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The moderating effect of age on the association between homocysteine levels, third ventricular width and cognitive function in Parkinson's disease

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Abstract

Objectives: This study aimed to explore the moderating effect of age on the relationships between homocysteine (Hcy) levels and cognitive function, as well as between third ventricular (V3) width and cognitive function in patients with Parkinson's disease (PD). *Methods:* We enrolled 237 PD patients and categorized them into two groups based on Montreal Cognitive Assessment (MoCA) scores: 65 patients with normal cognition (PDNC) and 172 patients with cognitive impairment (PDCI). All subjects underwent transcranial sonography and laboratory analysis to measure V3 width and Hcy levels, respectively. *Results:* Multiple regression analysis with interaction terms revealed significant moderating effects of age on both Hcy-cognition ($p < 0.001$) and V3-cognition ($p = 0.005$) relationships. Simple slope analysis demonstrated that the negative impacts of both V3 width and Hcy levels on cognitive function intensified with advancing age (V3: $\beta = -0.654$ in younger patients vs. $\beta = -1.260$ in older patients; Hcy: $\beta = -0.082$ in younger patients vs. $\beta = -0.531$ in older patients). No significant interaction was observed between V3 width and Hcy levels on cognitive function ($p = 0.074$).
Conclusions: Age significantly moderated the relationships between V3 width, Hcy levels, and cognitive function in PD patients, with older patients showing greater cognitive vulnerability to elevated Hcy and ventricular enlargement.

Keywords: Homocysteine, third ventricular width, transcranial sonography, cognitive impairment, Parkinson's disease, age moderation

INTRODUCTION

Parkinson's disease (PD) is a prevalent neurodegenerative disorder that significantly affects elderly individuals worldwide, with prevalence increasing from approximately 1% in those aged 60 years to 3-4% in individuals aged 80 years and above[1], growing evidence highlights the substantial impact of non-motor manifestations on patient quality of life. Among these, cognitive impairment represents one of the most debilitating complications, with mild cognitive impairment (MCI) affecting approximately 42.5% of patients even in early-stage PD based on MDS Task Force criteria[2], and the risk of progression to dementia increasing substantially with disease duration.[3] The development of cognitive dysfunction not only compromises patients' daily functioning but also substantially increases caregiver burden and healthcare costs.[4]

Despite extensive research, the pathophysiological mechanisms underlying cognitive decline in PD remain incompletely understood. Recent investigations have identified several potential biomarkers associated with cognitive deterioration. Elevated homocysteine (Hcy) levels have emerged as a significant risk factor for cognitive impairment in neurodegenerative disorders, including both Alzheimer's disease and PD-related dementia.[5,6]

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Concurrently, structural brain changes, particularly global brain atrophy reflected by ventricular enlargement, have been linked to cognitive decline progression. Transcranial sonography (TCS) measurement of third ventricular (V3) width has gained attention as an accessible, non-invasive biomarker for brain atrophy, correlating with both physiological aging and pathological neurodegeneration.[7] While previous studies have examined individual risk factors for cognitive impairment in PD, including age, education, psychiatric comorbidities, and metabolic parameters[8], limited research has investigated how these factors interact to influence cognitive outcomes. Age, in particular, represents a critical variable that may modify the relationship between biological markers and cognitive function. Understanding these age-dependent interactions could provide valuable insights for risk stratification and personalized therapeutic strategies.

The present study addresses this gap by investigating whether age moderates the associations between Hcy levels and cognitive function, and between V3 width and cognitive function in PD patients. Additionally, we explored potential interactions between Hcy levels and V3 width in relation to cognitive performance. By elucidating these complex relationships, we aim to contribute to more refined, age-tailored approaches for identifying and managing cognitive decline in PD.

METHODS

Subjects

We recruited 237 patients diagnosed with PD from The Second Affiliated Hospital of Soochow University. All participants met the UK Parkinson's Disease Society Brain Bank diagnostic criteria for PD.[9] Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), a validated screening tool that evaluates multiple cognitive domains including visuospatial/executive function, naming, memory, attention, language, abstraction, and orientation. One additional point was added for participants with ≤12 years of education to adjust for educational bias. Based on established criteria[10], patients scoring ≥26 were classified as PDNC (PD with normal cognition), while those scoring <26 were classified as PDCI (PD with cognitive impairment).

Exclusion criteria were: (1) comorbid neurological disorders other than PD (e.g., Alzheimer's disease, epilepsy, or primary psychiatric disorders); (2) current or recent use of medications known to affect Hcy levels, including vitamin B6, vitamin B12, or metformin; (3) acute or chronic hepatic or renal dysfunction; and (4) inadequate temporal bone acoustic windows precluding TCS examination.

Transcranial Sonography

TCS examinations were performed following standardized protocols established by the Ninth Meeting of the European Society of Neurosonology and Cerebral Hemodynamics.[11] Two experienced sonologists, each with >5 years of TCS experience and blinded to participants' cognitive status and clinical data, independently conducted all examinations using a 2.5 MHz phased-array transducer (Sequoia 512, Siemens Medical Solutions USA, Inc., 4V1C transducer).

For midbrain imaging, the transtemporal bone window in the axial plane was utilized with a penetration depth of 14-16 cm and dynamic range of 45-55 dB.[12] To visualize the ventricular plane, the ultrasound probe was tilted approximately 10°-20° upward from the midbrain plane. The third ventricle appeared as two parallel hyperechoic lines representing the interface between ependyma and cerebrospinal fluid. V3 width was measured as the minimal distance between the inner boundaries of these parallel lines, in accordance with consensus guidelines.[12]

Clinical assessment

All patients underwent comprehensive neurological examination by two movement disorders specialists. Demographic and clinical data were systematically recorded, including sex, age, disease duration, and years of education. Motor assessments were conducted while patients were in the "ON" medication state to standardize evaluation conditions and ensure optimal patient cooperation during both motor and cognitive testing, thereby minimizing potential confounding effects of severe OFF-state motor symptoms on cognitive performance and imaging quality. Parkinsonian motor symptoms were quantified using the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III), and disease severity was staged according to the modified Hoehn and Yahr scale (H-Y).[13]

Laboratory measurements

Fasting blood samples were obtained from all participants in the early morning following overnight fasting. Venous blood was collected and centrifuged within one hour of collection. Plasma Hcy levels, along with metabolic parameters including fasting blood glucose, triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), were measured using standard clinical laboratory protocols.

The study protocol was approved by the Ethics Committee of The Second Affiliated Hospital of Soochow University (JD-LK-2018-094-01), and written informed consent was obtained from all participants.

Statistical analysis

All statistical analyses were performed using R software version 4.5.1. Continuous variables were first assessed for normality using the Shapiro-Wilk test. Normally distributed variables are presented as mean ± standard deviation, while non-normally distributed variables are reported as median (interquartile range). Group comparisons employed independent samples t-tests for normally distributed variables, Mann-Whitney U tests for non-normally distributed variables, and chi-square tests for categorical variables.

To examine interaction effects, we constructed multiple linear regression models with MoCA scores as the dependent variable. Predictor variables included age, Hcy levels, V3 width, and their two-way interaction terms (Age × Hcy, Age × V3, V3 × Hcy), with years of education included as a covariate. All continuous variables were mean-centered prior to analysis to reduce multicollinearity. Model significance was evaluated using F-tests, and model fit was assessed by adjusted R^2. The significance of interaction terms was determined through t-tests. For statistically significant interactions, simple slope analyses were conducted at different moderator levels (mean ± 1 SD) using the emmeans and interactions packages, with 95% confidence intervals calculated. Interaction effects were visualized using the interact_plot function. Statistical significance was set at $p < 0.05$ (two-tailed).

RESULTS

Baseline characteristics

Of the 237 PD patients included in this study, 65 were classified as PDNC and 172 as PDCI. Baseline demographic and clinical characteristics are presented in Table 1. The two groups did not differ significantly in sex distribution, disease duration, UPDRS-III scores, or metabolic parameters including TG, TC, HDL-C, LDL-C, and fasting blood glucose (all $p > 0.05$).

Table 1: Baseline characteristics of PDNC and PDCI patients

	PDNC	PDCI	*p* value
Male sex	40 (61.5)	105 (61.0)	0.998
Age (y)	57 (52, 68)	69 (62, 73)	< 0.001*
PD duration (y)	2.28 (1.10, 3.50)	3 (1.27, 5)	0.154
Edu (y)	9 (6, 12)	7 (3, 12)	< 0.001*
MoCA	27 (26, 29)	20 (16, 23)	< 0.001*
V3 (cm)	4.1 (3.3, 5.1)	6.15 (4.4, 7.6)	< 0.001*
Hcy (μmol/L)	11.1 (9.1, 13.8)	13.95 (10.9, 17)	< 0.001*
H-Y stage	2 (1, 3)	2.5 (2, 3)	0.004*
UPDRS III	27 (17, 40)	30 (21, 43)	0.126
TG (mmol/L)	1.2 (0.95, 1.56)	1.12 (0.8, 1.53)	0.432
TC (mmol/L)	4.64 ± 1.05	4.48 ± 0.98	0.266
HDL-C (mmol/L)	1.2 (1.01, 1.4)	1.21 (1.03, 1.51)	0.317
LDL-C (mmol/L)	2.82 ± 0.88	2.62 ± 0.82	0.108
Blood glucose (mmol/L)	5.04 (4.81, 5.48)	5.23 (4.9, 5.89)	0.064

Data are given as mean ± SD, median (Q1, Q3), or n (%)
* Indicates statistical significance

However, PDCI patients were significantly older, had fewer years of education, and exhibited lower MoCA scores compared to PDNC patients (all $p < 0.001$). Importantly, PDCI patients demonstrated significantly elevated Hcy levels and larger V3 width (both $p < 0.001$). Disease severity, as measured by H-Y stage, was also significantly greater in PDCI patients compared to PDNC patients ($p = 0.004$).

Multiple regression analysis and interaction effects

The biomarkers examined in this study were plasma homocysteine (Hcy) levels and third ventricular (V3) width measured by transcranial sonography.Multiple linear regression analysis incorporating interaction terms revealed significant moderating effects of age on the relationships between both biomarkers and cognitive function. The overall regression model was highly significant ($F(6, 230) = 45.32$, $p < 0.001$, adjusted $R^2 = 0.536$). No significant interaction was observed between Hcy levels and V3 width in relation to cognitive function ($p = 0.074$) (Table 2).

The significant Age × Hcy interaction ($p < 0.001$) indicated that the negative association between Hcy levels and cognitive function was moderated by age. Simple slope analysis demonstrated that in younger patients (mean age - 1 SD), the relationship between Hcy and MoCA scores was relatively modest ($\beta = -0.082$), whereas in older patients (mean age + 1 SD), this negative association was substantially stronger ($\beta = -0.531$) (Table 3). This pattern suggests that elevated Hcy exerts a progressively greater detrimental effect on cognitive function with advancing age (Figure 1A).

Similarly, the significant Age × V3 interaction ($p = 0.005$) revealed age-dependent variation in the relationship between ventricular width and cognition. In younger patients, V3 width showed a moderate negative association with MoCA scores ($\beta = -0.654$). This relationship intensified markedly in older patients ($\beta = -1.260$), indicating that ventricular enlargement has a more pronounced cognitive impact in the elderly PD population (Figure 1B).

DISCUSSION

Principal findings

This study demonstrates that age significantly moderates the relationships between two important biomarkers—Hcy levels and V3 width—and cognitive function in PD patients. Our findings reveal that both elevated Hcy and increased ventricular width exert progressively

Table 2: Multiple linear regression analysis of factors associated with MoCA scores

	Model 1 (Age^c * Hcy^c)		**Model 2 (Age^c *$V3^c$)**		**Model 3 ($V3^c$ *Hcy^c)**	
	***β* (SE)**	***p* value**	***β* (SE)**	***p* value**	***β* (SE)**	***p* value**
Intercept	21.717 (0.281)	< 0.001*	21.720 (0.281)	< 0.001*	21.553 (0.277)	< 0.001*
Age^c	-0.231 (0.039)	< 0.001*	-0.151 (0.031)	< 0.001*	-	-
Hcy^c	-0.306 (0.061)	< 0.001*	-	-	-0.225 (0.061)	< 0.001*
$V3^c$	-	-	-0.955 (0.143)	< 0.001*	-1.19 (0.127)	< 0.001*
Edu^c	0.303 (0.054)	< 0.001*	0.246 (0.052)	< 0.001*	0.227 (0.052)	< 0.001*
Age^c * Hcy^c	-0.022 (0.005)	< 0.001*	-	-	-	-
Age^c * $V3^c$	-	-	-0.030 (0.010)	0.005*	-	-
$V3^c$ * Hcy^c	-	-	-	-	-0.054 (0.027)	0.074
Model Fit						
Adjust R^2	0.407		0.466		0.449	
F statistic	41.50		52.41		49.09	
p value	< 0.001*		< 0.001*		< 0.001*	

Edu as a covariate

Age^c, Hcy^c, $V3^c$, Edu^c, centralization of these variables

* Indicates statistical significance

- denotes non-inclusion of the variable in the corresponding model

Table 3: Moderating effect of age on the relationship between V3 width, Hcy levels and MoCA scores

	V3 width			Hcy levels		
	β (SE)	*p* value	95%CI	*β* (SE)	*p* value	95%CI
Low age ≤ 55 (y)	-0.654 (0.200)	< 0.001*	-1.05, -0.260	-0.082 (0.084)	0.335	-0.248, 0.085
Medium age 55-75 (y)	-0.955 (0.143)	< 0.001*	-1.24, -0.673	-0.306 (0.061)	< 0.001*	-0.427, -0.185
High age ≥ 75 (y)	-1.260 (0.152)	< 0.001*	-1.56, -0.957	-0.531 (0.085)	< 0.001*	-0.699, -0.363

* Indicates statistical significance

stronger negative effects on cognition with advancing age. These age-dependent interactions provide novel insights into the pathophysiology of cognitive decline in PD and suggest potential targets for age-stratified intervention strategies.

Homocysteine, age, and cognitive function

The observed interaction between age and Hcy levels in predicting cognitive outcomes aligns with emerging evidence linking hyperhomocysteinemia to accelerated cognitive decline in elderly populations.[14,15] Several pathophysiological mechanisms may explain this age-dependent vulnerability. First, elevated Hcy promotes oxidative stress through increased generation of reactive oxygen species and impaired antioxidant defense mechanisms.[16] While this process occurs in aging generally, the combination of age-related decline in cellular antioxidant capacity and PD-specific pathology (alpha-synuclein aggregation, mitochondrial dysfunction in dopaminergic neurons) may create a synergistic vulnerability. This convergence of aging and neurodegenerative processes could render older PD patients disproportionately susceptible to Hcy-mediated oxidative damage in already compromised brain regions such as the hippocampus and prefrontal cortex.[16] With advancing age, cellular antioxidant capacity naturally declines, potentially rendering older individuals more susceptible to Hcy-mediated oxidative damage in vulnerable brain regions such as the hippocampus and prefrontal cortex.

Second, hyperhomocysteinemia induces endothelial dysfunction and promotes cerebrovascular injury.[16,17] Age-related vascular changes, including arterial stiffening and reduced

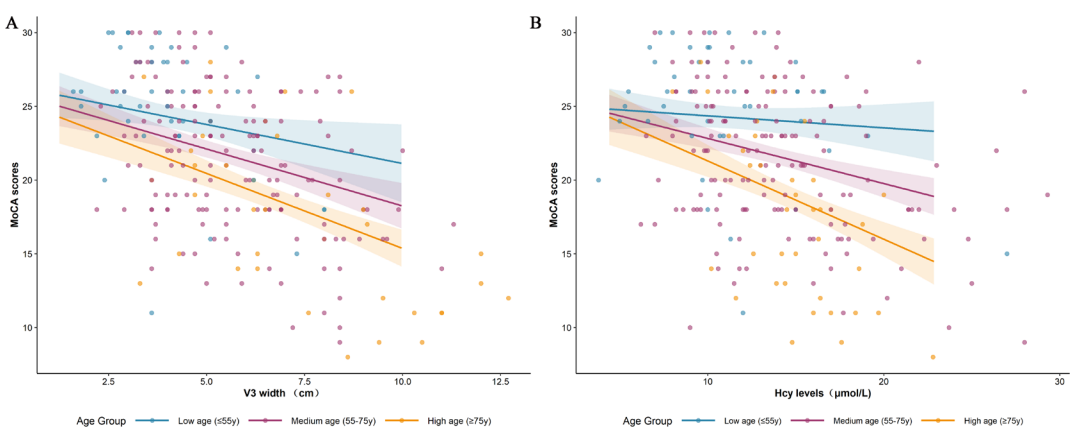

Figure 1. Relationship between each group.
A. Age moderates the relationship between homocysteine levels and cognitive function in Parkinson's disease. The plot illustrates the interaction effect, showing steeper negative slopes for the Hcy-cognition relationship in older compared to younger patients. B. Age moderates the relationship between third ventricular width and cognitive function in Parkinson's disease. The visualization demonstrates progressively stronger negative associations between V3 width and MoCA scores with advancing age.

cerebral blood flow autoregulation, may amplify the detrimental effects of Hcy on cerebral perfusion. This vascular-cognitive pathway appears particularly relevant in PD, where both alpha-synuclein pathology and vascular insufficiency may synergistically contribute to neurodegeneration.[18,19] The cerebrovascular hypothesis is further supported by evidence that Hcy correlates with white matter lesion burden and microinfarcts in aging brains.[20,21]

Third, Hcy interferes with methylation reactions crucial for neurotransmitter synthesis, myelin maintenance, and DNA repair.[22,23] Age-related decline in methylation capacity may exacerbate these disruptions, leading to cumulative neuronal dysfunction.[24] In the context of PD, where dopaminergic deficits already compromise cognitive reserve[25], additional Hcy-mediated metabolic perturbations may more readily manifest as clinically apparent cognitive impairment in older patients.

The observed interaction between age and Hcy levels in predicting cognitive outcomes aligns with emerging evidence linking hyperhomocysteinemia to accelerated cognitive decline in elderly populations.[14,15] This interaction suggests that Hcy thresholds for cognitive risk may need age-specific calibration, with lower levels potentially warranting intervention in elderly patients.

Ventricular enlargement, age, and cognitive decline

The age-moderated relationship between V3 width and cognitive function reflects the convergence of physiological aging and neurodegenerative processes. Third ventricular enlargement represents a surrogate marker for medial temporal lobe and periventricular white matter atrophy[26,27], regions critically implicated in memory and executive function. Several mechanisms may explain why this structural biomarker shows stronger cognitive associations in older PD patients.

From a neuroanatomical perspective, age-related brain atrophy follows a regionally heterogeneous pattern, with accelerated volume loss in subcortical structures including the thalamus, basal ganglia, and periventricular regions.[28] In PD patients, superimposed dopaminergic denervation and alpha-synuclein pathology may interact with age-related atrophy to produce disproportionate structural changes in areas adjacent to the third ventricle.[29,30] These regions include the medial dorsal thalamic nucleus and mammillothalamic tract, both integral to frontotemporal cognitive networks.[31,32]

Moreover, ventricular enlargement in older individuals often reflects not only neuronal loss but also more extensive white matter damage and reduced brain tissue elasticity. Age-related myelin degradation, when combined with PD-specific pathology, may compromise neural network integrity more severely than either process alone. This "double-hit" phenomenon could explain why equivalent degrees of ventricular dilation correlate with more severe cognitive impairment in elderly compared to younger PD patients.

The clinical utility of TCS-measured V3 width as a cognitive biomarker has been demonstrated in previous studies[33,34], but our findings highlight the necessity of age-adjusted interpretation. The steeper slope in older patients (β = -1.260 vs. -0.654 in younger patients) suggests that small incremental increases in ventricular width carry greater cognitive significance in the elderly population, potentially improving early detection of at-risk individuals.

Independence of Hcy and V3 pathways

Notably, we did not observe a significant interaction between Hcy levels and V3 width in their effects on cognition ($p = 0.074$). This finding suggests that these biomarkers influence cognitive function through largely independent, albeit possibly parallel, mechanisms. While Hcy primarily affects cognition through vascular injury and metabolic dysfunction, ventricular enlargement reflects structural neurodegeneration and network disruption. The lack of interaction implies that their combined effects may be approximately additive rather than synergistic, with each contributing independently to overall cognitive risk.

This independence has important clinical implications. Patients with elevated levels of both markers may face cumulative cognitive vulnerability through distinct pathophysiological pathways, suggesting that multifaceted intervention strategies addressing both vascular/metabolic and structural factors may be necessary for optimal cognitive preservation.

Educational attainment as cognitive reserve

Consistent with the cognitive reserve hypothesis, years of education emerged as a significant

protective factor against cognitive decline in our cohort. Higher educational attainment likely enhances neural efficiency and provides compensatory networks that maintain cognitive function despite underlying pathology.[35] This protective effect appeared consistent across age groups, underscoring the importance of considering premorbid cognitive reserve when assessing PD patients.

Clinical implications and future directions

These findings have several practical implications for clinical management of PD. First, our results support age-stratified monitoring protocols for cognitive decline. In elderly PD patients (particularly those >70 years), regular assessment of Hcy levels and TCS measurement of V3 width may facilitate early identification of individuals at heightened cognitive risk. Given the differential age-dependent effects we observed, risk prediction models incorporating age-biomarker interactions may demonstrate superior performance compared to models using biomarkers alone.

Second, the age-moderated Hcy-cognition relationship suggests potential therapeutic windows for intervention. In older PD patients with elevated Hcy, targeted B-vitamin supplementation (B6, B12, folate) aimed at lowering Hcy levels represents a potential strategy, though evidence for cognitive benefits remains inconsistent. While some trials in non-PD populations have shown modest improvements in cognitive outcomes with Hcy-lowering interventions[36,37], other studies have yielded negative results.[38] Whether similar approaches could benefit elderly PD patients with hyperhomocysteinemia requires validation through randomized controlled trials specifically designed for this population.

Third, the clinical significance of our findings should be interpreted within the context of our cognitive assessment methodology. The MoCA, while widely validated as a cognitive screening tool for PD populations, provides a global cognitive index rather than fine-grained assessment of specific cognitive domains. Comprehensive neuropsychological test batteries, in contrast, offer domain-specific measurements (e.g., Hopkins Verbal Learning Test for memory, Trail Making Test for executive function, Judgment of Line Orientation for visuospatial processing) with greater sensitivity to subtle deficits and ceiling effects. Future studies employing detailed neuropsychological assessments might reveal whether age-biomarker interactions differentially affect specific cognitive domains—for instance, whether Hcy shows stronger age-dependent associations with executive dysfunction while V3 width primarily impacts memory performance. Such domain-specific insights could refine targeted intervention strategies beyond what global screening tools can reveal.

Several limitations warrant consideration when interpreting our findings. First, the cross-sectional design precludes causal inference regarding the temporal relationships between age, biomarkers, and cognitive decline. Longitudinal studies tracking changes in Hcy, V3 width, and cognition over time are needed to establish whether age-related acceleration of cognitive decline can be attributed to these biomarkers or whether they simply co-vary with unmeasured progressive pathology.

Second, our sample was recruited from a single tertiary referral center in Suzhou, which may limit generalizability to other populations or healthcare settings. Regional differences in dietary patterns (affecting Hcy levels)[39], genetic backgrounds[40], and comorbidity profiles[41] could influence the strength or even presence of the observed interactions. Multicenter studies with diverse patient populations would strengthen external validity.

Third, while we adjusted for years of education, we did not include other potentially important variables such as APOE genotype, inflammatory markers, or detailed vascular risk profiles in our models. These unmeasured confounders might contribute to the observed associations and warrant investigation in future research.[42,43] Additionally, medication effects, particularly levodopa dosing and duration, were not systematically analyzed and could influence cognitive performance.[44,45]

Fourth, cognitive assessment relied solely on the MoCA, which, despite being well-validated for PD populations, provides a global cognitive index rather than domain-specific information. More comprehensive neuropsychological batteries examining distinct cognitive domains[46,47] (e.g., executive function, memory, visuospatial processing) might reveal differential age-biomarker interactions across cognitive dimensions.

Fifth, our sample size, while adequate for detecting the reported interactions, may have limited power to identify more subtle effects

or higher-order interactions (e.g., three-way interactions between age, Hcy, and V3). The non-significant Hcy × V3 interaction ($p = 0.074$) approaches borderline significance, suggesting this relationship merits re-examination in larger cohorts.

Finally, the accuracy of TCS measurements depends on examiner expertise and acoustic window quality. Although our sonologists were experienced and blinded to clinical data, inter-rater reliability was not formally assessed.[48] Furthermore, TCS cannot visualize certain brain structures with the resolution of MRI, limiting our ability to correlate V3 enlargement with specific regional atrophy patterns.

In conclusion, this study demonstrates that age significantly moderates the relationships between Hcy levels, V3 width, and cognitive function in PD patients. Both elevated Hcy and increased ventricular width showed progressively stronger negative associations with cognition in older individuals, highlighting age-dependent vulnerability to these risk factors. These findings underscore the importance of age-stratified approaches to cognitive risk assessment and suggest that elderly PD patients may particularly benefit from monitoring and interventions targeting Hcy and structural brain changes. Future longitudinal studies with larger, more diverse cohorts are needed to validate these interactions and determine whether biomarker-targeted interventions can modify age-related cognitive decline trajectories in PD.

DISCLOSURE

Ethics: This study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Soochow University (JD-LK-2018-094-01). Written informed consent was obtained from all participants.

Data availability: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Conflict of interest: None

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