White Matter Lesions Volume and Motor Performances in the Elderly

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Objectives: To investigate the cross-sectional and longitudinal associations between performance-based measures of motor function and volume of white matter lesions (WMLs), and to examine the influence of the localization of these lesions.
Methods: At baseline, motor performances (maximum walking speed, Tinetti gait and balance subscales) were assessed in 1,702 subjects aged 80 years or younger from the Dijon (France), France center of the Three-City study. Volumes of WMLs lesions (total, periventricular, deep) were measured using an automated method of tissue segmentation and quantification of lesion size. At 8-year follow-up, walking speed was evaluated in 1,086 subjects.
Results: At baseline, mean and 95% confidence interval (CI) walking speed was lower in subjects with total volumes of WMLs ≥90th percentile (1.50 [1.45–1.55] m/s) than in subjects with lower volumes (1.56 [1.55–1.58] m/s; $p = 0.004$). Baseline total volumes of WMLs above the 90th percentile predicted walking speed decline during follow-up (odds ratio [95% CI] for having the greatest walking speed decline = 2.3 [1.3–4.1], $p = 0.006$). Moreover, high volumes of periventricular but not deep WMLs were associated with slower walking speed at baseline ($p = 0.005$) and over time ($p = 0.001$), and with lower Tinetti gait subscore ($p = 0.02$).
Interpretation: Our study shows a cross-sectional and longitudinal association between high total volumes of WMLs, in particular volumes above the 90th percentile, and impaired mobility. These associations were independent of several confounders, including cognition, and were mainly accounted for by volumes of periventricular WMLs. These findings support the hypothesis of a vascular contribution to motor decline in the elderly.

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White matter lesions (WMLs) are abnormalities of the white matter often observed on brain magnetic resonance imaging (MRI) in the elderly. Their frequency is increased in persons with vascular risk factors, and they are considered to reflect cerebral small-vessel disease.[1,2] It is now well established that these lesions are associated with cognitive decline and dementia.[3,4] The emergence of potential therapies that could delay WMLs progression (eg, antihypertensive medication)[5] explains the growing interest in the relation between WMLs and other age-related phenomena, such as gait and balance impairment.

Gait and balance impairment are common in the elderly and can lead to falls, dependence, and death.[6] Their etiology is likely to be multifactorial, and there is emerging evidence that vascular factors are associated with motor impairment.[7–9] In addition, imaging studies have reported an association between WMLs and motor impairment[10–19]; however, the significance of their findings may be somewhat attenuated by small sample sizes or the use of qualitative or semiquantitative WML evaluation methods mainly based on visual rating scales.[20] Moreover, few have examined the association between WMLs and decline in physical performances, or investigated the effect of WMLs based on their periventricular or deep localization.

We undertook a cross-sectional and longitudinal study of a large sample of community-dwelling adults aged 65 years and older. Our aims were: 1) to evaluate the relation between performance-based measures of motor function and volume of WMLs using an automated method of tissue segmentation and quantification of volumes, and to investigate a potential dose effect; and 2) to examine the influence of WMLs localization.

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Material and Methods

Subjects

The Three-City (3C) study is a cohort study conducted in three French cities (Bordeaux, Dijon, Montpellier), designed to estimate the risk of dementia and cognitive impairment attributable to vascular factors.[21] Data reported in this article were obtained in Dijon, where a specific substudy on motor function was conducted. Eligibility criteria included living in the city and being registered on the electoral rolls in 1999, 65 years or older, and not institutionalized; 4,931 individuals were recruited (1999–2001). The cohort has been followed every 2 years. Data from the fourth follow-up examination at 8 years are included in this article for longitudinal analyses. The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre; each participant signed informed consent.

MRI

Exclusion criteria for the examination were: cardiac pacemaker, valvular prosthesis, or other internal electrical/magnetic devices; history of neurosurgery/aneurysm; claustrophobia; and presence of metal fragments (eyes, brain, spinal cord). Brain MRI was proposed to every participant aged ≤80 years enrolled between June 1999 and September 2000 (N = 2,763); 2,285 subjects (82%) accepted, but only 1,924 scans were performed because of financial limitations; 123 scans were not interpretable.

Briefly, MRI acquisition was performed on a 1.5T Magnetom (Siemens, Erlangen, Germany). A 3-dimensional (3D) high-resolution T1-weighted brain volume was acquired using a 3D inversion recovery fast spoiled-gradient echo sequence (repetition time [TR] = 97 milliseconds; echo time [TE] = 4 milliseconds; inversion time = 600 milliseconds; coronal acquisition). The axially reoriented 3D volume matrix size was 256 × 192 × 256, with a 1.0 × 0.98 × 0.98mm^3 voxel size. T2- and proton density (PD)-weighted brain volumes were acquired using a 2-dimensional dual spin echo sequence with 2 echo times (TR = 4,400 milliseconds; TE1 = 16 milliseconds; TE2 = 98 milliseconds). T2 and PD acquisitions consisted of 35 axial slices 3.5mm thick (0.5mm spacing between slices), having a 256 × 256 matrix size, and a 0.98 × 0.98mm^2 in-plane resolution. This coarse T2/PD image axial resolution was set to keep acquisition duration in elderly subjects to a minimum. Positioning in the magnet was based on the orbitomeatal line so that the entire brain, including cerebellum and mid-brain, was contained within the field of view of both the T1 and T2/PD weighted acquisitions. Each subject dataset (T1, T2, PD) was reconstructed and visually checked for major artifacts, before being sent to the database repository (Caen).

Fully automated image processing software was developed to detect, measure, and localize WMLs.[22] Image analysis contained three steps: 1) preprocessing (registration, non-brain tissue removal, bias field correction); 2) detection of WMLs in T2 images, including removal of false positives (FPs); and 3) postprocessing (generation of WMLs probability maps at the individual and sample levels, morphometry, and location and classification of WMLs). Inspection of initial results revealed at least two types of voxels wrongly classified as WMLs by the algorithm (FPs). First, some FPs originated from the cerebrospinal fluid (CSF)/Virchow robin spaces having intensities similar to those of WMLs on T2 images. Removal of such FPs led to better delineation of the CSF compartment border; this was achieved using SPM99 (Statistical Parametric Mapping) software. Using high-resolution T1 volumes, an optimized CSF mask was generated and aligned on the T2 volume using the spatial normalization matrix (SNM-1MNI), thereby allowing the identification and removal of WMLs with >50% of their voxels overlapping the CSF mask. Second, some FPs were voxels that were white matter but were not hyperintensities. Such FPs correspond to voxels having a very low intensity but a larger probability of belonging to the white matter lesions than to the white matter class (this may happen because WMLs voxels have a larger variance than those of white matter). Therefore, WMLs having a mean T2 signal intensity lower than that of white matter were excluded.

Morphologic parameters (center of mass coordinates, Euclidian distance to the ventricular system, principal axes dimension) were computed for each WML. When their distance to the ventricular system was <10mm, WMLs were labeled as periventricular; otherwise, they were labeled as deep.[23] Periventricular and deep volumes of WMLs were estimated by summing the volumes of all periventricular and deep lesions.

The presence of lacunar infarcts was assessed visually by a neurologist (Y.Z.) using a standardized assessment grid. Lacunar infarcts were defined as focal hyperintensities on T2-weighted images, ≥3mm in size, with corresponding prominent hypointensities on T1-weighted images, with the same density as the cerebrospinal fluid.

Motor Performances

Two tests were used at baseline to evaluate motor performances in subjects aged ≤85 years who visited the study center. Subjects were asked to walk a 6-m distance at their usual and maximum speed. Time to complete the test was recorded by a chronometer connected to two photoelectric cells placed at each extremity of a walkway, and walking speed was calculated. Because results related to WMLs were similar for usual and maximum walking speed, we present those based on maximum walking speed, hereafter referred to as walking speed. In addition, a simplified version of the Tinetti Performance-Oriented Assessment of Mobility Instrument was used.[24,25] The original scale has 20 items; we included 14 items (maximum score = 18) distributed into two subscores: gait (maximum = 5) and balance (maximum = 13). We assessed the complete scale in 100 subjects and found that the correlation between the complete and shortened versions was high (correlation coefficient = 0.95, $p < 0.0001$). At 8-year follow-up, only walking speed was assessed.

Covariates

Sociodemographic and medical data were collected at home by trained psychologists. Participants were asked whether they were treated for a number of conditions (eg, parkinsonism, hip fracture in the previous 2 years, myocardial infarction, stroke). Ischemic heart disease was defined as a history of myocardial infarction, bypass cardiac surgery, or angio-

plasty. Diabetes mellitus was defined as a glycemia ≥7mmol/L or use of antidiabetic treatment.[26] Systolic (SBP) and diastolic (DBP) blood pressure were measured; hypertension was defined by SBP ≥140mmHg or DBP ≥90mmHg, or by antihypertensive drug use. Depressive symptoms were evaluated using the Center for Epidemiological Studies–Depression scale.[27] Smoking status was categorized as never, former, and current smoking. Alcohol consumption was recorded as number of drinks/wk. Measures of weight and height were taken to compute body mass index (BMI). Use of psychotropic drugs (antidepressants, anxiolytics, benzodiazepines, hypnotics) and regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) for joint pain were recorded. Fasting plasma total homocysteine was measured. Participants underwent neuropsychological examination (Mini Mental State Examination,[28] Trail Making Test [TMT] parts A and B,[29] Isaac Set Test).[30]

Participants were screened for dementia.[21] Dementia diagnosis and classification were made by the 3C Study local investigators according to Diagnostic and Statistical Manual of Mental Disorders–IV criteria, and validated by a panel of independent neurologists.

Statistical Analysis

The cross-sectional relation between volume of WMLs and walking speed or Tinetti subscales was investigated using linear and logistic regression. In linear regression models, walking speed was considered as the dependent variable; we used a logarithmic transformation, because its distribution was not normal. Volume of WMLs (independent variable) was introduced in the models using the following categories: <25th, 25th–49th, 50th–74th, 75th–89th, and ≥90th percentiles. The 90th percentile threshold was chosen to examine the influence of the largest volumes. We used orthogonal contrasts to assess the shape of the relation between walking speed and the volume of WMLs and to perform class comparisons. Gait and balance Tinetti subscores had a highly skewed distribution; they were dichotomized at their 10th percentile (5 and 10, respectively), and considered as the dependent variables in logistic models. Geometric means, regression coefficients, and their 95% confidence intervals (CI) or odds ratios (OR) are presented depending on the models.

Because volumes of WMLs are highly correlated with total white matter volume, all analyses were adjusted for white matter volume. Age, gender, and education level are associated with physical performances and WMLs[31–33]; analyses were adjusted for these variables (model 1), after checking that there were no significant interactions with WMLs. We then added to this model variables associated with both WMLs and motor tests in univariate analyses ($p \leq 0.05$) (model 2); additional adjustment for the presence of lacunar infarcts was performed (model 3). Analyses restricted to subjects without lacunar infarcts are also reported.

Cognitive status is associated with WMLs and motor function.[3,34,35] Because we wanted to rule out the possibility that the association between WMLs and motor performances was explained by cognition, we identified the cognitive test that was more strongly associated with motor performances among all cognitive tests cited above. We stratified our analyses of the relation between walking speed and volumes of WMLs according to the median cognitive performance to assess whether the relation between the two variables was modified by cognition; when no interaction was observed, we adjusted our analyses by including the cognitive test in the model.

Three separate analyses were conducted to examine the influence of the localization of WMLs: 1) separate models were built for deep and periventricular volumes of WMLs, 2) we combined the two volumes dichotomized at their 90th percentile to create a 4-level variable, and 3) both volumes were entered in the same model.

In longitudinal analyses, we examined the mean annual rate of walking speed change (difference between baseline and follow-up walking speed divided by the delay between the measures). This variable was dichotomized at its 75th percentile (0.04m/s/yr) and considered as the outcome in logistic models. This threshold was used to define a group of persons with a significant decline that was also of sufficient size for the statistical analyses. Models were initially adjusted for age, gender, education level, baseline brain white matter volume, and baseline walking speed (model 1). We then added variables associated with both walking speed decline and volume of WMLs (model 2); we finally adjusted for the presence of lacunar infarcts (model 3) and baseline cognition. Analyses restricted to subjects without lacunar infarcts were also performed.

We performed sensitivity analyses by imputing missing values for walking speed at 8 years, based on all covariates included in model 2 (gender; education; baseline BMI, age, walking speed, diabetes, psychotropic drugs use, physical activity level, and total volume of WMLs) and the delay between the two examinations, using Proc MI and MIANALYZE in SAS v9.1. All analyses were performed using SAS v9.1 (SAS Institute, Inc., Cary, NC).

Results

Of 1,801 participants aged ≤80 years with an interpretable MRI, 1,745 had a motor test available. We excluded 43 subjects with conditions that affected motor function (parkinsonism, n = 21; stroke, n = 13; hip fracture, n = 2; dementia, n = 8). The baseline study sample included the remaining 1,702 persons (1,621 measures available for walking speed and 1,702 for the Tinetti subscales).

Baseline Characteristics

At baseline, median (interquartile range) total volume of WMLs was 4.0 (3.6) cm^3 (periventricular, 2.8 [2.8]; deep, 1.2 [1.1]). Median walking speed was 1.50 (0.39) m/s. Table 1 shows baseline participant characteristics. The cognitive test showing the strongest association with walking speed and volume of WMLs was the TMT-A. Nine percent of the participants had at least 1 lacunar infarct. They had higher volumes of WMLs, but they did not walk more slowly than subjects without lacunar infarcts; mean walking speed (95% CI) was 1.57 (1.52–1.62) m/s in subjects with lacunar infarcts and 1.56 (1.54–1.57) m/s in subjects

Table 1. **Baseline Characteristics of the Study Participants (N = 1,702)**

Characteristics	Overall	Walking Speed[a]		Total Volume of WMLs[a]	
		<Median, n=799	≥Median, n=822	≤Median, n=851	>Median, n=851
Age, yr, mean (SD)	72.4 (4.1)	73.3 (4.0)	71.3 (3.9)[b]	72.2 (4.2)	72.5 (4.0)[b]
Female gender, n (%)	1,031 (60.6)	630 (76.6)	351 (43.9)[b]	568 (66.7)	463 (54.4)[d]
Education level, n (%)					
Low	274 (16.1)	153 (18.7)	111 (13.9)	120 (14.1)	154 (18.1)
Medium low	750 (44.1)	395 (48.2)	311 (38.9)	404 (47.6)	346 (40.7)
Medium high	321 (18.9)	148 (18.0)	160 (20.0)	164 (19.3)	157 (18.5)
High (>12 yr)	355 (20.9)	124 (15.1)	217 (27.2)[b]	161 (19.0)	194 (22.8) [d]
Alcohol consumption ≥13 drinks/wk, n (%)	444 (28.2)	156 (20.5)	268 (36.3)[d]	214 (26.9)	230 (29.4)
Current smoker, n (%)	89 (5.2)	159 (19.5)	93 (11.8)	37 (4.3)	52 (6.1)[c]
Body mass index, kg/m^2, mean (SD)	25.4 (3.8)	25.7 (4.0)	25.0 (3.4)[b]	25.1 (3.7)	25.7 (3.8)[c]
TMT-A, s/correct connection, mean (SD)[e]	2.21 (0.85)	2.33 (0.84)	2.06 (0.84)[b]	2.18 (0.78)	2.24 (0.91)[b]
Depressive symptoms, n (%)	221 (13.2)	137 (16.9)	75 (9.5)[b]	107 (12.7)	114 (13.6)
Ischemic heart disease, n (%)	143 (8.4)	71 (8.6)	66 (8.3)[c]	75 (8.8)	68 (8.0)
Hypertension, n (%)	1,314 (77.2)	651 (79.2)	596 (74.6)[c]	625 (73.4)	689 (81.0)[c]
Diabetes mellitus, n (%)	138 (8.2)	70 (8.6)	59 (7.5)	60 (7.1)	78 (9.3)[c]
Homocysteine, μmol/L, mean (SD)	14.3 (5.0)	14.5 (5.5)	14.0 (4.5)[c]	14.1 (4.9)	14.5 (5.1)[d]
Psychotropic drug use, n (%)	397 (23.3)	232 (28.2)	151 (18.9)[b]	184 (21.6)	213 (25.0)[d]
Regular use of NSAIDs for joint pain, n (%)	255 (15.1)	155 (19.1)	85 (10.7)[b]	125 (14.7)	130 (15.5)
Regular physical activity, n (%)	573 (35.1)	209 (26.9)	341 (43.8)[b]	304 (36.9)	269 (33.3)[d]
Lacunar infarcts, n (%)	158 (9.3)	74 (9.0)	76 (9.5)	56 (6.5)	102 (12.0)[b]

Depressive symptoms are defined as a Center for Epidemiological Studies–Depression scale score ≥17 for men or ≥23 for women.
[a]For simplicity, we present the mean or percentage of each characteristic by walking speed and by total volume of WMLs dichotomized at their median (1.50m/s for walking speed and 4.0cm^3 for WMLs). The relation between each variable and walking speed or total volume of WMLs was studied using linear regression models adjusted for age, gender, and education level (and white matter volume for models including volume of WMLs). Walking speed and volume of WMLs were considered as dependent variables in each model.
[b]$p < 0.0001$.
[c]$p < 0.005$.
[d]$p < 0.05$.
[e]Time needed to make a correct connection (ratio of time to complete the part by number of correct connections) (second per correct connection).
WMLs = white matter lesions; SD = standard deviation; TMT-A = trail making test part A; NSAIDs = nonsteroidal anti-inflammatory drugs.

without ($p = 0.87$, adjusted for age, gender, and education level).

Cross-Sectional Association Between Total WML Volume and Motor Performance

Table 2 shows a decrease in mean walking speed across categories of volume of WMLs that was significant for volumes above the 75th percentile, after adjustment for age, gender, education, and brain white matter volume (model 1). After additional adjustment (model 2), the association between walking speed and WMLs volume remained significant only for the highest volumes. Adjustment for lacunar infarcts did not modify these findings (model 3); in analyses restricted to subjects without lacunar infarcts, there was an association between volumes of WMLs above the 90th percentile and walking speed (model 2, β [standard error {SE}] = −0.015 [0.007], $p = 0.03$).

There was no difference in mean walking speed across the first 4 categories of WMLs volume in the full adjusted model (model 2, Table 2). Subjects with WMLs ≥90th percentile walked more slowly than subjects with lower WMLs volumes grouped together (model 2, β [SE] = −0.017 [0.006], $p = 0.004$). Accordingly, orthogonal contrasts showed that the coding of the WMLs volume variable as a dichotomous variable (below and above the 90th percentile) provided the best fit.

Table 2. **Cross-Sectional Association Between Volumes of WMLs and Walking Speed**

Volume of WMLs[a]	No.	Geometric Mean of Walking Speed (95% CI) [m/s]	Model 1[b]		Model 2[c]		Model 3[d]	
			β (SE)	*p*	β (SE)	*p*	β (SE)	*p*
Total								
<25th percentile	405	1.55 (1.51–1.58)	Reference		Reference		Reference	
25th–49th percentile	405	1.58 (1.55–1.61)	0.003 (0.005)	0.57	0.007 (0.005)	0.14	0.007 (0.005)	0.14
50th–74th percentile	405	1.57 (1.54–1.60)	−0.005 (0.005)	0.31	0.000 (0.005)	0.93	−0.001 (0.005)	0.91
75th–89th percentile	243	1.56 (1.52–1.59)	−0.014 (0.006)	0.02	−0.005 (0.006)	0.43	−0.005 (0.006)	0.38
≥90th percentile	163	1.50 (1.45–1.55)	−0.026 (0.007)	0.0003	−0.016 (0.007)	0.02	−0.017 (0.007)	0.01
Lacunar infarcts								
No	1,471	1.56 (1.54–1.57)	—	—	—	—	Reference	
Yes	150	1.57 (1.52–1.62)	—	—	—	—	0.006 (0.006)	0.31
Periventricular								
<25th percentile	405	1.55 (1.52–1.58)	Reference		Reference		Reference	
25th–49th percentile	405	1.57 (1.54–1.60)	0.000 (0.005)	0.93	0.004 (0.005)	0.40	0.004 (0.005)	0.40
50th–74th percentile	405	1.57 (1.55–1.60)	−0.003 (0.005)	0.54	−0.001 (0.005)	0.92	−0.001 (0.005)	0.90
75th–89th percentile	243	1.56 (1.53–1.60)	−0.007 (0.006)	0.27	0.001 (0.006)	0.85	0.001 (0.006)	0.93
≥90th percentile	163	1.49 (1.44–1.54)	−0.024 (0.007)	0.0007	−0.016 (0.007)	0.02	−0.016 (0.007)	0.01
Lacunar infarcts								
No	1,471	1.56 (1.54–1.57)	—	—	—	—	Reference	
Yes	150	1.57 (1.52–1.62)	—	—	—	—	0.006 (0.006)	0.38
Deep								
<25th percentile	405	1.55 (1.52–1.58)	Reference		Reference		Reference	
25th–49th percentile	405	1.55 (1.52–1.57)	−0.009 (0.005)	0.10	−0.005 (0.005)	0.31	−0.005 (0.005)	0.32
50th–74th percentile	405	1.57 (1.54–1.60)	−0.007 (0.005)	0.17	0.000 (0.005)	0.96	0.000 (0.005)	0.96
75th–89th percentile	243	1.56 (1.52–1.60)	−0.019 (0.006)	0.002	−0.011 (0.006)	0.06	−0.011 (0.006)	0.06
≥90th percentile	163	1.56 (1.51–1.61)	−0.020 (0.007)	0.005	−0.013 (0.007)	0.07	−0.013 (0.007)	0.07
Lacunar infarcts								
No	1,471	1.56 (1.54–1.57)	—	—	—	—	Reference	
Yes	150	1.57 (1.52–1.62)	—	—	—	—	0.004 (0.006)	0.56

[a]Volume of WMLs is categorized according to the following percentile cutoffs: total WMLs volume: 25th = 2.8 cm^3, 50th = 4.0 cm^3, 75th = 6.4 cm^3, and 90th = 10.4 cm^3; periventricular WMLs volume: 25th = 1.8 cm^3; 50th = 2.8 cm^3, 75th = 4.6 cm^3, and 90th = 7.6 cm^3; deep WMLs volume: 25th = 0.8 cm^3, 50th = 1.2 cm^3, 75th = 1.8 cm^3, and 90th = 2.9 cm^3.
[b]Regression coefficients and *p* values were computed using linear regression models. Adjustment was made for age, gender, education level, and brain white matter volume.
[c]Additional adjustment was made for body mass index, homocysteine level, psychotropic drugs, hypertension, and physical activity.
[d]Additional adjustment was made for lacunar infarcts.
WMLs= white matter lesions; CI = confidence interval; SE = standard error.

The relation between walking speed and volumes of WMLs was not modified by median TMT-A ($p = 0.92$); after adjustment for median TMT-A, participants with total volumes ≥90th percentile walked more slowly than those with lower volumes (model 2, β [SE] = −0.015 [0.006], $p = 0.01$).

Compared with subjects with volumes of WMLs <90th percentile, those with higher volumes had a higher probability of having a low Tinetti gait (model 2, OR [95%CI] = 1.4 [0.8–2.3], $p = 0.19$) or balance subscore (model 2, OR [95%CI] = 1.3 [0.8–2.0], $p = 0.34$), but these relations were not statistically significant. Results remained unaltered after adjustment for lacunar infarcts and TMT-A (data not shown).

Volume of Periventricular WMLs Accounts for the Association With Motor Performance

When included in separate models, high volumes of both periventricular and deep WMLs were associated with slower walking speed (model 1, Table 2). After adjustment for confounders, volumes of deep WMLs ≥90th percentile were no longer associated with walking speed (mode 2); adjustment for lacunar infarcts did not alter these findings (model 3).

Subjects with periventricular WMLs volumes ≥90th percentile walked more slowly than subjects with lower (<90th percentile) periventricular WML volumes (model 2, β [SE] = −0.017 [0.006], $p = 0.005$), whereas there was no difference for deep WMLs (model 2, β [SE] = −0.009 [0.006], $p = 0.16$).

Again, orthogonal contrasts showed that the coding of the WML volume variable as a dichotomous variable (below and above the 90th percentile) provided the best fit.

Cognitive status did not modify these relations (interaction p values = 0.75–0.85); after adjustment for TMT-A, the relation between walking speed and periventricular WMLs remained significant for volumes ≥90th percentile (model 2, β [SE] = −0.014 [0.006], p = 0.01), whereas there was no association for deep WMLs (model 2, β [SE] = −0.005 [0.006], p = 0.37).

To disentangle the effect of periventricular versus deep WMLs, we combined the two volumes dichotomized at their 90th percentile in a 4-level variable (Fig 1). Compared with subjects with volumes of both periventricular and deep WMLs <90th percentile, subjects with larger volumes of periventricular WMLs (≥90th percentile) and lower volumes of deep WMLs (<90th percentile) had the slowest mean walking speed, followed by subjects with high volumes of both periventricular and deep WMLs, whereas there was no significant difference in mean walking speed for subjects with low volumes of periventricular WMLs and high volumes of deep WMLs. In addition, the association between periventricular WMLs and walking speed was not modified by deep WMLs (interaction p value = 0.37). When both periventricular WMLs and deep WMLs were included in the same model as continuous variables using z scores, the variance inflation factor did not detect major collinearity problems, and only periventricular WMLs were associated with walking speed (model 2, p = 0.02), whereas deep WMLs were not (model 2, p = 0.98). Results remained unaltered after adjustment for lacunar infarcts and TMT-A (data not shown).

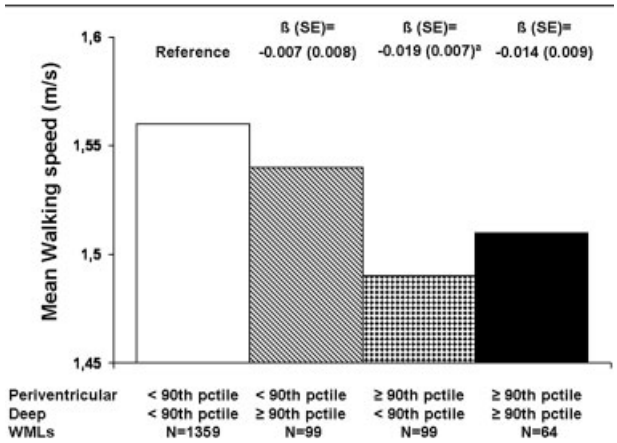

Fig 1. Influence of white matter lesions (WMLs) localization on walking speed. Walking speed means are adjusted for age, gender, education level, brain white matter volume, body mass index, hypertension, homocysteine level, psychotropic drugs use, and physical activity. [a]p Values < 0.05, for comparison with the reference category (volumes of periventricular and deep WMLs below the 90th percentile). SE = standard error; pctile = percentile. β = regression coefficient.

Low Tinetti gait subscores were associated with the volumes of periventricular WMLs ≥90th percentile (model 2, OR [95% CI] = 1.8 [1.1–2.8], p = 0.02). Results remained unaltered after adjustment for lacunar infarcts and TMT-A (data not shown). Volumes of periventricular WMLs were associated with low balance subscores in model 2 (OR [95% CI] = 1.6 [1.1–2.5], p = 0.03), but this association was no longer significant after controlling for cognition (p = 0.07). Volumes of deep WMLs were not associated with balance or Tinetti gait subscores (data not shown).

Association Between Baseline Volume of WMLs and Rate of Walking Speed Decline

Figure 2 shows the flowchart of participants selection for longitudinal analyses. Subjects without walking speed measures at 8 years were older, had a higher baseline prevalence of vascular risk factors, higher baseline WMLs volumes, and lower baseline walking speed and cognitive performances (results not shown). Characteristics of the 1,086 subjects included in longitudinal analyses are shown in Figure 2. Increasing age (p < 0.001) and BMI (p < 0.001), female gender (p < 0.001), lower education level (p < 0.001), diabetes (p = 0.02), smoking (p = 0.02), psychotropic drug (p = 0.02) and NSAIDs (p = 0.05) use, higher TMT-A (p = 0.04), low activity level (p = 0.004), and baseline walking speed (p < 0.001) were associated with greater walking speed decline. Walking speed decline was not associated with the presence of lacunar infarcts at baseline; mean decline (standard deviation [SD]) was 0.028 (0.036) m/s/yr in subjects with lacunar infarcts and 0.022 (0.034) m/s/yr in those without (p = 0.14)

Table 3 shows that subjects with total volumes of WMLs ≥90th percentile at baseline had over a 2-fold increased risk of decline in walking speed, compared with subjects with lower volumes of WMLs (model 1). Whereas a similar finding was observed for periventricular WMLs, no association was found for deep WMLs. Additional adjustment for variables associated with walking speed decline and volumes of WMLs (model 2), as well as for lacunar infarcts (model 3), did not modify the results. In analyses restricted to subjects without lacunar infarcts, ORs (model 2) were 2.6 (95% CI = 1.4–4.9, p = 0.003) for total WMLs volumes ≥90th percentile, 2.9 (95% CI = 1.5–5.5, p = 0.001) for periventricular WML volumes, and 1.7 (95% CI = 0.9–3.2, p = 0.12) for deep WML volumes. Adjustment for cognitive level did not modify these findings.

When volumes of periventricular and deep WMLs

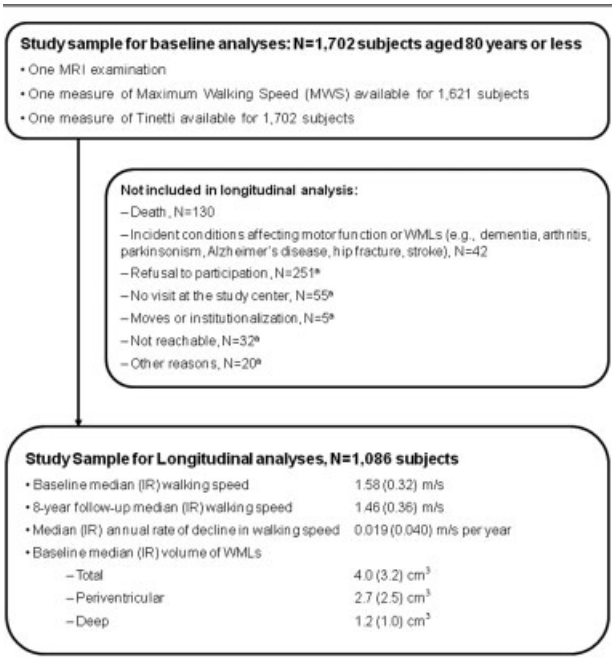

Fig 2. Flowchart of participant selection for longitudinal analyses. [a]Multiple imputation was used to impute missing values for walking speed for these subjects (n = 363) in sensitivity analyses. MRI = magnetic resonance imaging; white matter lesions = WMLs; IR = interquartile range.

were entered in the same model, only periventricular WMLs (model 2, OR [95% CI] for subjects with volumes ≥90th percentile = 2.9 [1.5–5.7], $p = 0.002$) predicted walking speed decline, whereas no association was found with volumes of deep WMLs (model 2, OR [95% CI] = 1.0 [0.5–2.0], $p = 0.99$). These relations were not modified by age, gender, education, or cognitive status, and adjustment for cognitive status yielded similar results (data not shown). For the 3 volumes, orthogonal contrasts showed that the coding of the WMLs volume variable as a dichotomous variable (below and above the 90th percentile) provided the best fit.

Sensitivity analyses were performed by: 1) imputing in 363 subjects (Fig 2) missing values for walking speed at 8 years; walking speed decline was associated with volumes of WMLs ≥90th percentile (model 2, OR [95% CI] = 2.5 [1.4–4.4], $p = 0.002$) and volumes of periventricular WMLs ≥90th percentile (model 2, OR [95% CI] = 2.8 [1.4–5.7], $p = 0.006$); 2) adjusting for cognitive status using the other tests of the cognitive battery instead of TMT-A; 3) using alternative thresholds (75th or 80th percentile) to dichotomize walking speed decline; and 4) including variables associated with either volume of WMLs or walking speed in multivariate models. Results found were always similar to those presented in this article (data not shown).

Discussion

In this large community-based cohort study, we found that higher volumes of WMLs were associated with slower walking speed (cross-sectional analyses) and greatest motor decline (longitudinal analyses). These associations were independent of many potential confounders, including vascular risk factors, the presence of lacunar infarcts, and cognitive status.

The difference in geometric means of walking speed between subjects with total volumes of WMLs above the 90th percentile and those in the first quartile was 9 cm. This difference was of a similar magnitude to the difference in walking speed between nonfallers (1.56 m/s) and recurrent fallers (1.48 m/s) in our study, thus suggesting that this difference may be clinically relevant.

We did not find a progressive decrease in walking speed or increasing motor decline with increasing WMLs volumes, and we found that only the highest total WMLs volumes were significantly associated with decreased walking speed or with motor decline. Statistical comparisons of models including different codings of the volumes of WMLs showed that the model including the volume of WMLs as a dichotomous variable (above and below the 90th percentile) provided the best fit. Therefore, our findings for WMLs are more suggestive of a threshold effect than of a dose-effect relation. A similar finding was reported in a study of the relation between WMLs and cognition.[36] Whereas a relationship between WMLs and motor dysfunction has been reported in some studies,[13–17] only 1 described a dose-dependent effect of white matter changes on measures of gait and balance,[18] but it was based on a visual evaluation of WMLs; most of the other studies did not investigate dose-effect relations.

The type of WMLs seems also to have importance, as worse motor performances were associated with higher volumes of periventricular WMLs but not with deep WMLs. Few studies have explored the influence of WML localization; 1 reason may be the difficulty of separating the effect of both volumes, especially if they are not measured precisely. Some studies found that periventricular WMLs were more influential on motricity than deep WMLs,[11,19] but others did not.[37,38] The explanation for these discrepancies may include differences in the assessment of WMLs or in participants characteristics, the limited assessment of confounders, and analyses of the role of periventricular lesions that do not take into account deep lesions and vice versa. It is also possible that the lack of association with deep WMLs in our study is related to lower volumes of deep WMLs compared with periventricular WMLs; however, this hypothesis is not supported by our analyses including the two types of volumes in the same model. Finally, our findings were independent of the definition of periventricular versus deep WMLs, as

Table 3. **Association Between Baseline Volumes of WMLs and Walking Speed Change at the 8-Year Follow-up**

Baseline Volume of WMLs[a]	%	Highest Walking Speed Decline[b]					
		Model 1[c]		Model 2[d]		Model 3[e]	
		OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Total							
<25th percentile	21.0	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)	
25th–49th percentile	25.7	1.4 (0.9–2.2)	0.13	1.4 (0.9–2.1)	0.18	1.4 (0.9–2.1)	0.18
50th–74th percentile	28.0	1.7 (1.1–2.7)	0.02	1.5 (0.9–2.4)	0.08	1.5 (0.9–2.4)	0.08
75th–89th percentile	19.0	1.2 (0.7–2.1)	0.51	1.1 (0.6–2.0)	0.72	1.1 (0.6–1.9)	0.73
≥90th percentile	33.9	2.6 (1.5–4.5)	0.001	2.3 (1.3–4.1)	0.006	2.3 (1.3–4.1)	0.007
Lacunar infarcts							
No		—	—	—	—	1.0 (Reference)	
Yes		—	—	—	—	1.1 (0.6–2.0)	0.74
Periventricular							
<25th percentile	18.1	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)	
25th–49th percentile	25.4	1.7 (1.1–2.6)	0.03	1.6 (1.0–2.6)	0.05	1.6 (1.0–2.6)	0.05
50th–74th percentile	28.4	2.0 (1.3–3.2)	0.003	1.9 (1.2–3.0)	0.008	1.8 (1.2–3.0)	0.01
75th–89th percentile	25.8	1.8 (1.1–3.1)	0.03	1.7 (0.9–2.9)	0.06	1.7 (0.9–2.9)	0.06
≥90th percentile	31.2	2.9 (1.6–5.2)	0.0003	2.7 (1.5–4.9)	0.001	2.7 (1.5–4.9)	0.002
Lacunar infarcts							
No		—	—	—	—	1.0 (Reference)	
Yes		—	—	—	—	1.1 (0.6–1.9)	0.82
Deep							
<25th percentile	22.9	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)	
25th–49th percentile	29.0	1.8 (1.2–2.8)	0.01	1.7 (1.1–2.6)	0.02	1.7 (1.1–2.7)	0.02
50th–74th percentile	23.6	1.2 (0.8–1.8)	0.47	1.0 (0.6–1.6)	0.96	1.0 (0.6–1.6)	0.96
75th–89th percentile	21.5	1.3 (0.8–2.3)	0.31	1.2 (0.7–2.0)	0.62	1.2 (0.7–2.0)	0.61
≥90th percentile	28.4	1.7 (0.9–3.0)	0.08	1.5 (0.8–2.8)	0.18	1.5 (0.8–2.7)	0.19
Lacunar infarcts							
No		—	—	—	—	1.0 (Reference)	
Yes		—	—	—	—	1.2 (0.7–2.1)	0.54

[a]Baseline volume of WMLs is categorized according to the following percentile cutoffs: total WMLs volume: 25th = 2.7 cm^3, 50th = 4.0 cm^3, 75th = 5.9 cm^3, and 90th = 9.5 cm^3; periventricular WMLs volume: 25th = 1.8 cm^3, 50th = 2.7 cm^3, 75th = 4.3 cm^3, and 90th = 7.0 cm^3; deep WMLs volume: 25th = 0.8 cm^3, 50th = 1.2 cm^3, 75th = 1.7 cm^3, and 90th = 2.7 cm^3.
[b]Decline (difference between baseline and follow-up walking speed divided by the delay between the two measures) > 75th percentile (0.04 m/s/yr).
[c]ORs (95% CI) were computed using logistic regression. Adjustment was made for age, gender, education level, baseline walking speed, and brain white matter volume.
[d]Additional adjustment was made for baseline body mass index, diabetes, physical activity, and psychotropic drugs use.
[e]Additional adjustment was made for lacunar infarcts at baseline.
WMLs = white matter lesions; OR = odds ratio; CI = confidence interval.

the results remained identical when the cutoff used to define these regions was changed. Furthermore, our estimates of volumes of periventricular and deep WMLs are in reasonable agreement with those reported by other studies relying on quantitative measurement.[3,39] The mechanisms linking WMLs and motor function are not well understood, but it has been suggested that WMLs might disrupt long loop reflexes mediated by deep white matter sensory and motor tracts that are involved in motor control, in particular those coming from the frontal regions. In hydrocephalus, it has been suggested that gait dysfunction may be related to the vulnerability of long descending motor tracts that arise from medial cortical areas involved in lower extremity motor control, pass close to the lateral ventricles, and enter the internal capsule. Similar mechanisms could be implicated in the association between WMLs and walking speed. Lesions of the superior fronto-occipital or longitudinal fasciculus and of the basal ganglia may also play a role.[13,14]

The presence of lacunar infarcts was assessed visually; 9% of the participants had at least 1 lacunar infarct. In agreement with other studies, subjects with lacunar infarcts had higher volumes of WMLs than

subjects without lacunar infarcts.[36] There was no significant difference in walking speed between subjects with and without lacunar infarcts. In analyses adjusted for lacunar infarcts or restricted to subjects without lacunar infarcts, our findings remained unchanged; therefore, the association between walking speed and volumes of WMLs was not explained by the presence of lacunar infarcts. A recent study of the cross-sectional relation between gait speed, WMLs (visual severity grade), and brain infarcts showed that when the two lesions were included in the same model, only WMLs remained associated with gait speed.[40]

In contrast with other studies,[10,13,41] volumes of WMLs were not associated with balance. However, the Tinetti balance subscale used in the present study is not sensitive to small balance impairments, compared with more sophisticated methods (eg, computerized posturography).

One of the strengths of our study is the use of an automated measurement method that provides a precise quantification and localization of WMLs. In addition, automated volumetric assessment is not prone to a ceiling effect, permits a better discrimination of lesion volume, and is reported to be more sensitive in detecting small group differences than visual scales.[20] Other strengths include the large sample size, longitudinal analyses that confirmed cross-sectional findings, use of performance-based measures of physical function that are more reliable than self-reports, and evaluation of various potential confounders including cognitive status.

Some limitations should be mentioned. First, we did not obtain a walking speed measure at follow-up for all the participants. However, we found similar results when we used multiple imputation methods to analyze the data. Second, as we only had 2 measures, we were unable to examine whether decline in walking speed was constant between the baseline and the follow-up examinations. Third, our automated method of image analysis does not allow studying the role of the regional localization of WMLs. Fourth, we did not assess mild parkinsonian symptoms using the Unified Parkinson Disease Rating Scale, because we did not consider that they could be assessed reliably by the interviewers. In addition, walking speed is easier and quicker to measure; it can be measured with greater reliability, and it is a continuous measure that offers several advantages for statistical analyses.

These findings support the hypothesis of a vascular contribution to motor decline in the elderly. Because a higher amount of baseline WMLs is associated with greater walking speed decline, and because the main predictor of progression of WMLs is the extent of baseline lesions, the next step could be to examine whether progression of periventricular WMLs is related to a greater motor decline. If so, halting or delaying the progression of these lesions (eg, through treatment of vascular risk factors) could be a potential strategy to prevent or delay motor decline.

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