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Association between mental disorders and trigeminal neuralgia: a cohort study and Mendelian randomization analysis

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Abstract

Background Clinical observational evidence suggests a close association between Trigeminal Neuralgia (TN) and Mental disorders (MDs). However, the causal relationship between the two remains unclear. This study aims to observe and analyse the associations between depression, anxiety, insomnia, and TN through clinical research. It also employs Mendelian randomization (MR) analysis to verify the potential genetic correlation between TN and various mental disorders. offering new insights for the diagnosis, prevention, and intervention strategies for TN.

Methods In the cohort study section, clinical data were collected from 154 patients with TN, all of whom were excluded from preoperative use of psychotropic drugs such as carbamazepine. The PHQ-9, GAD-7, and ISI scales were used to assess preoperative symptoms of depression, anxiety, and insomnia. Multivariable linear regression models were used to identify factors associated with questionnaire scores, with model performance evaluated by adjusted R^2, AIC, BIC, and p-values. Patients with significant positive symptoms preoperatively were followed up one-year after surgery, and non-parametric tests were employed to examine changes in mental disorder symptoms after pain relief. In MR analysis section, the main MR analysis methods include Inverse Variance Weighted (IVW), MR Egger, Weighted Median, Simple Mode, and Weighted Mode. The Benjamini–Hochberg (BH) method was used to adjust the p -values and control the false discovery rate (FDR). Subsequent sensitivity analyses involved Cochran's Q test, MR-Egger regression intercept, MR-pleiotropy residual sum and outlier test (MR-PRESSO).

Results Multiple linear regression analyses revealed that longer disease duration and greater involvement of trigeminal branches were consistently associated with higher PHQ-9, GAD-7, and ISI scores, while demographic factors and baseline BNI scores showed no significant predictive value. MR analysis indicated that autism (OR = 0.697, 95% CI [0.494–0.982], $P = 0.039$), schizophrenia (OR = 0.910, 95% CI [0.831–0.997], $P = 0.042$), and ADHD combined with OCD (OR = 0.175, 95% CI [0.044–0.693], $P = 0.013$) reduced the risk of TN. Conversely, bipolar disorder (OR = 1.249, 95% CI [1.016–1.535], $P = 0.034$), depression (OR = 2.375, 95% CI [1.043–5.409], $P = 0.039$), anxiety (OR = 1.174, 95% CI [1.008–1.368], $P = 0.039$), and insomnia (OR = 2.036, 95% CI [1.074–3.861], $P = 0.029$)increased the risk of TN. TN also elevated the risk of anxiety (OR = 1.43, 95% CI [1.04–1.96], $P = 0.034$), depression (OR = 1.00305, 95% CI [1.00036–1.00549], $P = 0.013$), and insomnia (OR = 1.00918, 95% CI [1.00236–1.01605], $P = 0.008$).

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Conclusions Longer disease duration and broader trigeminal nerve involvement were independently associated with increased severity of depressive, anxiety, and insomnia symptoms, highlighting the importance of early clinical intervention in patients with TN. And results of MR analysis provide evidence supporting a causal relationship between MDs and TN. In contrast to the traditional view that pain causes mood changes such as anxiety and depression, a variety of MDs such as anxiety, depression, and insomnia also alter the risk of developing TN.

Keywords Mental disorders, Depression, Anxiety, Insomnia, Trigeminal neuralgia, Mendelian randomization

Introduction

Trigeminal neuralgia (TN) is a functional neurogenic pain disorder characterized by recurrent, intense pain lasting for seconds or longer that occurs in the sensory distribution area of the trigeminal nerve. This pain can be triggered by specific stimuli, such as touching certain points on the face, lips, or gums, or even by chewing. Retrospective cohort studies in European populations indicate a lifetime prevalence of 0.16–0.3% and an annual incidence of 12.6–27.0 per 100,000 person-years for TN [1–4]. The high prevalence not only causes immense suffering for affected individuals but also imposes significant economic burdens on society as a whole. While the exact etiology of TN remains unclear, many researchers consider neurovascular compression syndrome (NCs) to be a direct cause [5]. Consequently, surgery has become the primary approach for treating TN. However, owing to the lack of clarity regarding specific causative factors, effective therapeutic options are currently unavailable for patients who do not respond to surgical or pharmacological interventions. Therefore, it is essential to delve into the etiology and risk factors for TN.

In recent years, the relationship between pain and mental disorders (MDs), particularly depression and anxiety, has garnered widespread attention. An increasing number of studies suggest a close association between these conditions. Gerrits et al. found that pain in six different body regions increases the risk of developing anxiety and depression, with a higher number of pain sites and greater pain intensity correlating with a higher risk [6]. Similarly, the prospective cohort study by Hu et al. demonstrated a significantly increased risk of depression in pain patients one year later [7]. A large-scale regional retrospective cohort study by Wu et al. demonstrated a significantly increased risk of depression, anxiety, and sleep disorders in patients with TN [8]. Moreover, a meta-analysis by Raggi et al. highlighted that psychosocial disorders are common comorbidities in patients with migraines [9].

Mendelian randomization analysis (MR) [10] is a data analysis method extensively employed in epidemiological research for assessing causal inference in etiological studies. This analysis uses genetic variations strongly associated with a specific exposure factor, often in the form of single nucleotide polymorphisms (SNPs), as instrumental variables (IVs). The primary aim is to infer the causal relationship between the exposure factor and a particular outcome. Because these genetic variations are present at birth and maintain relative stability throughout the entire life course, the association results obtained through MRs are less susceptible to reverse causation and confounding factors.

The MR analysis conducted by Yao et al. also indicated a potential causal relationship between multi-site bodily pain and depression, anxiety, and insomnia [11]. However, the potential causal link between TN and MDs remains unclear. To date, no studies have utilized MR analysis to investigate the potential causal relationship between TN and MDs.

This study included data from 154 TN patients and aimed to investigate the relationships between TN and depression, anxiety, and insomnia. We subsequently employed bidirectional two-sample MRs to investigate the potential causal relationships between TN and MDs.

Methods

Cohort study

Data collection

This study included patients with TN who were hospitalized at China-Japan Friendship Hospital between June 2023 and September 2023. Inclusion criteria: typical symptoms of TN. Exclusion criteria: (1) Diagnosed with mental illness before the onset of pain symptoms. (2) Treated with antipsychotic drugs (such as carbamazepine) within 3 months. All patients underwent a detailed medical interview, and demographic and clinical data, including age, sex, affected lateral, disease course, affected branches, and pain severity, were collected. Preoperative and postoperative pain severity were assessed via the Barrow Neurological Institute (BNI) pain intensity scale. Additionally, depression (PHQ-9), anxiety (GAD-7), and insomnia (ISI) were evaluated via standardized questionnaires.

The Patient Health Questionnaire-9 (PHQ-9) is used to assess the severity of depressive symptoms, with the following scoring criteria: 0–4 (grade 0) indicates no or minimal depression; 5–9 (grade 1) indicates mild depression; 10–14 (grade 2) indicates moderate depression; 15–19 (grade 3) indicates moderately severe depression; and 20–27 (grade 4) indicates severe depression. The Generalized Anxiety Disorder-7 (GAD-7) scale is used to evaluate the severity of anxiety symptoms, with

the following score ranges: 0–4 (grade 0) indicates no or minimal anxiety; 5–9 (grade 1) indicates mild anxiety; 10–14 (grade 2) indicates moderate anxiety; and 15–21 (grade 3) indicates severe anxiety. The Insomnia Severity Index (ISI) is used to assess the severity of insomnia and is scored as follows: 0–7 (grade 0) indicates no clinically significant insomnia; 8–14 (grade 1) indicates mild insomnia; 15–21 (grade 2) indicates moderate insomnia; and 22–28 (grade 3) indicates severe insomnia [12–14].

Follow-up

The follow-up cohort consisted of patients who, on the basis of preoperative questionnaire results, presented symptoms of depression, anxiety, and insomnia (defined as a PHQ-9 score ≥ 5, GAD-7 score ≥ 5, and ISI score ≥ 8). Data were collected via telephone follow-ups one year postoperatively, focusing primarily on pain recovery. Additionally, depression, anxiety, and insomnia were reassessed via the same questionnaires.

Statistical analysis

The analysis included measures such as the means, medians, standard deviations, ranges, and quartiles for continuous variables and frequency tables for categorical variables. The distribution of the data was assessed via normality tests, and appropriate descriptive statistics methods were applied to both normally and nonnormally distributed variables. For comparisons between groups of categorical data, we used Fisher's exact test for expected frequencies of < 5; otherwise, we used the chi-square test.

Regression analysis

Multiple linear regression models were constructed to explore the associations between patient characteristics and questionnaire scoring. Model 1 included demographic variables (age and gender). Model 2 incorporated clinically significant factors identified through univariate analysis, including disease duration, BNI scores, and affected nerve branches. Model 3 further adjusted for the affected side. To ensure model stability, variables with a variance inflation factor (VIF) > 5 were excluded to mitigate multicollinearity. Adjusted R^2, Akaike information criterion (AIC), Bayesian information criterion (BIC), and p-values were reported to evaluate model performance. A significance threshold of $p < 0.05$ was applied [15]. In our study, all the statistical analyses were performed via R software (version 4.3.2).

Mendelian randomization analysis

Data sources

This is a two-sample Mendelian randomization study following the Strengthening the Reporting of Mendelian Randomization Studies (STROBE-MR) guidelines [16]. In this study, we investigated various MDs, including attention-deficit/hyperactivity disorder (ADHD), anorexia nervosa (AN), autism, bipolar disorder (BD), narcolepsy, depression, attention-deficit/hyperactivity disorder comorbid with obsessive–compulsive disorder (ADHD & OCD), anxiety, schizophrenia, and insomnia. We conducted a forward MR analysis, considering MDs as exposures and TN as the outcome. Additionally, we performed a reverse MR analysis, with TN as the exposure and MDs as the outcome. In this study, the data utilized were derived from Genome-Wide Association Study (GWAS) data of European populations. Importantly, the populations for exposure and outcome were mutually independent in our analyses.

Except for depression, we conducted both forward and reverse MR analyses using the same dataset. The GWAS summary data for ADHD, AN, autism, BD, ADHD & OCD, and schizophrenia patients were obtained from the Psychiatric Genomics Consortium (PGC) (https://pgc.unc.edu/for-researchers/download-results/). The dataset for ADHD includes 20,183 cases and 35,191 controls [17], AN includes 3,495 cases and 10,982 controls [18], autism includes 14,525 cases and 14,890 controls, and BD includes 7,481 cases and 9,250 controls [19]. The ADHD & OCD dataset comprises 19,099 cases and 2,688 controls [20], whereas the schizophrenia dataset includes 76,755 cases and 2,436,499 controls [21]. For narcolepsy, anxiety, insomnia, and depression [22] in reverse MR, the GWAS summary data were sourced from the Pan-UK Biobank (https://pan.ukbb.broadinstitute.org). Narcolepsy includes 460,913 samples, anxiety includes 1,173 samples, and insomnia includes 462,341 samples. The GWAS summary data for depression in the forward MR analysis were obtained from The Within-family Consortium (https://www.withinfamilyconsortium.com/), comprising 47,517 samples [23]. The GWAS summary data for TN were sourced from the FinnGen database (https://www.finngen.fi/en/access_results) and included 1,777 cases and 360,538 controls [24] (Supplementary Table 1).

Instrumental variable selection

First, we selected SNPs with a p value less than 5e-08 as IVs strongly associated with MDs. We subsequently applied a threshold of r [2] less than 0.001 and excluded SNPs within a 10,000 kb range that were in linkage disequilibrium (LD) while also removing SNPs strongly correlated with the TN phenotype ($p < 5e\text{-}08$). The strength of the selected SNPs as IVs was assessed via the F statistic, which was calculated as β^2/SE^2, where β represents the effect size of the SNP on the exposure, and SE is the standard error of the β value [25–27]. We chose SNPs with an F statistic greater than 10. We extracted the selected SNPs from the GWAS data of TN, and those not found were excluded. The remaining SNPs were utilized as the final IVs for the MR analysis. If the number

of selected SNPs was less than 3, we gradually lowered the selection criteria and increased the p value threshold (specifically, at 1e–07, 2e–07, 5e–07, and 5e–06) until the number of SNPs for analysis reached 3 or more. Finally, we harmonized information from SNPs in MDs and TN for two-sample MR analysis. To address potential collinearity issues in MR analyses involving multiple mental disorders, we systematically screened all SNPs used as instrumental variables for overlap among different exposures. Upon identification of overlapping SNPs, we evaluated the strength of each SNP based on its F-statistic within respective disorders. SNPs with stronger instrumental strength for a particular disorder were retained exclusively for that disorder. In the reverse MRs, the TN was considered the exposure, and the MD was the outcome for IVs selection. This process resembled forward MRs, with the difference being the use of two p value standards (specifically, p values less than 5e-08 and p values less than 5e-06) for SNP selection.

Statistical analyses

We conducted a two-sample MR analysis using the harmonized SNPs. For exposures with three or more IVs, we applied five methods—inverse variance weighted (IVW), MR Egger, weighted median, simple mode, and weighted mode—for MR analysis. If sensitivity analysis indicated no significant heterogeneity among IVs, the results of the IVW method were considered; otherwise, the results of the weighted median method were adopted [28]. For exposures with two IVs, a fixed-effects IVW model was used for analysis. If there was only one IV, the Wald ratio method was employed [29]. To account for potential false positives arising from multiple MR comparisons, we applied the Benjamini–Hochberg (BH) procedure to adjust the p-values and control the false discovery rate (FDR). This correction was applied post hoc to the results of the MR analyses involving multiple MDs.

Sensitivity analyses of MR

When there were three or more SNPs, first, we employed Cochran's Q test to assess heterogeneity among IVs. If the p value was greater than 0.05, there was no heterogeneity among the IVs. Second, we used the MR–Egger regression intercept to test the horizontal pleiotropy of IVs. If the p value is greater than 0.05, we assume that the MR results are not influenced by horizontal pleiotropy. We subsequently conducted the MR-pleiotropy residual sum and outlier (MR-PRESSO) global test again to examine horizontal pleiotropy [30]. The MR-PRESSO outlier test was used to check for the existence of outlier SNPs. If outliers were detected, they were removed, and the MR analysis was conducted again. We consider horizontal pleiotropy unacceptable; therefore, regardless of the significance of MR results, the presence of horizontal pleiotropy suggests no association between exposure and outcome. Finally, we conducted a leave-one-out analysis to examine whether there were any IVs that exerted a substantial effect on the MR results. Cochran's Q test and leave-one-out analysis were performed when there were 2 SNPs. Sensitivity analysis could not be conducted when only one SNP was available (Fig. 1).

All analyses were conducted via R software version 4.3.2, with the primary utilization of the TwosampleMR package.

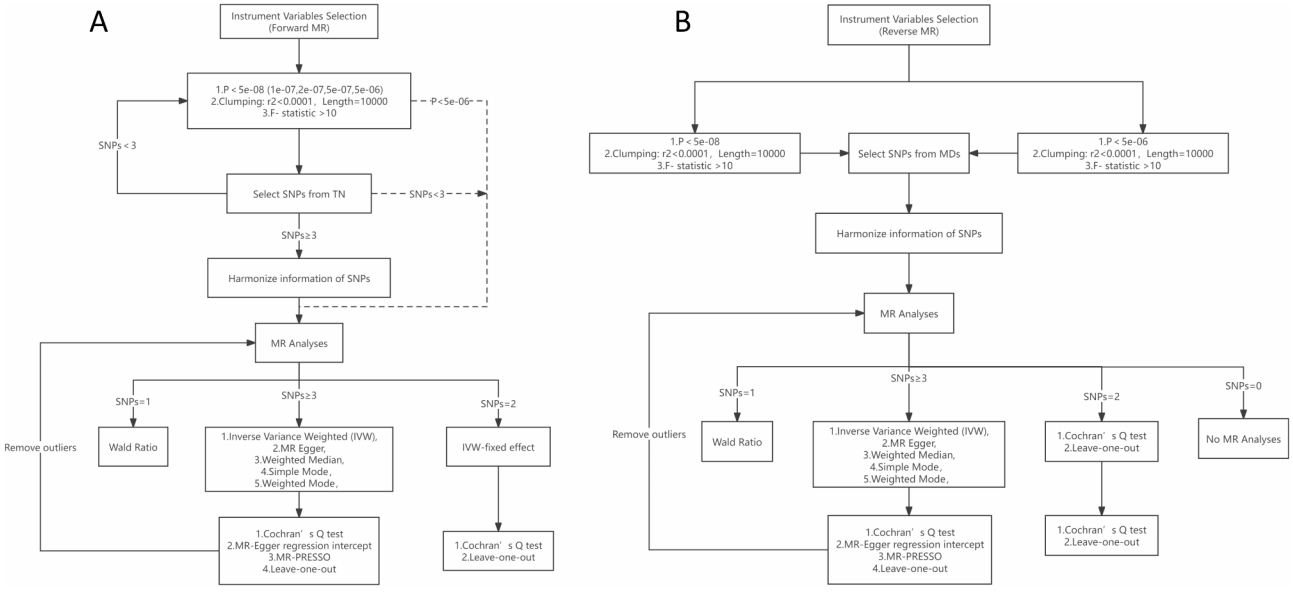

Fig. 1 Study design for the association between mental diseases and trigeminal neuralgia in our Mendelian randomization analysis. (**A**) Forward Mendelian randomization analysis; (**B**) Reverse Mendelian randomization analysis

Results

All patient demographic data

The baseline characteristics (Table 1) present key demographic and clinical characteristics of the sample population. The participants ($N = 154$) had a mean age of 61 years and a mean disease course of 36 years. The gender distribution revealed that 66.2% were female and 33.8% were male. In terms of pain location, 63.6% of patients reported pain on the right side, whereas 36.4% reported pain on the left side.

Difference analysis

Fifty-six of the 154 patients had significant preoperative depressive symptoms, with a PQH9 score of ≥ 5. Disease duration increased markedly with increasing depression grade ($p < 0.001$), and patients with more severe depression were more likely to have three affected branches ($p = 0.021$) and higher BNI pain scores ($p = 0.030$). (Table 2).

Forty-seven of the 154 patients had significant preoperative depressive symptoms with a GAD-7 score of ≥ 5. For anxiety, disease duration significantly increased with severity ($p < 0.001$), with higher anxiety grades linked to three affected branches ($p = 0.018$) and severe BNI pain scores ($p = 0.008$). Gender also showed a significant association, with females predominating in lower anxiety grades ($p = 0.030$). However, age and lateralization did not significantly differ. (Table 2).

Eighty-two of the 154 patients had significant preoperative depressive symptoms with an ISI score of ≥ 8. For insomnia, severity was strongly associated with increasing age ($p = 0.010$), longer disease duration ($p < 0.001$), and the involvement of three affected branches ($p = 0.008$). Severe insomnia grades were exclusively observed in patients with right-sided symptoms ($p = 0.013$) and were strongly linked to higher BNI pain scores ($p < 0.001$). The gender distribution did not differ significantly across insomnia grades. (Table 2).

Table 1 All patient demographics and baseline characteristics

Characteristic	$N = 154$[1]
Age	61 (55, 67)
Disease course	36 (12, 81)
Gender	
Female	102 (66.2%)
Male	52 (33.8%)
Lateral	
Left	56 (36.4%)
Right	98 (63.6%)
Affected branches	
1	26 (16.9%)
2	63 (40.9%)
3	65 (42.2%)
BNI Score	
III	59 (38.3%)
IV	52 (33.8%)
V	43 (27.9%)
PHQ9 Score	2.0 (1.0, 11.0)
Depression grade	
0 (0–4 score)	99 (64.3%)
1 (5–9 score)	10 (6.5%)
2 (10–14 score)	22 (14.3%)
3 (15–19 score)	19 (12.3%)
4 (20–27 score)	4 (2.6%)
GAD7 Score	3.0 (1.0, 11.0)
Anxiety grade	
0 (0–4 score)	99 (64.3%)
1 (5–9 score)	12 (7.8%)
2 (10–14 score)	35 (22.7%)
3 (15-21score)	8 (5.2%)
ISI Score	9 (4, 15)
Insomnia grade	
0 (0–7 score)	72 (46.8%)
1 (8–14 score)	41 (26.6%)
2 (15–21 score)	33 (21.4%)
3 (22–28 score)	8 (5.2%)

[1]Median (IQR); n (%)

Regression analysis

Supplementary Table 2 summarizes the results of multiple linear regression analyses assessing predictors of depressive (PHQ-9), anxiety (GAD-7), and insomnia (ISI) symptom severity. Across all regression models, multicollinearity diagnostics indicated no substantial concerns (VIF < 5) (Supplementary Table 3).

In predicting depressive symptoms (PHQ-9 scores), clinical variables demonstrated significant predictive value. Specifically, longer disease course and involvement of more extensively affected trigeminal branches were associated with higher PHQ-9 scores. Introduction of these clinical predictors in Model 2 notably enhanced the model's explanatory power, increasing the adjusted R^2 from essentially zero in Model 1 ($R^2 = 0.037$, adjusted $R^2 = -0.001$) to 0.435 ($R^2 = 0.509$). Addition of symptom laterality in Model 3 provided only marginal improvement (adjusted $R^2 = 0.427$; $R^2 = 0.513$). Demographic factors (age, gender), laterality, and baseline BNI scores did not significantly predict PHQ-9 scores.

For anxiety symptom severity (GAD-7 scores), disease course was a robust and consistent predictor in Models 2 and 3 ($\beta = 0.033$, $p < 0.001$), substantially increasing the explained variance from 9% in Model 1 to approximately 48% after adding clinical variables (disease course, affected branches, BNI scores, laterality). Other factors such as gender, age, baseline pain intensity (BNI scores), affected branches, and symptom laterality did not demonstrate statistical significance in predicting anxiety levels.

Table 2 Different demographics between patients with different levels of depression, anxiety and insomnia

MDs	Variables	Grade 1[1]	Grade 2[1]	Grade 3[1]	Grade 4[1]	pval
Depression	Age	62 (61, 64)	63 (54, 66)	64 (60, 74)	71 (60, 82)	0.630[2]
	Disease course	30 (11, 69)	72 (48, 120)	84 (66, 120)	276 (240, 312)	< 0.001[2]
	Gender					0.928[3]
	Female	5 (50.0%)	13 (61.9%)	10 (52.6%)	2 (50.0%)	
	Male	5 (50.0%)	8 (38.1%)	9 (47.4%)	2 (50.0%)	
	Lateral					0.426[3]
	Left	2 (20.0%)	8 (38.1%)	4 (21.1%)	0 (0.0%)	
	Right	8 (80.0%)	13 (61.9%)	15 (78.9%)	4 (100.0%)	
	Affected branches					0.021[3]
	1	3 (30.0%)	2 (9.5%)	0 (0.0%)	0 (0.0%)	
	2	5 (50.0%)	9 (42.9%)	5 (26.3%)	0 (0.0%)	
	3	2 (20.0%)	10 (47.6%)	14 (73.7%)	4 (100.0%)	
	BNI Score					0.030[3]
	III	6 (60.0%)	9 (42.9%)	4 (21.1%)	0 (0.0%)	
	IV	3 (30.0%)	5 (23.8%)	3 (15.8%)	0 (0.0%)	
	V	1 (10.0%)	7 (33.3%)	12 (63.2%)	4 (100.0%)	
Anxiety	Age	63 (55, 64)	62 (59, 71)	67 (60, 76)		0.513[2]
	Disease course	15 (6, 36)	72 (48, 120)	240 (195, 258)		< 0.001[2]
	Gender					0.030[3]
	Female	10 (83.3%)	18 (51.4%)	2 (25.0%)		
	Male	2 (16.7%)	17 (48.6%)	6 (75.0%)		
	Lateral					0.822[3]
	Left	4 (33.3%)	8 (22.9%)	2 (25.0%)		
	Right	8 (66.7%)	27 (77.1%)	6 (75.0%)		
	Affected branches					0.018[3]
	1	2 (16.7%)	5 (14.3%)	0 (0.0%)		
	2	7 (58.3%)	14 (40.0%)	0 (0.0%)		
	3	3 (25.0%)	16 (45.7%)	8 (100.0%)		
	BNI Score					0.008[3]
	III	6 (50.0%)	12 (34.3%)	0 (0.0%)		
	IV	5 (41.7%)	9 (25.7%)	1 (12.5%)		
	V	1 (8.3%)	14 (40.0%)	7 (87.5%)		
Insomnia	Age	63 (52, 70)	60 (58, 62)	76 (71, 78)		0.010[2]
	Disease course	36 (24, 60)	72 (48, 120)	240 (198, 258)		< 0.001[2]
	Gender					> 0.999[3]
	Female	22 (53.7%)	18 (54.5%)	4 (50.0%)		
	Male	19 (46.3%)	15 (45.5%)	4 (50.0%)		
	Lateral					0.013[3]
	Left	22 (53.7%)	14 (42.4%)	0 (0.0%)		
	Right	19 (46.3%)	19 (57.6%)	8 (100.0%)		
	Affected branches					0.008[3]
	1	6 (14.6%)	5 (15.2%)	0 (0.0%)		
	2	21 (51.2%)	9 (27.3%)	0 (0.0%)		0.008[3]
	3	14 (34.1%)	19 (57.6%)	8 (100.0%)		
	BNI Score					< 0.001[3]
	III	12 (29.3%)	10 (30.3%)	0 (0.0%)		
	IV	23 (56.1%)	8 (24.2%)	0 (0.0%)		
	V	6 (14.6%)	15 (45.5%)	8 (100.0%)		

[1]Median (IQR); n (%); [2]Kruskal-Wallis rank sum test; [3]Fisher's exact test

MD = Mental disorders

Regarding insomnia severity (ISI scores), younger age initially emerged as a significant predictor in Model 1 (β = 0.130, $p = 0.012$) but was no longer significant after adjusting for clinical variables. Disease course remained consistently significant across Models 2 (β = 0.028, $p < 0.001$) and 3 (β = 0.027, $p = 0.002$). The inclusion of clinical variables markedly improved explanatory power from 7.9% in Model 1 to approximately 42% in Models 2 and 3. Again, gender, preoperative pain intensity (BNI scores), number of affected branches, and symptom laterality were not significant predictors of ISI scores.

Overall, clinical characteristics—particularly disease duration and extent of affected trigeminal branches—emerged as the most influential predictors for psychological symptoms measured by PHQ-9, GAD-7, and ISI.

Follow-up

The analysis revealed a significant decrease in the PHQ-9 scores postoperation (mean difference = 10.89, SD = 4.97), with a t value of 16.11, degrees of freedom (df) = 53, and a p value < 0.001, indicating a substantial reduction in depressive symptoms. Similarly, the GAD-7 scores were significantly lower (mean difference = 8.82, SD = 3.51), t (54) = 18.65, $p < 0.001$, suggesting a notable improvement in anxiety levels. Finally, the ISI scores also significantly decreased following the intervention (mean difference = 10.46, SD = 5.08), with t (81) = 18.67 and $p < 0.001$, indicating a marked improvement in insomnia symptoms. These results indicate that pain relief had a significant positive effect on reducing symptoms of depression, anxiety, and insomnia in the patient cohort (Fig. 2).

Mendelian randomization analysis

Characteristics of the selected SNPs

In the forward MR analysis, multiple SNPs were identified as IVs for each of the MDs, except for Autism, which had 2 SNPs. For the other 9 MDs, the number of selected SNPs exceeded 3, all of which strongly correlated with

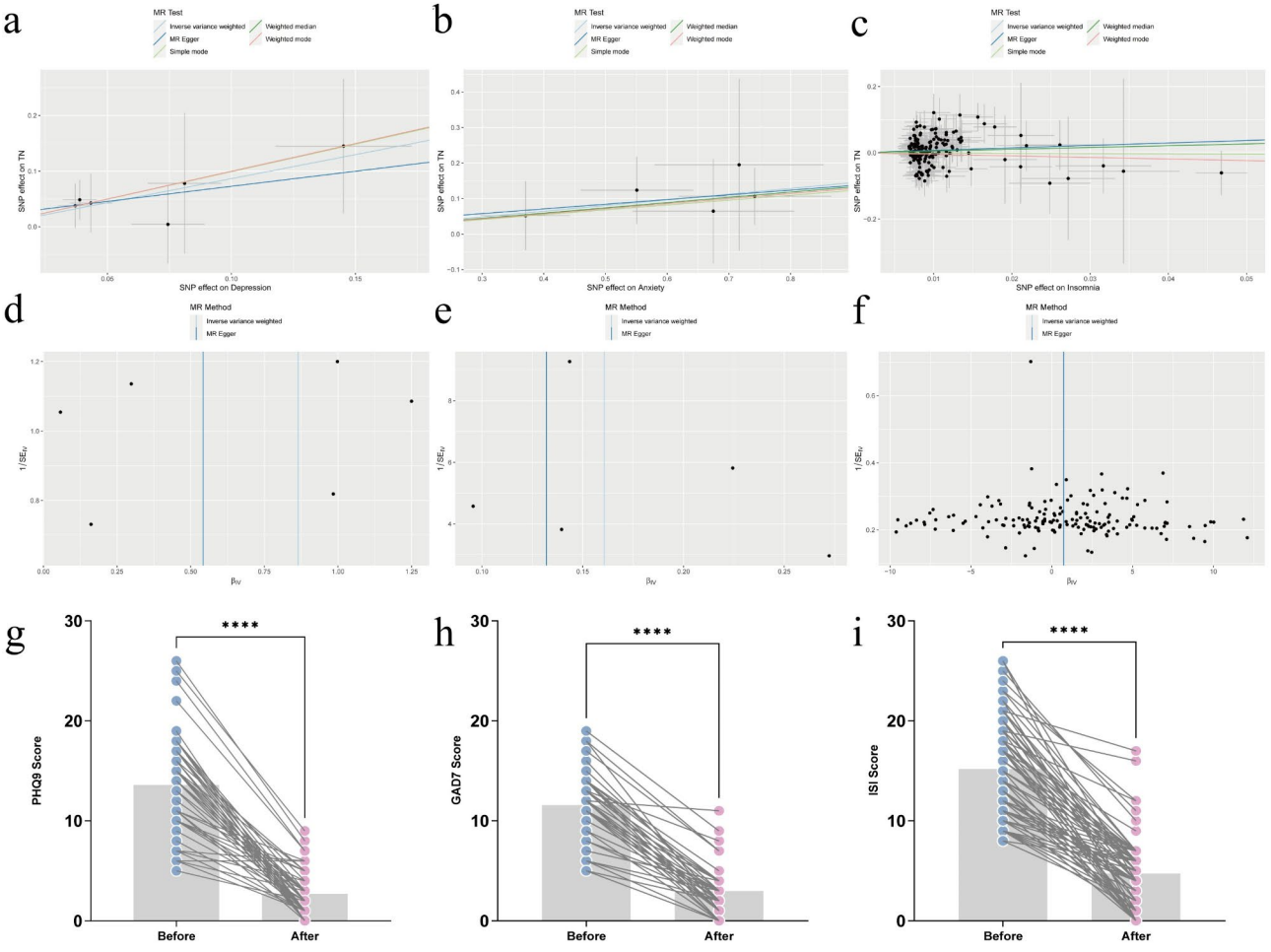

Fig. 2 Scatter plot showing the genetic associations of MDs and TN. (**a**) Depression related to TN, (**b**) anxiety related to TN, (**c**) insomnia related to TN. The funnel plot represents IVs for each significant causal association between MDs and TN. (**d**) Depression related to TN, (**e**) anxiety related to TN, (**f**) insomnia related to TN. Changes in mental health scores before and after surgery in patients with TN. (**g**) Depression scores (PHQ-9); (**h**) anxiety scores (GAD-7); (**i**) insomnia scores (ISI)

their respective MDs, were unrelated to TN, and were mutually independent. The F statistics for all IVs were greater than 10 (Supplementary Table 4).

In the reverse MR analysis, when a P value threshold of < 5e-08 was used, only 1 SNP was found in the TN, and it could not be identified in any of the MDs. When a P value threshold of < 5e-06 was used, after removing LD, 9 SNPs were retained. Harmonizing with all 10 MDs, more than 3 SNPs were still available as IVs (Supplementary Tables 5 and 6).

Potential relationships between MDs and TN

In the forward MR analysis, we observed that certain MDs had an impact on the risk of developing TN. Compared with the control group, autism (OR = 0.697, 95% CI [0.494–0.982], $P = 0.039$), schizophrenia (OR = 0.910, 95% CI [0.831–0.997], $P = 0.042$), and ADHD & OCD (OR = 0.175, 95% CI [0.044–0.693], $P = 0.013$) were associated with a reduced risk of TN. On the other hand, BD (OR = 1.249, 95% CI [1.016–1.535], $P = 0.034$), depression (OR = 2.375, 95% CI [1.043–5.409], $P = 0.039$), anxiety (OR = 1.174, 95% CI [1.008–1.368], $P = 0.039$), and insomnia (OR = 2.036, 95% CI [1.074–3.861], $P = 0.029$) increased the risk of TN (Fig. 3). ADHD, AN, and narcolepsy did not influence the risk of TN. In the reverse MR analysis, we found that TN increased the risk of anxiety (OR = 1.43, 95% CI [1.04–1.96], $P = 0.034$), depression (OR = 1.00305, 95% CI [1.00036–1.00549], $P = 0.013$), and insomnia (OR = 1.00918, 95% CI [1.00236–1.01605], $P = 0.008$) (Fig. 4). After applying false discovery rate (FDR) correction using the Benjamini–Hochberg method, the adjusted p-values for these associations were all above the conventional significance threshold (q > 0.05), with the lowest q-value being 0.060. Although

Exposure	Method	nSNP	P	OR(95%CI)
Autism	Inverse variance weighted	2	0.039	0.697(0.494 to 0.982)
Bipolar Disorder	Inverse variance weighted	4	0.035	1.249(1.016 to 1.535)
	MR Egger	4	0.489	0.761(0.403 to 1.438)
	Weighted median	4	0.100	1.231(0.961 to 1.576)
	Simple mode	4	0.164	1.507(0.973 to 2.336)
	Weighted mode	4	0.704	1.065(0.794 to 1.428)
Depression	Inverse variance weighted	6	0.039	2.375(1.043 to 5.409)
	MR Egger	6	0.616	1.720(0.243 to 12.184)
	Weighted median	6	0.062	2.709(0.950 to 7.727)
	Simple mode	6	0.207	2.692(0.705 to 10.278)
	Weighted mode	6	0.220	2.713(0.672 to 10.955)
ADHD & OCD	Inverse variance weighted	5	0.013	0.175(0.044 to 0.693)
	Weighted median	5	0.083	0.226(0.042 to 1.213)
	Simple mode	5	0.386	0.320(0.032 to 3.187)
	Weighted mode	5	0.417	0.331(0.030 to 3.625)
Anxiety	Inverse variance weighted	5	0.040	1.174(1.008 to 1.368)
	MR Egger	5	0.712	1.141(0.604 to 2.156)
	Weighted median	5	0.120	1.159(0.962 to 1.396)
	Simple mode	5	0.335	1.146(0.898 to 1.463)
	Weighted mode	5	0.243	1.153(0.940 to 1.415)
Schizophrenia	Inverse variance weighted	215	0.042	0.910(0.831 to 0.997)
	MR Egger	215	0.110	0.746(0.522 to 1.066)
	Weighted median	215	0.182	0.914(0.801 to 1.043)
	Simple mode	215	0.376	1.218(0.788 to 1.883)
	Weighted mode	215	0.527	1.145(0.754 to 1.740)
Insomnia	Inverse variance weighted	173	0.029	2.036(1.074 to 3.861)
	MR Egger	173	0.510	2.036(0.247 to 16.794)
	Weighted median	173	0.294	1.690(0.635 to 4.501)
	Simple mode	173	0.957	0.926(0.057 to 14.976)
	Weighted mode	173	0.694	0.625(0.061 to 6.448)

P<0.05 was considered statistically significant

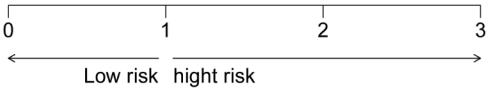

Fig. 3 Results of Mendelian randomization analysis with mental disorders as the exposure and TN as the outcome. The scale of the x-axis is logarithmic. nSNPs, number of SNPs used in MR; OR, odds ratio; CI, confidence interval. The P value requirement was relaxed to $< 5 \times 10^{-8}$

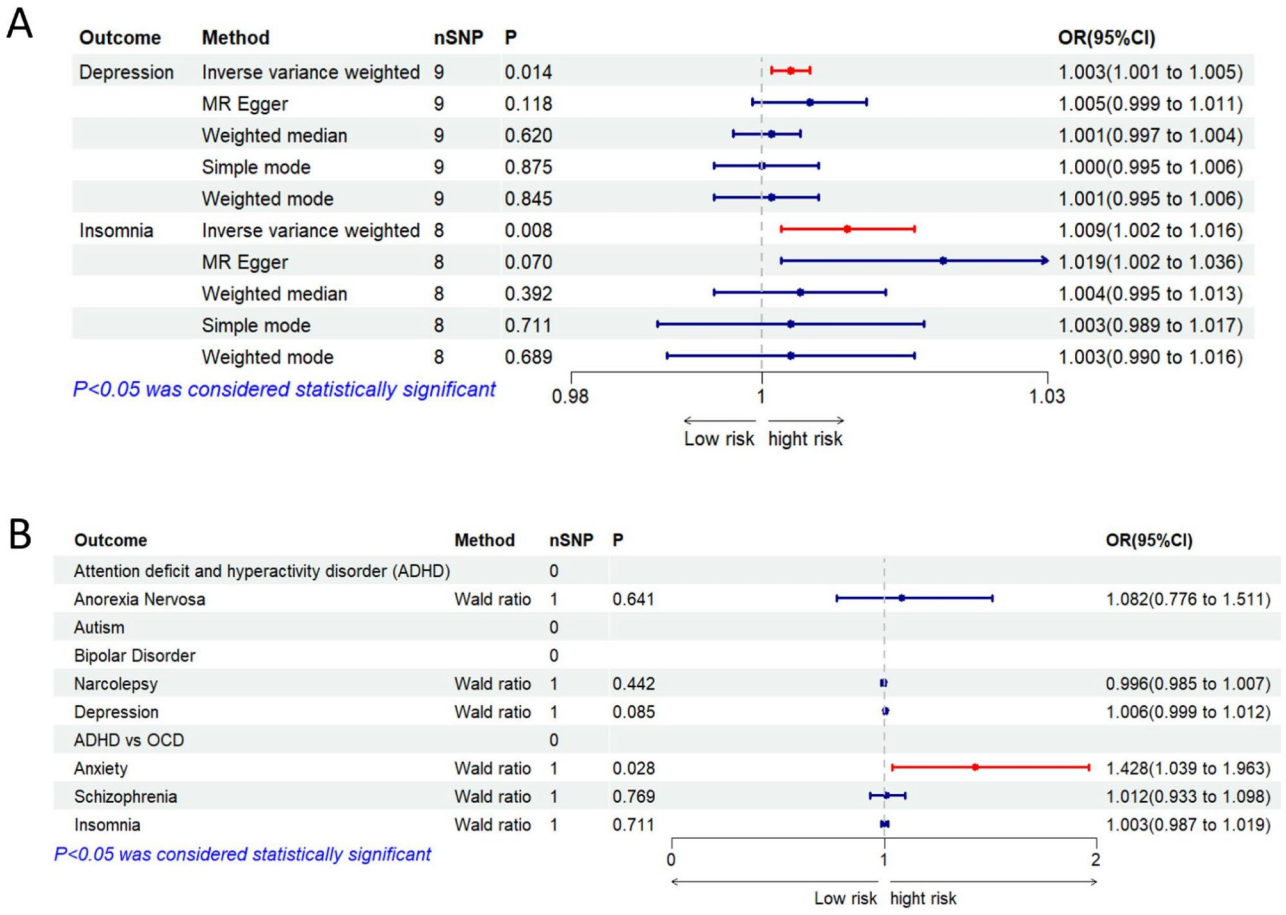

Fig. 4 Results of the Mendelian randomization analysis with mental disorders as the outcome and TN as the exposure. (**A**): The *P* value requirement was relaxed to $< 5 \times 10^{-8}$. (**B**): The *P* value requirement was relaxed to $< 5 \times 10^{-6}$

the associations did not remain statistically significant after correction, the direction and magnitude of effects remained consistent, suggesting potential biological relevance (Supplementary Table 7). The forest plot clearly depicts the effect of each SNP on the outcome (Supplementary Fig. 1). Scatter plot showing the genetic associations of MDs with the risk of TN (Fig. 3 and Supplementary Fig. 2).

Sensitivity analyses of MRs

In the forward MR analysis, the results of the Cochran's Q test indicated no significant heterogeneity among all included SNPs. Furthermore, the P values for the MR–Egger regression intercepts were all greater than 0.05, suggesting that our analysis results were not influenced by the pleiotropy of IVs (Table 3). The MR-PRESSO global test also revealed P values greater than 0.05, indicating that our results were not affected by SNP pleiotropy, and the MR-PRESSO outlier test suggested the absence of outliers in IVs (Table 4).

In the reverse MR analysis, both the Cochran's Q statistic and the MR–Egger regression intercept yielded good results (Table 3). However, in the reverse MR analysis with insomnia as the outcome, the MR–Egger regression intercept and MR-PRESSO global test suggested the presence of pleiotropy. Further MR-PRESSO outlier tests identified rs7565627 as an outlier. After removing this SNP and conducting MR analysis, the MR–Egger regression intercept and MR-PRESSO global test yielded highly satisfactory results (Table 4). Leave-one-out analysis (Supplementary Fig. 3) revealed that the absence of SNPs significantly influenced the results for both forward and reverse MRs. The funnel plot visually presents whether IVs exhibit heterogeneity (Fig. 3 and Supplementary Fig. 4). The sensitivity analysis results indicate the reliability of the causal relationships identified in the bidirectional MR analysis.

Discussion

A study on the impact of TN on patients utilizing the Hospital Anxiety and Depression Scale reported high prevalences of depression (36%) and anxiety (50%)[31]. Another study by Diana Mačianskytė et al., involving 30 TN patients, revealed that 30–47% of patients

Table 3 Pleiotropy and heterogeneity test of IVs

	MDs	Pleiotropy test		Heterogeneity test	
		MR-Egger		Inverse-variance weighted	
		Intercept	*p*	Q	Q_pval
Forward	Autism	0.036	0.381	0.951	0.329
	Bipolar Disorder	0.096	0.248	2.660	0.447
	Depression	0.018	0.740	0.959	0.966
	ADHD vs. OCD	0.234	0.580	1.507	0.825
	Anxiety	0.018	0.933	0.367	0.985
	Schizophrenia	0.012	0.261	204.641	0.494
	Insomnia	2.055E-06	0.999	155.633	0.583
Reverse	Depression	-0.001	0.429	5.296	0.725
	Insomnia	-0.003	0.269	7.408	0.388
	Anxiety	-0.004	0.528	6.861	0.839

Table 4 Result of MR-pleiotropy residual sum and outlier (MR-PRESSO)

Traits	global test	
	RSSobs	*P*
Forward (Exposure)		
Autism	6.656202	0.472
Bipolar Disorder	6.656202	0.476
Depression	1.490576	0.973
ADHD vs. OCD	2.426811	0.825
Anxiety	0.5754084	0.995
Schizophrenia	206.8564	0.496
Insomnia	157.7607	0.590
Reverse (Outcome)		
Depression	6.857275	0.751
Insomnia	9.819325	0.4209
Anxiety	NA	NA

When anxiety disorder is used as an outcome, there is only one instrumental variable, so MR-PRESSO test cannot be performed

experienced anxiety and depression [32]. In this study, among the 154 patients with TN, 56 (36.4%) had varying degrees of depressive symptoms, 47 (30.5%) had anxiety symptoms, and 82 (53.2%) had insomnia symptoms, which is consistent with the findings of previous studies.

On the basis of the results of the MR analysis, we observed a potential causal relationship between MDs and TN. Autism, ADHD & OCD, and schizophrenia were associated with a reduced risk of TN, whereas bipolar disorder, depression, anxiety disorder, and insomnia were associated with an increased risk of TN. Conversely, TN was found to increase the risk of anxiety, depression, and insomnia.

Scholars generally believe that TN increase the risk of developing MDs. Wu et al. reported that the proportion of TN patients with anxiety, depression, and insomnia was significantly greater than that of the control group [8]. However, it did not affect the incidence rates of schizophrenia or BD, which aligns completely with our analysis results. Notably, Wu et al. suggested that although their cohort study results indicated that TN does not affect the incidence of BD, this finding may be influenced by TN patients taking carbamazepine orally to treat TN. In our study, while the results of the reverse MRs suggest that TN does not affect the incidence of BD, in the forward MRs, BD significantly increases the incidence of TN. Therefore, our perspectives are consistent.

The central theory suggests that increased excitability of the central nervous system is one of the causes of TN. This alteration may be attributed to changes in central neurotransmitters. Research [33] has revealed a significant decrease in the levels of norepinephrine, serotonin, and dopamine metabolites in the cerebrospinal fluid of TN patients, resembling the central changes observed in depression, anxiety, and BD patients. This implies a potential mutual influence between the TN and these MDs. Additionally, substance P significantly increases in the cerebrospinal fluid of TN patients, and the elevation of calcitonin gene-related peptide in the neural pathways of TN model mice suggests the involvement of chronic inflammation in the pathogenesis of TN [33, 34]. Studies have also revealed a significant increase in the levels of cytokines such as IL-1β, TNF-α, CCL2, IL-17 A, IL-6, and CXCL8 in the saliva of TN patients, further supporting the notion of chronic inflammation in TN patients [35]. This is akin to the physiological and pathological processes observed in depression, anxiety, and BD [36–39]. Lv et al. reported that corticotropin-releasing hormone (CRH) mediates TN-related anxiety and depressive symptoms through a dedicated neural circuit from the ventral hippocampus (vHPC) to the medial prefrontal cortex (mPFC) [40].

Our study also revealed that autism, ADHD & OCD, as well as schizophrenia, appear to reduce the risk of TN. To our knowledge, this is the first study to propose such results. On the one hand, we posit that individuals with autism exhibit congenital abnormalities in the development of the nervous system, such as anomalies in gray matter with abnormal proliferation, disruptions in white matter structure, and atypical connections between

neurons [41]. We believe that these abnormalities lead to a weakened connection between neurons and the reduced responsiveness of the central posterior gyrus in the frontal lobe to abnormal impulses generated by lower-level neurons, thereby lowering the risk of developing TN. On the other hand, individuals with autism often experience dysregulation of the neurotransmitter system, particularly defects in the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) signalling pathway [42]. These alterations can result in emotional numbness and delayed pain perception in patients. The comorbidity of ADHD and OCD also reduces the risk of TN, but isolated ADHD does not affect the risk of TN. We attribute this to the weakened activity of central nervous system serotoninergic neurons and the involvement of chronic neural inflammation in the pathological processes of both disorders [43, 44]. The coexistence of ADHD and OCD enhances these pathological changes. However, this cannot explain why this would lead to a reduced risk of TN rather than an increased risk, as individuals with TN also exhibit decreased serotonin metabolite levels and chronic inflammation in the cerebrospinal fluid. With respect to the relationship between schizophrenia and TN, previous studies did not find any association between the two. However, our use of MRs to eliminate confounding biases revealed a significant decrease in the risk of TN in individuals with schizophrenia. The Ignition hypothesis proposed by Devor et al. suggests that injury leads to abnormal impulses in the afferent nerve fibres of the trigeminal ganglion or nerve roots, resulting in TN[34]. This change is mediated by glutamate [46]. On the other hand, schizophrenia is often associated with hyperactivity of central nervous system dopamine neurons and decreased glutamatergic neuronal function [47, 48]. Therefore, schizophrenia reduces the risk of developing TN.

Our analysis results indicate a bidirectional influence and mutual promotion between TN and insomnia. Insomnia is often characterized by excessive activity of the sympathetic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis [49–51]. On the one hand, studies have revealed heightened excitability of the sympathetic nervous system in the peripheral blood of TN patients, which persists and is not directly related to pain episodes [52]. These findings suggest that the excitability of the sympathetic nervous system is not only a consequence of neuropathic pain but may also play a role in its induction and maintenance. On the other hand, research suggests that sympathetic nerves within the vascular wall may act as a bridge in transmitting abnormal impulses between compressed nerve fibres [53]. Furthermore, insomnia is commonly a manifestation of various psychiatric disorders that often coexist with conditions such as depression, anxiety, and BD. These factors may contribute to the increased risk of TN in individuals with insomnia [54].

Previous research has indicated a significant association between TN and MDs, but the causative relationship remains unclear. Therefore, we employed the MR method for the first time to assess potential causal relationships between TN and MDs. MR analyses utilize stable and unchanging SNPs as IVs and cleverly analyse potential causal relationships on the basis of three main assumptions regarding exposure and outcome. We conducted multiple sensitivity tests to eliminate confounding biases and reverse causal influences. Therefore, our research approach is novel, and the results are credible.

Despite the meaningful results obtained in our study, several limitations should be acknowledged. Firstly, while the conclusion of a significant reduction in TN risk associated with the comorbidity of ADHD and OCD appears relatively robust, we have not fully explained the underlying reasons. Secondly, our MR analysis was based on GWAS summary statistics derived from European populations, whereas our clinical cohort consisted of individuals of Asian ancestry. This discrepancy may limit the external validity of our findings. Thirdly, MR analysis relies on SNPs identified through GWAS as IVs. As several MDs have not undergone large-scale GWASs, their potential associations with TN cannot be analysed via this method. Fourthly, as this was a retrospective cohort study, a priori sample size calculation was not performed. While this is commonly accepted in retrospective designs, the absence of a predefined sample size may limit the statistical power, particularly for detecting smaller effects. Lastly, although several MR associations reached statistical significance, the estimated effect sizes were relatively small. The clinical relevance and practical implications of these modest genetic effects require cautious interpretation and further validation. These limitations should be considered when interpreting and generalizing the study results.

Conclusion

In summary, we found strong associations between TN and depression, anxiety, and insomnia. A longer disease duration is a key predictor of depression, anxiety and insomnia. The results of MRs revealed potential causal relationships between TN and MDs. On the one hand, autism, schizophrenia, ADHD & OCD may reduce the risk of TN, whereas BD may increase the risk of TN. On the other hand, depression, anxiety, and insomnia, three types of MDs, mutually promote and cause TN, forming a bidirectional causal relationship. Our study provides a new perspective for investigating and understanding the pathophysiological mechanisms of TN. These findings highlight the importance of integrating MD evaluation

and management in TN treatment strategies, offering novel perspectives for addressing this complex condition.

Abbreviations

TN	Trigeminal neuralgia
MDs	Mental disorders
MRs	Mendelian randomization analysis
IVW	Inverse variance weighted
MR-PRESSO	MR-pleiotropy residual sum and outlier test
ADHD & OCD	Attention-deficit/hyperactivity disorder comorbid with obsessive–compulsive disorder
BD	Bipolar disorder
AN	Anorexia nervosa
NCs	Neurovascular compression syndrome
SNPs	Single nucleotide polymorphisms
GWAS	Genome–wide association study
LD	Linkage disequilibrium
GABA	Gamma-aminobutyric acid
HPA	Hypothalamic–pituitary–adrenal axis
VIF	Variance inflation factor
AIC	Akaike information criterion
BIC	Bayesian information criterion
BH	Benjamini–Hochberg
FDR	False discovery rate

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s10194-025-02026-y.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Supplementary Material 10

Supplementary Material 11

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Author contributions

J W: Conceptualization, Methodology, Formal analysis, Writing - Original Draft, Visualization; M L: Conceptualization, Writing - Review & Editing; Z Z: Methodology; Y D: Methodology, Writing - Review & Editing; Z Z: Formal analysis; H L: Data Curation; K Y: Data Curation; J L: Funding acquisition.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

This study was conducted as a retrospective analysis of clinical data, and informed consent was obtained from all participants. All personal information was anonymized to ensure the confidentiality and privacy of the participants. The study was approved by the Institutional Review Board (IRB) of China-Japan Friendship Hospital, Beijing, China, and was performed in accordance with the ethical standards of the Declaration of Helsinki. Mendelian randomization analysis utilizes summary data from various publicly available large-scale GWASs and does not include any individual-specific information. Patient consent was previously obtained in the original studies; therefore, this study does not require new patient consent. The GWASs also received ethical approval from the respective ethics review boards.

Consent for publication

All the authors of this study have read and approved the final manuscript. They consent to the publication of the research findings in The Journal of Headache and Pain.

Competing interests

The authors declare no competing interests.

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