, such as cardiovascular diseases, diabetes, psychiatric disorders, and many other complex diseases.[20,21] Our study aimed to use a two-sample MR approach to examine the causal relationships between lipid traits and the incidence of preeclampsia, GDM, and ICP. We also assessed how lipid-modifying drug targets could inform clinical strategies. These findings could offer valuable insights for developing more targeted and effective treatments to prevent and manage these complications in pregnant women.

Materials and Methods

Study Design

This two-sample MR study adhered to the guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology-Mendelian Randomization (STROBE-MR) framework (Table S1). [22] All these studies had been approved by the relevant institutional review boards and participants had provided informed consents. The study's workflow was illustrated in Figure 1.

Data Source

GWAS data for lipid levels of TC, HDL-C, LDL-C, and TG were from the Global Lipids Genetics Consortium (GLGC). The GLGC is one of the largest GWAS studies on blood lipid levels to date, including data from 60 studies with up to

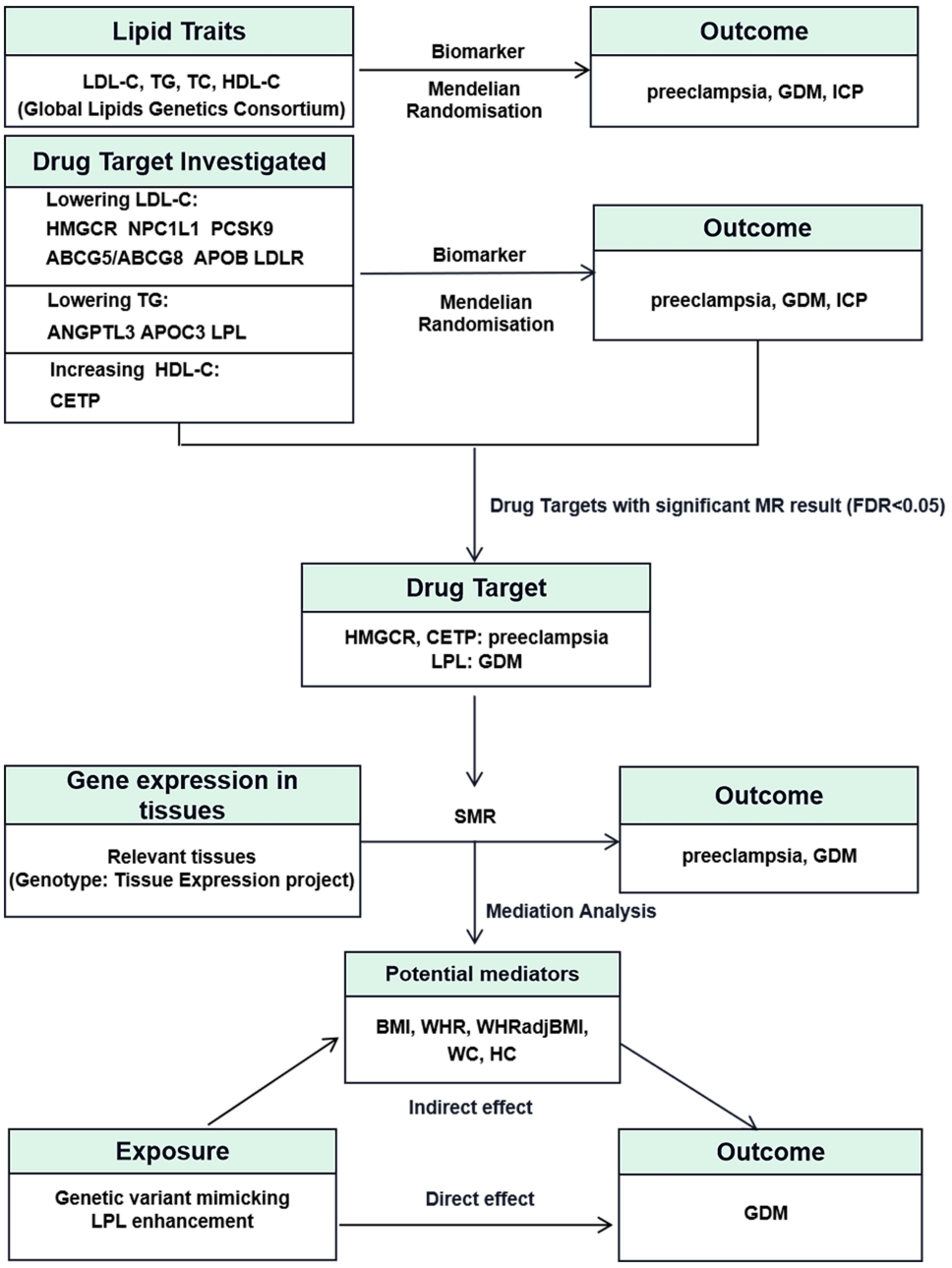

Figure 1 Workflow of the study design.

188,577 participants. The blood lipid levels are typically reported in milligrams per deciliter (mg/dL). The participants come from diverse genetic backgrounds, with the majority of studies focusing on European populations to ensure consistency in the analysis. The effect estimates were adjusted for age, age squared, sex, and population stratification, and participants using lipid-lowering medications were excluded when possible. Moreover, this lipid data were used to screen the gene targets of drugs with demonstrated effects on lipid levels in preparation for our subsequent drug-target MR analysis. Table S2 provides detailed information about this dataset.

The outcome of this investigation was preeclampsia, GDM, and ICP. The GWAS data for the three diseases were sourced from the FinnGen consortium R9 release,[23] encompassing preeclampsia (6663 cases and 194,266 controls), GDM (13,039 cases and 197,831 controls), and ICP (2003 cases and 130,682 controls). All cases were diagnosed and coded using the International Classification of Diseases (ICD-10) codes. Preeclampsia, GDM, and ICP were identified

using ICD-10 codes O14, O24.4, and O26.6, respectively. All enrolled participants in this study are of European descent. Adjustments were made for factors including sex, age, the first ten principal components, and genotyping batch. Detailed information about these datasets were presented in Table S2.

For mediation analysis, we selected five obesity-related phenotypes - body mass index (BMI), waist-to-hip ratio (WHR), WHR adjusted for BMI (WHRadjBMI), waist circumference (WC), and hip circumference (HC) - as potential mediators between *LPL* and the risk of GDM. Excessive weight gain during pregnancy is recognized as a significant risk factor for GDM. Research has demonstrated that women who experience excessive weight gain in early pregnancy are at an increased risk of developing GDM. Additionally, WHR, WHRadjBMI, WC, and HC were indicators of central obesity. Central obesity, particularly an increase in visceral fat, is recognized as a key driver of glucose metabolism abnormalities and a significant predictor of GDM development.[24] Understanding how these factors mediate the effects of lipid-targeting drugs on GDM could offer valuable insights into the underlying mechanisms. Summary statistics from large-scale GWAS by the Genetic Investigation of Anthropometric Traits (GIANT) consortium and UK Biobank[25] were used to identify genetic instruments for BMI (n=806,834), WHR (n=697,734), and WHRadjBMI (n=694,649). SNPs associated with WC (sample size = 462,166) and HC (sample size = 462,117) were extracted from the largest publicly available UK Biobank GWAS datasets and utilized as genetic instruments.[26] These datasets were chosen for their large sample sizes and public availability, which provided higher statistical power and improved the reliability of our results. Moreover, both datasets consist of independent cohorts of individuals of European descent, which helped minimize heterogeneity across studies. Specific data information of these data source were provided in Table S2.

Genetic Instrumental Variable Selection

Genetic instruments are composed of one or more genetic variants and are utilized as instrumental variables (IVs) in MR analysis due to their specific properties. For an IV to be valid in MR analysis, it must fulfill three core assumptions. First, the relevance assumption requires a significant association between the IV and the exposure of interest. Second, the independence assumption mandates that the IV is not linked to any confounding variables. Third, the IV must be independent of the outcome and exert its effect on the outcome exclusively through the exposure. To ensure the validity of our instrumental variables (IVs) in the MR analysis, we followed a rigorous quality control process. First, to meet the relevance assumption, we identified independent, eligible, and genome-wide significant single-nucleotide polymorphisms (SNPs) associated with TC, LDL-C, TG, and HDL-C levels, using a significance threshold of $p < 5\times10^{-8}$. We performed linkage disequilibrium (LD) clumping with an r^2 threshold of < 0.001 to ensure that the SNPs were independent and not in strong correlation with each other. Additionally, to address the independence assumption, we excluded SNPs that showed palindromic characteristics, which could lead to strand ambiguity. We also checked SNPs for potential pleiotropic effects using the PhenoScanner database, excluding those directly related to the outcomes (preeclampsia, GDM, ICP) or possibly influencing outcomes through confounding factors. To meet the exclusion restriction assumption, we ensured that the selected SNPs only affected the outcomes through the lipid traits and did not have a direct effect on the outcomes. Furthermore, we computed the F-statistic (β^2/SE^2) for each SNP. The F-statistic is calculated to evaluate whether the selected SNPs effectively serve as instrumental variables and meet the relevance assumption. An F statistic greater than 10 is generally considered indicative of strong instruments, minimizing the risk of weak instrument bias that could otherwise invalidate the results.[27]

For the identification of IVs for drug targets, we first used DrugBank (https://go.drugbank.com/) to identify the gene targets of lipid-modifying drugs. These drugs include both licensed and in-development treatments such as statins, ezetimibe, bile acid sequestrants, mipomersen, fibrates, and PCSK9 inhibitors. We categorized them into three groups based on their primary pharmacological effects: (1) LDL-C-lowering drugs targeting *ABCG5, ABCG8, APOB, HMGCR, LDLR, NPC1L1*, and *PCSK9*; (2) TG-lowering drugs targeting *APOC3, ANGPTL3, LPL*, and *PPARA;* and (3) HDL-C-increasing drugs targeting *CETP*.[28–31] The specific gene targets for these drugs are detailed in Table S3. Subsequently, we applied the same methodology as before to identify genetic variants which mimic the lipid-modifying effect of the drug targets.[32] Specifically, we first selected SNPs that are highly correlated ($p < 5\times10^{-8}$) with TG, LDL-C, and HDL-C levels in the GWAS meta-analysis from the GLGC. To ensure robustness, these SNPs were required to be within a 100 kb window, have an LD $r^2 \leq 0.2$, and a minor allele frequency (MAF) > 1%. These criteria ensure that the SNPs can be used

as proxies for lipid-modifying drug targets. F-statistic were also conducted for the weak-instrument test. However, since none of the genetic variants of *PPARA* were found in the variant selection process, it was excluded from further evaluation. Additionally, due to the close proximity of the *ABCG5* and *ABCG8* genes on chromosome 2 (located at positions 44,039,611–44,066,004 and 44,066,103–44,105,605, respectively), we combined variants near these genes in our analyses. Ultimately, the drug-target MR analysis consisted of ten drug target genes: *ABCG5/ABCG8, ANGPTL3, APOB, APOC3, CETP, HMGCR, LDLR, LPL, NPC1L1*, and *PCSK9*. Specific information about these drug targets can be found in Table S3. To ensure the accuracy of the selected drug target genetic variants, we tested them using coronary artery disease (CAD) as a positive control. For CAD, the summary-level data were sourced from the Coronary Artery Disease Genome-wide Replication and Meta-analysis plus the Coronary Artery Disease Genetics Consortium (CARDIoGRAMplusC4D).[33]

For drug target genes significantly associated with pregnancy complications, we further leveraged open-access eQTL data from the eQTLGen Consortium, encompassing 31,684 individuals,[34] and the Genotype-Tissue Expression project (GTEx-V8) , which comprises data from 838 donors across 49 tissue types,[35] to perform additional summary-data-based MR (SMR) analysis. In SMR analysis, we first selected eQTL SNPs (with a MAF >1%) that had a significant correlation ($p < 5.0\times10^{-8}$) with the expression of *HMGCR* and *CETP* in blood, as well as *LPL* and *CETP* in subcutaneous adipose tissue. Moreover, this study focused exclusively on cis-eQTLs, which are eQTLs located within 1 Mb of the encoded gene.

Statistical Analysis

We used the inverse-variance weighted Mendelian Randomization (IVW-MR) method as the primary approach to assess the collective influence of genetic factors associated with lipid traits and lipid-modifying drug targets on three pregnancy complications. This method combines all valid instruments by meta-analyzing SNP-specific Wald estimates, with each weighted by the inverse of its variance, providing a comprehensive evaluation of their effects.[36] To facilitate the interpretation of how lipid-modifying drug targets impact the risk of these complications, the odds ratios (ORs) were adjusted to reflect a 1-mmol/L change in genetically predicted lipid levels. This adjustment corresponds to 88.9 mg/dL for TG, 38.7 mg/dL for LDL-C, 40.0 mg/dL for HDL-C, and 41.8 mg/dL for TC. An OR greater than 1 indicates that for every 1 mmol/L increase in lipid levels, the disease risk increases, while an OR less than 1 suggests that higher lipid levels may be associated with a reduced disease risk. The Benjamini-Hochberg false-discovery rate (FDR) procedure was applied to adjust the raw p-values for multiple testing of four lipid traits and ten drug targets. The purpose of FDR correction is to reduce false discoveries arising from multiple testing, thereby enhancing the reliability of the results. FDR-adjusted p-values were considered significant if less than 0.05.

We also conducted several sensitivity analyses to assess the reliability and stability of the results. First, we used the weighted median method and MR-Egger regression to test the robustness of the IVW-MR analysis under less stringent assumptions. The weighted median method provides reliable estimates even when up to 50% of SNPs are invalid instruments, reducing bias from invalid instruments. MR-Egger regression not only gives effect estimates but also helps detect potential confounding by evaluating pleiotropy through its intercept term. Second, we employed Cochran's Q test to examine the heterogeneity between SNPs in the IVW-MR estimates. When heterogeneity exists and the effect of weighted median method was significant, we adopted the effect estimates of the weighted median method, which is reliable even when more than half of the SNPs are invalid or weak.[37] Third, we utilized Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO) to determine and rectify the horizontal pleiotropy and outliers.[38] Afterwards, to explore directional pleiotropy, MR-Egger intercepts[39] were employed and a p-value of less than 0.05 was taken as an indication of significant pleiotropy. Finally, we performed a "leave-one-out" analysis by systematically removing each SNP one at a time to assess the impact of each individual SNP on the primary causal association.

For drug targets found to be significantly correlated with pregnancy complications in the MR analysis, SMR was used to further investigate any existing relationships between gene expression and the diseases.[34] In SMR analysis, eQTL data were determined by a 1-standard deviation (SD) rise in the expression of genes for each additional effect allele. A threshold of 0.05 for p-values was used to determine statistical significance. Additionally, we conducted the heterogeneity in dependent instruments (HEIDI) test to examine potential linkage in the observed associations. A HEIDI test p-value below 0.05 suggests a high likelihood that two distinct genetic variants are strongly correlated, thereby

influencing the observed relationship.[40] SMR and HEIDI analyses were conducted as previously described (SMR software: http://cnsgenomics.com/software/smr/).

A two-step MR mediation analysis was performed to investigate if the five obesity-related risk factors (BMI, WHR, WHRadjBMI, WC, and HC) mediated *LPL*'s effects on GDM. The "total" effect of an exposure on an outcome encompasses both the "direct" effect and any "indirect" effects through mediators. In this study, a standard univariable MR analysis, the primary MR, was used to capture the "total" effect. In addition, to separate the "direct" effect and "indirect" effect, we used the "Two-Step Cis-MR technique".[41] The "product of coefficients" method was employed to estimate the indirect effect's beta, while the Delta method was used to calculate the standard error (SE) and confidence interval (CI).[42] The two-step MR approach minimizes the risk of confounding and reverse causation by first selecting genetic instruments that are strongly associated with the exposure. In the second step, it adjusts for potential mediators, reducing bias from unmeasured confounders that could otherwise affect the estimation of mediation effects in traditional observational analyses.

All analyses in this study were performed via "TwoSampleMR" (version 0.5.6), "Mendelian randomization" (version 0.5.1), "MR-PRESSO" (version 1.0) and "TwoStepCisMR" packages in R (version 4.2.1). All the aforementioned software packages are publicly available.

Results

Casual Effect of Lipid Traits on Pregnancy Complications

It was found that 81 SNPs showed a significant correlation with LDL-C, 55 with TG, 88 with TC, and 74 with HDL-C. The genetic proxies had F statistics ranging from 27.8 to 1663.1, indicating a low likelihood of weak instrument bias affecting our results (Tables S4–S7). Moreover, we found that higher level of genetically-determined HDL-C were related to a lower risk of preeclampsia (OR: 0.755, 95% CI: 0.639–0.891, p=0.001, FDR = 0.012) (Figure 2A and Table S8), as well as a reduced risk of GDM (OR: 0.835, 95% CI: 0.741–0.942, p=0.003, FDR=0.018) (Figure 2B and Table S8). Nevertheless, no causal link was found between lipid traits and ICP risk (Figure 2C and Table S8). Figure 2D and E displayed scatter plots illustrating the relationship between HDL-C and either preeclampsia or GDM.

Sensitivity analyses including MR Egger and weighted median provided additional evidence for the robustness of the results (Table S8). The leave-one-out analysis further confirmed the robustness of the results, demonstrating that no single SNP disproportionately influenced the overall causal estimates (Figure S1). This analysis helps ensure that the observed associations are not driven by outliers or a single strong instrumental variable, thus enhancing the reliability of our findings. In addition, the MR-Egger test (Table S9) revealed no pleiotropic SNPs in the MR study. The results of MR-PRESSO also indicated no horizontal pleiotropy in this MR analysis (Table S15). Nevertheless, the Cochran Q test revealed some heterogeneity between the four lipid traits and the three pregnancy complications (Table S9).

Casual Effect of Lipid-Modifying Drug Targets on Pregnancy Complications

We identified SNPs serving as genetic instruments for ten lipid-modifying drug targets: *ABCG5/ABCG8* (7 SNPs), *ANGPTL3* (3 SNPs), *APOB* (15 SNPs), *APOC3* (12 SNPs), *HMGCR* (5 SNPs), *LDLR* (12 SNPs), *LPL* (15 SNPs), *NPC1L1* (3 SNPs), *PCSK9* (11 SNPs), and *CETP* (37 SNPs). We also computed the F statistics of these genetic instruments to evaluate their strength. F statistics from 29.2 to 1837.0 indicated that instrument bias would not affect our analyses (Table S10). In addition, we performed positive control analyses to confirm the effectiveness of the genetic instruments. Apart from *ANGPTL3*, significant correlations between genetically determined drug targets and a lower risk of CAD were observed, demonstrating that our genetic instruments are effective for studying the impact of lipid-modifying drugs (Figure S2). Our primary results are illustrated in Figure 3, highlighting the associations between ten lipid-modifying drugs and the risk of three pregnancy complications. Genetic mimicry of *CETP* inhibition showed a strong relationship with a reduced risk of preeclampsia (OR: 0.863, 95% CI: 0.786–0.947, p=0.002, FDR=0.027) (Figure 3A and Table S11). In contrast, genetic proxies of *HMGCR* inhibition were associated with an increased risk of preeclampsia (OR: 1.700, 95% CI: 1.189–2.431, p=0.004, FDR=0.036) (Figure 3A and Table S11). Furthermore, genetic enhancement of *LPL* was significantly linked to a lower risk of GDM (OR: 0.681, 95% CI: 0.560–0.829, $p=1.290\times10^{-4}$,

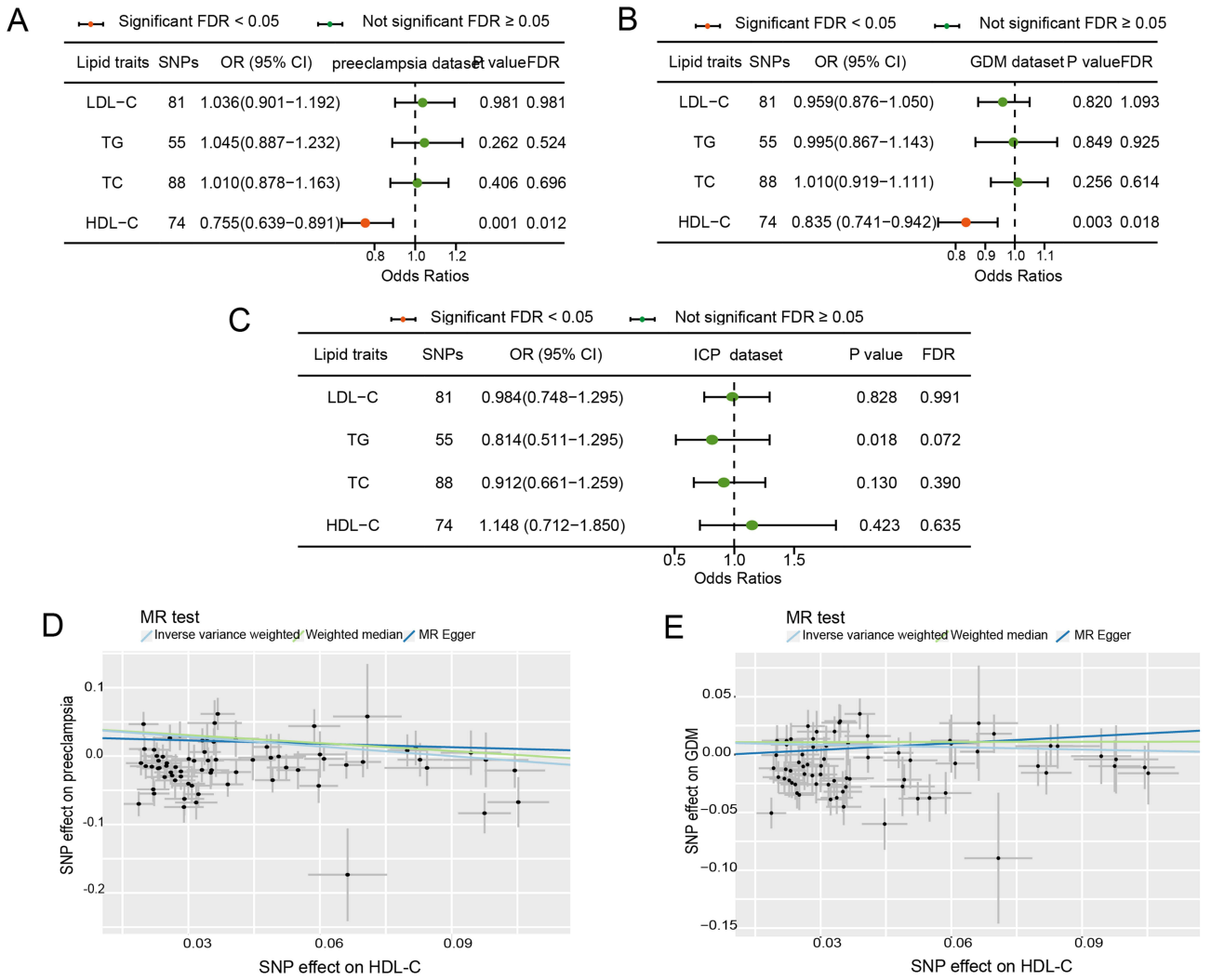

Figure 2 Association of four lipid traits with the risk of pregnancy complications in IVW-MR analysis. (**A**) The forest plot shows the correlation between the four lipid traits and the risk of preeclampsia; (**B**) and risk of GDM; (**C**) and risk of ICP; (**D**) Scatter plot showing the correlation between the effects of SNPs on HDL-C level and the effects of SNPs on preeclampsia; (**E**) Scatter plot showing the correlation between the effects of SNPs on HDL-C level and the effects of SNPs on GDM.

FDR=0.004) (Figure 3B and Table S12). However, no causal relationship was found between genetic mimicries of other drug targets and ICP (Figure 3C and Table S13).

Furthermore, we supplemented the IVW-MR method with alternative approaches such as weighted median and MR Egger methods. The results from the alternative methods consistently supported those obtained from IVW-MR, which underscores the robustness of our findings (Tables S11-S13). Sensitivity analysis using Cochran's Q statistic revealed there was no significant heterogeneity among the effects of the instrument SNPs (Table S14). Moreover, neither the MR-Egger intercept nor the MR-PRESSO test detected any evidence of pleiotropy, which increases the reliability of our causal estimates (Tables S14 and S15). Additionally, the leave-one-out plot suggested that individual SNP had no significant influence on the observed results (Figure S3).

SMR Analysis Between Gene Expression and Preeclampsia or GDM Risk

Given the causal relationships between *CETP, HMGCR*, and *LPL* with the risks of preeclampsia and GDM in IVW-MR analysis, we utilized genetic variations associated with the expression of *CETP, HMGCR*, and *LPL* in whole blood and subcutaneous adipose tissue to further validate their unique associations with the risks of preeclampsia and GDM. In SMR analysis, a 1-SD increase in *LPL* expression in subcutaneous adipose tissue was linked to a reduced risk of GDM (OR: 0.642,

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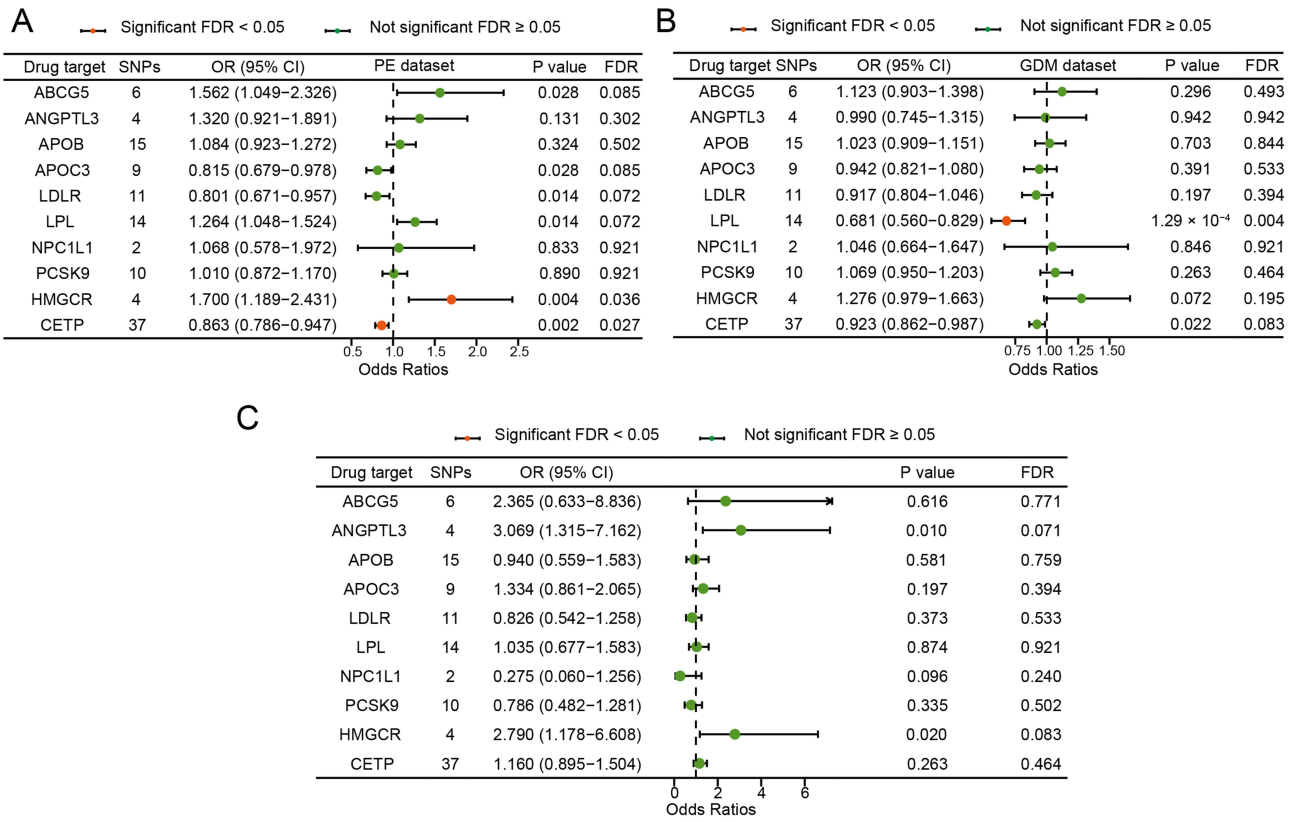

Figure 3 Association of nine drug targets with the risk of pregnancy complications in IVW-MR analysis. (**A**) The forest plot shows the correlation between a 1-mmol/L alteration in the lipid levels of ten lipid-modifying drug targets and the risk of preeclampsia; (**B**) and risk of GDM; (**C**) and risk of ICP.

95% CI: 0.454–0.909, p=0.010) (Table S16). In addition, while there was a possible negative correlation between *HMGCR* expression in whole blood and the risk of preeclampsia, it did not reach a statistically significant level (OR: 0.823, 95% CI: 0.617–1.099, p=0.187). Similarly, the relationship between *CETP* expression and preeclampsia risk in SMR analysis generally mirrored IVW-MR findings, though these results were not statistically significant (blood tissue: OR: 1.083, 95% CI: 0.826–1.421, p=0.563, adipose tissue: OR: 1.020, 95% CI: 0.893–1.165, p=0.774) (Table S16).

Mediation Analysis

To investigate the indirect effect of *LPL* on the outcome of GDM via risk factors (BMI, WHR, WHRadjBMI, WC, and HC), we carried out a mediation analysis using the effect estimates from two-step MR and the total effect from primary MR. From the mediation effect analysis, we derived β_{EM} (effects of exposure on mediator), β_{MO} (effects of mediator on outcome), and β_{EO} (effects of exposure on outcome). Using these coefficients, we computed the mediation effects of *LPL* on GDM ($\beta_{EM}\times\beta_{MO}/\beta_{EO}$). The mediation effect of *LPL* enhancement through WHRadjBMI accounts for approximately 5.7% (Figure 4A and Table S17), whereas the effect through WC is slightly lower, at 4.2% (Figure 4B and Table S17).

Discussion

This MR study offers convincing evidence of causal relationships between lipid traits and pregnancy complications, demonstrating the potential role of lipid-modifying drug targets in preeclampsia and GDM. These findings are of great significance for understanding the pathophysiology of pregnancy complications and guiding therapeutic interventions, particularly for preeclampsia and GDM.

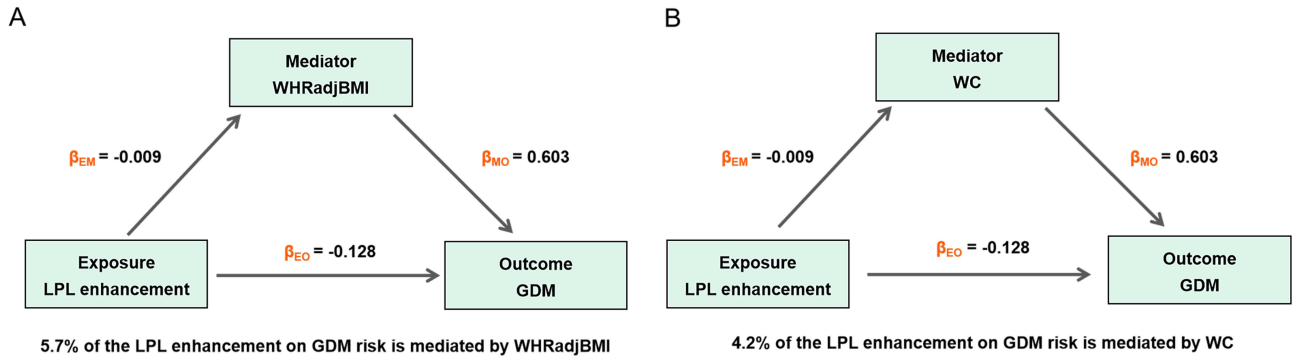

Figure 4 Mediation analysis of the effect of *LPL* on GDM via potential mediators. (**A**) *LPL* effect on GDM mediated by WC; (**B**) *LPL* effect on GDM mediated by WC.
Abbreviations: β_{EM}, effects of exposure on mediator; β_{MO}, effects of mediator on outcome; β_{EO}, effects of exposure on outcome.

HDL-C levels and the risk of preeclampsia and GDM

Firstly, our study revealed a significant association between increased HDL-C levels and reduced risks of preeclampsia and GDM. Specifically, each unit increase in HDL-C was linked to a 24.5% lower risk of preeclampsia and a 16.5% lower risk of GDM. Some observational studies have reported lower HDL-C levels in patients with preeclampsia and GDM,[43,44] which is consistent with our findings. Nevertheless, observational studies cannot rule out potential bias and confounding factors. Our MR study provided robust evidence, confirming a causal relationship between increased HDL-C levels and reduced risks of preeclampsia and GDM. This finding significantly contributes to the existing literature, particularly by being the first to establish a causal link between HDL-C and GDM, filling a gap in the field. HDL-C is an important plasma lipoprotein that protects vascular health through its role in promoting reverse cholesterol transport and exhibiting antioxidant effects.[45] Biologically, HDL-C may help reduce the risk of preeclampsia and GDM. It does so by improving endothelial function and reducing oxidative stress and inflammation, which are closely linked to the development of these conditions.[46,47] However, further research is needed to fully elucidate the underlying mechanisms.

Additionally, in the Cochran Q test, we observed significant heterogeneity between the four lipid traits and three pregnancy complications, which can be attributed to two main factors: First, the differential effects of genetic instruments on the exposure. Different genetic loci may influence the exposure through multiple biological pathways, introducing heterogeneity. Second, the relationship between the exposure and disease outcomes may be complex, involving non-linear effects or multiple intermediate mechanisms. Different genetic variants may be linked to specific biological processes, leading to variations in the exposure's effects on disease outcomes.[48] To address this heterogeneity, we employed random effects models which combines inter-group heterogeneity with intra-group heterogeneity and reduces bias. Therefore, despite the observed heterogeneity, the direction and magnitude of the causal effects remained consistent across the sensitivity analyses and statistical models, reinforcing the robustness of our conclusions and indicating that they reflect true biological relationships.

CETP Inhibition and the Risk of Preeclampsia

Moreover, our drug-target MR analysis revealed that genetic proxies for *CETP* inhibition was associated with a reduced risk of preeclampsia. This result aligned with the findings of a multi-ethnic MR study by Hosier et al, which reported that *CETP* inhibition, a drug target that increases HDL-C, may protect against preeclampsia.[49] These findings suggest that targeting *CETP* could be a promising therapeutic approach for preventing preeclampsia. *CETP* is a key plasma protein responsible for facilitating cholesterol exchange between HDL-C and LDL-C. By increasing HDL-C levels and decreasing LDL-C levels, *CETP* inhibition may improve vascular function and reduce inflammation and oxidative stress, thereby lowering the risk of preeclampsia.[50] Currently, studying the functional roles of *CETP* and its molecular mechanisms in lipid metabolism helps identify potential drug targets. These targets could improve lipid profiles and reduce cardiovascular risk.[51] However, research on *CETP* in the context of preeclampsia remains extremely limited. Future studies should include larger-scale cohort studies to further validate the relationship between *CETP* and

preeclampsia. Additionally, functional investigations are needed to elucidate the specific biological roles of *CETP* in the pathogenesis of preeclampsia.

HMGCR Inhibition and the Risk of Preeclampsia

We found that LDL-C reduction due to *HMGCR* inhibition was associated with an increased risk of preeclampsia, consistent with previous research findings. *HMGCR* is the rate-limiting enzyme in the cholesterol synthesis pathway, and its inhibition may affect placental function and development. Existing studies have indicated that disruptions in cholesterol metabolism may lead to placental dysfunction, contributing to the development of preeclampsia.[52] Furthermore, preeclampsia is linked to imbalances in anti-angiogenic and pro-angiogenic factors. Raghu et al demonstrated that *HMGCR* may play a role in the pathogenesis of preeclampsia by influencing this balance.[52] Statins, lipid-lowering drugs that reduce blood LDL-C levels by inhibiting *HMGCR* activity, have gained significant attention for their potential to prevent preeclampsia. Preclinical studies, primarily in animal models, suggest that statins may provide vascular protection through their cholesterol-lowering and pleiotropic effects, potentially benefiting the management of preeclampsia.[53] However, a high-quality RCT found that pravastatin did not reduce the risk of preeclampsia.[17] The inconsistent findings on statins' efficacy in preeclampsia may result from differences in study design, drug type, dosage, and patient characteristics. Our MR analysis provided robust genetic evidence linking *HMGCR* inhibition with an increased risk of preeclampsia. Moreover, our results aligned with concerns raised by existing guidelines and highlighted the complexity of lipid metabolism during pregnancy. While statins are widely used in lipid management outside of pregnancy, their use in pregnancy-related complications must be carefully considered. These findings underscore the need for caution in using statins for pregnancy complications. Future research could investigate whether *HMGCR* inhibition affects placental lipid metabolism and how it might influence placental function, potentially contributing to preeclampsia. Additionally, large-scale RCTs could help determine whether statins are effective and safe for preventing preeclampsia, taking into account patient characteristics and treatment regimens.

LPL Enhancement and the Risk of GDM

In recent years, research on GDM has increasingly focused on lipid metabolism regulation, expanding the understanding of its pathophysiology beyond glucose control.[54] However, the role of lipid-lowering therapies in GDM management remains unclear, and this gap in knowledge highlights the significance of our findings. For the first time, our two-sample MR analysis demonstrated that genetically mimicked *LPL* enhancement is associated with a reduced risk of GDM. Furthermore, SMR analysis showed that higher *LPL* expression in subcutaneous adipose tissue is closely linked to a lower risk of GDM. *LPL* is a key lipolytic enzyme that breaks TG in lipoproteins, maintaining lipid balance in the blood.[27] Recent studies have demonstrated that genetic variants of *LPL* can improve insulin resistance and increase insulin sensitivity, playing a critical role in the development of GDM.[55] Additionally, studies have shown that *LPL* expression in the placenta of GDM patients is reduced, which could be linked to disrupted lipid metabolism in the placenta.[55] These findings aligned with our MR results and suggested that *LPL*'s role in GDM is multifaceted, involving lipid metabolism, oxidative stress, and other factors. Targeting *LPL* could represent a promising therapeutic approach for GDM, offering potential benefits for both maternal and fetal health by improving metabolic control during pregnancy. Investigating whether increasing *LPL* activity can improve insulin sensitivity, placental function, and lipid metabolism may offer new strategies for better managing and preventing GDM, benefiting both mother and fetus.

Moreover, our mediation analysis revealed that the WHRadjBMI and WC are likely to partially mediate the effect of *LPL* enhancement on the reduced risk of GDM. This finding suggested that the influence of *LPL* on GDM risk reduction was not entirely direct but was partially channeled through its impact on these anthropometric measures. WHRadjBMI and WC are reflective of central adiposity, which is a significant determinant of insulin resistance and glucose intolerance-key pathophysiological mechanisms underlying GDM.[56] Thus, reducing WHRadjBMI and WC could help lower the risk of GDM. Specific interventions include diet control, moderate physical exercise, and early screening of weight and fat distribution during pregnancy to reduce central obesity and improve insulin sensitivity. Future research should focus on assessing the effectiveness of these strategies at different stages of pregnancy and in diverse populations, to refine early prevention and personalized treatment approaches for GDM.

Strengths and Limitations

Our study thoroughly investigated the causal effects of four genetically proxied lipid traits and widely prescribed lipid-modifying medications, including statins, fenofibrate, evinacumab, mipomersen, and anacetrapib, on pregnancy complications. Through comprehensive analysis, we made several innovative and exciting discoveries. We also conducted a series of sensitivity analyses to ensure the results were not compromised by potential bias factors. Additionally, our study focused on the European population, reducing the confounding factors from genetic background differences among different ethnic groups, making the results clearer and more accurate. However, there are also limitations in our study. Firstly, the diseases in the Finnish database were diagnosed using ICD codes, which are commonly used for disease classification. However, there may be variations in how different doctors or healthcare institutions apply these codes, which could introduce some bias. Despite this, the large sample size and rigorous methodology employed in our study help to mitigate the potential impact of these biases on our findings. Secondly, as the scope of our research was restricted to individuals of European descent, the applicability of our results to other ethnic groups remains uncertain. Genetic, environmental, and lifestyle factors differ across populations, which may affect the generalizability of our findings. To confirm whether these results hold true in non-European populations, further studies involving diverse ethnic groups are necessary. Thirdly, due to the absence of genetic variants for the *PPARA* gene during the variant selection process, it was not included in our analysis. Although this exclusion did not significantly impact the overall conclusions of our study, it is important to note that the omission of *PPARA* may have overlooked its potential role in the traits studied. Future research that includes this gene may provide further insights into its contribution. Fourthly, it's important to note that the OR value in the MR analysis only showed the causal link between genetically predicted lipid changes and disease risk, rather than absolute clinical risk in patients. More clinical trial data are needed to estimate the absolute risk reduction. Last, it is noteworthy that genetic variations reflect the influence of lifetime changes in lipid levels on the risk of preeclampsia and GDM, and the extent of this impact might not be equivalent to the immediate effects of lipid-modifying drugs.

Conclusion

In summary, our MR study provides novel insights into the causal relationships between lipid traits and pregnancy complications, highlighting potential therapeutic targets. Elevated HDL-C and genetic inhibition of *CETP* show promise in reducing the risk of preeclampsia, while *LPL* enhancement appears protective against GDM. Conversely, caution is warranted with *HMGCR* inhibition due to its association with an increased risk of preeclampsia. These findings highlight the potential for lipid-targeting interventions to improve maternal and fetal health by reducing the risk of pregnancy complications, offering new avenues for prevention and treatment strategies in clinical practice.

Abbreviations

LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; *HMGCR*, HMG-CoA reductase; *NPC1L1*, Niemann-Pick C1-like protein 1; *PCSK9*, proprotein convertase subtilisin/kexin type 9; *ABCG5*, ATP Binding Cassette Subfamily G Member 5; *ABCG8*, ATP Binding Cassette Subfamily G Member 8; *APOB*, Apolipoprotein B-100; *LDLR*, LDL Receptor; *ANGPTL3*, angiopoietin-like 3; *APOC3*, Apolipoprotein C-III; *LPL*, lipoprotein lipase; *CETP*, cholesteryl ester transfer protein; BMI, body mass index; WHR, waist-to-hip ratio; WHRadjBMI, WHR adjusted for BMI; WC, waist circumference; HC, hip circumference; GDM, gestational diabetes mellitus; and ICP, intrahepatic cholestasis of pregnancy; FDR, false discovery rate; SMR, summary-data-based Mendelian Randomization.

Data Sharing Statement

All the data is open to the public. Detailed information about these datasets can be found in Table S2.

Ethics Statement

This study was based on publicly available data and was exempt from ethical review according to Article 32, items 1 and 2 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (effective February 18, 2023), as the data used were anonymized and already ethically approved.

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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 declare no competing interests in this work.

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