

Original Article

The influence of genetic predisposition to oxidative stress on painful diabetic peripheral neuropathy: A Mendelian randomization study

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Abstract



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Genetic predisposition to oxidative stress (OS) may influence the risk of Painful Diabetic Peripheral Neuropathy (PDPN). This study employed a Mendelian Randomization (MR) approach to investigate the causal relationship between genetic predisposition to OS and PDPN. Genetic instruments associated with OS biomarkers were selected as exposures. Summary-level data on PDPN was obtained from the largest available genome-wide association study (GWAS). MR analyses were conducted using the inverse-variance weighted (IVW) method, with sensitivity analyses employing the MR-Egger, weighted median, and MR-PRESSO approaches. Genetic predisposition to increased glutathione S-transferase (GST) activity was associated with a reduced risk of PDPN (OR=0.66, 95%CI: 0.49-0.89, P=0.006). Higher ascorbate levels conferred a protective effect against PDPN (OR=0.83, 95%CI: 0.71-0.97, P=0.018). No significant association was observed between genetic predisposition to OS biomarkers and PDPN severity. Genetic predisposition to increased GST activity and higher ascorbate levels protect against the development of PDPN, suggesting a causal relationship.

Keywords: Oxidative Stress (OS), Painful Diabetic Peripheral Neuropathy (PDPN), Mendelian Randomization (MR).

1. Introduction

Painful Diabetic Peripheral Neuropathy (PDPN) emerges as a significant complication of diabetes, marked by nerve damage resulting from prolonged hyperglycemia [1]. This condition affects a considerable segment of the diabetic population, presenting with symptoms ranging from discomfort and numbness to severe neuropathic complications, profoundly impacting patients' quality of life [2-4]. Among the multiple etiological factors implicated in PDPN, oxidative stress (OS) stands out, characterized by an imbalance in the production and detoxification of reactive oxygen species (ROS) [5]. This oxidative imbalance is known to contribute to neuronal damage and accentuate diabetic symptoms [6], presenting a critical area of research in understanding and managing PDPN.

The role of genetic predisposition in PDPN, particularly in individual responses to OS, is an area of burgeoning interest. Genetic factors may significantly influence susceptibility to PDPN, an aspect that remains inadequately explored. Previous studies have identified several gene-

tic determinants that could affect an individual's risk of developing PDPN [7-9]. However, the causal relationship between these genetic factors and the condition has not been fully elucidated. This gap in understanding necessitates a methodological approach that can robustly infer causality.

Mendelian Randomization (MR), leveraging genetic variants as instrumental variables [10], offers a novel approach to elucidate causal relationships between exposures (e.g., OS) and outcomes (like PDPN). This method utilizes the random assortment of alleles at conception, mirroring randomized controlled trials. By applying MR, this study aims to investigate the causal impact of genetic predisposition to OS on PDPN development and severity.

The objectives of this study are multifaceted: firstly, to explore the extent to which genetic susceptibility to OS influences the risk of PDPN, and secondly, to determine the implications of these findings for future therapeutic strategies for diabetic patients. This groundbreaking research faces challenges, including the need for large sample sizes,

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addressing diverse genetic backgrounds, and interpreting MR findings. Acknowledging potential limitations, including confounding factors and the assumption of a linear relationship between genetic predisposition and oxidative stress, is crucial.

In summary, this study, through the lens of Mendelian Randomization, aims to unravel the complex interplay between genetic predisposition to OS and the risk of painful diabetic peripheral neuropathy. The findings could pave the way for targeted interventions and contribute significantly to the management of this debilitating complication in diabetic patients.

2. Materials and methods

2.1. Study design

In this study, a bidirectional MR design was strategically implemented to ascertain the potential causal effect of a carefully curated set of 11 oxidative stress injury biomarkers on DNP. The exhaustive list of these biomarkers includes but is not limited to, superoxide dismutase (SOD), glutathione S-transferase (GST), glutathione peroxidase (GPX), catalase (CAT), uric acid (UA), zinc, α -tocopherol, ascorbic acid, retinol, albumin, and total bilirubin (TBIL). The overarching goals of this MR analysis were to evaluate the assumptions associated with the methodology and elucidate the potential causal pathways linking these biomarkers with DNP. The MR hypotheses were clearly articulated as follows: 1. Genome-wide single-nucleotide polymorphisms (SNPs), culled from genome-wide association studies (GWAS), functioned as instrumental variables (IVs) and were associated with the exposure; 2. These IVs, in turn, were not associated with any potential confounders; and 3. These IVs influenced the risk of outcomes, such as DNP, solely through their exposure pathway.

2.2. Exposure data source

The available GWAS summarized oxidative stress injury biomarkers data were gained from the open data-

base (IEU OPEN GWAS PROJECT: <https://gwas.mrcieu.ac.uk/> (accessed on 20, Oct 2023)). To avoid bias from population heterogeneity, only European population summarized data were adopted. The detailed information on the GWAS datasets is described in Table 1.

Genetic determinants for 11 biomarkers linked to oxidative stress were sourced from recent Genome-Wide Association Studies (GWAS). These biomarkers include GST, CAT, SOD, GPX, UA, zinc, tocopherol, ascorbate, retinol, albumin, and bilirubin. The information for GST, CAT, SOD, and GPX originated from the INTERVAL research [11], while data on tocopherol and albumin were extracted from studies involving the Twins UK cohort and KORA [12]. Zinc data were compiled from a variety of consortia contributing to MR-Base [13], and the remaining biomarker data were acquired from the UK Biobank. The sample sizes for these biomarkers were: GST (3301 participants), CAT (3301 participants), SOD (3301 participants), GPX (3301 participants), UA (343,836 participants), zinc (2630 participants), tocopherol (6266 participants), ascorbate (64,979 participants), retinol (62,911 participants), albumin (115,060 participants), and bilirubin (342,829 participants).

2.3. Outcome data source

The available GWAS summarized DNP data were gained from the open database (IEU OPEN GWAS PROJECT: <https://gwas.mrcieu.ac.uk/> (accessed on 20, Oct 2023)). To avoid bias from population heterogeneity, only European population summarized data were adopted. The detailed information on the GWAS datasets is described in Table 2.

2.4. SNP selection

Initially, SNPs showing significant associations with the gut microbiome were chosen as IVs. Two thresholds were employed during the IV selection process. The first threshold involved selecting SNPs with a significance level below the genome-wide threshold of 5×10^{-8} as IVs

Table 1. Detailed information on GWAS data for Oxidative stress injury biomarkers.

Biomarkers	Ethnic	Participants	Web Source
GST	European	3301	https://gwas.mrcieu.ac.uk/datasets/prot-a-1283/
CAT	European	3301	https://gwas.mrcieu.ac.uk/datasets/prot-a-367/
SOD	European	3301	https://gwas.mrcieu.ac.uk/datasets/prot-a-2800/
GPX	European	3301	https://gwas.mrcieu.ac.uk/datasets/prot-a-1265/
UA	European	343,836	https://gwas.mrcieu.ac.uk/datasets/ukb-d-30880_raw/
Tocopherol	European	6266	https://gwas.mrcieu.ac.uk/datasets/met-a-571/
Zinc	European	2630	https://gwas.mrcieu.ac.uk/datasets/ieu-a-1079/
Ascorbate	European	64,979	https://gwas.mrcieu.ac.uk/datasets/ukb-b-19390/
Retinol	European	62,911	https://gwas.mrcieu.ac.uk/datasets/ukb-b-17406/
Albumin	European	115,060	https://gwas.mrcieu.ac.uk/datasets/met-d-Albumin/
Total bilirubin	European	342,829	https://gwas.mrcieu.ac.uk/datasets/ukb-d-30840_raw/

Note: GST, glutathione S-transferase; CAT, catalase; SOD, superoxide dismutase; GPX, glutathione peroxidase; UA, uric acid.

Table 2. Detailed information on GWAS data for DNP.

Ethnic	Participants	Web Source / GWAS ID
European	1419 cases / 195,047 controls	https://gwas.mrcieu.ac.uk/datasets/finn-b-G6_DIABETNEUR/
European	2843 cases / 271,817 controls	finngen_R9_DM_NEUROPATHY
European	111 cases / 374434 controls	finngen_R9_DM_AUTONOMIC

[14]. However, this initial selection resulted in a limited number of OS biomarker's SNP being considered as IVs. A second threshold was implemented to obtain more comprehensive results and explore additional relationships between OS and DPN. SNPs below the locus-wide significance level of 1×10^{-5} [15] were selected as the second set of IVs to identify potential causal associations. Several steps were taken to ensure the quality of the IVs used in the MR analysis. Firstly, the variants of interest were subjected to a minor allele frequency (MAF) threshold of 0.01 [15]. Additionally, it was crucial to assess the presence of linkage disequilibrium (LD) among the IVs, as strong LD can introduce bias. A clumping process with parameters $r^2 < 0.01$ and clumping distance = 10,000 kb was performed to evaluate LD between the selected SNPs [16].

Another essential consideration in MR analysis is the alignment of SNP effects on exposure and outcome. To prevent any distortion caused by strand orientation or allele coding, palindromic SNPs (e.g., those with A/T or G/C alleles) were excluded. Alleles were harmonized with the human genome reference sequence, and any ambiguous or duplicated SNPs were removed. We calculated the proportion of variance in the exposure explained by the genetic variants, using the following equation:

$$R^2 = 2 \times MAF \times (1 - MAF) \times \beta^2 .$$

To evaluate the strength of instrumental variables (IVs), the F-statistic was calculated using the formula:

$$F = \frac{R^2 \times (n-1-k)}{(1-R^2) \times k}$$

Here, N represents the sample size, and K represents the number of instruments. When the resulting F-statistic was greater than 10, it indicated the absence of significant weak instrumental bias. To assess the power of the MR estimates, an online calculator tool provided by Stephen Burgess was utilized.

Two regression tests, Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) [17] and Mendelian randomization-Egger (MR-Egger) [18], assessed potential horizontal pleiotropy effects. The MR-PRESSO outlier test calculated the pleiotropy significance of each SNP, while the MR-PRESSO global test evaluated overall horizontal pleiotropy. SNPs were sorted based on their MR-PRESSO outlier test p-values in ascending order and sequentially removed. After removing each SNP, the MR-PRESSO global test was conducted on the remaining SNPs. This recursive process was repeated until the p-value for the worldwide test was insignificant ($P > 0.05$). The final list of SNPs, free from pleiotropic effects, was then used for subsequent MR analysis [18].

2.5. MR analysis

To estimate the potential causal relationships between OS and PDPN, we employed a number of statistical techniques, including the fixed/random-effects inverse-variance weighted (IVW) test [19], weighted mode [20], MR-Egger regression, weighted median estimator (WME), and MR-PRESSO. We used the IVW method as the primary analysis because it provides the most accurate effect estimates and almost all meta-analyses used it as the primary method. The IVW method first calculates ratio estimates for individual SNPs using the Wald estimator and Delta method, and then combines these estimates to obtain the

primary causa estimate [19]. Cochran's Q test was used to test for heterogeneity among the SNPs we selected [21]; if heterogeneity exists ($P < 0.05$), the random-effects IVW method was elected; otherwise, the fixed-effects IVW method was used. Since IVW method results are susceptible to the influence of valid instruments and potential pleiotropic effects, we conducted sensitivity analyses to evaluate the association's robustness. First, we estimated associations using the weighted median method because it provided more reliable estimates of a causal effect in the absence of valid instruments. It could provide valid estimates of causal effect when less than 50 percent of the information originates from invalid instruments. Horizontal pleiotropy of SNPs may exist if the p-value of the intercept is less than 0.05.

To further assess the influence of potential directional pleiotropy, we scanned each SNP used as IVs for their potential secondary phenotypes using the GWAS Catalog (<http://www.ebi.ac.uk/gwas>, last accessed on Nov 6th, 2023). If the overlapped SNPs were found, the analysis would be re-run after rejecting these ones. The associations between OS and the risk of PDPN were depicted as ORs with 95% confidence intervals (CIs). All MR analyses were carried out utilizing R version 4.2.3 (<https://www.r-project.org/>) with the "Mendelian Randomization", "Tow-SampleMR", and "MRInstruments" packages.

2.6. Statistical analysis

In the described study, SNPs significantly associated with the gut microbiome were initially selected as instrumental variables (IVs) using two thresholds. The first threshold involved selecting SNPs with a significance level below 5×10^{-8} , but this yielded only a limited number of SNPs for the OS biomarker. To obtain a more comprehensive set, a second threshold of 1×10^{-5} was applied. The selected IVs were then rigorously assessed for minor allele frequency, linkage disequilibrium, and strand orientation to ensure quality and reliability in the Mendelian Randomization (MR) analysis. This process included harmonizing alleles with the human genome reference sequence and calculating the proportion of variance in the exposure explained by these genetic variants. The strength of the IVs was evaluated using the F-statistic, and tools like MR-PRESSO and MR-Egger were employed to address potential horizontal pleiotropy effects. For the MR analysis, various statistical methods like inverse-variance weighted (IVW) test, weighted mode, MR-Egger regression, and weighted median estimator were used to estimate the potential causal relationships, ensuring robustness through sensitivity analyses and considering heterogeneity among SNPs. The associations were presented as odds ratios with 95% confidence intervals, utilizing R software and specific MR analysis packages.

3. Results

3.1. Causal Effect of Genetically Predicted OS Injury Biomarkers on PDPN

We performed a two-sample MR analysis of three different sources of PDPN databases with biomarkers of OS in 11. The results showed that PDPN data originating from `finngen_R9_DM_AUTONOMIC` was associated with GST, a biomarker of OS (OR=1.064, 95% CI=1.002-1.129). Indicating that OS would increase the risk of developing PDPN by 1.064-fold (Figure 1). In contrast, data

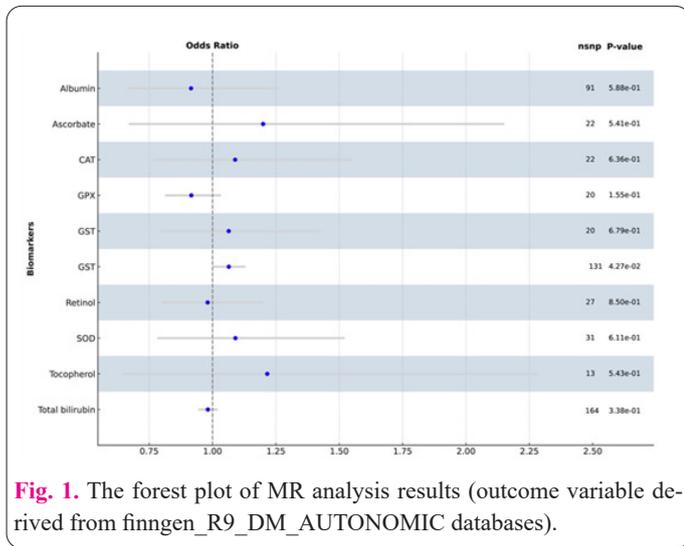


Fig. 1. The forest plot of MR analysis results (outcome variable derived from finngen_R9_DM_AUTONOMIC databases).

derived from finngen_R9_DM_AUTONOMIC found an association between a different OS biomarker and PDPN. The results showed that Retinol increased the risk of PDPN by 2.103-fold (95% CI=1.102-4.012), but notably, the presence of Ascorbate, an OS biomarker, reduced the risk of PDPN by 0.102-fold (95% CI=0.013-0.781) (Figure 2). We also analysed PDPN data derived from finngen_R9_DM_NEUROPATHY, however, we were not able to find any statistically significant results in this database. All of the above results were derived from IVW statistical analyses (Figure 3).

3.2. Description of overall trends

Although IVW was used as the primary test for evaluating the results of MR analyses, scatter plots of all MR analyses were plotted in order to assess the results of MR analyses under other tests. The results showed that GST, CAT, GPT, Ascorbate and Retinol, which are biomarkers of OS, presented the possibility of being a potential risk factor for PDPN, i.e., all the results showed a smooth upward trend in general, and therefore, we have some evidence to believe that the development of OS will increase the risk of developing PDPN (Figure 4).

4. Discussion

Our study employed an MR approach to investigate the influence of genetic predisposition to OS on the development and severity of Painful PDPN. By analyzing genetic variants associated with OS biomarkers, we aimed to elucidate potential causal relationships and provide new insights into PDPN pathogenesis.

The findings of our study align with and extend previous research on the role of OS in the pathogenesis of Painful PDPN [22,23]. While earlier studies have highlighted the contribution of OS to PDPN [24,25], our research uniquely utilizes a MR approach to investigate the genetic predisposition to OS as a potential risk factor for PDPN. This approach enables a more rigorous examination of causality compared to observational studies [26].

Our study found associations between specific genetic markers related to OS biomarkers, such as GST and ascorbate, and the risk of PDPN. These results can be interpreted in the context of the established role of OS in neuronal damage [27-29]. For instance, the association of GST, a key enzyme in detoxifying reactive oxygen species, suggests that individuals with certain genetic variants may

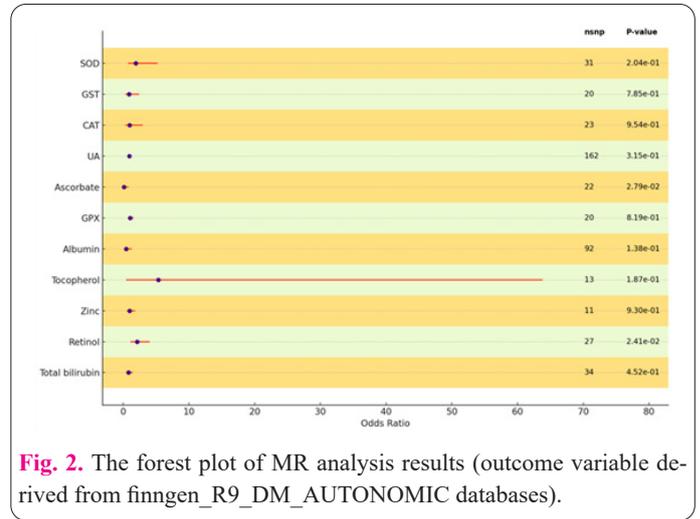


Fig. 2. The forest plot of MR analysis results (outcome variable derived from finngen_R9_DM_AUTONOMIC databases).

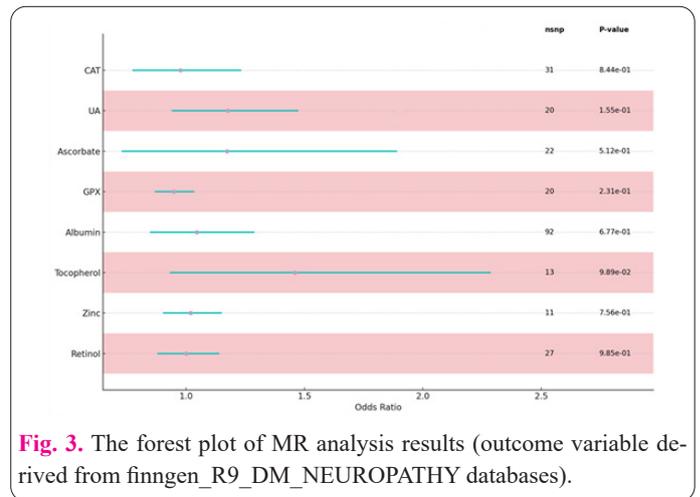


Fig. 3. The forest plot of MR analysis results (outcome variable derived from finngen_R9_DM_NEUROPATHY databases).

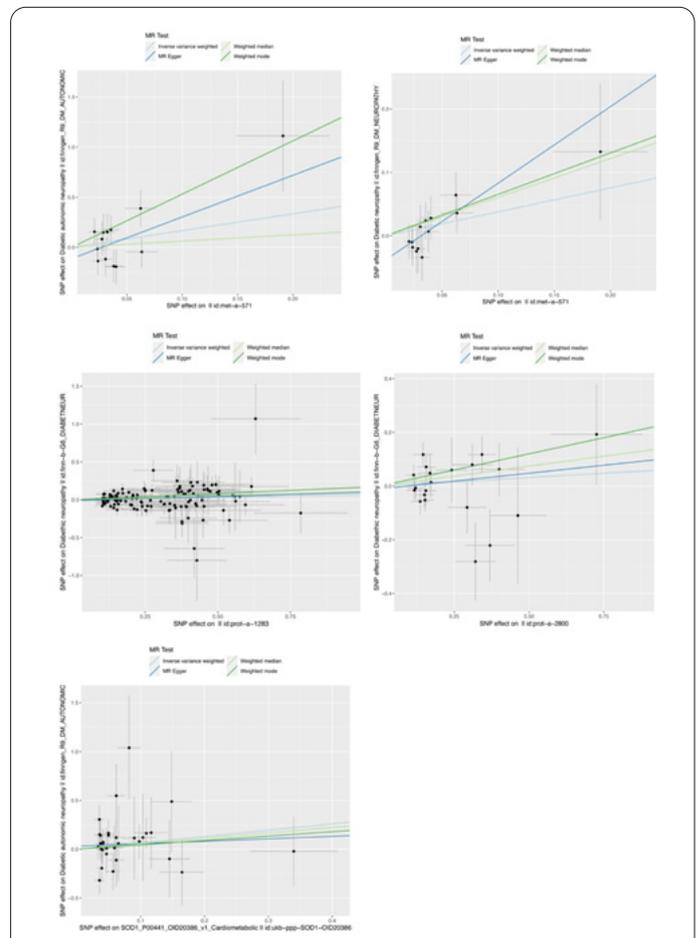


Fig. 4. The scatter plot of main MR analysis results.

have a reduced capacity to mitigate OS, thereby increasing their risk of PDPN [30,31].

The variation in associations across different biomarkers can be attributed to the multifaceted nature of OS and its interaction with other diabetic complications [32]. Genetic factors that influence individual response to OS, such as variations in antioxidant enzyme activity or ROS detoxification pathways, could explain the differential risk of PDPN [27]. Additionally, these differences may be influenced by lifestyle factors, metabolic control in diabetes, and other genetic predispositions that were not directly assessed in our study [33,34].

Our findings necessitate further research to validate these associations in diverse populations and to explore the interplay between genetic predisposition to OS and other risk factors for PDPN. Future studies should also focus on the longitudinal assessment of these biomarkers in diabetic patients to understand the progression of PDPN and its relation to OS. Furthermore, investigating the mechanisms by which these genetic variants influence OS and PDPN could offer insights into potential therapeutic targets.

While our study provides significant insights, it is not without limitations. The reliance on existing GWAS data may limit the generalizability of our findings to diverse populations. Furthermore, the MR approach, while robust, is dependent on the quality and completeness of the genetic instruments used. Thus, there is a need for comprehensive and well-characterized datasets to enhance the accuracy of MR analyses.

5. Conclusion

In summary, our study contributes to the growing body of evidence on the genetic factors influencing the risk of PDPN, emphasizing the role of oxidative stress. These insights enhance our understanding of PDPN pathogenesis and suggest avenues for personalized interventions targeting individuals with a higher genetic predisposition to OS-related damage in the context of diabetes.

Conflict of interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

No human or animals were used in the present research.

Informed consent

The authors declare not used any patients in this research.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request

Authors' contributions

Liyang Zou and Jiangyi Yu designed the study and performed the experiments, Duosheng Zhu collected the data, Min Gong analyzed the data, Liyang Zou and Jiangyi Yu prepared the manuscript. All authors read and approved the final manuscript.

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