In shape: a novel approach to white matter hyperintensity analysis

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CHAPTER 4

A MORE IRREGULAR SHAPE OF WHITE MATTER HYPERINTENSITIES IS ASSOCIATED WITH COGNITIVE DECLINE OVER 5 YEARS IN COMMUNITY-DWELLING OLDER ADULTS

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Under review.

4.1 ABSTRACT

A previous study has shown that WMH shape is associated with long-term risk for dementia after 10 years in community-dwelling older adults. However, the exact association with decline in different cognitive domains remains unknown. The current study aimed to investigate the association of WMH shape and decline in three cognitive domains over 5 years' time in community-dwelling older adults.

The association of baseline WMH shape (solidity, convexity, concavity index, fractal dimension, and eccentricity) and cognitive decline over 5.2 ± 0.3 years (domains: memory, executive function, and processing speed) were investigated using linear regression models in the Age, Gene/Environment Susceptibility-Reykjavik (AGES) study (n = 2560).

A more irregular shape of periventricular/confluent WMH was related to cognitive decline in the memory domain (lower solidity (B: -0.04 (95% CI: -0.07—-0.01); p=0.005), lower convexity (-0.07 (-0.10—-0.04); p<0.001), a higher concavity index (-0.09 (-0.12—-0.06); p<0.001), and a higher fractal dimension (-0.07 (-0.10—-0.04); p<0.001)), the executive function domain (lower convexity ((-0.04 (-0.07—-0.01); p=0.009), a higher concavity index (-0.04 (-0.07—-0.01); p=0.003), and a higher fractal dimension (-0.04 (-0.07—-0.01); p=0.009)), and the processing speed domain (lower solidity (-0.04 (-0.07—-0.02); p<0.001), lower convexity (-0.06 (-0.08—-0.03); p<0.001), a higher concavity index (-0.08 (-0.10—-0.05); p<0.001), and higher fractal dimension (-0.06 (-0.09—-0.04); p<0.001)) over 5.2 years. No associations were found between deep WMH shape and cognitive decline in any of the cognitive domains.

These findings show that WMH shape patterns may be indicative of relatively short-term cognitive decline in community-dwelling older adults. This supports the evidence of WMH shape being a valuable marker that may be used to assess and predict cognitive outcome related to cerebrovascular disease progression.

4.2 INTRODUCTION

Cerebral small vessel disease (SVD) is associated with cognitive decline and is an important contributor to occurrence of dementia in older adults.[1,2] A key MRI marker of SVD is white matter hyperintensities (WMH), which become evident as hyperintense lesions on T2-weighted MRI scans. Total WMH volume is a commonly used MRI marker and is related to cognitive decline.[3,4] However, WMH volume is a relatively crude marker that only shows a moderate association with cognitive decline and is also not specific for underlying pathophysiological changes. In recent studies, WMH shape has been introduced as a more descriptive measure related to severity and progression of WMH compared to WMH volume alone.[5–7] For example, a more irregular shape of periventricular/confluent WMH has been associated with an increased long-term risk for ischemic stroke and mortality.[5] Furthermore, our previous study showed that a more irregular shape of periventricular/confluent WMHs was associated with an increased long-term dementia risk in community-dwelling older adults over 10 years.[6] However, the association between WMH shape and decline in different cognitive domains remains unknown. We hypothesized that a more irregular WMH shape is associated with increased cognitive decline over 5.2 years, especially in the memory domain. The current study therefore aimed to investigate the association of WMH shape and decline in three cognitive domains over 5 years' time in community-dwelling older adults.

4.3 METHODS

4.3.1 Participants & study design

The study is based on the AGES-Reykjavik study cohort.[8] This study was approved by the Icelandic National Bioethics Committee, VSN:00-063, and the institutional review board responsible for the National Institute on Aging (NIA) research. All participants signed informed consent prior to any experiments. Baseline brain MRI scans were acquired from 2002 to 2006. Five years later the follow-up visit took place from 2007 to 2011. The participants underwent cognitive testing at baseline and follow-up. A total of 2560 participants were included in the current study. A flow-chart describing the exclusion of participants for the current study is shown in supplementary figure S.4.9.1.

4.3.2 Baseline characteristics and cardiovascular risk factors

Education level and smoking status were collected via questionnaires. The highest completed education level (primary school, secondary school, college or university) was entered. Non-smokers were defined as persons who never smoked, former regular smokers of at least 100 cigarettes or 20 cigars in a lifetime were categorized

as former smokers, and the last category were current smokers. Body mass index (BMI) was calculated based on the measured participant's height (cm) and weight (kg). Systolic and diastolic blood pressure were measured with a standard mercury sphygmomanometer, and the mean of two measurements was calculated. Hypertension was defined based on self-report and/or use of antihypertensive medication, and/or measured systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg. Diabetes mellitus was defined based on self-report, use of anti-diabetic medication, or fasting blood glucose level >7.0 mmol/L. Coronary artery disease was defined based on self-report plus the use of nitrates, a history of a bypass operation, and/or evidence of myocardial infarction on electrocardiogram.

4.3.3 MRI acquisition protocol

MRI scans were performed on a 1.5 Tesla Signa Twinspeed system (General Electric Medical Systems, Waukesha, Wisconsin). Sequences included in the protocol: a 3D T1-weighted, spoiled-gradient echo sequence (repetition time = 21 ms; time to echo = 8 ms; field of view = 240 mm; slice thickness = 1.5 mm; voxel size = 0.94 × 0.94 × 1.50 mm^3) and a fluid attenuated inversion recovery (FLAIR) sequence (repetition time = 8000 ms; time to echo = 100 ms; field of view = 220 mm; 3 mm interleaved slices; voxel size = 0.86 × 0.86 × 3.00 mm^3).

4.3.4 WMH markers

An in-house developed pipeline was used to calculate WMH shape markers, as described previously.[6] In brief, WMH were segmented automatically from FLAIR MRI scans using the LST toolbox[9] in SPM12. Lateral ventricles were segmented from T1 scans and these ventricle masks were inflated with 3 and 10 mm. The inflated ventricle masks were used to classify WMHs into periventricular, confluent, or deep WMH (figure 4.1, supplementary figure S.4.9.2). Convexity, solidity, concavity index, and fractal dimensions were determined based on the segmentations of the periventricular/confluent WMHs.[6] A lower convexity and solidity, and higher concavity index and fractal dimension indicate more irregular shapes. For deep WMH fractal dimensions and eccentricity were calculated.[6] Higher eccentricity indicates a rounder shape, and a higher fractal dimension indicates a more irregular shape of deep WMH. The formulas of the WMH shape markers are shown in figure 4.1. Moreover, total WMH volume, as well as the volumes of periventricular/confluent and deep WMH were calculated.

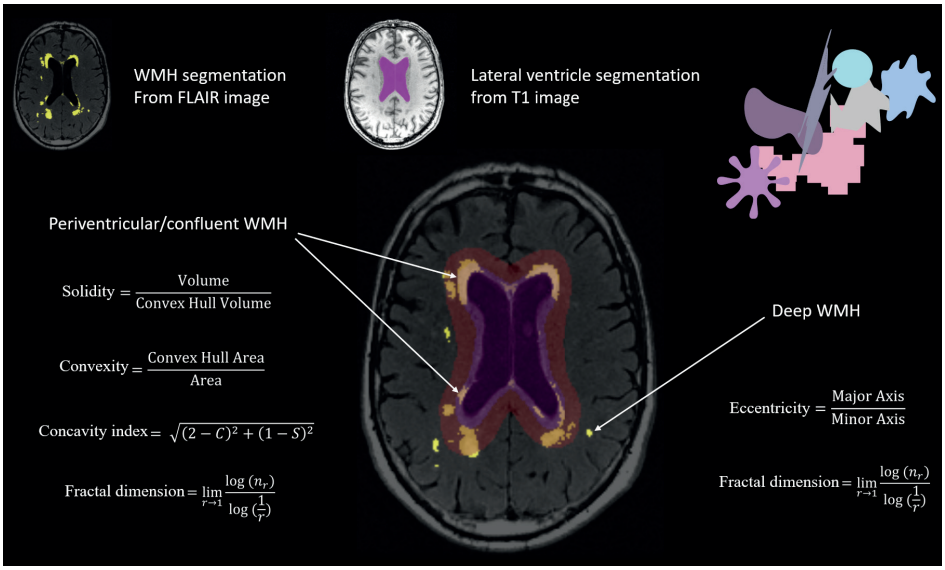

Figure 4.1. Illustration of the calculation of WMH shape markers from brain MRI scans. WMHs are automatically segmented from FLAIR images. The lateral ventricles are automatically segmented from T1 images and inflated in order to aid delineation of periventricular/confluent WMHs. Based on the segmentations, the shape markers (for periventricular/confluent WMH: solidity, convexity, concavity index, and fractal dimension; for deep WMH: eccentricity and fractal dimension) are calculated using the formula's shown in the figure.

4.3.5 Neuropsychological testing

Based on a cognitive test battery the composite scores were calculated for three cognitive domains: memory, executive function, and processing speed.[10–12] Immediate- and delayed-recall portions of the California Verbal Learning Test[13] were included in the memory composite score. The executive domain score included the Digits Backward Test[14], the Spatial Working Memory Test of the Cambridge Neuropsychological Test Automated Battery[15], and the Stroop Test, Part III (word-color interference). The processing speed domain score included the Digit Symbol Substitution Test[14], the Figure Comparison Test[16] and the Stroop Test[17] Part I (word naming) and Part II (color naming). Domain scores were calculated by converting raw scores on each test to standardized z-scores and averaging the z-scores across the tests in each composite score per participant. Change in cognitive function was determined per domain by subtracting the baseline scores from the follow-up scores.

4.3.6 Statistical analysis

To aid comparability of the results, solidity and convexity were inverted for the linear regression analyses. Solidity and WMH volumes were multiplied by 100 and natural log transformed due to non-normal distribution. Z-scores of WMH shape

markers and WMH volumes were calculated to aid comparability. Linear regression analyses were run to study the association of WMH shape and cognitive change per domain, corrected for age, sex, education, time to follow-up, and baseline cognitive domain scores. In secondary analysis to test for WMH volume independency of the associations between WMH shape and cognitive decline, WMH volume as a percentage of intracranial volume was added as an additional covariate to the linear regression models used in the main analysis. As a frame of reference linear regression analyses for WMH volumes were performed as secondary analyses, additionally corrected for intracranial volume. A p value <0.05 was considered statistically significant.

4.3.7 Sensitivity analysis

Different methods to analyze cognitive change over time were used in previous studies. To test the robustness of the linear regression models we therefore performed sensitivity analyses. To this end, linear regression analyses were run with the follow-up domain scores as dependent variable, WMH shape as independent variable and corrected for age, sex, education, time to follow-up, and baseline domain scores.

4.4 RESULTS

Baseline characteristics of the participants (n=2560) can be found in table 4.1. Mean age at baseline was 74.7 ± 4.8 years of age, and 61% of the participants were females. The cognitive decline (in z-scores) over 5.2 ± 0.3 years was -0.28 ± 0.98 in the memory domain, -0.25 ± 0.69 for executive function, and -0.32 ± 0.60 for processing speed. The z-scores per cognitive domain at baseline and follow-up for all participants per cognitive domain can be found in figure 4.2.

4.4.1 WMH Shape and cognitive decline

4.4.1.1 Memory domain

A more irregular shape of periventricular/confluent WMH expressed as a lower solidity (B: -0.04 (95% CI: -0.07—-0.01); p=0.005), lower convexity (-0.07 (-0.10—-0.04); p<0.01), a higher concavity index (-0.09 (-0.12—-0.06); p<0.001), and a higher fractal dimension (-0.07 (-0.10—-0.04); p<0.001) was related to cognitive decline in the memory domain over 5.2 years (table 4.2). No associations were found for deep WMH shape.

4.4.1.2 Executive function domain

A more irregular shape of periventricular/confluent WMH expressed as a lower convexity (-0.04 (-0.07—-0.01); p=0.009), a higher concavity index; (-0.04 (-0.07—-0.01); p=0.003), and a higher fractal dimension (-0.04 (-0.07—-0.01); p=0.009)

was related to cognitive decline in the executive function domain over 5.2 years (table 4.2). No associations were found for deep WMH shape.

4.4.1.3 Processing speed domain

A more irregular shape of periventricular/confluent WMH expressed as a lower solidity (-0.04 (-0.07—-0.02); p<0.001), a lower convexity (-0.06 (-0.08—-0.03); p<0.001), a higher concavity index (-0.08 (-0.10—-0.05); p<0.001), and a higher fractal dimension (-0.06 (-0.09—-0.04); p<0.001) was significantly associated with cognitive decline over 5.2 years in the processing speed domain (table 4.2). No associations were found for deep WMH shape.

Table 4.1. Baseline characteristics of the study sample.

Baseline characteristics	**Total n = 2560**
Age (years)	74.7 ± 4.8
Females	1562 (61%)
BMI (kg/m^3)	27.2 ± 4.1
Hypertension	1978 (77%)
Diabetes type 2 diabetes	228 (9%)
Cholesterol (mmol/L)	5.69 ± 1.13
Smoking status	
Never	1141 (44%)
Former	1145 (45%)
Current	274 (11%)
Coronary artery disease	402 (16%)
Time to follow-up (years)	5.2 ± 0.3
Total WMH volume (ml)	17.44 ± 15.94
Periventricular/confluent WMH volume (ml)	15.93 ± 15.54
Deep WMH volume (ml)	1.51 ± 1.37
Periventricular/confluent WMH	
Solidity	0.19 ± 0.12
Convexity	1.03 ± 1.18
Concavity index	1.27 ± 1.15
Fractal dimension	1.71 ± 1.54
Deep WMH	
Eccentricity	0.61 ± 0.07
Fractal dimension	1.69 ± 0.13

Data are indicated as mean ± SD or frequency (%). WMH: white matter hyperintensities.

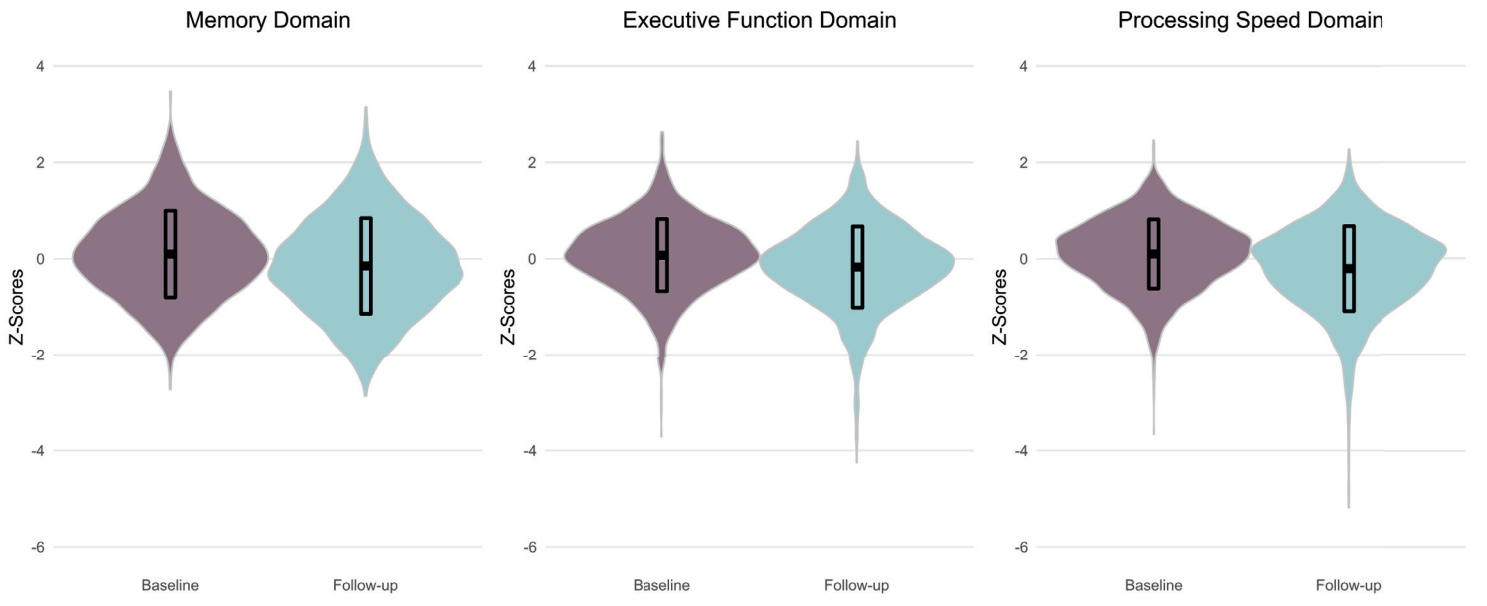

Figure 4.2. Violin plots including z-scores and standard deviation per cognitive domain (memory, executive function and processing speed) at baseline and follow-up.

4.4.1.4 Secondary analysis

In secondary analysis to test for WMH volume independency of the found associations of WMH shape and cognitive decline, we showed that these associations were for a small part WMH volume dependent. The results slightly attenuated, but stayed statistically significant in the memory domain (except for solidity) and the processing speed domain (supplementary table S.4.9.1). In the executive function domain all statistical significance was lost. Deep WMH eccentricity was found to be associated with cognitive decline in the memory domain, a finding that did not appear in the main results.

4.4.2 WMH volumes and cognitive decline

In secondary analyses, total WMH volume (memory domain: -0.10 (-0.13—-0.07); $p < 0.001$; executive function domain: -0.05 (-0.08—-0.02); $p < 0.001$; processing speed domain: -0.08 (0.10—-0.05); $p < 0.001$), the volume of periventricular/confluent WMH (memory domain: -0.10 (-0.13—-0.07); $p < 0.001$; executive function domain: -0.05 (-0.07—-0.02); $p < 0.003$; processing speed domain: -0.08 (0.10—-0.05); $p < 0.001$), and the volume of deep WMH (memory domain: -0.04 (-0.07—-0.02); $p = 0.002$; executive function domain: -0.04 (-0.06—-0.01); $p = 0.007$; processing speed domain: -0.04 (-0.06—-0.01); $p = 0.002$) were significantly associated with cognitive decline in the memory, executive function and processing speed domain (table 4.3).

4.4.3 Sensitivity analysis

To test the robustness of our results for a different method to analyse cognitive change, sensitivity analyses were performed. These results were quite comparable to our main results (supplementary table 4.9.2).

Table 4.2. Linear regression results for baseline WMH shape and decline in cognitive domain scores over 5.2 years.

	Memory (n=2340)	Executive function (n=2356)	Processing speed (n=2443)
Periventricular/confluent WMH			
Solidity	-0.04 (-0.07—-0.01) **	-0.01 (-0.04—0.02)	-0.04 (-0.07—-0.02)***
Convexity	-0.07 (-0.10—-0.04) ***	-0.04 (-0.07—-0.01)**	-0.06 (-0.08—-0.03)***
Concavity index	-0.09 (-0.12—-0.06) ***	-0.04 (-0.07—-0.01) **	-0.08 (-0.10—-0.05)***
Fractal dimension	-0.07 (-0.10—-0.04) ***	-0.04 (-0.07—-0.01)**	-0.06 (-0.09—-0.04)***
Deep WMH			
Eccentricity	-0.01 (-0.04—0.02)	-0.01 (-0.04—0.02)	-0.01 (-0.04—-0.01)
Fractal dimension	0.01 (-0.02—0.04)	0.02 (-0.01—0.05)	0.02 (-0.01—0.04)

Linear regression models for the association between WMH shape and cognitive change over 5.2 years in each cognitive domain, controlled for age, sex, education, time to follow-up, and cognitive domain scores at baseline. The sample size varies per domain due to missing data in the cognitive domain scores. Solidity and convexity were inverted to aid in the comparability of the direction of effect. *<0.05; **<0.01; ***<0.001.

Table 4.3. Linear regression results for baseline WMH volume and decline in cognitive domain scores over 5.2 years.

WMH volume	Memory (n=2340)	Executive function (n=2356)	Processing speed (n=2443)
Total WMH volume	-0.10 (-0.13—-0.07)***	-0.05 (-0.08—-0.02)***	-0.08 (-0.10—-0.05)***
Periventricular/confluent WMH volume	-0.10 (-0.13—0.07)***	-0.05 (-0.07—-0.02)**	-0.08 (-0.10—-0.05)***
Deep WMH volume	-0.04 (-0.07—-0.02) **	-0.04 (-0.06—-0.01)**	-0.04 (-0.06—-0.01)**

Linear regression models for the association between WMH volume and cognitive change over 5.2 years in each cognitive domain, controlled for age, sex, education, time to follow-up, cognitive domain scores at baseline, and intracranial volume. The sample size varies per domain due to missing data in the cognitive domain scores. *<0.05; **<0.01; ***<0.001

4.5 DISCUSSION

We showed that a more irregular shape of periventricular/confluent WMH was related to cognitive decline in the memory domain, the executive function domain, and the processing speed domain over 5.2 years in community-dwelling older adults. No associations were found between deep WMH shape and cognitive decline in any of the cognitive domains. Our secondary analyses showed that a higher total, periventricular/confluent, and deep WMH volume was associated with cognitive decline in the memory domain, the executive function domain, and the processing speed domain over 5.2 years.

Previously, we found that a more irregular shape of periventricular/confluent WMHs was associated with an increased long-term dementia risk over 10 years in the same dataset.[6] However, which cognitive functions mediate this association at a more short-term (5 years) remained unclear. A recent cross-sectional study in patients with manifest arterial disease using the same WMH shape markers showed that a more irregular shape of periventricular/confluent WMH was related to decreased executive functioning and memory performance.[18] Moreover, another cross-sectional study in cognitively impaired individuals showed that mental speed and fluid abilities showed a stronger association to a more irregular shape of WMH (based on a confluency sum score) than WMH volume.[19] To the best of our knowledge, our study is the first to investigate WMH shape and cognitive decline over time in domain scores in community-dwelling older adults. Our study showed that WMH shape markers are associated with decline in individual cognitive domains over time. As these associations were largely independent of WMH volume, this suggests that WMH shape conveys additional information about WMHs, which is not captured by WMH volume alone.

In previous studies periventricular/confluent WMH burden or volume showed a stronger association with cognitive functioning and cognitive decline compared to deep WMH burden or volume.[20,21] In a longitudinal study in the general population (n=563), with a similar age and comparable population to our study, periventricular WMH burden was associated with cognitive decline over nearly 10 years, but deep WMH burden was not.[20] While deep WMH are often found in regions of short-looped U-fibers connecting different cortical regions, periventricular WMH largely involve regions of long associating fibers with subcortical nuclei and other more distant brain regions.[22,23] Therefore, changes in a long fiber region may have more severe consequences, and also cognitive reserve mechanisms may suffer more from changes in periventricular regions compared to deep white matter regions. Another explanation could be that periventricular/confluent WMH are typically larger in volume compared to deep WMH and therefore involve a larger area of the brain. In our study, we found that both periventricular/confluent WMH volume and deep WMH volume are related to cognitive decline in all three domains (memory, executive function, and processing speed), most pronounced in the memory and processing speed domains. In a previous meta-analysis in relatively healthy older adults without cognitive impairment from 60 years of age, WMH volume and burden were also related to cognitive decline in three cognitive domains (memory, attention and executive function), slightly more pronounced for the domain attention and executive function.[3]

In the present study, the effect sizes of the associations between WMH shape and cognitive decline showed differences between cognitive domains. The effect sizes for the associations of WMH shape with memory and processing speed were roughly similar, while the effect sizes for executive function were relatively smaller. An explanation could be that different WMH shape patterns are related to different underlying pathology resulting in different effects on the brain, and possibly on different cognitive domains. SVD is a whole-brain disease and with MRI we are only able to capture the tip of the iceberg of the disease process. WMH shape could therefore convey additional information on why some cognitive domains are affected earlier or to a greater extent than others.

In our study the effect sizes of the association between WMH markers and cognitive decline per domain are quite similar for WMH shape compared to WMH volume, especially for the WMH shape marker concavity index. As these associations were largely independent of WMH volume, this shows that WMH shape is an important and relevant additional marker besides WMH volume alone. Furthermore, in otherwise healthy older adults WMHs are commonly seen and at the moment the exact prognostic meaning for an individual is unclear. Since not all individuals with WMH will eventually develop cognitive decline or dementia, it is challenging to successfully identify individuals who are at a higher risk. Specific WMH patterns—defined by type and shape—may improve this early identification within risk-MR-phenotypes.

A important strength of our study is the large cohort from the general population, which gives the study a large external validity and aids generalizability. Moreover, automated image processing techniques, in combination with extensive visual quality checks are other strengths of our study. Furthermore, the study contains a full neuropsychological assessment at two time points (baseline and follow-up). The use of a 1.5T MRI system could be considered a limitation of our study. While these systems were standard at the time of data collection, most 1.5T research MRI scanners have now been replaced with 3T MRI systems. Another limitation of our study could be selective loss to follow-up as participants who develop the most cognitive decline over time are most likely to be lost-to-follow-up. Nevertheless, despite these limitations significant associations between WMH shape markers and cognitive decline in different domains were found in our study.

In conclusion, our findings show that WMH shape patterns may be indicative of relatively short-term cognitive decline in community-dwelling older adults. This supports the evidence of WMH shape being a valuable marker that may be used to assess and predict cognitive outcome related to cerebrovascular disease progression.

4.6 ACKNOWLEDGEMENTS

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4.7 DISCLOSURES

M.J.P. van Osch reports to be an unpaid member of a clinical trial steering committee of Alnylam.

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4.9 SUPPLEMENTARY MATERIAL

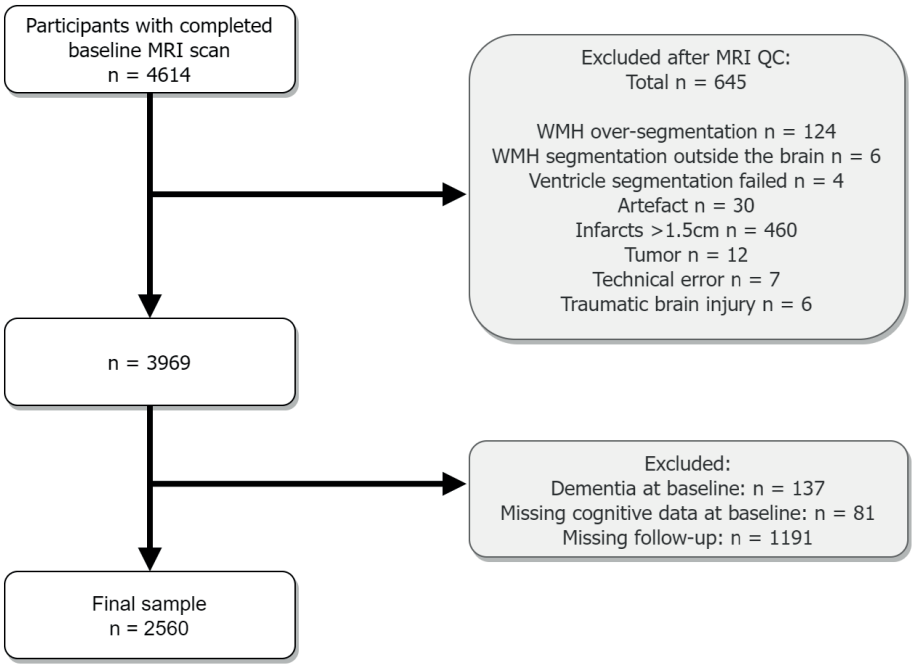

Figure S.4.9.1. Flow-chart showing the inclusion and exclusion of participants in the current study.

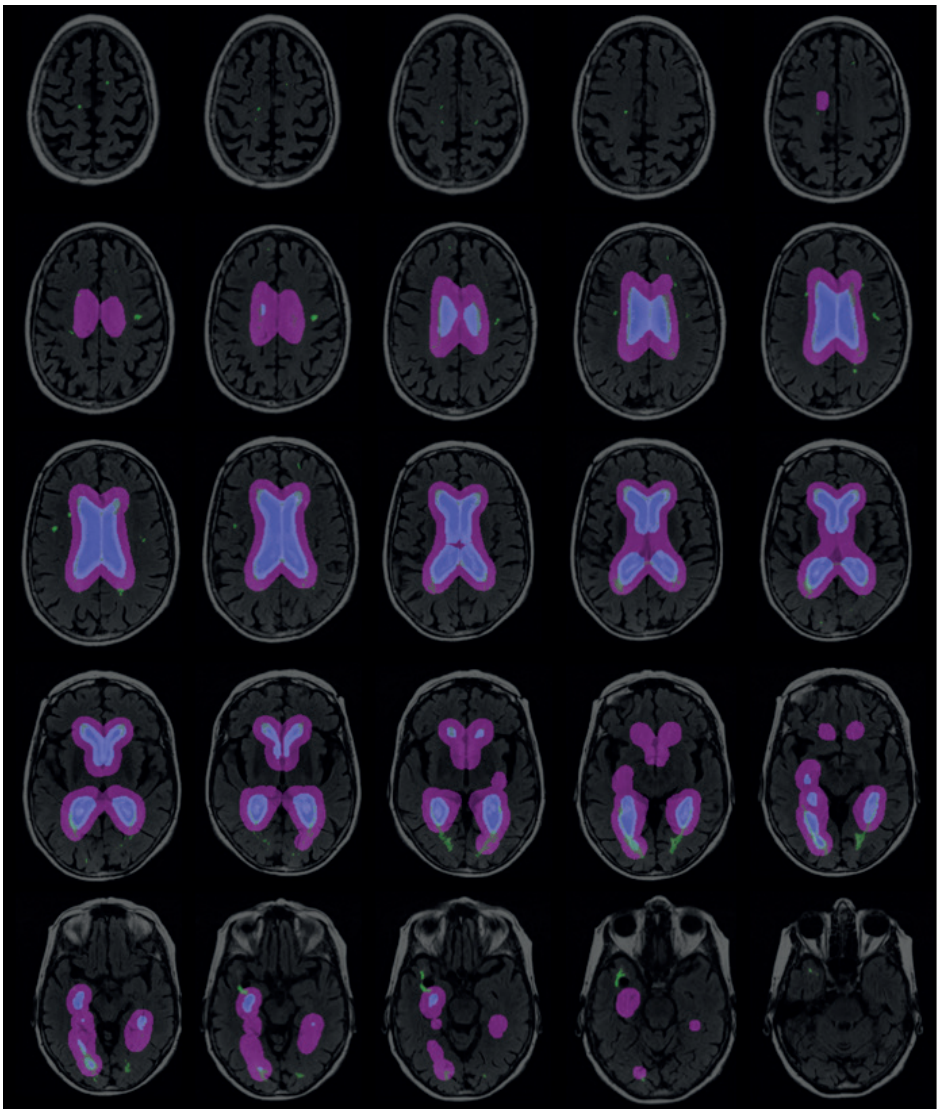

Figure S.4.9.2. Illustration of the results of the WMH shape image processing pipeline showing different brain slices with automatic segmentations. Green: white matter hyperintensities. Blue: 3 mm inflated lateral ventricle segmentation. Purple: 10 mm inflated lateral ventricle segmentation.

Table S.4.9.1. Secondary analysis to test WMH volume-dependency of the associations with the WMH shape markers.

	Memory (n=2340)	Executive function (n=2356)	Processing speed (n=2443)
Periventricular/confluent WMH			
Solidity	-0.03 (-0.06—0.00)	-0.00 (-0.03—0.03)	-0.03 (-0.06—-0.01)**
Convexity	-0.05 (-0.08—-0.01)*	-0.03 (-0.06—-0.01)	-0.05 (-0.07—-0.02)**
Concavity index	-0.07 (-0.11—-0.03)***	-0.03 (-0.07—0.01)	-0.07 (-0.10—-0.04)***
Fractal dimension	-0.05 (-0.08—-0.01)*	-0.02 (-0.06—-0.01)	-0.05 (-0.08—-0.02)**
Deep WMH			
Eccentricity	-0.04 (-0.07—-0.01)*	-0.02 (-0.05—-0.01)	-0.02 (-0.05-0.00)
Fractal dimension	0.03 (0.00—0.06)	0.02 (-0.01—0.05)	-0.04 (0.00—0.05)

Sensitivity analyses were performed to test the WMH volume-dependency of WMH shape markers. Linear regression models for the association between WMH shape and cognitive change were performed for each cognitive domain with follow-up domain score as dependent variable and WMH shape as independent variable, controlled for age, sex, education, time to follow-up, baseline domain score, and baseline WMH volume as percentage of intracranial volume. The sample size varies per domain due to missing data in the cognitive domain scores. Solidity and convexity were inverted to aid in the comparability of the direction of effect. *<0.05; **<0.01; ***<0.001.

Table S.4.9.2. Sensitivity analyses for baseline WMH shape markers and decline in cognitive domain scores after 5.2 years.

	Memory (n=2340)	Executive function (n=2356)	Processing speed (n=2443)
Periventricular/confluent WMH			
Solidity	-0.04 (-0.07—-0.01) **	-0.01 (-0.04—0.02)	-0.04 (-0.07—-0.02)***
Convexity	-0.07 (-0.10—-0.04)***	-0.04 (-0.07—-0.01)**	-0.06 (-0.08—-0.03)***
Concavity index	-0.09 (-0.12—-0.06)***	-0.04 (-0.07—-0.01)**	-0.08 (-0.10—-0.05)***
Fractal dimension	-0.07 (-0.10—-0.04)***	-0.04 (-0.07—-0.01)**	-0.06 (-0.09—-0.04)***
Deep WMH			
Eccentricity	-0.01 (-0.04—0.02)	-0.01 (-0.04—0.02)	-0.01 (-0.04—0.01)
Fractal dimension	0.01 (-0.02—0.04)	0.02 (-0.01—0.05)	0.02 (-0.01—0.04)

Sensitivity analyses were performed to test the robustness of our results for a different method to analyse cognitive change. Linear regression models for the association between WMH shape and cognitive change were performed for each cognitive domain with follow-up domain score as dependent variable and WMH shape as independent variable, controlled for age, sex, education, time to follow-up, and baseline domain score. The sample size varies per domain due to missing data in the cognitive domain scores. Solidity and convexity were inverted to aid in the comparability of the direction of effect. In the executive function domain, however, there was a slight attenuation in the results and significance was lost for the association between periventricular/confluent WMH and change in executive function. *<0.05; **<0.01; ***<0.001.