Brain White Matter Hyperintensities, Executive Dysfunction, Instability, and Falls in Older People: A Prospective Cohort Study

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Background. White matter hyperintensities (WMHs) are associated with fall risk factors in older people including reduced cognitive functioning and impaired balance and gait. This prospective study investigated relationships between WMHs, sensorimotor performance, executive functioning, and falls in a large sample of community-living older people.

Methods. Two hundred and eighty-seven community-dwelling people aged 70–90 years, underwent structural magnetic resonance imaging and assessments of executive function (Trail-Making Tests), sensorimotor performance (Physiological Profile Assessment), and prospective monitoring of falls. Total WMH volume was quantified using an automated method. Fallers were defined as people who had at least one injurious or two noninjurious falls during the 12-month follow-up period.

Results. Participants with severe WMH burden (WMH volumes as a percentage of intracranial volume in the fourth quartile) performed poorly in the Trail-Making Test and Physiological Profile Assessment (p < .05) and had an increased risk of falls during the 12-month follow-up (relative risk = 1.63, 95% confidence interval 1.11–2.40). The association between WMHs and falls was little changed after adjusting for Trail-Making Test and Physiological Profile Assessment scores, age, sex, education, and a range of cardiovascular risk factors (relative risk = 1.55, 95% confidence interval 1.06–2.26).

Conclusions. Greater WMH burden predicts falls over 12 months, and the association between greater burden of WMHs and falls appears to be independent of reduced executive function and sensorimotor performance. Strategies to reduce the development and progression of WMHs may contribute to future falls prevention in older people.

Key Words: White matter hyperintensities—Aged—Accidental falls—Cognition—Balance—Executive function.

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FALLS are a common clinical problem, with approximately one in three older community-dwelling people falling annually (1). Falls and fall-related injuries, such as fractures, are leading causes of morbidity and mortality in older populations (1). Consequently, the identification of fall risk factors amenable to intervention is of importance in terms of the development and implementation of effective fall prevention strategies. Impairments of balance and gait are well-described risk factors for falls (1–3), and more recently, the importance of executive function has also been highlighted in this regard (2,4).

Age-related cerebral white matter hyperintensities (WMHs), commonly seen on brain magnetic resonance imaging (MRI) in older people, have been recognized as a sign of small vessel disease and are associated with vascular risk factors, such as hypertension (5,6). An increasing body of research has indicated that impaired balance, gait, and mobility and reduced executive functioning are key clinical manifestations of WMHs (7–10). Several cross-sectional studies (9,11–15) and one prospective study (16) have suggested a relationship between falls and greater volumes of WMHs. However, it remains unclear whether this relationship is mediated through impaired physical or cognitive pathways.

The main purpose of this longitudinal study was to investigate the relationship between WMHs and falls in nondemented community-dwelling older people. First, we aimed to confirm the cross-sectional relationship between greater volumes of WMHs and fall risk factors, that is, executive function and sensorimotor performance. Second, we aimed to investigate whether greater volumes of WMHs are related to falls during...
a 12-month follow-up and whether the relationship between WMHs and falls is moderated by executive function or sensorimotor performance. Finally, we investigated whether there is a threshold effect of WMHs on fall risk, in that an increased risk of falling may only be manifested in people with severe WMH burden.

**METHODS**

**Participants**

Two hundred and eighty-seven people aged 70–90 years participated in a cohort study with a 12-month follow-up for falls. Participants were those who consented to undergo both an MRI and a falls risk assessment from a cohort of 1,037 nondemented community-dwelling men and women living in eastern Sydney and participating in the ongoing Sydney Memory and Ageing Study (MAS). The detailed methodology of this study has been published elsewhere (17). Participants were recruited randomly through the electoral roll for this study, with enrollment being compulsory for Australian citizens. People were excluded from the study if they had a previous diagnosis of dementia, psychosis, multiple sclerosis, motor neuron disease, developmental disability, progressive malignancy, a Mini-Mental State Examination (18) score of <24 adjusted for age, education, and non-English speaking background (19) at study entry or if they had received a diagnosis of dementia after comprehensive assessment. Participants were excluded from the study if they had cardiovascular, neurological, or major musculoskeletal impairments that precluded them from walking 20 m without a walking aid, or they had a contraindication to an MRI scan, such as a pacemaker or other metallic implants. The Human Studies Ethics Committee at the University of New South Wales approved the study, and informed consent was obtained from all participants.

**Measures**

At baseline, all participants underwent an extensive assessment of medical, physical, and cognitive measures by trained researchers.

*Medical assessment.*—A complete medical history was recorded during a face-to-face interview including medical conditions, medication use, and falls history in the year prior to the study. Presence of hypertension, hypercholesterolemia, diabetes, and cardiovascular disease were based on self-report of a diagnosed medical condition (eg, answering “yes” to the question: “has a doctor ever told you that you have high blood pressure?”). Levels of disability were assessed using the 12-item World Health Organization Disability Assessment Schedule (WHODAS II, total score range 0–36 (20)). Detailed information on frequency and duration of physical activity was assessed with the Incidental and Planned Exercise Questionnaire (21).

*Executive function.*—Executive function was quantified using the Trail-Making Test (TMT, parts A and B), which addresses three key executive processes (22): (i) working memory, (ii) set shifting, and (iii) response inhibition. Part A requires participants to draw lines connecting numbers (eg, 1-2-3), and part B requires participants to draw lines connecting alternating letters and numbers (eg, 1-A-2-B). The difference between the two parts was calculated to isolate the executive component of this test—TMT (23). The TMT was selected as our previous research has found this test (cut-point of 50s) provides the best neuropsychological measure for discriminating between fallers and nonfallers (2).

*Sensorimotor performance.*—The Physiological Profile Assessment (PPA) (Neuroscience Research Australia, Sydney, NSW, Australia) was used to obtain an estimate of physiological falls risk. The PPA comprises five validated measures of sensorimotor function (3): (i) visual contrast sensitivity (assessed using the Melbourne Edge Test), (ii) proprioception (measured using a lower limb–matching task, with errors in degrees recorded using a protractor inscribed on a vertical clear acrylic sheet placed between the legs), (iii) quadriceps strength (measured isometrically in the dominant leg with participants seated with the hip and knee flexed 90°), (iv) simple reaction time (measured using a light as stimulus and a finger press as response), and (v) postural sway (path area in square millimeters, measured using a sway meter recording displacements of the body at the level of the pelvis with participants standing on a foam rubber mat with eyes open). Weighted contributions from these measures can discriminate between older fallers and nonfallers with an accuracy of up to 75% (3).

**MRI Acquisition and Image Analysis**

MRI scans were performed on a Philips 3T Achieva Quasar Dual scanner (Philips Medical Systems, Best, The Netherlands) located at Neuroscience Research Australia, Sydney. Acquisition parameters have been reported previously in the Sydney MAS protocols (17). For reasons outside the control of the researchers, the original scanner was replaced by a Philips 3T Achieva Quasar Dual scanner in the late stage of the study. As participant recruitment was random, no systematic sampling bias was likely due to the scanner change (24). Participants scanned with the two different scanners were compared on social, demographic, and imaging parameters, and there were no significant differences in age, sex, and years of education. Volumes of gray matter, white matter, cerebrospinal fluid, and total intracranial volume (ICV) were not significantly different between the scanners after controlling for age, education, and sex. Furthermore, analyses of five healthy participants who were scanned on
WMHs predict falls in older adults

Methods

Participants and Procedures

Participants were recruited from the Sydney Memory and Ageing Study (MAS; N = 1,047) cohort study with a 12-month follow-up for falls. Presence of hypertension, hypercholesterolemia, diabetes, and cardiovascular disease were based on self-report of a diagnosed medical condition (e.g., answering “yes” to the question: “has a doctor ever told you that you have high blood pressure?”). Levels of disability were assessed using the PPA comprised of five validated tests: (i) a modified version of the Digit Symbol Substitution Test (18) score of <24 adjusted for overlapping variables with right-skewed distributions. Independent sample t-tests were performed to compare our sample (N = 287) with the entire MAS cohort (N = 1,037) and fallers with nonfallers. Chi-square analysis was used to compare groups on categorical measures.

Statistical Analysis

The data were analyzed using PASW Statistics 18 (SPSS Inc., Chicago, IL) and SAS v9.1 (SAS Institute Inc., Cary, NC). Log transformations were used for continuous scaled variables with right-skewed distributions. Independent sample t-tests were performed to compare our sample (N = 287) with the entire MAS cohort (N = 1,037) and fallers with nonfallers. Chi-square analysis was used to compare groups on categorical measures.

As there was the potential for a threshold effect (16), WMH burden expressed as a percentage of ICV was entered in the models in the following categories: less than 50th percentile (reference), 50th–75th percentile, and greater than 75th percentile (Figure 1). Multivariate linear regression analyses were used to examine the associations between WMHs and physical (PPA) and executive (Trails B–A) performance adjusting for age, gender, education, and other potential confounding factors.

Modified Poisson regression analysis (27) was used to calculate relative risk ratios for the relationship between WMHs and falls, first controlling for age, gender, education, disability, and cardiovascular risk factors and then controlling for sensorimotor performance and executive function. In a final model, interaction terms WMH × PPA and WMH × Trails B–A were entered to investigate potential moderating effects of physiological or cognitive pathways for the relationship between WMH and falls.

Results

Sample Characteristics

MRI scans and falls follow-up data were available for 287 participants who comprised the sample. Compared with the whole MAS cohort (N = 1,037), this sample was younger (77.8 ± 4.5 vs 79.2 ± 4.9 years, t(1,035) = −4.14, p < .001); however, no significant differences were found for gender (women: 53.7% vs 55.9%, χ² = .52), education levels (11.5 ± 3.5 vs 11.6 ± 3.5 years, t(1,035) = −0.35, p = .73), or

WMHs were delineated from coronal plane 3D T1-weighted and Fluid Attenuated Inversion Recovery (FLAIR) structural image scans by using a computer algorithm (Figure 1). The automatic quantification of WMHs was carried out in the following steps that have been described in detail previously (25): (i) coregistration of each participant’s FLAIR images to their corresponding T1-weighted structural images; (ii) spatial transformation of T2 FLAIR and T1 images into Montreal Neurological Institute space; (iii) generation of a brain mask to remove nonbrain tissue by segmenting both T1-weighted and FLAIR images into gray matter, white matter, and cerebrospinal fluid; (iv) initial detection and grading of candidate WMH clusters employing a parametric method from T2 FLAIR images; and (v) visual inspection of the extracted WMH map and manual removal of voxels misclassified as WMH.

Figure 1. Examples of axial T1-weighted, FLAIR, and white matter hyperintensities (WMHs) segmentation on FLAIR image slices at the level of the ventricle show participants with WMH burden in the (A) first quartile, (B) second quartile, (C) third quartile, and (D) fourth quartile, respectively. FLAIR = fluid attenuated inversion recovery.

both scanners within 2 months did not reveal a significant scanner difference.

Falls Follow-up

A fall was defined as “an unexpected event in which the person comes to rest on the ground, floor, or lower level” (26). Fall frequency during 1 year of follow-up was ascertained with monthly falls diaries (26). Participants were also asked whether they suffered any physical injuries as a result of the fall, including bruises, lacerations, or fractures. If a diary was not returned within 2 weeks of the end of each month, participants were contacted by telephone to complete the survey. Previous studies have found that single fallers are more similar to nonfallers than to recurrent fallers on a range of medical, physical, and psychological risk factors. In this study, fallers were defined as people who had at least one injurious or two noninjurious falls during the 12-month follow-up period as we considered that single fallers should not be categorized as nonfallers when an injury occurred (2).

Figure 1. Examples of axial T1-weighted, FLAIR, and white matter hyperintensities (WMHs) segmentation on FLAIR image slices at the level of the ventricle show participants with WMH burden in the (A) first quartile, (B) second quartile, (C) third quartile, and (D) fourth quartile, respectively. FLAIR = fluid attenuated inversion recovery.
Mini-Mental State Examination scores (28.1 ± 1.4 vs 28.0 ± 1.6, t(1,035) = 1.27, p = .20). The prevalence of hypertension (57.3% vs 62.2%, p = .15), diabetes (12.2% vs 11.8%, p = .55), hypercholesterolemia (58.9% vs 60.8%, p = .58), and cardiovascular disease (27.9% vs 31.7%, p = .23) was similar between our subsample and whole cohort. Fewer participants included in our sample were taking six or more medications (40.1% vs 47.6%, p = .03) and antidepressants (5.6% vs 11.1%, p < .01). The mean total volume of WMHs for our study sample was 8.6 mL (±12.8) compared with 10.1 mL (±16.3) for the whole MAS cohort with available data (N = 542; p = .24).

Relationships Between WMHs and Executive and Physical Function

Tables 1 and 2 summarize the multivariate linear regression model findings for the relationships between WMHs and executive and sensorimotor functioning (Tables 1 and 2). The mean WMH volume of the reference group (<.33% ICV) was 1.9 ± 1.5 compared with 7.6 ± 2.0 mL in the moderate WMH group (.33%–.70% ICV) and 22.9 ± 19.2 mL in the severe WMH group (> .70% ICV).

The analyses revealed that participants with severe WMH burden (in the fourth quartile) performed significantly worse in the tests of executive function (Table 1; Model 1) and sensorimotor function compared with participants in the reference group (Table 2; Model 1). These associations remained significant after adjustment for sex, age and education (Model 2), and cardiovascular risk factors (Model 3).

The Relationship Between WMHs and Falls

During the 12-month follow-up, four people were lost to follow-up. Of the remaining 283 participants with complete follow-up, 125 (44.2%) fell at least once, of which 53 (18.7%) had two or more falls and 84 (29.7%) reported at least one injurious fall. In total, 99 (35.0%) participants had multiple noninjurious falls or at least one injurious fall during 1-year follow-up period. Univariate analyses showed that those who suffered multiple noninjurious falls or at least one injurious were more likely to be women (p = .031) and have poorer scores on the WHODAS (p = .025), TMT (p = .036), and PPA assessments (p < .001). No participants suffered a stroke in the follow-up period.

A modified Poisson regression model adjusting for age, sex, education (Table 3; Model 2), and other covariates (Table 3; Model 3), indicated that the severe WMH group was at an increased risk of suffering multiple or injurious falls when compared with the reference group. This association was little changed after additional adjustments for the PPA and TMT assessments (Table 3; Model 4), which suggests that the contributing effect of WMH on falls was independent of these factors. This was confirmed by nonsignificant interaction terms: WMH × PPA and WMH × Trails B-A (Table 3; Model 4).

Discussion

Our study used a prospective design to investigate the relationship between WMHs and falls in nondemented community-dwelling older adults. In accord with previous

Table 1. Multivariate Linear Regression Output for the Relationship Between WMHs and Trail-Making Test (B-A)

<table>
<thead>
<tr>
<th>WMH Severity Group</th>
<th>Mean (SD) of Executive Function (s)</th>
<th>β (SE)</th>
<th>p</th>
<th>β (SE)</th>
<th>p</th>
<th>β (SE)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50th Percentile</td>
<td>64.34 (41.57)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50th-74th Percentile</td>
<td>74.87 (44.16)</td>
<td>10.324 (7.641)</td>
<td>.178</td>
<td>8.392 (7.643)</td>
<td>.273</td>
<td>9.246 (7.688)</td>
<td>.230</td>
</tr>
<tr>
<td>≥75th Percentile</td>
<td>88.03 (70.61)</td>
<td>23.140 (7.797)</td>
<td>.003</td>
<td>19.286 (7.942)</td>
<td>.016</td>
<td>17.837 (7.985)</td>
<td>.026</td>
</tr>
</tbody>
</table>

Notes: Regression coefficients and p values were calculated using multiple linear regression models. WMH = white matter hyperintensities.

* Adjusted for intracranial volume (ICV).
† Adjusted for ICV, sex, age, and education.
‡ Adjusted for ICV, sex, age, education and history of hypertension, cerebrovascular disease, transient ischemic attacks, heart disease, and diabetes.

Table 2. Multivariate Linear Regression Output for the Relationship Between WMHs and Physiological Profile Assessment (PPA) Score

<table>
<thead>
<tr>
<th>WMH Severity Group</th>
<th>Mean (SD) of PPA (SD)</th>
<th>β (SE)</th>
<th>p</th>
<th>β (SE)</th>
<th>p</th>
<th>β (SE)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50th Percentile</td>
<td>0.38 (0.83)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50th-74th Percentile</td>
<td>0.42 (0.90)</td>
<td>0.021 (0.125)</td>
<td>.868</td>
<td>−0.060 (0.136)</td>
<td>.658</td>
<td>−0.040 (0.138)</td>
<td>.769</td>
</tr>
<tr>
<td>≥75th Percentile</td>
<td>0.74 (0.88)</td>
<td>0.322 (0.127)</td>
<td>.012</td>
<td>0.319 (0.149)</td>
<td>.033</td>
<td>0.321 (0.152)</td>
<td>.036</td>
</tr>
</tbody>
</table>

Notes: Regression coefficients and p values were calculated using multiple linear regression models. Higher scores in PPA indicate impaired physiological function.

* Adjusted for intracranial volume (ICV).
† Adjusted for ICV, sex, and age.
‡ Adjusted for ICV, sex, age, psychoactive medication use and history of arthritis, hypertension, cerebrovascular disease, transient ischemic attacks, heart disease, and diabetes.
In summary, the study findings indicate that greater WMH burden predicts falls over 12 months, and the association between high volumes of WMHs and falls appears to be

Table 3. Modified Poisson Regression Output for the Models Relating to the Relative Risks (RRs) of Suffering Multiple or Injurious Falls During the 1-Year Follow-up Period

<table>
<thead>
<tr>
<th>WMHs Severity Group</th>
<th>Model 1 *</th>
<th>Model 2 †</th>
<th>Model 3 ‡</th>
<th>Model 4 §</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>RR (95% CI)</td>
<td>p</td>
<td>RR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>&lt;50th Percentile</td>
<td>30.0% (42)</td>
<td>Reference</td>
<td>1.33 (0.88–2.01)</td>
<td>.182</td>
</tr>
<tr>
<td>50th–74th Percentile</td>
<td>38.9% (28)</td>
<td>Reference</td>
<td>1.63 (1.11–2.40)</td>
<td>.012</td>
</tr>
<tr>
<td>≥75th Percentile</td>
<td>42.3% (30)</td>
<td>Reference</td>
<td>1.54 (0.96–2.47)</td>
<td>.076</td>
</tr>
<tr>
<td>PPA</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>WMH × PPA</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>WMH × TMT</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Notes: RR and 95% confidence interval (CI) were calculated using modified Poisson regression models. WMHs = white matter hyperintensities.

* Adjusted for intracranial volume (ICV).
† Adjusted for ICV, sex, age, and education.
‡ Adjusted for ICV, sex, age, education, physical activity and disability, psychoactive medication use and history of hypertension, cerebrovascular disease, transient ischemic attacks, heart disease, and diabetes.
§ Based on Model 3 with additional adjustments for Physiological Profile Assessment (PPA, median cutoff score: 0.37) and Trail-Making Test (TMT, cutoff score: 50s).

findings (8,9,28), we found that people with severe WMH burden had significantly poorer executive function and sensorimotor performance compared with the mild WMH burden group (Tables 1 and 2). Furthermore, the study participants with severe WMH burden had a 55% greater risk of suffering multiple or injurious falls when compared with participants with mild WMH burden during the 12-month follow-up period while adjusting for confounding factors (Table 3). Our study also supported a threshold effect between WMHs and falls because an increased risk was apparent only in individuals with severe levels of WMHs.

Many studies have shown that reduced sensorimotor performance is a key risk factor for falls (1–3). However, the structural and functional integrity of brain neural networks is also necessary for processing sensorimotor input from vision, proprioception, and peripheral sensation and, therefore, for maintaining balance control (29). Planning, control, and execution of movements also relies on frontal executive function, and impairments in this area are likely to increase falls risk (4,30–32). WMH may represent ischemic damage to periventricular and subcortical white matter tracts that carry executive and sensorimotor information from the frontal cortex to lower centers. Damage to these tracts may result in functional deficits that may predispose elderly people to falls (33). However, our analyses suggested that WMHs, cognitive (executive) functioning, and sensorimotor impairments were independently associated with falls (Table 3; Model 4). Therefore, it remains unclear through which mechanisms WMHs lead to falls in healthy older adults.

Only one previous study (the TASCOG Study) has reported an association between WMHs and prospectively determined falls (16). In this study, increased risk was only evident in the subset of people who had not previously fallen. In the current study, greater WMHs increased the risk of falls not only in previous nonfallers (data not shown) but also in the total sample, where fall risk doubled for people with severe WMH burden. Mean WMH volume was lower in our sample compared with the TASCOG study sample (8.6 vs 12.6 mL), even though our sample was older (mean age: 77.8 ± 4.5 vs 72.3 ± 7.0 years). This suggests that our sample was healthier, and it is possible that this factor and/or differences in the faller outcome measure used in the two studies may account for the slightly divergent study findings.

The main strengths of the study include the comprehensive medical, executive, and sensorimotor assessments in a large community-based cohort and a prospective follow-up of falls, in addition to MRI scans. This enabled us to adjust for some important covariates associated with WMHs and falls. This study also has certain limitations. The sample largely consisted of healthy community-dwelling older people. Even though the demographic, health, and medical characteristics of the participants included in the study were similar to those in the MAS cohort and other published studies (8,16), we acknowledge that the exclusion of participants who were unable to undergo MRI and additional assessments could influence the representativeness of the sample. Second, we did not include lacunar infarcts in the analysis, which might potentially underestimate the effect of small vessel disease on fall risk.

The study findings have clinical implications in relation to cardiovascular health. WMHs, sensorimotor performance, and executive function may share common pathophysiological processes with shared end points including an increased risk of falls. WMHs are arguably a surrogate for hypertensive microangiopathy (34) and are consistently found to be associated with hypertension (35,36). Studies have also reported that severe WMHs significantly increase the risk of dementia (37)—a strong risk factor for falls (38). Tight control of traditional vascular risk factors may, therefore, have benefits that extend beyond stroke and myocardial disease and include preservation of physical performance and reduction in falls risk (39,40).

In summary, the study findings indicate that greater WMH burden predicts falls over 12 months, and the association between high volumes of WMHs and falls appears to be
independent of reduced executive and physiological function. Attention to known risk factors for WMHs, such as the management of long-term hypertension, may contribute to future fall prevention in older people.

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Conflict of Interest
The Physiological Profile Assessment is commercially available through Neuroscience Research Australia.

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References