Article

Discovery Medicine 2025; 37(201): 2283–2293
https://doi.org/10.24976/Discov.Med.202537201.194

Association Between Polypharmacy and Gait Performance in Older Adults With Cerebral Small Vessel Disease

Wei Wei[1,†], Hong-yang Xie[1,†], Cui-qiao Xia[1], Nan Zhang[1], Jun-jie Cao[1], Hong-yi Zhao[1,2], Yong-hua Huang[1,*]

[1]Department of Neurology, Chinese PLA General Hospital, 100010 Beijing, China
[2]Department of Neurology, NO 984 Hospital of PLA, 100094 Beijing, China
*Correspondence: huangyh@163.com (Yong-hua Huang)
[†]These authors contributed equally.

Submitted: 11 July 2025 Revised: 28 August 2025 Accepted: 10 September 2025 Published: 20 October 2025

Background: The practice of polypharmacy is prevalent among older adults and has been associated with mobility decline and cognitive impairment. However, its effects on gait performance in patients with cerebral small vessel disease (CSVD)—a population inherently vulnerable to gait disturbances—remain poorly understood. This study investigated the impact of polypharmacy on gait performance during single-task walking (STW) and dual-task walking (DTW) in patients with CSVD, and identified neuroimaging correlates associated with polypharmacy.

Methods: A total of 126 hospitalized individuals with CSVD were recruited. Based on the number of regularly used medications that had been in use for ≥2 weeks, patients were classified into three groups: non-polypharmacy (≤4 drugs, *n* = 47), polypharmacy (5–9 drugs, *n* = 49), or hyper-polypharmacy groups (≥10 drugs, *n* = 30). Gait speed and its coefficient of variation (CV) were recorded during STW and DTW. Magnetic resonance imaging was used to evaluate white-matter hyperintensities, lacunar infarcts, and cerebral microbleeds, which were integrated into a total CSVD burden score (0–3).

Results: During STW, the hyper-polypharmacy group had significantly slower gait speed (0.70 ± 0.20 m/s) compared to the non-polypharmacy and polypharmacy groups (both >0.91 m/s, $p < 0.001$). In DTW, gait speed decreased and CV increased across all groups, with the most pronounced impairments in the hyper-polypharmacy group (DTW speed: 0.59 ± 0.15 m/s; CV: 16.03%). Linear regression revealed that medication count was negatively associated with gait speed (STW $\beta = -5.622$, $p < 0.001$; DTW $\beta = -8.484$, $p < 0.001$) and positively with gait variability during DTW ($\beta = 0.246$, $p < 0.001$). The total CSVD score was independently associated with polypharmacy ($p = 0.036$).

Conclusion: The study confirmed a relationship between polypharmacy and locomotion in CSVD patients. Furthermore, total CSVD score—but not any single neuroimaging biomarker—is independently associated with the presence of polypharmacy.

Keywords: cerebral small vessel disease; polypharmacy; gait speed; coefficient of variation; cross-sectional study

Introduction

Cerebral small vessel disease (CSVD) is a common disorder among older individuals, with its prevalence increasing significantly with age [1]. It is a major contributor to stroke and dementia and can be identified by neuroimaging markers such as small subcortical infarcts, white matter hyperintensities (WMHs), lacunar infarctions (LIs), enlarged perivascular spaces, cerebral microbleeds (CMBs), and atrophy [2]. The prevalence of WMH increases from 5% at age 50 to nearly 100% by age 90 [3], and CMB incidence rises from approximately 6.50% at ages 45–50 to around 36.00%–38.00% in those over 80 years old [4].

Although movement disorders and cognitive impairment are hallmark features of CSVD [5], they are frequently underrecognized through the sole detection by conventional diagnostic approaches [6]. Recent advances in neuroimaging, including the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) criteria, diffusion-weighted imaging, and dynamic contrast-enhanced magnetic resonance imaging (MRI), have significantly enhanced the precision of CSVD diagnosis, disease monitoring, and evaluation of blood-brain barrier integrity [7,8]. Additionally, dual-task walking (DTW)—which evaluates gait performance under simultaneous cognitive or motor demands, has emerged as a sensitive tool for identifying mobility impairments in CSVD. Because walking and secondary tasks rely on shared neural resources, DTW poses particular challenges for individuals with CSVD, offering insight into their functional limitations [9].

Gait, a complex movement controlled by both motor and central neural functions [10], serves as an impor-

tant health indicator in older adults [11]. While studies on community-dwelling elderly individuals suggest that polypharmacy negatively impacts mobility [12,13], its effect on CSVD patients remains unclear. CSVD-related subcortical damage, particularly in the frontal cortex and basal ganglia, contributes to slow walking speed, raising the question of whether polypharmacy exacerbates this impairment [11]. A similar association between polypharmacy, slow gait, and recurrent falls has also been reported in older adults with HIV [14]. Given evidence that deprescription benefits patients with multiple comorbidities [15], exploring the relationship between polypharmacy and gait performance may inform strategies to prevent CSVD progression.

Polypharmacy, commonly defined as the concurrent use of five or more medications [16], has been associated with adverse outcomes such as falls, frailty, gait slowing, and cognitive decline [13,17–19]. Hyper-polypharmacy, defined as the use of ten or more medications, is linked to even poorer prognoses [20]. However, the specific impact of polypharmacy on the clinical characteristics of CSVD remains poorly understood. This study aims to investigate gait alterations in CSVD patients with polypharmacy during single-task walking (STW) and DTW. Furthermore, it seeks to identify neuroimaging biomarkers associated with polypharmacy in older Chinese adults with CSVD. By elucidating these relationships, our findings may inform deprescription strategies and support targeted interventions to mitigate the negative effects of polypharmacy on mobility and disease progression.

Materials and Methods

Participants

A total of 126 patients diagnosed with CSVD treated at the Department of Neurology, Chinese People's Liberation Army (PLA) General Hospital between January 1, 2022, and June 1, 2023, were enrolled. Patients fulfilling the following criteria were included: (1) the ability to independently ambulate for a distance of 30 steps with or without holding a tray; (2) the ability to comprehend and accurately execute commands; and (3) age over 50 years, accompanied by at least one imaging manifestation associated with CSVD, such as WMHs, LIs, or CMBs. Notably, if WMHs were at a minimal level of 1 and no other discernible markers were present, patients must exhibit at least one vascular risk factor, such as hypertension, diabetes, hyperlipidemia, or similar distinguished conditions, to be eligible for inclusion [5,21]. Exclusion criteria of this study are as follows: (1) noticeable deficiency in receptive language abilities hindering comprehension and adherence to commands; (2) confirmed diagnosis of mild cognitive impairment or dementia; and (3) recent acute cerebral ischemic or bleeding episodes, leukoencephalopathy with demyelinating or genetic etiology, major psychiatric disorders, nonvascular-induced gait disorders, and contraindications to MRI utilization.

A comprehensive collection of personal data was conducted, including key factors such as age, gender, educational level, and the presence of any comorbid conditions. To assess cognitive function, participants underwent the clock drawing test (CDT), the trail-making test-part B (TMT-B) [22], and the verbal fluency test (VFT) [23].

The VFT evaluates language fluency by counting the number of animals named within one minute. The TMT-B measures executive function by assessing the time required to complete the trail-marking test. In CDT, a transformed score was utilized to assess visual-spatial abilities, with lower scores indicating reduced proficiency. Points are allocated based on the accuracy and complexity of the clock dials generated by the participants [24].

An a priori sample size calculation was performed using G*Power 3.1 (Heinrich Heine University Düsseldorf, Düsseldorf, Germany) to ensure adequate statistical power. Based on an expected medium-to-large effect size (Cohen's $f = 0.30$), $\alpha = 0.05$, power = 0.80, the minimum required total sample size was 111 participants. The final sample (n = 126) exceeded this threshold, indicating sufficient power to detect clinically meaningful group differences in gait performance.

CSVD Neuroimaging Markers

Neuroimaging procedures were conducted with a 3.0 T MRI scanner (Siemens AG, Erlangen, Bavaria, Germany). The protocol included T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and susceptibility-weighted imaging (SWI) sequences. All scans were independently evaluated by two board-certified neurologists blinded to clinical information. In case of disagreement, a third senior neurologist was consulted to reach consensus.

The grading of WMHs was based on the Fazekas scale (range: 0–3), a widely accepted tool in CSVD research [25]. Additionally, we recorded the presence of CMBs and LIs. To quantify total CSVD burden, we applied a validated composite scoring system, in which one point was assigned for each of the following features: (1) two or more LIs, (2) presence of CMBs, and (3) WMH with severity measured in terms of Fazekas grade 2 or 3, yielding a total score ranging from 0 to 3 [26]. This scoring rule has been widely adopted in previous studies [26] to reflect the overall extent of small vessel pathology and its association with clinical outcomes.

Based on total CSVD scores, participants were classified into three groups: mild (score = 0), moderate (score = 1), and severe (score = 2 or 3).

STW and DTW Protocols

The gait characteristics of all participants were assessed under two distinct conditions: (1) walking without any additional tasks, and (2) walking while performing a cognitive task involving three consecutive subtractions from a randomly selected number (90, 95, 100, or 105), referred to as cognitive DTW.

As previously described, participants were instructed to complete 30 strides along a designated walkway under STW and DTW conditions [27,28]. A starting and a finish line were marked on the walkway. The participants were required to take five preparatory steps before the starting line, walk 30 strides between the two marked lines, and continue with taking five additional steps beyond the finish line. To minimize the effects of acceleration and deceleration, only the 30 strides in the central section were analyzed. In the DTW assessment, the participants were instructed to perform both walking and the cognitive tasks simultaneously, without prioritizing either activity.

Gait Parameters of Participants With CSVD

Gait-related data were collected using the MiniSun Intelligent Device for Energy Expenditure and Activity System (IDEEA®, Model 3.1, MiniSun LLC, Fresno, CA, USA). Gait variability (%) was determined from the coefficient of variation (CV), a common metric for this phenomenon. Additionally, recognizing the inherent interdependence between the bilateral legs, we calculated the CV for each side using the formula:

$$\text{Stride CV} = \frac{\text{stdev}\ (stride)}{\text{mean}\ (stride)} \times 100\%$$

Definition of Polypharmacy

To obtain comprehensive insights into the medication history of the participants, we collected information from their medical records and medication diaries. Only medications that were regularly used for at least two consecutive weeks prior to gait assessment were considered eligible and included in the analysis. To avoid misclassification due to transient prescriptions, short-term medications such as antibiotics for acute illnesses and drugs prescribed on an "as-needed" basis were excluded. Topical medications were also excluded. Patients practicing polypharmacy, which is defined as concurrent use of five or more regularly scheduled medications, were divided into three groups based on a previous study [29]: non-polypharmacy ($\leq$4 medications, n = 47), polypharmacy (5–9 medications, n = 49), and hyper-polypharmacy groups ($\geq$10 medications, n = 30).

Statistical Analysis

To assess the normality of data distribution, we employed the Shapiro–Wilk test. Normally distributed variables are expressed as mean $\pm$ standard deviation (SD), while non-normally distributed variables are presented as median and interquartile range (IQR). Categorical data are expressed as frequencies. Group comparisons for continuous variables were conducted using one-way analysis of variance (ANOVA) for normally distributed data, or the Kruskal–Wallis H test for non-normally distributed data. For comparisons between two groups, t-test or Mann–Whitney U test was applied, depending on the distribution. The t-test was used for analyzing normally distributed data, while the nonparametric Mann-Whitney U test was applied for data with skewed distribution. The chi-squared test was applied for comparing categorical variables. To determine gait performance across conditions and polypharmacy status, generalized estimation equations (GEE) were employed, incorporating walking condition (STW vs. DTW) and polypharmacy group as within-subject and between-subject factors, respectively. Post-hoc tests with Bonferroni correction were used to adjust for multiple comparisons in the presence of significant interactions. Linear regression analysis was employed to assess associations between the number of medications and gait speed or CV. Furthermore, logistic regression analyses evaluated the relationship between neuroimaging markers and polypharmacy risk.

To control for potential confounders, particularly the number of comorbidities and performance on the TMT-B, these variables were included as covariates in the GEE and linear regression models. Interaction terms were tested to identify any effect modifications. Sensitivity analyses excluded participants with extreme values, and subgroup analyses explored effects within specific strata. Additional adjustments were made for age, gender, medication types, physical activity levels, and socioeconomic status to ensure an accurate and unbiased assessment of the relationship between polypharmacy and gait parameters in CSVD patients. All statistical analyses were performed using SPSS version 23.0 (SPSS Inc., Armonk, NY, USA), with $p < 0.05$ set as the statistical significance threshold.

Results

Participants' Characteristics

As shown in Table 1, the entire cohort of CSVD patients (n = 126) had a mean age of 66.10 $\pm$ 8.30 years, comprising 38.09% of female. Among them, 47 patients were classified as engaging in non-polypharmacy, 49 patients as practicing polypharmacy, and 30 patients as practicing hyper-polypharmacy. There were no significant differences across the three groups in age, sex, years of education, CDT scores, or VFT. However, significant group differences were found in the number of comorbidities ($p < 0.001$) and TMT-B performance (p = 0.001).

Post-hoc analyses indicated that patients in the hyper-polypharmacy group had significantly more comorbidities than those in the non-polypharmacy ($p < 0.001$) and polypharmacy groups ($p < 0.001$). The number of comorbidities was also higher in the polypharmacy group than in the non-polypharmacy group (p = 0.001). Regarding TMT-B, patients in the hyper-polypharmacy group performed significantly worse than both the non-polypharmacy ($p < 0.001$) and polypharmacy groups (p = 0.045), whereas no significant difference was found between the non-polypharmacy and polypharmacy groups (p = 0.078).

Table 1. Characteristics and neuroimaging biomarkers of participants in this study.

Variables	Non-polypharmacy group (n = 47)	Polypharmacy group (n = 49)	Hyper-polypharmacy group (n = 30)	F/χ^2-value	p-value	Post-hoc comparisons
Sex (female), n (%)	20 (42.55%)	17 (34.69%)	11 (36.67%)	0.662	0.718	
Duration of education (years)	12.00 (9.00, 12.00)	12.00 (9.00, 12.00)	12.00 (9.00, 12.00)	2.778	0.249	
Age (years)	63.30 ± 7.77	64.94 ± 8.06	67.73 ± 7.70	2.913	0.058	
Number of comorbidities	2.00 (1.00, 2.00)	2.00 (2.00, 3.00)	3.00 (2.75, 4.00)	35.341	<0.001	Non vs. Hyper: $p < 0.001$ Poly vs. Hyper: $p < 0.001$ Non vs. Poly: $p = 0.001$
VFT score	17.74 ± 3.40	16.94 ± 4.07	15.87 ± 3.51	2.360	0.099	
CDT score	12.00 (11.00, 13.00)	12.00 (11.00, 13.00)	11.00 (10.00, 13.00)	3.824	0.148	
TMT-B score	76.00 (57.00, 86.00)	78.00 (62.00, 97.00)	94.50 (76.00, 103.30)	13.858	0.001	Non vs. Hyper: $p < 0.001$ Poly vs. Hyper: $p = 0.045$ Non vs. Poly: NS

Note: Data are presented as mean ± standard deviation (SD), median (interquartile range, IQR), or n (%). Group comparisons were conducted using one-way ANOVA for normally distributed continuous variables, the Kruskal–Wallis test for non-normally distributed continuous variables, and the chi-square test for categorical variables.

Abbreviations: CDT, clock drawing test; VFT, verbal fluency test; TMT-B, trail-making test-part B; F, value from one-way analysis of variance; χ^2, chi-square.

Gait Performance Across Different Polypharmacy Groups Under STW and DTW Conditions

Table 2 presents the gait parameters (speed and CV) across the polypharmacy groups during STW and DTW after adjusting for comorbidities and executive function. GEE analysis results (Table 3) revealed significant main effects and interactions effects between group (polypharmacy status) and condition (STW vs. DTW) for both gait speed and its CV, which remained robust after covariate adjustment (Table 4).

Under the STW condition, only the hyper-polypharmacy group exhibited slower gait speed compared with both the non-polypharmacy (p = 0.005) and polypharmacy groups ($p < 0.001$). During DTW, both gait speed and CV differed significantly between the hyper-polypharmacy group and the non-polypharmacy ($p < 0.001$) and polypharmacy groups ($p < 0.05$). Notably, DTW performance also differed between the non-polypharmacy and polypharmacy groups ($p < 0.05$), indicating a dose–response relationship between medication load and motor-cognitive interference. Post-hoc comparisons of within-group changes further revealed that only the polypharmacy and hyper-polypharmacy groups exhibited significant declines in gait speed and increases in CV from STW to DTW ($p < 0.05$). In contrast, no significant within-group change was observed in the non-polypharmacy group (Table 2).

Linear regression analysis was conducted to examine the association of the number of medications with both gait speed and CV, with adjustments for TMT-B and the number of comorbidities. The results are summarized in Tables 5,6. Linear regression of the STW and DTW data revealed that gait speed was negatively associated with the number of medications (Table 5, model 1), and the association remained significant after adjustment (Table 5, model 2). Furthermore, the number of medications was positively associated with gait variability in both conditions (Table 6, model 1). This association remained significant in the DTW condition after adjustment, but it was no longer observed in the STW condition (Table 6, model 2).

Neuroimaging Biomarkers Associated With Polypharmacy

We also investigated group differences in neuroimaging biomarkers (Table 7). Significant differences were observed in the total CSVD burden score and the presence of LIs among the three groups (p = 0.001 and p = 0.035, respectively). To further explore these associations, logistic regression analyses were performed using total CSVD score and LIs status of polypharmacy (Table 8). In these models,

Table 2. Comparison of gait speed and variability across different polypharmacy groups under STW and DTW conditions (adjusted for comorbidities and TMT-B).

Variables	Non-polypharmacy group ($n = 47$)	Polypharmacy group ($n = 49$)	Hyper-polypharmacy group ($n = 30$)	Overall test (F/χ^2, p)	Between-group comparisons (p)
STW					
Speed (m/s)	0.91 ± 0.17	0.92 ± 0.19	0.70 ± 0.20	$F = 70.971$, $p < 0.001$	Hyper vs. Non: 0.005; Hyper vs. Poly: <0.001; Non vs. Poly: 0.931
Speed CV (%)	8.04 (6.67, 10.67)	7.84 (5.73, 13.38)	13.26 (8.23, 16.26)	$\chi^2 = 3.905$, $p = 0.052$	Hyper vs. Non: 0.023 Hyper vs. Poly: 0.012 Non vs. Poly: 0.882
DTW					
Speed (m/s)	0.89 ± 0.16	0.77 ± 0.18	0.59 ± 0.15	$F = 63.300$, $p < 0.001$	Hyper vs. Non: <0.001; Hyper vs. Poly: <0.001; Non vs. Poly: 0.026
Speed CV (%)	7.32 (5.93, 9.52)	10.71 (6.93, 14.53)	16.03 (12.75, 24.50)	$\chi^2 = 20.200$, $p < 0.001$	Hyper vs. Non: <0.001; Hyper vs. Poly: 0.039; Non vs. Poly: 0.025
STW vs. DTW (within-group)					
Speed (m/s)	$t = 0.587$, $p = 0.558$	$t = 4.012$, $p < 0.001$	$t = 2.410$, $p = 0.019$		-
Speed CV (%)	$z = 1.885$, $p = 0.060$	$z = 5.734$, $p = 0.017$	$z = 6.650$, $p = 0.010$		-

Abbreviations: CV, coefficient of variation; DTW, dual-task walking; STW, single-task walking; TMT-B, trail-making test-part B; F, value from one-way analysis of variance; χ^2, chi-square.

the group with a total CSVD score of 2 (indicating severe burden) served as the reference. Both lower total CSVD scores (score = 0 and 1) were significantly associated with reduced odds of polypharmacy in both unadjusted and adjusted models ($p < 0.05$). These associations remained robust after adjustment for potential confounders, including number of comorbidities and executive function. LI presence was marginally associated with polypharmacy in the adjusted model ($p = 0.096$), but did not reach statistical significance. Representative neuroimaging examples of these CSVD markers were illustrated in Fig. 1.

Discussion

To the best of our knowledge, this is the first study to investigate the relationship between polypharmacy and gait parameters in individuals with CSVD under both STW and DTW conditions. Previous investigations have confirmed a relationship between polypharmacy and slow gait speed in community-dwelling older adults [12,13], as well as in patients with cognitive impairment during STW conditions [29]. Gait speed is influenced by cognition, particularly executive function [30], whose impairment is a primary clinical feature of CSVD [5]. Therefore, individuals with CSVD are anticipated to walk at a slower pace compared to healthy individuals [6]. It is crucial to determine whether polypharmacy affects gait speed in CSVD patients already practicing slow-paced walking. Our findings showed that hyper-polypharmacy was associated with slower gait speed only under the STW condition, whereas significant differences in both gait speed and

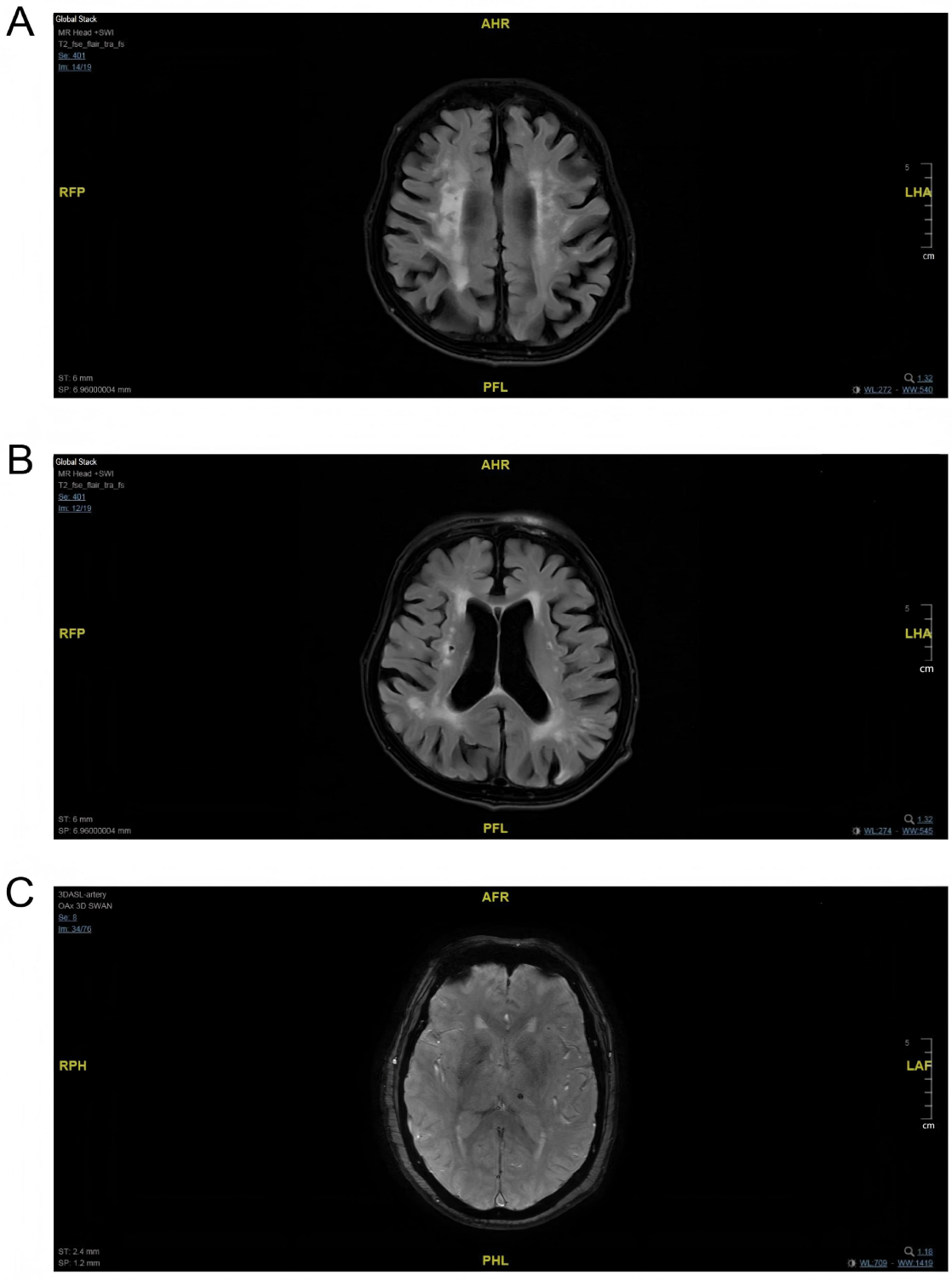

Fig. 1. Representative MRI features of cerebral small vessel disease. (A) White matter hyperintensities in the periventricular and deep white matter regions. (B) Lacunar infarcts appearing as small, round hypointense lesions in the basal ganglia. (C) Cerebral microbleeds detected on susceptibility-weighted imaging as punctate hypointense foci. Abbreviations: MRI, magnetic resonance imaging; AHR, anterior head right; LHA, left head anterior; RFP, right foot posterior; PFL, posterior foot left; AFR, anterior front right; PHL, posterior head left; RPH, right posterior head; LAF, left anterior front; ST, slice thickness; SP, slice spacing.

Table 3. Summary of GEE analysis results for speed and its CV.

Variables		Speed	Speed CV
Main effect			
Group	χ^2	49.560	30.507
(polypharmacy status)	p	<0.001	<0.001
Condition	χ^2	78.315	7.201
(STW vs. DTW)	p	<0.001	0.007
Interaction			
Group × condition	χ^2	42.690	15.647
	p	<0.001	0.001
	Partial η^2	0.267	0.086

Abbreviations: CV, coefficient of variation; DTW, dual-task walking; GEE, generalized estimation equation; STW, single-task walking; χ^2, chi-square; η^2, eta-squared.

Table 4. Summary of GEE analysis results for speed and its CV with adjustments for comorbidities and TMT-B.

Variables		Speed	Speed CV
Main effect			
Group	χ^2	23.926	13.090
(polypharmacy status)	p	<0.001	0.001
Condition	χ^2	78.315	7.201
(STW vs. DTW)	p	<0.001	0.007
Interaction			
Group × condition	χ^2	42.690	15.647
	p	<0.001	0.001
	Partial η^2	0.214	0.064

Abbreviations: CV, coefficient of variation; DTW, dual-task walking; GEE, generalized estimation equation; STW, single-task walking; TMT-B, trail-making test-part B; χ^2, chi-square; η^2, eta-squared.

speed CV were observed among all three groups during DTW. The polypharmacy and hyper-polypharmacy groups demonstrated slower speed and greater variability in DTW compared to STW, whereas the non-polypharmacy group showed no such differences. Moreover, the number of medications was negatively associated with gait speed in both STW and DTW and positively correlated with speed CV in DTW, even after adjusting for confounders. Notably, polypharmacy was independently associated with total CSVD scores, with this correlation remaining significant after adjusting for executive function impairment and other factors. These findings highlight the importance of cautious medication management to minimize gait-related impairments in CSVD patients. Future longitudinal studies should investigate causality and explore interventions like deprescription to improve mobility and overall outcomes in this population.

CV is another important parameter and serves as a significant predictor of falls [31]. However, research on the impact of polypharmacy on gait speed CV is limited, with only one study reporting this effect in community-dwelling older adults [13], which revealed a higher incidence (>3%) of elevated speed CV during STW among individuals taking more medications. In contrast, our findings revealed no significant differences in speed CV among the three groups during STW, nor was it correlated with medication count after controlling for confounders. As a sensitive indicator of motor dysfunction in individuals with CSVD [32], gait variability was significantly elevated during STW, even more in those not engaging in polypharmacy. This suggests that the disease itself may overshadow the effect of polypharmacy, unlike in community-dwelling older adults. DTW, widely recognized for its sensitivity to subtle gait changes in CSVD, provides important clinical insights [6]. While one study found no significant decline in gait speed during cognitive DTW in community-dwelling older adults, a reanalysis using a stricter definition of polypharmacy (≥8 medications) revealed a significant reduction in gait speed [12]. Another study reported reduced prefrontal cortex activation during cognitively demanding DTW tasks in individuals practicing polypharmacy [33]. Notably, in CSVD patients, both polypharmacy status and medication count appear to affect gait during cognitive DTW, with significant difference in gait variability between DTW and STW.

A plausible explanation is that while CSVD itself contributes to CV, intergroup differences remain subtle. STW, as a semi-automatic task with low cognitive demand, may not be sensitive enough to detect subtle changes, whereas DTW, which requires greater cognitive engagement, provides a more effective assessment. Walking without performing a secondary task in STW is largely automatic, whereas DTW requires intact cognitive function to compete for attentional resources, thus enabling revelation of subtle gait impairments [30].

Our findings showed that individuals in the polypharmacy and hyper-polypharmacy groups exhibited slower gait speeds and greater variability during DTW compared to STW, whereas those in the non-polypharmacy group did not, supporting the notion of limited neural resource availability in CSVD patients engaging in polypharmacy. Therefore, careful monitoring of gait patterns in CSVD patients and minimizing cognitive distractions while walking should be prioritized.

Additionally, previous research has demonstrated that comorbidity significantly impacts gait speed [34]. In this study, comorbid conditions differed significantly among CSVD patients with polypharmacy, and our results confirmed that polypharmacy status and medication count were associated with walking speed and its CV, regardless of severity of comorbidities. However, as we did not assess comorbidity severity, its influence cannot be entirely ruled out. It is also plausible that the prescription of multiple medications may reflect more advanced or complex disease status, which may contribute to impaired gait performance. Moreover, medication type also affects gait, with anti-

Table 5. Linear regression models examining the association between gait speed and polypharmacy under both STW and DTW conditions.

Variables		Model 1			Model 2		
		β	p	95% CI	β	p	95% CI
Number of medications	STW speed	–8.962	<0.001	(–12.203, –5.720)	–5.622	<0.001	(–8.393, –2.851)
	DTW speed	–12.493	<0.001	(–15.342, –9.643)	–8.484	<0.001	(–11.253, –5.715)

Note: Model 2 was adjusted for all confounding factors, including the number of comorbidities and TMT-B.
Abbreviations: DTW, dual-task walking; STW, single-task walking; TMT-B, trail-making test-part B; β, standardized regression coefficient; CI, confidence interval.

Table 6. Linear regression models examining the association between speed CV and polypharmacy under both STW and DTW conditions.

Variables		Model 1			Model 2		
		β	p	95% CI	β	p	95% CI
Number of medications	STW speed CV	0.177	0.002	(0.065, 0.289)	0.083	0.077	(–0.009, 0.175)
	DTW speed CV	0.322	<0.001	(0.264, 0.379)	0.246	<0.001	(0.191, 0.300)

Note: Model 2 was adjusted for all confounding factors, including the number of comorbidities and TMT-B.
Abbreviations: CV, coefficient of variation; DTW, dual-task walking; STW, single-task walking; TMT-B, trail-making test-part B; β, standardized regression coefficient; CI, confidence interval.

Table 7. Distribution of neuroimaging biomarkers and total CSVD score across polypharmacy groups.

Variables		Non-polypharmacy group	Polypharmacy group	Hyper-polypharmacy group	χ^2-value	p-value
WMHs	0	10	7	3	6.136	0.408
	1	16	16	7		
	2	14	15	9		
	3	7	11	11		
LIs	Positive	24	32	24	6.728	0.035
CMBs	Positive	17	26	17	4.036	0.133
Total score	0	15	11	4	19.326	0.001
	1	20	10	4		
	2	12	28	22		

Note: Total CSVD score ranges from 0 to 3, with 1 point assigned for each of the following: ≥2 LIs, presence of CMBs, or WMHs of grade 2–3.
Abbreviations: CMBs, cerebral microbleeds; CSVD, cerebral small vessel disease; LIs, lacunar infarctions; WMHs, white matter hyperintensities; χ^2, chi-square.

Table 8. Logistic regressions analyses of the association between neuroimaging biomarkers of CSVD and polypharmacy.

Variables		Model 1				Model 2			
		β	p	OR	95% CI	β	p	OR	95% CI
Total score (Ref: 2)	0	–1.217	0.001	0.296	(0.122, 0.720)	–1.035	0.036	0.355	(0.135, 0.934)
	1	–1.519	0.001	0.219	(0.091, 0.528)	–1.068	0.028	0.344	(0.132, 0.893)
	2	0		1	Reference	0		1	Reference
LIs (Ref: positive)	Negative	–0.397	0.301	0.672	(0.317, 1.426)	–0.699	0.096	0.497	(0.218, 1.133)
	Positive	0		1	Reference	0		1	Reference

Note: Model 2 was adjusted for all confounding factors, including the number of comorbidities and TMT-B. Reference categories: Total CSVD score = 2 (severe burden); LIs = positive (presence of ≥2 lacunes).
Abbreviations: CSVD, cerebral small vessel disease; LIs, lacunar infarctions; TMT-B, trail-making test-part B; β, standardized regression coefficient; CI, confidence interval; OR, odds ratio.

cholinergic drugs, for example, impairing cognitive functions such as attention and executive function—both of which are essential for gait regulation [35]. Since detailed data on specific medication classes (e.g., anticholinergics,

sedatives), dosages, or adherence levels were not collected for the present study, we were unable to examine their individual contributions to gait impairment. Future prospective studies should systematically evaluate the effects of these high-risk medications and consider adherence as a potential confounding factor to better characterize their influence on gait and cognitive-motor performance in CSVD patients.

Importantly, a longitudinal study demonstrated a dose-dependent effect, where each additional medication increased the likelihood of gait decline [13]. Our cross-sectional study further confirmed the relationship between medication count and gait speed in both STW and DTW. Additionally, a geriatric clinic study showed that reducing medication improved mobility and nutritional status without significantly affecting cognition or gait speed. Moreover, baseline gait speed has been identified as a predictor of WMH progression [36,37]. These findings suggest that deprescription could help prevent gait deterioration linked to CSVD progression. Future cohort studies should evaluate the effectiveness of deprescription in mitigating polypharmacy-related gait decline and disease progression in CSVD patients.

The relationship between neuroimaging markers of CSVD and polypharmacy remains unclear due to limited attention to this issue. To date, very few studies have explored this association. This study is the first to demonstrate that polypharmacy in CSVD patients is associated with higher total neuroimaging scores, including WMHs, CMBs, and Lis. These imaging markers were also found to be independent risk factors for reductions in gait performance.

CSVD encompasses various pathophysiological mechanisms, and the total burden score offers a more comprehensive assessment of cerebrovascular damage than individual biomarkers [26]. A higher total burden score is linked to greater symptom severity, potentially leading to increased medication use, which may further contribute to disease progression. Thus, regulating medication load based on total CSVD scores is crucial. However, this study did not establish a longitudinal link between neuroimaging markers and polypharmacy, highlighting the need for future research to track neuroimaging changes in CSVD patients with and without polypharmacy.

Our study presents the first evidence of the relationship between quantitative gait parameters, neuroimaging biomarkers, and polypharmacy in Chinese individuals with CSVD. By assessing the relationship between polypharmacy and gait performance while adjusting for executive function and comorbidities, this study provides novel clinical insights. However, our study has several limitations. Firstly, the cross-sectional design limits our ability to establish causality between polypharmacy and gait impairment in CSVD patients; longitudinal data would be necessary to confirm these relationships over time. Secondly, potential sources of bias or confounding factors may have influenced our results. The inclusion criteria, which required participants to ambulate independently for a distance of 30 steps and comprehend commands, may have excluded individuals with more severe impairments, potentially skewing the findings. Third, despite the adjustment for multiple covariates, unmeasured confounders such as comorbidity severity, frailty, and lifestyle factors may still have influenced the results. Additionally, we did not account for the specific types and dosages of medications, which could have varying effects on gait and cognitive function. Finally, while we controlled for several confounding variables, other unmeasured factors, such as the severity of comorbid conditions and lifestyle differences, might have impacted our outcomes. Future research should focus on longitudinal studies to investigate how medication changes affect gait and disease progression in CSVD patients. In addition, to deepen our understanding of polypharmacy's impact, future research should include participants with varying levels of disease severity and incorporate multidimensional medication data into the analyses. Deprescription strategies and advanced neuroimaging techniques for monitoring brain changes should be explored to optimize treatment plans and interventions.

Conclusion

Our study demonstrates a clear association between polypharmacy and impaired gait performance in older adults with CSVD, particularly under cognitively demanding dual-task conditions. Among a range of neuroimaging markers tested, only the total CSVD score showed an independent association with polypharmacy, suggesting that cumulative cerebrovascular damage may contribute to increased medication burden. These findings underscore the importance of medication reviews and targeted gait assessments in this high-risk population. Future longitudinal studies are needed to clarify causal relationships and evaluate whether deprescription strategies can mitigate mobility decline and disease progression.

Availability of Data and Materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

WW and HX were responsible for the data collection and manuscript writing. NZ and JC contributed to data collection, processing, and critical revision of the manuscript. CX was responsible for data analysis and also contributed to manuscript drafting. YH and HZ were responsible for the study design and critical revision of the manuscript. All authors contributed to the article, reviewed, and approved the final version. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This clinical study was designed and performed in accordance with the Declaration of Helsinki and approved by the Academic Ethics Committee of the Biological Sciences Division of the Seventh Medical Center of the PLA General Hospital (Beijing, China) (2022-098). All the participants provided written informed consent.

Acknowledgment

Not applicable.

Funding

This study was supported by the Wu Jieping Medical Foundation (Grant No. 320.6750.18456 and Grant No. 320.6750.2023-3-37).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Rodriguez L, Araujo AT, D Vera D, Rodríguez Gelvez A, Camacho PA, Mantilla DE, *et al*. Prevalence and imaging characteristics of cerebral small vessel disease in a Colombian population aged 40 years and older. Brain Communications. 2024; 6: fcae057. https://doi.org/10.1093/braincomms/fcae057.

[2] Clancy U, Kancheva AK, Valdés Hernández MDC, Jochems ACC, Muñoz Maniega S, Quinn TJ, *et al*. Imaging Biomarkers of VCI: A Focused Update. Stroke. 2024; 55: 791–800. https://doi.org/10.1161/STROKEAHA.123.044171.

[3] Karvelas N, Elahi FM. White Matter Hyperintensities: Complex Predictor of Complex Outcomes. Journal of the American Heart Association. 2023; 12: e030351. https://doi.org/10.1161/JAHA.123.030351.

[4] Akirov A. Amyloid Burden on PET and Other Risk Factors for Cerebral Microbleeds. Neurology Advisor. 2020. Available at: https://www.neurologyadvisor.com/news/amyloid-burden-on-pet-and-other-risk-factors-for-cerebral-microbleeds/ (Accessed: 19 September 2025).

[5] Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, *et al*. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. The Lancet Neurology. 2013; 12: 822–838. https://doi.org/10.1016/S1474-4422(13)70124-8.

[6] Wardlaw JM, Debette S, Jokinen H, De Leeuw FE, Pantoni L, Chabriat H, *et al*. ESO Guideline on covert cerebral small vessel disease. European Stroke Journal. 2021; 6: CXI–CLXII. https://doi.org/10.1177/23969873211012132.

[7] Duering M, Biessels GJ, Brodtmann A, Chen C, Cordonnier C, de Leeuw FE, *et al*. Neuroimaging standards for research into small vessel disease-advances since 2013. The Lancet Neurology. 2023; 22: 602–618. https://doi.org/10.1016/S1474-4422(23)00131-X.

[8] van den Brink H, Doubal FN, Duering M. Advanced MRI in cerebral small vessel disease. International Journal of Stroke: Official Journal of the International Stroke Society. 2023; 18: 28–35. https://doi.org/10.1177/17474930221091879.

[9] Wong PL, Cheng SJ, Yang YR, Wang RY. Effects of Dual Task Training on Dual Task Gait Performance and Cognitive Function in Individuals With Parkinson Disease: A Meta-analysis and Meta-regression. Archives of Physical Medicine and Rehabilitation. 2023; 104: 950–964. https://doi.org/10.1016/j.apmr.2022.11.001.

[10] Hernandez-Navarro A, Ros-Alsina A, Yurtseven M, Wright M, Kumru H. Non-invasive cerebral and spinal cord stimulation for motor and gait recovery in incomplete spinal cord injury: systematic review and meta-analysis. Journal of Neuroengineering and Rehabilitation. 2025; 22: 53. https://doi.org/10.1186/s12984-025-01557-4.

[11] Takakusaki K, Takahashi M, Kaminishi K, Fukuyama S, Noguchi T, Chiba R. Neural mechanisms underlying upright bipedal gait: role of cortico-brainstem-spinal pathways involved in posture-gait control. Ageing and Neurodegenerative Diseases. 2024; 4: 14. https://doi.org/10.20517/and.2023.45.

[12] George C, Verghese J. Polypharmacy and Gait Performance in Community-dwelling Older Adults. Journal of the American Geriatrics Society. 2017; 65: 2082–2087. https://doi.org/10.1111/jgs.14957.

[13] Montero-Odasso M, Sarquis-Adamson Y, Song HY, Bray NW, Pieruccini-Faria F, Speechley M. Polypharmacy, Gait Performance, and Falls in Community-Dwelling Older Adults. Results from the Gait and Brain Study. Journal of the American Geriatrics Society. 2019; 67: 1182–1188. https://doi.org/10.1111/jgs.15774.

[14] Kosana P, Wu K, Tassiopoulos K, Letendre S, Ma Q, Paul R, *et al*. Polypharmacy Is Associated With Slow Gait Speed and Recurrent Falls in Older People With HIV. Clinical Infectious Diseases: an Official Publication of the Infectious Diseases Society of America. 2024; 78: 1608–1616. https://doi.org/10.1093/cid/ciad782.

[15] Pereira A, Veríssimo M, Ribeiro O. Influence of chronic medical conditions on older patients' willingness to deprescribe medications: a cross-sectional study. BMC Geriatrics. 2024; 24: 315. https://doi.org/10.1186/s12877-024-04891-9.

[16] Kim S, Lee H, Park J, Kang J, Rahmati M, Rhee SY, *et al*. Global and regional prevalence of polypharmacy and related factors, 1997-2022: An umbrella review. Archives of Gerontology and Geriatrics. 2024; 124: 105465. https://doi.org/10.1016/j.archger.2024.105465.

[17] Keller MS, Qureshi N, Mays AM, Sarkisian CA, Pevnick JM. Cumulative Update of a Systematic Overview Evaluating Interventions Addressing Polypharmacy. JAMA Network Open. 2024; 7: e2350963. https://doi.org/10.1001/jamanetworkopen.2023.50963.

[18] Park HY, Park JW, Song HJ, Sohn HS, Kwon JW. The Association between Polypharmacy and Dementia: A Nested Case-Control Study Based on a 12-Year Longitudinal Cohort Database in South Korea. PloS One. 2017; 12: e0169463. https://doi.org/10.1371/journal.pone.0169463.

[19] Delara M, Murray L, Jafari B, Bahji A, Goodarzi Z, Kirkham J, *et al*. Correction: Prevalence and factors associated with polypharmacy: a systematic review and meta-analysis. BMC Geriatrics. 2022; 22: 742. https://doi.org/10.1186/s12877-022-03388-7.

[20] Lutsey PL, Misialek JR, Whitsel EA, Lakshminarayan K, Kucharska-Newton AM, Windham BG, *et al*. Polypharmacy and Potentially Inappropriate Medications in Adults ≥75 Years of Age by Dementia and Frailty Status: The ARIC Study. Mayo Clinic Proceedings. 2025; 100: 1551–1562. https://doi.org/10.1016/j.mayocp.2024.11.030.

[21] Okawa R, Hayashi N, Takahashi T, Atarashi R, Yasui G, Mihara B. Comparison of qualitative and fully automated quantitative tools for classifying severity of white matter hyperintensity. Journal of Stroke and Cerebrovascular Diseases: the Offi-

cial Journal of National Stroke Association. 2024; 33: 107772. https://doi.org/10.1016/j.jstrokecerebrovasdis.2024.107772.

[22] Arbuthnott K, Frank J. Trail making test, part B as a measure of executive control: validation using a set-switching paradigm. Journal of Clinical and Experimental Neuropsychology. 2000; 22: 518–528. https://doi.org/10.1076/1380-3395(200008)22:4;1-0;FT518.

[23] Canning SJD, Leach L, Stuss D, Ngo L, Black SE. Diagnostic utility of abbreviated fluency measures in Alzheimer disease and vascular dementia. Neurology. 2004; 62: 556–562. https://doi.org/10.1212/wnl.62.4.556.

[24] Vishnevsky G, Fisher T, Specktor P. The clock drawing test (CDT) in the digital era: Underperformance of Generation Z adults. Journal of the Neurological Sciences. 2024; 467: 123289. https://doi.org/10.1016/j.jns.2024.123289.

[25] Pradeep A, Raghavan S, Przybelski SA, Preboske GM, Schwarz CG, Lowe VJ, *et al*. Can white matter hyperintensities based Fazekas visual assessment scales inform about Alzheimer's disease pathology in the population? Alzheimer's Research & Therapy. 2024; 16: 157. https://doi.org/10.1186/s13195-024-01525-5.

[26] Amin Al Olama A, Wason JMS, Tuladhar AM, van Leijsen EMC, Koini M, Hofer E, *et al*. Simple MRI score aids prediction of dementia in cerebral small vessel disease. Neurology. 2020; 94: e1294–e1302. https://doi.org/10.1212/WNL.0000000000009141.

[27] Ma R, Zhào H, Wei W, Liu Y, Huang Y. Gait characteristics under single-/dual-task walking conditions in elderly patients with cerebral small vessel disease: Analysis of gait variability, gait asymmetry and bilateral coordination of gait. Gait & Posture. 2022; 92: 65–70. https://doi.org/10.1016/j.gaitpost.2021.11.007.

[28] Xia C, Xie H, Li T, Ding Y, Zhào H, Huang Y. Spatiotemporal gait characteristics during single- and dual-task walking are associated with the burden of cerebral small vessel disease. Frontiers in Neurology. 2023; 14: 1285947. https://doi.org/10.3389/fneur.2023.1285947.

[29] Umegaki H, Yanagawa M, Komiya H, Matsubara M, Fujisawa C, Suzuki Y, *et al*. Polypharmacy and gait speed in individuals with mild cognitive impairment. Geriatrics & Gerontology International. 2019; 19: 730–735. https://doi.org/10.1111/ggi.13688.

[30] Lim YW, Huang SL, Liu YC. The role of executive function domains on cognitive and gait performance during dual task walking in healthy young adults: A preliminary study. Gait & Posture. 2025; 121: 325–331. https://doi.org/10.1016/j.gaitpost.2025.06.009.

[31] Yin L, Nam H, Wei Y, Feng T, Li F, Wang Y, *et al*. Gait and balance metrics comparison among different fall risk groups and principal component analysis for fall prediction in older people. Age and Ageing. 2025; 54: afaf076. https://doi.org/10.1093/ageing/afaf076.

[32] Lai X, Qiao LY, Rau PLP, Liu Y. Gait Disturbances in Older Adults With Cerebral Small Vessel Disease: Mixed Methods Study Using Smartphone Sensors and Video Analysis. JMIR Formative Research. 2025; 9: e58864. https://doi.org/10.2196/58864.

[33] George CJ, Verghese J, Izzetoglu M, Wang C, Holtzer R. The effect of polypharmacy on prefrontal cortex activation during single and dual task walking in community dwelling older adults. Pharmacological Research. 2019; 139: 113–119. https://doi.org/10.1016/j.phrs.2018.11.007.

[34] Wei MY, Kabeto MU, Langa KM, Mukamal KJ. Multimorbidity and Physical and Cognitive Function: Performance of a New Multimorbidity-Weighted Index. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2018; 73: 225–232. https://doi.org/10.1093/gerona/glx114.

[35] Huang AR, Mallet L, Rochefort CM, Eguale T, Buckeridge DL, Tamblyn R. Medication-related falls in the elderly: causative factors and preventive strategies. Drugs & Aging. 2012; 29: 359–376. https://doi.org/10.2165/11599460-000000000-00000.

[36] Zhang W, Shen H, Yao X, Liu F, Wang S, Yang Y, *et al*. Clinical and Diffusion Tensor Imaging to Evaluate Falls, Balance and Gait Dysfunction in Leukoaraiosis: an Observational, Prospective Cohort Study. Journal of Geriatric Psychiatry and Neurology. 2020; 33: 223–230. https://doi.org/10.1177/0891988719874132.

[37] Heiland EG, Welmer AK, Kalpouzos G, Laveskog A, Wang R, Qiu C. Cerebral small vessel disease, cardiovascular risk factors, and future walking speed in old age: a population-based cohort study. BMC Neurology. 2021; 21: 496. https://doi.org/10.1186/s12883-021-02529-6.