Journal of Multidisciplinary Healthcare

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ORIGINAL RESEARCH

Unraveling Genetic Causality Between Type 2 Diabetes Mellitus and Hemiplegia Based on Mendelian Randomization

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Purpose: Observational studies have shown a high comorbidity rate between type 2 diabetes mellitus (T2DM) and hemiplegia, but the causal relationship between the two remains to be proven. Therefore, we performed two-sample Mendelian randomization (MR) analysis to explore the causal relationship between T2DM and hemiplegia.

Methods: Genome-wide association study (GWAS) data related to hemiplegia was obtained from the FinnGen study. We also obtained GWAS data for T2DM from the IEU OpenGWAS project. Single nucleotide polymorphisms (SNPs) that were closely associated with T2DM were selected as instrumental variables (IVs) ($P < 5\times10^{-8}$, $r^2 < 0.001$). The causal effects were evaluated using inverse variance weighted (IVW), MR-Egger, weighted median, simple mode, and weighted mode. Subsequently, Cochran's Q statistic was used to calculate the magnitude of heterogeneity and the MR-Egger method was used to detect level pleiotropy to ensure the reliability of the results. A leave-one-out sensitivity analysis was conducted to assess stability.

Results: A total of 170 independent SNPs were selected as IVs to assess the genetic causality between T2DM and hemiplegia. Our findings suggest that genetic liability to T2DM has been linked with increased risk of hemiplegia (IVW: OR = 1.168, 95% confidence interval [CI], 1.025–1.331, $P = 0.020$; weighted median: OR = 1.257, 95% CI = 1.023–1.544, $P = 0.030$). Results of comprehensive sensitivity analysis were consistent with the main causality estimate. There was no significant heterogeneity or horizontal pleiotropy bias in this result.

Conclusion: This study shows a causal relationship between T2DM and hemiplegia, indicating that T2DM increases the risk of hemiplegia, which may provide guidance for additional hemiplegia screening in T2DM patients.

Keywords: type 2 diabetes mellitus, hemiplegia, Mendelian randomization, IEU OpenGWAS, genetic causality

Introduction

Hemiplegia refers to central nervous system damage caused by various reasons, including stroke, traumatic brain injury, tumor, infection, and autoimmune disorders, leading to paralysis of one upper and lower limb, often accompanied by brain nerve damage.[1,2] Stroke is the second leading cause of death after ischemic heart disease, accounting for 9% of the deaths worldwide. The World Health Organization (WHO) estimated that 15 million people suffer from stroke each year worldwide. Of these, over 6 million die and 5 million are permanently disabled.[3] Craniocerebral injury is a common

Received: 28 May 2025
Accepted: 2 August 2025
Published: 7 August 2025

surgical emergency with a mortality rate of 30%–50%, and most patients with traumatic brain injury exhibit various functional impairments, including hemiplegia.[4,5]

Type 2 diabetes mellitus (T2DM) has gradually become one of the chronic diseases that seriously endanger human life and health and global social and economic development.[6,7] The recent findings of the International Diabetes Federation (IDF) on diabetes epidemiology indicated that 536.6 million cases were reported worldwide in 2021, and this number is projected to increase to 783.2 million by 2045 (with a prevalence rate of 12.2%).[8] Previous studies have demonstrated a causal association between T2DM and various cerebrovascular diseases, including cerebral infarction and stroke.[9,10] T2DM may lead to hemiplegia through mechanisms such as chronic hyperglycemia, which can cause endothelial dysfunction and increase the risk of thrombosis and atherosclerosis, contributing to stroke and subsequent hemiplegia.[11,12] However, the relationship between T2DM and hemiplegia has not been established. To our knowledge, no Mendelian randomization (MR) study has previously investigated the causal relationship between T2DM and hemiplegia. We focused specifically on hemiplegia rather than broader stroke phenotypes because hemiplegia represents a more specific and severe form of stroke-related disability, which is particularly relevant for understanding the potential causal pathways and clinical implications of T2DM on stroke outcomes.

MR is a research method that uses genetic variation as instrumental variables (IVs) and follows Mendelian law, which states that the corresponding alleles are randomly assigned during embryonic development.[13,14] It eliminates the influence of confounding factors on the results, thereby enhancing the strength of causal inference evidence and achieving the goal of simulating randomized controlled trials. The most commonly used genetic variation is single-nucleotide polymorphisms (SNPs).[15] In this study, we used large-scale genome-wide association studies (GWAS) data and performed a two-sample MR analysis to investigate the causal effect of T2DM on hemiplegia.

Methods

Study Design

This study aimed to explore the causal relationship between T2DM and hemiplegia by using a two sample MR analysis. The MR analysis follows three important assumptions: (1) correlation assumption: IVs are strongly correlated with exposure ($P < 5\times10^{-8}$); (2) independence assumption: IVs are independent of observed or unobserved hybrid factors; (3) exclusivity assumption: IVs only affect results through exposure. The overview of the design flowchart for MR analysis in this study is presented in Figure 1.

Data Source

The GWAS data for T2DM (ebi-a-GCST90018926) and hemiplegia (finn-b-G6_HEMIPLE) were obtained from the IEU OpenGWAS Project Data Platform.[16,17] The data on T2DM included 38,841 patients and 451,248 controls, with a total of 24,167,560 SNPs. Hemiplegia data included 217,787 samples and 16,380,462 SNPs. All participants were of European ancestry. As this study was based on a re-analysis of previously conducted and published GWASs data, ethical clearance was not required. This is in accordance with national legislative guidelines, specifically items 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects promulgated on February 18, 2023, in China, which exempt studies using publicly available, de-identified data from the requirement for ethical approval.

IVs Selection

The IVs used in this study were selected from the corresponding GWAS as SNPs that are statistically significant to the whole genome ($P < 5 \times 10^{-8}$).[18] Using the "clump_data" function in the R software, linkage disequilibrium (LD) was removed, and independent SNPs were determined for each feature ($r^2 = 0.001$ and clump distance > 10000 kb). The threshold of $r^2 < 0.001$ was chosen to ensure that the selected SNPs are highly independent, minimizing the potential for linkage disequilibrium to confound the analysis. The F-statistic ($F = \beta^2/SE^2$) was used to evaluate the strength of the association between the SNPs and exposure factors. An F-statistic threshold of >10 was selected to ensure that the instrumental variables are strongly associated with the exposure, thereby reducing the risk of weak instrument bias,

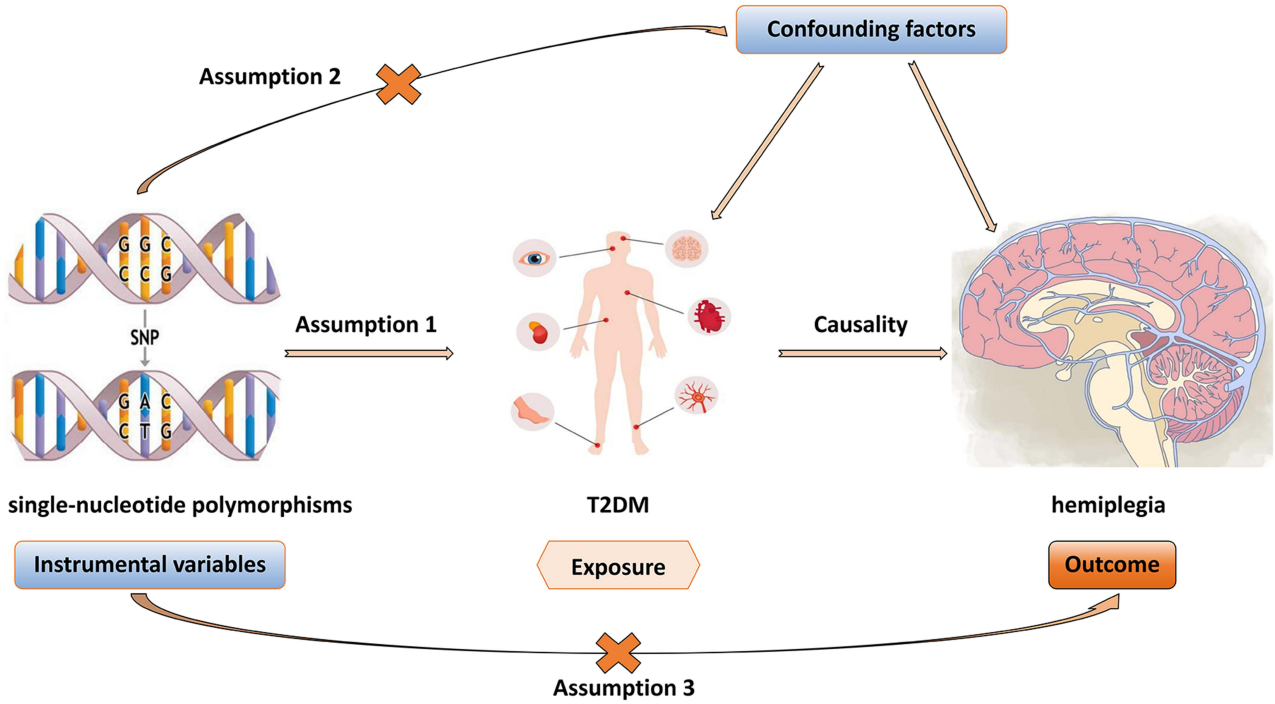

Figure 1 A Mendelian randomization study revealing causality between T2DM and hemiplegia.

which can lead to imprecise causal effect estimates. SNPs with an F-statistic < 10 were excluded (considered to have weaker associations). β represents the allelic effect value, while SE is the standard error.

Statistical Analysis

To comprehensively and accurately estimate the causal effects, the inverse variance weighted (IVW) method was used, supplemented by the MR-Egger, weighted median, simple mode, and weighted mode methods. We employed a fixed-effect IVW model to account for the consistency in the effect sizes across the instrumental variables. Due to differences in analysis platforms, selected populations, and SNPs, there may be heterogeneity in MR analysis results, leading to bias in the estimation of causal effects. Therefore, Cochran's Q test is necessary to evaluate the heterogeneity of IVs.[19] A $P < 0.05$ indicated heterogeneity. Horizontal pleiotropy occurs when genetic variation affects outcomes through pathways other than exposure. Violation of "no level of validity" (Assumption 3 above) may lead to a significant bias in the MR estimation. Therefore, when calculating the intercept of the MR-Egger regression, no significant difference from zero indicated no horizontal pleiotropy, while a $p < 0.05$ indicated horizontal pleiotropy. We developed the MR pleiotropy residual sum and outlier (MR-PRESSO) test to detect horizontal pleiotropic outliers.[20] The Global test was used to detect horizontal pleiotropy and outliers in IVs ($P < 0.05$), while the distortion test was used to detect significant differences in results before and after removing outliers. Moreover, the "leave on one out" method was used to evaluate the effect of a single SNP on the regression coefficients. Individual SNPs were removed in sequence, and the remaining SNPs were used to calculate the causal effect estimates. The IVW method was used to evaluate the impact of individual SNPs on overall estimates. All analyses were conducted using the "TwoSampleMR" and "MRPRESSO" packages in R software (version 4.3.3).

Results

Acquisition of IVs

After screening, a total of 185 SNPs significantly associated with T2DM were ultimately included in this study (Table S1). The value of F-statistic corresponding to each SNP is all significantly greater than 10, indicating that these 185 SNPs are all IVs strongly correlated with T2DM, and the possibility of weak instrumental bias is relatively small. Then, 178 out of the total SNPs

https://doi.org/10.2147/JMDH.S543296

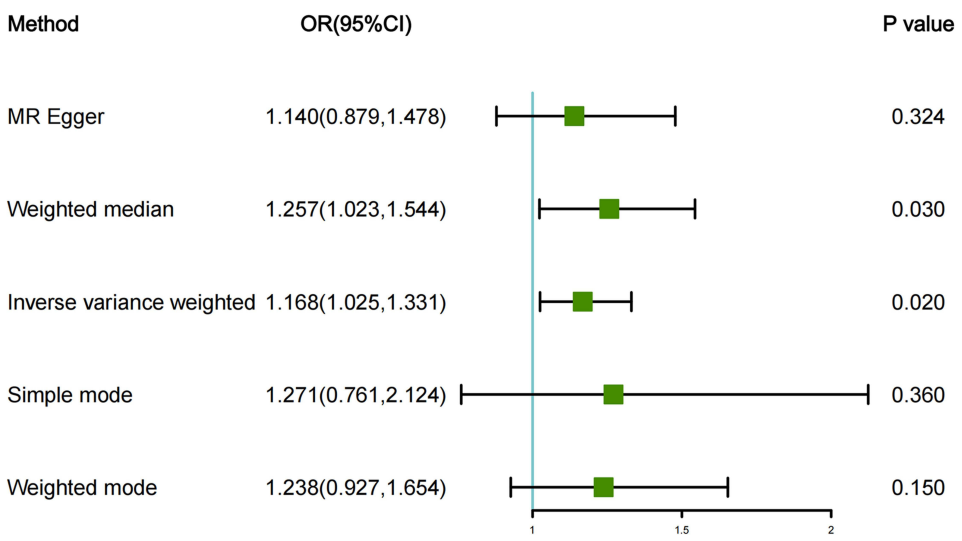

Figure 2 Forest plot for the effect of T2DM on hemiplegia.

were extracted from the hemiplegia GWAS data (Table S2). The following palindromic SNPs were excluded: rs243018, rs11001398, rs6538804, rs12662968, rs703981, rs4711750, rs4358140, and rs7258722. Finally, 170 independent SNPs were selected as IVs to evaluate the genetic association between T2DM and hemiplegia. The effect of each SNP on hemiplegia is displayed in Table S3.

Causal Relationship Between T2DM and Hemiplegia

The IVW analysis results showed a significant correlation between T2DM and an increased risk of hemiplegia (OR = 1.168, 95% CI = 1.025–1.331, P = 0.020) (Figure 2). The weighted median analysis results (OR = 1.257, 95% CI = 1.023–1.544, P = 0.030) also confirmed the association between T2DM and hemiplegia. While these findings suggest a potential causal relationship, the P-values are borderline significant, indicating that the evidence, though suggestive, is not overwhelmingly strong. In addition, the dataset filtered by MR-PRESSO was not significantly affected by external disturbances, which increased the reliability of the results of this study (Figure 3).

Sensitivity Analysis

In Cochran's Q-test, no heterogeneity was found in any IVs (P > 0.05), indicating that there was no heterogeneity in the results between T2DM and hemiplegia (MR-Egger: Q=164.265, Q-P value=0.567; IVW: Q=164.310, Q-P=0.588), and the symmetry of the funnel plot also confirmed this result (Figure 4). However, we acknowledge that the funnel plot displays asymmetry, with one outlier SNP effect estimate falling below −5.0, significantly deviating from the central trend. This asymmetry raises concerns about potential pleiotropy, outlier influence, or weak instrument bias. To address these concerns, we conducted additional analyses using the MR-Egger regression and MR-PRESSO tests. The MR-Egger intercept test showed no significant horizontal pleiotropy (MR-Egger intercept = 0.002083105, P = 0.832), indicating that the observed asymmetry is unlikely due to pleiotropy. Furthermore, the MR-PRESSO global test (172.915, P = 0.642) did not detect significant outliers, suggesting that the outlier SNP does not significantly influence the overall results. Additionally, the leave-one-out method showed that removing the outlier SNP did not significantly alter the IVW analysis results, further supporting the robustness of our findings (Table S4). These comprehensive sensitivity analyses provide additional assurance that our results are reliable and not unduly influenced by potential biases.

Discussion

Our study provides the first genetic evidence supporting a causal relationship between T2DM and hemiplegia using MR. This result challenges the current understanding by suggesting a direct causal pathway from T2DM to hemiplegia, which

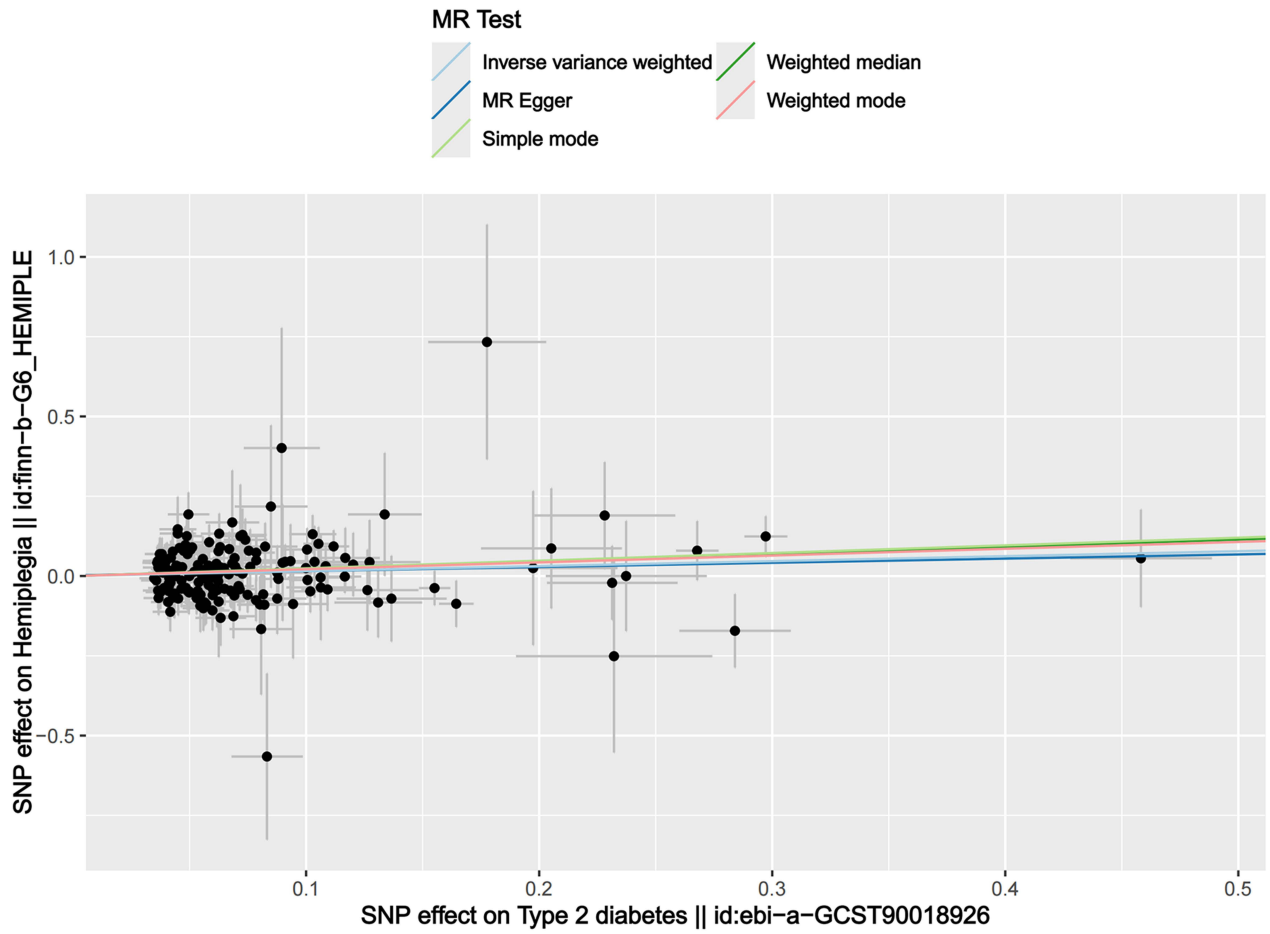

Figure 3 Scatter plot of MR analysis results.

has implications for both preventive and therapeutic strategies. While observational studies have documented comorbidity[21,22] and established T2DM as a risk factor for stroke—a primary cause of hemiplegia[23,24]—the direct causal link between T2DM and hemiplegia itself remained unproven due to residual confounding. By leveraging genetic instruments, our MR analysis overcomes this limitation and demonstrates that lifelong genetic predisposition to T2DM elevates hemiplegia risk (IVW OR=1.168, P=0.020). This finding extends beyond cerebrovascular-specific pathways and implies T2DM may independently contribute to hemiplegia through systemic mechanisms.

T2DM-associated hemiplegia might be mediated by systemic biological pathways, including inflammatory responses and gut microbiota interactions. Inflammatory dysregulation represents one plausible mechanism: multiple studies report elevated serum TNF-α[25,26] and IL-6[27,28] in T2DM patients. These cytokines could contribute to neurological damage, as evidenced by IL-6 elevations (723 pg/mL) in cerebrospinal fluid during hemiplegic episodes[29] and 2.8-fold higher TNF-α mRNA in hemiplegic muscle.[30] Concurrently, gut microbiota dysbiosis—characterized by altered abundance in T2DM[31,32]—might influence hemiplegia susceptibility through neurotransmitter signaling (eg, serotonin and calcitonin gene-related peptide).[33,34] Specifically, microbiota-derived metabolites could affect neural pathways via inflammatory molecules or hormonal cross-talk.[35,36] While these pathways are biologically plausible, they remain hypothetical and warrant experimental validation.

It is also well-documented that T2DM contributes to hemiplegia through a sequence of vascular events: chronic hyperglycemia leads to endothelial damage, which in turn promotes atherosclerosis, cerebral infarction, and ultimately hemiplegia.[2,37,38] This vascular pathway is supported by considerable evidence and highlights the importance of

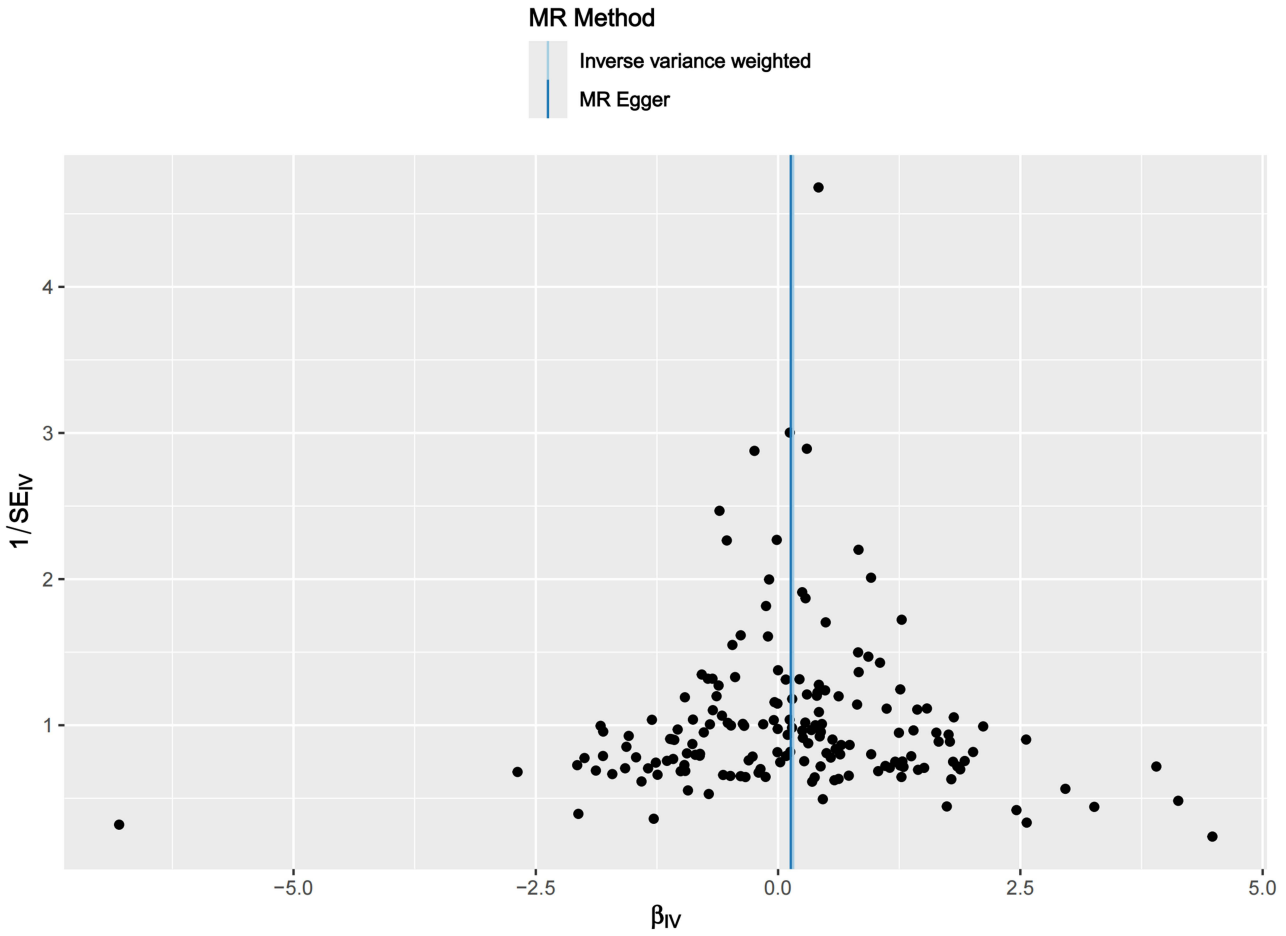

Figure 4 The overall heterogeneity test of the effect of T2DM on hemiplegia.

glycemic control in preventing stroke and its complications. Collectively, these mechanisms may underlie the observed association between T2DM and hemiplegia, though further research is needed to elucidate the precise pathways involved.

We acknowledge the multifactorial nature of hemiplegia, which can result from various conditions, including tumors or trauma. To address the potential for horizontal pleiotropy, we conducted sensitivity analyses using MR-Egger regression and the MR-PRESSO test. These analyses did not detect significant horizontal pleiotropy, suggesting that the observed association between T2DM and hemiplegia is unlikely to be confounded by these factors. However, we recognize the importance of considering these multifactorial causes and recommend further research to evaluate their potential contributions to the risk of hemiplegia.

An important difference between MR studies and randomized control trial (RCT) is that MR studies describe the association between lifelong exposure to T2DM alleles in the general population, while RCT can fully evaluate the role of T2DM in preventing or treating hemiplegia. Finally, based on the following two points, MR may be an ideal research design for understanding hemiplegia risk factors: (1) a long incubation period from onset to diagnosis; (2) MR can estimate the lifetime exposure of risk factors. MR studies have reduced the likelihood of inherent biases in observational studies. In this study, we reduced the pleiotropy of genetic variation by excluding some variations. In addition, The MR-Egger method does not support imbalanced pleiotropy. Sensitivity analysis also adds credibility to our results.

While our study provides valuable insights, it is important to acknowledge several limitations that may affect the generalizability and interpretation of our findings. The analysis was restricted to the European population, which limits the applicability of our results to other racial and ethnic groups. Additionally, despite efforts to identify potential alternative SNPs, not all exposed SNPs were included in the final GWAS dataset, potentially affecting the statistical

power to detect subtle effects. Furthermore, the use of publicly available GWAS data means that we could not control for all potential confounding factors, which may introduce some bias into our estimates. These limitations highlight the need for further research to validate our findings in more diverse populations and settings.

Conclusion

In summary, this study concluded through the MR analysis that there is a positive causal relationship between T2DM and the risk of hemiplegia. This discovery may have some enlightening implications for the prevention and treatment strategies of hemiplegia, but more scientific support is still needed to confirm it.

Data Sharing Statement

Data supporting the results of this study can be obtained on reasonable request to the corresponding author Xiaoxin Wu (xiaoxinwu@zju.edu.cn).

Ethics Approval

This research utilizes publicly accessible, abstract-level data derived from comprehensive genome-wide association studies (GWAS). In accordance with national legislative guidelines, specifically items 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects promulgated on February 18, 2023, in China, this study is exempt from the requirement for ethical approval.

Acknowledgments

We would like to thank all the participants of this project and investigators for collecting the data. We thank Home for Researchers editorial team (www.home-for-researchers.com) for language editing service.

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.

Funding

This work was supported by National Key R&D Program of China (2024YFC2309904 and 2024YFC3506600). The funding sources had no role in the study design; in the writing of the report; or in the decision to submit the paper for publication.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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