Genetic Association Between Hypothyroidism and the Risk of Trigeminal Neuralgia: A Two-Sample Mendelian Randomisation Study

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ABSTRACT

Objective: To use Mendelian randomisation (MR) for determining the causal relationship between hypothyroidism and trigeminal neuralgia (TN).

Study Design: Analytical study.

Place and Duration of the Study: Department of Neurosurgery, Yantai Yuhuangding Hospital, Yantai, Shangdong, China, from January to April 2024.

Methodology: Fifty hypothyroidism-related single nucleotide polymorphisms (SNPs) were retrieved as instrumental variables (IVs) from the genome-wide association studies (GWAS). MR analysis was conducted using summary statistics from GWAS in the European individuals. The inverse variance weighted (IVW) method was the main tool for finding causality. Other MR methods supported the IVW results and helped confirm the causality results. The additional methods strengthened the findings. Finally, multiple sensitivity studies were conducted to evaluate stability, heterogeneity, and horizontal pleiotropy.

Results: The IVW method showed a strong link between hypothyroidism and TN ($p = 0.009$). MR-Egger regression revealed that directional pleiotropy was unlikely to bias the results ($p = 0.351$). Evidence of a causal relationship between hypothyroidism and TN was also found using the weighted median ($p = 0.008$) and weighted mode ($p = 0.016$) approaches. Although the simple model showed a null causal effect, it showed a trend similar to that of several other methods.

Conclusion: The results of the MR study corroborate the possibility that hypothyroidism and the risk of TN are directly related.

Key Words: *Hypothyroidism, Trigeminal neuralgia, Mendelian randomisation, Single nucleotide polymorphisms, Genetics*.

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INTRODUCTION

Trigeminal neuralgia (TN) is a neurological condition that causes severe facial pain, typically seen in older individuals. The pain experienced with TN is sharp and sudden, often described as stabbing or electric-like. Everyday activities such as eating or talking can trigger these intense episodes of pain. Treatment for TN may include medications, injections, or surgery to manage the symptoms effectively and improve the individual's daily life.[1-3] Clinical research has focused on primary TN, which includes both idiopathic and classical forms, and the antiepileptic medicine carbamazepine is the first-line pharmacological treatment for TN. Surgical procedures are reserved for individuals who do not react to or cannot properly tolerate medical therapies.[4]

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Doctors use various magnetic resonance imaging (MRI) techniques to pinpoint the blood vessels compressing the trigeminal nerve. They rely on three-dimensional time-of-flight magnetic resonance angiography to identify the culprit vessel. Additionally, phase-contrast MRI helps visualise veins, while three-dimensional T2-weighted MRI sequences focus on studying different nerve segments. These methods provide detailed information essential for planning the best treatment for TN.[5] The process of selecting patients for microvascular decompression may be facilitated using standardised MRI criteria to detect neurovascular compression.[6] Not only are pharmaceutical and surgical treatments being explored, but there has also been an increasing amount of research on TN in recent years. However, thorough and rigorous evaluation of the state of the field and new trends in TN research are lacking. Many TN cases have no apparent cause, and the aetiopathogenesis of this condition is unknown. There is evidence from certain studies that there may be a correlation between hypothyroidism and TN.[7] Based on the results of this retrospective investigation, TN and hypothyroidism have a bidirectional association and should be assessed together when one of the two is present. Considering that this study was the first to raise the possibility of a connection between hypothyroidism and TN, a two-sample Mendelian randomisation (TSMR) study was conducted to examine the possibility of a causal relationship.

In order to uncover genotype-phenotype correlations, genome-wide association studies (GWASs) have tested millions of genetic variants throughout the genomes of several individuals during the past ten years, revolutionising the area of complex disease genetics. GWASs offer an unbiased method for examining the genetic causes of complex disorders.[8]

A method frequently used to look into potential causes of disease and exposure is Mendelian randomisation (MR) analysis. It exploits the intrinsic features of common genetic variations for modifiable exposure of interest.[9] TSMR analysis can be used to generate a single causal estimate by combining single-nucleotide polymorphism (SNP) exposure and SNP-outcome relationships from different GWASs. With the rapid growth of GWASs on exposures and illnesses, large-scale summary statistics have been more widely available.[10] Due to this, TSMR analysis is now feasible with significantly more statistical power. This work intended to provide a useful theoretical framework for the relationship between hypothyroidism and the onset and development of TN. The objective of this study was to use MR for determining the causal relationship between hypothyroidism and TN.

METHODOLOGY

MR analysis was used in this work to thoroughly evaluate the causal link between TN and hypothyroidism. The dataset for this study was assembled using GWASs. There was no need for additional ethical approval or informed consent because the MR analyses were conducted using publicly accessible summary statistics in a two-sample manner. This study was conducted in accordance with STROBE-MR guidelines.[11]

These assumptions are crucial for making valid causal inferences in studies using MR.[12] The first assumption requires a strong relationship between the instrumental variable (IV) and the exposure. The second assumption demands no connection between the IV and any other factors influencing the outcome. The third assumption asserts that the IV solely impacts the outcome through the exposure. These criteria ensure the reliability of MR investigations in determining causal relationships.

A summary of TN data based on the TN phenotype was obtained from a recent meta-analysis of GWASs in the UKB (United Kingdom Biobank) and FinnGen, which includes 195,847 participants of the European ancestry.[13] The main database sources for the present study are detailed in Table I.

Genetic tools for hypothyroidism were selected from the largest meta-analysis of GWAS which included 410,141 individuals of the European ancestry.[14]

In order to meet the first MR assumption, which states that SNPs must have a substantial correlation with hypothyroidism, SNPs that were significantly associated with the condition were first chosen at the genome-wide level ($p < 5 \times 10^{-8}$, $r^2 < 0.001$, clumping distance = 100,000 kb). Second, the authors used Phenoscanner (https://www.PhenoScanner.medschl.cam.ac.uk/) to investigate the relationship between genetic variation and known confounders to confirm the second MR hypothesis. The analysis showed no significant associations between the SNPs and potential confounders. This examination aimed to demonstrate that the genetic variations were not influenced by factors that could impact the results.

Because every SNP in the hypothyroidism GWASs had genome-wide significance for hypothyroidism, 50 SNPs were selected for further analysis.

The F-statistic was calculated to test the connection hypothesis. An F value greater than 10 would suggest no weak IV bias. This was done to check if the selected IVs were biased. The formula used was F equals β^2 divided by SE^2, with β being the value of the exposed SNPs and SE being the value of the exposed SNPs. This calculation helped determine the presence of weak IV bias in the chosen IVs.[15]

By using 50 SNPs as IVs in a TSMR, analysis revealed a strong link between hypothyroidism and the development of TN. This suggests that hypothyroidism could be a contributing factor to TN. These findings shed light on the potential impact of hypothyroidism on TN development, emphasising the need for additional research to delve deeper into this relationship.

Table I: Summary of the GWAS included in this study.

Traits	GWAS ID	Sample size	Number of variants	Population	Gender	Year
Hypothyroidism	ebi-a-GCST90018862	410, 141	24, 138, 872	European	Males and Females	2021
Trigeminal neuralgia	finn-b-G6_TRINEU	195, 847	195, 847	European	Males and Females	2021

Table II: The MR estimates from each method of assessing the causal effect of hypothyroidism on the risk of TN.

MR method	Number of SNPs	Beta	SE	Association p-value	Heterogeneity p-value	Cochran Q statistic	OR	95% confidence interval
IVW	50	0.192	0.074	0.009	0.913	36.202	1.212	1.048-1.127
Weighted median	50	0.295	0.111	0.008	-	-	1.343	1.081-1.669
Weighted mode	50	0.339	0.135	0.016	-	-	1.137	1.077-1.830
Simple mode	50	0.364	0.219	0.104	-	-	0.936	1.072-2.212
MR-Egger	50	0.325	0.159	0.047	0.913	35.313	1.404	1.013-1.889

Beta, β coefficient; MR, Mendelian randomisation; SE, Standard error; SNPs, Single nucleotide polymorphisms.

In multiple regression analysis, using different methods can increase statistical power. IVW, MR-Egger regression, weighted median, simple mode, and weighted mode analyses were employed. These techniques help address various factors and yield more reliable results. By pooling data from different sources, the authors can better grasp the connections between variables. This comprehensive approach enhances the accuracy of the study's findings.

MR-Egger regression, weighted median, weighted mode, simple mode, and inverse-variance weighted (IVW) analyses were performed. In multiple regression analysis, several variations increase statistical power; nevertheless, there is a chance that these variations contain pleiotropic genetic variants that are invalid IVs.[16] Even when up to 50% of the study's data are genetic variants that are invalid IVs, the weighted median estimator reliably calculates the causal influence.[17] Pleiotropy was examined and corrected using the weighted median and MR-Egger regression techniques.

The weighted median estimator approach has the advantage of maintaining a better estimate precision when compared to the MR-Egger analysis. In order to evaluate and account for the existence of imbalanced pleiotropy, the MR-Egger methodology includes outline information estimations of causal effects from multiple individual variants and introduces a parameter for this bias.[18] The MR software tool, a component of the R open-source software environment, was used to perform MR analysis using summary data. GWASs were used to assemble the software used in this study. Statistical significance was set at $p < 0.05$.

To assess the heterogeneities among SNPs, the authors employed Cochran's Q-statistics and the I^2 statistic. The authors also ran a leave-one-out analysis to investigate the likelihood that the causal connection was caused by a single SNP. Horizontal pleiotropy was identified by computing the MR-Egger regression intercept. Horizontal pleiotropy was evident and the MR results were unreliable if the p-value for the MR-Egger regression intercept was less than 0.05.[18] Radial regression for MR-Egger and inverse variance weighted models was produced, along with radial graphs using radial MR. These graphs have the benefits of being coding invariant and enhancing the visual identification of outliers. The contribution of every SNP to Cochran's Q-statistic was measured, and SNPs with significant contributions were labelled as outliers according to the user-selected significance level, which is usually a Bonferonni correction.[11] To estimate the adjusted results and exclude anomalous SNPs (outliers), the MR-PRESSO outlier test and Radial-MR techniques were applied.

The mRnd statistical efficacy calculator, available online at https://cnsgenomic.com/shiny/mRnd/, was used to calculate the statistical efficacy. The TwoSampleMR, Radial-MR, and MR-PRESSO packages in R (version 4.3.3) were used for all MR correlation analyses.

RESULTS

Fifty hypothyroidism-related SNPs were extracted as IVs from the GWASs after removing IVs with linkage disequilibrium ($r^2 < 0.001$, $p < 5 \times 10^{-8}$, Clumping distance = 100,000 kb). In order to estimate the modified results and eliminate outliers or anomalous SNPs, Radial-MR and the MR-PRESSO outlier test were utilised (Figure 1).

Since F >10 of the SNPs part of the analysis demonstrated that there was no minor skewing of the results, the study's findings were found to be valid. The validity of the findings was confirmed using two-sample MR. Every SNP locus impact on TN was determined. Figure 2 displays the outcomes.

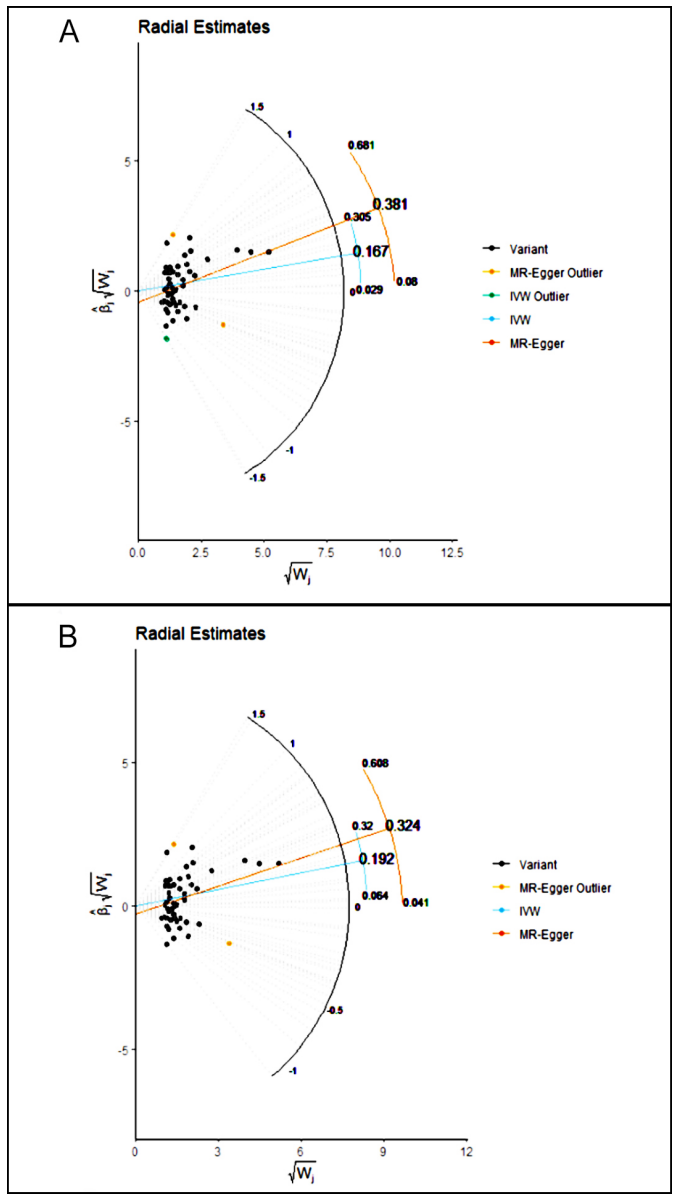

Figure 1: Radial regression for MR-Egger and IVW models is produced along with radial graphs using radial MR. (A) Shows the visualisation outliers detected by perform radial MR; (B) Shows the graph after removing outliers.

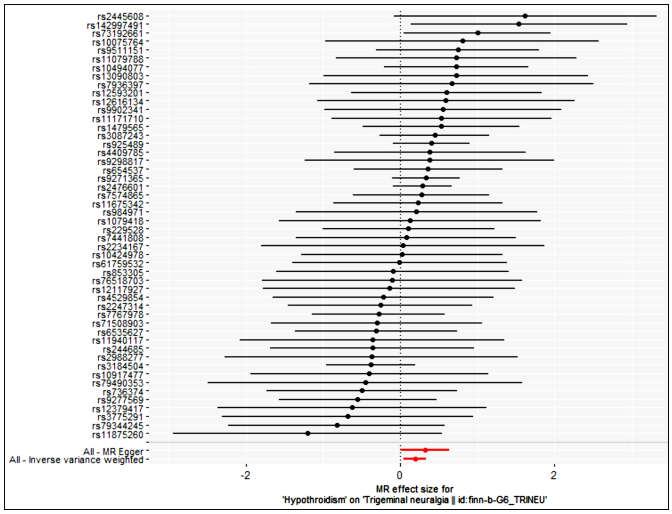

Figure 2: Forest plot of the causal effects of hypothyroidism associated SNPs on TN.

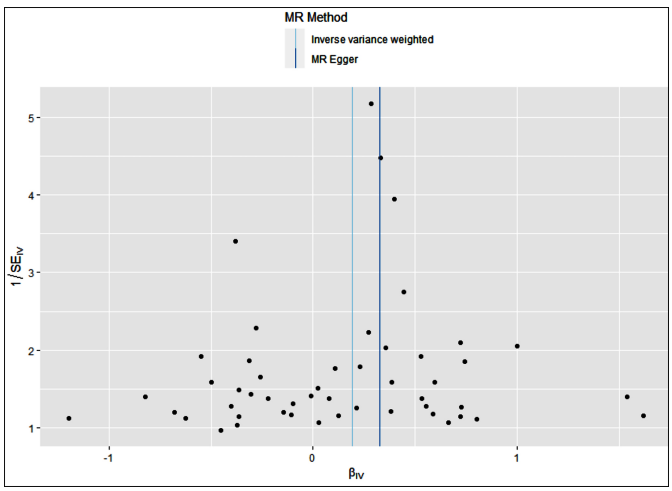

Figure 3: Funnel plot assessing heterogeneity. Blue line represents the IVW estimate and dark blue line represents the MR-Egger estimate.

The IVW technique provided evidence for a causal relationship between TN and hypothyroidism (OR = 1.212, 95% CI: 1.048-1.127, p = 0.009), indicating that the likelihood of getting TN increases with exposure to hypothyroidism. The MR-Egger technique proposed a hypothesis that hypothyroidism and TN are causally related (OR = 1.404, 95% CI: 1.013-1.889, p = 0.047). It revealed that directional pleiotropy did not bias the results (intercept = -0.016; p = 0.351). With the MR-PRESSO assay, no potential horizontal pleiotropy was discovered (p = 0.899). In addition, the funnel plot (Figure 3) demonstrated a lack of bias. Hypothyroidism and TN were causally associated using the weighted median technique (OR = 1.343, 95% CI: 1.081-1.669, p = 0.008). Weighted mode analysis also revealed a positive causal relationship between hypothyroidism and TN (OR = 1.137, 95% CI: 1.077-1.830, p = 0.016).

Despite the fact that the straightforward approach did not reveal a causal link between TN and hypothyroidism (OR = 0.936, 95% CI: 1.072-2.212, p = 0.104), it followed a trend similar to that of several other methods (Table II).

While the IVW, MR-Egger, weighted median, and weighted mode approaches showed a negative causal effect of hypothyroidism on TN risk, the basic technique revealed a null causal effect. Compared to the simple method analysis, the weighted median estimator maintains greater precision in the estimates.[17] Consequently, the MR analysis findings showed a causal link between TN and hypothyroidism.

Heterogeneity is the degree of variability in the causal estimates found for each SNP, or the degree of consistency in the causal estimate across all SNPs. Based on individual variations, Cochran's Q test did not reveal any evidence of heterogeneity between the IV estimations (Table II). The IVW point estimate was not being driven by a single SNP, according to the leave-one-out study. Even though directed horizontal pleiotropy, which can lead to bias in MR approaches, was inferred by asymmetry in the funnel plot, the MR-Egger regression test and funnel plot did not provide any indication of asymmetry.

DISCUSSION

Although the research of Jannetta *et al*. has mostly focused on identifying classical TN, it has also led to the development of an efficient therapeutic approach utilising cerebral microvascular decompression surgery.[18] However, this does not explain or account for some of the causes of idiopathic TN.

The possibility of bias associated with observational studies is decreased because, to the best of the authors' knowledge, this is the first study to establish a causal connection between hypothyroidism and TN using the MR paradigm. Strong evidence was discovered to support the hypothesis that hypothyroidism increases TN risk.

Five different estimate techniques were employed for the MR analysis: Simple mode, weighted mode, IVW methodology, weighted median methodology, and MR-Egger regression test. Among them, only the simple method failed to prove that hypothyroidism and TN are causally related; however, the trend remained consistent with other findings. Thus, this research confirmed a positive causal relationship between hypothyroidism and TN. Sensitivity analyses, which reverse causation and eliminate bias from confounding variables, also supported this positive association.

However, the precise association between hypothyroidism and TN remains unclear. There are in-depth studies correlating hypothyroidism with migraines and tension headaches. One of the most prevalent signs of hypothyroidism, affecting about one-third of patients, is a migraine or tension headache.[19] Concurrently, it was discovered that the prevalence of hypothyroidism in the groups with tension headaches and migraines was greater than that in the general population, and comparable to that previously reported in the literature.[20] Evidence suggests that individuals with hypothyroidism have a higher incidence of TN.[7]

A possible link between hypothyroidism and TN has also been described in animal studies. Thyroid hormones, primarily in the central nervous system, are important growth and development factors. The absence of thyroid hormones reduces the volume of neurons and a number of glial cells and may result in myelination abnormalities. Behavioural testing has shown that hypothyroidism can reduce the effects of neuropathy by increasing the threshold for injurious sensations but can also enhance the expression of phospholipid basic protein and activator of transcription factor 3; thereby potentiating the effects of TN.[21]

Diffuse peripheral sensory and motor neuropathy are consequences of hypothyroidism, which typically affect nerve fibres in the distal extremities. In a study by Salas-Lucia, a considerable number of myelinated fibres and segmental demyelination were observed in the peroneal nerve of hypothyroid rats.[22] In contrast, neurophysiological, neuroimaging, and histological studies have found demyelination at the site of trigeminal nerve entrance into the pons, and central myelin formed by oligodendroglia replaces the Schwann cell myelin sheath of the trigeminal nerve. This transitional area is susceptible to injury, particularly to demyelination. Demyelination is typically brought on by vascular compression at the location closest to the nerve entering the pons.[2] Thus, the authors postulated that hypothyroidism may worsen or accelerate the onset of one of the elements that contribute to the appearance of classical TN.

Trigeminal nerve innervation in the affected area has trigger sites that may cause TN. Painful episodes can result from non-harmful stimuli, such as eating, brushing teeth, and wind, as well as from uncommonly harmful mechanical stimuli. The lips, nose, and the area surrounding the mouth are the most common trigger points.[23]

It has been argued that the skin biopsies from the limbs of patients with hypothyroidism found abnormally low intraepidermal nerve fibre density in up to 60% of the distal limbs and 20% of the proximal limbs. This suggests that peripheral fine nerve fibre damage occurs during hypothyroidism, which may be the primary peripheral factor causing nociception and allergies in hypothyroid rats. Sensitivity in rats with hypothyroidism.[24] This may play a role in hypothyroidism-related TN.

According to some studies, patients with TN may exhibit reduced volume or increased excitability in some cortical and subcortical cerebral areas; nevertheless, these alterations are likely the result of the tolerance of the brain regions to repeated stimulation.[2] However, in patients with hypothyroidism, these cortical regions are also covered by patches of structurally altered grey matter.[25]

There is not enough information from this study to pinpoint the exact role that low hypothyroidism might have in Tennessee. Consequently, more research is required to determine the precise role that hypothyroidism plays in the pathogenesis of TN. To provide new ideas and strategies for clinical diagnosis, treatment, and prevention of TN, more research is needed on the roles and mechanisms of hypothyroidism in the aetiology of TN.

There were certain restrictions on this investigation. First, the participants in the TN investigations were of the European descent. Further research including alternative populations is necessary to confirm this link in different ethnic groups, as ethnicity may influence causality. Second, a precise causal association may have been established through subgroup analysis; however, this was not possible owing to a lack of thorough clinical data. Third, the fact that different approaches produce different outcomes raises some concerns. Because this yields only the method with the lowest p-value, it is illogical to argue that a more exact approach should be used.

CONCLUSION

MR analysis revealed a favourable correlation between hypothyroidism and the likelihood of TN occurrence. Therefore, keeping an eye on hypothyroidism may help to identify the likelihood that TN will manifest. Furthermore, because different ethnic groups, nations, and regions have diverse genetic makeup, more research on other populations is required.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

CY, WZ: Methodology, software, and investigation.
YL, WK: Formal analysis and writing of the original draft.
YBW: Conceptualisation and supervision.
All authors approved the final version of the manuscript to be published.

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