Original Article

Associations between maternal gestational diabetes mellitus and offspring cerebral palsy: a two-sample Mendelian randomization study

Honghao Peng[1#], Yun Shu[2#], Siyu Lu[1], Qiongli Fan[1], Yuping Zhang[1], Li Ming[1], Zhifeng Wu[1]^

[1]Department of Pediatrics, Second Affiliated Hospital of the Army Medical University, Chongqing, China; [2]Medical College of Acu-Moxi and Rehabilitation, Guangzhou University of Chinese Medicine, Guangzhou, China

Contributions: (I) Conception and design: H Peng, Z Wu; (II) Administrative support: Y Shu; (III) Provision of study materials or patients: L Ming; (IV) Collection and assembly of data: H Peng; (V) Data analysis and interpretation: Y Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Li Ming, MD; Zhifeng Wu, MD. Department of Pediatrics, Second Affiliated Hospital of the Army Medical University, 2-V Xinqiao Street, Sha-Ping-Ba District, Chongqing 400037, China. Email: 710315177@qq.com; wuzhifeng@tmmu.edu.cn.

Background: Observational studies on the association between gestational diabetes mellitus (GDM) during pregnancy and pediatric neurological disorders (PNDs) such as cerebral palsy (CP), autism spectrum disorders (ASD), and epilepsy (EP) in offspring have yielded mixed findings, creating ambiguity in causal interpretations. The direct link between GDM and these PNDs remains unclear. Elucidating this connection is vital for developing effective early intervention strategies during pregnancy to mitigate the risk of PNDs in the offspring. This study utilizes a two-sample (2-sample) Mendelian randomization (MR) approach to investigate the causal relationship between GDM and its impact on CP, ASD, and EP in offspring.

Methods: We employed 2-sample MR using 6 single nucleotide polymorphisms (SNPs) strongly associated with GDM. Summary-level data for CP, ASD, and EP were obtained from the Integrative Epidemiology Unit (IEU) Open Genome-Wide Association Study (GWAS) project, encompassing sample sizes of 217,278, 46,351, and 463,010, respectively. The robustness of our findings was assessed using the inverse variance-weighted (IVW) method along with additional sensitivity analyses.

Results: The results demonstrate that GDM is associated with a higher risk of offspring CP as determined by the IVW method [odds ratio (OR): 1.74; 95% confidence interval (CI): 1.27–2.37; P<0.001]. In contrast, no association was observed between GDM and ASD or EP. Additionally, alternative methods for sensitivity analyses showed consistent results, and there was no pleiotropy detected using MR-Egger regression (P=0.48).

Conclusions: This study provides strong evidence supporting a positive causal relationship between genetically predicted GDM and the increased risk of offspring CP, with no observed correlation found with ASD or EP.

Keywords: Gestational diabetes mellitus (GDM); cerebral palsy (CP); autism spectrum disorder (ASD); epilepsy (EP); Mendelian randomization (MR)

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^ ORCID: 0000-0003-3096-6175.

Introduction

Gestational diabetes mellitus (GDM) is characterized by elevated blood glucose levels detected during pregnancy (1). It affects approximately 16.7% of all pregnancies and poses risks for both the mother and child (2). The global incidence of GDM is on the rise, with notable disparities across regions and populations (3). Maternal GDM increases the risks of adverse perinatal outcomes such as cesarean delivery, macrosomia, large for gestational age (LGA), neonatal hypoglycemia, hyperinsulinemia, hyperbilirubinemia, neonatal respiratory distress syndrome, preterm birth, shoulder dystocia, and birth injuries (1-8). However, its long-term impacts on offspring, including cerebral palsy (CP), autism spectrum disorders (ASD), and epilepsy (EP), remain poorly understood due to challenges in observational studies caused by lengthy research cycles and numerous confounding factors. Existing case-control and cross-sectional studies, along with other non-Mendelian randomization (non-MR) research, present conflicting conclusions regarding the association between maternal GDM and offspring neurodevelopmental outcomes (1,4,5,7,8).

Highlight box

Key findings

- Strong causal relationship between genetically predicted gestational diabetes mellitus (GDM) and increased risk of offspring cerebral palsy (CP).
- No observed correlation between GDM and offspring autism spectrum disorders (ASD) or epilepsy.
- Mendelian randomization (MR) provides new insights into the genetic predisposition for GDM and offspring pediatric neurological disorders (PNDs).

What is known and what is new?

- Observational studies have provided inconsistent findings on the association between GDM and PNDs in offspring.
- MR approach, which is less susceptible to biases and confounders often present in observational studies, has not previously been applied to investigate the relationship between GDM and offspring CP, ASD, and epilepsy.

What is the implication, and what should change now?

- The findings suggest that effective management of gestational diabetes during pregnancy could be an opportunity for early intervention to reduce the risk of CP in offspring.
- Public health strategies should now consider the potential implications of these findings for the prevention and early detection of CP among children of mothers with gestational diabetes.

CP is a permanent motor disorder that significantly affects individuals and their families (1). Preventing the occurrence of CP in offspring is crucial, particularly in low- and middle-income countries, where incidence rates can reach as high as 3.4‰ among live births. Although Europe and Australia have experienced a decline in pre-/perinatal CP cases, postneonatal rates have remained stable (9). Current estimates indicate that CP affects approximately 1–4‰ of live births, highlighting the urgent need for further investigation into its underlying causes (10). Environmental factors such as perinatal asphyxia were once seen as the main causes of CP (11). New research (12), however, suggests a complex interaction of genetic and metabolic factors, especially related to maternal conditions such as GDM. Using genetic tools to explore the link between GDM and CP could reveal key mechanisms, aiding in the development of preventive strategies and better outcomes for future generations. ASD encompasses various social interaction and communication difficulties (13,14). ASD has been on the rise globally, with a significant increase in prevalence observed in both the United States and China, raising worldwide concern. During 2014 to 2016, China witnessed a notable increase in ASD prevalence, ranging from 0.12% to 0.70% (15). On another note, EP is a chronic neurological condition characterized by recurrent, unprovoked seizures (16). In China, almost 10 million people are affected by EP, and among children, the reported prevalence rate ranges from 3.9‰ to 5.1‰. Children with EP may experience pediatric neurological disorders (PNDs) that can influence their perception and cognitive development (17,18). CP, ASD, and EP collectively represent three PNDs, imposing substantial challenges in medical management, often necessitating lifelong care and intervention (19-22). Current multidisciplinary treatment approaches remain arduous (23). Annually, these disorders incur significant economic burden, encompassing direct medical costs and productivity losses, totaling billions of dollars (20). Identification of genetic risk factors and their preventive implications hold promise in mitigating the onset of these chronic conditions, thereby significantly enhancing population health quality.

MR offers a promising method in epidemiology to assess causal relationships using genetic variants as instrumental variables (IVs), thereby reducing biases from measurement errors and confounding factors such as socioeconomic status and behavioral influences (24). To our knowledge, MR has not yet been applied to explore the relationship between GDM and offspring PNDs such as CP, ASD, and

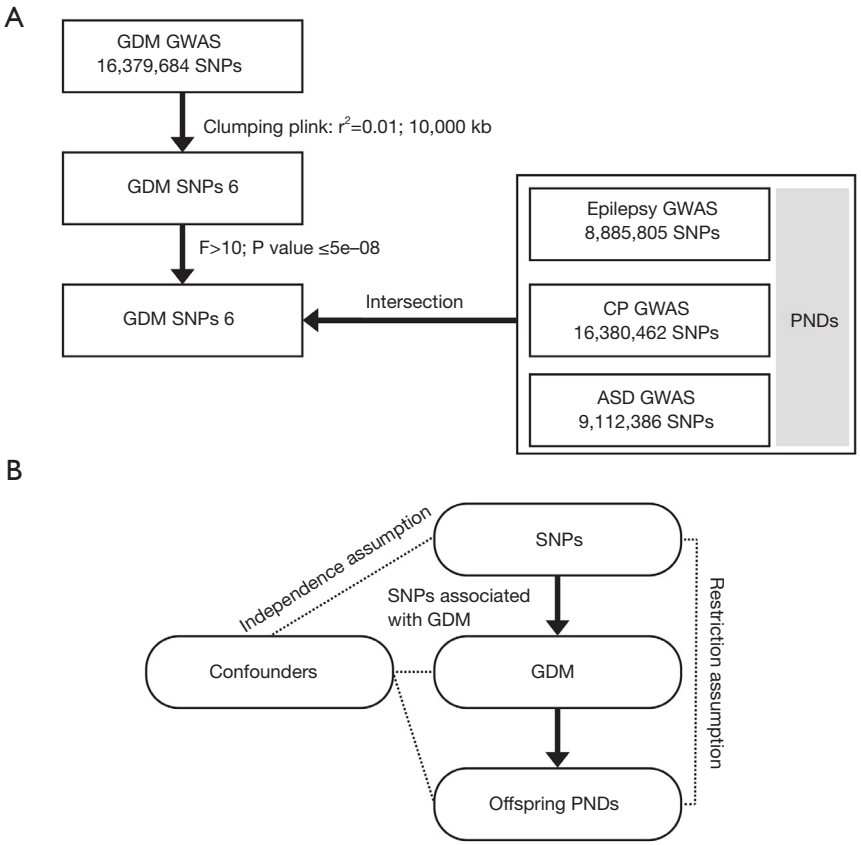

Figure 1 Overall design of MR analyses in the present study. (A) Experimental workflow. (B) Assumptions underlying the MR analysis. The dashed lines denote factors that do not interact, whereas the solid lines indicate factors that do interact. GDM, gestational diabetes mellitus; GWAS, Genome-Wide Association Study; SNPs, single nucleotide polymorphisms; CP, cerebral palsy; ASD, autism spectrum disorders; PNDs, pediatric neurological disorders; MR, Mendelian randomization.

EP. Applying MR in investigating these associations may offer robust genetic evidence, addressing existing etiological gaps and potentially providing more cost-effective strategies for disease prevention to safeguard offspring health. This study aimed to use a two-sample (2-sample) MR approach to elucidate the causal relationship between GDM and CP, ASD, and EP, thereby offering clarity and valuable insights into the intricate dynamics between maternal health and child neurodevelopment. We present this article in accordance with the STROBE-MR reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-260/rc).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study design overview is illustrated in *Figure 1A*, including the assessment of maternal exposure to GDM as the primary exposure factor. The outcomes in offspring, encompassing CP, ASD, and EP, were evaluated using an MR approach. The data incorporated in the research were sourced from the Integrative Epidemiology Unit (IEU) open Genome-Wide Association Study (GWAS) project (https://gwas.mrcieu.ac.uk/); no further ethical approval from an institutional review board was necessary.

Utilizing GWAS data, this study explores associations between maternal genetic variants and offspring three PNDs. The MR analysis adopts a 2-sample design, employing genetic variation as IVs to assess causal relationships.

Outcome source

For this study, we utilized several GWAS datasets.

Specifically, the GDM and CP datasets were sourced from the latest and most comprehensive FinnGen consortium dataset. The GDM dataset included 116,363 participants with 6,033 cases, whereas the CP dataset comprised 217,278 participants with 286 cases. The ASD data, encompassing 46,351 participants (18,382 cases), were obtained from the Psychiatric Genomics Consortium, representing the most recent and extensive dataset from 2017. For EP, we utilized the authoritative 2018 dataset from the Medical Research Council IEU (MRC-IEU), which included 463,010 participants (2,326 cases) (Table S1). Although the most recent EP data are updated to 2021, they are not from an authoritative institution or organization. Consequently, we selected the 2018 MRC-IEU data, which is deemed more authoritative and reliable compared to the latest dataset. All data were derived from reputable institutions adhering to internationally recognized diagnostic standards and data collection protocols, with multiple rounds of review and quality control, ensuring high data reliability. Furthermore, we evaluated the possibility of sample overlap in our datasets, which came from different consortia: FinnGen for GDM and CP, the Psychiatric Genomics Consortium for ASD, and MRC-IEU for EP. The distinct origins suggest minimal overlap. A sensitivity analysis showed no significant heterogeneity or pleiotropy due to overlap.

IVs selection

Genetic variants associated with GDM were identified from a GWAS involving 116,363 European individuals. In the primary analysis, six single nucleotide polymorphisms (SNPs) were selected as IVs for GDM, all of which reached the significance level with a threshold of P<5e−8 (Table S2). No linkage disequilibrium (LD) (r^2 threshold <0.001) was found among these instrumental SNPs for GDM. We used the PhenoScanner V2 database (http://www.phenoscaner.medschl.cam.ac.uk/) to ascertain potential IVs based on their associations with confounding factors. Our screening process revealed that none of the candidate SNPs exhibited associations with phenotypes that could introduce genetic confounding effects. Consequently, the identified instruments were confirmed to be free from confounding influences related to GDM. Our analysis confirmed that none of the SNPs were associated with phenotypes that could confound GDM, validating the robustness of our IVs. To evaluate weak IVs bias, the F-statistics were computed to measure the strength of the IVs used in the study. The F-statistics values ranged from 679.68 to 5,747.07, as shown in Table S3. These values all surpassed the assumption threshold of F>10, ensuring the validity of the MR analyses. To assess potential horizontal pleiotropy, the study further investigated other related phenotypes of IVs, which we selected in this study, utilizing the GWAS catalog (https://www.ebi.ac.uk/gwas/). This analysis was carried out to confirm whether the IVs could be influencing the outcomes through alternative pathways beyond the main intended causal effect (Table S4).

Statistical analysis

The analysis utilized the "MR" and "MR pleiotropy residual sum and outlier (MRPRESSO)" packages in R software version 4.3.0 (https://cran.r-project.org/). The MR study was conducted following three assumptions (*Figure 1B*). The primary method used for MR was the inverse variance-weighted (IVW) method. This method provides a reliable means of stably identifying of the correlation between GDM and the increased risk of the offspring CP when the IVs are not pleiotropic. To ensure the robustness of the results, sensitivity analyses were performed, including the weighted median method, weighted mode method, simple mode method, and the MR-Egger method. Moreover, the Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) method was utilized to detect and correct for potential pleiotropic effects by identifying and removing possible outliers from the analysis.

We used the PhenoScanner V2 database to rigorously screen our candidate SNPs for potential confounding associations. This confirmed that none of the selected SNPs were linked to phenotypes that could cause genetic confounding, ensuring the integrity of our findings.

Lastly, in terms of exclusion restriction, we provided detailed evidence demonstrating that the genetic instruments used in this study are not associated with offspring PNDs through pathways independent of maternal GDM. This was achieved by carefully addressing and controlling for potential pleiotropy using the MR-PRESSO method. By identifying and correcting for both pleiotropic effects and outliers, we ensured the validity and accuracy of our findings.

Results

The association of GDM with three offspring PNDs are shown in *Figure 2*. The Cochran's Q test results indicated no significant evidence for heterogeneity in the outcomes

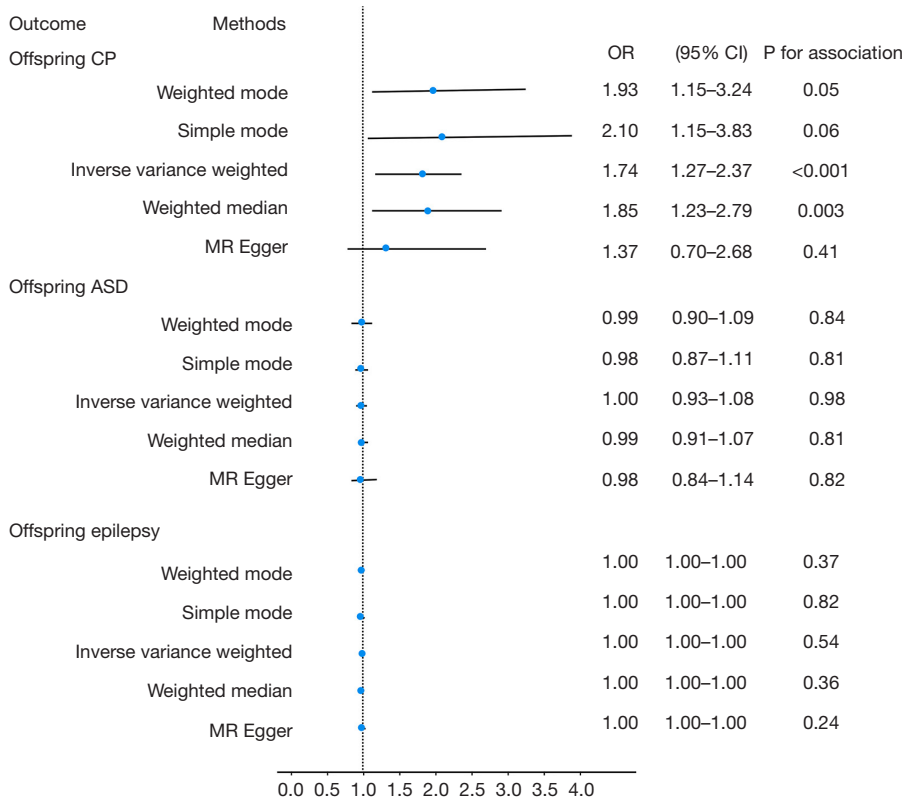

Figure 2 MR estimates from instrument variants for GDM on risk of offspring CP. MR, Mendelian randomization; GDM, gestational diabetes mellitus; CP, cerebral palsy; ASD, autism spectrum disorders; OR, odds ratio; CI, confidence interval.

of CP, ASD, or EP (CP: P=0.47; ASD: P=0.67; EP: P=0.87, *Table 1*). As a result, the fixed-effect IVW model was selected for the MR analysis. This choice was made to provide a consistent estimate of the association between GDM and the risk of these three PNDs when the IVs are not showing substantial heterogeneity. GDM was found to be significantly associated with an increased risk of offspring CP by the IVW method [odds ratio (OR): 1.74; 95% confidence interval (CI): 1.27–2.37; P<0.001, *Table 1*]. The positive slope of the fitted curve in the scatter plot of *Figure 3* indicates that GDM increases the risk of offspring CP, as described by the association between SNP effects on CP and SNP effects on GDM, suggesting an unfavorable influence. Sensitivity analysis showed similar results with various methods, including weighted mode, simple mode, weighted median, and MR Egger (OR: 1.93, 95% CI: 1.15–3.24, P=0.05 by weighted mode; OR: 2.10, 95% CI: 1.15–3.83, P=0.06 by simple mode; OR: 1.85, 95% CI: 1.23–2.79, P=0.003 by weighted median; OR: 1.37, 95% CI: 0.70–2.68, P=0.41 by MR Egger). No potential directional pleiotropy was detected using MR-Egger regression, as indicated by a P value for the intercept of 0.48 (*Table 1*). The leave-one-out analysis further strengthened the evidence for a consistent inverse association between GDM and the risk of offspring CP (Figure S1).

The results did not demonstrate significant correlations of GDM with other PNDs, such as ASD or EP (ASD: OR: 1.00, 95% CI: 0.93–1.08, P=0.98; EP: OR: 1.00, 95% CI: 1.00–1.00, P=0.54; *Table 1*; *Figure 2*). The null findings, indicating no significant associations between GDM and ASD or EP, were consistently supported by various methods, including the weighted median method, simple mode method, weighted mode method, and MR-Egger method (*Table 1*; *Figure 2*). The MR-Egger regression analysis did not show any apparent signs of horizontal pleiotropy, further supporting the validity of the results (ASD: P=0.80; EP: P=0.26, *Table 1*). This robustness indicates that the lack of significant associations between GDM and ASD or EP is not affected by the presence of SNPs in LD. Taken together, the study findings consistently

Table 1 MR analysis of GDM with 3 offspring PNDs risk

Risk factors	Number of SNPs	OR	95% CI	P for association	P for MR Egger intercept	P for heterogeneity test
CP						
MR Egger	6	1.37	0.70–2.68	0.41	0.48	0.47
Weighted median	6	1.85	1.23–2.79	0.003		
Inverse variance-weighted	6	1.74	1.27–2.37	<0.001		0.52
Simple mode	6	2.10	1.15–3.83	0.06		
Weighted mode	6	1.93	1.15–3.24	0.05		
ASD						
MR Egger	4	0.98	0.84–1.14	0.82	0.80	0.67
Weighted median	4	0.99	0.91–1.07	0.81		
Inverse variance-weighted	4	1.00	0.93–1.08	0.98		0.83
Simple mode	4	0.98	0.87–1.11	0.81		
Weighted mode	4	0.99	0.90–1.09	0.84		
Epilepsy						
MR Egger	4	1.00	1.00–1.00	0.24	0.26	0.87
Weighted median	4	1.00	1.00–1.00	0.36		
Inverse variance-weighted	4	1.00	1.00–1.00	0.54		0.45
Simple mode	4	1.00	1.00–1.00	0.82		
Weighted mode	4	1.00	1.00–1.00	0.37		

MR, Mendelian randomization; GDM, gestational diabetes mellitus; PNDs, pediatric neurological disorders; SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; CP, cerebral palsy; ASD, autism spectrum disorder.

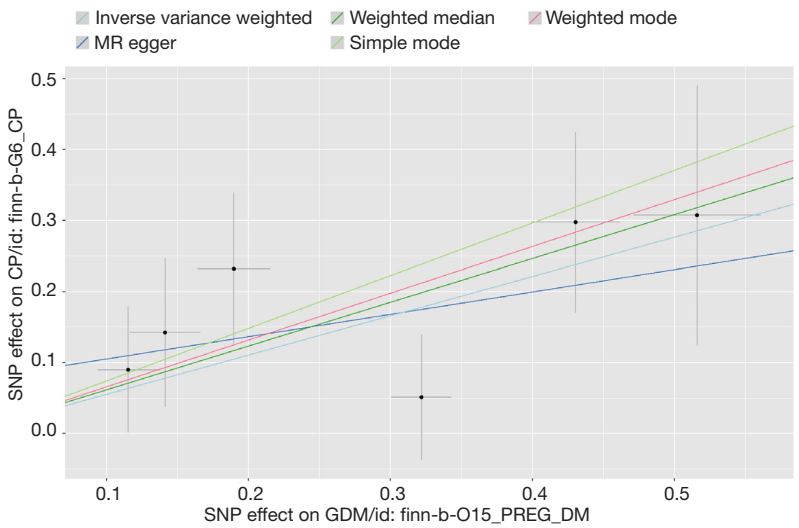

Figure 3 MR estimates from instrument variants for GDM on risk of offspring CP was described in the association between SNP effect on CP and SNP effect on GDM. MR, Mendelian randomization; GDM, gestational diabetes mellitus; CP, cerebral palsy; SNP, singlenucleotide polymorphism.

suggest that GDM does not have a substantial impact on the risk of developing ASD or EP in offspring based on the current analysis and dataset.

Discussion

Existing non-MR studies have investigated the association between GDM and PNDs in offspring, such as CP, ASD, and EP (1,4,5,7,8). However, the results have been conflicting and inconclusive. The relationship between GDM and ASD in offspring has been extensively studied. A meta-analysis incorporating 12 articles from 16 studies revealed a significant link between GDM and ASD, with a relative risk (RR) of 1.48, indicating a 62% increased risk of ASD among children born to mothers with GDM compared to those without (RR: 1.48; 95% CI: 1.24–1.77) (8). Similarly, a retrospective cohort study illustrated that GDM correlated with an elevated risk of ASD in offspring, but did not indicate a significant association between GDM and EP (4). Conversely, Perea *et al.* reported in their cohort study that GDM did not significantly elevate the risk for ASD [hazard ratio (HR): 1.46, 95% CI: 0.74–2.84] (7). These conflicting findings underscore the complexity of researching the relationship between maternal GDM and ASD in offspring.

Existing literature indicates that children of women with EP are at higher risk for EP, and certain antiepileptic drugs used during pregnancy negatively impact offspring's PNDs (25,26). However, research exploring the link between maternal GDM and offspring EP remains scarce. In contrast, studies investigating the link between maternal GDM and offspring CP have been reported significant findings. In a cross-sectional study conducted in the Republic of Kazakhstan, several risk factors associated with CP was identified, among which GDM was notably linked to increased CP risk in offspring (27). Schneider *et al.* reported that women over 35 years old faced higher GDM risk (OR: 1.9, 95% CI: 1.3–2.8) and were more likely to have children with CP (28). These findings hint at a potential correlation between maternal GDM and CP in offspring. However, contrasting results emerged from a population-based cohort study evaluating the risk of CP in utero exposure to maternal diabetes, which revealed an elevated risk of CP in offspring of mothers with pregestational diabetes, with an adjusted HR of 1.84 (95% CI: 1.59–2.14). Surprisingly, no significant association was found between GDM and CP, with an adjusted HR of 0.91 (95% CI: 0.77–1.06) (1). These cohort studies present mixed outcomes, showing both positive and negative associations between maternal GDM and CP in offspring, leading to confusion.

The aforementioned findings highlight the challenges faced by current non-MR studies, characterized by issues such as confounding variables and the lack of enduring longitudinal data. Predominantly featuring case-control or cross-sectional designs, these investigations provide valuable insights but struggle to definitively establish a causal relationship between GDM and PNDs. Ongoing research utilizing non-MR approaches to investigate the association between GDM and specific PNDs in offspring remains inconclusive, frequently yielding conflicting results impacted by confounding elements.

Our study aimed to explore this association using a 2-sample MR approach, a more robust method that minimizes confounding factors common in observational studies. To our knowledge, this is the first MR study to investigate the association of maternal GDM with offspring outcomes of ASD, CP, and EP. Our MR study revealed a significant association between GDM and increased risk of CP in offspring (OR: 1.74; 95% CI: 1.27–2.37; P<0.001) using the IVW method, suggesting a potential causal link. The directionality of this relationship is consistent with the majority of existing non-MRI data on genetically determined glucose levels during pregnancy and the risk of CP in offspring. The complex molecular pathways linking GDM to CP involve hyperglycemia-induced oxidative stress, inflammation, and endothelial dysfunction during fetal environment, disrupting normal brain development (6,29). According to authoritative literature, apart from common environmental factors, genomic factors can also cause CP (30). Recent genetic studies have identified pathogenic and likely pathogenic variants associated with CP, partially elucidating certain genetic mechanisms (31,32). Yet, further foundational research is essential to validate these genetic findings and explore clinical implications.

Our MR analysis, by leveraging genetic variants as IVs, strengthens causal inference while minimizing confounding from maternal lifestyle and environmental factors (33-35). This approach supports the preventive role of optimal glucose control during pregnancy in reducing CP risk. Despite mixed results from observational studies, our MR findings underscore a causal relationship between GDM and CP in offspring, emphasizing the critical need for effective glucose management during pregnancy to mitigate CP risk. Future studies employing longitudinal designs and considering potential mediators are crucial to

fully elucidate underlying mechanisms and develop targeted interventions.

In contrast, our study did not identify a causal relationship between GDM and offspring ASD or EP using MR analysis. Several factors may explain this absence of association. Firstly, the instruments utilized in MR analysis may inadequately capture the intricate genetic landscape of GDM and its potential relationship with ASD or EP. The pleiotropic effects of genetic variants and potential interactions between genetic and environmental factors could confound MR analysis. Secondly, the lack of association may reflect the genuine absence of a causal link between GDM and ASD or EP. Although GDM might be linked to CP, its direct causal impact on other PNDs remains uncertain. This supposition finds support in studies showing that behavioral traits of ASD in children born prematurely, including those exposed to GDM, resemble those in term-born ASD children (5). Our study's findings underscore the significance of considering maternal risk factors, including GDM, in understanding and managing CP incidence. Future research should delve deeper into genetic foundations and explore additional mediators to refine preventive strategies and clinical care.

Limitations

The present study has some limitations, including the need to investigate the causal relationship between GDM and other types of PNDs in offspring, such as developmental delay and attention-deficit/hyperactivity disorder, for a larger GWAS sample size, potential pleiotropy, limited applicability to non-Europeans populations, and lack of exploration of potential mediating factors, such as maternal lifestyle, nutritional status, and prenatal care, that may influence the relationship between GDM and PNDs, such as CP, ASD, and EP. Additionally, 2-sample MR analysis cannot discern whether the identified causal effect is of parental origin, and it may be influenced by dynastic effects and assortative mating (36). Despite these limitations, our study provides valuable new insights into the relationships between GDM and offspring CP. It contributes to a better understanding of the etiology of CP and adds to the existing knowledge about the potential impact of GDM on the risk of PNDs in children. The findings can form a valuable foundation for future research in this area, and further investigations using different methodologies might provide a more comprehensive understanding of the complex relationships between GDM and various PNDs.

Conclusions

The study demonstrated that GDM was correlated with an increased risk of offspring CP using 2-sample MR methods. Our research highlights the importance of proper management and monitoring of glucose levels during pregnancy to mitigate the risk of CP in offspring. Absolutely, further studies are warranted to delve deeper into how GDM influences the occurrence and development of offspring CP. Large-scale randomized controlled trials involving human participants and scientific animal experiments can provide valuable insights into the underlying mechanisms and causality.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-260/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-260/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-260/coif). The authors have no conflicts of interest to declare.

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

revised in 2013).

References

1. Ahmed A, Rosella LC, Oskoui M, et al. In utero Exposure to Maternal Diabetes and the Risk of Cerebral Palsy: A Population-based Cohort Study. Epidemiology 2023;34:247-58.
2. Gao S, Su S, Zhang E, et al. The effect of circulating adiponectin levels on incident gestational diabetes mellitus: systematic review and meta-analysis. Ann Med 2023;55:2224046.
3. Wu S, Li L, Hu KL, et al. A Prediction Model of Gestational Diabetes Mellitus Based on OGTT in Early Pregnancy: A Prospective Cohort Study. J Clin Endocrinol Metab 2023;108:1998-2006.
4. Chen KR, Yu T, Lien YJ, et al. Childhood neurodevelopmental disorders and maternal diabetes: A population-based cohort study. Dev Med Child Neurol 2023;65:933-41.
5. Jo H, Eckel SP, Chen JC, et al. Gestational diabetes mellitus, prenatal air pollution exposure, and autism spectrum disorder. Environ Int 2019;133:105110.
6. Lorenc A, Otto-Buczkowska E. Maternal Diabetes Mellitus – Risk Factor for Fetus and Infant. Endocrinol Diab 2018;5:1-7.
7. Perea V, Urquizu X, Valverde M, et al. Influence of Maternal Diabetes on the Risk of Neurodevelopmental Disorders in Offspring in the Prenatal and Postnatal Periods. Diabetes Metab J 2022;46:912-22.
8. Wan H, Zhang C, Li H, et al. Association of maternal diabetes with autism spectrum disorders in offspring: A systemic review and meta-analysis. Medicine (Baltimore) 2018;97:e9438.
9. McIntyre S, Goldsmith S, Webb A, et al. Global prevalence of cerebral palsy: A systematic analysis. Dev Med Child Neurol 2022;64:1494-506.
10. Alharbi SM, Alluheybi AA, AlHarbi AA, et al. Common chronic conditions in pediatric primary care. Int J Community Med Public Health 2022;9:3911-6.
11. Chin EM, Gorny N, Logan M, et al. Cerebral palsy and the placenta: A review of the maternal-placental-fetal origins of cerebral palsy. Exp Neurol 2022;352:114021.
12. Basu AP, Low K, Ratnaike T, et al. Genetic investigations in cerebral palsy. Dev Med Child Neurol 2024. [Epub ahead of print]. doi: 10.1111/dmcn.16080.
13. Kuo HY, Liu FC. Pathophysiological Studies of Monoaminergic Neurotransmission Systems in Valproic Acid-Induced Model of Autism Spectrum Disorder. Biomedicines 2022;10:560.
14. van Eijk L, Zietsch BP. Testing the extreme male brain hypothesis: Is autism spectrum disorder associated with a more male-typical brain? Autism Res 2021;14:1597-608.
15. Zhou H, Xu X, Yan W, et al. Prevalence of Autism Spectrum Disorder in China: A Nationwide Multi-center Population-based Study Among Children Aged 6 to 12 Years. Neurosci Bull 2020;36:961-71.
16. Fisher RS. Redefining epilepsy. Curr Opin Neurol 2015;28:130-5.
17. Ding D, Zhou D, Sander JW, et al. Epilepsy in China: major progress in the past two decades. Lancet Neurol 2021;20:316-26.
18. Zhang M, Zhang H, Hu S, et al. Investigation of Anxiety, Depression, Sleep, and Family Function in Caregivers of Children With Epilepsy. Front Neurol 2021;12:744017.
19. Atar E, Dilekçi E, Özsoy Ünübol T, et al. Caregiver burden in cerebral palsy: Validity and reliability of the Turkish version of caregiver difficulties scale. Child Care Health Dev 2022;48:465-73.
20. Begley C, Wagner RG, Abraham A, et al. The global cost of epilepsy: A systematic review and extrapolation. Epilepsia 2022;63:892-903.
21. Cirnigliaro M, Chang TS, Arteaga SA, et al. The contributions of rare inherited and polygenic risk to ASD in multiplex families. Proc Natl Acad Sci U S A 2023;120:e2215632120.
22. Zhao Y, Su B, Zhu D, et al. Medical service utilization and costs of autism spectrum disorder: Evidence from hospital records in Beijing, China. Autism Res 2023;16:1462-74.
23. Hutson J, Stommes P, Wickboldt T, et al. Suitability of quality of life outcome measures for children with severe cerebral palsy receiving postural care interventions: a scoping review. Assist Technol 2023. [Epub ahead of print]. doi: 10.1080/10400435.2023.2240876.
24. Iob E, Pingault JB, Munafò MR, et al. Testing the causal relationships of physical activity and sedentary

behaviour with mental health and substance use disorders: a Mendelian randomisation study. Mol Psychiatry 2023;28:3429-43.
25. Vajda FJE, O'Brien TJ, Graham JE, et al. Seizures in infancy in the offspring of women with epilepsy. Acta Neurol Scand 2020;141:33-7.
26. Lee SK. Issues of Women with Epilepsy and Suitable Antiseizure Drugs. J Epilepsy Res 2023;13:23-35.
27. Zhakupova M, Nurbakyt A, Ospanova D, et al. Epidemiology of cerebral palsy in the Republic of Kazakhstan: Incidence and risk factors. Heliyon 2023;9:e14849.
28. Schneider RE, Ng P, Zhang X, et al. The Association Between Maternal Age and Cerebral Palsy Risk Factors. Pediatr Neurol 2018;82:25-8.
29. Fox A, Doyle E, Geary M, et al. Placental pathology and neonatal encephalopathy. Int J Gynaecol Obstet 2023;160:22-7.
30. Jin SC, Lewis SA, Bakhtiari S, et al. Mutations disrupting neuritogenesis genes confer risk for cerebral palsy. Nat Genet 2020;52:1046-56.
31. Moreno-De-Luca A, Millan F, Pesacreta DR, et al. Molecular Diagnostic Yield of Exome Sequencing in Patients With Cerebral Palsy. JAMA 2021;325:467-75.
32. Kapanova G, Malik S, Adylova A. Underlying causes of cerebral palsy: public health perspectives. Folia Neuropathol 2021;59:386-92.
33. Duan C, Shi J, Yuan G, et al. Causal Association Between Heart Failure and Alzheimer's Disease: A Two-Sample Bidirectional Mendelian Randomization Study. Front Genet 2021;12:772343.
34. Martin SS, Blaha MJ. Genetically low triglycerides and mortality: further support for "the earlier the better"? Clin Chem 2014;60:705-7.
35. Xu Q, Ni JJ, Han BX, et al. Causal Relationship Between Gut Microbiota and Autoimmune Diseases: A Two-Sample Mendelian Randomization Study. Front Immunol 2021;12:746998.
36. Sadik A, Dardani C, Pagoni P, et al. Parental inflammatory bowel disease and autism in children. Nat Med 2022;28:1406-11.

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