BMC Pregnancy and Childbirth

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Association between gestational diabetes mellitus and offspring health: a two-sample mendelian randomization study

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Abstract

Background Gestational diabetes mellitus (GDM) constitutes a significant contributor to maternal and fetal morbidity, which is observed to be associated with future risks of offspring health. Nevertheless, it is essential to acknowledge that observational findings may be susceptible to residual confounding and bias.

Methods To investigate the association of GDM with offspring health, a genome-wide genetic association study employing Mendelian Randomization (MR) is conducted between May 31 and November 30, 2023. The inverse-variance-weighted (IVW) is utilized in the primary analysis stage. The study data of the majority patients are European ancestry, which are sourced from the IEU open genome-wide association study project.

Results Genetically predicted GDM is associated with an increased risk of various short- and long-term health problem in offspring. For fetal and neonatal conditions, GDM is linked to an elevated risk of preterm delivery [odd ratio (OR) = 1.150, false discovery rate (FDR)-adjusted $P_{IVW} = 0.009$] and placental disorders (OR = 2.143, FDR-adjusted $P_{IVW} = 0.028$). In respiratory diseases, it is associated with a higher likelihood of influenza (OR = 1.175, FDR-adjusted $P_{IVW} = 0.008$), bacterial pneumonia (OR = 1.141, FDR-adjusted $P_{IVW} = 0.008$), congenital malformations of the respiratory system (OR = 1.673, FDR-adjusted $P_{IVW} = 0.033$), influenza with pneumonia (OR = 1.078, FDR-adjusted $P_{IVW} = 0.008$), and need for non-invasive ventilation (OR = 1.265, FDR-adjusted $P_{IVW} = 0.028$). In terms of neurodevelopmental and psychiatric outcomes, GDM is linked to a higher risk of cerebral palsy (OR = 1.721, FDR-adjusted $P_{IVW} = 0.008$). For urinary conditions, GDM increases the risk of acute tubulo-interstitial nephritis (OR = 1.098, FDR-adjusted $P_{IVW} = 0.008$). No association is identified between genetically predicted GDM and major digestive diseases, such as gastroesophageal reflux, or cardiovascular conditions in offspring.

Conclusions The findings of this study provide genetic evidence supporting an association between GDM and higher risk of offspring diseases. This supports classification of GDM as risk factors for short- and long-term offspring health.

Keywords Two-sample mendelian randomization study, Causal association, Genetic analyses, Gestational diabetes mellitus

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Background

Gestational diabetes mellitus (GDM) is a metabolic disorder characterized by glucose intolerance and hyperglycemia that arises either at the onset of pregnancy or is first diagnosed during gestation. As a prevalent complication of pregnancy, GDM is influenced by a complex interplay of genetic, environmental, and lifestyle factors [1–3]. The condition affects approximately 4% to 8% of pregnancies, with prevalence rates varying based on diagnostic criteria and the populations studied [1]. According to estimates from 2015, nearly 33% of pregnant individuals with GDM in the United States experience adverse pregnancy outcomes and maternal complications. Additionally, around 25% of infants born to individuals with GDM experience poor perinatal outcomes [4]. Moreover, the prevalence of GDM has increased by over 30% in the past one to two decades in several countries, including those in the developing world, contributing to the emergence of a global epidemic [5].

GDM is linked to an elevated risk of short- and long-term adverse health outcomes in the offspring [6]. Offspring born to individuals with GDM exhibits an increased likelihood of experiencing adverse perinatal outcomes, including encompassing shoulder dystocia, neonatal hypoglycemia, stillbirth, growth abnormalities (both large and small for gestational age), preterm birth, low Apgar scores, and admission to the neonatal intensive care unit [4, 6–9]. Over the long term, exposure to GDM is anticipated to potentially predispose both the mother and her child to non-communicable diseases later in life and metabolic risks, including early-onset type 2 diabetes, obesity and cardiometabolic disorders in later life [3, 6, 10]. Long-term adverse consequences observe in offspring also encompass cardiovascular abnormalities, glucose/insulin dysfunction, allergic/respiratory health issues, and neurodevelopmental outcomes [10]. Increasing evidence suggests that disruption of hypothalamic development and function, including epigenetic modifications, as well as nutritional and environmental factors, and metabolic reprogramming, are involved in the pathogenesis of offspring diseases associated with GDM [10–13]. However, several considerations arise: (1) A systematic analysis of studies investigating the causal relationship between gestational diabetes and the risk of short- and long-term outcomes in offspring is currently lacking; (2) Observational studies are susceptible to potential confounders or reverse causality bias, hindering the establishment of reliable conclusions. Consequently, there is a need for further clarification regarding the causal impact of GDM on the risk of short- and long-term consequences for offspring.

Mendelian randomization (MR) emerges as a novel approach to investigate the causal association between GDM and the short- and long-term consequences for offspring. MR studies leverage genetic variations linked to modifiable exposures to evaluate the causal association between the exposure and disease outcome, with the goal of mitigating potential biases stemming from confounding and reverse causation [14]. MR offers a more robust understanding of the impact of these exposures on outcomes, as germline genetic variants are randomly inherited from parents to offspring. Consequently, these variants should not be associated with potential confounding factors influencing exposure–outcome associations. The genetic variant serves as a tool to establish a connection between the proposed risk factor and outcome, allowing for the estimation of this effect with less confounding and bias compared to conventional epidemiological approaches [15].

MR has been applied to investigate the causal association between GDM and various diseases, including obesity [16], autoimmune diseases [17], and gut microbiota [18]. However, there is a limited body of genetic studies investigating the relationship between GDM and the health status of their offspring. In this study, a two-sample MR analysis is conducted using genome-wide association studies (GWASs) summary statistics to assess the causal association between GDM and short- and long-term consequences for offspring.

Methods

This study employs deidentified summary-level data that have been publicly released, with ethical approval obtained in all original studies. The GWASs summary-level data employs in this study are sourced from the IEU Open GWAS project. Data analysis for this study takes place between May 31 and November 30, 2023.

Study design

To explore the associations between GDM and the short- and long-term consequences for offspring, two-sample MR analysis based on the summary statistics of GWASs is conducted comprehensively. In an instrumental variable setting, MR utilizes genetic variants as proxies for specific modifiable risk factors to estimate and test for a causal effect with an outcome. The random allocation of genetic variants at conception, following Mendel's laws, ensures independence from any confounding factors, resembling a randomized controlled trial. Furthermore, if the core assumptions (relevance, independence, and exclusion restriction assumptions) are satisfied, this study design addresses reverse causation, a potential issue in observational studies. Figure 1 illustrates the study design along with the crucial MR assumptions: (1) instrumental variables (IVs) are associated with the exposure factors, (2) IVs are not related to any confounding factors, and (3)

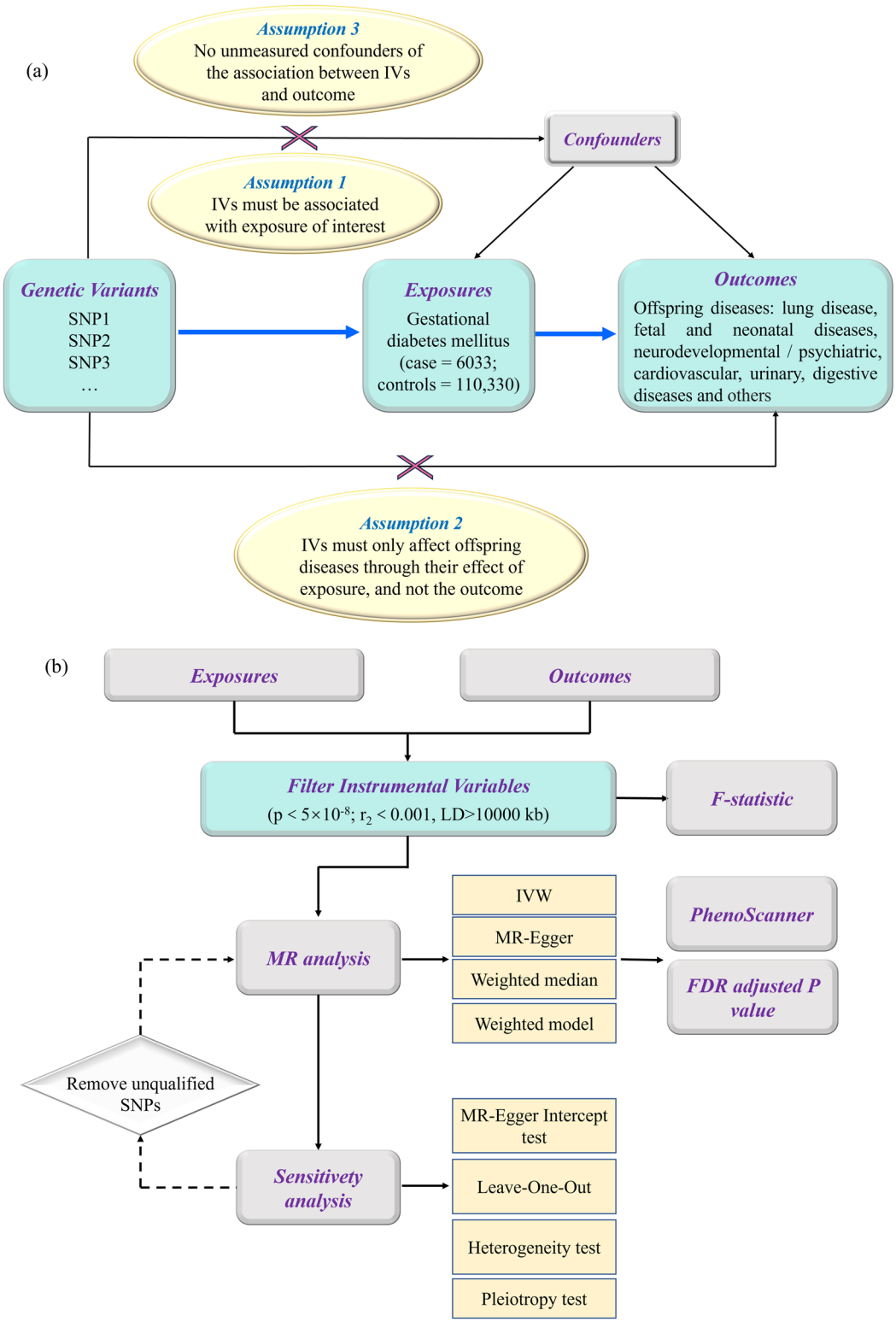

Fig. 1 Study overview and mendelian randomization model. **a** Workflow of present study and basic assumption of mendelian randomization (MR) model; **b** Workflow of the MR analysis**.** Abbreviations: MR, Mendelian randomization; SNP, single nucleotide polymorphisms; IVs, instrumental variables; LD, linkage disequilibrium; IVW, inverse variance weighting

IVs only affect the outcome through the pathway of the exposure factors [19].

Data sources and instruments

GDM genetic instrument selection

The genetic information regarding GDM as the exposure variable is derived from the largest GWAS sourced from the FinnGen biobank through the IEU Open GWAS project. This study includes 16,379,684 single nucleotide polymorphisms (SNPs) and involves 116,363 participants. The dataset for GDM, identified with the GWAS-ID of finn-b-O15_PREG_DM, comprises 6,033 cases of GDM among 116,363 women, exclusively comprising individuals of European descent. A genetic instrument for GDM is constructed from summary statistics, employing independent ($r^2=0.001$; distance, 10,000 kilobases) genome-wide significant variants ($P<5\times10^{-8}$) as the exposure, following a previously described methodology [20]. Additional details are provided in supplemental Table 1. The F-test evaluates the validity of the instruments by calculating the strength of the association between the IVs and the exposure factors. A larger F-statistic indicates a stronger association between the IVs and the exposure, thereby reducing the risk of bias from weak instruments. An F statistic exceeding 10 generally is considered as meeting the criteria for a robust association, which is a function of the magnitude and precision of the genetic effect on the trait: $F=\text{beta}^2 / \text{se}^2$. The R^2 values are estimated using the formula $R^2=2\times\text{EAF}\times(1—\text{EAF})\times\text{beta}^2$, where EAF is the effect allele frequency (EAF) of the SNP and beta is the estimated effect of SNP on trait [19]. The summary data for both GWAS analyses can be accessed from the open-access GWAS dataset at https://gwas.mrcieu.ac.uk/.

Outcome selection

Statistics for short- and long-term consequences for offspring, including lung disease, fetal and neonatal diseases, neurodevelopmental / psychiatric disease, cardiovascular system disease, urinary diseases, digestive diseases, and others, from published GWASs are collected. The GWAS summary statistics (Table 1) for these consequences are extracted by the IEU Open GWAS project.

For lung disease, the GWAS datasets includes the following cases and controls: 3,025 cases and 131,051 controls for childhood asthma (age < 16 years old), 205 cases and 218,587 controls for congenital malformations of the respiratory system, 1,107 cases and 186,723 controls for bronchiectasis, 7,987 cases and 188,868 controls for bacterial pneumonia, 4,262 cases and 188,868 controls for all influenza, 29,924 cases and 188,868 controls for influenza and pneumonia, 3,279 cases and 108,701 controls for continuous positive airway pressure, 1,254 cases and 108,701 controls for non-invasive ventilation, and 625 cases and 217,231 controls for invasive ventilation.

Regarding fetal and neonatal diseases, the sample sizes for datasets on preterm birth, placental disorders, digestive system disorders of the fetus and newborn, and transitory endocrine and metabolic disorders specific to the fetus and newborn are as follows: 104,106 (5,480 cases, 98,626 controls), 104,349 (102 cases, 104,247 controls), 218,792 (143 cases, 218,649 controls), and 218,792 (137 cases, 218,655 controls), respectively. The GWAS summary-level data for lung disease and fetal and neonatal diseases are extracted from the FinnGen biobank by the IEU Open GWAS project.

The outcomes of interest also include neurodevelopmental and psychiatric diseases, cardiovascular diseases, urinary diseases, digestive diseases, and hypothyroidism (both congenital and acquired). Summary-level data for these outcomes are sourced from the IEU GWAS database, with detailed information for each GWAS outcome provided in Table 1. In cases where instrumental SNPs are absent in the outcome dataset, proxy SNPs are applied based on a linkage disequilibrium cut-off of $R^2\geq0.8$. To ensure that genetic associations reflects the same effect allele, all instrumental variables for each trait are harmonized.

Mendelian randomization analysis

To evaluate the causal relationship between GDM (as the exposure factor) and disease risk in offspring, four analytical methods are applied. We use "phenoscanner" to eliminate confounding factors of GDM, including women age, body mass index, ethnicity, gestational age at onset, hypertension, preeclampsia, in vitro fertilization treatment etc. These methods include inverse variance weighting (IVW), MR-Egger, weighted mode (WMO), and weighted median (WME). Visualization of MR results, comprising scatter plots, forest plots, and sensitivity analysis plots, are facilitated using the "TwoSampleMR" package in the R programming language. Primarily, a generalized IVW approach to MR (IVW MR) under a multiplicative random-effects model serves as the principal analysis. False discovery rate (FDR) adjustment is applied to all *P*-value thresholds, with significance set at $P<0.05$ and FDR adjusted $P<0.05$ indicating outcome. Heterogeneity among SNP estimates is assessed using Cochrane's Q test in conjunction with IVW and MR-Egger methods, with a significance threshold of $P<0.05$ indicating the presence of heterogeneity. Pleiotropy occurs when a genetic variant (instrumental variable) affects the outcome through multiple biological pathways, rather than exclusively via the exposure of interest. This violation of the independence and exclusivity

Table 1 Study characteristics for gestational diabetes mellitus and offspring's diseases[a]

Disease	Cohort	Year	GWAS ID	Population	Number of SNP	No. Sample size	Cases	Controls
Exposure								
Diabetes mellitus in pregnancy	IEU	2021	finn-b-O15_PREG_DM	EUR	16,379,684	116,363	6033	110,330
Outcomes								
Lung Disease								
Childhood asthma (age < 16) (more controls excluded)	IEU	2021	finn-b-ASTHMA_CHILD_EXMORE	EUR	16,379,765	134,076	3,025	131,051
Congenital malformations of the respiratory system	IEU	2021	finn-b-Q17_CONGEN_MALFO_RESPI_SYSTEM	EUR	16,380,466	218,792	205	218,587
Bronchiectasis	IEU	2021	finn-b-J10_BRONCHIECTASIS	EUR	16,380,375	187,830	1,107	186,723
Bacterial pneumoniae	IEU	2021	finn-b-J10_PNEUMOBACT	EUR	16,380,385	196,855	7,987	188,868
All influenza	IEU	2021	finn-b-J10_INFLUENZA	EUR	16,380,378	193,130	4,262	188,868
Influenza and pneumonia	IEU	2021	finn-b-J10_INFLUPNEU	EUR	16,380,466	218,792	29,924	188,868
Continuous positive airway pressure	IEU	2021	finn-b-CPAP	EUR	16,379,284	111,980	3,279	108,701
Non-invasive ventilation	IEU	2021	finn-b-NIV	EUR	16,379,226	109,955	1,254	108,701
Invasive ventilation	IEU	2021	finn-b-INV_VENT	EUR	16,380,462	217,856	625	217,231
Fetal and Neonatal Diseases								
Preterm labour and delivery	IEU	2021	finn-b-O15_PRETERM	EUR	16,379,340	104,106	5,480	98,626
Placental disorders	IEU	2021	finn-b-O15_PLAC_DISORD	EUR	16,379,357	104,349	102	104,247
Digestive system disorders of fetus and newborn	IEU	2021	finn-b-P16_DIGES_SYSTEM_DISORD_FETUS_NEWBO	EUR	16,380,466	218,792	143	218,649
Transitory endocrine and metabolic disorders specific to fetus and newborn	IEU	2021	finn-b-P16_TRANSITO_ENDOCR_METABOLIC_DISORD_SPECIFIC_FETUS_NEWBO	EUR	16,380,466	218,792	137	218,655
Neurodevelopmental / Psychiatric Disease								
Cerebral palsy	IEU	2021	finn-b-G6_CP	EUR	16,380,462	217,278	286	216,992
Specific development disorders of speech and language	IEU	2021	finn-b-F5_SPEECH	EUR	16,380,459	217,658	829	216,829
Hyperkinetic disorders	IEU	2021	finn-b-KRA_PSY_HYPERKIN	EUR	16,380,466	218,792	955	217,837
Disorders of psychological development	IEU	2021	finn-b-F5_PSYCHDEV	EUR	16,380,466	218,792	1,963	216,829
Emotional disorders starting during childhood or adolescence	IEU	2021	finn-b-KRA_PSY_CHILDEMOT	EUR	16,380,466	218,792	805	217,987
Specific development disorders of scholastic skills	IEU	2021	finn-b-F5_SCHOLA	EUR	16,380,460	217,428	599	216,829
Social disorders starting during childhood or adolescence	IEU	2021	finn-b-KRA_PSY_CHILDSOC	EUR	16,380,466	218,792	129	218,663
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	IEU	2021	finn-b-F5_BEHEMOCHILD	EUR	16,380,466	218,792	3,029	215,763
Cardiovascular system								
Ischemic heart diseases	IEU	2021	finn-b-I9_ISCHHEART	EUR	16,380,466	218,792	30,952	187,840
Congenital malformations of heart and great arteries	IEU	2021	finn-b-CONGEN_HEART_ARTER	EUR	16,380,466	218,792	1,994	216,798
Chronic heart failure	IEU	2021	ebi-a-GCST90018806	EUR	24,178,220	486,160	14,262	471,898

Table 1 (continued)

Disease	Cohort	Year	GWAS ID	Population	Number of SNP	No. Sample size	Cases	Controls
Hypertrophic cardiomyopathy	IEU	2021	ebi-a-GCST90018861	EUR	24,199,797	489,727	507	489,220
Hypertensive Heart Disease	IEU	2021	finn-b-I9_HYPTENSHD	EUR	16,380,199	166,775	3,938	162,837
Atherosclerotic heart disease	IEU	2021	ukb-b-7436	EUR	9,851,867	463,010	5,771	457,239
Heart valve problem or heart murmur	IEU	2021	ebi-a-GCST90038612	EUR	9,587,836	484,598	3,742	480,856
Urinary diseases								
Urinary tract infection or kidney infection	IEU	2021	ebi-a-GCST90013940	EUR	11,037,313	397,867	NA	NA
Pyelonephritis	IEU	2021	ebi-a-GCST90018909	EUR	24,185,354	462,487	7,992	454,495
Acute tubulo-interstitial nephritis	IEU	2021	finn-b-N14_PYELONEPHR	EUR	16,380,447	212,244	11,216	201,028
Chronic tubulo-interstitial nephritis	IEU	2021	finn-b-N14_CHRONTUBULOINTNEPHRITIS	EUR	16,380,412	202,648	620	201,028
Acute glomerulonephritis	IEU	2021	ebi-a-GCST90018788	EUR	24,199,179	475,529	274	475,255
Chronic glomerulonephritis	IEU	2021	ebi-a-GCST90018820	EUR	24,199,034	475,821	566	475,255
Congenital malformations of the urinary system	IEU	2021	finn-b-Q17_CONGEN_MALFO_URINARY_SYSTEM	EUR	16,380,466	218,792	813	217,979
Digestive diseases								
Gastroesophageal reflux disease	IEU	2021	ebi-a-GCST90000514	EUR	2,320,781	602,604	129,080	473,524
Chronic gastritis	IEU	2021	ebi-a-GCST90018825	EUR	24,189,505	445,096	3,645	441,451
Peptic ulcer	IEU	2021	finn-b-K11_PULC	EUR	16,380,374	189,825	130	189,695
Inflammatory bowel disease	IEU	2021	ebi-a-GCST90038683	NA	9,587,836	484,598	4,101	480,497
Nonalcoholic fatty liver disease	IEU	2021	ebi-a-GCST90054782	EUR	9,097,254	377,998	4,761	373,227
Cirrhosis	IEU	2021	finn-b-CIRRHOSIS_BROAD	EUR	16,380,466	218,792	1,931	216,861
Other								
Hypothyroidism (congenital or acquired)	IEU	2021	finn-b-HYPOTHYROIDISM	EUR	16,378,441	86,169	26,342	59,827

Abbreviations: IEU ieu open gwas project, *ADHD* attention-deficit hyperactivity disorder, *OLS* ordinary least squares, *SNP* single nucleotide polymorphism, *EUR* European

[a] Overview of genetic data sets used in the mendelian randomization analyses. The number of cases and controls is reported for case–control studies, with total sample size reported for all studies

assumptions is assessed using the MR-Egger intercept test, with a *P*-value < 0.05 indicating the presence of pleiotropy [21]. For sensitivity analysis, the "leave-one-out" method is employed. This involves systematically removing the results associated with individual SNPs, assessing whether they are outliers, and observing the stability of the results after each SNP's removal. Additionally, the R programming language is utilized to generate a funnel plot, enabling assessment of SNP symmetry and evaluation of result reliability. In this study, all statistical analyses are carried out in R, version 4.3.0 (R Foundation for Statistical Computing), utilizing the TwoSampleMR and Mendelianrandomization packages.

Functional enrichment analysis

In our MR analysis, functional enrichment analysis is performed on the genes mapped by the IVs of GDM. The analysis is conducted using Bioinformatics (https://www.bioinformatics.com.cn/). Gene Ontology (GO) Biological Processes (BP), Cellular Components (CC), Molecular Functions (MF), KEGG pathways, and Heat Map are employed for enrichment analysis through the "clusterProfiler" R package. A significance threshold of $P < 0.05$ is applied, and the top 10 significant GO terms and pathways are visualized using the R package.

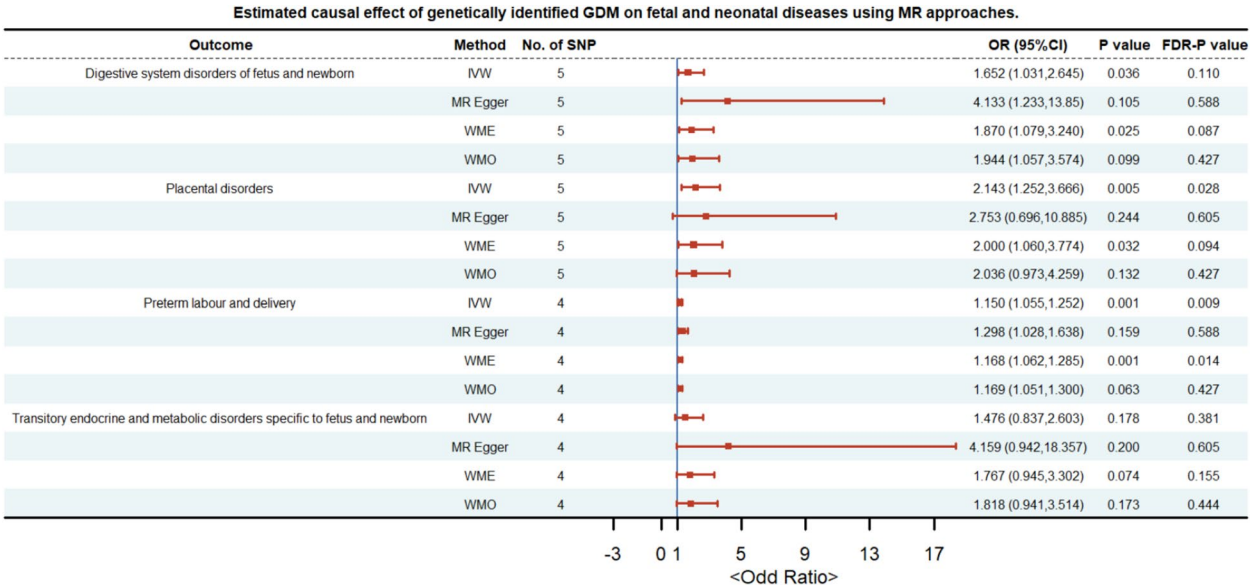

Fig. 2 Estimated causal effects between gestational diabetes mellitus (GDM) and fetal and neonatal diseases for the offspring using different mendelian randomization (MR) methods. Abbreviations: GDM, gestational diabetes mellitus; MR, mendelian randomization; SNP, single nucleotide polymorphism; IVW, inverse variance weighting; WME, weighted median; WMO, weighted mode; OR, odd ratio; FDR, False discovery rate

Results

Following screening, five independent SNPs associated with GDM are identified, and all these SNPs are included in the analyses. The F-statistics for the IVs are consistently > 10, indicating that the potential bias from weak instruments may not be substantial. Moreover, there is no evidence of pleiotropic effects as detected by the heterogeneity test and the MR-PRESSO global test ($P > 0.05$), as outlined in Supplementary Table 2 and 3. Further details regarding the included SNPs can be found in Supplementary Table 1 and Supplementary Table 4.

The mendelian randomization study identifies a significant association between gestational diabetes mellitus and an increased risk of both premature delivery and placental disorders

The MR estimation values from different methods are presented in Fig. 2. The main finding using the IVW method shows that GDM is causally linked with an elevated risk of placental disorders [odd ratio (OR) = 2.143, 95% CI: 1.252–3.666, $P = 0.005$, FDR-adjusted $P = 0.028$, IVW] and preterm labor (OR = 1.150, 95% CI: 1.055–1.252, $P = 0.001$, FDR-adjusted $P = 0.009$, IVW). However, GDM is not associated with an increased risk of transitory endocrine and metabolic disorders specific to the fetus and newborn (OR = 1.476, 95% CI: 0.837–2.603, FDR-adjusted $P = 0.381$, IVW) or digestive system disorders in the fetus and newborn (OR = 1.652, 95% CI: 1.031–2.645, FDR-adjusted $P = 0.110$, IVW) (Fig. 2). The MR-PRESSO analysis indicates no significant horizontal pleiotropic outliers Supplementary Table 3. Furthermore, the leave-one-out analysis demonstrates that no single instrumental SNP can significantly influence the causal effect estimation. Detailed data are available in Supplementary Figure 1.

Gestational diabetes mellitus is found to be associated with a heightened risk of several long-term pulmonary diseases, along with cerebral palsy in the mendelian randomization study

The MR analysis indicates a significant causal effect, demonstrating a risk-increasing association between genetic liability to GDM and lung diseases, as well as neurodevelopmental and psychiatric disorders (Fig. 3). Specifically, for lung diseases, GDM is causally linked to an increased risk of several conditions: influenza (OR = 1.175, 95% CI: 1.069–1.292, $P = 0.001$, FDR adjusted $P = 0.008$, IVW), bacterial pneumonia (OR = 1.141, 95% CI: 1.062–1.226, $P = 0.0003$, FDR adjusted $P = 0.008$, IVW), congenital malformations of the respiratory system (OR = 1.673, 95% CI: 1.149–2.435, $P = 0.007$, FDR adjusted $P = 0.033$, IVW), influenza with pneumonia (OR = 1.078, 95% CI: 1.032–1.125, $P = 0.001$, FDR adjusted $P = 0.008$, IVW), and non-invasive ventilation (OR = 1.265, 95% CI: 1.073–1.491, $P = 0.005$, FDR adjusted $P = 0.028$, IVW). Interestingly, no causal relationship was found between GDM and conditions such as bronchiectasis (OR = 1.210, 95% CI: 0.915–1.601, $P = 0.181$, FDR adjusted $P = 0.381$, IVW), childhood asthma (age < 16) (OR = 1.133, 95% CI: 0.927–1.385, $P = 0.224$, FDR adjusted $P = 0.416$, IVW),

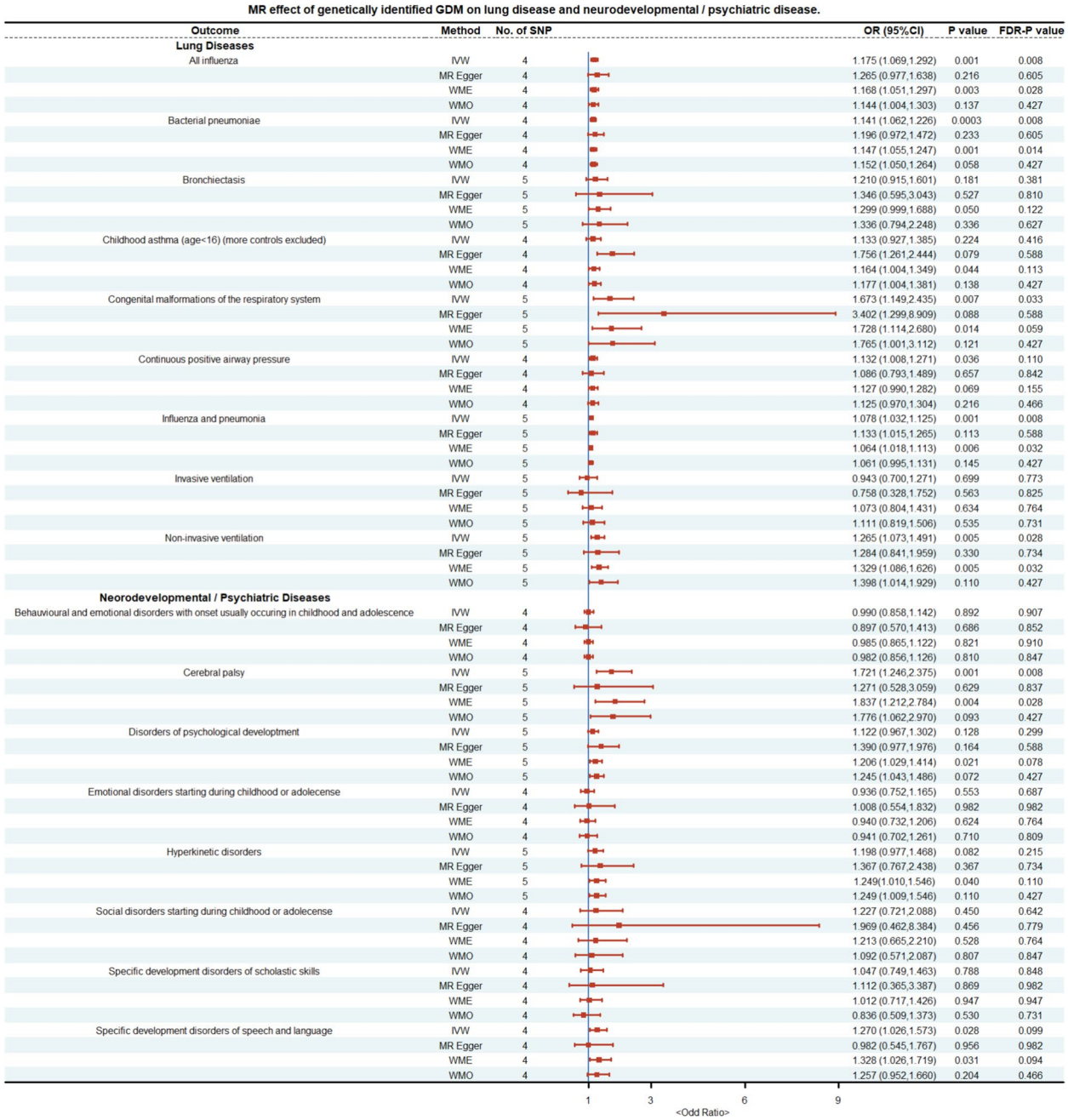

Fig. 3 Estimated causal effects between gestational diabetes mellitus (GDM) and lung disease and neurodevelopmental /psychiatric disease for offspring using different mendelian randomization (MR) methods. Abbreviations: GDM, gestational diabetes mellitus; MR, mendelian randomization; SNP, single nucleotide polymorphism; IVW, inverse variance weighting; WME, weighted median; WMO, weighted mode. OR, odd ratio; FDR, False discovery rate

continuous positive airway pressure (OR = 1.132, 95% CI: 1.008–1.271, $P = 0.036$, FDR adjusted $P = 0.110$, IVW), and invasive ventilation (OR = 0.943, 95% CI: 0.700–1.271, $P = 0.699$, FDR adjusted $P = 0.773$, IVW) (Fig. 3).

The comprehensive causal analysis reveals a significant association between GDM and specific neurodevelopmental and psychiatric disorders in offspring (Fig. 3). Notably, the analysis finds a link to cerebral palsy (OR = 1.721, 95% CI: 1.246–2.375, $P = 0.001$, FDR adjusted $P = 0.008$, IVW) (Fig. 3). These findings indicate that a history of GDM may elevate the risk of certain neurodevelopmental and psychiatric disorders in

children (Fig. 3 and Supplementary Figures 1–4). However, no significant associations are identified between GDM and other neurodevelopmental or psychiatric disorders, including various behavioral and emotional disorders typically emerging in childhood and adolescence, disorders of psychological development, emotional disorders beginning in childhood or adolescence, hyperkinetic disorders, social disorders starting in early life, specific developmental disorders of speech and language, and specific developmental disorders related to academic skills (all FDR adjusted $P > 0.05$, IVW) (Fig. 3).

Gestational diabetes mellitus shows no significant causal effect on most cardiovascular, digestive, and urinary diseases, with the exception of acute tubulo-interstitial nephritis in the mendelian randomization study

This study extensively investigates the causal impact of GDM on various offspring diseases, including cardiovascular, urinary, digestive diseases, and hypothyroidism, using two-sample MR study. Detailed findings are illustrated in Fig. 4 and Supplementary Table 4. According to the IVW approach, the MR analysis involving five SNPs indicates a significant causal link between GDM and acute tubulo-interstitial nephritis, with an OR of 1.098 (95% CI: 1.041–1.159, $P = 0.001$, FDR-adjusted $P = 0.008$). This finding is supported by the weighted median analysis, which shows an OR of 1.127 (95% CI: 1.049–1.210, $P = 0.001$, FDR-adjusted $P = 0.014$). Scatter and forest plots illustrate a statistically significant association between genetic susceptibility to GDM and offspring diseases (shown as Supplementary Figures 2 and 3). There is no evidence of heterogeneity in effect estimates across variants ($P > 0.05$) as indicated in Supplementary Table 2, and the funnel plot visualization can be found in Supplementary Figure 4. The MR-PRESSO method also don't identify any abnormal instrumental variables, as shown in Supplementary Table 3. Furthermore, results from the leave-one-out sensitivity analysis indicate that the relationship between GDM and offspring diseases is not influenced by any single SNP (Supplementary Figure 1). Notably, MR-Egger regression shows no evidence of directional pleiotropic effects in genetic variation ($P > 0.05$), as indicated in Supplementary Table 2. This strongly supports the robustness of the analysis.

Furthermore, no evidence is found to support a causal relationship between GDM and several cardiovascular diseases, including chronic heart failure (OR = 1.017, 95% CI: 0.963–1.075, $P = 0.544$, FDR-adjusted $P = 0.687$, IVW), congenital malformations of the heart and great arteries (OR = 0.964, 95% CI: 0.828–1.121, $P = 0.632$, FDR-adjusted $P = 0.717$, IVW), heart valve issues or murmurs (OR = 1.000, 95% CI: 0.999–1.000, $P = 0.347$, FDR-adjusted $P = 0.540$, IVW), atherosclerotic heart disease (OR = 1.001, 95% CI: 1.000–1.002, $P = 0.237$, FDR-adjusted $P = 0.416$, IVW), hypertensive heart disease (OR = 1.030, 95% CI: 0.925–1.147, $P = 0.589$, FDR-adjusted $P = 0.706$, IVW), ischemic heart disease (OR = 1.056, 95% CI: 0.970–1.149, $P = 0.209$, FDR-adjusted $P = 0.416$, IVW), and hypertrophic cardiomyopathy (OR = 0.888, 95% CI: 0.719–1.095, $P = 0.266$, FDR-adjusted $P = 0.430$, IVW). Additionally, no significant association is found between GDM and hypothyroidism, as well as various digestive and urinary diseases. This includes chronic gastritis, cirrhosis, inflammatory bowel disease, nonalcoholic fatty liver disease, peptic ulcer, acute glomerulonephritis, chronic glomerulonephritis, chronic tubulo-interstitial nephritis, congenital malformations of the urinary system, pyelonephritis, and urinary tract infections or kidney infections (all FDR-adjusted $P > 0.05$, IVW) (Fig. 4).

Pathway enrichment

To investigate the role of the identified five genes from the IVs in specific biological pathways (Fig. 5A), we conduct enrichment analyses for GO terms and KEGG pathways. The GO analysis indicates that the outcomes associated with GDM in offspring are involved in processes such as peptide transport, amide transport, antigen processing and presentation of exogenous antigens, endocytic vesicle membranes, endocytic vesicles, β-catenin-TCF complexes, major histocompatibility complex (MHC) class II protein complexes, and peptide antigen binding (Fig. 5C-D). Additionally, the KEGG enrichment analysis highlights significant pathways related to disease mechanisms, with notable pathways including antigen processing and presentation (Fig. 5B).

Discussion

In this study, we employ Mendelian randomization to investigate whether GDM influences the incidence of offspring diseases. Our results indicate that GDM is associated with an increased risk of various outcomes, including fetal and preterm complications, lung diseases, and cerebral palsy (CP). However, genetic predisposition to GDM does not appear to be linked with an increased risk of cardiovascular diseases, urinary system disorders, or hypothyroidism in offspring.

Our findings indicate a significant correlation between GDM and specific fetal and neonatal diseases, such as preterm labor delivery and placental disorders. These associations align with previous observational studies that reported an increased risk of these conditions in individuals with GDM [22–24]. For instance, Riskin et al. [22] demonstrated a higher prevalence of prematurity in pregnancies with GDM (11.3%) and pregestational diabetes mellitus (PGDM) (31.9%) compared to

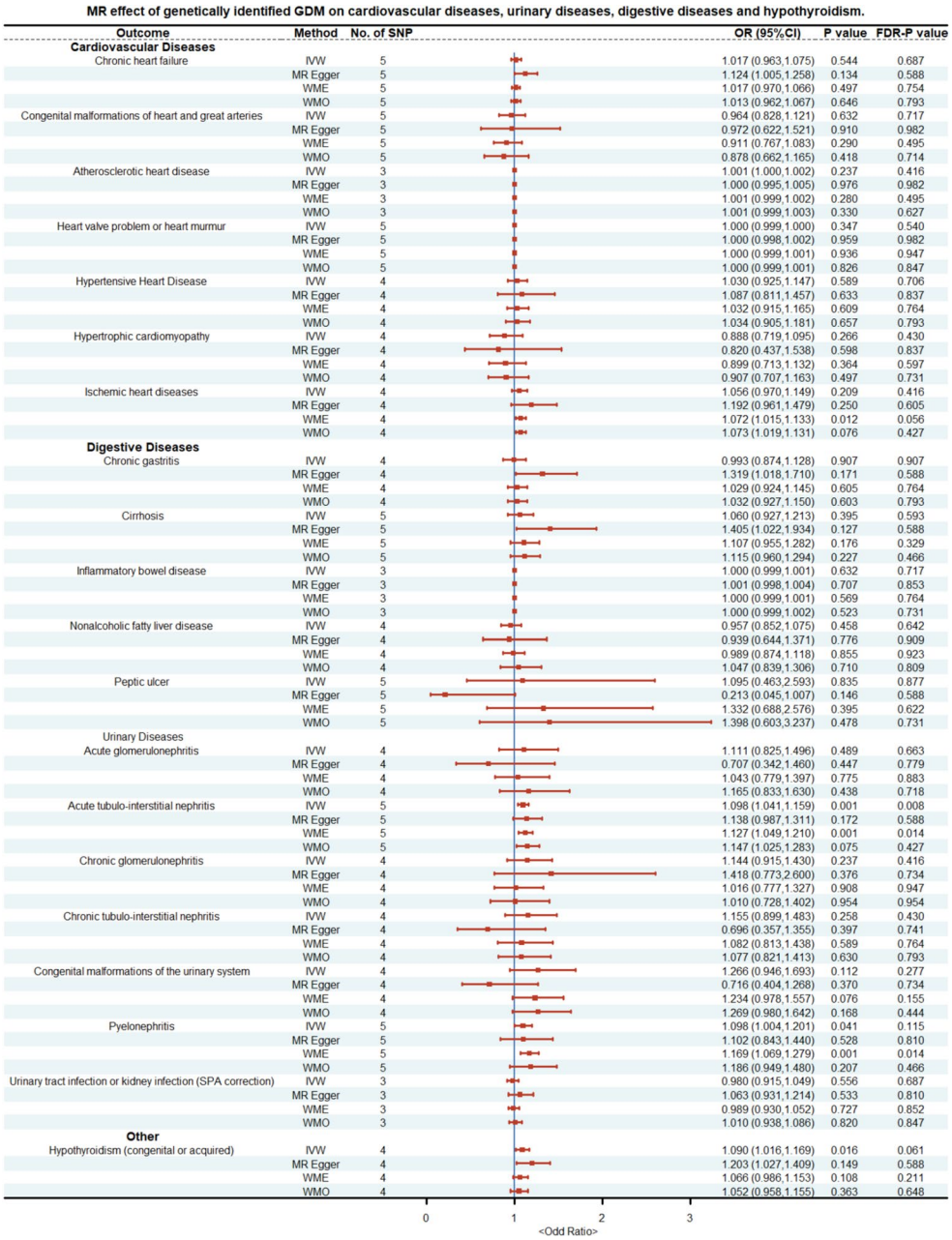

Fig. 4 Estimated causal effects between gestational diabetes mellitus (GDM)and cardiovascular diseases, urinary diseases, digestive diseases and hypothyroidism for the offspring using different mendelian randomization (MR) methods. Abbreviations: GDM, gestational diabetes mellitus; MR, mendelian randomization; SNP, single nucleotide polymorphism; IVW, inverse variance weighting; WME, weighted median; WMO, weighted mode. OR, odd ratio; FDR, False discovery rate

controls (4.9%). Soliman et al. [23] similarly observed a significantly elevated rate of preterm delivery in women with PGDM and GDM (13.7% and 9%, respectively) compared to controls. Simmons et al. [24] conducted a multicenter randomized controlled trial focusing on the treatment of glucose metabolism in the first trimester of pregnancy across 17 centers. The study revealed that the early treatment group exhibited a lower incidence of adverse pregnancy outcomes (including gestational age < 37 weeks and so on), compared to the control group. Moreover, GDM has been linked to various histological changes in the placenta, such as alterations in placental thickness, hypervascularization, necrosis, and syncytial nodes. These changes include modifications in

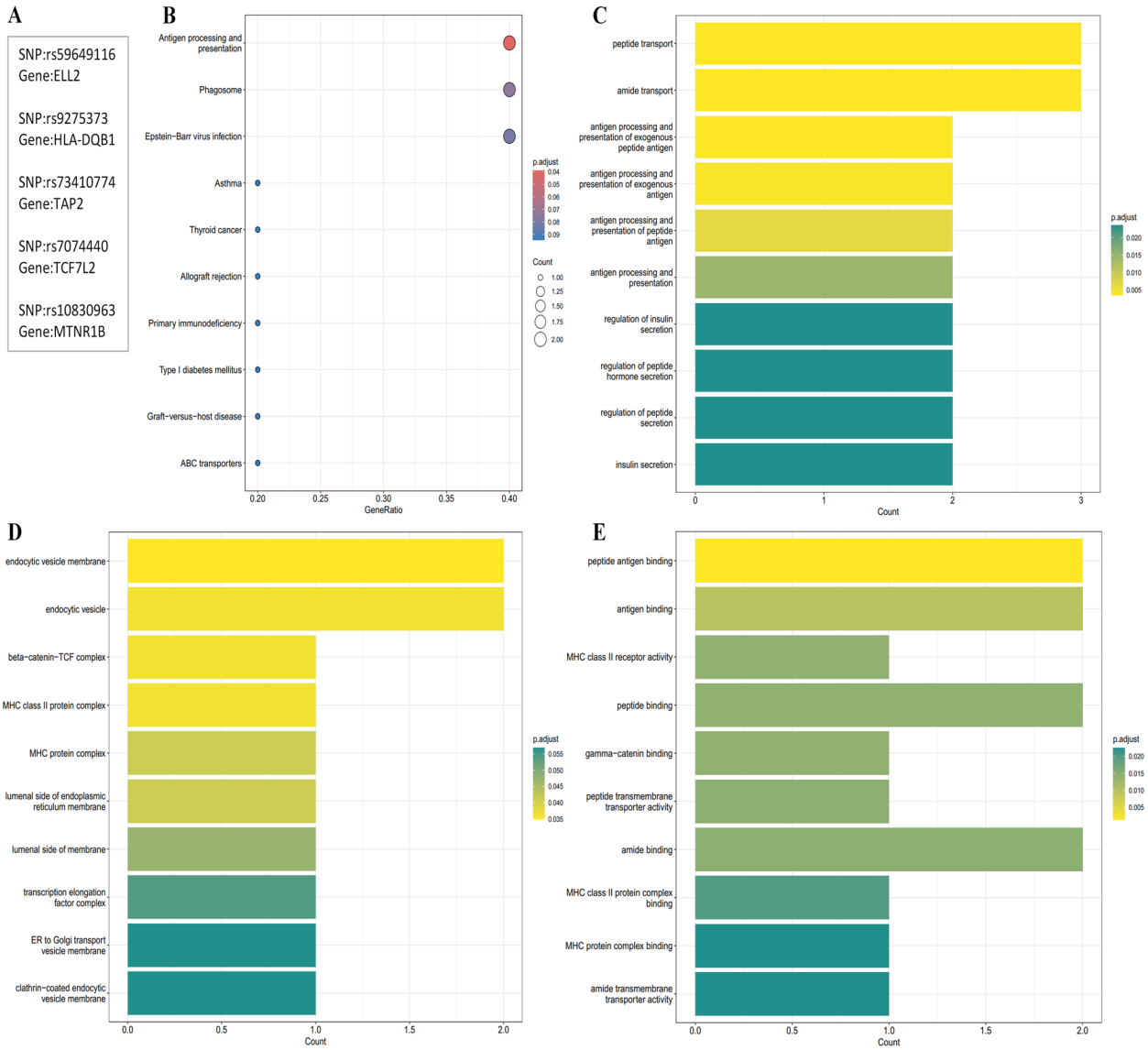

Fig. 5 The enrichment analysis of Gene Ontology (GO) terms for key genes related to offspring diseases associated with gestational diabetes mellitus (GDM). **A** 5 genes annotated with single nucleotide polymorphisms of instrumental variables. **B** KEEG pathway of 5 genes. **C** GO biological processes analysis of 5 genes. **D** GO cellular components analysis of 5 genes. **E** GO molecular functions analysis of 5 genes. Abbreviations: GDM, gestational diabetes mellitus; SNP, single nucleotide polymorphism; GO, Gene Ontology

placental surface area and volume, an increased volume of the intervillous space and terminal villi, elevated numbers of syncytiotrophoblasts, fibrinoid areas, and glycogen deposits [25]. The observed association between GDM and placental abnormalities may be attributed to several potential mechanisms, including inflammation, dysregulation of transforming growth factor-β (TGF-β) and collagen pathways, as well as mitochondrial dysfunction [25–27]. However, further research is crucial to gain a deeper understanding of the complex relationship between GDM and fetal and neonatal health. Investigating the underlying mechanisms and identifying potential preventive strategies will be pivotal in advancing our knowledge of maternal and child health in this critical area.

In this study, MR analysis is performed on GDM and various lung diseases in offspring, and it is found that GDM significantly increases the risk of influenza, influenza with pneumonia, bacterial pneumonia, congenital malformations of the respiratory system and non-invasive ventilation. These findings are consistent with prior observational studies, which have also reported an

elevated risk of these respiratory conditions in individuals with GDM [28–31]. GDM is a significant risk factor associated with respiratory diseases, including respiratory distress syndrome and pneumonia, in a prospective observational study [31]. However, the association between GDM and the need for mechanical ventilation remains controversial. Our MR study provides no evidence of a causal relationship between GDM and invasive ventilation. Neonates born to mothers with GDM do not show a significantly increased likelihood of requiring mechanical ventilation compared to those born to mothers without diabetes, as suggested by a retrospective cohort study [32]. But, a recent meta-analysis that synthesized data from 156 studies involving over 7.5 million pregnant women found that neonates born to mothers with GDM who received insulin therapy had a significantly higher risk of requiring intensive care unit (ICU) hospitalization compared to those born to non-GDM mothers [33]. Therefore, further multicenter, large-sample, randomized controlled trials are warranted to explore the relationship between pregnancy-related diabetes, including GDM, and the severity of respiratory diseases in offspring.

Our MR study findings suggest a causal relationship between GDM and an increased risk of CP in offspring. Supporting this, a study investigating risk factors for CP in children aged 0–6 years in China identified exposure to intrauterine hyperglycemia during pregnancy as a factor that elevated the risk of CP in offspring [34]. Similarly, a population-based birth cohort study involving 2,110,177 children reported that maternal pre-gestational diabetes mellitus (PGDM) was associated with an increased risk of CP [35]. However, our MR genetic analysis results indicate that GDM is not associated with other neurodevelopmental or psychiatric disorders. Further investigation using large genetic databases is essential to better understand the potential relationship between GDM and conditions such as ADHD, epilepsy, autism spectrum disorder (ASD), and other neurodevelopmental or psychiatric disorders.The mechanisms underlying the observed association between GDM and neurodevelopmental or psychiatric diseases may involve several factors, including oxidative stress [36, 37], fetal hypoxia [38], epigenetic alterations such as histone methylation leading to embryonic damage [36], and mitochondrial dysfunction [38]. To better understand these complex relationships, further experimental studies are warranted. Continued research in this area will provide deeper insights into the molecular and cellular processes involved, potentially guiding the development of targeted interventions and preventive strategies for the long-term health of offspring.

Our MR study utilizes genetic databases to investigate the relationship between GDM and the risk of cardiovascular diseases, urinary tract disorders, and hypothyroidism. Our MR study finds no genetic relationship between GDM and most cardiovascular diseases, urinary tract diseases, or hypothyroidism. However, the results of our MR analysis are inconsistent with findings from observational studies [28, 39–45]. This conclusion contrasts with the findings of some previous observational studies for several reasons: (i) The MR analysis employed in this study utilizes SNPs derived from the GWAS database as instrumental variables, which effectively mitigates the bias of confounding factors such as lifestyle and social environment that can influence disease outcomes. This approach ensures a more robust estimation of the causal relationship. (ii) Our study benefits from a large sample MR analysis, which provides more statistical power and is inherently more reliable compared to previous observational studies with smaller sample sizes. Additionally, observational and cohort studies, while valuable, often fail to establish causality or the chronological order of events. In contrast, MR analysis is specifically designed to infer causal relationships, offering a more rigorous framework for understanding the associations between GDM and offspring health outcomes. It has the shortcomings of geographic restrictions. The causal association identified in our MR study between GDM and acute tubulo-interstitial nephritis lacks corroborating evidence from similar clinical research. Further research is needed to explore the complex relationship between GDM and various health outcomes in offspring. Ongoing investigations utilizing genetic databases can enhance our understanding of the underlying mechanisms and contribute to the development of effective preventive strategies.

This study provides evidence indicating a causal association between GDM and the risk of both short- and long-term consequences for offspring of European ancestry. A principal strength of this research lies in the application of the MR method to assess the causal relationship between GDM and offspring risk within the same study population. The MR approach leverages the random assortment and fixation of alleles at conception, thereby minimizing biases related to confounding factors and reverse causality. In addition, the emphasis on a population of European ancestry enhances the internal validity of the findings by minimizing potential biases associated with population stratification. The reliance on genetic factors offers a unique perspective, as alleles are unaffected by environmental influences post-conception. However, despite these strengths, it is important to acknowledge potential limitations. The generalizability of the findings to diverse ethnicities may be constrained, and extending the application of the MR method to different populations can yield a more comprehensive

understanding of the causal relationship. Continued research efforts and additional studies will be crucial for validating and expanding upon the insights derived from this investigation.

Conclusions

In conclusion, our findings indicate that GDM is associated with an increased risk of various diseases in offspring, including fetal and neonatal conditions, lung diseases, and certain neurodevelopmental disorders, as determined by MR analysis. Consequently, there is a pressing need to improve the management of patients with GDM to reduce the likelihood of both short- and long-term adverse consequences for their offspring. Furthermore, acknowledging the genetic differences among various ethnic groups, countries, and regions, additional studies involving diverse populations are essential to validate and expand upon these findings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-025-07423-4.

Supplementary Material 1.

Acknowledgements
This work was supported by National Key Research and Development Program (2021YFC2701702) and National Natural Science Foundation of China (8227061448 and 82201909).

Authors' contributions
Mi Yan, Zhengdong Chen and Jia Tang: drafted the initial manuscript, analysis the data and reviewed and revised the manuscript. Xinyu Duan, Wenjie Peng, Rui Liu, and Wanwei Li analysis the data. Yanfei Liu and Zhangxue Hu: reviewed and edited the manuscript. All authors were involved in designing and conducting the study as well as writing and proofing the manuscript. The author(s) read and approved the final manuscript.

Funding
This work was supported by National Key Research and Development Program (2021YFC2701702) and National Natural Science Foundation of China (8227061448 and 82201909).

Data availability
The summary data for both GWAS analyses that support the findings of this study can be accessed from the open-access GWAS dataset at https://gwas.mrcieu.ac.uk/.

Declarations

Ethics approval and consent to participate
This study utilized deidentified summary-level data that have been publicly released, with ethical approval obtained in all original studies.

Consent for publication
The manuscript is approved by all authors for publication.

Competing interests
The authors declare no competing interests.

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Received: 16 January 2024 Accepted: 5 March 2025
Published online: 19 March 2025

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