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Article

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Posted Date: November 26th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11268347/v1

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Additional Declarations: No competing interests reported.

Internal Jugular Vein Stenosis Mediates Cognitive Impairment Through Cerebrospinal Fluid Circulation Disorder: A Cross-Sectional Mediation Analysis Study

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Abstract

Previous studies have confirmed a significant correlation between extrinsic compression-induced internal jugular vein (IJV) stenosis and cognitive impairment; however, the underlying neurostructural mechanisms remain unclear. Cerebrospinal fluid (CSF) circulation disorder may be a key link connecting impaired venous outflow to structural brain changes. This study investigated whether CSF circulation disorder mediates the relationship between IJV stenosis and cognitive impairment. A total of 92 patients with atlas transverse process compression-induced IJV stenosis was enrolled. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), and standardized ventricular volume was measured as a structural proxy for CSF circulation disorder. Mediation analysis was performed using structural equation modeling with 5,000 Bootstrap resamples, adjusting for age, sex, and years of education. IJV stenosis degree was negatively correlated with MoCA score ($r = -0.242$, $p = 0.020$) and positively correlated with ventricular volume ($r = 0.274$, $p = 0.008$). After controlling for covariates, IJV stenosis remained an independent predictor of MoCA score ($\beta = -0.351$, $p < 0.001$), with its effect attenuated by 26% after adding ventricular volume. The indirect effect was significant ($\beta = -0.090$, 95% CI: [-0.182, -0.026]), accounting for 25.6% of the total effect. These findings suggest that CSF circulation disorder partially mediates the relationship between IJV stenosis and cognitive decline, providing new evidence for the CSF dynamic mechanisms of venous-origin cognitive impairment.

Keywords: internal jugular vein stenosis; cognitive impairment; cerebrospinal fluid circulation disorder; ventricular enlargement; mediation analysis

Introduction

The internal jugular vein (IJV) serves as the primary conduit for cerebral venous drainage, playing a critical role in cerebral metabolic waste clearance, intracranial pressure regulation, and CSF reabsorption[1]. When the IJV is narrowed by extrinsic compression from the atlas transverse process, venous outflow resistance increases significantly, cerebral venous drainage function is impaired, and metabolic waste may accumulate in the brain[2,3]. Recent studies have gradually revealed a potential association between cerebral venous system dysfunction and cognitive decline. Animal experiments have shown that jugular vein ligation mouse models exhibit significant learning and memory impairment[4,5]. Clinical studies have found that patients with Alzheimer's disease and mild cognitive impairment have significantly smaller cross-sectional areas of the cerebral venous drainage system compared to cognitively normal individuals[6]. Additionally, jugular venous reflux

and venous hypertension caused by heart failure are also significantly associated with cognitive deficits[7,8]. Primiani et al. reported a case of cognitive decline caused by jugular vein stenosis that was relieved after surgical decompression[9], further suggesting a potential role of venous factors in cognitive impairment.

Our previous study (Peng et al., 2026) systematically confirmed at the clinical level a significant correlation between atlas transverse process compression-induced IJV stenosis and cognitive impairment, and preliminarily observed cognitive improvement after surgical decompression[10]. However, the mechanism by which IJV stenosis leads to cognitive decline remains unclear.

Cognitive decline is closely related to impaired clearance of cerebral metabolic waste, such as amyloid-beta, and current research indicates that CSF circulation plays an important role in cerebral metabolic waste clearance[11]. Under physiological conditions, CSF is secreted by the choroid plexus, flows through the ventricular system, and returns to the venous sinuses via arachnoid granulations or meningeal lymphatics, maintaining a dynamic balance between production and absorption[12-14]. When IJV stenosis elevates venous sinus pressure, the pressure gradient across the exchange interface decreases, CSF reabsorption is impeded, intraventricular CSF accumulation increases, and passive ventricular dilation may occur[15,16]. Animal experiments have also confirmed that jugular vein ligation can significantly increase ventricular volume, accompanied by alterations in CSF circulation dynamics5. In clinical diagnosis, changes in the morphology and size of the ventricle are often used as important indicators for assessing intracranial pathology. Therefore, standardized ventricular volume (absolute ventricular volume / total intracranial volume × 100%) can serve as a structural proxy for CSF circulation disorder—its enlargement reflects passive accumulation following impaired CSF reabsorption due to elevated venous pressure, representing an imaging manifestation of CSF circulation dynamics disturbance. Previous studies have confirmed that ventricular enlargement is significantly associated with cognitive decline[17], and in patients with idiopathic intracranial hypertension (IIH) and venous outflow disorders, ventricular dilation is also an important imaging marker of disease severity[13,18,19].

Based on the above, we propose the research hypothesis that IJV stenosis, by elevating venous pressure and causing CSF circulation disorder (with the ventricular enlargement as the structural manifestation of CSF circulation disorder), subsequently drives cognitive impairment. To test this hypothesis, this study employed a cross-sectional mediation analysis, using standardized ventricular volume as an operational indicator of CSF circulation disorder, to systematically examine its mediating effect between IJV stenosis and cognitive function, aiming to provide new evidence for the CSF dynamic mechanisms of "venous-origin cognitive impairment."

Methods

Study Design and Participants

This cross-sectional study consecutively enrolled patients presenting to the Department of Neurosurgery at Beijing Shijitan Hospital, Capital Medical University, between September 2025 and March 2026. Inclusion criteria were: (1) age 18–75 years; (2) CT venography (CTV)-confirmed atlas transverse process compression-induced IJV stenosis; (3) no history of cerebral infarction, Alzheimer's disease, or other neurological disorders known to cause cognitive decline. Exclusion criteria were: (1) other venous outflow abnormalities such as venous sinus stenosis, venous sinus thrombosis, or arteriovenous malformations; (2) severe heart failure, hepatic or renal insufficiency, or terminal illnesses such as malignant tumors; (3) severe hearing or visual impairment or inability

to cooperate with neuropsychological assessment. A total of 92 patients were ultimately enrolled. All patients provided written informed consent. The study protocol was approved by the Ethics Committee of Beijing Shijitan Hospital, Capital Medical University (Approval No. IIT2025-021-003). All experiments were performed in accordance with relevant guidelines and regulations, and informed consent was obtained from all participants.

Imaging Assessment

Calculation of Internal Jugular Vein Stenosis Degree

All patients underwent CTV examination. Following the method of our previous study[10], the cross-sectional areas of bilateral IJV stenosis were measured on axial images using Fiji software (ImageJ). The IJV stenosis degree (IJVS degree) was calculated using the following formula:

$$\text{IJVS degree} = 1 - \frac{S1 + S2}{\text{S3} + S4 + S5 + S6}$$

S1 is the residual area at the right-sided narrowest segment;
S2 is the residual area at the left-sided narrowest segment;
S3 is the normal area above the right-sided stenosis;
S4 is the normal area below the right-sided stenosis;
S5 is the normal area above the left-sided stenosis;
S6 is the normal area below the left-sided stenosis.

Structural Indicator of CSF Circulation Disorder—Standardized ventricular volume Measurement

All patients underwent cranial MRI examination. T1-weighted three-dimensional magnetization-prepared rapid acquisition gradient-echo (MPRAGE) images were acquired on a 3.0 Tesla scanner (MAGNETOM Skyra, Siemens Healthineers, Erlangen, Germany). Automated segmentation of the ventricles and total intracranial volume was performed using FreeSurfer software (version 7.2)[20]. The standardized ventricular volume was calculated as:

$$\text{Standardized ventricular volume} = \frac{\text{absolute ventricular volume}}{\text{total intracranial volume}}$$

Ventricular enlargement was used here as a structural proxy for CSF circulation disorder. All segmentation results were reviewed and confirmed by a neuroradiologist.

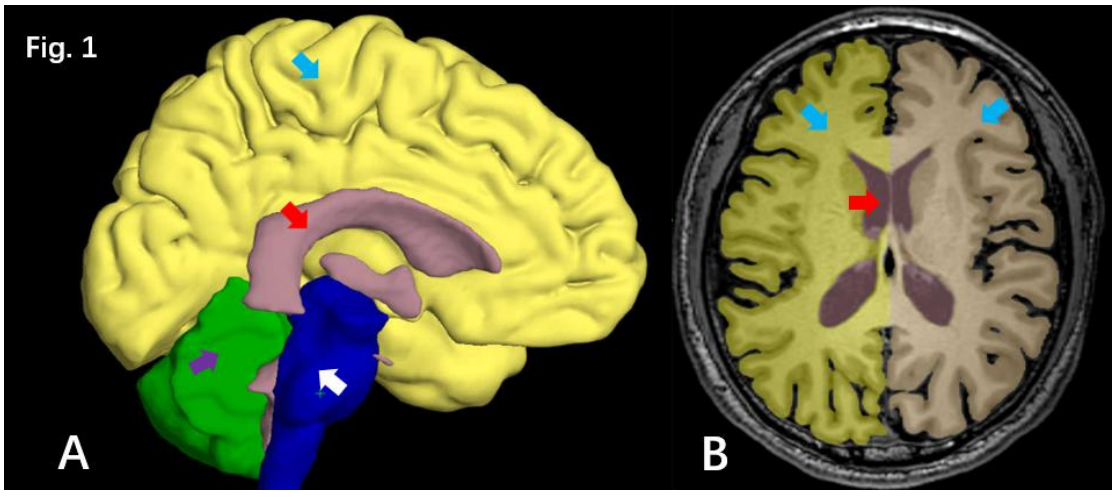

Figure 1 Automated segmentation of the ventricles and intracranial structures based on MRI. (A)

Red arrow indicates the ventricles; blue arrow indicates the telencephalon; purple arrow indicates the cerebellum; white arrow indicates the brainstem. (B) Red arrow indicates the lateral ventricles; blue arrow indicates the telencephalon. All segmentations were performed using FreeSurfer software (version 7.2) and were used to calculate the standardized ventricular volume (absolute ventricular volume / total intracranial volume). Segmentation of the telencephalon, cerebellum, brainstem, and total intracranial volume was used to determine the denominator for standardization, while segmentation of the lateral ventricles was used to calculate the absolute ventricular volume.

Cognitive Function Assessment

Cognitive function was assessed in all patients using the Beijing version of the Montreal Cognitive Assessment (MoCA). Assessments were conducted by trained neurologists in a quiet environment, and assessors were blinded to imaging data.

Statistical Analysis

Statistical analyses were performed using SPSS 27.0 and R 4.4.2 software (lavaan package). Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range, IQR). Hierarchical multiple linear regression was used to examine the independent predictors of MoCA score, with variables entered in sequential blocks: demographic covariates were entered first, followed by IJV stenosis degree, then standardized ventricular volume, and finally the interaction term between years of education and IJV stenosis degree. To reduce multicollinearity between the interaction term and main effect terms, the relevant variables were centered before constructing the interaction term. Variance inflation factor (VIF) was reported in all regression models, with VIF < 5 considered acceptable. Mediation analysis was conducted using structural equation modeling, with standardized ventricular volume as the mediator and MoCA score as the outcome, adjusting for demographic covariates. The Bootstrap method (5,000 resamples) was used to estimate the 95% confidence interval (CI) of the indirect effect; an interval excluding 0 was considered indicative of a significant mediation effect. All tests were two-sided, with a significance level set at $\alpha = 0.05$.

Results

Baseline Characteristics

A total of 92 patients (34 males, 58 females) were enrolled, with a mean age of 54.17 ± 12.56 years and a median education of 12.00 years (IQR: 9.00–16.00). The mean MoCA score for the entire cohort was 22.76 ± 2.86, below the normal reference value (26). The IJV stenosis degree was 0.36 ± 0.21, and the median standardized ventricular volume was 0.017 (IQR: 0.014–0.024) (Table 1).

Table 1 Baseline characteristics of patients

Variable	All patients (n=92)
Age, mean (SD)	54.17 (12.56)
Gender (Male/Female)	92 (34/58)
Education, median (IQR)	12.00 (9.00-16.00)
MoCA, mean (SD)	22.76 (2.86)
IJVS degree, mean (SD)	0.36 (0.21)
Ventricle, median (IQR)	0.017 (0.014-0.024)

Note: Education, years of education; MoCA, Montreal Cognitive Assessment; IJVS degree, internal

jugular vein stenosis degree; Ventricle, standardized ventricular volume.

Correlation Analysis of Core Variables

Spearman correlation analysis was performed for age, sex, years of education, MoCA score, IJV stenosis degree, and standardized ventricular volume (Table 2), and scatter plots were generated (Figure 2).

For demographic variables, years of education was significantly positively correlated with MoCA score ($r = 0.59$, $p < 0.01$), and age was significantly negatively correlated with MoCA score ($r = -0.58$, $p < 0.01$) and significantly positively correlated with standardized ventricular volume ($r = 0.48$, $p < 0.01$).

For the correlation between IJV stenosis degree and ventricular volume and cognitive function: IJV stenosis degree was significantly negatively correlated with MoCA score ($r = -0.24$, $p < 0.05$) and significantly positively correlated with standardized ventricular volume ($r = 0.27$, $p < 0.05$). Standardized ventricular volume was significantly negatively correlated with MoCA score ($r = -0.56$, $p < 0.01$). These correlations provided preliminary supporting evidence for subsequent mediation analysis.

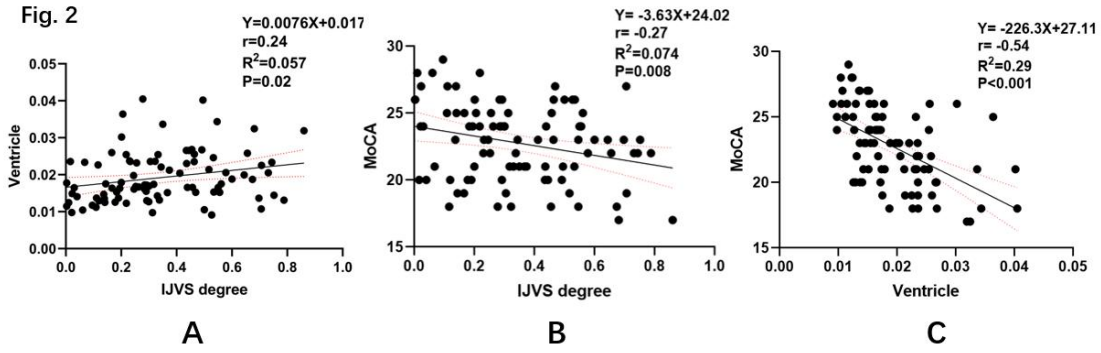

Figure 2 Scatter plots showing correlations between IJV stenosis degree, ventricular volume, and MoCA score in the total cohort (n = 92). (A) Correlation between IJV stenosis degree and ventricular volume (r = 0.24, p = 0.02). (B) Correlation between IJV stenosis degree and MoCA score (r = -0.27, p = 0.008). (C) Correlation between ventricular volume and MoCA score (r = -0.54, p < 0.001). Solid lines represent linear regression fits; red dashed lines represent 95% confidence intervals. IJVS degree, internal jugular vein stenosis degree; Ventricle, standardized ventricular volume; MoCA, Montreal Cognitive Assessment.

Table 2 Correlation analysis of core variables

Variable	Age	Gender	Education	MoCA	IJVS	Ventricle
Age	1.00					
Gender	-0.16	1.00				
Education	-0.64**	0.24*	1.00			
MoCA	-0.58**	0.11	0.59**	1.00		
IJVS degree	-0.20	0.34**	-0.04	-0.24*	1.00	
Ventricle	0.48**	0.03	-0.36**	-0.56**	0.27*	1.00

*Note: *p < 0.05, **p < 0.01. Values are Spearman correlation coefficients (n = 92). Education, years of education; Ventricle, standardized ventricular volume; IJVS degree, internal jugular vein stenosis degree. MoCA, Montreal Cognitive Assessment.*

Patients were divided into a lower stenosis group (n = 46) and a higher stenosis group (n = 46) based on the median IJV stenosis degree (Table 3), and box plots were generated (Figure 3). The two groups were balanced and comparable in age, sex, and years of education (all $p > 0.05$). Compared with the lower stenosis group, the higher stenosis group had significantly lower MoCA scores (22.04 ± 2.64 vs. 23.48 ± 2.92, $p = 0.015$) and significantly larger standardized ventricular volume (0.021 ± 0.0069 vs. 0.018 ± 0.0065, $p = 0.047$).

Table 3 Comparison between lower and higher stenosis groups

Variable	Lower Stenosis Groups	Higher Stenosis Groups	T/Z	P
Cases	46	46		
Age, mean (SD)	56.52 (11.20)	51.83 (13.51)	1.82	0.073
Gender (Male/Female)	18/28	15/31	0.42	0.51
education, median (IQR)	12.00 (12.00-16.00)	12.00 (11.25-16.00)	0.16	0.87
IJVS degree, mean (SD)	0.17 (0.11)	0.52 (0.14)	-13.7	<0.0001
Ventricle, mean (SD)	0.018 (0.0065)	0.021 (0.0069)	-2.01	0.047
MoCA, mean (SD)	23.48 (2.92)	22.04 (2.64)	2.46	0.015

Note: Patients were divided into lower and higher stenosis groups based on the median IJVS degree. Between-group comparisons were performed using independent samples t-test, Mann-Whitney U test, or chi-square test, as appropriate. IJVS degree, internal jugular vein stenosis degree; Ventricle, standardized ventricular volume; Education, years of education; MoCA, Montreal Cognitive Assessment.

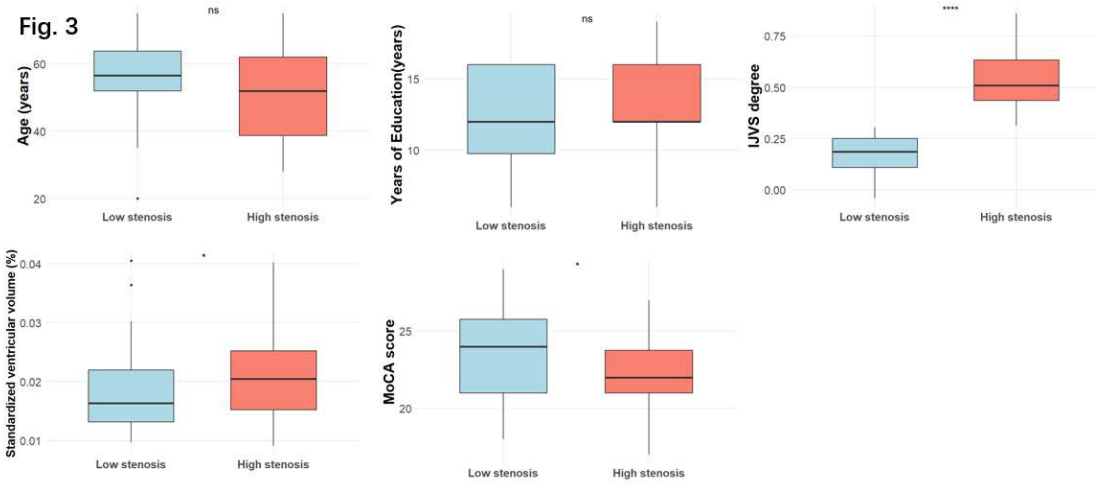

Figure 3 Boxplots comparing variables between the lower and higher stenosis groups. The lower stenosis group (n = 46) and higher stenosis group (n = 46) were balanced and comparable in age, sex, and years of education (all $p > 0.05$). Compared with the lower stenosis group, the higher stenosis group had significantly higher IJVS degree ($p < 0.001$), significantly lower MoCA score ($p < 0.05$), and significantly larger standardized ventricular volume ($p < 0.05$). The horizontal line

*within each box represents the median; the top and bottom edges represent the interquartile range; whiskers extend to the most extreme values within 1.5 times the interquartile range; dots represent outliers. ns, not significant; *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. IJVS, internal jugular vein stenosis; MoCA, Montreal Cognitive Assessment.*

Hierarchical Regression Analysis of IJV Stenosis and Ventricular Volume on Cognitive Function

With MoCA score as the dependent variable, hierarchical linear regression analysis was performed, as shown in Table 4.

Block 1 included age, sex, and years of education, with model $R^2 = 0.423$ ($p < 0.001$), in which age ($\beta = -0.293$, $p = 0.006$) and years of education ($\beta = 0.439$, $p < 0.001$) were significant predictors, while sex had no significant predictive effect ($p = 0.425$).

Block 2 further included IJV stenosis degree, with model R^2 increasing to 0.524, $\Delta R^2 = 0.102$ ($p < 0.001$), and IJV stenosis degree showing a significant independent negative predictive effect on MoCA score ($\beta = -0.351$, $p < 0.001$).

Block 3 further included standardized ventricular volume, with model R^2 increasing to 0.572, $\Delta R^2 = 0.047$ ($p = 0.003$). In the final model, age ($\beta = -0.269$, $p = 0.012$), years of education ($\beta = 0.343$, $p < 0.001$), IJV stenosis degree ($\beta = -0.260$, $p = 0.002$), and standardized ventricular volume ($\beta = -0.261$, $p = 0.003$) were all independent predictors of MoCA score, while sex remained non-significant ($p = 0.542$).

Block 4 further included the centered interaction term between years of education and IJV stenosis degree, with model R^2 increasing to 0.574, $\Delta R^2 = 0.002$ ($p = 0.557$), and the interaction term coefficient did not reach statistical significance ($\beta = -0.041$, $p = 0.557$). This result indicates that years of education had no significant moderating effect on the relationship between IJV stenosis and cognitive function. All predictors had VIF < 2.3, indicating no multicollinearity.

Notably, after adding ventricular volume, the standardized regression coefficient of IJV stenosis degree decreased from -0.351 to -0.260 (attenuation of approximately 26%), suggesting that ventricular enlargement may partially mediate the detrimental effect of IJV stenosis on cognitive function.

Table 4 Hierarchical linear regression analysis of MoCA scores

Variable	Block 1 (β)	Block 2 (β)	Block 3 (β)	Block 4 (β)	VIF
Age	-0.293**	-0.410***	-0.269*	-0.268*	2.220
Gender	-0.067	0.052	0.048	0.047	1.279
Education	0.439***	0.328**	0.343**	0.341**	2.037
IJVS degree	—	-0.351*	-0.260**	-0.259**	1.476
Ventricle	—	—	-0.261**	-0.261**	1.717
Education _ c × IJVS degree _ c	—	—	—	-0.041	1.353
R^2	0.423***	0.524***	0.572***	0.574***	—
ΔR^2	—	0.102***	0.047**	0.002	—

*Note: *p < 0.05, **p < 0.01, ***p < 0.001. Values are standardized regression coefficients (β). Education_c and IJVS degree_c are centered variables of years of education and IJVS degree, respectively. IJVS degree, internal jugular vein stenosis degree; Ventricle, standardized ventricular volume; Education, years of education; MoCA, Montreal Cognitive Assessment. VIF, variance inflation factor; ΔR^2 represents the increment in R^2 relative to the previous model.*

Mediation Analysis of Ventricular Enlargement

Structural equation modeling was used to examine the mediating effect of standardized ventricular volume between IJV stenosis and cognitive function, adjusting for age, sex, and years of education. The Bootstrap method with 5,000 resamples was used to estimate the 95% confidence interval of the indirect effect (Table 5, Figure 4).

The path coefficient from IJV stenosis degree to standardized ventricular volume was statistically significant (path a: $\beta = 0.346$, $p < 0.001$), and the path coefficient from standardized ventricular volume to MoCA score was also statistically significant (path b: $\beta = -0.261$, $p = 0.006$).

After controlling for standardized ventricular volume, the direct effect of IJV stenosis degree on MoCA score remained statistically significant (path c': $\beta = -0.259$, $p = 0.004$). The Bootstrap 95% confidence interval for the indirect effect (IJV stenosis degree → standardized ventricular volume → MoCA score) was [-0.182, -0.026], excluding 0, indicating a significant mediation effect with an effect size of -0.090. The total effect was -0.351 (95% CI: [-0.504, -0.186], $p < 0.001$). The mediation effect accounted for 25.6% of the total effect.

Fig. 4

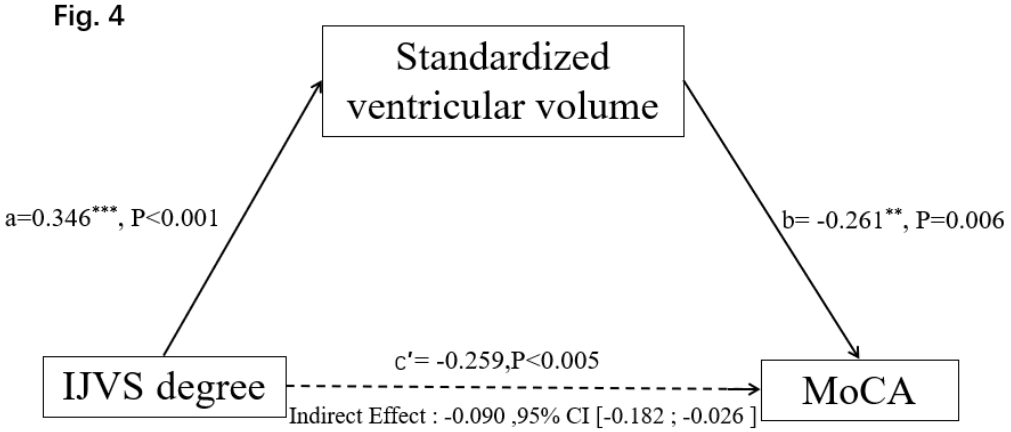

*Figure 4 Mediation model showing the role of standardized ventricular volume between IJV stenosis degree and cognitive function. Standardized coefficients are shown. Path a represents the effect of IJV stenosis degree on standardized ventricular volume (β = 0.346, p < 0.001); path b represents the effect of standardized ventricular volume on MoCA score (β = -0.261, p = 0.006); path c' represents the direct effect of IJV stenosis degree on MoCA score after controlling for standardized ventricular volume (β = -0.259, p = 0.004). The indirect effect via ventricular enlargement was significant (β = -0.090, 95% CI: [-0.182, -0.026]), accounting for 25.6% of the total effect. *p < 0.05, **p < 0.01, ***p < 0.001. IJV, internal jugular vein; MoCA, Montreal Cognitive Assessment; CI, confidence interval.*

Table 5 Mediation analysis of ventricular volume between IJV stenosis and MoCA score

Effect Type	Path	Estimate	Std. Err	Z	Bootstrap 95% CI	P	Std. Coefficient (β)
Path a	IJVS degree → Ventricle	0.011	0.003	4.088	[0.006, 0.016]	<0.001	0.346

Effect Type	Path	Estimate	Std. Err	Z	Bootstrap 95% CI	P	Std. Coefficient (β)
Path b	Ventricle → MoCA	-109.2	39.529	-2.764	[-196.1,- 40.48]	0.006	-0.261
Direct effect (c′)	IJVS degree→ MoCA	-3.437	1.186	-2.897	[-5.641, -1.021]	0.004	-0.259
Indirect effect	IJVS degree → Ventricle → MoCA	-1.192	0.532	-2.245	[-2.389,-0.348]	0.025	-0.090
Total effect	IJVS degree → MoCA (direct + indirect)	-4.631	1.061	-4.365	[-6.675,-2.445]	<0.001	-0.351

Note: Bootstrap resampling was performed 5,000 times. The model was adjusted for age, sex, and years of education. IJVS degree, internal jugular vein stenosis degree; Ventricle, standardized ventricular volume; MoCA, Montreal Cognitive Assessment. CI, confidence interval; Std., standardized. CFI, comparative fit index; RMSEA, root mean square error of approximation. Model fit indices: CFI = 1.000, RMSEA = 0.000 (saturated model).

Discussion

This study used standardized ventricular volume as a structural proxy for CSF circulation disorder to systematically investigate the mediating pathway by which compressive internal jugular vein (IJV) stenosis leads to cognitive impairment through CSF circulation disorder. The main findings were as follows: (1) IJV stenosis degree was significantly negatively correlated with MoCA score and significantly positively correlated with standardized ventricular volume (an indicator of CSF circulation disorder); (2) hierarchical regression showed that, after controlling for age, sex, and years of education, IJV stenosis degree was an independent negative predictor of MoCA score ($\beta = -0.351$, $p < 0.001$), and its effect was attenuated by approximately 26% after adding ventricular volume; (3) standardized ventricular volume played a significant partial mediating role between IJV stenosis and cognitive function (indirect effect $\beta = -0.090$, 95% CI: [-0.182, -0.026]), with the mediation effect accounting for 25.6% of the total effect. These findings reveal for the first time at the clinical level the intermediate pathway through which IJV stenosis drives cognitive impairment via CSF circulation disorder, providing new direct evidence for the CSF dynamic mechanisms of "venous-origin cognitive impairment."

The association between IJV stenosis and cognitive function was robust in this expanded cohort. Building on an expanded sample size, this study reconfirmed the robust association between IJV stenosis and cognitive impairment. Correlation analysis showed that IJV stenosis degree was significantly negatively correlated with MoCA score ($r = -0.242$, $p = 0.020$), and hierarchical regression analysis further confirmed that it remained an independent predictor of MoCA score after controlling for age, sex, and years of education ($\beta = -0.351$, $p < 0.001$). This result is highly consistent with our team's previous exploratory findings based on 47 samples—in the previous study, the partial correlation coefficient between IJV stenosis degree and MoCA score was -0.66 ($p <$

0.001), and the MoCA total score of the higher stenosis group was significantly lower than that of the lower stenosis group[10] After expanding the sample size to 92 in this study, although the correlation coefficient was somewhat attenuated (r = -0.24), the independent predictive effect of stenosis degree on cognition remained highly statistically significant, confirming the cross-sample robustness of this association. The calculation method and grouping criteria for stenosis degree were consistent between the two studies, providing a stable phenomenological basis for subsequent mechanistic exploration.

CSF circulation disorder played a significant partial mediating role between IJV stenosis and cognitive function. The core finding of this study is that CSF circulation disorder (manifested structurally as ventricular enlargement) plays a significant partial mediating role between IJV stenosis and cognitive function. In hierarchical regression, after adding ventricular volume, the standardized coefficient of IJV stenosis decreased from -0.351 to -0.260 (attenuation of approximately 26%); mediation analysis further quantified this effect, with an indirect effect of β = -0.090 (95% CI: [-0.182, -0.026]), accounting for 25.6% of the total effect. Two independent analytical pathways mutually corroborate each other, jointly supporting that CSF circulation disorder plays a partial mediating role between stenosis and cognition.

The three key path coefficients of this study provide direct evidence for the impact of IJV stenosis on CSF dynamics. First, the positive predictive effect of IJV stenosis on ventricular volume (path a: $\beta = 0.346$, $p < 0.001$) indicates that greater stenosis severity is associated with more pronounced ventricular dilation. This result quantitatively confirms the first link in the chain of "elevated venous pressure → impaired CSF absorption → passive ventricular dilation" hypothesized in the background15—if stenosis merely increased venous resistance without affecting CSF dynamics, path a should not be significant. Moreover, this mechanism has been fully supported in studies of IIH and venous sinus stenosis[12,18,21]. Lenck et al.'s 2026 study published in Nature Neuroscience clearly demonstrated that venous outflow obstruction can lead to fluid accumulation in the brain parenchyma by affecting dural lymphatic function and CSF dynamics[22]. Zhou et al. also found that intracranial hypertension induced by IJV stenosis can be resolved by stent placement, suggesting a clear causal relationship between venous pressure and CSF circulation[23]. Second, the negative predictive effect of ventricular volume on MoCA score (path b: $\beta = -0.261$, $p = 0.006$) validated the structure-function association between ventricular enlargement and cognitive impairment, consistent with previous findings on ventricular volume and dementia conversion risk17. On the one hand, within the limited intracranial volume, an enlarged ventricle directly compresses surrounding white matter and nerve fiber tracts, leading to neurological dysfunction[24,25]. On the other hand, an increasing number of studies have indicated a clear correlation between ventricular enlargement and cognitive decline. A study published in Nature Human Behaviour reported that enlarged inferior lateral ventricular volume can predict AD risk[26], and Gong Q's team, by observing ventricular volume in AD patients in relation to cognitive function, cortical amyloid-beta changes, and glymphatic clearance efficiency, demonstrated a clear correlation between ventricular enlargement and cognitive decline[27]. Third, the significant indirect effect confirmed by the Bootstrap method further integrated the above two associations into a complete pathway of "stenosis → ventricular enlargement → cognitive decline," elevating the hypothesis from theoretical deduction to quantifiable statistical evidence.

Sex, education, and age showed distinct relationships with the mediation pathway. The mediation model in this study adjusted for age, sex, and years of education, but the complex relationships among these three factors, IJV stenosis degree, and cognition warrant further discussion.

Regarding years of education, the correlation coefficient between Education and MoCA score was $r = 0.604$ ($p < 0.001$), making it the strongest cognitive protective factor in this study. To examine whether education moderated the detrimental effect of IJV stenosis on cognition, we included a centered interaction term between years of education and IJV stenosis degree in the hierarchical regression. The results showed that the interaction term coefficient did not reach statistical significance ($\beta = -0.041$, $p = 0.557$), and the model R^2 did not show significant improvement ($\Delta R^2 = 0.002$, $p = 0.557$). This result indicates that the protective effect of years of education on cognition is independent of the severity of IJV stenosis—education may exert its protective effect through an independent cognitive reserve mechanism[28,29], rather than by attenuating the detrimental effect of stenosis itself. This finding has clinical implications: regardless of educational level, the risk of cognitive impairment in patients with IJV stenosis requires equal attention.

Regarding age, Age was highly correlated with Ventricle ($r = 0.48$) and MoCA ($r = -0.58$), but not significantly correlated with IJV stenosis degree ($r = -0.20$, $p > 0.05$). Elderly individuals inherently exhibit ventricular enlargement and cognitive decline due to aging[30,31], and IJV stenosis may produce a superimposed effect on top of natural aging, thereby accelerating cognitive decline[32].

Regarding sex, male patients in this cohort had significantly higher IJV stenosis degree than females ($r = 0.34$, $p < 0.01$), but sex was not directly associated with MoCA score ($r = 0.11$, $p > 0.05$), and sex consistently showed no significant predictive effect in hierarchical regression. This suggests that sex may indirectly affect cognition through IJV stenosis degree—that is, males may have more severe CSF circulation disorder due to thicker atlas transverse process bone and greater bony compression[33].

The mechanisms by which IJV stenosis leads to cognitive impairment can be integrated into a hierarchical framework**.** Integrating the findings of this study with previous literature, the mechanisms by which IJV stenosis leads to cognitive impairment can be organized into a hierarchical framework in which hemodynamic disturbance is the initiating factor. IJV stenosis increases venous outflow resistance, leading to elevated cerebral venous and venous sinus pressure[23]. Recent studies generally support that the primary route of CSF absorption is through dural lymphatic vessels rather than arachnoid granulations[16,22]. Therefore, elevated venous pressure may affect CSF dynamics primarily by impairing dural lymphatic function, producing two downstream consequences.

First, impaired CSF reabsorption leads to intraventricular CSF accumulation and passive dilation. This pathway is supported by the significant mediation effect observed in this study, which accounted for 25.6% of the total effect of IJV stenosis on cognition. Second, impaired interstitial fluid drainage leads to decreased clearance of metabolic waste, including β-amyloid[34]. This pathway was not directly measured in this study but may contribute to the remaining 74.4% of the direct effect of IJV stenosis on cognition, and warrants investigation in future studies.

CSF circulation disorder may subsequently impair cognitive function through several mechanisms: periventricular white matter fiber stretching due to ventricular enlargement[35]; compression of

adjacent structures such as the thalamus and hippocampus[36]; and impaired clearance of metabolic waste[27]. Persistent venous hypertension may also compromise blood-brain barrier integrity and promote neuroinflammation[4]. These pathways may ultimately converge to produce cognitive decline, although direct evidence for these mechanisms in the context of IJV stenosis is currently lacking and requires further investigation.

This study has the following limitations. First, the cross-sectional design cannot establish causality, and the statistical inference of mediation analysis needs to be further verified with longitudinal data. Although mediation analysis provides mechanistic evidence at the methodological level, the ultimate establishment of causality still requires prospective cohort studies or interventional studies. Second, the sample size is relatively limited (N = 92). Although it meets the basic statistical requirements for mediation analysis, statistical power is insufficient for covariate stratification analysis and subgroup analysis. In particular, for potential effect modifiers such as age and sex, adequate stratified testing cannot be performed. Third, this study did not include a healthy control group, limiting the specificity assessment of the results. Including a healthy control group would help clarify whether the effects of IJV stenosis on ventricles and cognition are independent of normal aging processes. Fourth, this study did not directly measure hemodynamic parameters (such as venous pressure, cerebral blood flow, etc.), limiting the quantitative assessment of the hemodynamic impact of IJV stenosis. Future studies should combine phase-contrast MRI or invasive pressure measurement to establish a complete evidence chain of stenosis degree–hemodynamics–brain structure–cognitive function.

This study used standardized ventricular volume as a structural proxy for CSF circulation disorder and found that CSF circulation disorder plays a significant partial mediating role between internal jugular vein stenosis and cognitive decline, with approximately one-quarter of the cognitive impairment effect explainable through the pathway of ventricular enlargement. These findings suggest that internal jugular vein stenosis may contribute to cognitive impairment by affecting CSF circulation dynamics, providing preliminary evidence for the CSF dynamic mechanisms of "venous-origin cognitive impairment." The non-mediated effect may be related to dural lymphatic dysfunction and blood-brain barrier disruption. Future studies incorporating longitudinal follow-up and direct measurements of hemodynamic and lymphatic function are warranted to further validate and extend this mechanistic pathway.

Data Availability

The participant-level clinical and imaging datasets generated and analysed during the current study are not publicly available due to patient-privacy-related ethical restrictions. De-identified datasets supporting the conclusions of this study are available from the corresponding author on reasonable request. Data requests should specify the research purpose and will be subject to review by the institutional ethics committee of Beijing Shijitan Hospital.

References

1 Zivadinov, R. & Chung, C. P. Potential involvement of the extracranial venous system in central nervous system disorders and aging. *BMC Med* **11**, 260, doi:10.1186/1741-7015-11-260 (2013).

2 Almegren, M. O. Cerebral venous thrombosis: A comprehensive narrative review. *Brain Circ*

11, 178-186, doi:10.4103/bc.bc_158_24 (2025).

3 Kotani, J. *et al.* Effects of bilateral jugular vein ligation on intracranial pressure and cerebrospinal fluid outflow resistance in cats. *Br J Oral Maxillofac Surg* **30**, 171-173, doi:10.1016/0266-4356(92)90151-8 (1992).

4 Fulop, G. A. *et al.* Cerebral venous congestion promotes blood-brain barrier disruption and neuroinflammation, impairing cognitive function in mice. *GeroScience* **41**, 575-589, doi:10.1007/s11357-019-00110-1 (2019).

5 Wei, H. *et al.* Cerebral venous congestion alters brain metabolite profiles, impairing cognitive function. *J Cereb Blood Flow Metab* **43**, 1857-1872, doi:10.1177/0271678x231182244 (2023).

6 Pardo, K. *et al.* Alzheimer's disease patients have smaller venous drainage system compared to cognitively healthy controls. *Alzheimers Dement* **21**, e14551, doi:10.1002/alz.14551 (2025).

7 Beggs, C. *et al.* Jugular venous reflux and brain parenchyma volumes in elderly patients with mild cognitive impairment and Alzheimer's disease. *BMC Neurol* **13**, 157, doi:10.1186/1471-2377-13-157 (2013).

8 Kong, S., Gootee, E., Williams, N., Gottesman, R. F. & Johansen, M. C. Congestive heart failure and its associations with cognition and cerebral blood flow. *Brain Circ* **11**, 30-38, doi:10.4103/bc.bc_86_24 (2025).

9 Primiani, C. T., Lawton, M., Hillis, A. E. & Hui, F. K. Pearls & Oy-sters: Cerebral Venous Congestion Associated With Cognitive Decline Treated by Jugular Release. *Neurology* **99**, 577-580, doi:10.1212/wnl.0000000000201037 (2022).

10 Peng, X. *et al.* Surgical treatment for cognitive impairment caused by internal jugular vein stenosis: a clinical study of atlas transverse process resection. *Front Neurol* **17**, 1776658, doi:10.3389/fneur.2026.1776658 (2026).

11 Sakka, L., Coll, G. & Chazal, J. Anatomy and physiology of cerebrospinal fluid. *Eur Ann Otorhinolaryngol Head Neck Dis* **128**, 309-316, doi:10.1016/j.anorl.2011.03.002 (2011).

12 Bothwell, S. W., Janigro, D. & Patabendige, A. Cerebrospinal fluid dynamics and intracranial pressure elevation in neurological diseases. *Fluids Barriers CNS* **16**, 9, doi:10.1186/s12987-019-0129-6 (2019).

13 Eide, P. K., Quesada, C. L. V. & Ringstad, G. Cerebrospinal Fluid-Mediated Brain Clearance: Insights from Human Studies. *Annu Rev Physiol* **88**, 297-320, doi:10.1146/annurev-physiol-043024-120520 (2026).

14 Lenck, S. *et al.* Idiopathic intracranial hypertension: The veno glymphatic connections. *Neurology* **91**, 515-522, doi:10.1212/wnl.0000000000006166 (2018).

15 Yamada, S. & Mase, M. Cerebrospinal Fluid Production and Absorption and Ventricular Enlargement Mechanisms in Hydrocephalus. *Neurologia medico-chirurgica* **63**, 141-151, doi:10.2176/jns-nmc.2022-0331 (2023).

16 Adigun, O. O. & Al-Dhahir, M. A. in *StatPearls* (StatPearls Publishing
Copyright © 2026, StatPearls Publishing LLC., 2026).

17 Carmichael, O. T. *et al.* Cerebral ventricular changes associated with transitions between normal cognitive function, mild cognitive impairment, and dementia. *Alzheimer Dis Assoc Disord* **21**, 14-24, doi:10.1097/WAD.0b013e318032d2b1 (2007).

18 Liu, Y. *et al.* Pathogenesis and management of idiopathic intracranial hypertension: A narrative review. *Brain Circ* **12**, 246-256, doi:10.4103/bc.bc_13_25 (2026).

19 Alperin, N. *et al.* Evidence for altered spinal canal compliance and cerebral venous drainage in

untreated idiopathic intracranial hypertension. *Acta Neurochir Suppl* **114**, 201-205, doi:10.1007/978-3-7091-0956-4_39 (2012).

20 Lewis, C. J. *et al.* A Case for Automated Segmentation of MRI Data in Neurodegenerative Diseases: Type II GM1 Gangliosidosis. *NeuroSci* **6**, doi:10.3390/neurosci6020031 (2025).

21 Capel, C. *et al.* Cerebrospinal Fluid and Cerebral Blood Flows in Idiopathic Intracranial Hypertension. *Acta Neurochir Suppl* **126**, 237-241, doi:10.1007/978-3-319-65798-1_48 (2018).

22 El Kamouh, M. R. *et al.* Cerebral venous blood flow regulates intracerebral pressure and brain clearance via meningeal lymphatic vessels. *Nat Neurosci* **29**, 2190-2203, doi:10.1038/s41593-026-02358-1 (2026).

23 Zhou, D. *et al.* Intracranial hypertension induced by internal jugular vein stenosis can be resolved by stenting. *Eur J Neurol* **25**, 365-e313, doi:10.1111/ene.13512 (2018).

24 Ribeiro, M., Yordanova, Y. N., Noblet, V., Herbet, G. & Ricard, D. White matter tracts and executive functions: a review of causal and correlation evidence. *Brain* **147**, 352-371, doi:10.1093/brain/awad308 (2024).

25 Nestor, S. M. *et al.* Ventricular enlargement as a possible measure of Alzheimer's disease progression validated using the Alzheimer's disease neuroimaging initiative database. *Brain* **131**, 2443-2454, doi:10.1093/brain/awn146 (2008).

26 Ge, Y. J. *et al.* Genetic architectures of cerebral ventricles and their overlap with neuropsychiatric traits. *Nature human behaviour* **8**, 164-180, doi:10.1038/s41562-023-01722-6 (2024).

27 Yin, H. *et al.* Choroid plexus remodeling linked to impaired CSF-mediated clearance and Alzheimer's disease progression. *Alzheimers Dement* **22**, e71606, doi:10.1002/alz.71606 (2026).

28 Li, H. *et al.* Impacts of education level on Montreal Cognitive Assessment and saccades in community residents from Western China. *Clin Neurophysiol* **161**, 27-39, doi:10.1016/j.clinph.2024.02.017 (2024).

29 Li, F. *et al.* The moderating effect of cognitive reserve on cognitive function in patients with Acute Ischemic Stroke. *Front Aging Neurosci* **14**, 1011510, doi:10.3389/fnagi.2022.1011510 (2022).

30 Brain growth charts, discovery gap - the week in infographics. *Nature*, doi:10.1038/d41586-022-01038-x (2022).

31 Jin, S. *et al.* The mechanisms, hallmarks, and therapies for brain aging and age-related dementia. *Sci Bull (Beijing)* **69**, 3756-3776, doi:10.1016/j.scib.2024.09.005 (2024).

32 Stamenkovic, S. *et al.* Impaired capillary-venous drainage contributes to gliosis and demyelination in mouse white matter during aging. *Nat Neurosci* **28**, 1868-1882, doi:10.1038/s41593-025-02023-z (2025).

33 Asukai, M. *et al.* Sex-Related Differences in the Developmental Morphology of the Atlas: A Computed Tomography Study. *Spine* **43**, 699-704, doi:10.1097/brs.0000000000002388 (2018).

34 Ding, J., Zhao, C., Hao, X. & Jiao, H. Glymphatic and meningeal lymphatic dysfunction in Alzheimer's disease: Mechanisms and therapeutic perspectives. *Alzheimers Dement* **21**, e70709, doi:10.1002/alz.70709 (2025).

35 Guillamón-Vivancos, T., Aníbal-Martínez, M., Puche-Aroca, L., Martini, F. J. & López-Bendito, G. Sensory modality-specific wiring of thalamocortical circuits. *Nature reviews. Neuroscience* **26**, 623-641, doi:10.1038/s41583-025-00945-y (2025).

36 Williams, V. J. *et al.* Postshunt lateral ventricular volume, white matter integrity, and intellectual

outcomes in spina bifida and hydrocephalus. *J Neurosurg Pediatr* **15**, 410-419, doi:10.3171/2014.10.Peds13644 (2015).

Author Contributions

X.P. and J.X. contributed equally to this work. X.P. performed the investigation and wrote the original draft, and contributed to writing – review & editing. J.X. contributed to conceptualization, investigation, methodology. S.L. and ZY contributed to data curation and supervision. G.Z. contributed to supervision and writing – review & editing. Y.D. contributed to supervision and writing – review. X.J. contributed to resources and writing – review & editing. Z.H. contributed to funding acquisition, resources, supervision, and writing – review & editing. All authors reviewed and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (NSFC) (Grant No. 82171858 to ZH) and the Beijing Hospitals Authority Clinical Medicine Development of Special Funding Support (Grant No. ZLRK202512 to ZH). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Additional Information

Competing interests

The author(s) declare no competing interests.

Figure Legends

Figure 1 Automated segmentation of the ventricles and intracranial structures based on MRI. (A) Red arrow indicates the ventricles; blue arrow indicates the telencephalon; purple arrow indicates the cerebellum; white arrow indicates the brainstem. (B) Red arrow indicates the lateral ventricles; blue arrow indicates the telencephalon. All segmentations were performed using FreeSurfer software (version 7.2) and were used to calculate the standardized ventricular volume (absolute ventricular volume / total intracranial volume). Segmentation of the telencephalon, cerebellum, brainstem, and total intracranial volume was used to determine the denominator for standardization, while segmentation of the lateral ventricles was used to calculate the absolute ventricular volume.

Figure 2 Scatter plots showing correlations between IJV stenosis degree, ventricular volume, and MoCA score in the total cohort (n = 92). (A) Correlation between IJV stenosis degree and ventricular volume ($r = 0.24$, $p = 0.02$). (B) Correlation between IJV stenosis degree and MoCA score ($r = -0.27$, $p = 0.008$). (C) Correlation between ventricular volume and MoCA score ($r = -0.54$, $p < 0.001$). Solid lines represent linear regression fits; red dashed lines represent 95% confidence intervals.

IJVS degree, internal jugular vein stenosis degree; Ventricle, standardized ventricular volume; MoCA, Montreal Cognitive Assessment.

Figure 3 Boxplots comparing variables between the lower and higher stenosis groups. The lower stenosis group (n = 46) and higher stenosis group (n = 46) were balanced and comparable in age, sex, and years of education (all $p > 0.05$). Compared with the lower stenosis group, the higher stenosis group had significantly higher IJVS degree ($p < 0.001$), significantly lower MoCA score ($p < 0.05$), and significantly larger standardized ventricular volume ($p < 0.05$). The horizontal line within each box represents the median; the top and bottom edges represent the interquartile range; whiskers extend to the most extreme values within 1.5 times the interquartile range; dots represent outliers. ns, not significant; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. IJVS, internal jugular vein stenosis; MoCA, Montreal Cognitive Assessment.

Figure 4 Mediation model showing the role of standardized ventricular volume between IJV stenosis degree and cognitive function. Standardized coefficients are shown. Path a represents the effect of IJV stenosis degree on standardized ventricular volume ($\beta = 0.346$, $p < 0.001$); path b represents the effect of standardized ventricular volume on MoCA score ($\beta = -0.261$, $p = 0.006$); path c' represents the direct effect of IJV stenosis degree on MoCA score after controlling for standardized ventricular volume ($\beta = -0.259$, $p = 0.004$). The indirect effect via ventricular enlargement was significant ($\beta = -0.090$, 95% CI: [-0.182, -0.026]), accounting for 25.6% of the total effect. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. IJV, internal jugular vein; MoCA, Montreal Cognitive Assessment; CI, confidence interval.