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Unveiling taurine's protective role in ischemic stroke: insights from bidirectional Mendelian randomization and LC–MS/MS analysis

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Abstract

Ischemic stroke remains a leading cause of mortality and disability globally, emphasizing the urgent need for innovative preventative and therapeutic strategies. Taurine, a critical amino sulfonic acid, has garnered attention for its neuroprotective effects, yet its precise role in ischemic stroke remains elusive. This study utilized a bidirectional Mendelian Randomization (MR) approach to explore the causal relationship between plasma taurine levels and ischemic stroke risk, employing genome-wide association study (GWAS) datasets. In parallel, a novel high-sensitivity liquid chromatography-tandem mass spectrometry (LC–MS/MS) method was developed to quantify plasma taurine levels in ischemic stroke patients and healthy controls. Our findings reveal a significant inverse association between taurine levels and stroke risk, with IVW analysis showing beta = -0.001 and $P = 0.0085$. Furthermore, LC–MS/MS analysis demonstrated that plasma taurine levels in patients with ischemic stroke were notably lower at 36.07 ± 5.37 μmol/L compared to controls at 108.66 ± 25.11 μmol/L, confirming taurine's potential as a protective factor. These results suggest taurine as a promising biomarker and therapeutic target for stroke prevention and recovery. This study not only highlights the importance of taurine in cerebrovascular health but also provides a foundation for personalized intervention strategies.

Keywords Ischemic stroke, Taurine, Mendelian randomization, LC–MS/MS, Neuroprotection

Introduction

Ischemic stroke is one of the leading causes of disability and mortality worldwide, imposing a significant burden on public health systems and patients' quality of life [1]. Although acute therapeutic interventions such as thrombolysis and mechanical thrombectomy have improved outcomes for some patients, long-term prevention and treatment strategies remain challenging [2]. Therefore, identifying novel biomarkers and developing effective interventions are essential to reducing the risk of stroke and improving patient management [3, 4].

Taurine, a vital amino sulfonic acid, plays multiple roles in maintaining cellular homeostasis, including regulating calcium metabolism, mitigating oxidative stress, and

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controlling osmotic balance [5, 6]. Its neuroprotective effects have attracted increasing interest, particularly for potential applications in cardiovascular and neurological disorders [7, 8]. Furthermore, a systematic review by Tzang et al. emphasizes the cardiovascular benefits of taurine across different demographic groups, providing substantial evidence of its efficacy from a global perspective [9]. However, the precise role of taurine in the onset and progression of ischemic stroke remains unclear, and further investigation into its levels and association with stroke risk is warranted.

Observational studies exploring the relationship between taurine levels and stroke risk are often limited by confounding variables and reverse causation [10]. To overcome these limitations, Mendelian randomization (MR), a genetic approach to causal inference, has emerged as a powerful tool [11]. MR utilizes genetic variants as instrumental variables(IVs), reducing the impact of confounding and mitigating reverse causality, thereby providing more reliable evidence for causal relationships between exposure and outcome [12].

To further elucidate the relationship between taurine levels and stroke, we developed a liquid chromatography-tandem mass spectrometry (LC–MS/MS) method for high-sensitivity and high-specificity quantification of plasma taurine [13]. Using this method, we analyzed plasma samples from 45 ischemic stroke patients and 45 healthy controls, comparing taurine concentrations between the two groups. This approach not only offers robust data on taurine metabolism but also lays the groundwork for exploring personalized interventions.

Given the importance of taurine in regulating metabolism and providing neuroprotection, clarifying its association with stroke risk holds significant academic and clinical value [14, 15]. If low taurine levels are confirmed as a risk factor for ischemic stroke, taurine supplementation through dietary interventions or pharmacological means could serve as a promising strategy for stroke prevention and treatment [9]. These findings will provide theoretical support for clinical applications and may drive the development of personalized medical approaches to reduce stroke incidence and improve patient outcomes.

Materials and methods

Mendelian randomization framework

This study applies a bidirectional MR framework to explore the causal relationship between taurine levels and ischemic stroke incidence. MR analysis serves to emulate a randomized control trial by using genetic variants as IVs, thereby minimizing biases from confounding factors and reverse causation. The process adheres to the three fundamental assumptions of classical MRanalysis [16]: (1) the IVs have a direct impact on the exposure; (2) the IVs are independent of any confounding factors; and (3) the IVs affect the risk of outcomes exclusively through their influence on the exposure, without involvement of alternative pathways. In this bidirectional approach, we analyze both directions: taurine levels affecting stroke and stroke influencing taurine levels. This ensures a comprehensive understanding of any causal effects between the two variables. The study was conducted in alignment with the principles outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [17] and the extended version specifically designed for MR studies, STROBE-MR to ensure comprehensive and transparent reporting of our methodology and findings [18]. Figure 1 illustrates the framework employed in our bidirectional Mendelian randomization analysis.

Data resources

We utilized data from the UK Biobank, one of the largest and most comprehensive biobanks worldwide, which was initiated in 2006 and includes extensive health data and biological samples from over 500,000 participants across the UK [19]. For this analysis, we also accessed datasets from the European Bioinformatics Institute (EBI) database, a leading repository for genomic and genetic research [20]. Specifically, we focused on datasets pertaining to Cerebral Infarction (CI) (ukb-d-I63) and Taurine levels (TL) (ebi-a-GCST90026035). The UK Biobank dataset, published in 2018, encompasses 10,889,323 genetic variants from participants of European ancestry [21], while the EBI dataset, published in 2021, contains 6,856,779 genetic variants, also from individuals of European descent [22].

In this study, we employed SNPs as IVs to conduct a two-sample MR analysis. To minimize potential bias from population stratification, we limited our selection to datasets exclusively involving European ancestry. All data were sourced from publicly available databases, and details of each dataset are provided in Table 1. As all datasets used in this study were ethically approved and made available for research purposes, no additional institutional ethical review was required.

Identification of genetic IVs

A systematic selection process was employed to identify appropriate IVs. SNPswere chosen based on strict criteria within the GWAS datasets, prioritizing those with genome-wide significance ($p < 5 \times 10^{-5}$) and independent associations ($R^2 < 0.001$, kb $= 10{,}000$), ensuring no linkage disequilibrium (LD) [23]. SNPs absent in the GWAS datasets or those with mirror-image alleles were also discarded. Additionally, all included SNPs had a minor allele frequency (MAF) of no less than 0.01,

Table 1 Overview of the dataset characteristics

Phenotype	Group ID	Database	Year	Number of SNPs	Population
CI	ukb-d-I63	UK Biobank	2018	10,889,323	European
TL	ebi-a-GCST90026035	EBI Database	2021	6,856,779	European

CI Cerebral Infarction, *TL* Taurine levels, *EBI* European Bioinformatics Institute

ensuring their reliability and absence of bias. To ensure consistency between exposure and outcome data, SNPs with palindromic structures and intermediate allele frequencies were excluded from the analysis. Additionally, SNPs linked to both the exposure and the outcome were identified and eliminated using the PhenoScanner database (www.phenoscanner.medschl.cam.ac.uk/), thereby reducing potential biases and maintaining the integrity of the analysis [13]. The relevance of the selected IVs to the exposure was further evaluated by calculating the *F*-statistic and variance explained (R^2) [24]. R^2 was determined using the formula $R^2 = \beta^2 \times (1 - \mathrm{EAF}) \times 2 \times \mathrm{EAF}$, where EAF represents the effect allele frequency. The F-statistic, calculated as $F = R^2 \times (N - K - 1)/[K \times (1 - R^2)]$, where N is the GWAS sample size for the exposure and K is the number of SNPs associated with the exposure, was used to ensure the strength of the instruments [25]. SNPs with F-statistics greater than 10 were considered robust IVs, minimizing the risk of weak instrument bias and ensuring the validity of the MR analysis [26].

Statistical methods for MR analysis

Our primary approach utilized inverse variance weighting (IVW) as the central method for MR analysis, combining SNP-specific Wald ratios through a meta-analytic framework [27]. To ensure the robustness and reliability of our results, we applied several complementary analytical techniques: 1. The MR-Egger regression, a method capable of detecting and adjusting for horizontal pleiotropy, despite its reduced statistical power [28]; 2. The simple mode, weighted median, and weighted mode approaches, which enhance the MR-Egger method by addressing specific limitations. Furthermore, we employed the maximum likelihood method to integrate data from multiple genetic variants into a unified causal inference. This approach not only improves the type 1 error rate in finite sample scenarios but also provides a complementary perspective to the MR-Egger regression, enhancing the robustness of causal estimates [29].

Sensitivity analysis

To ensure the robustness of the MR results, we implemented several sensitivity analyses [30]. MR-Egger regression allowed us to detect pleiotropy by testing whether the intercept deviated from zero, signaling if any SNPs influenced the outcome through non-target pathways [31]. MR-PRESSO further enhanced the analysis by identifying and correcting outliers, thereby reducing bias. We used Cochran's Q test to assess heterogeneity across the instrumental variables, guiding whether to apply a random-effects (IVW-RE) or fixed-effects (IVW-FE) model [32, 33]. Additionally, leave-one-out analysis ensured that no single SNP dominated the overall effect by recalculating estimates after sequentially excluding each SNP [34]. To complement these methods, we created funnel and scatter plots to visually inspect the presence of publication bias and the directionality of individual SNP effects [35]. This multi-layered approach provided comprehensive validation, ensuring the reliability of our findings on the causal relationship between taurine levels and ischemic stroke.

Statistical approach

All statistical analyses were conducted using R software (Version 4.2.1), employing the Two-Sample MR (0.5.6), MR-PRESSO (1.0), and mr.raps packages [36]. To align exposure and outcome datasets, the harmonize_data function from the Two-Sample MR package was utilized, ensuring data consistency and reliability. Two-sided *P*-values were computed, with $p < 0.05$ indicating statistical significance. Furthermore, to enhance transparency and reproducibility, all scripts and codes used for these analyses are publicly accessible.

LC–MS/MS

International standards

In the development and validation of our LC–MS/MS method, we followed the International Conference on Harmonisation (ICH) guidelines, specifically the ICH Q2(R1) guideline.

Relevant reagents (and chemical reagents)

Standards for Taurine (#T818825, 99% purity) were supplied by MACKLIN. Isotope-labeled internal standards, Taurine-d4 (#IR-15344, 100% purity) were acquired from ISOREAG. All chemicals were stored at a temperature range of 2–8 °C until use. Methanol and formic acid were

obtained from Thermo Fisher Scientific for subsequent analysis.

Chromatography and mass spectrometry conditions

Chromatographic separation was conducted using a high-performance liquid chromatography (HPLC) system with a ChromCore HILIC-Amide column (3 μm, 2.1 ×100 mm). The column temperature was set to 40 °C, and the flow rate was maintained at 0.4 mL/min. The mobile phases consisted of 0.1% formic acid in water (Phase A) and 0.1% formic acid in acetonitrile (Phase B). The gradient elution began with 90% B, decreased to 45% B over 1.5 min, returned to 90% B at 2.7 min, and was held constant until the end of the 3.5-min runtime.

Mass spectrometric analysis was carried out using Thermo Scientific™ *TSQ Altis*™. Detection was achieved through selected reaction monitoring (SRM). The electrospray ionization source operated in positive ion mode. Key operational parameters included a sheath gas flow rate of 45 arbitrary units, an ion spray voltage of 3500 V, and a scan gas flow rate of 5 arbitrary units. The ion transfer tube temperature was maintained at 350 °C, while the evaporator temperature was set to 450 °C. The auxiliary gas flow rate was adjusted to 15 arbitrary units. Both Q1 and Q3 quadruple were configured at a resolution of 0.7 full width at half maximum (FWHM).

The analysis was performed in multiple reaction monitoring (MRM) mode, targeting specific ion transitions. For taurine, the transitions monitored were m/z 124.1 → 80.1 and 107.1, while for its isotope-labeled counterpart taurine-d4, the transitions were m/z 128.1 → 80.1 and 107.1. The collision energies applied were 20 V and 13 V for taurine and taurine-d4.

Method verification

The method was validated following international standards, evaluating parameters such as linearity, specificity, precision, accuracy, stability, recovery, and matrix effects. Precision and accuracy were assessed both within-day and between-day by analyzing six replicates of quality control samples at three separate time points. Calibration curves demonstrated linearity across the entire concentration range, employing a $1/x^2$ weighting factor for curve fitting.

Sample pre-processing

We combined 150 μL of the internal standard solution (taurine-d4 internal standard solution prepared from methanol and acetonitrile in 1:2 ratio) with 50 μL of the clinical plasma sample. This mixture was thoroughly vortexed for approximately 1 min to ensure complete mixing. Following mixing, the samples were centrifuged at 14,000 rpm and 4 °C for 10 min. This step is crucial for precipitating the proteins and ensuring that the supernatant, which contains the analytes of interest, is free from protein interference. Post-centrifugation, 150 μL of the clear supernatant was carefully transferred into a clean sample vial to avoid any precipitated protein carry-over. This supernatant was then analyzed using LC–MS/MS.

Quantification of plasma taurine levels

Study population and sampling

Patients diagnosed with cerebral infarction were enrolled in this study, with plasma samples collected for the precise determination of taurine concentrations following a comprehensive explanation of the study protocol. To establish a baseline reference, plasma taurine levels were also measured in healthy volunteers. The study adhered to the ethical principles outlined in the 1964 Declaration of Helsinki and its subsequent revisions. All procedures were approved by the Ethics Committee of the Central Hospital of Shenyang Medical College under ethical approval number MR-21-23-023372. Informed consent was obtained from all participants prior to their inclusion in the study.

Preparation of plasma

Blood samples were collected into tubes containing ethylenediaminetetraacetic acid (EDTA) and gently mixed. Plasma was separated by centrifugation at 1500 ×g for 15 min at 4 °C. The resulting plasma was aliquoted and stored at −80 °C to preserve analyte integrity. To prevent degradation, repeated freeze–thaw cycles were meticulously avoided.

LC–MS/MS analysis and method verification

As above.

Statistical analyses

The taurine concentration data were analyzed statistically and presented as mean ± standard deviation (SD). Differences in taurine levels between cerebral infarction patients and healthy controls were assessed using suitable statistical methods, such as paired t-tests or ANOVA, with the significance level (α) predefined.

Results

The effect of taurine levels on cerebral infarction

Following a rigorous screening process, instrumental variables (IVs) for taurine levels were identified from the GWAS database. This process involved selecting 85 SNPs after removing palindromic variants and applying a MAF threshold greater than 0.01, utilizing the two-sample MR function in the R package. To further ensure the reliability of the IVs, SNPs associated with cerebral infarction risk factors were excluded using the PhenoScanner

Table 2 Various Mendelian randomisation methods assessed the relationship between TL and CI

NO.SNPs	IVW[a]		Simple mode[a]		Weighted median[a]		MR-Egger[a]		Weighted mode[a]	
	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*
TL-CI 84	−0.001	0.0085	−0.0005	0.808	−0.0015	0.096	−0.0033	0.026	−0.001	0.621
CI-TL 67	0.72	0.512	2.22	0.59	0.83	0.604	1.291	0.607	2.22	0.571

CI Cerebral Infarction, *TL* Taurine levels, *p* p-value, *IVW* Inverse Variance Weighting, *SE* Standard Error

[a] No MR-PRESSO outliers were exposed (NA)

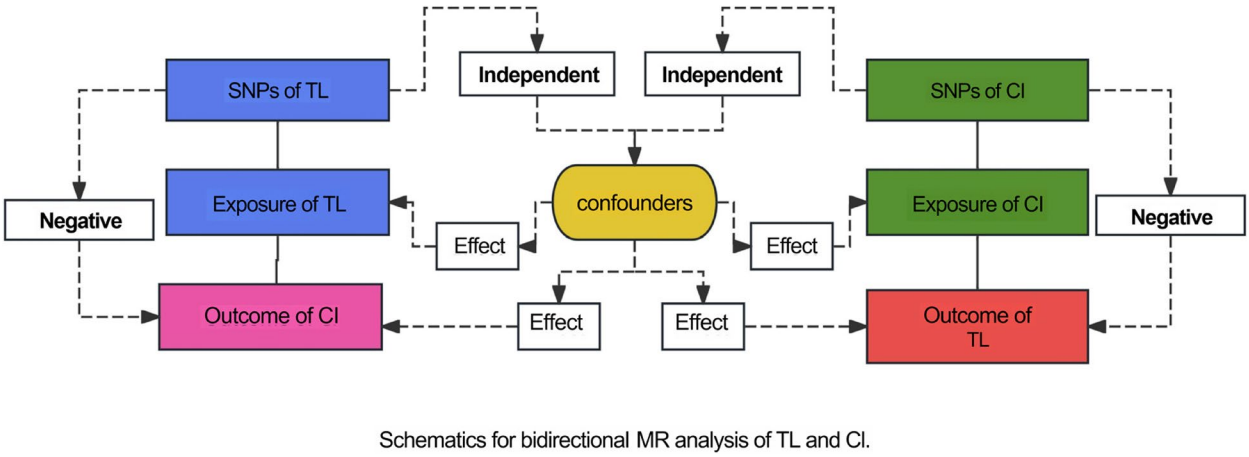

Fig. 1 Diagram illustrating the bidirectional MR analysis of taurine levels and cerebral infarction risk. All included SNPs satisfy the three core assumptions of Mendelian randomization. Single nucleotide polymorphisms (SNPs); Taurine levels (TL); Cerebral infarction (CI)

database. The final set of robust IVs, characterized by *F*-statistics exceeding 10, is detailed in the Results section. Additional information on the SNPs related to taurine levels is available in Table S1 of Additional File 1.

Our MR analysis utilized five distinct methodologies to investigate the causal relationship between taurine levels and cerebral infarction risk. The findings, as presented in Table 2 and Figs. 1, 2 and 3, revealed a significant inverse association, with higher taurine levels linked to a lower risk of cerebral infarction (IVW, beta = −0.001, $p = 0.0085$). The maximum likelihood approach further confirmed this relationship (beta = −0.001, $p = 0.0089$). These results underscore the potential protective effect of taurine against cerebral infarction.

Heterogeneity analysis using the MR-Egger and IVW methods showed no significant inconsistencies in the results ($p > 0.05$). Additionally, MR-Egger regression was utilized to evaluate the presence of horizontal pleiotropy in the data, and the results confirmed its absence ($p > 0.05$), as detailed in Table 3. The leave-one-out analysis, visualized in Additional file 2, Figure S1(A), demonstrated that no single SNP exhibited a disproportionate impact on the association between taurine levels and cerebral infarction. Additionally, funnel plot analysis Additional file 2, Figure S2(A) provided further evidence against the presence of horizontal pleiotropy. Moreover, the MR-PRESSO outlier and global tests confirmed that there were no detectable outliers or significant heterogeneity in the analysis.

These findings highlight the potential protective role of taurine against Cerebral infarction, providing a valuable basis for future research and preventative approaches aimed at improving cerebrovascular health.

The effect of cerebral infarction on taurine levels

IVs for cerebral infarction were meticulously selected from the GWAS database through a comprehensive screening process. Initially, 67 SNPs were identified after excluding palindromic variants and applying a MAF threshold of >0.01, using the two-sample MR function in the R package. To enhance the reliability of these IVs, SNPs linked to risk factors for cerebral infarction were filtered out via the PhenoScanner database. The final robust set of IVs, all with *F*-statistics greater than 10, is presented in the Results section. Detailed information on the SNPs associated with taurine levels can be found in Table S1 of Additional File 1.

To explore the causal relationship between cerebral infarction and taurine levels, our MR analysis employed five different methodologies. The results, detailed in

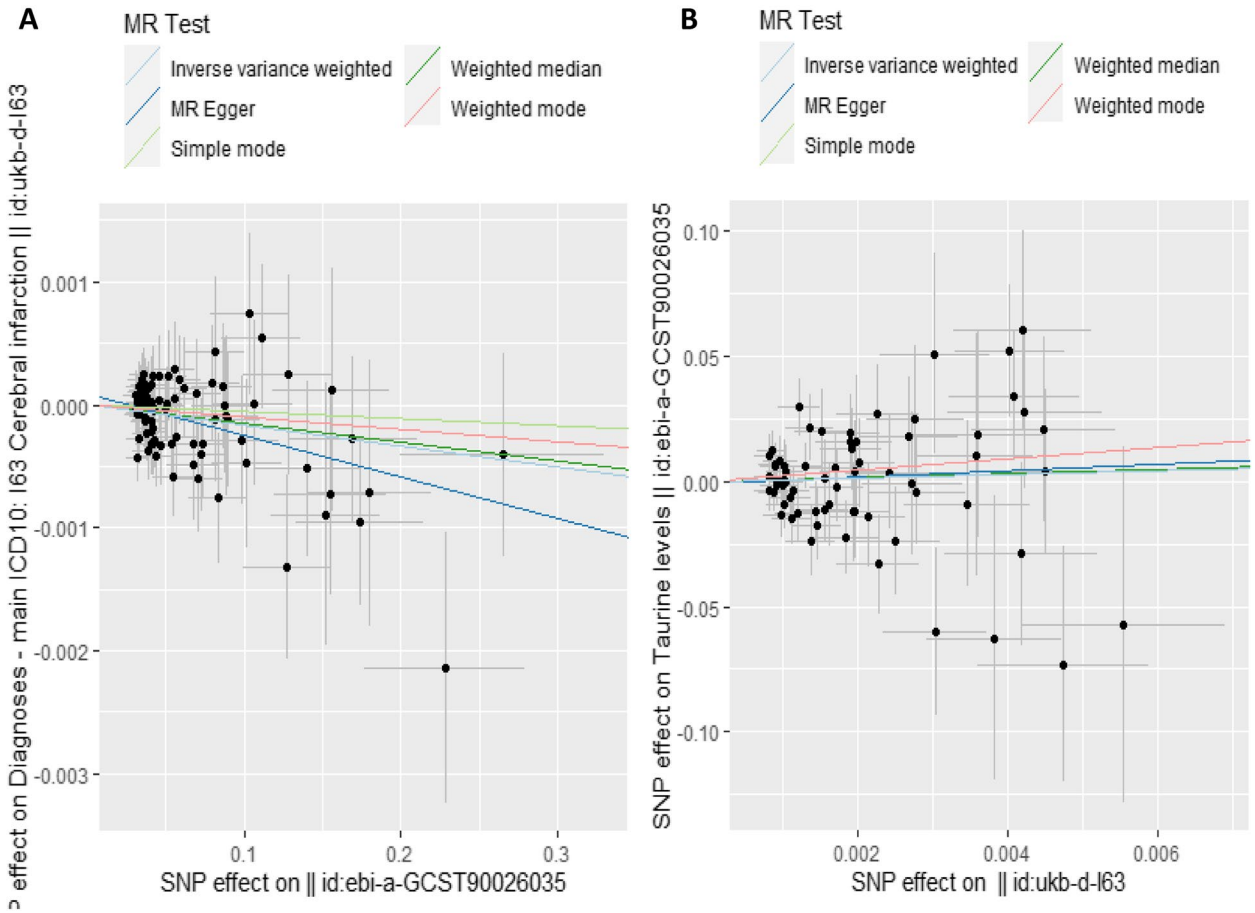

Fig. 2 Scatter plot illustrating the causal relationship between taurine levels and cerebral infarction in the initial Mendelian randomization analysis. **A** Taurine levels-Cerebral infarction; **B** Cerebral infarction-Taurine levels

Table 2 and Figs. 2–3. There was no significant causal relationship between cerebral infarction and taurine levels (IVW, $p = 0.512$).

Heterogeneity analyses performed using the MR-Egger and IVW methods showed no significant differences in the results ($p > 0.05$). Additionally, MR-Egger regression was utilized to examine the presence of horizontal pleiotropy, with results confirming its absence ($p > 0.05$), as presented in Table 3. The leave-one-out visualization technique further verified that no individual SNPs had a disproportionate effect on the association between taurine levels and cerebral infarction (Additional file 2, Figure S1B). Funnel plot analysis also supported the absence of horizontal pleiotropy (Additional file 2, Figure S2 B). Finally, the MR-PRESSO outlier and global tests confirmed that no outliers or significant heterogeneity were detected in the analysis.

These findings suggest that taurine attenuates the effects of cerebral infarction, while cerebral infarction does not have an effect on taurine levels. This provides new directions for future research, including exploring strategies to maintain or increase taurine levels and its therapeutic potential in the prevention of cerebral infarction.

LC–MS/MS

Specificity

As illustrated in Figure S3, the retention times of taurine and taurine-d4 under the specified conditions were 2.23 min and 2.23 min, respectively. These results demonstrate that endogenous components in blank plasma do not interfere with the measurement of taurine concentration.

Calibration curve and minimum quantifiable limit

A total of six concentration levels of QC working solutions, STD01 (8 μmol/L), STD02 (16 μmol/L), STD03 (40 μmol/L), STD04 (80 μmol/L), STD05 (200 μmol/L), and STD06 (400 μmol/L) were spiked into blank plasma for pretreatment. Taurine demonstrated excellent linearity within the concentration range of 8 to 400 μmol/L. The calibration curve equation was $y = 2.302 \times 10^{-2}x—1.754 \times 10^{-2}$ ($R^2 = 0.9997$), with a lower limit of quantification

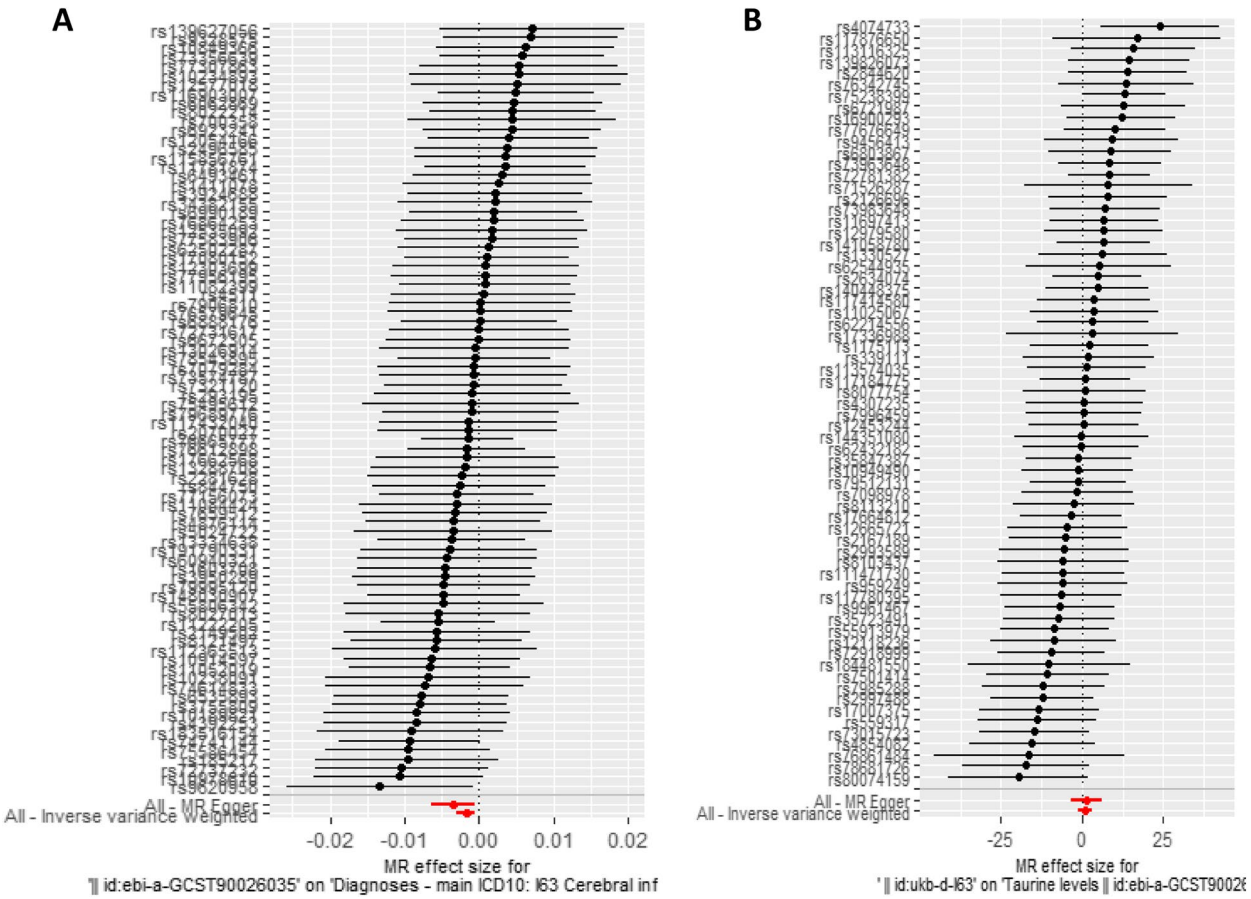

Fig. 3 Forest plot showing the individual SNP effects and the combined MR estimates for the causal influence of taurine levels and cerebral infarction. **A** Taurine levels and Cerebral infarction; **B** Cerebral infarction and Taurine levels; The black lines depict the 95% confidence intervals (CI) for each allele, with their lengths reflecting the range of the CI. The overall MR estimate is represented by a red line, extending across the entire 95% confidence interval

Table 3 Heterogeneity and horizontal pleiotropy check between TL and CI

Exposure outcome		Horizontal pleiotropy test (MR-Egger)			Heterogeneity test (IVW)		Heterogeneity test (MR-Egger)	
		Intercept	SE	*P*	*Q*	*p*	*Q*	*p*
TL	CI	9.005e-5	7.24e-05	0.21	50.88	0.997	49.34	0.998
CI	TL	−0.0008	0.003	0.802	65.5	0.46	65.44	0.46

CI Cerebral Infarction, *TL* Taurine levels, *p p*-value, *IVW* Inverse Variance Weighting, *SE* Standard Error, Cochran, *Q* s Q test

(LLOQ) of 8 μmol/L. These findings confirm the strong linear relationship for taurine concentrations between 8 and 400.0 μmol/L.

Accuracy and precision

The quality control samples of taurine at low, medium, and high concentrations exhibited intra- and inter-day standard deviations (SD) within 10%. Detailed data are provided in Table S3.

Stability

The QC working solutions at three concentration levels, QCL, QCM and QCH, were spiked into blank plasma and pretreated separately to investigate their stability when placed at room temperature for 4 h as well as in the sampler for 24 h. The results showed that the plasma samples containing taurine were stable for 4 h at room temperature and 24 h in the autosampler. The results showed that the plasma samples containing taurine were

stable for 4 h at room temperature with accuracies ranging from 97.92% to 98.49%, and were stable after 24 h in the autosampler with accuracies ranging from 96.47% to 99.13% (Table S4).

Matrix effect

QC working solutions at three concentration levels, QCL, QCM and QCH, were spiked to six different sources of blank plasma and water, pretreated, and the matrix effect was evaluated by calculating the internal standard-corrected matrix factor. The internal standard-corrected matrix factors for different spiked concentrations of taurine in plasma and plasma-free matrices were in the range of 1.02–1.13 with RSD ≤6.59. The above results indicated that all matrix effects of taurine were small and would not affect the analysis of the assay results (Table S5).

Extraction recovery

Plasma and plasma supernatant samples were configured with QC working solutions at three concentration levels, QCL, QCM and QCH, pretreated, and the extraction recoveries of each analyte and its internal standard were determined. The results showed that the recoveries of taurine ranged from 91.47% to 93.60% (Table S6).

Plasma taurine concentration

This study focused on examining plasma taurine levels across different groups, including healthy individuals and patients with cerebral infarction. The average plasma taurine concentration was 108.66 ± 25.11 μmol/L in healthy individuals, compared to 36.07 ± 5.37 μmol/L in cerebral infarction patients. Notably, taurine levels were significantly lower in the plasma of cerebral infarction patients than in healthy individuals. These findings suggest a reduction in taurine levels in the plasma of individuals with cerebral infarction. This observation aligns with the results of our Mendelian randomization analysis, which indicated that lower taurine concentrations are more likely to contribute to the occurrence of cerebral infarction, highlighting taurine as a potential causal factor.

Discussion

In this study, we employed bidirectional MR analysis in combination with high-sensitivity LC–MS/MS detection to systematically explore the causal relationship between plasma taurine levels and the risk of ischemic stroke. By utilizing genetic variants from large-scale GWAS databases as IVs, MR analysis effectively mitigates biases commonly found in observational studies, such as confounding factors and reverse causality [37, 38]. Moreover, the bidirectional MR design further strengthens the robustness of the causal inference by examining the relationship in both directions [39]. Sensitivity analyses likewise showed that the results of this study were reliable.

Our results demonstrate a significant inverse association between higher taurine levels and reduced stroke risk, independent of metabolic changes following the occurrence of stroke. This suggests that maintaining adequate taurine levels not only prevents ischaemic stroke, but also plays a beneficial role in potential therapeutic strategies. Furthermore, it suggests that reduced taurine levels may be a causative factor rather than a consequence of cerebral infarction. This study deepens our understanding of taurine as a potential metabolic regulator and provides new perspectives for the future development of preventive and therapeutic approaches to ischaemic stroke, reinforcing the value of taurine as a potential therapeutic target.

Taurine has gained significant attention in the field of neurological disorders, particularly for its potential role in ischemic stroke prevention and therapy [5, 40]. Studies suggest that taurine supplementation may provide neuroprotection by stabilizing cell membranes, regulating neurotransmitter balance, and controlling neuronal excitability [41]. Its role is especially prominent in neurodegenerative diseases such as Parkinson's and Alzheimer's, where it has been associated with reduced inflammation and slower cognitive decline [42, 43]. In ischemic stroke models, such as the middle cerebral artery occlusion (MCAO) model, taurine supplementation has been shown to reduce infarct size, enhance brain tissue recovery, and improve motor function following ischemic events [44, 45]. This neuroprotective effect is likely due to its ability to mitigate oxidative stress and support vascular health, which correlates with reduced stroke incidence [46, 47]. Epidemiological studies also indicate that higher plasma taurine levels are linked to a lower risk of cardiovascular and cerebrovascular events, supporting the hypothesis that taurine plays a preventive role [48, 49]. Despite these promising findings from observational studies and animal experiments, further randomized controlled trials (RCTs) are required to establish taurine's efficacy in humans conclusively. Research in countries such as Japan and South Korea has already integrated taurine into functional foods and supplements, targeting cognitive function and stress relief while enhancing cardiovascular health [50]. However, in Western countries, taurine's role in cerebrovascular disease prevention remains an emerging area of investigation, with ongoing clinical studies aimed at validating these initial findings [51, 52].

According to previous observational studies, taurine levels are associated with cardiovascular and neurological health. However, these studies are often subject to

confounding factors and reverse causality, which undermine the reliability of their conclusions. To overcome these limitations, this study applied bidirectional MR analysis, utilizing genetic instrumental variables to minimize the influence of confounders and ensure the robustness of causal inference [53]. Additionally, LC–MS/MS quantification was employed to precisely measure plasma taurine levels, further validating the relationship between taurine and the risk of ischemic stroke.

Current research on taurine and ischaemic brain infarction is gradually revealing its potential in neuroprotection and disease intervention. Taurine is an endogenous amino acid that is widely distributed in mammalian tissues, especially in the brain, heart and white blood cells [54, 55].

Taurine plays a significant role in promoting neuroplasticity and axonal growth, contributing to both acute neuroprotection and long-term recovery following ischemic stroke [56, 57]. Its protective effects extend beyond reducing acute damage by supporting neuroplasticity during the recovery phase, enhancing axonal sprouting in both the ipsilateral and contralateral cortices [58]. This axonal remodeling is closely tied to taurine's ability to improve mitochondrial energy metabolism [59, 60]. By upregulating the expression of mitochondrial biogenesis markers such as PGC-1α and TFAM, taurine promotes mitochondrial function, ensuring energy supply and neuronal health, which are essential for axonal regeneration and neuronal survival [61, 62]. Neuroplasticity and axonal sprouting are critical for motor function recovery in stroke patients [63, 64]. Studies in animal models demonstrate that taurine-treated groups exhibit superior motor function recovery, corresponding to an increase in axonal growth compared to control groups [65, 66]. These findings indicate that taurine enhances the brain's self-repair mechanisms, making it a promising therapeutic agent for speeding up neurological recovery after stroke. Its role in post-stroke rehabilitation highlights its dual value as a neuroprotective supplement and a strategy to efficiently restore function. This aligns with our results, further confirming taurine's therapeutic potential in cerebral infarction.

Taurine also contributes to ischemic stroke recovery by supporting mitochondrial function. Mitochondrial dysfunction following stroke often leads to energy metabolism disturbances and neuronal death [67]. Taurine mitigates these effects by restoring mitochondrial function, ensuring that neurons maintain energy balance and reduce the risk of apoptosis induced by ischemia–reperfusion injury [68]. Specifically, taurine increases the mitochondrial DNA copy number and enhances the expression of key mitochondrial biogenesis proteins, both of which are essential for mitochondrial health and energy production [69, 70]. The mitochondrial support extends beyond energy regulation, as taurine also plays a role in promoting the survival and functionality of newly generated neurons [71]. Research shows that taurine's mitochondrial protection enhances neuronal survival and helps restore motor and cognitive functions after ischemic injury. By improving mitochondrial efficiency, taurine supports recovery from ischemic strokes, proving its potential as a therapeutic agent for post-stroke rehabilitation.

Ischemic stroke is often accompanied by severe oxidative stress and inflammatory responses, which exacerbate brain injury [72]. Taurine plays a critical role in reducing oxidative stress, as it can neutralize free radicals and limit lipid peroxidation, thereby protecting neurons from further damage [73]. In addition, taurine has been shown to suppress the release of pro-inflammatory cytokines and inhibit the activation of the NF-κB signaling pathway, which is a key regulator of inflammation [74]. This helps mitigate the inflammatory response that follows ischemic injury. By minimizing post-stroke inflammation, taurine not only alleviates acute brain damage but also promotes functional recovery in the later stages [75]. This dual mechanism—targeting both oxidative stress and inflammation—positions taurine as a promising neuroprotective agent for reducing secondary damage after stroke. Its ability to intervene in these critical processes offers potential for use in therapeutic strategies aimed at improving recovery outcomes in stroke patients.

Taurine also exerts neuroprotective effects by maintaining membrane stability and regulating calcium homeostasis [76]. By stabilizing cell membranes, taurine helps prevent ionic imbalance across the membrane, which is critical for reducing neuronal damage during ischemic stroke [77]. Ischemic injury often leads to an influx of sodium and calcium ions, triggering excitotoxicity and resulting in neuronal death [78]. As an osmotic regulator, taurine ensures cells maintain appropriate ion concentrations, minimizing cellular swelling and reducing apoptosis [79]. This membrane-stabilizing function is particularly essential during ischemia–reperfusion injury, where neurons are at heightened risk of damage due to both ion imbalance and the increased production of reactive oxygen species (ROS) [80]. Taurine helps mitigate these effects by stabilizing membrane integrity and limiting oxidative stress, thereby preventing further injury. In addition to alleviating acute damage, taurine's ability to maintain membrane stability supports long-term tissue repair and functional recovery [81]. Taurine's dual role in reducing acute injury and promoting recovery makes it a strong candidate for therapeutic stroke interventions. It alleviates neurological damage during acute cerebral infarction and enhances tissue repair and functional recovery. These

effects substantiate taurine's use in stroke management and suggest its future role in personalized treatment strategies. Our study confirms the causal link between high plasma taurine levels and a reduced risk of cerebral infarction, highlighting taurine's potential in prevention and treatment and guiding future clinical research.

Our study has several notable strengths. First, we used bidirectional MR analysis to investigate the causal relationship between taurine levels and ischemic stroke risk, ensuring that the findings are not affected by confounding factors or reverse causation, strengthening the causal inference. Second, we leveraged the latest and most comprehensive GWAS datasets to select IVs, ensuring that there was no overlap between the exposure and outcome data, which enhances the reliability and generalizability of our results. Additionally, we applied multiple MR methods and sensitivity analyses, such as MR-Egger and IVW approaches, to verify the robustness and consistency of our findings. In our study, significant findings were obtained using both the IVW and MR-Egger methods, indicating statistically meaningful results. However, the robustness of our conclusions remains strong, as IVW and MR-Egger are recognized as reliable and widely used methods in MR analyses, particularly when the instrumental variables meet MR assumptions [82]. Although small beta values may indicate limited effect sizes, they still carry clinical significance. As emphasized in statistical literature, including "Principles of Biostatistics," small yet statistically significant effects are meaningful and reflect real associations rather than random variation [83]. In the context of our findings, even subtle changes in taurine levels could have important implications for stroke prevention and treatment, suggesting that these small modulations might play a valuable role in clinical settings. A key highlight of this study is the development and application of a novel taurine quantification method using LC–MS/MS technology, which enabled us to precisely measure taurine levels in clinical blood samples. This combination of clinical sample analysis with high-precision mass spectrometry not only ensures the reliability of the exposure measurements but also bridges the gap between genetic findings and real-world clinical relevance. Lastly, by integrating genetic and clinical data, our study goes beyond theoretical causal inference, offering insights with practical implications for both prevention and treatment strategies for ischemic stroke. These features collectively enhance the robustness, reproducibility, and translational potential of our findings, paving the way for future targeted interventions and clinical applications.

Despite the strengths of our study, several limitations must be acknowledged. First, although multiple strategies, including sensitivity analyses, were employed to detect and minimize pleiotropy, it is not possible to entirely exclude its potential influence. MR-Egger regression and other tests revealed limited evidence of horizontal pleiotropy, but residual pleiotropic effects could still affect the precision of our causal estimates. Second, the majority of participants included in the GWAS datasets used in our analysis were of European ancestry, potentially limiting the generalizability of our results to other populations. To overcome this limitation, future research should aim to incorporate multi-ethnic GWAS datasets, enabling more comprehensive insights and broader applicability across diverse groups. In addition, although we have performed mass spectrometry in the Chinese population, we still need to further expand the sample size. Third, the effect sizes (beta values) identified in our findings were relatively small, though statistically significant. These modest effect sizes should be interpreted with caution, and further investigation is necessary to determine their practical implications for clinical settings. Additionally, MR analyses rely heavily on genetic instruments. This approach may encounter challenges when suitable genetic variants are lacking or when sample sizes are limited. MR assumes consistent effects of genetic instruments on exposure, yet genetic heterogeneity could introduce bias, complicating the interpretation of results. Given the promising results of taurine's neuroprotective effects, future research should focus on expanding the sample diversity to include multi-ethnic cohorts, which would help in verifying and possibly enhancing the generalizability of our conclusions. Furthermore, optimizing the dosage of taurine for different population groups through clinical trials is essential to tailor therapeutic interventions effectively. Conducting randomized controlled trials will be crucial to ascertain the clinical efficacy and safety of taurine supplementation in stroke prevention and treatment. By addressing these aspects, we aim to refine the understanding of taurine's role in neuroprotection and encourage robust, inclusive research efforts in this promising area. Mechanistic research, such as functional genomics and metabolomic studies, would also provide deeper insights into the biological pathways linking taurine levels and ischemic stroke, supporting the development of more targeted therapeutic interventions.

Conclusion

Our study establishes the causal protective effect of taurine in reducing ischemic stroke risk, validated through bidirectional MR analysis. By seamlessly integrating genetic data with advanced LC–MS/MS quantification, we bridged the divide between genomic insights and practical clinical applications. Our findings offer novel perspectives for personalized stroke prevention and therapeutic strategies, while laying a solid groundwork for future clinical interventions and research endeavors aimed at enhancing patient outcomes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12263-025-00769-6.

Additional file 1.

Additional file 2.

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Authors' contributions
This study was conceptualized and designed by Tianyi Wang and Xuyang Huang. Sample collection was carried out by Xuyang Huang, while Tianyi Wang contributed to data organization. Xinyue Zhang and Na Li were responsible for conducting the experiments. Data analysis and interpretation were performed by Kaizhi Lu. The manuscript was drafted by Tianyi Wang, Xuyang Huang, and Xinyue Zhang.Yong Zeng supervised the project and provided critical revisions to enhance its intellectual depth. All authors reviewed and approved the final manuscript, taking accountability for every aspect of the work. Tianyi Wang and Xuyang Huang share co-first authorship.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The data used in the MR analyses are publicly available at the summary level, negating the requirement for additional ethical approval. Ethical clearance and informed consent for each included study were documented in their respective original publications. All studies were conducted in accordance with the principles of the Declaration of Helsinki. For the plasma detection experiment, this study adhered to the ethical principles outlined in the 1964 Declaration of Helsinki and its subsequent revisions. All research procedures were approved by the Ethics Committee of the Central Hospital of Shenyang Medical College, with the ethical approval number MR-21-23-023372. Informed consent was obtained from all participants prior to the commencement of the study.

Competing interests
The authors declare no competing interests.

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