# Deep frontal and periventricular age related white matter changes but not basal ganglia and infratentorial hyperintensities are associated with falls: cross sectional results from the LADIS study

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## ABSTRACT

**Background:** Global age related white matter changes (ARWMC) are associated with progressive gait disturbances and falls, hypothesised to result from interruptions of cortico-subcortical circuits controlling balance, posture and locomotion.

**Methods:** The location of ARWMC in a large cohort of elderly non-disabled individuals with reported falls was analysed, using the cross sectional data of the Leukoaraiosis and Disability (LADIS) study. Detailed anatomical distributions of ARWMC assessed by MRI studies were analysed with respect to falls and balance performance.

**Results:** The severity of global ARWMC was significantly associated with a history of falls in the year prior to study inclusion (22.2% in the mild, 31.6% in the moderate and 37.3% in the severe ARWMC group according to the Fazekas scale; $p = 0.002$). Analysing the anatomical distribution of ARWMC, using the semiquantitative Scheltens scale, in multivariate analysis, periventricular ($p = 0.006$) and frontal deep ($p = 0.033$) ARWMC were independently associated with falls. Furthermore, logistic regression identified frontal deep ($p = 0.003$) ARWMC, but not basal ganglia and infratentorial hyperintensities, as significantly associated with balance disturbances.

**Conclusion:** The association of frontal and periventricular ARWMC with falls supports the hypothesis that interruption of frontal subcortical motor circuits lead to balance disturbances and hence to an increased risk for falls in ARWMC.

Changes in the cerebral white matter, also called leukoaraiosis,[1] are detected frequently on brain imaging of elderly persons and are known to be associated with several vascular risk factors.[1–4] Apart from hypertension, age is one of the most important factors linked with leukoaraiosis and therefore the term age related white matter changes (ARWMC) has been introduced to define these structural alterations[5] and to separate them from other diseases of the white matter observed in younger patients.[6]

One of the key clinical features associated with ARWMC are motor abnormalities such as gait[7–10] and balance impairment,[10 11] which lead to considerable medical and socioeconomic problems. Recurrent falls are associated with physical decline and disability, resulting in psychosocial problems and a significant reduction in quality of life.[12] In addition, falls are correlated with an increased injury related mortality[13] and notable medical expenses due to hospitalisation caused by fall related injuries.[12 14]

Various risk factors for falls have been proposed, among them visual impairment, functional limitations in daily living, an abnormal postural sway and an increased gait and stride variability.[12 15 16] Several neurodegenerative disorders, such as Parkinson's disease,[17] Alzheimer's dementia and various conditions associated with cerebellar ataxia,[18] but also psychiatric diseases such as depression, are correlated with an increased risk of falls.

Direct evidence for the association of ARWMC with falls is scarce but has been derived from several studies showing associations between ARWMC and gait and balance disturbances.[7 18–21] Interruption of frontal lobe circuits and descending motor fibres has been discussed as the most probable cause of balance disturbances and falls in ARWMC.[10 19] These involve the prefrontal dorsolateral cortex[22] but data correlating motor performance with the precise topography of ARWMC are scarce to date.[21 23]

In the present study, the association of ARWMC with balance disturbances and the rate of falls in a large cohort of elderly non-disabled individuals were analysed using the cross sectional data of the Leukoaraiosis and Disability in the Elderly (LADIS) study. The purpose of this paper was to define the detailed anatomical distribution of ARWMC to ascertain the structural and functional relationship hypothesised.

## METHODS

### Sample and protocol

Data were derived from the LADIS study. In this multinational study, 11 European centres collaborate with the purpose of assessing the role of ARWMC as an independent predictor of transition to disability in the non-disabled elderly.[6]

In total, 639 elderly individuals were enrolled in a hospital based setting, presenting with no or mild disability in the instrumental activities of daily living, defined as no impairment at all or only 1 item compromised in the instrumental activities of daily living scale.[24] At baseline, MRI studies following a standard protocol[6] were performed

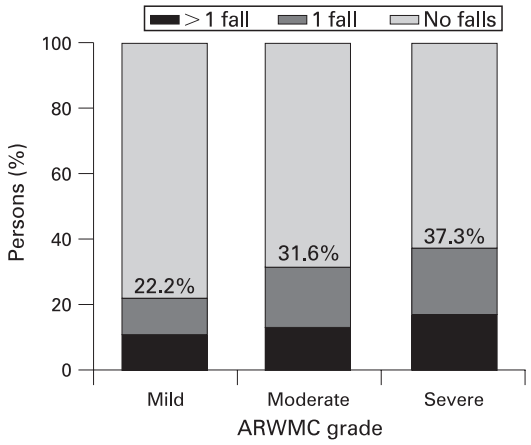


**Figure 1** Rate of patients with a history of falls in the year prior to study inclusion in the three age related white matter changes (ARWMC) severity groups (mild, moderate, severe), according to the Fazekas scale.

and the degree of ARWMC severity was categorised into three groups (mild, moderate and severe) using the visual scale of Fazekas.[25] Inclusion and exclusion criteria have been described in detail previously.[6]

At baseline and during the yearly follow-up, an extensive set of clinical and functional tests was performed. This included a structured and comprehensive questionnaire to assess vascular risk factors and comorbidity, as well as different global functioning, and cognitive, motor, psychiatric and quality of life measures, which were reviewed with the patient and a relative at baseline and every year during the 3 year follow-up period. Both the occurrence and frequency of falls were documented as separate items in this structured questionnaire.

**Table 1** Independent effect of ARWMC, comorbidities and other factors on falls

| | Univariate | Multivariate* | |
|---|---|---|---|
| **Factor** | **OR (95% CI)** | **OR (95% CI)** | **p Value†** |
| ARWMC (Fazekas scale >1) | 1.82 (1.28–2.60) | 1.60 (1.07–2.41) | 0.024 |
| Lacunes (≥ n = 1) | 1.25 (0.88–1.76) | 1.14 (0.76–1.69) | 0.533 |
| Complaints of gait disturbance | 3.17 (2.22–4.53) | 2.82 (1.83–4.35) | <0.001 |
| Female gender | 1.81 (1.27–2.58) | 1.74 (1.14–2.65) | 0.011 |
| Age ≥75 years | 1.35 (0.96–1.91) | 1.13 (0.76–1.68) | 0.551 |
| Memory impairment | 1.72 (1.19–2.48) | 1.22 (0.79–1.88) | 0.376 |
| Syncopal events | 1.78 (1.15–2.74) | 1.57 (0.96–2.57) | 0.072 |
| Vertigo | 1.64 (1.10–2.44) | 1.01 (0.64–1.60) | 0.971 |
| Depression | 1.38 (0.95–2.00) | 0.94 (0.61–1.45) | 0.764 |
| Stroke | 0.97 (0.66–1.42) | 0.82 (0.52–1.29) | 0.387 |
| Cardiac arrhythmias | 1.07 (0.69–1.65) | 0.91 (0.55–1.50) | 0.721 |
| Hypertension | 1.18 (0.81–1.73) | 1.22 (0.79–1.90) | 0.375 |
| Diabetes mellitus | 1.04 (0.64–1.69) | 0.93 (0.53–1.61) | 0.789 |
| Osteoarthritis | 1.17 (0.80–1.72) | 0.80 (0.51–1.24) | 0.312 |
| Hearing loss | 1.09 (0.77–1.53) | 1.04 (0.69–1.56) | 0.862 |
| Visual loss | 1.50 (0.97–2.31) | 0.98 (0.59–1.62) | 0.942 |
| Physical activity | 0.48 (0.34–0.69) | 0.60 (0.39–0.93) | 0.023 |

*Binary logistic regression model (stepwise selection of variables, model included the variables: age ≥75 years, sex, ARWMC severity, lacunes, hypertension, diabetes mellitus, syncopal events, cardiac arrhythmias, peripheral vascular disease, osteoarthrosis, stroke, transient ischaemic attack; complaints of gait disturbance, memory impairment, depression, vertigo, hearing loss, visual loss and physical activity; centre origin was included as a covariable).
†p values refer only to the multivariate analysis.
ARWMC, age related white matter changes.

To assess physical performance and postural control, a previously described test battery,[9] including the Short Physical Performance Battery (SPPB)[26] and the single leg stance time as a simple test for balance ability[7] was used. This test battery comprised timed clinical tests assessing locomotion (walking speed), and balance and postural control (single leg stance time, tandem stance, chair stands), all of which are supposedly controlled by cortico-subcortical functional loops.

### MRI scans and visual ratings

All persons underwent cerebral MRI following a standard protocol. Scans were evaluated centrally at the Image Analysis Centre of the Vrije Universiteit Medical Centre, Amsterdam, The Netherlands.[27] Visual ratings of ARWMC were carried out at this centre by a single rater who was blinded to the clinical details. Apart from assessment of the degree of global ARWMC and severity according to the Fazekas scale, the anatomical distribution of ARWMC was described using the semiquantitative Scheltens scale.[28] In this scale, the severity of hyperintensities in the different anatomical areas of the brain is scored separately, including three periventricular regions, four areas of deep white matter, five areas of the basal ganglia and four different infratentorial regions.

The number of lacunes was counted in each of the same anatomical regions but not subdivided by side of brain.[27]

During the evaluation of the follow-up MRI scans, baseline MRI rating was corrected in 22 scans. This correction was necessary because of a mistake in the data processing, not because they were misclassified. The correction proved not to affect the main results of the baseline analyses but resulted in small differences in some data reported in the present paper compared with those reported in previous publications.

### Statistical analysis

A non-parametric Kruskal–Wallis test was conducted to compare the rate of falls between the different ARWMC severity groups. Furthermore, non-parametric Mann–Whitney U tests were used to compare the means of the single leg stance time and the SPPB subscore "standscore" in patients with and without falls and in the different groups of ARWMC severity, respectively. To determine differences between the mean single scores of the Scheltens scale in patients with and without falls, univariate non-parametric Mann–Whitney U tests and a multivariate binary logistic regression model were used.

To describe variations in different factors depending on the history of falls, univariate analyses were performed using odds ratios (ORs) with 95% confidence intervals (CIs). Subsequently a binary logistic regression model was carried out to test independently the effect of factors associated with falls in order to obtain adjusted ORs. Finally, a binary logistic regression model was used to determine the independent association of severe hyperintensities in different brain regions according to the Scheltens scale with a diminished balance ability, ascertained by the single leg stance time.

All statistical analyses were calculated using SPSS for Windows, V.15 (SPSS Inc, Chicago, Illinois, USA).

## RESULTS

In total, 639 individuals with a mean age of 74.1 (5.0) years were included in the study (288 men and 351 women). According to the Fazekas scale, 284 people (44.4%) had mild, 197 (30.8%) moderate and 158 (24.7%) severe ARWMC at baseline.

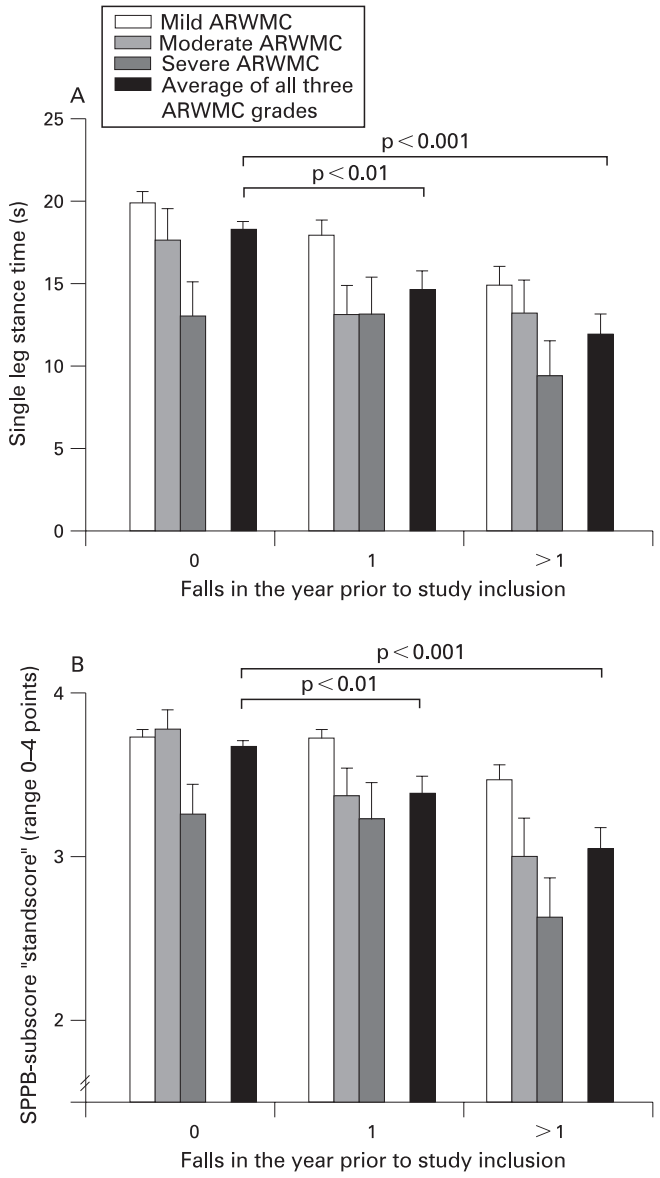


**Figure 2** Mean single leg stance time (A) and the standing balance subscore of the Short Physical Performance Battery (SPPB) (B), dependent on the rate of falls in the year prior to study inclusion. Values are mean (SEM) for the different severities of age related white matter changes (ARWMC) according to the Fazekas scale, separately for the three groups (mild, moderate and severe), and the averaged values of all three degrees of ARWMC severity.

At first, a statistically significant association of global ARWMC with a positive history of falls in the year prior to study inclusion (fig 1) was found. The rate of falls was 22.2% in the mild, 31.6% in the moderate and 37.3% in the severe ARWMC group ($p = 0.002$).

Using a binary logistic regression model to study the impact of comorbidity (table 1), apart from moderate to severe ARWMC, complaints of gait disturbance and female gender were identified as independent factors for an increased rate of falls in the year prior to study inclusion. The association of memory impairment, syncopal events and vertigo with falls found in univariate analysis was no longer significant in the multivariate binary logistic regression model. Detection of lacunes on MRI as the second main type of vascular pathology seen in the white matter was not associated with an increased rate of falls. Physical activity was associated with a significant lower rate of falls (OR 0.60 (95% CI 0.39 to 0.93); $p = 0.023$).

In fig 2, the single leg stance time (fig 2A) and the standing balance subscore of the SPPB (fig 2B) as simple tests for balance ability are plotted against the rate of falls in the year prior to study inclusion. Compared with those without a history of falls (mean 18.2 (SEM 0.5) s), the mean single leg stance time was significantly reduced both in individuals with a history of multiple falls (11.9 (1.2) s; $p<0.001$) and in those with a single fall (14.6 (1.1) s; $p<0.01$) in the previous year (fig 2A). Furthermore, within each of these three groups, the single leg stance time was significantly correlated with the severity of ARWMC ($p<0.05$ in the Kruskal–Wallis test, respectively).

Likewise, the standing balance subscore of the SPPB (fig 2B) was significantly reduced in individuals with a history of multiple falls (3.05 (0.13); $p<0.001$) and a single fall (3.38 (0.11); $p<0.01$), compared with those without falls (3.67 (0.03)) in the previous year.

Analysing the detailed anatomical distribution of ARWMC, as assessed by the Scheltens scale (table 2), falls were associated with increased scores in the ratings of periventricular ARWMC (frontal caps, occipital caps and lateral ventricle bands) as well as frontal and parietal deep ARWMC. In contrast, falls did not show a significant correlation with temporal and occipital deep ARWMC, basal ganglia lesions or infratentorial foci of ARWMC in the present cohort. In a multivariate binary logistic regression model, only periventricular ($p = 0.006$) and frontal deep ARWMC ($p = 0.033$) remained significantly associated with falls.

In table 3, the independent effect of the anatomical distribution of ARWMC on balance ability, as reflected by single leg stance time, using a binary logistic regression model, is presented. Similar to the results observed for the rate of falls, a significant association of severe frontal deep ARWMC ($p = 0.003$) and a trend for severe hyperintensities located in the internal capsule ($p = 0.057$) with a diminished balance ability, determined by a reduced single leg stance time under 15 s, was demonstrated. However, temporal and occipital deep ARWMC, other basal ganglia lesions and infratentorial ARWMC were not associated with significant balance disturbances.

## DISCUSSION

Further to the previously reported association of ARWMC with global motor impairment and gait disturbances,[9] this study has demonstrated that falls are significantly associated with the global severity of ARWMC in a cross section of a large cohort of 639 elderly persons. Furthermore, the rate of falls and the severity of ARWMC were significantly associated with balance disturbances.

Apart from other sources of falls, such as orthopaedic diseases, visual impairment or peripheral neuropathies, gait disturbances are an important determinant of falls. However, we found that ARWMC represent a further independent risk factor for falls. Thus we postulate that comparable with other movement disorders such as Parkinson's disease,[29] impairment of postural control, which is not necessarily closely related to the severity of gait dysfunction, should be the most important cause of falls in patients with ARWMC. Clinically, early identification of patients with ARWMC at risk of falls using simple clinical tests, such as the single leg stance time, might be of relevance.

Using a novel approach in a large study, detailed anatomical studies of ARWMC have confirmed the hypothesis that falls and balance disturbances are associated primarily with frontal

**Table 2** Mean single scores and subscores of the Scheltens scale in patients with and without falls in the year prior to study inclusion

| Scheltens scale item | Falls in the year prior to study inclusion | | p Value* Univariate | p Value† Multivariate |
|---|---|---|---|---|
| | No | Yes | | |
| PVH frontal caps | 1.35 (1.30–1.41) | 1.52 (1.44–1.59) | 0.004 | |
| PVH occipital caps | 1.47 (1.43–1.53) | 1.60 (1.53–1.67) | 0.016 | |
| PVH lateral bands | 1.23 (1.18–1.28) | 1.40 (1.33–1.48) | 0.001 | |
| PVH subscore | 4.06 (3.94–4.17) | 4.52 (4.33–4.70 | <0.001 | 0.006 |
| WMH frontal | 3.77 (3.62–3.94) | 4.30 (4.07–4,52) | <0.001 | 0.033 |
| WMH parietal | 3.54 (3.36–3.73) | 3.93 (3.64–4.23) | 0.009 | 0.122 |
| WMH occipital | 0.34 (0.25–0.43) | 0.47 (0.29–0.66) | 0.740 | 0.856 |
| WMH temporal | 1.73 (1.57–1.89) | 1.99 (1.72–2.27) | 0.184 | 0.675 |
| WMH subscore | 9.39 (8.92–9.85) | 10.67 (9.94–11.41) | 0.004 | |
| BG caudate nucleus | 0.06 (0.02–0.09) | 0.07 (0.01–0.13) | 0.922 | 0.870 |
| BG putamen | 0.40 (0.31–0.49) | 0.40 (0.25–0.54) | 0.899 | 0.246 |
| BG globus pallidus | 0.18 (0.12–0.24) | 0.19 (0.10–0.28) | 0.886 | 0.402 |
| BG thalamus | 0.37 (0.28–0.46) | 0.49 (0.34–0.65) | 0.190 | 0.851 |
| BG internal capsule | 2.20 (2.01–2.38) | 2.52 (2.21–2.83) | 0.079 | 0.512 |
| BG subscore | 3.21 (2.91–3.51) | 3.68 (3.17–4.19) | 0.129 | |
| ITF cerebellar | 0.09 (0.05–0.14) | 0.18 (0.08–0.28) | 0.576 | 0.312 |
| ITF mesencephal | 0.10 (0.04–0.15) | 0.28 (0.14–0.42) | 0.214 | 0.069 |
| ITF pontine | 0.60 (0.49–0.71) | 0.88 (0.65–1.10) | 0.182 | 0.525 |
| ITF medullar | 0.02 (0.00–0.04) | 0.00 | 0.896 | 0.999 |
| ITF subscore | 0.81 (0.65–0.96) | 1.33 (1.00–1.66) | 0.066 | |
| Total Scheltens Score‡ | 17.46 (16.65–18.27) | 20.20 (18.82–21.57) | 0.001 | |

Values are means (95% CI).
*Univariate Mann–Whitney U test.
†Multivariate binary logistic regression with a history of falls as the dependent variable and grouped PVH subscore as well as the different WMH, BG and ITF single item scores as independent variables (range 0–6 points for each score).
‡Total score, range 0–84 points.
BG, basal ganglia hyperintensities, range 0–6 points for every item and 0–30 points for grouped subscore; ITF, infratentorial foci of hyperintensities, range 0–6 points for every item and 0–24 points for grouped subscore; PVH, periventricular hyperintensities, range 0–2 points for every item and 0–6 points for grouped subscore; WMH, deep white matter hyperintensities, range 0–6 points for every item and 0–24 points for grouped subscore.

deep and periventricular ARWMC. These lesions involve the cortico-subcortical circuit for motor control[22] and result in disturbances of a widespread subcortical motor network as the most likely cause of balance disturbances and falls in ARWMC.[7 19 30 31] The observations are mainly in line with the results of a previous study comprising 28 elderly individuals with various degrees of impaired mobility.[23]

Different frontal lesions such as bilateral subdural haematomas, tumours or hydrocephalus are well known to be associated with gait and balance disturbances.[32] Periventricular as well as frontal and parietal deep ARWMC might interfere with long loop reflexes critical for gait and balance mediated by deep white matter sensory and motor tracts.[30] In normal pressure hydrocephalus, characterised by a ''frontal'' gait disorder similar to that in ARWMC, gait dysfunction and balance disturbances have been attributed to interruptions of corticocortical fibres projecting to the frontal cortex or lesions of frontocerebellar pathways.[32] Lesions in the frontal deep white matter and lateral to the frontal horns of the ventricles may also affect the fronto-occipital fasciculus and the more laterally located superior longitudinal fasciculus[33] that are involved in sensorimotor integration and postural control. Another traditional hypothesis for the cause of gait disturbances in hydrocephalus is the effect on the descending motor tracts related to lower extremity control, arising from medial cortical areas and passing close to the lateral ventricle before entering the internal capsule.[34] However, according to the present results, a direct effect on the descending motor fibres in the areas of the internal capsule, pons and medulla oblongata seem to be of minor importance for balance disturbances and the risk of falls.

The exact pathophysiology and biology of how ARWMC affect frontal circuits is unclear. In a combined MRI and positron emission tomography study, Tullberg *et al*[35] demonstrated that white matter lesions were associated with frontal hypometabolism, irrespective of their location. Given that the frontal and periventricular areas are the predominant locations for ARWMC,[35] it could simply be that ARWMC in these regions are good estimates of global ARWMC magnitude. However, the results of the current study reveal that only frontal ARWMC are associated with balance disturbances despite considerable ARWMC scores even in other brain areas such as the periventricular and parietal white matter as well as the basal ganglia region. This clearly points to a specific role of frontal ARWMC in the occurrence of balance disturbances, most likely by direct interruption of frontal cortico-subcortical circuits responsible for motor control.

Apart from complaints of gait disturbance and female gender, no further independent factors or comorbidities associated with an increased rate of falls were found in the cohort. This is in contrast with previous studies which identified several risk

**Table 3** Independent association of severe hyperintensities in different brain regions with a diminished balance ability

| Scheltens scale item | OR (95% CI)* | p Value* |
|---|---|---|
| PVH subscore | 1.06 (0.70–1.63) | 0.777 |
| WMH frontal | 1.93 (1.25–2.97) | 0.003 |
| WMH parietal | 0.88 (0.57–1.35) | 0.547 |
| WMH occipital | 0.96 (0.34–2.69) | 0.934 |
| WMH temporal | 1.24 (0.68–2.24) | 0.480 |
| BG putamen | 0.19 (0.02–1.92) | 0.160 |
| BG thalamus | 1.24 (0.25–6.06) | 0.791 |
| BG internal capsule | 1.57 (0.99–2.51) | 0.057 |
| ITF cerebellar | 1.36 (0.10–18.02) | 0.816 |
| ITF mesencephal | 1.15 (0.23–5.77) | 0.868 |
| ITF pontine | 1.30 (0.56–3.67) | 0.620 |

Independent association of severe hyperintensities in different brain regions with a diminished balance ability.
*Binary logistic regression model with balance disturbances (defined as single leg stance time <15 s) as the dependent variable.
BG, severe basal ganglia hyperintensities (subscore >4 points for every item; the items BG caudate nucleus and BG globus pallidus have been excluded from the model because of absence of scores >4 points in these regions); ITF, severe infratentorial foci of hyperintensities (subscore >4 points for every item, the item ITF medullar has been excluded from the model because of absence of scores >4 points in this region); PVH, severe periventricular hyperintensities (grouped PVH subscore >4 points); WMH, severe deep white matter hyperintensities (subscore >4 points for every item).

factors for falls in elderly persons, in particular reduced vision, decreased hearing, cognitive impairment, depression and neuromuscular disorders.[12 15 36 37] A probable explanation for this discrepancy could be that individuals in the LADIS study were not disabled or only mildly disabled in activities of daily living, thus very few of those included persons had any of these risk factors for falls to a significant degree on enrolment.

Physical activity appeared to be clearly associated with a reduced rate of falls, supporting published data indicating that exercise, in particular when combined with balance training, could reduce the risk of falls[38 39] and mobility impairment.[40] Assuming a possible beneficial effect of physical activity on falls and motor performance in ARWMC, this observation might have clinical implications. Nevertheless, the causal direction in this association remains unclear. It needs to be discussed more openly if the fear of falls and motor disturbances restrain patients from partaking in physical activity.

Among the strengths of the current study are the large sample size and the detailed MRI protocol with centralised analysis, which guaranteed reliability and accuracy of ARWMC scorings and identification of even small effects of ARWMC on motor performance. Furthermore, because of the relatively strict inclusion and exclusion criteria, the results of the present study are less biased by interacting effects of multiorgan disease in geriatric patients, unlike previous studies.[15 36 37]

Limitations of the present study include its cross sectional design as well as the retrospective assessment of falls based on patient history and an additional report of an informant. Furthermore, although the visual rating scales used here to assess ARWMC had the problem of non-linearity and possible ceiling effects, their equal validity in comparison with a complex volumetry in association with different clinical parameters was demonstrated previously in the LADIS study.[41] In addition, the results of the multivariate statistical model estimating the influence of the anatomical distribution of ARWMC could be biased because of collinearities between the different Scheltens scale subscores, hampering a reliable evaluation of individual regression coefficients. Finally, a possible limitation for the generalisability of the results to a general population may be patient selection in a hospital based setting and the inclusion criterion of not being disabled. Individuals were required to have minor motor disturbances on enrolment and thus the extent of association between the severity of ARWMC and balance disturbances with falls may have been underestimated.

The longitudinal design of the LADIS study with a follow-up of 3 years, including cerebral MRI scans for quantification of the progression of ARWMC, will show if falls and disturbances in postural control are predictors of a transition to disability in elderly subjects with ARWMC. It will possibly also enable us to see which ARWMC, in terms of location and severity, will lead to new falls. Perspective functional MRI studies, including diffusion tensor magnetic resonance tractography, that allow detailed visualisation of different white matter fasciculi and pathways and its affect on ARWMC,[42] will help to further specify the localisation of strategic white matter lesions and its correlation with motor disturbances.

In conclusion, for the first time using detailed anatomical studies of ARWMC in a large cohort of elderly non-disabled individuals, a significant association between falls and balance disturbances and primarily frontal deep and periventricular ARWMC was demonstrated. The present data confirm the hypothesis that these lesions interfere with the cortico-subcortical circuit for motor control, resulting in disturbances of a widespread subcortical motor network, and thus are the most likely cause of balance disturbances and falls in ARWMC.

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