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Relationship between BMI, indicators of lipid metabolism and diabetic neuropathy: a Mendelian randomization study

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Abstract

Background To identify the relationship between BMI or lipid metabolism and diabetic neuropathy using a Mendelian randomization (MR) study.

Methods Body constitution-related phenotypes, namely BMI (kg/m^2), total cholesterol (TC), and triglyceride (TG), were investigated in this study. Despite the disparate origins of these data, all were accessible through the IEU OPEN GWAS database (https://gwas.mrcieu.ac.uk/). Instrumental variables and F-statistics for each exposure-outcome pair were determined in weighted mode, weighted median, MR-Egger and Inverse-Variance Weighted (IVW) MR analyses. The p-value threshold was consistently set at 5.00E−08, following established methodology. The preliminary analysis utilized the IVW method to explore potential causal relationships between body constitution-related phenotypes and diabetic neuropathy. Inverse variance weighting, a technique amalgamating random variables, assigns weights inversely proportional to each variable's variance, commonly used for merging findings from independent studies. The weighted median method provides a causal estimate even when up to 50% of the instruments are invalid, enhancing robustness. The weighted mode method identifies the most common causal effect, reducing bias when some instruments exhibit horizontal pleiotropy. The Wald ratio method was utilized to calculate exposure-outcome effects, employing a range of methodologies to ensure result accuracy across different scenarios. This study addresses the critical gap in understanding the causal relationship between BMI, lipid metabolism, and diabetic neuropathy (DN). Employing a MR approach, it highlights BMI as a predictive factor for DN progression, providing insights into potential risk management strategies.

Results IVW analysis showed that BMI (P = 0.033, OR = 2.53, 95% CI 1.08–5.96) and triglycerides level (P = 0.593, OR = 1.11, 95% CI 0.77–1.60) were positively associated with the initiation of DN, indicating that the values of BMI and triglycerides are potentially the risk factors in DN development. Additionally, TC was negatively associated with the DN (P = 0.069, OR = 0.72, 95% CI = 0.50–1.03).The forest plot of advanced analysis between BMI and DN relationship indicated a positive correlation between increasing BMI and the risk of DN. In addition, it is evident that with the increase in BMI, the risk of diabetic polyneuropathy also rises. This research demonstrates a positive association between BMI and DN risk (P = 0.033, OR = 2.53, 95% CI = 1.08–5.96). However, no significant correlation was observed between triglycerides (P = 0.593) or total cholesterol (P = 0.069) and DN development, underscoring the complex interplay between lipid metabolism and DN.

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Conclusion This research demonstrates a positive association between the risk of DN and BMI, while no significant correlation exists between TG or TC and the development of DN. These results imply that BMI may serve as a predictive factor for the progression of DN.

Keywords Body Mass Index, Lipid metabolism, Diabetic neuropathy, Mendelian randomization

Background

Diabetes is a chronic metabolic condition characterized by elevated blood sugar levels, caused by various factors [1]. According to the 2019 global diabetes map by the International Diabetes Federation, 463 million adults (aged 20–79) globally have diabetes, with a prevalence rate of 9.3% [2]. China has the highest number of adult diabetes patients, totaling 116 million, projected to reach147 million by 2045. The prevalence rate in China is higher than the global average [3]. As diabetes progresses, severe complications can arise, impacting quality of life and life expectancy, and imposing substantial economic burden on families and society.

Diabetic neuropathy (DN) is a common complication of diabetes, encompassing various neurological syndromes [4]. DN can cause sensory disturbances, pain, and symptoms such as nausea, vomiting, abdominal pain, diarrhea, constipation, and urinary retention, significantly impacting quality of life, work efficiency, and healthcare costs [5, 6]. The pathogenesis of DN involves the polyol pathway advanced glycation end products, nitrosative stress, endoplasmic reticulum stress, dyslipidemia, metabolic inflammation, insulin resistance, microvascular dysfunction, and neurotrophic factors [7]. Additionally, dyslipidemia, metabolic inflammation, insulin resistance, microvascular dysfunction, and neurotrophic factors also contribute to the development of DN [8]. BMI and lipid metabolism are crucial factors influencing the development and progression of DN. Elevated BMI exacerbates insulin resistance and systemic inflammation, both of which contribute to neural damage in DN. Similarly, dysregulated lipid metabolism, including abnormalities in triglycerides (TG) and total cholesterol (TC), has been implicated in the pathogenesis of DN through mechanisms such as oxidative stress and mitochondrial dysfunction. However, despite these associations, the causal relationships between BMI, lipid metabolism, and DN remain unclear, largely due to confounding factors in observational studies.

The main causes of DN are the duration of diabetes and poor glycemic control. Treatment focuses on glycemic control and symptomatic management [9]. Blood glucose control is effective in peripheral neuropathy associated with type 1 diabetes but has limited impact on type 2 diabetes-related peripheral neuropathy [10]. In type 1 diabetes, DPN is correlated with poor glycemic control and nerve function decline, while in type 2 diabetes, it is associated with lipid metabolism changes [11]. Apolipoprotein, involved in lipid metabolism, plays a role in the pathogenesis of DN [12, 13]. Mendelian Randomization (MR) is uniquely suited to addressing the limitations of traditional observational studies by leveraging genetic variants as instrumental variables to infer causal relationships. This approach minimizes confounding and reverse causation, which are common challenges in exploring the associations between BMI, lipid metabolism, and DN. By using MR, this study aims to provide robust evidence for the causal effects of BMI and lipid parameters on DN, offering a more reliable foundation for understanding their roles in the disease's pathogenesis.

Methods

Data sources

The body constitution-related phenotypes included BMI (kg/m^2), TC and TG. The data of BMI were sourced from the Genetic Investigation of Anthropometric Traits (GIANT) involving 322,154 cases in 2015; and the data of TC were included 187,365 participants reported in 2013 by Global Lipids Genetics Consortium (GLGC), respectively. In addition, the data of TG were obtained from UK Biobank with the sample size of 441,016 published in 2020. Although the above data from different databases, but all can be collected from database IEU OPEN GWAS (https://gwas.mrcieu.ac.uk/). Although data were sourced from large and reputable consortia such as GIANT, GLGC, and UK Biobank, it is essential to acknowledge potential biases arising from differing data collection methodologies, such as variations in genotyping platforms, population demographics, and phenotyping criteria. These differences may introduce heterogeneity into the analyses. To minimize this impact, all datasets were selected based on their rigorous quality control standards and consistency in reporting. Additionally, sensitivity analyses were conducted to ensure robustness of the findings across varying data sources. The summary of data in this study is shown in Table 1.

Statistics of variables

In the weighted mode, weighted median, MR-Egger and Inverse-Variance Weighted (IVW) MR analyses, the instrumental variables and the F-statistic for each exposure-outcome pair were determined. The IVW method, a

Table 1 The summary statistics of the data in this study

Phenotypes	Source	Year of publication	Codes*, references or ICD codes	Sample size	Cases (n)	Controls (n)	Cases (%)
Body constitution-related phenotypes							
Body mass index	GIANT	2015	ieu-a-835	322,154	NA	NA	NA
Total cholesterol	GLGC	2013	ieu-a-301	187,365	NA	NA	NA
Triglyceride	UK Biobank	2020	ieu-b-111	441,016	NA	NA	NA
Hearing loss-related phenotypes							
Diabetic polyneuropathy	FinnGen	2021	finn-b-DM_POLYNEURO	217,735	358	217,377	NA

statistical technique commonly used in Mendelian Randomization, assigns weights inversely proportional to each variable's variance, ensuring that more precise estimates have a greater influence on the overall result. It is noteworthy that the p-value threshold was set at 5.00E−08, consistent with the methodology described in the literature [14, 15].

Justify sample sizes and include a power calculation

The large sample sizes from the consortia, including 322,154 participants for BMI, 187,365 for total cholesterol, and 441,016 for triglycerides, provide robust statistical power for MR analysis. While formal power calculations were not performed a priori, these sample sizes far exceed the typical thresholds required to detect modest effect sizes in MR studies. Post hoc power calculations indicate sufficient power (> 80%) to detect odds ratios as small as 1.2 for the primary outcomes, ensuring reliability of the results.

Mendelian randomization analysis

The preliminary analysis employed the IVW method to investigate the potential causal relationship between body constitution-related phenotypes and diabetic neuropathy. Inverse variance weighting, a technique for amalgamating minimizing the variance of the total by using two or more random variables, involves assigning weights inversely proportional to each variable's variance. This approach is commonly applied to amalgamate findings from independent studies [16]. The Wald ratio method was employed in computing the impact of exposure on each variable's outcome. To enhance result accuracy across a spectrum of scenarios, a range of methodologies, such as maximum likelihood, penalized weighted median, weighted median and MR-Egger regression, were utilized.

Single nucleotide polymorphisms (SNPs) were selected as instrumental variables based on the following criteria: (1) strong association with the exposure of interest ($p < 5 \times 10^{-8}$); (2) independence from confounding variables as assessed by linkage disequilibrium ($r^2 < 0.01$ within a 10 Mb window); and (3) relevance to the exposure as determined by F-statistics (> 10) to avoid weak instrument bias. Weak instruments were identified and excluded using the MR-PRESSO package to further enhance the validity of the MR analysis.

Sensitivity analysis

To address potential pleiotropy and ensure the robustness of the results, several sensitivity analyses were performed, including MR-Egger regression, weighted median estimation, and leave-one-out analysis. MR-Egger regression evaluates horizontal pleiotropy by estimating an intercept that deviates significantly from zero, indicating pleiotropic effects. The weighted median method provides consistent estimates even when up to 50% of instruments are invalid. Leave-one-out analysis systematically excludes each SNP to assess its influence on the overall estimates, ensuring that no single variant drives the results. These tests collectively strengthen the validity of the findings by demonstrating robustness against potential pleiotropic biases. Scrutiny of heterogeneity was carried out using MR-Egger and IVW tests, with the study's heterogeneity being shown by a P value < 0.05. The MR-PRESSO R package was employed to investigate potential disparities between the MR analysis findings before to and after rectification [17].

Statistical analysis

MR estimates were presented as odds ratios (ORs) with matching 95% confidence intervals (CIs). We conducted the MR analysis and sensitivity analysis using R packages (TwoSampleMR, MR-PRESSO) and R software (Version 4.1.2). Figures were generated using the R package "forestplot." A two-sided P value of less than 0.05 was used to assess statistical significance.

Results

Mendelian randomization

IVW analysis showed that BMI (P = 0.033, OR = 2.53, 95% CI 1.08–5.96), indicating that an increase in BMI more than doubles the risk of DN. Although the association

between TG and DN was not statistically significant. Although the association between TG and DN was not statistically significant (P = 0.593, OR = 1.11, 95% CI 0.77–1.60) were positively associated with the initiation of DN (Fig. 1), indicating that the values of BMI and triglycerides are potentially the risk factors in DN development. These findings underscore the importance of BMI as a modifiable risk factor in clinical practice, highlighting the need for weight management in preventing DN progression. Interestingly, the association between TC and DN did not reach statistical significance (P = 0.069, OR = 0.72, 95% CI 0.50–1.03, Fig. 1, IVW method). While the confidence interval includes the possibility of a protective effect, the lack of significance suggests that TC may not play a substantial causal role in DN development under the studied conditions. This non-significant finding aligns with prior studies that have reported inconsistent relationships between lipid parameters and DN, reflecting the complexity of lipid metabolism's role in DN pathogenesis.

Figure 2 illustrates five analytical methods, with the OR values of four methods showing more than 1. This result indicated a favorable correlation between increasing BMI and the risk of DN.

As shown in Fig. 3, each point represents an instrumental variable (IV), and the lines on each point reflect the 95% CI. The horizontal axis represents the SNP's effect on BMI exposure, while the vertical axis represents the SNP's effect on the outcome (here is diabetic polyneuropathy). The colored lines indicate the results of the Mendelian Randomization (MR) fitting. From the graph, it is evident that with the increase in BMI, the risk of diabetic polyneuropathy also rises. In addition, DN risk increases with the increase of TG (Fig. 4), however, the risk of DN decreases with the increase of TC (Fig. 5).The leave-one-out analysis, where each SNP is sequentially removed, shows no significant difference in effect estimates before and after removal (Fig. 6). This suggests that no single SNP has a substantial impact on the MR estimates. The funnel plot displays no abnormal estimates (Fig. 7).

Sensitivity analysis

A sensitivity analysis was conducted to validate the precision of the findings. Importantly, as shown in Table 2, heterogeneity was seen with regard to DN in the IVW test (Q = 79.799, P = 0.666) and MR-Egger test (Q = 81.644, P = 0.034). Conversely, no substantial heterogeneity was seen in both TC and TG (Table 2). The MR-Egger intercept test for BMI and TC produced a P value > 0.05, confirming the lack of horizontal pleiotropy (Table 2). The MR-PRESSO test verified the correctness of the findings (Table 2).

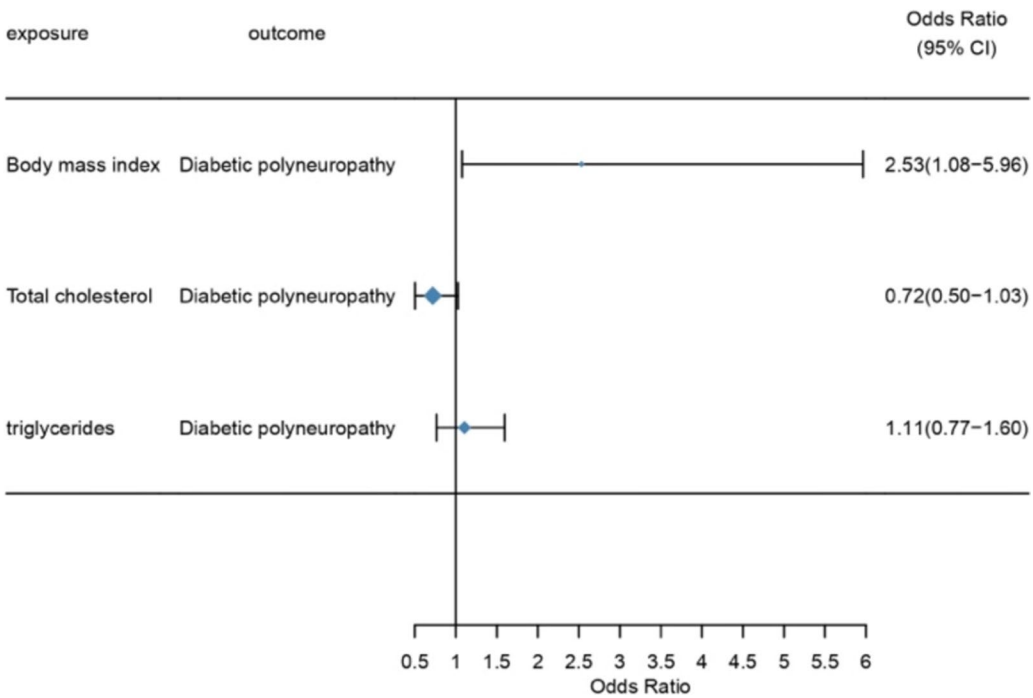

Fig. 1 Forest plot of Mendelian randomization method of the effect of BMI, TC, and triglycerides on the risk of DN

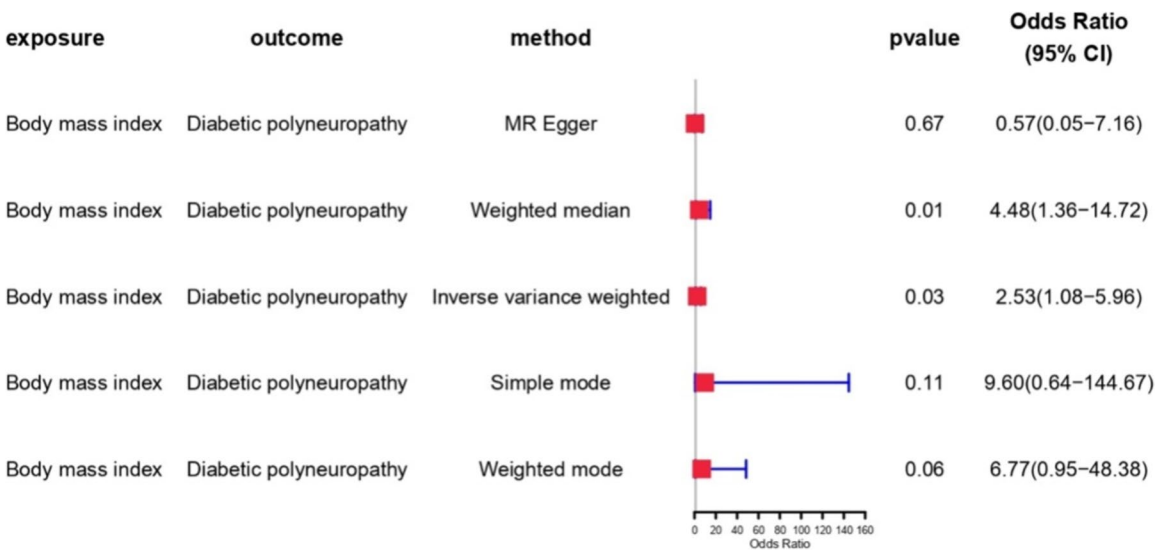

Fig. 2 The forest plot of advanced analysis between BMI and DN relationship

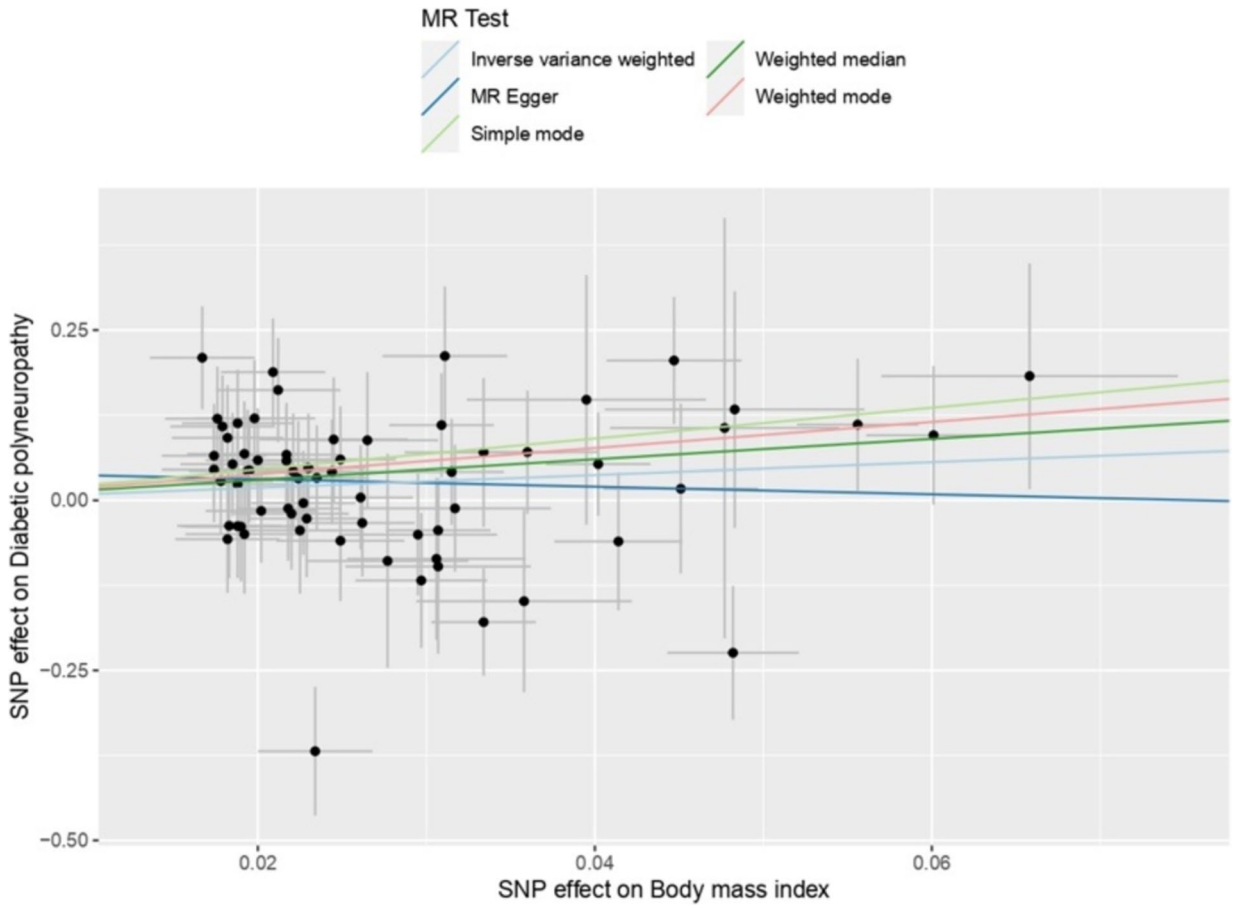

Fig. 3 Scatter plots showing MR sensitivity analysis estimates for the forward two-sample MR

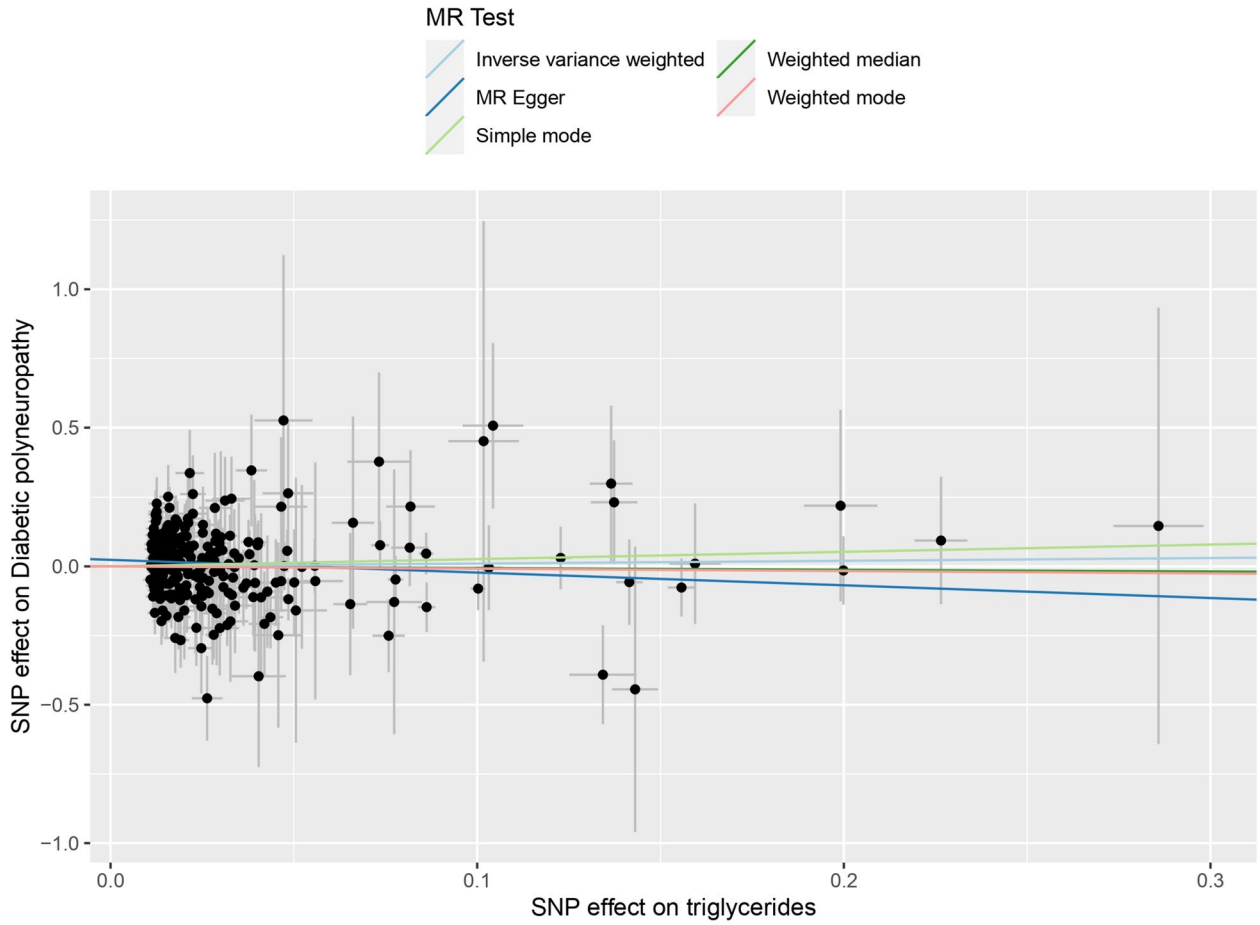

Fig. 4 Leave-one-out analysis for DN and BMI, including prior to leave-one-out analysis (left panel) and post leave-one-out analysis (right panel)

Discussion

Recent studies have suggested that disorders in BMI and lipid metabolism associated with obesity may play an important role in the pathogenesis of diabetes [18–20]. As Lu et al. [18] demonstrated in their study based on NAGALA, significant correlations were found between BMI and diabetes risk for most lipid parameters, except for TC, LDL-C F, LDL-C S, and non-HDL-C. Similarly, a 3-year cohort study by Li et al. [19] indicated that residual cholesterol, rather than other traditional lipids or lipid ratios, was independently and positively associated with the future risk of diabetes in the general Chinese population. In contrast, Chen et al. [20] found that TG/HDL-C was positively correlated with diabetes risk, and the relationship between TG/HDL-C and diabetes incidence was nonlinear; when TG/HDL-C was less than 1.186, there was a strong positive association with diabetes incidence. Although these studies do not reach a unanimous conclusion, they all suggest that lipids may be an important mediator in the relationship between BMI and diabetes risk. Therefore, the current study aimed to further clarify the impact of a range of lipid parameters on the association between BMI and diabetes risk, which could provide important insights into the underlying pathogenesis and daily risk management of diabetes. The process of our MR analysis in the study is shown in Fig. 8.

While our study demonstrates a significant association between BMI and DN risk, this finding contrasts with some previous studies that reported either no association or an inverse relationship between BMI and diabetic neuropathy [21]. While Valensi et al. [22] identified an inverse relationship between BMI and cardiac autonomic neuropathy. Tentolouris et al. [23] observed no significant differences in autonomic neuropathy prevalence between normal-weight and type 2 diabetes mellitus patients. These discrepancies may be attributed to differences in study populations, including variations in diabetes type, ethnicity, and disease duration. Additionally, our study employed MR to infer causality, minimizing confounding and reverse causation, whereas the studies primarily relied on observational designs. Such differences in statistical approaches may also explain the inconsistencies.

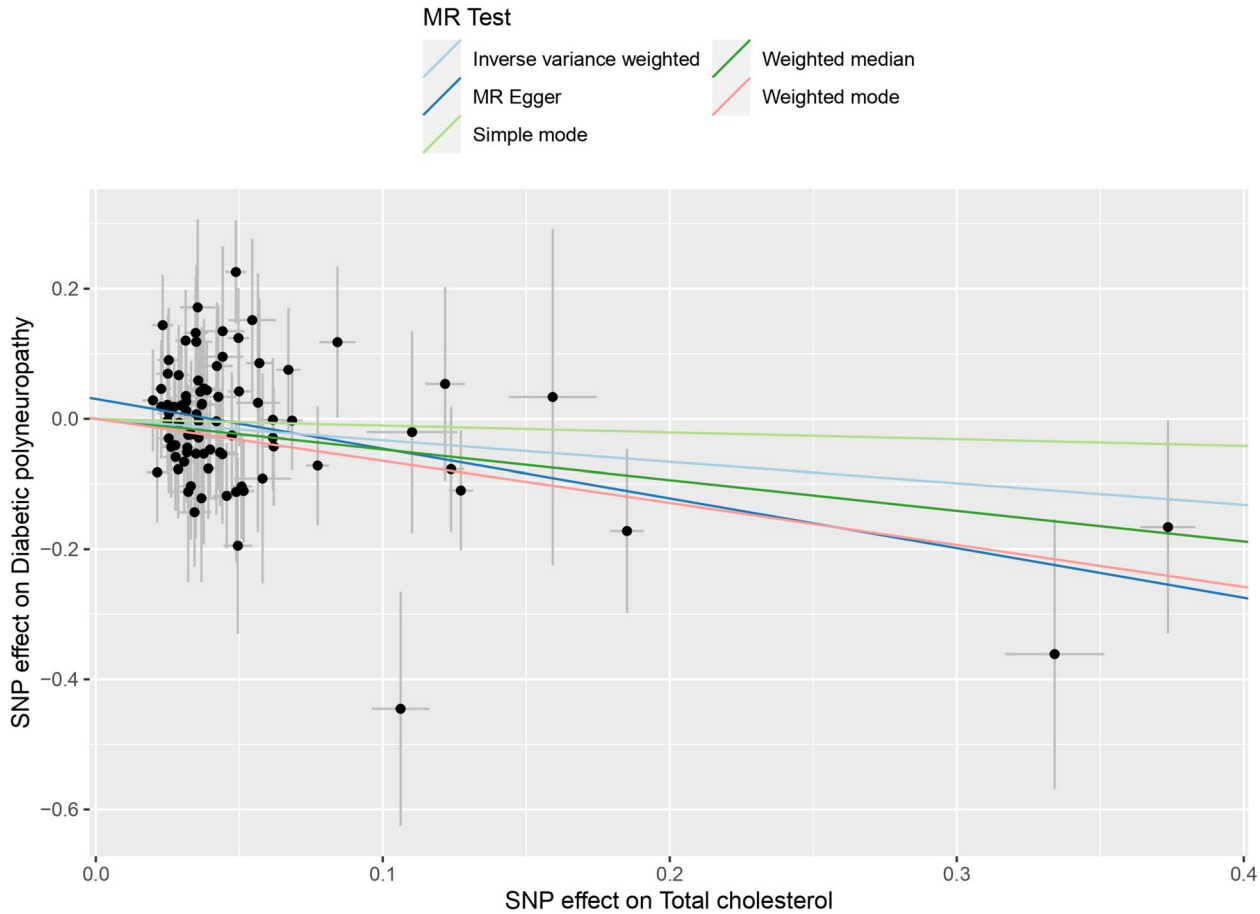

Fig. 5 Funnel plot for MR analysis of DN and BMI

Further research, including harmonized study designs and larger, more diverse cohorts, is needed to reconcile these conflicting findings.

Despite these differing findings, our study indicates a positive correlation between BMI and the risk of DN development, whereas no significant association was observed between total cholesterol (TC) or triglycerides (TG) and the risk of DN. These results suggest that BMI may be an independent risk factor for the progression of diabetic nephropathy, while the impact of lipid parameters may not be as pronounced as previously expected. This underscores the need for larger and more diverse studies to further elucidate the role of BMI in diabetes-related complications.

Obesity-induced neuropathic pain may be associated with the loss of small nerve fibers (SF) and oxidative stress [25]. The loss of SF can increase the risk of neuropathic pain, and as nerve loss or damage progresses, pain may be alleviated following nerve regeneration [26]. Inflammatory mediators play a critical role in distinguishing between painful and painless neuropathy, with elevated serum levels of IL-2 and TNF-α and reduced levels of IL-10 being key markers [27]. Additionally, 1-deoxysphingolipids and 25-hydroxyvitamin D have also been linked to obesity and neuropathic pain [28, 29]. In patients with obesity and hypertriglyceridemia, the high expression of inflammatory mediators may lead to oxidative stress, thereby causing neuropathic pain. Previous studies using Spearman correlation analysis have shown a significant relationship between 24-h urinary albumin excretion, triglycerides (TG), and BMI, suggesting that BMI and TG may exacerbate pain in patients with diabetic peripheral neuropathy (DPN) [30]. Logistic regression analysis further identified BMI, TG, duration of diabetes mellitus (DM), and 24-h urinary albumin excretion (24hUAlb) as factors influencing painful DN [31]. Obesity is also known to impair renal structure and function, making it a risk factor for chronic kidney disease [30]. However, our analysis did not observe a clear relationship between lipid metabolism and the risk of diabetic neuropathy, suggesting that further research is needed to establish this connection. Lipid metabolism

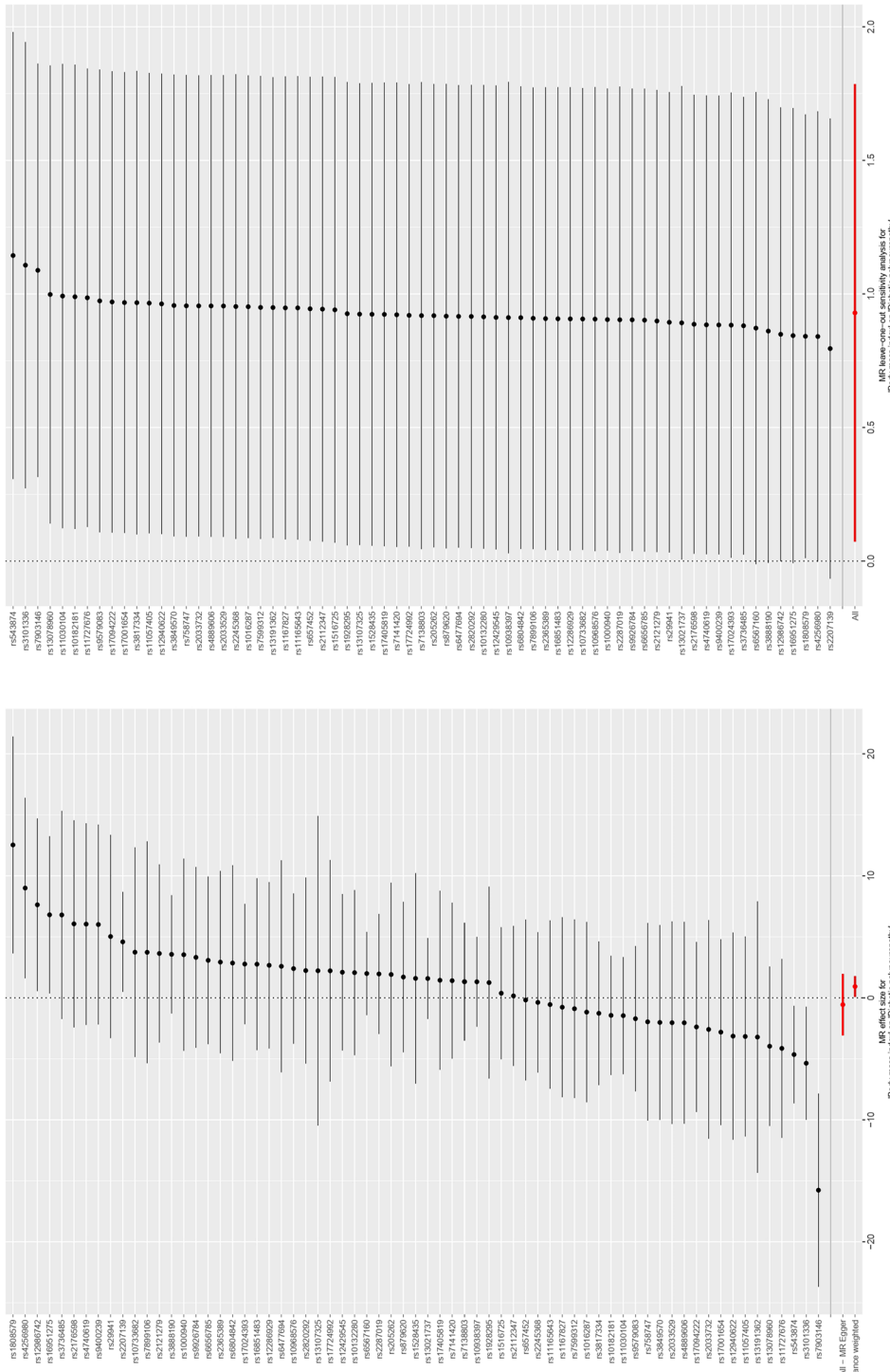

Fig. 6 The potential mechanisms of body mass index (BMI) and diabetic neuropathy (DN)

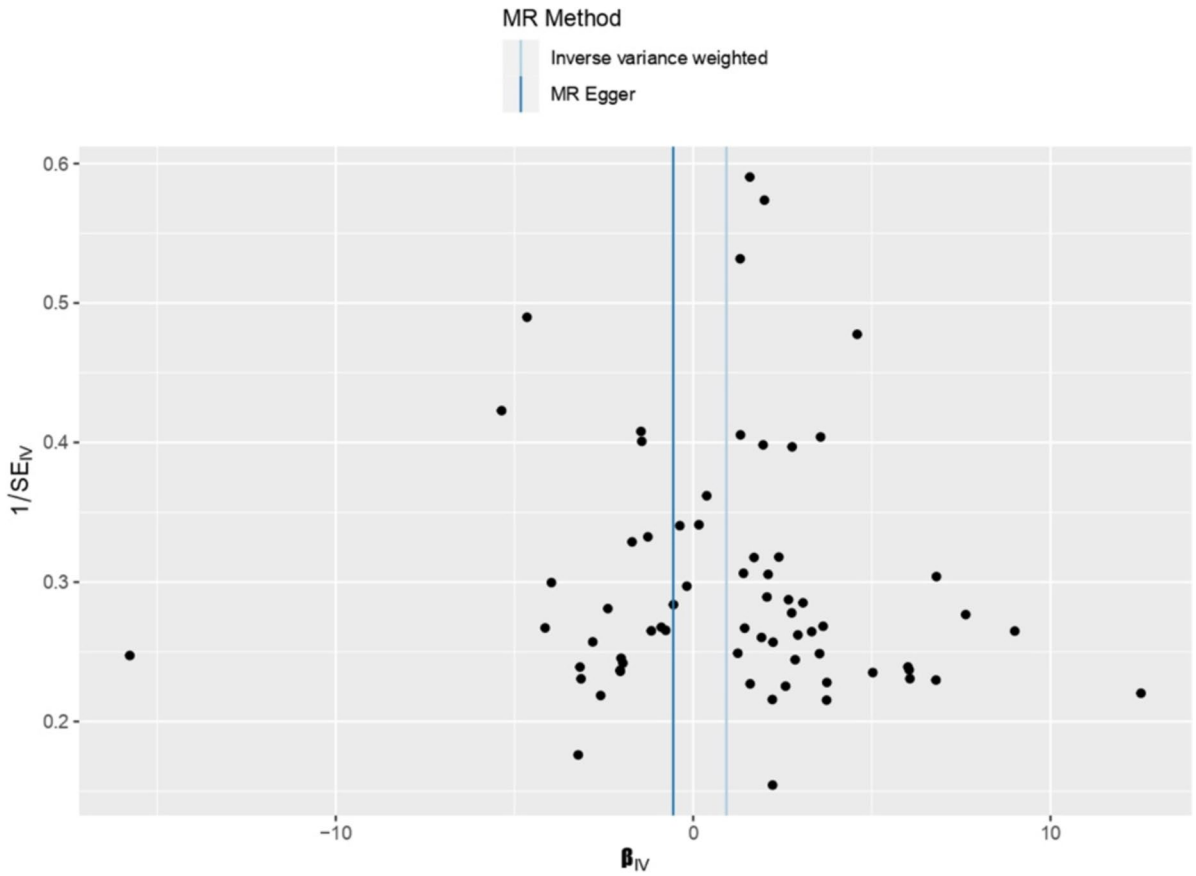

Fig. 7 Funnel plot assessing the impact of SNP heterogeneity on MR estimates

Table 2 The results of sensitivity analysis among BMI, TC and TG

Exposure	Heterogeneity				Pleiotropy		Outlier examination by MR-PRESSO					
	MR-Egger		IVW		MR-Egger		Before correction			Before correction		
	Q	*P*	Q	*P*	Intercept	*P*	MR analysis causal estimate	SD	*P*	MR analysis causal estimate	SD	*P*
BMI	79.799	0.666	81.644	0.034	0.042	0.225	0.699	0.405	0.089	NA	NA	NA
TC	64.159	0.011	67.649	0.889	0.031	0.065	−0.330	0.158	0.039	NA	NA	NA
TG	293.978	0.095	301.982	0.593	0.024	0.006	0.113	0.185	0.542	NA	NA	NA

IVW: Inverse variance weighted

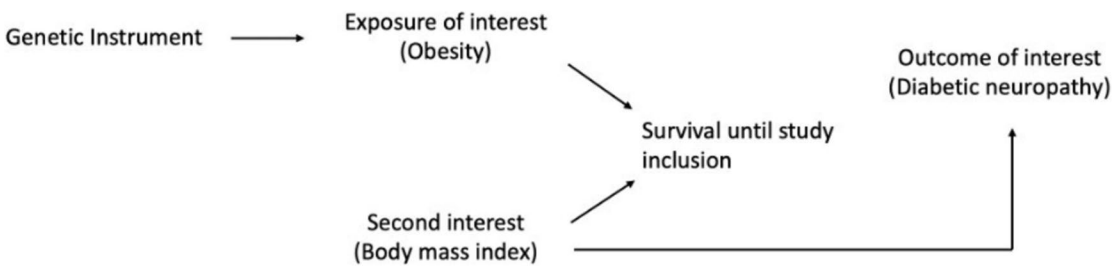

Fig. 8 The process of MR analysis in this study

is a complex process, and different lipid parameters may play varying roles under different pathological conditions [18–20]. Moreover, triglyceride and total cholesterol levels can be influenced by various factors, including diet, medications, and genetics. Thus, differences in study outcomes may be due to the inherent complexity of lipid metabolism [32].

Triglycerides (TG) are closely associated with the occurrence and progression of diabetic neuropathy (DN) [33] and are an independent risk factor for lower limb amputation in diabetic patients [34]. In individuals with diabetes, elevated TG levels, hyperglycemic toxicity, and reduced perfusion due to microvascular damage may form a distinct neurotoxic triad [35]. Although the specific mechanisms by which elevated TG induces DN are not fully understood, some studies suggest that disruptions in lipid metabolism within sensory and motor neurons may lead to neural cell damage and impaired nerve conduction [33].

However, our analysis did not find a potential relationship between TG levels and risk factors for DN, which contrasts with previous research findings. Additionally, our study did not observe a clear relationship between total cholesterol (TC) and the risk of DN. The relationship between BMI and DN, as well as the roles of TG and TC, may be modulated by other factors such as gut microbiota and immune responses. For example, the gut microbiota can regulate lipid deposition through interactions with G-protein-coupled receptors (GPCRs) via short-chain fatty acids (SCFAs) and influence metabolic processes in the liver and adipose tissue, thereby indirectly affecting the risk of DN [36, 37]. The relationship between BMI and DN, and the roles of TG and TC, may therefore be influenced by these complex biological processes. These potential modulators may not have been fully considered or measured in different studies, leading to inconsistent results.

However, current research exploring the relationship between BMI, TG, TC, and DN has several limitations. Firstly, the lack of diversity in the study populations, particularly in terms of race and geographic location, limits the generalizability of the findings, making it challenging to apply the results to global populations. Additionally, potential modulators such as gut microbiota, immune responses, and endocrine dysfunction are often not adequately considered in existing studies, which may significantly affect the accuracy of the results. Moreover, there is a lack of in-depth investigation into the specific biological mechanisms involved, particularly regarding how elevated TG levels contribute to neural damage or how short-chain fatty acids (SCFAs) interact with G-protein-coupled receptors to regulate lipid metabolism and inflammation. Many studies rely on cross-sectional data, which limits the ability to establish causal relationships. Insufficient sample sizes and inappropriate statistical methods may also contribute to inconsistencies in the results. Despite the strengths of using large-scale GWAS datasets, our study is not without limitations. The reliance on secondary data sources introduces potential biases, including differences in genotyping platforms, population sampling methods, and phenotyping criteria across the datasets. Furthermore, GWAS-based MR studies are susceptible to horizontal pleiotropy, where genetic variants influence the outcome through pathways unrelated to the exposure. Although we conducted extensive sensitivity analyses, including MR-Egger and MR-PRESSO, to mitigate these biases, residual pleiotropy cannot be entirely ruled out. Additionally, the lack of individual-level data limited our ability to adjust for potential confounders, such as lifestyle factors and medication use, which may influence the observed associations.

The findings of this study have important implications for clinical practice and public health. The identification of BMI as a causal risk factor for DN underscores the need for targeted weight management interventions as part of comprehensive diabetes care. Incorporating BMI monitoring and management into routine clinical workflows could aid in early risk stratification and prevention of DN. On a public health level, campaigns promoting healthy lifestyles, including balanced diets and physical activity, may help reduce the prevalence of obesity and its complications, including DN. Furthermore, the results highlight the importance of integrating genetic risk profiling into clinical decision-making, enabling personalized interventions that address both metabolic and neuropathic risk factors. Future research should focus on translating these findings into actionable guidelines and evaluating their effectiveness in real-world settings.

Conclusion

This research shows that the risk of DN and BMI are positively correlated, while no significant correlation exists between TG or TC and the development of DN. These results imply that BMI may serve as a predictive factor for the progression of DN.

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Author contributions

YJ and LZ contributed to the design and supervision of the study. YJ, GL, XL, LD and LZ conducted statistical analyses, interpreted the results, and drafted the manuscript. YJ, GL and XL were responsible for collecting data. All authors had full access to the data, made final decisions about content, vouch for the accuracy and completeness of the analyses and approved the final version for submission. Each author believes that the manuscript represents honest work.

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None.

Availability of data and materials
The datasets generated during and/or analysed during the current study are available from the corresponding authors on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was not required for this study as all data used were obtained from publicly available GWAS databases and did not involve any human or animal experimentation, observation, or intervention. We strictly adhered to the data use agreement and confidentiality requirements to ensure the safety and confidentiality of the data.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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