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MRI correlates of cognitive decline in CADASIL
A 7-year follow-up study

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ABSTRACT

Background: Cognitive decline is one of the clinical hallmarks of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a cerebrovascular disease caused by NOTCH3 mutations. In this 7-year follow-up study, we aimed to determine whether there are associations between the different radiologic hallmarks in CADASIL and decline in specific cognitive domains.

Methods: Twenty-five NOTCH3 mutation carriers and 13 controls had standardized neuropsychological testing and MRI examinations at baseline and after a follow-up of 7 years. To identify longitudinal associations between MRI abnormalities and cognitive decline, correlation analysis was used.

Results: At follow-up, mutation carriers showed a decline in global cognitive function (CAMCOG, \( p < 0.01 \)) and in the cognitive domains language, memory, and executive function, compared to controls. Cognitive decline, especially executive dysfunction, was associated with increase in lacunar infarcts, microbleeds, and ventricular volume. In contrast, WMHs and brain atrophy were not associated with cognitive decline.

Conclusion: Increase in lacunar infarcts, microbleeds, and ventricular volume, but not white matter lesions or atrophy, are associated with cognitive decline in the process of CADASIL in younger-aged, mildly affected patients with CADASIL. Neurology 2009;72:143–148

GLOSSARY

ANOVA = analysis of variance; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CAMCOG = Cambridge Cognitive Examination; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; MC = mutation carrier; MMSE = Mini-Mental State Examination; nonMC = non-mutation carrier; WMH = white matter hyperintensity; WMS = Wechsler Memory Scale.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary microangiopathy caused by mutations in the NOTCH3 gene. One of the clinical hallmarks of CADASIL is cognitive dysfunction. Most patients develop a marked and progressive cognitive decline before the age of 60. Cognitive dysfunction in CADASIL usually starts with impairment of executive functions which slowly progresses to global impairment of all cognitive domains.

Although several studies have demonstrated that general cognitive decline in CADASIL is associated with a number of CADASIL-associated MRI abnormalities, the exact mechanism that leads to this cognitive decline remains unclear. Two recent studies showed that lacunar infarct load is independently associated with cognitive dysfunction in CADASIL. In other studies it was found that whole brain volume and diffusion tensor imaging parameters are associated with global cognitive dysfunction. The main limitations of these studies are their cross-sectional or short follow-up design, as well as that only general cognitive decline was measured, and not specific cognitive domains.

The possible relationship between decline in...
diverse cognitive domains and radiologic hallmarks of CADASIL, i.e., lacunar infarcts, white matter hyperintensities (WMHs), and microbleeds, has not been investigated yet.

The aim of this study is to investigate longitudinal associations between radiologic changes and cognitive decline in CADASIL over a 7-year interval.

**METHODS Patients.** Participants were drawn from a Dutch CADASIL cohort evaluated at baseline in 1999/2000, which included 40 symptomatic and asymptomatic NOTCH3 mutation carriers (MCs) and 22 non-mutation carriers (nonMCs) from 15 unrelated families. All living participants were invited for a follow-up visit. Informed consent was obtained from the participant or from a family member if the participant was unable to provide informed consent. A total of 38 participants from 12 unrelated families consented to participate in the follow-up study. Twenty-five were MCs and 13 were nonMCs, the latter serving as controls. The medical ethics committee of the Leiden University Medical Center approved the study.

We took a full medical history of all participants and obtained their medical records from their physicians and general practitioners. Clinical, neuropsychological, and radiologic examinations were performed blinded to NOTCH3 mutation status.

**Neuropsychological assessment.** All individuals followed a standardized neuropsychological test battery, lasting 3 hours, at baseline and at follow-up. Details regarding administration, scoring, and clinical value of the administered neuropsychological tests have been extensively described by Spreen and Strauss. Global cognitive functioning was assessed using the Cambridge Cognitive Examination (CAMCOG), which incorporates the Mini-Mental State Examination (MMSE). The CAMCOG provides a total score for global cognitive functioning as well as subscores for specific cognitive functions (orientation, attention, memory, language, praxis, gnosia, calculation, abstract thinking).

Memory was additionally evaluated using the Wechsler Memory Scale (WMS). For testing of executive function we used the Trail Making Test A, a test of processing speed with relatively low executive burden, Trail Making Test B, a test of processing speed with relatively high executive burden, and the color-interference section of the Stroop Color and Word test.

For data analysis we used MMSE and CAMCOG as overall scores and we used the subscores that correspond to the five domains of cognition according to the DSM classification of dementia: memory, language, gnosia, praxis, and executive function. Raw scores of the tests were used, except for the WMS “memory quotient” which was conventionally transformed into a scaled score. Trail Making Test A and B scores were also analyzed after transformation to a logarithmic scale, because of a skewed distribution to the right, caused by long task completion times in patients with severe executive dysfunction. Since results were similar with and without using this transformation, only the non-transformed scores are shown.

**MRI. Image acquisition.** A uniform MRI protocol was performed on the same 1.5 T MR system (Philips Medical Systems, Best, The Netherlands) at the baseline and the follow-up examination. No significant hardware updates have been made to the scanner in the 7-year follow-up interval. The protocol included axial T1, T2, FLAIR, and T2* GE sequences. See e-Methods on the Neurology® Web site at www.neurology.org for additional details.

**Image postprocessing.** For volumetric MRI measurements of brain parenchyma, CSF, and WMHs we used locally developed semiautomated segmentation software (SNIPER, Software for Neuro-Image Processing in Experimental Research) that combines knowledge-based fuzzy clustering and region-growing techniques. Measurements were performed on dual spin-echo and FLAIR images. The FLAIR and proton density MRI were registered affine to the T2-weighted MRI using 12 degrees of freedom. The T1 sequences were not used for segmentation.

As a first step the intracranial volume was determined after skull stripping. In the second step brain parenchyma and CSF were segmented separately. Then CSF was separated into ventricular CSF and CSF surrounding the brain (peripheral CSF). Manual correction steps were used between these steps to correct for random segmentation errors. Brain atrophy was defined as follows: brain atrophy = (intracranial volume − brain parenchymal volume)/intracranial volume × 100%. Ventricular CSF volume and peripheral CSF volume were also expressed as percentage of total intracranial volume.

The final segmentation step was segmentation of WMHs. Proton density, T2, and FLAIR images were used for WMH segmentation. WMHs were defined as white matter areas with increased signal intensity on all three sequences. The software computed an additional T2/proton density image to distinguish the lesions from CSF. Volume of WMH was corrected for total brain volume by dividing the individual volume of WMH by total brain volume and expressed in percent.

The number of lacunar infarcts and microbleeds were counted on a digital workstation by one observer (M.L.), according to scoring criteria previously described (for more details, see e-Methods). A second observer (M.v.B.) reviewed the scores and in case of conflicting scores agreement was reached with a third observer (J.v.d.G.). All observers were blinded to patient data. After manual identification of lacunar infarcts, they were also marked on the MRI segmentations.

**Statistics.** Statistical analysis was performed by M.K. Liem, I.L. van der Neut, and J. van der Grond, all from the Department of Radiology of the Leiden University Medical Center. Statistical analysis was performed using the SPSS-14 statistical software package (SPSS Inc., Chicago, IL). Differences between MCs and nonMCs in demographic variables, MRI parameters, and neuropsychological testing results at baseline were analyzed using Student t tests for the normally distributed continuous variable Wechsler Memory Scale memory quotient, Mann–Whitney U test for the other non-normally distributed continuous variables, and χ² tests for categorical variables. In order to detect possible effects of selection bias on the study population, we also compared age and neuropsychological testing scores at baseline between MCs who did and who did not provide follow-up data, using Student t test for age and Wechsler Memory Scale memory quotient and Mann–Whitney U test for the other variables. Changes in neuropsychological testing results between baseline and follow-up were calculated for nonMCs. The mean change in nonMCs was considered to be a result from aging and learning effect, and was used as a correction factor for the neuropsychological testing scores of the MCs. Each individual MC testing score at follow-up was corrected by adding the mean change of the nonMC group to that score. The resulting differences in neuropsychological testing results in MCs were tested with repeated measurements analysis of variance (ANOVA) for Wechsler Memory Scale memory quotient and paired samples...
Table 1 Neuropsychological testing results at baseline and follow-up (n = 38)

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Measure</th>
<th>NonMC (n = 13), mean (SD)</th>
<th>MC (n = 25), mean (SD)</th>
<th>Corrected difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td>Baseline</td>
</tr>
<tr>
<td>Global</td>
<td>MMSE</td>
<td>28 (1.2)</td>
<td>28 (1.4)</td>
<td>28 (1.4)</td>
</tr>
<tr>
<td></td>
<td>CAMCOG total</td>
<td>95 (4.5)</td>
<td>96 (5.1)</td>
<td>94 (5.4)</td>
</tr>
<tr>
<td>Language</td>
<td>CAMCOG language</td>
<td>27 (2.2)</td>
<td>28 (1.9)</td>
<td>27 (2.5)</td>
</tr>
<tr>
<td>Praxis</td>
<td>CAMCOG gnosis</td>
<td>9.9 (0.3)</td>
<td>9.6 (0.9)</td>
<td>9.6 (0.9)</td>
</tr>
<tr>
<td>Memory</td>
<td>WMS-MQ</td>
<td>110 (12.2)</td>
<td>117 (16.1)</td>
<td>106 (14)</td>
</tr>
<tr>
<td>Executive function</td>
<td>Trails A, speed (sec)</td>
<td>29 (1.0)</td>
<td>30 (1.1)</td>
<td>38 (17)</td>
</tr>
<tr>
<td></td>
<td>Trails A (errors)</td>
<td>0</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Trails B, speed (sec)</td>
<td>73 (2.4)</td>
<td>70 (15)</td>
<td>92 (153)</td>
</tr>
<tr>
<td></td>
<td>Trails B (errors)</td>
<td>0.2 (0.1)</td>
<td>0.1 (0.1)</td>
<td>0.4 (0.1)</td>
</tr>
<tr>
<td></td>
<td>Stroop interference</td>
<td>39 (1.5)</td>
<td>32 (10)</td>
<td>40 (17)</td>
</tr>
</tbody>
</table>

Baseline–follow-up comparisons: paired samples t test for WMS-MQ; Paired samples Wilcoxon test for the other variables.

*Difference corrected for change in nonMCs.
†Difference (p < 0.01) between baseline and follow-up.
‡Difference (p < 0.05) between baseline and follow-up.

NonMC = non-mutation carriers; MC = mutation carriers; MMSE = Mini-Mental State Examination; CAMCOG = Cambridge Cognitive Examination; WMS-MQ = Wechsler Memory Scale memory quotient.

Wilcoxon tests for the other variables. Differences in MRI parameters between baseline and follow-up were tested also with repeated measurements ANOVA for normally distributed variables and with paired samples Wilcoxon tests for the other non-normally distributed variables. To correct for possible age differences between the MC and nonMC group, covariance analysis with age as a covariate was also used when needed. The 7-year differences in MRI parameters were correlated with differences in neuropsychological testing results using Pearson correlation coefficient for correlations between Wechsler Memory Scale memory quotient and brain atrophy, central atrophy, or peripheral atrophy, and using Spearman correlation coefficient for all other correlations. In order to determine the relative contribution of each MRI variable to cognitive decline, an additional multivariate analysis was performed, using multiple linear regression analysis of variables that showed an association (p < 0.05) on univariate analysis. Significance thresholds for associations between MRI parameters and cognitive decline were set at p < 0.01. Associations with a p value between 0.01 and 0.05 were considered as trends.

RESULTS Patients. Of the 62 original participants, 7 died during the follow-up period. Of the 55 remaining participants, 38 consented to participate in the follow-up study. Reasons for not participating were severe disease (3), disease-related immobility (2), hospital anxiety (2), and lack of interest or motivation (8). Two individuals did not provide a reason for nonparticipation. Of the 24 people who did not participate, 15 were MCs. These MCs were significantly older (nonparticipants: mean age 51.4, SD 9.5; participants: mean age 42.2, SD 9.5) and had worse cognitive testing scores (CAMCOG total, p = 0.02; CAMCOG language, p = 0.04; CAMCOG praxis, p = 0.04; WMS memory quotient, p = 0.01; TMT-A, p = 0.03) than MCs who participated in the follow-up study.

Of the 38 participants in the follow-up study, 25 were NOTCH3 mutation carriers. The average time between the two examinations was 7.1 years (range 6.4–7.6). There were no significant differences in age, gender, years of secondary education, and age between MCs and nonMCs, although the average age in the MC group was slightly higher than in the nonMC group (MCs: mean 42.2, SD 9.5; nonMCs: mean 36.7, SD: 8.4).

Neuropsychological test results of the MC and nonMC group at baseline and follow-up are shown in table 1. No significant differences in test results were found at baseline. At follow-up, MCs had a decrease in CAMCOG total score (p < 0.01), CAMCOG language subscore (p < 0.01), WMS-MQ (p < 0.05), and Stroop interference score (p < 0.05).

The MRI characteristics of the MC and nonMC group at baseline and follow-up are shown in table 2. MCs demonstrated an increase in lacunar infarcts (p < 0.01), WMHs (p < 0.01), and microbleeds (p < 0.05) at follow-up. NonMCs had no lacunar infarcts or microbleeds and no significant WMHs at baseline or follow-up. At baseline, level of brain atrophy, ventricular volume, and peripheral CSF volume was similar between MCs and nonMCs. At follow-up, ventricular volume had increased significantly only in MCs, whereas the level of brain atrophy increased by the same amount in both MCs and nonMCs. The yearly rate of brain atrophy was 1.7 mL per year for both MCs and nonMCs.

The associations between the changes in MRI parameters and neuropsychological testing results in MCs after the 7-year follow-up are shown in table 3. A decrease in global cognitive functioning was associated with an increase in microbleeds (CAMCOG: p = 0.005) and showed a trend toward an association with increase in lacunar infarcts (CAMCOG: p = 0.026) and increase in ventricular volume (MMSE: p = 0.025; CAMCOG: p = 0.022). Global cognitive decline was not associated with changes in WMH volume, brain atrophy, or peripheral CSF volume. Cognitive decline in the memory domain was associated with increase in microbleeds (p = 0.005), showed a trend toward an association with increase in ventricle volume (p = 0.02), but was not associated with increase in WMH volume, brain atrophy, or peripheral CSF volume. Decrease of executive function testing scores was associated with increase in lacunar infarcts (Stroop interference: p = 0.005), microbleeds (TMT-B: p = 0.007; Stroop...

*p < 0.01 between MCs and nonMCs at baseline.
†Difference (p < 0.01) between baseline and follow-up.
‡Difference (p < 0.05) between baseline and follow-up.

NonMC = non-mutation carriers; MC = mutation carriers; WMH = white matter hyperintensity.

decline, especially in the executive function domain (TMT-B and Stroop: p < 0.01).

**DISCUSSION** This study shows that in addition to lacunar infarcts, cognitive decline in mild CADASIL is also associated with microbleeds and ventricular volume, especially executive dysfunction. In contrast, WMHs and brain atrophy are not associated with cognitive decline.

This association between microbleeds and cognitive decline in CADASIL has not been described before. In this study we found that, next to global cognitive decline, the decline in the specific cognitive domains of executive function and memory are most strongly associated with an increase in microbleeds. Possibly, this association can be explained by focal tissue damage caused by microbleeds that leads to cognitive dysfunction, as has been suggested by studies in the general population. However, it is also possible that they are a proxy measure of vascular pathology and subcortical white matter injury, rather than a major cause of focal tissue damage.

Another finding in this study is the association between ventricular volume and cognition in CADASIL, as shown on both univariate and multivariate analysis. This is in line with a general population study showing that ventricular volume is an important determinant of cognitive decline. Associations between ventricular volume and cognition have also been described in other diseases such as Alzheimer disease and normal pressure hydrocephalus. However, the pathophysiologic mechanism behind this association is unknown. The increasing ventricular volume in NOTCH3 MCs may

### Table 2  
**MRI characteristics at baseline and follow-up (n = 38)**

<table>
<thead>
<tr>
<th>MRI parameter</th>
<th>NonMC (n = 13)</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>MC (n = 25)</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMH volume, % (SD)</td>
<td></td>
<td>0.0</td>
<td>0.0</td>
<td>5.0 (3.9)‡</td>
<td>7.4 (5.3)‡</td>
<td></td>
</tr>
<tr>
<td>Infarcts, n (range)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>6.2 (0–27)*</td>
<td>9.9 (0–38)*</td>
<td></td>
</tr>
<tr>
<td>Microbleeds, n (range)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>1.6 (0–35)</td>
<td>3.5 (0–40)†</td>
<td></td>
</tr>
<tr>
<td>Brain atrophy, % (SD)</td>
<td></td>
<td>19.2 (1.7)</td>
<td>20.0 (1.3)†</td>
<td>17.4 (2.9)</td>
<td>18.2 (3.2)†</td>
<td></td>
</tr>
<tr>
<td>Ventricular volume, % (SD)</td>
<td></td>
<td>1.9 (0.7)</td>
<td>2.1 (1.0)</td>
<td>2.5 (1.0)</td>
<td>2.9 (1.4)†</td>
<td></td>
</tr>
<tr>
<td>Peripheral CSF volume, % (SD)</td>
<td></td>
<td>17.3 (1.9)</td>
<td>17.9 (1.7)</td>
<td>14.9 (3.0)</td>
<td>15.2 (2.9)†</td>
<td></td>
</tr>
</tbody>
</table>

WMS completed by 24 mutation carriers, Stroop test by 22 mutation carriers, Trail-Making Test by 22 mutation carriers. Pearson correlation coefficient for WMS-MQ with NBV, VV, PCSF. Spearman rho for all other correlations. Only p values lower than 0.05 are shown.

*p < 0.05, †p < 0.01 in multivariate analysis.

WMS-MQ = Wechsler Memory Scale memory quotient.

### Table 3  
**Correlations between changes in MRI parameters and changes in neuropsychological test results in mutation carriers (n = 25)**

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Measure</th>
<th>Δ Infarcts</th>
<th>Δ WMH volume</th>
<th>Δ Microbleeds</th>
<th>Δ Brain atrophy</th>
<th>Δ Ventricular volume</th>
<th>Δ Peripheral CSF volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>Δ MMSE</td>
<td>−0.39</td>
<td>−0.19</td>
<td>−0.30</td>
<td>−0.17</td>
<td>−0.45</td>
<td>0.025</td>
</tr>
<tr>
<td>Global</td>
<td>Δ CAMCOG total</td>
<td>−0.45</td>
<td>0.026</td>
<td>−0.26</td>
<td>−0.54 (0.005</td>
<td>−0.09</td>
<td>−0.46</td>
</tr>
<tr>
<td>Language</td>
<td>Δ CAMCOG language</td>
<td>−0.41</td>
<td>0.041</td>
<td>−0.13</td>
<td>−0.25</td>
<td>−0.20</td>
<td>−0.36</td>
</tr>
<tr>
<td>Gnosis</td>
<td>Δ CAMCOG gnosis</td>
<td>−0.22</td>
<td>−0.02</td>
<td>−0.25</td>
<td>−0.17</td>
<td>−0.29</td>
<td>−0.09</td>
</tr>
<tr>
<td>Praxis</td>
<td>Δ CAMCOG praxis</td>
<td>−0.05</td>
<td>0.12</td>
<td>−0.38</td>
<td>−0.47 (0.02</td>
<td>−0.32</td>
<td>0.41</td>
</tr>
<tr>
<td>Memory</td>
<td>Δ WMS-MQ</td>
<td>−0.21</td>
<td>0.02</td>
<td>−0.55 (0.005</td>
<td>−0.22</td>
<td>−0.46</td>
<td>0.023*</td>
</tr>
<tr>
<td>Executive function</td>
<td>Δ Trails A (speed)</td>
<td>−0.02</td>
<td>−0.16</td>
<td>0.01</td>
<td>−0.14</td>
<td>0.32</td>
<td>0.01</td>
</tr>
<tr>
<td>Executive function</td>
<td>Δ Trails A (errors)</td>
<td>−0.06</td>
<td>−0.33</td>
<td>0.15</td>
<td>−0.42</td>
<td>0.31</td>
<td>0.26</td>
</tr>
<tr>
<td>Executive function</td>
<td>Δ Trails B (speed)</td>
<td>0.34</td>
<td>0.19</td>
<td>0.56 (0.007*</td>
<td>0.33</td>
<td>0.55</td>
<td>0.008*</td>
</tr>
<tr>
<td>Executive function</td>
<td>Δ Trails B (errors)</td>
<td>0.38</td>
<td>0.16</td>
<td>0.14</td>
<td>−0.08</td>
<td>0.32</td>
<td>0.18</td>
</tr>
<tr>
<td>Executive function</td>
<td>Δ Stroop interference</td>
<td>0.57</td>
<td>0.005</td>
<td>0.25</td>
<td>0.62 (0.002</td>
<td>0.16</td>
<td>0.48</td>
</tr>
</tbody>
</table>

*p < 0.05, †p < 0.01 in multivariate analysis.
be secondary to other MRI abnormalities in CADASIL. WMHs, lacunar infarcts, and microbleeds are mainly located in deep white matter tracts or in gray matter structures that surround the ventricles. Damage to these structures may cause central atrophy, leading to enlarged ventricles with relatively little change in peripheral CSF volumes. The results of the multivariate analysis indicated that of all neuroradiologic findings ventricular enlargement is the main determinant of cognitive decline.

Our data also demonstrate that an increase in lacunar infarcts is associated with cognitive decline, whereas increase in WMHs is not. This confirms the findings from recent cross-sectional studies showing lacunar infarcts, and not WMHs, to be the main predictor of cognitive decline.\(^{5,6}\)

We found no significant role for brain atrophy on cognition. This is in contrast to the findings of one recent study demonstrating an association between brain atrophy and cognitive decline in CADASIL.\(^7\) It is possible that this difference is caused by the smaller sample size in our study. However, it should be noted that our results do show an effect of ventricular enlargement on cognition, which can be considered a measure of central atrophy. In our study the amount of ventricular CSF volume reflects only 15% of the total amount of CSF volume. It is possible that the changes in ventricular volume are too small too cause a measurable change in total CSF volume and total brain volume. The previous research looked at global atrophy, without distinguishing between central atrophy and peripheral atrophy. It is unclear what the results would have been if ventricular volume was included separately in that study. Global brain atrophy is likely to correlate with cognitive decline in an older, more impaired CADASIL sample.

It should be noted that even with 7 years of follow-up the overall rate of cognitive decline in our research population was relatively small, even in sensitive measures of executive function such as the Trail Making Test B. Possible explanations for this are that our study population also included younger MCs who do not have any noticeable cognitive dysfunction and that there may be a selection bias, because of loss to follow-up of MCs with rapid disease progression. Another possible explanation for the low rate of cognitive decline may be a learning effect, as the cognitive testing scores in the control group show a slight improvement at follow-up for most cognitive tests. After correcting for this improvement, a significant decline in MCs was found in three out of five cognitive domains. The correlations we found mainly involved executive dysfunction and memory, which is in agreement with the profile of cognitive dysfunction early in the CADASIL disease process.\(^24\)

Our finding that the rate of cognitive decline was highest in the language domain may seem to disagree with this early cognitive profile in CADASIL. However, it should be noted that the CAMCOG language subtest also includes a test of word fluency, which is a test that measures both language and executive function. Additional analysis of the different subtests of CAMCOG language revealed that word fluency was the main contributor to this decline in CAMCOG language score. Word fluency also contributed most to the significant association between CAMCOG language and lacunar infarcts.

A limitation of this study is the relatively small study population, which may have limited the statistical power to prove some correlations between MRI parameters and cognitive decline. Another limitation is the small age difference between MCs and non-MCs, which may have affected analysis of cognitive testing scores. However, a strength of our study is the longitudinal design, which allowed us to measure the effect of relatively small changes in MRI parameters on cognitive performance within the same individual. This advantage is especially important in our study population, because CADASIL is known for the large interindividual variability in MRI parameters and clinical phenotype.\(^25\) No long-term follow-up studies describing the correlations between changes in MRI parameters and cognition have been performed before.

Another potential problem is that multiple statistical tests were used to associate MRI parameters and neuropsychological testing results. This may have resulted in false positive findings. We applied an a priori control of the alpha level to 0.01 to decrease this risk. However, it should be noted that the total number of significant associations and trends toward associations for specific MRI parameters was much higher than the rate of 5% false positives that would be expected on the basis of chance. Lacunar infarcts, microbleeds, and ventricular volume showed 27%, 36%, and 45% positive associations with neuropsychological testing results. In contrast, the three other MRI variables only showed 2 out of 33 associations (6%) which did not reach the significance threshold of \(p < 0.01\). Therefore, we believe that the overall results of this study are realistic and cannot be explained by chance alone.

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</tr>
</thead>
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