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Cerebral White Matter Lesions, Gait, and the Risk of Incident Falls

A Prospective Population-Based Study

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Background and Purpose—The association between cerebral white matter lesions (WMLs) and the risk of falls in older people is uncertain, with no supporting prospective evidence. We aimed to determine the risk of incident falls associated with WML volume, and the interactions between WML volume, gait, and other sensorimotor factors leading to falls.

Methods—We conducted a prospective, population-based study (n=294, mean age 72.3 years, independently mobile). Volumetric MRI, computerized gait measures, and sensorimotor measures of falls risk were obtained at baseline. Incident falls were recorded prospectively over a 12-month period. Using regression modeling, we estimated the risk of incident falls associated with baseline WML volume.

Results—Increasing baseline WML volume was independently associated with any incident fall ($P=0.01$) and multiple incident falls ($P=0.02$). The risk of incident falls was doubled in people with lesion volumes in the highest quintile of its distribution compared with the lowest (adjusted relative risk, 2.32; 95% CI, 1.28–4.14). Greater lesion volume was also associated with poorer gait and greater gait variability (both $P<0.001$). The effect of WML volume on the risk of falls was magnified in people with poorer quadriceps muscle strength ($P=0.03$) and greater gait variability ($P=0.001$).

Conclusions—These data provide the first prospective evidence to our knowledge demonstrating that WMLs are strong risk factors for falls in the general older population. WMLs present potential therapeutic targets for interventional trials in falls prevention. **(*Stroke*. 2009;40:000-000.)**

Key Words: falls ■ gait ■ population-based ■ prospective studies ■ white matter lesions

White matter lesions (WMLs) are seen as hyperintense signals on T2-weighted MRI brain scans and are almost ubiquitously present in people older than age 65 years.[1] Their underlying pathophysiology is suspected to be disease of the small cerebral blood vessels, with hypertension consistently identified as a risk factor.[2]

Falls and gait disorders are major public health problems that lead to significant injury and disability in older people.[3] The incidence of falls is ≈30% per year in people 65 years and older and is expected to increase further as populations age.[4] They often result in hospitalization and institutionalization and are expensive, with their annual costs estimated to increase in the United States to $32 billion by 2020.[5] Thus, there is a need to fully understand mechanisms underlying falls in older people.

WMLs have been postulated to increase the risk of falls and gait decline possibly by affecting motor control.[1] However, the association between WML and falls is yet to be prospectively demonstrated. Moreover, there are limited data indicating that WMLs are associated with declining gait speed and balance.[6–9] The effect of WML on stride-to-stride gait variability, an important predictor of falls,[10] has been examined in only a single study.[11] It is also important to examine the relationships between WMLs, gait, and other physiological factors (eg, muscle strength) leading to falls. Delaying the progression of WML may become a key approach in falls prevention, and such data may assist in the design of such interventional trials.[12]

We aimed to study the associations of the volume of WMLs (WMLV) with incident falls and gait (including gait variability) in a randomly selected population-based sample. We also examined the relative contributions of WMLV, gait, and other sensorimotor factors to the risk of falling.

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Materials and Methods

Sample

The sample consisted of the first 307 participants in the population-based Tasmanian Study of Cognition and Gait study conducted in Tasmania, Australia. Southern Tasmania has a total population of 239 444 people, including 46 159 who are aged 60 years and older.[13] Beginning in January 2005, we randomly selected residents between 60 and 86 years from the Tasmanian electoral roll. They were excluded if they lived in nursing homes, were unable to walk unaided, or could not undergo MRI. The Southern Tasmanian Human Research Ethics Committee approved the study and written informed consent was obtained.

MRI Scanning and Processing

We obtained MRI scans at baseline using a 1.5-T General Electric scanner with the following sequences: high-resolution T1-weighted spoiled gradient echo (TR, 35 ms; TE, 7 ms; flip angle, 35°; field of view, 24 cm; voxel size, 1 mm^3) comprising 120 contiguous slices; T2-weighted fast-spin echo (TR, 4300 ms; TE, 120 ms; NEX, 1; turbo factor, 48; voxel size, 0.90×0.90×3 mm); fluid-attenuated inversion recovery (TR, 8802 ms; TE, 130 ms; TI, 2200 ms; voxel size, 0.50×0.50×3 mm).

The following steps were used to identify WML. First, tissue classification was performed on the T1 scan using the algorithm implemented in the Statistical Parametric Mapping software version 5.[14] All scans were bias-corrected using the method of Styner et al[15] and coregistered to the fluid-attenuated inversion recovery scan in native space. An automated detection algorithm was applied to the coregistered fluid-attenuated inversion recovery images to generate a conservative segmentation of WML regions using a 2-dimensional watershed transform from markers applied to each slice.[16] An adaptive boosting statistical classifier[17] based on a randomly chosen training subset of 45 manually segmented scans (mean age, 74 years; SD, 7.9; 21 male; median WML volume, 10.6 mL; interquartile range, 5.4 to 33.8) was used to determine which regions corresponded to real WML. To avoid misclassification, the results were visually inspected and further manually segmented by one of the authors (J.S.) with excellent test–retest reliability over an average interval of 1 week (intraclass correlation coefficient for WMLV=0.98; 95% CI, 0.97–0.99). WMLV and total brain volume (TBV) were computed by a standard voxel counting algorithm. All procedures were blinded to age, sex, and outcome measures.

Gait Measurement

We measured gait at baseline using the 4.2-m *GAITRite* system (CIR Systems Inc), an electronic carpet walkway. The *GAITRite* has excellent validity against gold standard motion analysis.[18] Participants performed 6 walks at preferred pace and the following gait variables were averaged over the walks: speed (cm/sec), distance divided by ambulation time; cadence (steps/min), number of steps in 1 minute; step length (cm), distance between heel-center of 1 foot to that of the opposite foot during gait; step width (cm), perpendicular distance from heel point of 1 footfall to the line of progression of the opposite foot; and double support time (sec), the time that both feet are in contact with the ground during a gait cycle. For gait variability, stride-to-stride differences were calculated for stride length, stride time, and step width for each participant, and the mean of the stride-to-stride differences for each was calculated using data from all 6 walks. The SD of the mean was used as the measure of variability in each of the 3 measures.

Falls

We recorded falls that occurred during each of the 12 months after enrollment using a standardized falls diary that was mailed back to research staff.[4] A fall was defined as a slip or trip, which led to a loss of balance and caused the participant to land on the floor, ground, or lower level based on the standard definition by ProFaNE (Prevention of Falls Network Europe).[19] Participants were telephoned regularly to remind them to record falls. Those who did not respond on time were contacted by telephone for the information. Incident falls were defined as those occurring in people without a self-reported history of falls. Participants who fell more than once were termed as having multiple falls.

Other Measurements

At baseline, we also measured height (cm), weight (kg), and the following sensorimotor components of the Physiological Profile Assessment of falls risk:[20] quadriceps strength (kg), visual edge contrast sensitivity (dB), simple motor reaction time (msec), lower limb proprioception (degrees), and body sway (mm). Participants also performed the Digit Symbol Coding Test, an established test of cognitive speed and sustained attention.[21]

Self-reported history of lower limb arthritis, hypertension, hypercholesterolemia, smoking, diabetes mellitus, ischemic heart disease, stroke, and falls in the preceding 12 months were recorded. To estimate potential nonresponse bias, age, sex, medical history, and history of falls were also recorded using a brief telephone questionnaire among those unwilling to participate.

Statistical Methods

We used the Fisher exact test or *t* test to compare relevant characteristics between groups. Similar to previous work on cognition,[22] we categorized WMLV into fifths of its distribution for analyzing its associations with falls and gait.

Because convergence difficulties were experienced when fitting a multivariable log binomial model to estimate relative risk, we used a generalized linear model with a Poisson distribution and log-link function[23] to estimate the association between WMLV and incident falls, adjusting first for age, sex, and TBV, and then additionally for other physiological predictors of falls risk and duration of follow-up. The analyses were repeated after further adjusting for self-reported history of stroke. To investigate whether the findings may have been biased because respondents were younger than nonrespondents, the regression analyses were repeated with participants weighted by the multiple $w_{ij}=N_{ij}/n_{ij}$, where N_{ij} represents the number of eligible subjects (respondents and nonrespondents) in a particular age (i) and sex (j) category, and n_{ij} represents the number of respondents in that category.

Given their high correlation with each other, individual gait variables (cadence, step length, step width, and double support time) and gait variability measures (stride length, stride time, and step width variability) were first subjected to factor analyses generating a gait factor and a gait variability factor. Gait speed was not used in generating the former because it is explained totally by cadence and step length. We then computed standardized summary gait scores (termed gait score and gait variability score respectively) from these 2 factors using Thomson's regression method.[24]

Univariable and multivariable linear regression were performed to examine the effect of WMLV on the summary gait scores adjusting first for age, sex, and TBV, and then additionally for other confounding physiological sensorimotor variables. Two-way interactions between variables were examined. Fractional polynomial regression was used to assess for nonlinearity. For both gait and gait variability, no fit-improving transformations were identified. A partial *F* test was used in each of the multivariable models to test for the significance of the additional contribution of WMLV over and above other variables in the model. Finally, we used multivariable linear regression to develop a fuller model examining the relationships between WMLV, summary gait scores, and other physiological variables in predicting incident falls. Standard regression diagnostics were used to estimate model fit and examine for collinearity, leverage, consistency, and influence. Analyses were performed using STATA version 8.2 (Statacorp).

Results

Sample Characteristics

The sample response proportion was 57% (307 responders/541 eligible). Thirteen participants were excluded from fur-

Table 1. Sample Characteristics

Variable	Male, n=163	Female, n=131	All, n=294
Age, mean (SD)	72.3 (6.9)	72.1 (7.2)	72.3 (7.0)
Height, cm, mean (SD)	172.6 (6.5)	158.9 (5.4)	166.5 (9.1)
Weight, kg, mean (SD)	82.3 (13.2)	70.1 (13.0)	76.9 (14.4)
WMHV, mL	12.7 (10.4)	12.5 (9.6)	12.6 (10.0)
TBV, mL	1510.5 (118)	1337.1 (109)	1433.4 (143.1)
Gait measures, mean (SD)			
Speed, cm/sec	115.1 (18.2)	110.8 (19.9)	113.2 (19.1)
Cadence, steps/min	106.7 (8.5)	114.8 (10.6)	110.3 (10.3)
Step length, cm	64.6 (7.8)	57.6 (7.3)	61.5 (8.3)
Step width, cm	10.8 (2.8)	8.6 (2.5)	9.8 (2.9)
DST, sec	0.26 (0.04)	0.25 (0.06)	0.26 (0.05)
Stride length variability	3.84 (1.42)	3.91 (1.51)	3.87 (1.45)
Stride time variability	0.03 (0.01)	0.03 (0.02)	0.03 (0.01)
Step width variability	2.26 (0.96)	2.36 (1.74)	2.31 (1.36)
Sensorimotor measures, mean (SD)			
Visual edge contrast sensitivity, dB	20.4 (2.1)	20.9 (2.4)	20.7 (2.3)
Quadriceps strength, kg	36.2 (12.9)	25.6 (8.9)	31.5 (12.5)
Simple motor reaction time, msec	220 (39)	235 (38)	227 (39)
Proprioception, deg	1.6 (1.0)	1.3 (1.1)	1.4 (1.1)
Body sway, mm	28.9 (10.5)	28.1 (12.3)	28.6 (11.3)
Self-reported medical history, n (%)			
Hypertension	73 (44.8)	66 (50.4)	139 (47.3)
Diabetes	29 (11.7)	13 (9.9)	32 (10.8)
Hypercholesterolemia	67 (41.1)	50 (38.1)	117 (39.8)
Ever-smoker	102 (62.6)	47 (35.9)	149 (50.7)
IHD	42 (25.8)	18 (13.7)	60 (20.4)
Lower limb arthritis	48 (29.5)	43 (32.8)	91 (30.9)
Falls in previous year	25 (15.3)	24 (18.3)	49 (16.7)

DST indicates double support time; IHD, ischemic heart disease.

ther analyses: 1 with cerebral tumor, 7 with MRI confirmed stroke lesions, 1 with a large arachnoid cyst, 3 with extremely slow gait (≤50 cm/sec, 1 with Parkinson disease), and 1 with insufficient gait data. Of the remaining 294, the mean age was 72.3 (SD, 7.0) years (Table 1) and the mean and median WMLV were 12.6 mL (SD, 10.0) and 9.2 mL (interquartile range, 3.0–47.9), respectively. Nonresponders were older ($P<0.001$) but were similar to responders with respect to sex ($P=0.20$), history of hypertension ($P=0.38$), diabetes mellitus ($P=0.51$), ischemic heart disease ($P=0.63$), stroke ($P=0.53$), ever-smoking ($P=0.30$), and previous falls ($P=0.90$).

WMLV and Falls

The mean duration of follow-up was 318 days (SD, 112) with all participants contributing to the analyses. During this time, 105 participants (36%) experienced at least 1 fall and 32 (11%) experienced >1 fall. The median WMLV was significantly greater in those who experienced multiple falls (12.2 mL) compared with those who fell once (9.8 mL) or not at all (8.6 mL; $P=0.01$). Excluding 49 participants with a history of falls, 77 (31%) had an incident fall and 22 (11%) had multiple incident falls during follow-up. The proportions of participants experiencing an incident fall and multiple incident falls increased significantly with increasing category of baseline WMLV (both P for trend <0.05; Figure). After adjusting for age, sex, TBV, other physiological variables, and duration of follow-up, increasing WMLV was associated with a greater risk of any incident fall ($P=0.01$; Table 2) and multiple incident falls ($P=0.02$). The risk of any fall (adjusted relative risk, 2.18; 95% CI, 1.27–3.71), and incident falls (adjusted relative risk, 2.32; 95% CI, 1.28-4.14) during follow-up were approximately doubled in people with WMLV in the highest quintile of its distribution compared with the lowest. These risk estimates were similar after adjusting for self-reported history of stroke. Weighted analyses examining for nonresponse bias increased the risk estimates for incident falls slightly (relative risk, 2.34; 95% CI, 1.26–4.34).

WMLV and Gait

In factor analyses, the individual gait variables yielded a single gait factor explaining 55% of their overall variance (loadings for cadence, 0.81; step length, 0.58; step width, −0.43; double support time, −0.93). The gait variability measures yielded a single variability factor explaining 70% of their variance (loadings for stride length variability, 0.84; stride time variability, 0.87; step width variability, 0.80). The direction of loadings indicated that higher gait scores represented a better gait pattern and that higher gait variability scores represented greater overall gait variability.

Greater WMLV was associated with a poorer gait score ($P<0.001$; Figure) even after adjustment for age, sex, and TBV, and other physiological variables ($P=0.004$; Table 3). Age modified the effect of WMLV on the gait score, such that the association was greater with increasing age. In the final model, the age×WMLV interaction term ($P=0.004$), male gender ($P<0.001$), lower TBV ($P=0.001$), greater body weight ($P<0.001$), poorer quadriceps strength ($P<0.001$), and simple motor reaction time ($P=0.02$) were significantly associated with a poorer gait score. Greater WMLV was associated with a greater gait variability score ($P<0.001$; Figure) and remained associated in multivariable regression (Table 3), along with greater age ($P<0.001$), male gender ($P=0.007$), TBV ($P=0.02$), greater body weight ($P=0.008$), and greater height (0.007). These associations of WMLV with gait were substantially attenuated by adjusting for the Digit Symbol Coding Test score with the coefficient for Digit Symbol Coding Test score remaining unchanged relative to its unadjusted value, suggesting that attention and cognitive speed may mediate the effect of WMLV on gait.

WMLV, Gait, and Physiological Sensorimotor Factors Involved in Falls

In a full model incorporating WMLV, demographic variables, TBV, gait, and other physiological variables, the risk of incident falls associated with WMLV was significantly greater in those with poorer quadriceps strength

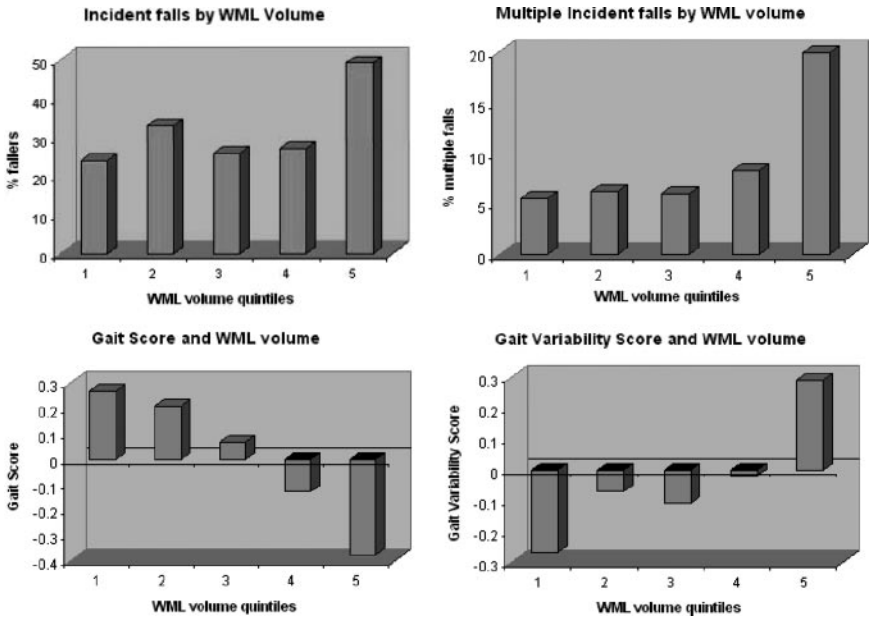

Figure. WMLV, falls, and gait.

(WMLV×quadriceps strength interaction, $P=0.03$) and in those with greater gait variability (WMLV×gait variability score interaction, $P=0.001$), indicating shared pathways involving WMLV and these factors in leading to falls. The gait score and other physiological factors did not add to model fit.

Discussion

We have provided the first prospective evidence to our knowledge demonstrating that WMLs increase the risk of incident falls in the general older population. We have also provided novel evidence of their adverse effect on gait and gait variability in older people and have shown that there may be interactions involving WMLV, quadriceps muscle strength, and gait variability, leading to falls.

The strengths of our study are its prospective design, the population-based nature of the sample, the use of volumetric MRI and computerized gait measures in a large sample, and the blinding of MRI analysis to outcome measurement. We avoided misclassification of WMLs by careful manual editing of the automated segmentation by a single expert with high reproducibility. The blinding of segmentation to outcome minimized systematic measurement bias. Any small segmentation errors are likely to have been randomly distributed, potentially resulting in an underestimation of associations.

A limitation of the study was the moderate sample response rate, which, however, is very similar to that obtained in other measurement-intensive brain imaging studies of older populations.[25,26] The associations were unaffected by the sensitivity analysis weighted by age and sex, further supporting the validity of the findings. Although it is often difficult to accurately estimate the impact of nonresponse bias, responders and nonresponders in this study were highly comparable with respect to self-reported medical history and previous falls, arguing against significant selection bias in terms of overall health. Although nonresponders were older, we did not find within-sample evidence that age may have modified the association between WMLV and incident falls. The use of self-reported falls may also raise the possibility of bias in outcome measurement. However, self-report is the only feasible method of recording falls in population-based samples,[4]and we used accepted methods of ensuring accuracy and completeness of information, including a diary and regular telephone calls.[4] Importantly, the segmentation of WMLs was performed blinded to age, sex, and outcome measurements, further protecting against bias.

To our knowledge, this is the first prospective demonstration of the association between WMLV and falls. In a single,

Table 2. Baseline WMLV and the Risk of Incident Falls (n=245)

		Relative Risk, (95% CI)		
WMLV Category	Falls (n)/Total (N)	Unadjusted	Adjusted for Age, Sex and TBV	Adjusted for Age, Sex, TBV, Physiological Variables,* and Duration of Follow-Up
<6.2 mL	13/54	1.00	1.00	1.00
6.2–8.0 mL	16/48	1.38 (0.75, 2.59)	1.40 (0.76, 2.61)	1.42 (0.79, 2.56)
8.1–10.6 mL	13/50	1.08 (0.55, 2.10)	1.12 (0.42, 2.18)	1.21 (0.65, 2.23)
10.7–16.5 mL	13/48	1.12 (0.58, 2.18)	1.19 (0.60, 2.34)	1.40 (0.68, 2.66)
>16.5 mL	22/45	2.03 (1.15, 3.53)	2.16 (1.19, 3.94)	2.32 (1.28, 4.14)
Test for trend		$P=0.05$	$P=0.04$	$P=0.01$

*Quadriceps strength, visual contrast sensitivity, simple reaction time, proprioception, and body sway.

Table 3. Baseline WMLV, Gait and Gait Variability (n=294)

Outcome	WMLV Category	Regression Coefficient† (95% CI) Unadjusted	Model 1 Adjusted for Age, Sex, and TBV	Model 2 Adjusted for Age, Sex, TBV, and Other Physiological Variables*†
Gait score	<6.2 mL	...	...	...
	6.2–8.0 mL	−0.06 (−0.40, 0.29)	−0.03 (−0.36, 0.29)	−0.05 (−0.36, 0.27)
	8.1–10.6mL	−0.19 (−0.54, 0.15)	−0.12 (−0.46, 0.22)	−0.08 (−0.41, 0.24)
	10.7–16.5mL	−0.41 (−0.76, −0.05)	−0.21 (−0.56, 0.14)	−0.08 (−0.41, 0.24)
	>16.5 mL	−0.66 (−1.00, −0.31)	−0.41 (−0.77, −0.05)	−0.48 (−0.83, −0.14)
Test for trend		$P<0.001$	$P=0.01$	$P=0.004$
Variability score	<6.2 mL	...	...	...
	6.2–8.0 mL	0.19 (−0.07, 0.47)	0.17 (−0.09, 0.43)	0.21 (−0.05, 0.46)
	8.1–10.6mL	0.16 (−0.11, 0.42)	0.10 (−0.17, 0.37)	0.12 (−0.14, 0.38)
	10.7–16.5mL	0.25 (−0.02, 0.52)	0.08 (−0.19, 0.36)	0.13 (−0.15, 0.39)
	>16.5 mL	0.67 (0.38, 0.95)	0.42 (0.12, 0.72)	0.51 (0.21, 0.80)
Test for trend		$P<0.001$	$P=0.04$	$P=0.02$

*For gait score, age, sex, TBV, weight, quadriceps strength, and simple motor reaction time were other significant predictors; †for gait variability score, age, sex, TBV, height, and weight were other significant predictors.

Adjusted r^2 for gait score model 1=12%; model 2=25%.

Adjusted r^2 for gait variability score, model 1=12%; model 2=18%.

small, cross-sectional study, the visually estimated degree of white matter hypodensity on CT was greater in those with a history of falls than in people with no previous falls.[27] We used volumetric MRI, which is superior to CT at detecting WML, to demonstrate a statistically linear association between WMLV and incident falls. However, the principal association was seen among those with relatively large lesion volumes (≥16 mL), raising the possibility that there may be a threshold effect. However, those with increasing WMLV were more likely to have multiple falls, supporting a dose–response relationship, and providing a potential explanation for the recent finding of an elevated fracture risk in those with severe WMLs.[29] Our findings parallel those from population-based studies of WMLs and cognition in which the effects on cognition were seen predominantly in those with highest lesion loads.[22,28] The persistence of the association after exclusion of people with previous falls supports a temporal relationship between WML and incident falls. There is strong biological plausibility in this relationship given that WMLs may disrupt important cerebral white matter connections that assist in motor control and balance.[8,9] Overall, these results support the notion that WML are causal risk factors for falls and highlight the possibility that slowing WML progression may be a key strategy to prevent falls. Control of blood pressure has been associated with a reduced future risk of having severe WML.[30] In a substudy of PROGRESS (Perindopril Protection Against Recurrent Stroke Study), there were encouraging indications that blood pressure lowering may stop or delay the progression of WML.[31] Future large-scale trials of this nature should consider the addition of falls as an outcome measure.

Our data provide novel evidence for the effect of WMLV on overall gait variability, adding significantly to the recently reported association between step length variability and visually graded WMLs.[11] Whereas changes in absolute gait measures (eg, gait speed) may represent a conscious response to accommodate a fear of falling, gait variability is a more reliable measure of intrinsic motor control and thus may be a better functional indicator of the effects of WMLs.[10,32] We confirmed previous findings of an association between increasing WMLV and poorer absolute gait measures.[6–9] Interestingly, the associations between WMLs and the summary gait scores were substantially mediated by their effect on sustained attention and processing speed. Attentional and executive cognitive systems play an important role in maintaining gait and postural control in older people.[33,34] The effect of attentional systems on late-life disability are also known to be partially mediated by gait speed.[35] WMLs may contribute to gait dysfunction in older people by disrupting cortical–subcortical connections that serve such cognitive systems.[3] It remains to be clarified whether the effect of WML on gait is influenced by their topographical location or whether progression of WML leads to gait decline. Our results show that quadriceps strength and gait variability modify the effect of WMLs on the risk of falls. Interventions designed to improve strength and gait variability therefore may be able to offset some of the adverse effects of WMLs. Therefore, falls prevention in older people may be most effective if it is multidimensional, incorporating strategies to slow the progression of WMLs (eg, antihypertensive therapy), increase quadriceps strength, and reduce gait variability (eg, resistance training).

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Disclosures

None.

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