Journal of the Neurological Sciences 406 (2019) 116439

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Can transcranial Doppler ultrasound be used for screening cerebral small vessel diseases in the community?

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ARTICLE INFO

Keywords:
White matter hyperintensity
Small vessel diseases
Vascular dementia
Screening
Transcranial Doppler ultrasound

ABSTRACT

Objectives: Elderly persons harbouring severe white matter hyperintensity (WMH), a radiological manifestation of cerebral small vessel disease (SVD), have an increased risk of dementia, stroke and poor functional outcomes. A simple screening tool will enhance their recruitment into preventive trials for SVD. We explored the clinical utility of the pulsatility index (PI) of the middle cerebral artery (MCA), obtained from transcranial Doppler ultrasound (TCD), in identifying severe WMH among community elderly persons with vascular risk factors.
Methods: Three hundred and thirty-one dementia- and stroke-free community elderly subjects with hypertension and/or diabetes mellitus underwent TCD to obtain the MCA PI. The WMH volume on 3.0 Tesla MRI was quantified and normalized to each subject's brain volume. The normalized WMH volumes were classified as low (< 14.5 ml, 1 standard deviation [SD] above the mean, 84th percentile) or high (≥ 14.5 ml). The severity of WMH was also rated visually with the Fazekas score. Logistic regression and receiver-operator characteristics (ROC) analysis were performed to evaluate the association between the MCA PI and the severity of WMH.
Results: The MCA PI was not an independent predictor of severe WMH. An MCA PI ≥ 1.095 detected high normalized WMH volumes with an area under the curve (AUC) of 0.553 (95% CI 0.473–0.633), sensitivity of 0.556, and specificity of 0.523. ROC analysis of the MCA PI in predicting high Fazekas scores yielded similar findings.
Conclusion: In stroke- and dementia-free elderly persons with vascular risk factors, the MCA PI was unable to identify severe WMH. (Word count: 260).

1. Introduction

Cerebral small vessel disease (SVD) is arguably the commonest brain disease among elderly persons and predicted to incur an enormous burden as the society ages. SVD is a result of multiple pathophysiological processes, ranging from ischemia, inflammation and endothelial dysfunction to blood-brain barrier leakage and venous insufficiency [1]. The most widely used neuroimaging marker of SVD is

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https://doi.org/10.1016/j.jns.2019.116439
Received 3 June 2019; Received in revised form 21 August 2019; Accepted 28 August 2019
Available online 29 August 2019

the age-related white matter hyperintensity (WMH), which appears as areas with high signal intensities ≥5 mm on fluid attenuated inversion recovery (FLAIR) images of T2-weighted Magnetic Resonance Imaging (MRI). Severe WMH predicts an increased risk of stroke, dementia and death [2]. Longitudinal studies demonstrate that the progression of WMH is an independent contributor to cortical atrophy and cognitive decline [2,3].

Over 90% of the elderly population harbor WMH. Confluent WMH, a result of small punctate WMH merging into extensive patches, are observed in a third of the elderly population and associated with a host of poor functional outcomes, such as urinary incontinence, gait disturbances, falls and depression [4–7]. As WMH takes years to evolve before symptoms appear, there exists a golden window for early therapeutic intervention. Whereas age and hypertension are consistently identified as the top risk factors of WMH [8], associations with diabetes mellitus, cholesterol, smoking, and homocysteinemia are also reported [9]. The progression of WMH may be retarded by modifying these vascular risk factors. Previous cohort studies have shown that optimal blood pressure control [9], statins [10], homocysteine-lowering therapy by B vitamins [11], multi-domain vascular care [12], and remote ischemic conditioning may slow the progression of WMH [13]. Their efficacies await clarification by randomized controlled trials in subjects with severe WMH.

The European Task Force on age-related WMH recommended that clinical trials on SVD should target patients with severe WMH in 2004 [14]. While recognising the clinical significance of WMH, the American Heart Association/American Stroke Association (AHA/ASA) did not recommend population screening for severe WMH as no clinical trials had demonstrated a reduction of adverse health outcomes from early screening. Nevertheless, a recent AHA/ASA guideline began to call for such trials [15].

The recruitment of subjects into the preventive trials for SVD is precluded by a lack of simple screening tool for asymptomatic elderly persons with severe WMH. MRI is impractical for community screening in view of its high monetary and time cost. The pulsatility index (PI), as defined by Gosling and King [16], can be obtained easily from transcranial Doppler ultrasound (TCD) and appears to be an attractive screening tool. A higher PI reflects an increased downstream resistance in the cerebral circulation, which is often due to SVD-related narrowing of the distal cerebral vessels.

Distal branches of the middle cerebral artery (MCA) supply the bulk of the cortical and subcortical regions responsible for sensory perception, psychomotor activity, language processing, and memory. Our pilot study of 159 elderly subjects suggested the MCA PI was able to guide selective MRI scanning for elderly persons with asymptomatic severe WMH and facilitate their recruitment into clinical trials for SVD [17]. In this study, we aimed to evaluate the clinical utility of the MCA PI in identifying severe WMH among a larger sample of community elderly persons with vascular risk factors.

2. Methods

2.1. Subjects

Subjects were recruited from the CU-RISK (The **C**hinese **U**niversity of **H**ong **K**ong- **R**isk **I**ndex for **S**ubclinical brain Lesions in Hong **K**ong) study [7], which is a population-based, cross-sectional study approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Ethics Committee. Subjects were recruited on a voluntary basis by convenient sampling between November 2011 and April 2015 from community centres in Shatin. The inclusion criteria were 1) age 60–90; 2) Chinese ethnicity; 3) diagnosis of hypertension (HT) and/or diabetes mellitus (DM); 4) presence of at least one viable temporal window for TCD and 5) obtainment of written informed consent. We excluded patients with 1) history of stroke; 2) diagnosis of dementia according to Diagnostic and Statistical Manual of Mental Disorders (4th edition); 3) Mini-mental State Examination (MMSE) score ≤ 22; 4) > 50% intracranial large artery stenosis on TCD or on MRA; 5) contraindications for MRI or 6) atrial fibrillation.

2.2. Data collection

Demographic factors and medical history were collected and Montreal Cognitive Assessment Hong Kong Version (HK-MoCA) were administered by skilled psychologists [19]. Blood pressure was measured using the standard procedure recommended by the AHA [19]. Fasting blood was collected to measure the lipid and glucose profile.

2.3. TCD and MRI examination

One experienced technician performed TCD by directing a 2-MHz pulsed Doppler hand-held probe to the temporal window above each zygomatic arch to detect the blood flow in the MCA. Time-averaged peak systolic flow velocity, mean flow velocity and PI were generated automatically. The PI was captured at the depth of 64 mm in 320 (96.7%) subjects. For the 11 (3.32%) subjects whose signals were undetectable at 64 mm, the PI was captured at the depth of 52 mm instead. Paired *t*-test did not find any significant difference between the PI measured at these two depths. The mean of the bilateral PI was taken for the subsequent analysis for subjects with viable temporal windows on both sides of the skull. For the 57 (17.2%) subjects with a viable temporal window on only one side of the skull, the unilateral PI was taken as the mean PI. No significant difference was found by independent samples *t*-test between the PI obtained from both temporal windows ($N = 274$), left temporal window alone ($N = 32$) and right temporal window alone ($N = 25$).

T1-, T2-weighted, FLAIR, susceptibility-weighted imaging sequences and time-of-flight MR angiograms were produced by 3.0 Tesla 3-dimensional MRI (Philips 3 T Achieva system 8-channel multi-coil) for all 331 subjects. The severity of WMH was assessed by the normalized total WMH volume, deep and periventricular WMH volume (as percentages of the whole intracranial volume) and Fazekas score. The WMH volume on the FLAIR sequences was normalized automatically by an in-house developed pipeline (AccuBrain®) (Appendix A) [21–24]. Visual rating with the 4-point Fazekas score was performed by two double-blinded technicians on the axial FLAIR sequences with a high inter-rater agreement (inter-class correlation 0.93, 95% CI 0.50–0.98) [24].

2.4. Data analysis

The normalized total WMH volumes were classified as low (< 14.5 ml, i.e. < 1 standard deviation [SD] above the mean or < 84th percentile) or high (≥14.5 ml). The classification of the deep and periventricular WMH volumes as low (< 1.73% of whole intracranial volume for deep WMH, i.e. < 84th percentile; < 0.477% of total intracranial volume for periventricular WMH, i.e. < 84th percentile) or high (≥1.73% for deep WMH; ≥0.477% for periventricular WMH) followed a similar method. For the visual rating, severe WMH was defined as a Fazekas global score of ≥2.

Logistic regression was carried out in two steps. Firstly, the demographic factors, vascular risk factors and cognitive performance scores were tested against a high WMH volume by univariate logistic regression. Factors associated with a high WMH volume ($p < .10$) were entered into multiple-variable logistic regression in a forward manner to test for an independent association with a high WMH volume. The MCA PI yielding the greatest sensitivity and specificity in predicting a high normalized total WMH volume and high Fazekas score, respectively, were identified by receiver-operator characteristics (ROC). Statistical analyses were performed with IBM SPSS Statistics 21 and $p < .05$ was taken as statistically significant.

Table 1
Demographic and clinical background of community-dwelling subjects ($N = 331$).

	Mean (SD)	Missing data (%)
Demographic factors		
Age	72.1 (5.02)	0
Male (%)	47.0	0
Years of education	8.28 (4.83)	0
Vascular risk factors		
Body mass index (kg/m^2)	24.1 (3.22)	0
Diabetes mellitus (%)	35.2	1 (0.302)
Fasting blood glucose (mmol/L)	6.01 (1.14)	11 (3.32)
Glycated haemoglobin (%)	6.31 (0.706)	3 (0.91)
Hypertension (%)	93.7	0
Systolic blood pressure (mmHg)	143 (17.0)	4 (1.21)
Diastolic blood pressure (mmHg)	79.7 (9.43)	4 (1.21)
Hyperlipidaemia (%)	42.0	0
Total cholesterol (mmol/L)	4.74 (0.901)	0
Triglyceride (mmol/L)	1.32 (0.763)	0
High-density lipoprotein (mmol/L)	1.51 (0.424)	0
Low-density lipoprotein (mmol/L)	2.64 (0.766)	0
Vitamin B12 deficiency (%)	2.42	0
Vitamin B12 (mmol/L)	402.8 (201.4)	0
Folic acid deficiency (%)	0	0
Folic acid (mmol/L)	30.4 (8.46)	0
Cognitive performance		
HK-MoCA[a] score	23.0 (3.72)	1 (0.302)
Measures of WMH[c] severity		
Fazekas global score	1.23 (0.813)	0
Normalized total WMH[c] volume (ml)	8.31 (11.0)	2 (0.604)
Deep WMH volume (% of whole intracranial volume)	1.09 (0.837)	0
Periventricular volume (% of whole intracranial volume)	0.303 (0.177)	0
Cerebral perfusion		
MCA PI[b]	1.11 (0.238)	0

[a] Montreal cognitive assessment-Hong Kong version.
[b] Pulsatility index of the middle cerebral artery. The mean of the bilateral pulsatility indices was used if the subject had viable temporal windows for transcranial Doppler ultrasonography on both sides. Otherwise, a unilateral pulsatility index was used for analysis.
[c] White matter hyperintensity.

3. Results

Among the 500 initially recruited subjects, seven (1.4%) withdrew due to old age or cardiac stenting. Another 149 (29.8%) and 13 (2.6%) subjects were excluded due to the absence of a viable temporal window and suboptimal quality of MRI scans, respectively. Three hundred and thirty-one stroke- and dementia-free elderly subjects with vascular risk factors remained in the study. Subject characteristics were summarized in Table 1.

The visually rated Fazekas score demonstrated a strong correlation with the normalized total WMH volume acquired by an automated method (Pearson's correlation 0.607, $p < .001$), indicating a high level of agreement between the two measures of severity of WMH.

Age (odds ratio [OR] 1.10, 95% confidence interval [CI] 1.04–1.17, $p = .001$) and HK-MoCA score (OR 0.902, 95% CI 0.835–0.973, $p = .008$) were associated with a high normalized total WMH volume in univariate logistic regression. Their independent association with the high normalized total WMH volume was established by multiple-variable logistic regression after adjusting for blood pressure and glycated haemoglobin (HbA1c) concentration on an a-priori basis (OR 1.09, 95% CI 1.02–1.16, $p = .009$ for age; OR 0.911, 95% CI 0.836–0.993, $p = .035$ for HK-MoCA score). It is noteworthy that vascular risk factors, such as blood pressure, HbA1c and total cholesterol concentration, did not demonstrate any significant associations with the normalized total WMH volume (Table 2). The MCA PI had no significant association with the normalized WMH volume in either univariate or multiple-variable logistic regression (Tables 1 and 2).

Table 2
Univariate logistic regression of demographic factors, vascular risk factors and MCA PI[a] in predicting high normalized WMH[b] volume ($N = 331$).

	p	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Demographic factors				
Age	0.001	1.10	1.04	1.17
Male (%)	0.932	1.03	0.572	1.84
Years of education	1.00	1.00	0.941	1.06
Vascular risk factors				
Body mass index (kg/m^2)	0.401	1.04	0.950	1.14
Fasting blood glucose (mmol/L)	0.320	0.868	0.656	1.15
HbA1c (%)	0.680	1.09	0.724	1.64
Systolic BP (mmHg)	0.666	0.996	0.979	1.01
Diastolic BP (mmHg)	0.349	0.985	0.954	1.02
Total cholesterol (mmol/L)	0.863	1.03	0.744	1.42
Triglyceride (mmol/L)	0.682	0.918	0.609	1.38
High-density lipoprotein (mmol/L)	0.18	1.57	0.812	3.02
Low-density lipoprotein (mmol/L)	0.836	0.960	0.655	1.41
Vitamin B12 (mmol/L)	0.617	1.00	0.998	1.00
Folic acid (mmol/L)	0.266	1.02	0.985	1.06
Cognitive performance				
HK-MoCA[c] score	0.008	0.902	0.835	0.973
Cerebral perfusion				
MCA PI[a]	0.424	1.59	0.511	4.94

[a] Pulsatility index of the middle cerebral artery. The mean of the bilateral pulsatility indices was used if the subject had viable temporal windows for transcranial Doppler ultrasonography on both sides. Otherwise, a unilateral pulsatility index was used for analysis.
[b] White matter hyperintensity. A high normalized WMH volume was defined as normalized WMH volume ≥ 14.5 ml.
[c] Montreal cognitive assessment-Hong Kong version.

The current understanding of the pathophysiology of regional WMH is that deep WMH results from chronic ischemic insults whereas periventricular WMH results more from fluid accumulation associated with reduced integrity of the ventricular ependyma. [25]. If this is true, we expect the deep WMH volume to have a higher association with perturbations in cerebral perfusion, and thus, with the MCA PI than the WMH of other brain regions. Nevertheless, logistic regression of the MCA PI against a high deep WMH volume and high periventricular WMH volume, respectively, failed to establish any statistically significant association (Table 3).

The lack of association between the MCA PI and the severity of WMH was confirmed by a small area under the curve (AUC) of 0.553 (95% CI 0.473–0.633) in the ROC analysis. An MCA PI ≥1.095 predicted high normalized total WMH volume with a sensitivity of 0.556, specificity of 0.523, positive predictive value of 0.182 and negative predictive value of 0.858. The ROC analysis with Fazekas score yielded similar findings, with an AUC of 0.536 (95% CI 0.470–0.602), sensitivity of 0.514, specificity of 0.477, positive and negative predictive values 0.346 and 0.686, respectively (Fig. 1). This suggests that a physiological measure of vascular resistance may not reflect the structural alterations in the white matter on neuroimaging.

4. Discussion

This is the largest community-based study investigating the ability of the MCA PI in identifying severe WMH in community elderly persons with vascular risk factors. The MCA PI had no independent association with severe WMH and demonstrated suboptimal AUC, sensitivity and specificity for predicting severe WMH.

Table 3
Logistic regression of the MCA PI[a] in predicting high deep WMH volume[b] and high periventricular WMH volume[c] (N = 331).

	p	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Univariate logistic regression				
High deep WMH volume	0.872	1.11	0.328	3.72
High periventricular WMH volume	0.431	0.577	0.146	2.27
Multiple-variable logistic regression (after adjusting for age and vascular risk factors)				
High deep WMH volume	0.551	0.646	0.153	2.72
High periventricular WMH volume	0.098	0.220	0.037	1.32

[a] Pulsatility index of the middle cerebral artery. The mean of the bilateral pulsatility indices was used if the subject had viable temporal windows for transcranial Doppler ultrasonography on both sides. Otherwise, a unilateral pulsatility index was used for analysis.

[b] A high deep white matter hyperintensity volume was defined as ≥1.73% of the whole intracranial volume.

[c] A high periventricular white matter hyperintensity volume was defined as ≥0.477% of the whole intracranial volume.

Previous small cohort studies of Caucasian subjects with recent stroke established an association between the MCA PI and a visually rated severity of WMH [26]. A study of 100 Chinese post-stroke subjects by our group also found that an MCA PI ≥1.15 differentiated patients with severe WMH (AUC 0.85, sensitivity 73.7% and specificity 82.0%) [28]. On the other hand, a pilot study of 54 middle-aged stroke-free hypertensive Caucasian male subjects was unable to recognise any significant association between the MCA PI and WMH volume [28]. The pronounced discrepancy across studies may be accounted for by their differences in subject characteristics. First and foremost, post-stroke subjects tended to harbor more extensive WMH and have poorer control of vascular risk factors than asymptomatic subjects. In our current sample of asymptomatic, stroke- and dementia-free subjects, a ceiling effect in the WMH volume might have attenuated its association with the MCA PI. Moreover, vasospasm following recent stroke could lead to intense fluctuations in cerebral vessel impedance and thus variations in the MCA PI over time, which might have confounded the association between the MCA PI and severity of WMH in post-stroke subjects [27].

Nevertheless, the MCA PI also exhibited potential utility in identifying asymptomatic SVD in our pilot study of 159 Chinese community-dwelling stroke-free elderly subjects. An MCA PI ≥1.04 differentiated those with and without severe WMH with an AUC of 0.70 and negative predictive value of 85.6% [18]. It is noteworthy that the subjects of this pilot study harbored less WMH (mean absolute WMH volume 2.60 ml, SD 1.50 ml) and their WMH volume was not adjusted for the individuals' brain volume. Our current study suggested that the MCA PI might not be able to predict severe WMH over a broader range of WMH volumes. Normalizing the absolute WMH volume to each subject's brain size might also affect the strength of its association with the MCA PI, which is a crude index obtained from the TCD without adjusting for an individual's body height, weight or brain size.

The clinical utility of MCA PI obtained from TCD in detecting severe WMH was also bound by technical limitations. TCD was unsuccessful in insonating the MCA in 31.0% of our potential subjects due to a lack of temporal window, a proportion comparable to the previously reported failure rate of 10–35% in Asian populations [29]. In addition, the MCA PI varied within a narrow range, which limited the effect size and statistical power of our analysis.

Methodological limitations of our study included the recruitment of subjects by convenience sampling. Volunteer subjects might be more health-conscious than an average elderly person with vascular risk factors in the community. For the methodology, in order to exclude the possibility that a supposedly significant association between the MCA PI and normalized WMH volume was diluted by the WMH in the cerebellum, a region not supplied by the MCA, the original FLAIR images of 33 randomly selected subjects (10% of the included subjects in this study) were screened for the presence of the infratentorial WMH. None of this subset of subjects harbored any infratentorial WMH, confirming that the lack of association between the MCA PI and the severity of WMH represented a true non-alignment between the measure of cerebral perfusion and the neuroimaging manifestation of SVD. The finding that the vascular risk factors known to contribute to SVD did not reach statistical significance in their association with severe WMH in this study may be attributed to the fact that diabetes mellitus and hypertension were generally in satisfactory control among this cohort of

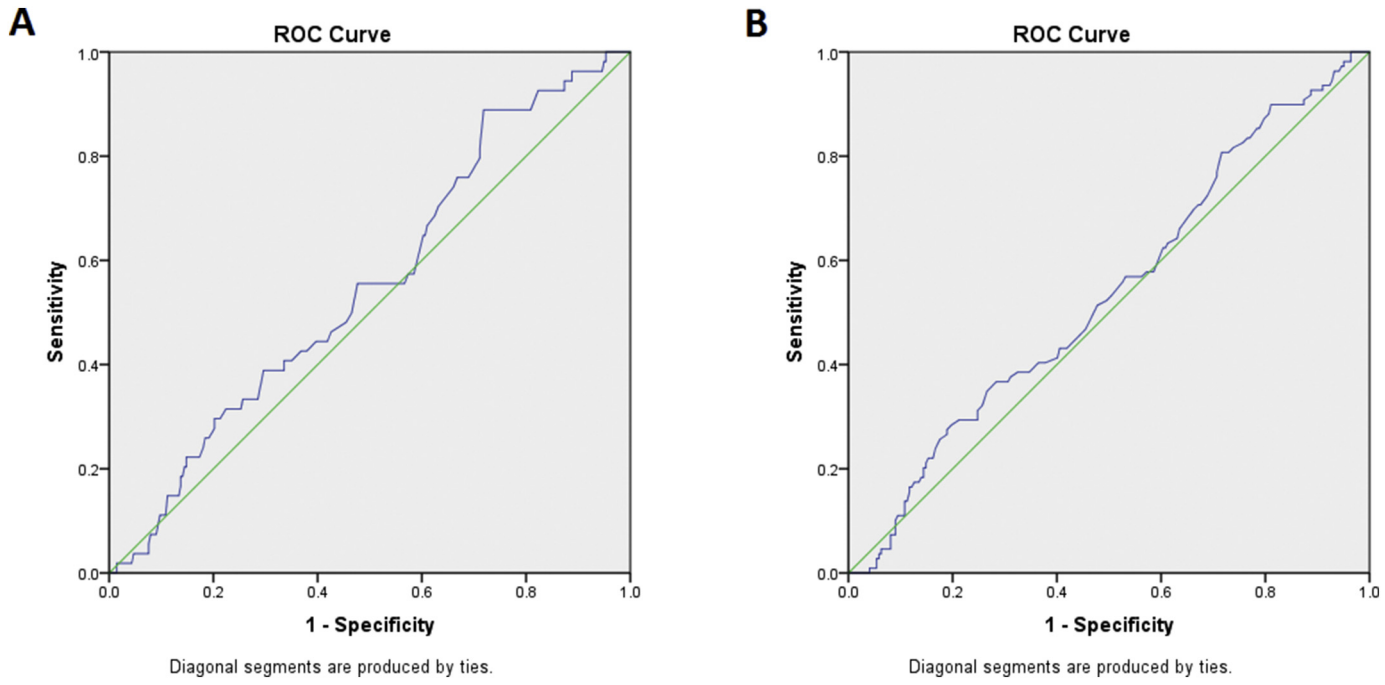

Fig. 1. Area under the curve of the MCA PI for identifying severe WMH as defined by A. normalized total WMH volume ≥ 14.5 ml, and B. Fazekas (global) score ≥ 2.

subjects (Table 1). Moreover, certain confounders, such as hypoxia and hypercapnia in chronic obstructive pulmonary disease, anaemia and migraine, remained uncontrolled. These comorbidities could impair cerebral autoregulation, superimposing the background loss of vascular elasticity from chronic atherosclerosis and creating sharp changes in the MCA PI [30–32]. Further studies with optimal control of the confounders are needed to confirm the lack of association between the MCA PI and WMH severity in asymptomatic elderly persons carrying vascular risk factors.

5. Conclusions

In stroke- and dementia-free elderly persons with vascular risk factors, the MCA PI was unable to identify severe WMH. Longitudinal studies will help to elucidate the time course of the disturbances in the MCA PI relative to the progression of WMH and the onset of SVD symptoms. At this stage, we recommended against the use of MCA PI alone in the community screening of asymptomatic SVD.

Source of funding

This study was supported by the National Key Research and Development Program of China (2016YFC1300600), the Hong Kong General Research Fund (HHSRF 09100131), the Lui Che Woo Institute of Innovative Medicine, and Therese Pei Fong Chow Research Centre for Prevention of Dementia (in memory of Donald H. K. Chow).

Disclosure

The authors reported no conflicts of interest

Appendix A

A.1. Generation of WMH lesion maps

In brief, WMH lesion maps were generated in two steps: Segmentation and registration.

WMH is defined as hyperintensity on MRI FLAIR image. Segmentation of WMH was done using a coarse-to-fine mathematical morphology pipeline [20]. Calculations of WMH volume excluded acute infarcts, which present as hyperintense regions on both FLAIR and DWI images. Segmentation results were rigorously checked and corrections were made where necessary.

The FLAIR images were first linearly registered to the T1 images of the subjects and further registered to the 1-mm T1 MNI-152 (Montreal Neurological Institute) template [21]. The registration procedure was performed by Elastix, with a linear registration followed by a non-linear registration [22], and the resulting transformations were combined to transform the corresponding lesion maps of WMH to the MNI-152 template. An age-specific MRI template was used as an intermediate before the final registration to MNI-152 standard space as all study subjects were elderly persons [23].

Quality checks of the registration results were performed by comparing the location of the lesion maps on native scan to that on MNI-152 template standard space. Manual correction of the mapped lesions was performed if necessary. These WMH lesion maps were normalized during the registration step and adjusted for individual brain size differences.

Resulting lesion maps were quantified by multiplying the number of voxels of WMH by the number of voxel spacing.

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