Progression of White Matter Hyperintensities of Presumed Vascular Origin Increases the Risk of Falls in Older People

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Background. Greater volume of cerebral white matter hyperintensities (WMH) of presumed vascular origin may affect postural control and gait. WMH measured at one time point predicts an increased risk of incident multiple falls. However, it is unknown whether WMH progression increases falls risk. We hypothesized that the progression of WMH would be associated with a greater risk of multiple falls.

Methods. A population-based sample aged more than 60 years was randomly selected from the electoral roll and followed up 2.5 years apart with two phases of measurement. Magnetic resonance imaging scans from both time points were subjected to automated segmentation to derive WMH volumes. Falls were recorded prospectively over 12 months after the second magnetic resonance imaging measurement. A generalized linear model was used to estimate the relative risk of multiple falls associated with WMH progression adjusted for confounders.

Results. There were 187 people (mean age 70.4, SD 6.5) with a mean follow-up of 2.5 (SD 0.4) years. Over 12 months, 35 (18.7%) participants reported multiple falls. A greater progression of WMH was associated with an increased risk of multiple falls (adjusted relative risk 1.30, 95% confidence interval 1.00–1.70, p = .05) independent of baseline WMH volume, duration of follow-up, age, sex, and total intracranial volume. This association was unchanged when adjusted for medical history, peripheral sensorimotor factors, gait speed, cognition, medications, mood, and magnetic resonance imaging infarcts.

Conclusion. Greater WMH progression independently increased the risk of multiple falls. Interventions to slow the progression of WMH may be successful in reducing this risk.

Key Words: Falls—Brain aging—Epidemiology—Imaging—White matter hyperintensities.

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FALLS are extremely common in older people. More than 30% of those aged more than 60 years who live at home experience a fall within a 1-year period (1). The adverse outcomes of falls include injury, hospitalization, nursing home admission, and mortality (2). A fall can also lead to significant fear and restriction of activities, resulting in a decline in mobility and loss of independence. Apart from environmental factors that may cause falling, a greater understanding of intrinsic (host) mechanisms is necessary. There is an increasing awareness that age-related brain changes may play an important mechanistic role.

White matter hyperintensities (WMH) of presumed vascular origin (3) are commonly found as hyperintense areas on T2-weighted magnetic resonance imaging (MRI) brain scans of older people and may disrupt white matter tracts that are important for motor control (4). To support this view, higher volumes of WMH are associated with poorer balance, gait (4–7), cognitive function (8), and disability (9), and therefore, might ultimately contribute to falls risk. Previous studies relating WMH with falls have mainly ascertained a history of falls (10–12) rather than prospectively determining falls incidence. Two prospective studies provide evidence that larger volumes of WMH measured at one point in time are associated with an increased future risk of multiple falls (13,14). However, there have been no studies relating progression of WMH with falls incidence. Such a longitudinal study would provide stronger evidence for causality in the relationship.

Our aim was to investigate the association between progression of WMH and the risk of multiple falls in a
longitudinal prospective population-based study of older people. We hypothesized that a greater progression of WMH would be associated with an increased risk of multiple falls.

METHODS

Participants
Participants aged 60–85 years were randomly selected from the Southern Tasmanian electoral roll into the Tasmanian Study of Cognition and Gait (TASCOG). Southern Tasmania has a population of 46,159 aged at least 60 years of age mainly of Caucasian descent. Participants were excluded if they had any contraindications to an MRI scan, lived in a nursing home, a prior history of dementia, Parkinson’s disease, or stroke. Survivors among those who participated in the baseline phase (phase 1) were re-approached for a second set of measurements approximately 2.5 years later (phase 2). The Southern Tasmanian Health and Medical Human Research Ethics Committee approved this study. Written and informed consent was obtained from all participants. Procedures followed were in accordance with institutional guidelines.

MRI Scanning and Processing
MRI was performed at baseline phase 1 and phase 2 using a single 1.5-Tesla scanner (LX Horizon, General Electric, Milwaukee, WI) with the following sequences: high-resolution T1-weighted spoiled gradient echo (repetition time 35 milliseconds, echo time 7 milliseconds, flip angle 35°, field of view 2 4 4 mm; voxel size 1 mm³) comprising 120 contiguous slices; T2-weighted fast spin echo (repetition time 4,300 milliseconds, echo time 120 milliseconds, one excitation, turbo factor 48; voxel size 0.90 × 0.90 × 3 mm); fluid-attenuated inversion recovery (repetition time 8,802 milliseconds, echo time 130 milliseconds, time interval 2,200 milliseconds; voxel size 0.50 × 0.50 × 3 mm), gradient echo (repetition time 800 milliseconds, echo time 15 milliseconds, flip angle 30°; voxel size 0.93 × 0.93 × 7 mm).

All scans were registered to a standard 152-brain Montreal Neurological Institute template in stereotaxic coordinate space. Using T1 sequences and methods based on statistical parametric mapping software (SPM5), brain tissue was classified as gray matter, white matter, or cerebrospinal fluid. Fully automated morphological segmentation with adaptive boosting classification was applied to fluid-attenuated inversion recovery and T1- and T2-weighted scans to identify WMH. WMH volumes estimated using this approach have a close correspondence with expert manual segmentation (intraclass correlation 0.90, 95% confidence interval [CI] = 0.80–0.95, n = 30; 15). Two stroke experts (V.S., T.P.) determined the presence and number of MRI infarcts by consensus, with infarct defined as a hypointensity ≥ 3 mm in diameter on T1-weighted and fluid-attenuated inversion recovery images, with a surrounding hyperintense rim on fluid-attenuated inversion recovery, taking care not to misclassify perivascular spaces as infarcts (16).

Falls
Falls were recorded prospectively over 12 months commencing after the second MRI scan. A fall was defined as “an unexpected event in which the participant comes to rest on the ground, floor, or lower level (17).” Participants kept a diary of all falls and were sent a monthly questionnaire to complete regarding the occurrence of falls. They were followed up by phone each month if they did not return the questionnaire. Those who fell more than once over the 12-month follow-up period were classified as multiple fallers. Multiple falls were chosen as the outcome measure because they are more likely to be related to intrinsic and biological risk factors for falls such as impaired balance and gait than single falls (18).

Other Measures
Self-reported medical history of hypertension, hypercholesterolemia, smoking, diabetes mellitus and acute myocardial infarct, stroke, dementia, and Parkinson’s disease were recorded with a standardized questionnaire. Tests of executive function and attention included the Controlled Word Association Test (19), Category Fluency (animals; 19), the Victoria Stroop test (20), and the Digit Span subtest of the Wechsler Adult Intelligence scale-III; tests of processing speed included the Symbol Search and Digit Symbol Coding subtests of the Wechsler Adult Intelligence scale-III (21); visual spatial function was tested with the Rey Complex Figure test; memory was tested using the Hopkins Verbal Learning Test – Revised (verbal memory) generating scores for total immediate recall and delayed (22); mood was measured using the Geriatric Depression scale (short version; 23). Sensorimotor risk factors for falling (reaction time, quadriceps strength, edge contrast sensitivity, proprioception, and postural sway) were measured using the protocols of the Short Physiological Profile Assessment (24). Gait speed was measured on a GAITRite computerized walkway (CIR Systems, Pennsylvania). The use of psychoactive or antihypertensive medication (antidepressants, antipsychotics, sedative/hypnotics, antiepileptics, antiparkinsons, or narcotics) was recorded at interview using a standard questionnaire.

Statistical Analysis
We first compared the characteristics of people lost to follow-up with those included in the study with a t test or Chi square test. We used a generalized linear model with modified Poisson distribution, log link function, and robust error variance (25) to estimate the risk of multiple falls associated with WMH progression. Based on baseline WMH volume is a strong predictor of WMH progression (26), we calculated WMH progression as a percentage of baseline WMH volume using the formula.
\[ \Delta \text{WMH} = \left( \frac{\text{WMH}_{\text{follow-up}} - \text{WMH}_{\text{baseline}}}{\text{WMH}_{\text{baseline}}} \right) \times 100. \]

We categorized \( \Delta \text{WMH} \) into quarters for all analyses to more clearly quantify its association in models with falls. The model was first adjusted for age, sex, duration of follow-up, and total intracranial volume. Further adjustment was made for medical history, sensorimotor measures, gait speed, cognitive function, mood, and MRI infarcts at phase 2 if the addition of each variable changed the coefficient of WMH measure by greater than 10%. In addition to estimating the effects of WMH progression, we also examined whether quarters of WMH volume at phase 2 were prospectively associated with the risk of multiple falls. We performed further sensitivity analysis for the analysis with quarters of WMH percentage progression excluding those with a previous fall. To account for the possibility that the findings may have been biased from losses to follow-up, we performed analysis using inverse propensity weighting (27). Complete cases are weighted by the inverse of their probability of being a complete case, with those that have a low probability of being a complete case receiving a larger weight. Regression models controlling baseline information were used to estimate the probability of response, and the reciprocals of these propensities were used as weights in the analysis of risk (27). Data were analyzed using STATA version 10.1 (StataCorp, Texas).

**RESULTS**

Of the initial 387 people with MRI scans recruited to TASCOG, 353 met the inclusion criteria for this analysis (Figure 1). At follow-up, 237 (67.1%) participants completed an MRI, of whom 50 were excluded because of inadequate scan quality (movement artifact). Therefore, 187 participants (mean age 70.5, SD 6.5 years) were included in the final analysis. The mean follow-up period between phase 1 and phase 2 measurements was 2.5 ± 0.4 years. When compared with people included in the study, those lost to follow-up were older (\( p < .001 \)), more likely to have a baseline history of acute myocardial infarct (\( p = .01 \)), lower mood (\( p = .04 \)), silent infarcts on MRI (\( p < .001 \)), be on antihypertensive medication (\( p = .01 \)), have poorer scores on the Physiological Profile Assessment Z score (\( p = .006 \)), Hopkins intermediate (\( p = .002 \)), Hopkins delay (\( p < .001 \)), digit symbol coding (\( p = .002 \)), symbol search (\( p < .001 \)), Digit Span (\( p = .02 \)), Category Fluency (\( p = .007 \)), and Rey complex figure (\( p = .005 \)) tests (Table 1). There were no statistically significant differences in other characteristics. WMH volume (divided into quarters) at phase 2 was not associated with risk of multiple falls (RR = 1.20, 95% CI = 0.92–1.59; \( p = .18 \)).

**WMH Progression and Falls**

Only three participants (1.6%) had incomplete falls data. Of these, one participant completed 6 of the 12 questionnaires and two participants completed 11 of the 12 questionnaires, and none reported a fall. A total of 68 (36.4%) participants reported a fall in the 12-month period after the second MRI scan. Of these, 35 (18.7%) participants reported multiple falls. The mean change in WMH volume was 0.99 mL (\( SD 2.6 \)). The mean percentage change...
Table 1. Sample Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lost to Follow-Up (n = 166)</th>
<th>Total Included Sample (n = 187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>73.2 (7.0)</td>
<td>70.5 (6.5)</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>68 (50.0)</td>
<td>90 (48.1)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27.9 (4.5)</td>
<td>27.5 (4.1)</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>23 (13.8)</td>
<td>16 (8.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>88 (53.0)</td>
<td>84 (44.9)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>61 (36.8)</td>
<td>80 (42.8)</td>
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<tr>
<td>Ever smoker</td>
<td>88 (53.0)</td>
<td>90 (48.1)</td>
</tr>
<tr>
<td>Acute myocardial infarct</td>
<td>27 (16.3)</td>
<td>14 (7.5)</td>
</tr>
<tr>
<td>Psychoactive medication’</td>
<td>33 (19.9)</td>
<td>30 (16.2)</td>
</tr>
<tr>
<td>BP lowering medication’</td>
<td>98 (58.3)</td>
<td>84 (45.4)</td>
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<tr>
<td>Geriatric depression score, mean (SD)</td>
<td>2.0 (1.9)</td>
<td>1.5 (1.9)</td>
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<tr>
<td>Other characteristics, mean (SD)</td>
<td></td>
<td></td>
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<tr>
<td>Gait speed, cm/s</td>
<td>114.1 (22.9)</td>
<td>119.3 (18.8)</td>
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<tr>
<td>Physiological Profile Assessment, Z score</td>
<td>−0.17 (0.83)</td>
<td>−0.41 (0.79)</td>
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<tr>
<td>COWAT, number correct</td>
<td>35.6 (12.1)</td>
<td>37.8 (13.2)</td>
</tr>
<tr>
<td>Category fluency, number correct</td>
<td>16.8 (4.8)</td>
<td>18.1 (4.3)</td>
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<tr>
<td>Stroop color time (s)</td>
<td>38.0 (14.5)</td>
<td>35.1 (14.2)</td>
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<tr>
<td>Symbol Search, score</td>
<td>21.8 (7.5)</td>
<td>24.4 (7.1)</td>
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<td>Digit Symbol coding, correct response</td>
<td>48.5 (14.3)</td>
<td>53.3 (14.3)</td>
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<tr>
<td>Digit Span, score</td>
<td>15.4 (3.6)</td>
<td>16.4 (3.9)</td>
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<tr>
<td>HVLT—immediate, score</td>
<td>21.4 (5.9)</td>
<td>23.4 (5.9)</td>
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<tr>
<td>HVLT—delay, score</td>
<td>7.2 (6.7)</td>
<td>8.3 (7.9)</td>
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<tr>
<td>Rey complex Figure test, score</td>
<td>31.4 (5.4)</td>
<td>32.8 (4.1)</td>
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<tr>
<td>MRI measures, mean (SD)</td>
<td></td>
<td></td>
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<tr>
<td>WMH volume, mL</td>
<td>7.42 (7.58)</td>
<td>6.18 (6.60)</td>
</tr>
<tr>
<td>Silent infarcts, n (%)</td>
<td>27 (16.67)</td>
<td>15 (8.02)</td>
</tr>
<tr>
<td>TIV volume, mL</td>
<td>1427.7 (1614.5)</td>
<td>1434.3 (1263.4)</td>
</tr>
</tbody>
</table>

Notes: BMI = body mass index; BP = blood pressure; COWAT = Controlled Oral Word Association Test; HVLT = Hopkins Verbal Learning Test; TIV = total intracranial volume; WMH = white matter hyperintensities.

*Two missing data for total included in sample.

relative to baseline volume was 17.7% (SD 52.6). Greater baseline WMH volume was associated with a larger change in WMH volume measured as a continuous variable over time (β = 0.16, 95% CI = 0.11–0.21; p < .001).

The proportion of participants experiencing multiple falls was greatest in the third and fourth quarter of percentage of WMH progression (Figure 2). After adjustment for age, sex, total intracranial volume, and duration of follow-up, there was a greater risk of multiple falls with increasing quarters of WMH progression (adjusted relative risk = 1.30, 95% CI = 1.00–1.70; p = .05). Table 2 shows the relative risk of multiple falls for each individual quarter of percentage WMH progression in relation to the reference quarter. The addition of medical history, silent infarcts, and other risk factors for falls at time point 2 (sensorimotor factors, cognitive function, gait speed, mood, MRI infarcts) had little or no effect on the strength of this association. There were no interactions between covariates and WMH progression. Weighted analysis for nonresponse bias did not substantially alter the results (RR = 1.30, 95% CI = 0.98–1.71). In the sensitivity analysis performed after excluding those with previous falls (n = 80), the trend toward increased risk for new falls persisted but was no longer statistically significant (RR = 1.45, 95% CI = 0.88–2.40; p = .15). The risk of multiple falls was similar between the first and second, and between the third and fourth quarters. When the percentage of WMH progression was dichotomized at >11.9% (start of the third quarter), the relative risk of multiple falls for those participants with >11.9% WMH progression was RR 1.89 (95% CI = 1.01–3.53; p = .045).

**Discussion**

We provide the first evidence to support an association between greater WMH progression and an increased risk of multiple falls in older people. This association was independent of baseline WMH volume, vascular history, silent MRI infarcts, and other risk factors for falls. These findings support a causal relationship between WMH progression and the occurrence of multiple falls. In addition to potential cognitive benefits, treatments designed to slow the progression of WMH may also contribute to reducing the risk of multiple falls, which are a major public health problem.

The longitudinal design is a major strength of this study, providing a better framework for establishing a causal relationship between WMH and the risk of falls compared with cross-sectional measurement of WMH. Falls were prospectively ascertained with a high response, minimizing measurement bias associated with reliance on a history of falling. Our sample was randomly selected from the population, making the results more generalizable to community-dwelling elders than highly selected clinic-based or volunteer samples. We applied the same fully quantitative and automated method of segmentation to both baseline and follow-up scans, thus minimizing measurement error in estimating WMH volumes. We adjusted for several important confounding factors in our analysis and also examined carefully for interactions. We performed sensitivity analysis excluding those with previous falls. Although the results were no longer significant, this may have been due to reduced power,
It may be that WMH progression is more important than association between WMH at time point 2 and risk of falls. Some participants, although older, having greater vascular risk, poorer cognitive function, and MRI infarcts. Therefore, although our results may not be generalizable to such individuals, it is possible that we have underestimated the strength of the association between WMH progression and falls. Some participants (n = 64; 34.3%) had no change or an apparent improvement in WMH burden over time, their mean baseline volume being 4.6 mL (SD 3.8). This may be due to segmentation error in those with small periventricular WMH volumes. Finally, we were unable to examine location of WMH progression. However, a previous study has demonstrated strong correlations between regional and total WMH progression.

Our finding that WMH progression increases the risk of falls adds substantially to previous findings from the few studies using a single measurement of WMH volume at baseline to predict falls (13,14). In those studies, the greatest risk of falls occurred in those with the largest burden of WMH (13,14). Similarly, diffuse (or confluent) WMH measured on a three-point visual rating scale was also associated with incident hip fractures, most likely a consequence of falling, in older people (29). We did not find a significant association between WMH at time point 2 and risk of falls. It may be that WMH progression is more important than burden at one point in time. Alternatively, the lack of an association may reflect a reduced sample size. In our study, we found the greatest risk of falls in those with the greatest progression, which in turn was most likely to occur among those with the largest baseline WMH volume. We also found a linear trend in the risk of falls with increasing quarters of WMH progression. However, as the risk was similar in the top two-quarters of WMH progression, the sample was dichotomized, with progression >1.9% increasing the risk of multiple falls by 89%. Taken as a whole, the body of evidence in the field now suggests that it is those with confluent WMH (corresponding to a Fazekas rating of 3 or more; 30) that are most at risk of multiple falls, possibly by virtue of being more at risk of white matter tract disconnection, and by being most at risk of WMH progression (26). WMHs are most commonly found in periventricular and anterior subcortical areas that may disrupt frontal–subcortical or long descending motor fibers important for postural control (4,31). A greater burden of WMH is associated with impaired balance (5), gait (5), cognitive function (32), and several other known risk factors for falls. However, our findings suggest an effect of WMH progression on the risk of falling, which is independent of such factors.

Our study provides evidence to strengthen the concept that strategies to slow the progression of WMH may be important for not just preserving cognitive function in older age, but also preventing a major health event such as a fall. However, there is little direct evidence supporting treatments to prevent or slow WMH progression. In cohort studies, older people with well-controlled hypertension were found to have a reduced risk of developing WMH (33) compared with those with uncontrolled untreated hypertension (34). Post hoc analysis in a randomized controlled trial in stroke patients provided suggestive evidence that blood pressure control can slow WMH progression (35). In another post hoc analysis of patients with asymptomatic middle cerebral artery stenosis, the use of a statin was associated with slower WMH progression only among those with severe baseline WMH (36). Further randomized controlled trials are required to establish whether such, and other treatments, may slow WMH progression, with some currently underway (37). It is also possible that WMH progression is a marker for increased frailty and risk for falling, rather than being directly causal. If such a view were adopted, more general interventions such as strength and balance training may build physical reserve and offset any increase in the risk of falls in those people prone to WMH progression.

**Summary**

In conclusion, this longitudinal study provides the first evidence that greater progression of WMHs increases the risk of multiple falls. Interventions to slow the progression of WMHs may hold promise in reducing this risk in older people.
WMH AND RISK OF FALLS IN OLDER PEOPLE

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