

Exploring the Link Between Diabetes, Herpes Zoster, and Post-Herpetic Neuralgia: Insights From Mendelian Randomization

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Background: Diabetes mellitus (DM), herpes zoster (HZ) and its sequelae, post-herpetic neuralgia (PHN), are common in elderly individuals. Previous observational studies have shown that the prevalence of HZ and PHN in conjunction with DM is increasing. Nonetheless, few studies have investigated the causal relationships between DM and the risk of HZ and PHN.

Methods: A two-sample Mendelian randomization (TSMR) analysis was conducted on genome-wide association study (GWAS) data. We obtained four separate datasets for DM: type 1 diabetes (T1D), type 2 diabetes (T2D), mother diabetes mellitus (mother-DM) and father diabetes mellitus (father-DM), and two independent datasets for HZ and anti-varicella-zoster virus IgG (VZV-IgG), a single GWAS for PHN. The inverse variance weighted (IVW), MR-Egger, weighted median and weighted mode analyses were used to estimate the causality.

Results: Genetically predicted T1D increased the level of VZV-IgG (IVW: OR=1.011, 95% CI 1.006–1.016, $P_{\text{FDR}}=8.44 \times 10^{-6}$). T2D (IVW: OR=1.313; 95% CI 1.043–1.655, $P_{\text{FDR}}=0.041$), mother-DM (IVW: OR=7.909; 95% CI 1.232–50.777, $P_{\text{FDR}}=0.039$), and father-DM (IVW: OR=11.798; 95% CI 2.051–67.874, $P_{\text{FDR}}=0.023$) increased the risk of PHN. No reverse causality was found between HZ, PHN, and DM.

Conclusion: Our research reveals a causal link between genetically determined T1D and increased VZV-IgG levels. Additionally, genetically predicted T2D and a family history of DM increase the risk of PHN. These discoveries deepen our comprehension of the underlying causes of HZ and PHN.

Keywords: diabetes mellitus, herpes zoster, post-herpetic neuralgia, two-sample Mendelian randomization

Introduction

Varicella-Zoster virus (VZV), also known as HHV-3, is a human α -herpesvirus in the Herpesviridae family. It is a double-stranded DNA virus that causes contagious chickenpox in children. The virus remains latent in the roots of the sensory nerve ganglion and dermatomes and can reactivate in adults, particularly in elderly individuals, when immunity weakens, causing herpes zoster (HZ).¹ The major manifestation of HZ is a cluster of rashes on the skin accompanied by severe pain at the corresponding site, affecting 15% to 30% of the global population at least once during their lifetime.² A frequent and potentially exacerbating consequence of HZ is post-herpetic neuralgia (PHN), which affects an estimated 15–40% of HZ patients.³ PHN is characterized by continuous pain for more than 3 months, even a decade after the resolution of the HZ rash.⁴ The pain is often described as burning, electric shock, stabbing, or tearing and is frequently accompanied by depression, anxiety, insomnia, and even suicidal thoughts.⁵ Although varicella vaccination has been used since 1995, the global occurrence of HZ continues to increase.⁶ Moreover, herpes, including both HZ and PHN, ranks among the top 10 costliest dermatological conditions.⁷

Diabetes mellitus (DM) is a prevalent chronic metabolic disorder that usually arises from injured insulin-producing islet β -cells or decreased insulin sensitivity, thus leading to type 1 diabetes (T1D) and type 2 diabetes (T2D), respectively.⁸ It has been reported that there are 521 million individuals with DM worldwide, of which 96% have T2D, and the number is predicted to be 1.31 billion in 2050.⁹ DM patients are often accompanied by compromised immune homeostasis^{10–13} and are more susceptible to viral infections such as VZV, with a slower recovery rate.¹⁴ These patients have more severe and prolonged clinical symptoms and are more likely to experience sequelae.¹⁵ Managing DM patients with HZ and PHN can be challenging because it can be hindered by complications of diabetes in the nervous system.¹⁶ Furthermore, PHN can exacerbate the already diminished quality of life experienced by DM patients.¹⁷

The risk of HZ and PHN is greater in diabetic patients than in controls.^{18–20} However, other studies reported a negative association between them.²¹ These observational studies may interfere with reverse causality and unmeasured confounding factors. Randomized controlled trials (RCTs) are the gold standard for testing causality but have extensive costs and time. Hence, we employed MR analyses in this domain. Using genetic variants as instrumental variables (IVs), MR provides an effective methodology for assessing the link between exposure and outcome,²² avoiding the limitations of observational studies and RCTs.

Methods

Study Design

Our study applied bidirectional two-sample Mendelian randomization (TSMR), adhering to the STROBE-MR guidelines (Table S1).²³ Genetic variants are deployed as instrumental variables (IVs) to evaluate the exposure's causal effect on the outcome. Qualified IVs must meet three fundamental criteria: (1) Relevance: the IVs must intimately link to the exposure (DM). (2) Independence: the IVs should be unrelated to any potential confounders (such as weak immune function due to HIV infection, immunosuppressive medication, autoimmune diseases, malignant tumors, or organ transplantation)²⁰ that could distort the relationship between exposure and outcome. (3) Exclusivity: IVs can only affect the outcome (HZ, PHN) through exposure (DM) without any direct link to the outcome²⁴ (Figure 1).

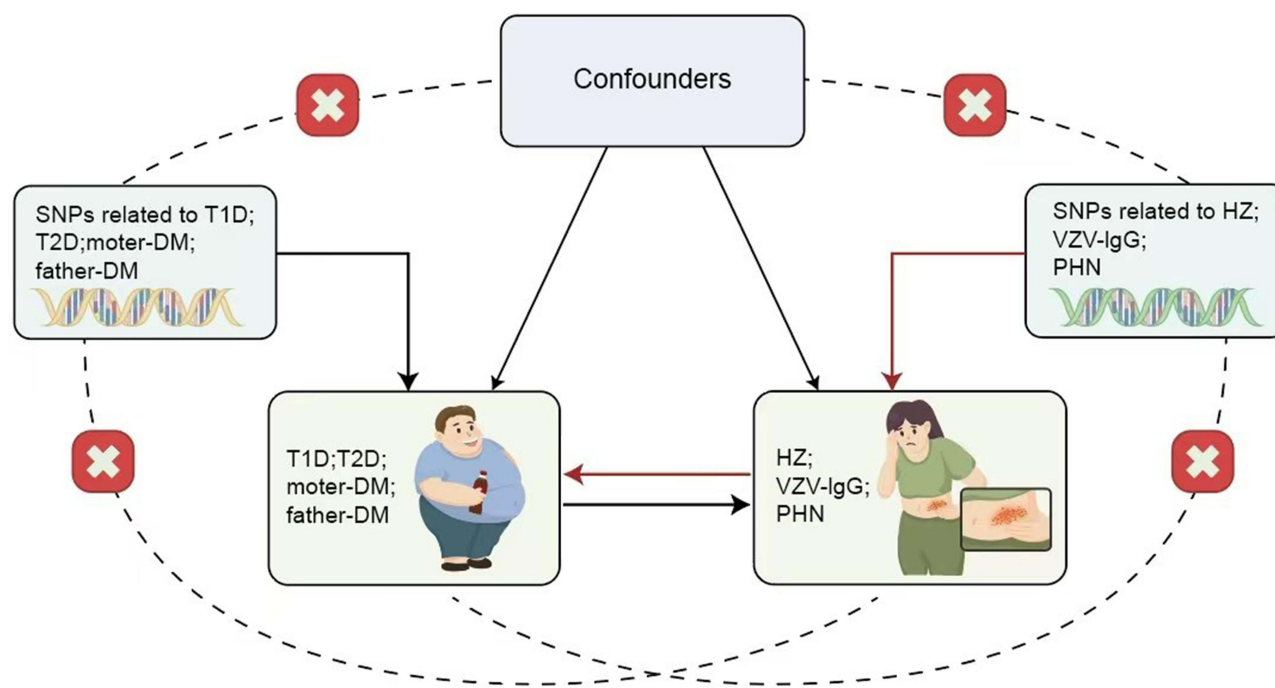


Figure 1 Basic assumptions of Mendelian randomization.

Abbreviations: T1D, type 1 diabetes; T2D, type 2 diabetes; mother-DM, mother-diabetes mellitus; father-DM, father-diabetes mellitus; HZ, herpes zoster; VZV-IgG, anti-varicella zoster virus IgG seropositivity; PHN, post-herpetic neuralgia; SNP, single-nucleotide polymorphism.

Data Source

For the HZ, GWAS summary statistics data were obtained from the FinnGen consortium (<https://r10.finnngen.fi/>), including data from 401866 European individuals (5488 cases and 396,378 healthy controls), classified as having certain infectious and parasitic diseases (AB1).²⁵ An additional GWAS dataset of anti-varicella herpesvirus IgG seropositivity (VZV-IgG) was added to enhance our findings (<https://gwas.mrcieu.ac.uk/>). This GWAS dataset is focused on 13 pathogens to define 46 phenotypes via 10,000 serological evaluations of infectious illness, with an extensive genotyping analysis that profiled 8,735 European participants and a scan of 9,170,312 single-nucleotide polymorphism (SNP) SNPs. For PHN, we searched many GWAS data resources. Nevertheless, we only found an available dataset from the FinnGen consortium, which represented a total of 360,894 Europeans with 356 cases and 360,538 controls, categorized as VI Diseases of the nervous system (G6_).²⁵ Summary details are given in Table 1.

For the DM, both the T1D and T2D datasets were obtained (<https://gwas.mrcieu.ac.uk/>). The GWAS summary data of 18,942 T1D cases versus 501,638 healthy controls of European individuals were obtained from 9 cohorts, including 59,999,551 SNPs.²⁶ For T2D, a meta-analysis of GWAS data was acquired, which incorporated 3 GWAS datasets of European volunteers: DIAbetes Genetics Replication and Meta-analysis (DIAGRAM consortium, stage 1 [12,171 cases/56,862 controls], stage 2 [22,669 cases/58,119 controls]),²⁷ Genetic Epidemiology Research on Aging (GERA consortium, 6905 cases/46,983 controls),²⁸ and the UK Biobank (UKB, 21,147 cases/434,460 controls),²⁹ including 16 million SNPs in 62,892 T2D cases vs 596,424 healthy controls of European ancestry.³⁰ To enhance our findings, we used datasets on the family history of DM from the UKB (<http://www.nealelab.is/uk-biobank>). Participants with any parent affected by DM were grouped as having a family predisposition to DM, as determined through self-reported information by answering, “Has/did your father/mother ever suffer from diabetes?”. The summary GWAS data, arrays of 488,018 individuals (38,850 cases of paternal DM and 361,837 controls), and 492,745 participants (40,091 cases of maternal DM and 383,801 controls) in the UKB were meta-analyzed (<http://biobank.etsu.ox.ac.uk/>) (Table 1). Notably, there was no sample overlap among the DM, HZ, and PHN datasets employed in this study. Z score normalization was used to standardize the primary GWAS data for further analysis.

Selection of IVs

The IVs utilized in the present study were meticulously chosen according to the standards mentioned above: (1) Relevant with exposure defined as $P < 5 \times 10^{-8}$ for T1D, T2D, mother-DM and father-DM; because no relevant SNPs were identified with $P < 5 \times 10^{-8}$ for HZ, VZV-IgG and PHN, we chose $P < 5 \times 10^{-6}$ for HZ, $P < 5 \times 10^{-5}$ for VZV-IgG and $P < 1 \times 10^{-5}$ for PHN according to relevant MR studies;^{31–33} with an assessment of linkage disequilibrium (LD, kb=10,000, $r^2 < 0.001$). Those SNPs linked to the confounders mentioned above (2 Independence)²⁰ or outcomes (3 Exclusivity) identified in the Phenoscanner database were meticulously excluded. We subsequently undertook a harmonization

Table 1 A Comprehensive Summary of the GWAS Datasets Employed in the MR Analysis

Trait	GWAS ID	Year	Sample size (Cases/Controls)	SNPs	Population	Sex	Category	PMID
T1D	ebi-a-GCST90014023	2021	18,942/501,638	5,99,99,551	European	Both	Binary	34012112
T2D	ebi-a-GCST006867	2018	62,892/596,424	50,53,015	European	Both	Binary	30054458
mother-DM	ukb-b-16451	2018	40,091/383,801	98,51,867	European	Both	Binary	NA
father-DM	ukb-b-20211	2018	38,850/361,837	98,51,867	European	Both	Binary	NA
HZ	finngen_R10_ABI_ZOSTER	2023	5,488/396,378	NA	European	Both	Binary	36653562
VZV-IgG	ebi-a-GCST90006928	2020	8,735	91,70,312	European	Both	Continuous	33204752
PHN	finngen_R10_G6_POSTZOST	2023	356/360,538	1,63,80,406	European	Both	Binary	36653562

Abbreviations: T1D, type 1 diabetes; T2D, type 2 diabetes; mother-DM, mother-diabetes mellitus; father-DM, father-diabetes mellitus; HZ, herpes zoster; VZV-IgG, anti-varicella zoster virus IgG seropositivity; PHN, postherpetic neuralgia; NA, not applicable.

process to ensure allelic consistency between the SNP-DM and the SNP-HZ and SNP-PHN statistics. We calculated the strength of the IVs via a formula ($F = (\beta^2/se^2)$).³⁴ $F < 10$ may suggest weak IVs, which could introduce bias into the results. Therefore, a degree of caution is warranted when interpreting outcomes.³⁵

Statistical methods

We performed four MR methods to evaluate the causal association between the DM and the inclination to affect the HZ and develop the PHN. Our primary MR analysis was conducted via the IVW method, with further evaluation provided by MR-Egger,³⁶ weighted medians,³⁷ and weighted modes.³⁸ For counts of SNPs less than 3, we performed the Wald ratio method by calculating the separate effect size for the SNP linked to the outcome and the exposure. When an abundance of more than three SNPs was accessible, the Wald estimates underwent a meta-analysis utilizing the IVW approach. The IVW method yields an unbiased estimate if there is no horizontal pleiotropy or if it is counterbalanced.³⁹ Because the type of disease data was dichotomous, we displayed our results as ORs±95% CIs. The Cochran Q statistic and MR Egger intercept, in conjunction with the MR-PRESSO global test, were used to assess heterogeneity and pleiotropy.⁴⁰ Additionally, a leave-one-out analysis was conducted to assess the sensitivity of our results. A Benjamini-Hochberg false discovery rate (FDR) correction method was used to correct for bias in multiple comparisons. A potential link was considered when $P_{\text{FDR}} > 0.05$ but $P < 0.05$. R software (version 4.3.3) in conjunction with the R packages “TwoSampleMR”, “MR PRESSO”, and “MR Radial” were applied in the MR study’s statistical analysis.

Results

Screening of IVs

In forward MR, for HZ, 83, 113, 23, and 27 SNPs that were closely associated with T1D, T2D, mother DM, and father DM, respectively, were used as outcomes. In addition, VZV-IgG was regarded as the outcome, and we obtained 57, 111, 16, and 19 SNPs that were closely associated with T1D, T2D, maternal DM, and paternal DM, respectively. For PHN to be seen as the outcome, we extracted 82, 113, 23, and 27 SNPs that were intimately linked with T1D, T2D, mother DM, and father DM, respectively.

In reverse MR, HZ was considered an exposure, and we identified 13, 9, 12, and 12 SNPs associated with T1D, T2D, mother DM, and father DM, respectively. The exposure to VZV-IgG yielded 89, 18, 78, and 78 SNPs for the same conditions. Furthermore, when PHN served as an exposure, we discovered 12, 4, 11, and 11 SNPs related to T1D, T2D, mother DM, and father DM, respectively.

The identified SNPs served as robust IVs, as indicated by a high F statistic exceeding the threshold of 10 (Table S2). This study included a comprehensive set of 27 MR analyses, as shown in Table S3.

The Causal Effect of DM on HZ, VZV-IgG, and PHN

We present the TSMR and related sensitivity analysis outcomes for the relationships between DM and HZ and between DM and PHN. Our analysis identified 4 significant causal relationships at a P value and P_{FDR} threshold of less than 0.05 (Figures 2a, 3 and Table S3). There was no association between genetic variations in T1D and the risk of HZ or PHN, as the results of the IVW method revealed (T1D for HZ: OR=0.999, 95% CI 0.983–1.014, $P=0.854$; T1D for PHN: OR=1.031, 95% CI 0.952–1.117, $P=0.455$). These findings are fully aligned with the results from the MR-Egger, weighted median, and weighted mode methods. Conversely, genetically predicted T1D patients presented a significant increase in the level of VZV-IgG, even after FDR control (OR=1.011, 95% CI 1.006–1.016, $P=2.11 \times 10^{-6}$, $P_{\text{FDR}}=8.44 \times 10^{-6}$), a result that was consistent across all three alternative MR methods.

When IVW was used as the dominant method, genetically predicted T2D, as well as maternal and paternal DM, had no causal associations with HZ (T2D: OR=0.996, 95% CI: 0.940–1.056, $P=0.897$; mother-DM: OR=0.959, 95% CI: 0.571–1.612, $P=0.875$; father-DM: OR=0.967, 95% CI: 0.618–1.515, $P=0.885$) or VZV-IgG levels (T2D: OR=0.995, 95% CI: 0.979–1.011, $P=0.539$; mother-DM: OR=0.973, 95% CI: 0.837–1.131, $P=0.718$; father-DM: OR=0.977, 95% CI: 0.849–1.125, $P=0.750$). These insignificant results were corroborated by the other MR methods. However, our results indicate a significant causal effect of T2D, mother-DM, and father-DM on the risk of PHN, with ORs of 1.313 (95% CI

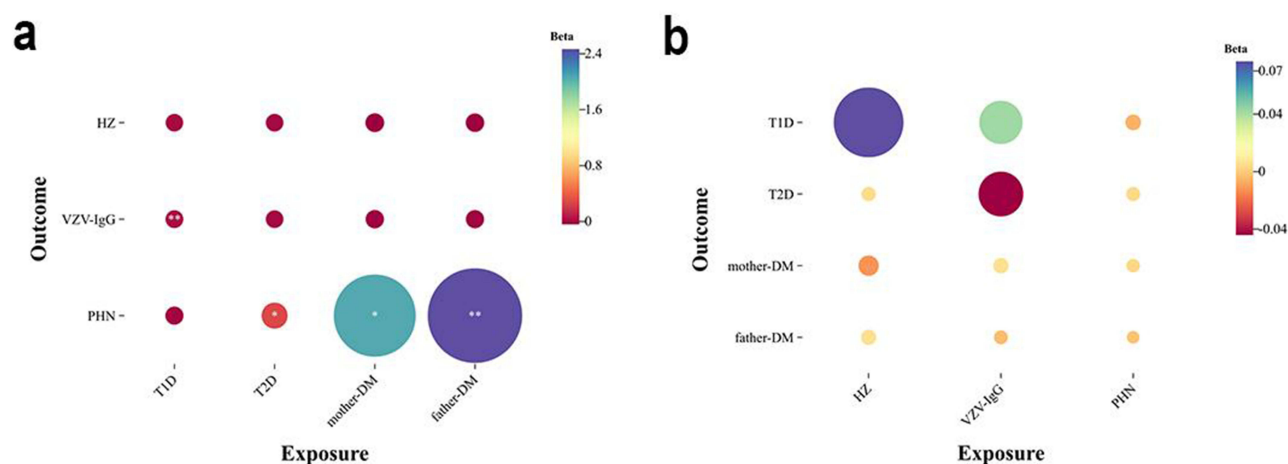


Figure 2 Forward (a) and reverse (b) MR (IVW method) assessments of the link between DM and the risk of developing HZ, VZV-IgG, and PHN. * $p < 0.05$; ** $p < 0.01$. **Abbreviations:** MR, Mendelian randomization; IVW, inverse variance weighting; DM, diabetes mellitus; T1D, type 1 diabetes; T2D, type 2 diabetes; mother-DM, mother-diabetes mellitus; father-DM, father-diabetes mellitus; HZ, herpes zoster; VZV-IgG, anti-varicella zoster virus IgG seropositivity; PHN, post-herpetic neuralgia; IVW, inverse variance weighting.

1.043–1.655, $P_{\text{FDR}}=0.041$), 7.909 (95% CI 1.232–50.777, $P=0.029$, $P_{\text{FDR}}=0.039$), and 11.798 (95% CI 2.051–67.874, $P=0.006$, $P_{\text{FDR}}=0.023$), respectively (Figures 2a, 3 and Table S3).

Notably, for PHN as an outcome, 83 SNPs were extracted from the T1D-associated dataset. Moreover, the results of the MR Egger intercept test were $P=0.032$. After excluding the outlier SNP (rs1794269), the MR-Egger P value was 0.144, suggesting that there were no further outlier SNPs. The secondary IVW results ($P=0.455$) were in line with the primary analysis ($P=0.507$). Furthermore, MR PRESSO ($P=0.527$) exerted no pleiotropy, indicating the limited impact of heterogeneity on the whole judgment. Other MR analyses with a Q statistic P value above 0.05 indicated no obvious heterogeneity (Table S4). All MR Egger intercept tests showed a P value above 0.05, demonstrating null pleiotropy among SNPs and reinforcing the qualification and robustness of the MR analysis findings (Table S4). In addition, no single SNP clearly influenced the association according to leave-one-out analyses (Figures S1–S6).

Causal Effects of HZ, VZV-IgG, and PHN on DM

Later, we initiated a reverse MR approach to test the causal links between HZ, VZV-IgG, PHN and DM. No significant causal relationship features were identified at the P value threshold of less than 0.05 (Figures 2b, 3 and Table S3). The IVW results provided no indication of a causal effect between these conditions (Figure 3, Table S3), and other MR methods did not yield clearly different outcomes. Moreover, when T1D was considered an outcome, 13 SNPs from the HZ-associated dataset showed significant pleiotropy (MR-PRESSO $P=0.011$) and heterogeneity (Cochran's Q test: $P_{\text{MR-Egger}}=0.006$, $P_{\text{MR-IVW}}=0.009$). After excluding the outlier SNP (rs81302), no evident pleiotropy or heterogeneity remained, as determined by the MR mentioned above methods, with the secondary IVW results ($P=0.065$) aligning with the primary IVW analysis ($P=0.259$). Additionally, 22 SNPs from the VZV-IgG-associated dataset demonstrated significant pleiotropy ($P_{\text{MR-PRESSO}}=0.001$), and heterogeneity was examined by Cochran's Q test ($P_{\text{MR-Egger}}=0.002$, $P_{\text{MR-IVW}}=0.002$). Following the exclusion of outlier SNPs (rs11205012, rs4546984, rs62473135, and rs9879045) identified by MR-PRESSO and radial MR ($P < 0.05$, Table S5, Figure S7), no statistical pleiotropy or heterogeneity was found via the MR methods mentioned above, and the secondary IVW results ($P=0.669$) were consistent with the primary IVW analysis ($P=0.708$). The subsequent MR-Egger analyses and Cochran's Q test revealed no pleiotropy or heterogeneity ($P > 0.05$), reinforcing the robust MR results. Leave-one-out analyses confirmed the absence of bias from any SNP exhibiting obvious heterogeneity (Table S4 and Figures S8–S13).

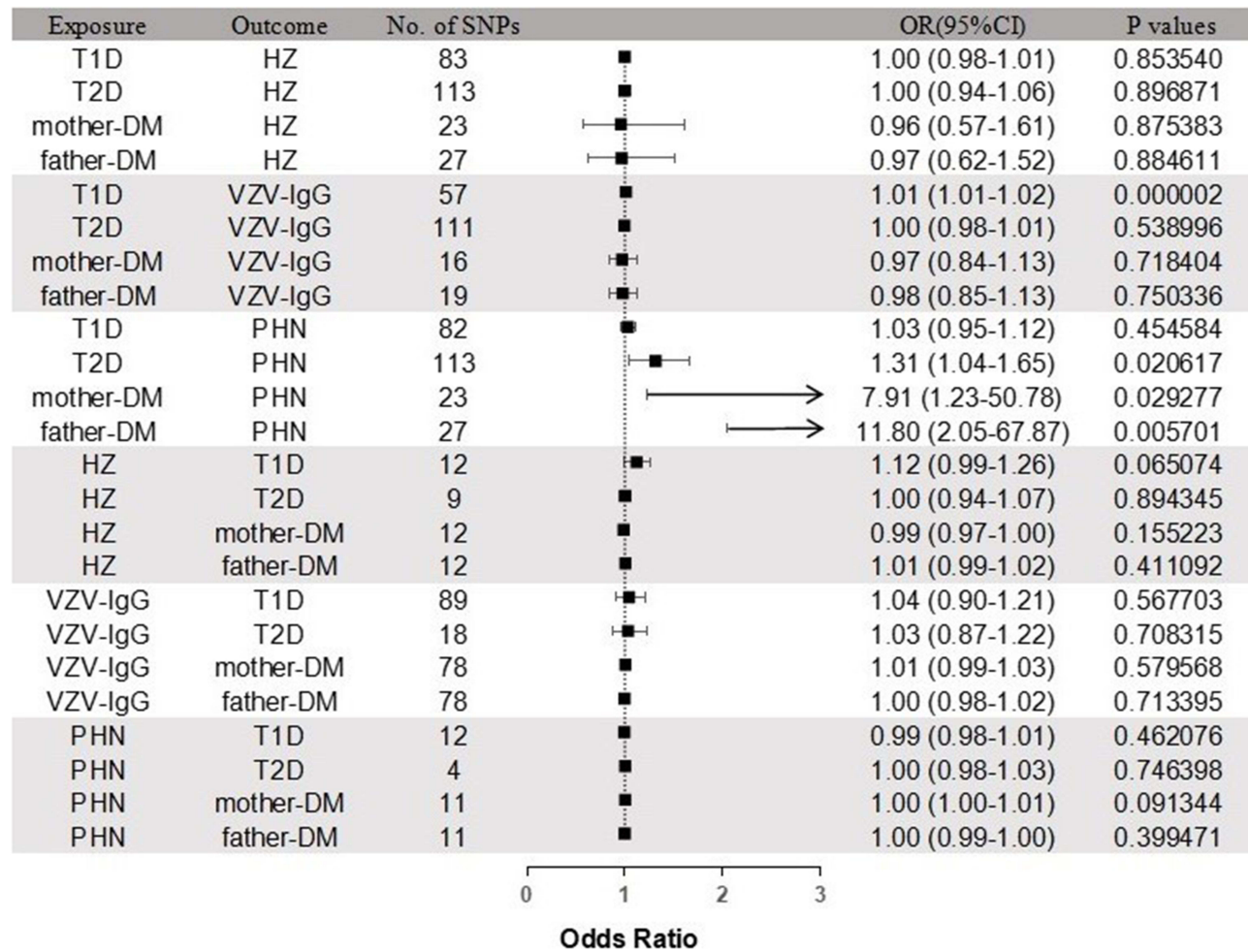


Figure 3 Quantification of the causal nexus between DM and HZ, VZV-IgG levels, and PHN via IVW methods. The results are presented as ORs with 95% CIs. **Abbreviations:** MR, Mendelian randomization. DM, diabetes mellitus; T1D, type 1 diabetes; T2D, type 2 diabetes; mother-DM, mother-diabetes mellitus; father-DM, father-diabetes mellitus; HZ, herpes zoster; VZV-IgG, anti-varicella zoster virus IgG seropositivity; PHN, post-herpetic neuralgia; IVW, inverse variance weighting. OR, odds ratio; CI, confidence interval.

Discussion

Individuals with DM sometimes encounter VZV infections, potentially resulting in serious complications such as PHN.⁴¹ While numerous investigations have suggested a link between DM and HZ/PHN, definitive causality remains understudied. In this work, we employed the TSMR to check the causal relationships between the DM and the HZ and PHN. Notably, our findings substantiate a causal influence of T1D on elevated VZV-IgG levels, as well as the impact of T2D and maternal and paternal history of DM on the increased risk of PHN. Conversely, HZ and its complication, PHN, were found to have no significant influence on DM.

The impact of diabetes on the progression to HZ or PHN has been examined predominantly through observational and cohort studies. A study from Taiwan revealed that individuals with T1D are at a notably elevated risk of HZ, with a 35% increase in risk. Additionally, the increase in risk for those with T2D is less notable, with a 9% surge risk in HZ.¹⁹ A UK study⁴² assessed the risk factors for HZ, indicating a link between T1D and HZ, whereas a null association was observed between T2D and HZ. These results are consistent with our finding that T1D increases the level of VZV-IgG. However, this consensus is not universal. A previous study conducted in America involving a sample size of 20,397 did not find a correlation between T1D and HZ,²⁰ a similar result was found in another study from Belgium with 77 participants.⁴³ The discrepancies in these findings might be attributed to differences in sample sizes, study designs, and the characteristics of the populations studied. These elements may plausibly account for the absence of a significant association in our

MR analysis concerning the causal impact of T1D on HZ. Importantly, observational studies often have limited sample sizes, confounding factors, and the possibility of reverse causality. In contrast, the MR findings from our study offer more reliable evidence for making causal inferences, providing a stronger basis for understanding the relationship between T1D and the risk of HZ.

While the exact way in which DM increases the risk of HZ has not been completely identified, some plausible explanations have emerged. Compared with healthy individuals, DM patients have a weaker defense against infectious disease. Owing to the fragile function of cell-mediated immunity,⁴⁴ lower expression of Toll-like receptor-2 (a key innate immune receptor that affects pathogen recognition),⁴⁵ impaired macrophage glycolysis and reserve capacity that affects phagocytosis,¹² dysfunction of natural killer cells,⁴⁶ and neutrophil hypofunction arise from inhibition of neutrophil degranulation,¹¹ decreased reactive oxygen species production⁴⁷ and impaired formation of extracellular traps.⁴⁸ Moreover, the levels of interleukins (IL-1, IL-6) secreted by peripheral blood mononuclear cells are lower in T1D patients than in T2D patients and healthy controls,¹³ whereas IL-6 has an important effect on the induction of antibody production and the development of T cells.⁴⁹ Autoimmune defects in T1D result in weaker macrophage/monocyte function.⁵⁰ These findings could explain why diabetic people, especially T1D patients, are more susceptible to HZ than are T2D patients and controls, as supported by observational studies conducted in Taiwan^{19,51} and England.⁵² This finding is also in line with our findings that genetically predicted T1D results in an amplified level of VZV-IgG, whereas T2D does not.

Currently, few studies have examined the connection between diabetes and PHN, with results that are not uniform. DM is correlated with a 45% increased likelihood of HZ and an 18% increased chance of PHN development compared with those without DM.⁵³ Additionally, a retrospective study noted that the wider the fluctuations in blood sugar levels are, the greater the inclination toward PHN in DM-associated HZ patients.⁵³ Moreover, a Taiwanese study revealed that the use of metformin, a common medication for T2D, exhibited a considerably protective effect against PHN.⁵⁴ These findings provide further evidence for the potential connection between T2D and PHN. Matching the findings from several studies that have shown that diabetes confers a greater risk of PHN^{41,55}, our study revealed that causal evidence of T2D and a family history of DM increases the risk of PHN. Using extensive GWAS with a larger sample size ranging from 360,894–659,316, we obtained a more reliable result.

The connection between DM and PHN is believed to be rooted in several physiological mechanisms. Persistent inflammation in diabetic patients may lead to nerve harm and hyperreaction to pain, which may explain the increasing prevalence of PHN in this population.⁵⁶ Additionally, high blood sugar levels can activate a metabolic pathway known as the polyol pathway, which can impair cellular functions and potentially lead to PHN.⁵⁷ Research involving laboratory animals and human trials indicates that even short-term spikes in blood sugar can trigger increased activity in small-diameter pain fibers, contributing to neuropathic pain.⁵⁸ Furthermore, diminished expression of cell adhesion factors in diabetic mice results in reduced protective infiltration of CD45+ leukocytes and CD8+ T cells and a marked increase in pro-inflammatory cytokines in the brain.⁵⁹ In addition, damage to the microvasculature can cause neurons to become stressed in T2D patients,^{60,61} resulting in increased viral loads and severe symptoms that exacerbate the odds of PHN. Specifically, we found evidence that genetically predicted T2D was associated with a greater risk of PHN, which was confirmed by an additional two GWAS datasets from mothers and fathers with DM.

This study has several inherent limitations. First, the datasets for DM, HZ, and PHN were derived primarily from European cohorts; although we selected GWAS data for these diseases with extremely large sample sizes, potential limitations in primary data quality may still limit the validity of extrapolating the results of this study. Future studies employing local GWAS data are necessary to confirm the generalizability of these findings. Second, the modest sample size of PHN cases within the Finnish Genetics database (n=356) could restrict the statistical robustness of our MR analysis. Despite these constraints, other suitable PHN GWAS datasets have yet to be identified to enhance our discoveries. Third, parental DM datasets were collected from self-reported information, and no specific diabetes type was indicated. On the basis of estimates of diabetes incidence, T1D accounts for <10% of all diabetes cases, and T2D accounts for 90% of adult diabetes cases with a clear genetic predisposition.⁶² We are confident that the majority of parents with T2D are likely to be at increased risk for individual PHN. Fourth, we found that DM did not affect HZ, whereas T1D could cause a significant increase in the level of VZV-IgG, which may be due to the following reasons: 1.

The sample sizes were different, the sample size of HZ was 5488, and the sample size of VZV-IgG was 8735; 2. The ways of confirming the diagnosis were different, the clinician made the diagnosis of HZ, and the clinic visit of HZ patients with mild symptoms was rare; therefore, we can speculate that the prevalence of HZ was underestimated, which led to reporting bias, whereas VZV-IgG was clearly diagnosed via laboratory ELISA. Further extensive and well-defined studies on VZV infection using GWAS data are essential to develop the application of MR in this domain. Fifth, a common challenge in MR is the unpredicted potential pleiotropy that can confound the effect of exposure on outcome. To limit this risk, a thorough pleiotropy analysis was performed, scrutinizing the phenotype associations of each SNP. Drawing from the current body of knowledge, we identified no other traits with confirmed direct impacts on DM or HZ and PHN, suggesting that our approach effectively controls for horizontal pleiotropy.

Conclusion

This study represents the most comprehensive MR analysis conducted to date, exploring the causal connections between the four DM types and HZ and PHN. Our findings indicate a pronounced link between T2D and PHN; moreover, a family history of DM increases the risk of PHN. This outcome is less prone to biases from confounding factors and reverses causality, offering a more reliable perspective than numerous preceding traditional observational studies.^{41,55,63,64} Additionally, the insights gleaned from our study shed more light on the origins of PHN and highlight the need for further investigation into the potential mechanisms that result in the onset of PHN. These findings also suggest that diabetic patients, especially the offspring of diabetic parents, should focus on preventive guidance for herpes zoster and PHN in their old age. Specific measures include regular monitoring of blood glucose levels and immune function (eg, white blood cell function, T-cell activity, etc.) for a comprehensive assessment of the patient's immune status; active and effective control of blood glucose and enhancement of the immune system; strengthening health education on herpes zoster; and administration of herpes zoster vaccines.

Ethics Statement

In compliance with national regulations, specifically Items 1 and 2 of Article 32 of [The Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects] dated February 18, 2023 in China, our research is exempt from additional ethical approval. This exemption is based on the fact that our study utilizes data that are both legally obtained and publicly available, and employs anonymized information. Throughout the research process, there is no potential for harm to subjects, and the study does not involve any sensitive personal information or commercial interests.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; Xueying Yang, Dairui Li, Yuqing Chen, Xuerong Zhang and Qiong Zhao took part in drafting, revising or critically reviewing the article; Xueying Yang, Dairui Li, Yuqing Chen, Xuerong Zhang and Qiong Zhao gave final approval of the version to be published; Xueying Yang, Dairui Li, Yuqing Chen, Xuerong Zhang and Qiong Zhao have agreed on the journal to which the article has been submitted; and X ueying Yang, Dairui Li, Yuqing Chen, Xuerong Zhang and Qiong Zhao agree to be accountable for all aspects of the work.

Disclosure

The authors affirm that this research was carried out autonomously, devoid of any business or monetary affiliations that might be interpreted as a conflict of interest.

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