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Impact of Small Vessel Disease Progression on Long-term Cognitive and Functional Changes After Stroke

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Abstract

Background and Objectives

The severity of white matter hyperintensities (WMH) at presentation with stroke associates with post-stroke dementia and dependency. However, WMH can decrease or increase after stroke, prediction of cognitive decline is imprecise, and there are few data assessing longitudinal interrelationships between changing WMH, cognition, and function after stroke, despite the clinical importance.

Methods

We recruited patients within three months of a minor ischaemic stroke, defined as NIHSS score <8 and not expected to result in a modified Rankin Score (mRS) >2. Participants repeated MRI at one year, and cognitive and mRS assessments at one and three years. We ran longitudinal mixed-effects models assessing change in Addenbrooke's Cognitive Examination-Revised (ACE-R) and modified Rankin Scores (mRS). For mRS, we assessed longitudinal WMH volumes (cube root; percentage intracranial volume [ICV]), adjusting for age, NIHSS, ACE-R, stroke subtype, and time to assessment. For ACE-R, we additionally adjusted for ICV, mRS, premorbid IQ, and vascular risk factors. We then used a multivariate model to jointly assess changing cognition/mRS, adjusted for prognostic variables, using all available data.

Results

We recruited 264 patients; mean age was 66.9 (SD 11.8); 41.7% were female; median mRS 1 (IQR 1-2). One year after stroke, normalised WMH volumes associated more strongly with one-year ACE-R ($\beta = -0.259$, 95% confidence interval

[CI] -0.407 to -0.111 more WMH per 1-point ACE-R decrease, $p=0.001$) compared to subacute WMH volumes and ACE-R ($\beta=0.105$, 95%CI -0.265 to 0.054, $p=0.195$). Three-year mRS associated with three-year ACE-R ($\beta=-0.272$, 95%CI -0.429 to -0.115, $p=0.001$). Combined change in baseline-one-year jointly assessed ACE-R/mRS associated with fluctuating WMH volumes ($F=9.3$, $p=0.03$).

Discussion

After stroke, fluctuating WMH mean that one-year, but not baseline, WMH volumes associate strongly with contemporaneous cognitive scores. Co-varying longitudinal decline in cognition and independence post-stroke, central to dementia diagnosis, is associated with increasing WMH volumes.

Introduction

Cerebral small vessel disease (SVD) is common in patients with stroke and is a common cause of stroke and vascular dementia.¹ White matter hyperintensities (WMH), a key feature of SVD, have been shown to decrease as well as increase in stroke,² cognitively impaired,^{3,4} older community-dwelling adults investigated for neurological or cognitive symptoms,⁵ and healthy adults (mean age 63).⁶ It is not clear how the timing of SVD lesion change relates to the clinical development of stroke and dementia.

To diagnose dementia, evidence of coexisting decline in both cognitive and functional ability is required. After stroke, we usually define functional status according to the degree of post-stroke disability measured by the modified Rankin Scale (mRS), i.e. the level of independence in carrying out activities of daily living. In particular, 'mild neurocognitive disorder' is distinguished from 'major neurocognitive disorder' by the presence of increasing dependence.^{7,8} This is particularly relevant after stroke, as

both worsening mRS and cognitive impairment are common and interrelated three years after minor stroke.⁹ However, it is not known whether SVD progression might influence the interaction of these impairments.

In cross-sectional studies, worse white matter hyperintensities (WMH) at stroke presentation are associated with worse cognition assessed concurrently as well as long term.^{10,11} However, it is less clear whether longitudinal WMH change predicts coexistent post-stroke cognitive or functional impairment. Relatively small MRI studies assessing WMH progression and post-stroke cognitive decline have not detected a longitudinal association, however follow-up sample sizes may have been underpowered, ranging from n=30 to n=94 participants¹²⁻¹⁷ (systematic search for relevant papers and summary of their characteristics are described in eTable 1 and eTable 2 in the Supplement). Additionally, we and others showed recently that WMH can decrease as well as increase long term^{2,5} and, although the reasons are poorly understood, fluctuations in WMH have not been accounted for in longitudinal studies. Although numerous studies have assessed baseline WMH and mRS change after stroke,¹⁰ we are not aware of any studies that have assessed WMH progression and mRS change after stroke (eTable 1, eTable 2 in the Supplement), or if WMH progression or severity at specific time-points affects variation between both mRS and cognition post-stroke, despite these measures being collected increasingly by ongoing studies.^{18,19}

The present in-depth analysis builds on previous work from the Mild Stroke Study-2⁹ on one- and three-year outcomes after stroke which included predictors of cognition and cognition-mRS relationships,⁹ but did not assess longitudinal change incorporating all three elements of cognition, mRS and WMH.

We aimed to determine whether WMH associations with cognition and mRS vary at different time-points post-stroke; whether associations vary according to intra-individual trajectories; whether longitudinal WMH volume change associates with change in cognition and mRS as a co-primary, co-varying endpoint; and whether any associations more strongly drive change in cognition or mRS.

Methods

Participants and design

We prospectively recruited 264 patients presenting to stroke services in Edinburgh, UK with acute minor ischaemic stroke. All patients were dementia-free at recruitment and were treated with secondary stroke prevention according to guidelines. Participants had baseline assessments 1-3 months post-stroke including MRI, cognitive, and mRS assessments. Participants repeated MRI at one year and repeated cognitive and mRS assessments at one and three years. Figure 1 shows variables collected at each visit.

Longitudinal cognitive, mRS, and other clinical assessments

Study procedures including baseline variables and stroke subtyping have been described in full previously.^{2,9,20-22} Participants underwent the Addenbrooke's Cognitive Examination–Revised version (ACE-R) at all three visits. The ACE-R is sensitive to multi-domain cognitive impairment post-stroke, similar to the Montreal Cognitive Assessment.²³ We assessed the mRS at all three visits. We collected NIHSS at baseline and one year. At baseline, participants completed the National Adult Reading Test (NART), a durable measure of premorbid intelligence.²²

Magnetic Resonance Imaging

MRI acquisition

Participants had brain MRI at baseline and were invited to repeat MRI one year later, all performed on the same 1.5T scanner (Signa LX; General Electric, Milwaukee). MRI included 3D T1-, T2-, and gradient recalled echo T2*-weighted, fluid-attenuated inversion recovery (FLAIR), and diffusion tensor imaging sequences using a self-shielding gradient and 8-channel phased-array head coil (details described previously).²⁴

MRI analysis

We analysed all images according to the Standards for Reporting Vascular changes on nEuroimaging (STRIVE),²⁵ using validated computational pipelines and visual assessments. Image analysis methods are outlined in full elsewhere.²⁴ In brief, we co-registered structural sequences at both time points using FSL-FLIRT. Total brain WMH volumes were quantified semi-automatically using paired T2-weighted, FLAIR and T2*-weighted images. WMH were carefully distinguished from the site of all chronic, index, and incident stroke lesions to avoid distorting WMH volume measurements.²⁶ This was guided by visual checks of DWI, T2-weighted and FLAIR images in discussion with a neuroradiologist (JMW).²⁶

We extracted baseline intracranial volume (ICV) semi-automatically using the T2*-weighted sequence followed by manual correction. All results were checked and manually edited independently and blinded to all clinical information.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by Lothian Ethics Medical Research Committee (REC 09/81101/54) and NHS Lothian R&D Office (2009/W/NEU/14). All participants gave written informed consent.

Statistical analysis

Data preparation

We used all available data at each time-point. To improve model fit, we transformed WMH volumes, calculating the cube root and expressing the result as % ICV, described in previous analyses.² We also rescaled ICV to ensure model convergence, due to the difference in magnitude vs other variables, dividing by 1000 to improve model fit. To avoid model overfitting, we calculated a baseline vascular risk factor composite sum score.²⁷ This score assigned equal weight to hypertension, hyperlipidaemia, diabetes mellitus, and smoking history. We created WMH volume change quintiles between baseline and one year for display purposes but we used continuous WMH volume measurements for all statistical analyses. Years since stroke was categorised as 0 (baseline visit was 1-3 months post-stroke) vs 1-year visit.

Models

Figure 1 describes the cross-sectional and longitudinal data analyses.

First, we assessed whether cross-sectional WMH volume-cognition-mRS associations are stronger or weaker at the different key time-points after stroke. To achieve this, we ran linear models with ACE-R at each visit and ordinal regression models with mRS at each visit (Figure 1), all adjusted for key factors which we outline below.

Secondly, we assessed *longitudinal change according to intra-individual trajectories*.

To do this, we performed mixed-effects analyses. To assess cognitive decline, we used a linear mixed-effects model (lme4,²⁸ R) with longitudinal change in ACE-R score between baseline and one year as the dependent variable. Since data for

participants who did not attend follow-up visits or who died after baseline (n=5 at one year; n=22 at three years) are not missing at random, we did not perform multiple imputation or last observation carried forward in accordance with guidance^{29,30} and therefore visits with missing data for such participants were not used. However, where available, baseline and/or one-year data for these participants were still used in the mixed-effects models. In keeping with previous analyses of post-stroke cognitive course,⁹ we adjusted for normalised longitudinal WMH volumes, baseline and one-year mRS, time since stroke (baseline vs 1 year), and the following baseline variables: age, NART score, stroke subtype, vascular risk factors, and ICV (to account for original brain size).²⁵

To assess worsening mRS, we performed mixed-effects ordinal regression analysis (mixor,³¹ R) with longitudinal mRS change between baseline and one year (dependent variable). In this model, we adjusted for normalised longitudinal WMH volumes (baseline to one year), baseline and one year ACE-R, NIHSS, time since stroke (baseline vs 1 year), and baseline age and stroke subtype. For participants who died after baseline or one-year follow-up, we used any available baseline or one-year data collected when these patients were alive in mixed-effects models. We did not adjust for sex since it appears not to predict long-term independence³² or cognitive function¹¹ after stroke. For this ordinal analysis, we standardised normalised WMH volumes using Z-scores. This minimises the parameter scaling issues with ordinal dependent variables that can hinder model convergence.

Finally, to assess co-varying change in cognition and mRS between baseline and one year, we created a multivariate mixed-effects model combining cognitive and mRS scores as a co-primary outcome. We fitted baseline and one-year normalised WMH volumes, NIHSS, time since stroke (baseline vs 1 year), and the following

baseline variables: age, ICV, stroke subtype, and vascular risk factor score as fixed effects. We built the model using ASReml-R version 4.³³ This analysis included baseline and one-year data since we collected imaging data at these visits only. We excluded individual participants' time-points that did not contain a one-year WMH volume measurement (n=68/264) or baseline vascular risk factor sum score (n=2/264). For all mixed-effects analyses, we fitted individual participants as random effects. The benefit of this approach is that it assesses intra-individual variation over time. We reported conditional F-test and p-values for fixed effects. We chose predictors based on previous research⁹ and did not perform power calculations on existing data as per recommended practice.³⁴

Data availability

Anonymized data not published within this article can be made available by request from any qualified investigator.

Results

We collected mRS, imaging, and cognitive data at baseline (mRS n=264; imaging: n=264; cognitive n=157), one year (mRS n=264; imaging: n=196; cognitive n=151), and three years post-stroke (mRS n=222; no imaging; cognitive n=152).

Participants who did not attend one-year follow-up (n=68/264) were older (mean age 69.9 [SD 13.3] vs 65.8 [11.1]), had lower ACE-R scores (mean 83 [SD 9.7] vs 88.8 [7.6]), and had similar WMH volumes (median 13.4 [IQR 5.0-36.8] vs 12.8mL [4.4-33.7]) and vascular risk factor scores (mean 1.8 [SD 1.0] vs 1.6 [0.8]) at baseline than participants who did attend. Participants who did not attend three-year cognitive follow-up (n=112/264) were older at baseline (68.6 [SD 12.5] vs 65.6 [11.0]), had similar baseline ACE-R scores (86.9 [8.6] vs 88.7 [7.8]), higher baseline WMH

volumes (median 17.8 [IQR 5.9-40] vs 12.3mL [3.8-29.4]), and similar vascular risk factor scores (mean 1.8 [1.0] vs 1.6 [0.94]) than those who did. Differences are shown in eTable 3 in the Supplement. At one year follow-up, 5/264 (1.9%) had died. At three-year follow-up, 22/222 had died (9.9%).

At baseline, the mean age was 66.9 (SD 11.8) years; 41.7% were female; median mRS was 1 (IQR 1-2); median NIHSS was 1 (IQR 0-2); median WMH volume was 13.1ml (IQR 4.5–34ml); median WMH as %ICV was 0.89 (IQR 0.31-2.38), and mean ACE-R was 88.1 (SD 8.1). Stroke subtype was lacunar in 44.6%. Population characteristics at baseline are shown in Table 1.

Over follow-up, the mean difference in WMH volumes between baseline and one year was 1.31mL (SD 8.68) with maximum 29.1mL growth and maximum 31.9mL shrinkage. The mean change in ACE-R scores from baseline to three years was -0.17 (SD 5.93), with a maximum increase of 20 and maximum decrease of 24 points. The median change in mRS from baseline to three years was 0 (IQR -1 to 0), with a maximum increase of three and maximum decrease of four points. Figure 2 shows the distribution of change in these variables during follow-up. Figure 3 shows ACE-R and mRS interrelationships at each visit according to WMH change quintiles. See eTable 4 in the Supplement for mean WMH volumes, cognitive and mRS scores at each time-point.

Between baseline and one- or three-year follow-up, n=95/195 (48.7%) participants had a ≥ 1 -point increase in mRS and 76/148 (51.3%) had a ≥ 1 -point decrease in ACE-R. Considered together, n=28/137 (20.4%) participants had a combined increase in mRS with decrease in ACE-R, potentially meeting DSM-V diagnostic criteria for dementia.

Multivariable analyses

Cross-sectional WMH, cognition, and mRS at baseline/one year/three years

First, we performed cross-sectional analyses of ACE-R associations at baseline, one, and three-year visits (eTable 5 in Supplement, Figure 4A-C). At baseline, ACE-R scores were very weakly associated with WMH volumes (cube root as % ICV) ($\beta = 0.105$, 95% confidence interval [CI] -0.265 to 0.054 more WMH per 1-point ACE-R decrease, $p = 0.195$). At one year, associations between ACE-R scores and WMH volumes were more apparent ($\beta = -0.259$, 95%CI -0.407 to -0.111 more WMH per 1-point ACE-R decrease, $p = 0.001$). The ACE-R/WMH association predominated over ACE-R associations with age, mRS, ICV, vascular risk factors, and stroke subtype. Since participants did not undergo imaging at three years, we included normalised WMH volumes from the one-year visit in the three-year model. We did not detect any associations between one-year WMH and three-year ACE-R scores. Assessing ACE-R and mRS relationships, we did not find any association between ACE-R and mRS scores at baseline. However, we detected an ACE-R/mRS trend at one year, and a strong association emerged at three years ($\beta = -0.272$, 95% CI -0.429 to -0.115, $p = 0.001$; eTable 5 in Supplement, Figure 4A-C).

We then ran cross-sectional ordinal regression models of mRS associations at baseline, one, and three years (eTable 6 in Supplement). We used one-year WMH volumes and NIHSS scores in the three-year model. WMH were not associated with mRS at any time-point (one-year OR 1.01, 95% CI 0.99-1.02). NIHSS was contemporaneously associated with mRS at baseline (OR 4.19, 95% CI 2.89-6.25), one year (OR 4.28, 95% CI 2.89-6.25), and three years (OR 3.08, 95% CI 2.51-7.59).

Longitudinal WMH, cognition, and mRS between baseline and one year

Secondly, we assessed longitudinal change according to intra-individual trajectories.

We used mixed-effects models to assess ACE-R, mRS and WMH volumes at baseline and one year. Changing ACE-R scores associated most strongly with age ($\beta = -0.30$, 95% CI -0.44 to -0.16, $p < 0.001$) and NART scores ($\beta = 0.53$, 95% CI 0.40-0.66, $p < 0.001$), followed by change in normalised WMH volumes between baseline and one year ($\beta = -0.113$, 95% CI -0.233-0.007, $p = 0.065$; Figure 4D, eTable 7).

ACE-R change was more strongly associated with WMH volume change than with mRS change, time since stroke, ICV, vascular risk factors, and stroke subtype.

Change in mRS from baseline to one year was associated most strongly with NIHSS and WMH volumes, with a trend towards cortical (rather than lacunar) stroke subtypes (eTable 8 in the Supplement).

Longitudinal WMH and combined, co-varying cognitive/mRS endpoint between baseline and one year

Finally, in multivariate change-change analysis, individuals with change in both ACE-R and mRS between baseline and one year were more likely to have had a baseline-one-year change in their WMH volumes and a baseline-one-year change in their NIHSS scores, compared with individuals without any change in ACE-R and mRS (Table 2). Worsening ACE-R/mRS was also more likely in participants with lower ICV and participants who were older at baseline. Co-variation between ACE-R and mRS was stronger at the one-year than at the baseline visit.

Table 2 shows the contribution of each variable driving ACE-R change and mRS change between baseline and one year, e.g. change between baseline-one-year WMH volumes and co-varying ACE-R/mRS during the same time period is more strongly driven by WMH:mRS (standardised mRS change = 1.81 [95% CI 0.35-3.26])

than by WMH:ACE-R (standardised ACE-R change -0.99 [95% CI -3.13-1.15]). In contrast, co-varying ACE-R/mRS change associations with baseline ICV and age are more strongly associated with changing ACE-R than with changing mRS.

Discussion

We found that co-varying longitudinal change in cognition and mRS post-stroke independently associates with change in total WMH volumes between baseline and one year. In the subacute phase post-stroke, cross-sectional cognitive scores are most strongly associated with age and pre-morbid cognitive ability (NART), followed by WMH volume. However, by one year, the WMH-cognition cross-sectional association is considerably stronger and supersedes all other factors (Figure 4).

Longitudinal change in cognitive scores associates most strongly with age and NART, followed by change in WMH volumes, then mRS, baseline ICV, baseline vascular risk factors, stroke subtype, and timing (baseline vs 1 year) since stroke. A WMH-mRS association emerges over time that was not detectable on cross-sectional analyses, reflecting that WMH and mRS are dynamic and effects may take longer to emerge and stabilise.

Of particular relevance to dementia after stroke, we show that longitudinal change in co-varying cognition and mRS in the first year post-stroke is associated with age, ICV, change in WMH volumes and NIHSS.

These findings highlight the role of SVD in evolving vascular cognitive impairment and physical dysfunction after stroke, suggesting that individuals with WMH progression post-stroke are more likely to develop a simultaneous decline in cognition and mRS compared to individuals with unchanging WMH after accounting

for demographics and risk factors. This analysis builds on the recent finding in the same population that cognitive impairment after lacunar stroke is more related to background SVD than to index lesion location.³⁵ Notwithstanding that, considering the range of all subtypes of stroke, lesion location does appear to play a role in post stroke cognitive impairment.³⁶ These findings add clarity to the time-course of vascular cognitive impairment and the impact of WMH progression in the first year after stroke, both increases and decreases, suggesting that clinical evidence of SVD-related cognitive or mRS change becomes progressively apparent in the chronic rather than subacute phase post-stroke (Figure 3).

Our research findings in context

Our finding of associations between cognitive decline and WMH progression was not detected in most previous longitudinal imaging studies after stroke.^{12-14,16,17} These differences may be due to variation in follow-up sample sizes, cognitive measures, methods of assessing WMH change, lower drop-out rates, and follow-ups at the same vs separate scanners. Moreover, the interval between stroke presentation and baseline MRI assessment is an important factor (eTable 2) as SVD lesions are dynamic.¹ When assessing post-stroke cognition, it is important to adjust for factors that associate with pre-morbid cognitive ability,²² later-life cerebrovascular disease,^{41,42} and cognitive decline.⁴² One previous study adjusted for ICV and education¹² and another adjusted for premorbid IQ.³⁷

Apart from WMH, there are a broader range of SVD features that require further longitudinal attention in relation to combined cognitive decline³⁷ and worsening mRS after stroke. Such features, including lacunes, perivascular spaces, and microbleeds are part of the total SVD picture.²⁵ Total baseline SVD scores are associated with lower cognitive ability in older adults⁴³ and with worse prognosis in stroke patients.⁴⁴

Further work is required to establish how total longitudinal SVD changes might relate to clinical outcomes.

Strengths and limitations

This study uses a statistical approach combining cognition and mRS as a co-primary outcome, paralleling real-world DSM-V diagnostic criteria⁷ for the clinical diagnosis of dementia. We used a well-validated approach to quantify WMH volumes at two time-points with improved retention (n=196/264) for follow-up MRI compared with previous longitudinal SVD studies assessing cognition after stroke (n=94/115 at one year and 74/115 at two years;^{14,37} n=52/101;¹² n=101/189 [CT-based];³⁸ 52/81 at five years¹⁷), and comparable to non-stroke longitudinal MRI studies.^{5,39,40}

Our study had limitations. We did not invite participants to attend MRI at three years: longer-term WMH volumes would have strengthened our analysis and better reflected the dynamic changes of WMH, cognition, and mRS at all three time-points. Not all participants completed cognitive assessments (eTable 3 in the Supplement) because we introduced cognitive tests after the 1st patients had joined the study but completion rates for mRS were good (84% at three years; eTable 3). We did not include depression as a covariate: depression is common post-stroke, has associations with worse WMH and has implications for cognitive dysfunction and dependence.

Implications for post-stroke cognitive impairment and dependence

This study found that the key components of the dementia syndrome, combined decline in cognition and independence, are associated with the presence and progression of WMH in the year after a stroke. One-year, but not baseline, WMH volumes associate strongly with contemporaneous cognitive scores, superseding

other clinical factors. This suggests that dynamic WMH in the weeks after a stroke do not reflect permanent brain damage but by one year, perhaps when any modifiable component of WMH such as interstitial oedema has cleared,^{45,46} WMH volumes may more closely represent the underlying 'permanent' damage and hence better correlate with cognition. Studies evaluating patients for as long as possible post-stroke, i.e. to three years and beyond, are needed to capture the full long-term implications.

These results call for an acceleration of research into processes driving SVD-related cognitive decline. The emergence of a WMH-cognitive association one year after a stroke represents a short but achievable therapeutic window for halting SVD progression and potentially preserving cognitive ability and independence post-stroke.

Future research targets

It would be useful to determine whether a combined, co-varying cognitive and mRS outcome could predict conversion to incident dementia in the longer term. We should encourage consistent analysis of levels of independence alongside cognitive ability in stroke research. A more detailed spatial analysis assessing patterns with persisting WMH vs WMH that dynamically appear and disappear would give more precise insights into the influence of SVD on the clinical course after a stroke.

Moreover, an analysis of whether WMH lesions behave differently adjacent to vs remote from the stroke lesion, whether this impacts on lesion evolution, and whether this influences outcomes after stroke, is required.

Despite secondary prevention, vascular risk factors were not associated with change in cognitive scores in our study. This reinforces that finding alternative treatment approaches to target the underlying pathophysiology of SVD is particularly important.

We need to closely track the natural history of dementia post-stroke and determine whether clinically and radiologically distinct dementia subtypes emerge over time. Identifying subgroups will allow future triage of clinical presentations to appropriate services, the development of disease-specific management strategies, and targeted entry into future research trials.

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Figure Legends

Figure 1 Study and analysis flow chart

Age=age at recruitment; diabetes mellitus defined as a previous diagnosis or diagnosed at stroke presentation in accordance with the World Health Organization criteria; hypertension defined as a previous diagnosis or blood pressure of $\geq 140/90$ mm Hg at presentation, hyperlipidemia defined as a previous diagnosis or cholesterol >5 mmol/L at presentation; smoking status defined as self-report of current, ex-smoker $<$ one year ago, ex-smoker $>$ one year ago, or never smoker; stroke subtyping defined previously,²⁰ ICV as outlined in Methods.

ACE-R = Addenbrooke's Cognitive Assessment – Revised, mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale

Figure 2 Distribution of change in WMH volumes (baseline-one-year), ACE-R scores and mRS (baseline-three-years)

Figure 3 Cross-sectional correlations between ACE-R scores and mRS at each time-point (A) baseline, (B) one-year, and (C) three-year visits, divided into panels by extent of baseline-one-year WMH change; Q5=greatest WMH increase Q1 = greatest WMH reduction. Note that participants with mRS 5 or 6 did not complete ACE-R

Figure 4 Cross-sectional and longitudinal associations with ACE-R scores (A-C)

Linear models: ACE-R associations at (A) baseline, (B) one year, (C) three years, and (D) mixed-effects model: intra-individual changing ACE-R associations between baseline and one year. Note that we used one-year WMH volumes in (C)

Table 1. Population characteristics at baseline visit, n=264

	Lacunar (N=118)	Cortical (N=146)	Overall (N=264)
Age (years) Mean (SD)	64.9 (11.8)	68.5 (11.7)	66.9 (11.8)
Female	51 (43.2%)	59 (40.4%)	110 (41.7%)
Diabetes	12 (10.2%)	18 (12.3%)	30 (11.4%)
Hypertension	82 (69.5%)	109 (74.7%)	191 (72.3%)
Hyperlipidaemia	73 (61.9%)	88 (60.3%)	161 (61.0%)
Atrial fibrillation	7 (5.9%)	18 (12.3%)	25 (9.5%)
Ex-smoker:>one year ago	31 (26.3%)	42 (28.8%)	73 (27.7%)
Never smoker	35 (29.7%)	52 (35.6%)	87 (33.0%)
Ex-smoker:<one year ago	5 (4.2%)	7 (4.8%)	12 (4.5%)
Current smoker	46 (39.0%)	44 (30.1%)	90 (34.1%)
Vascular sum score, Mean [SD]	1.77 (0.98)	1.85 (0.96)	1.8 (0.97)
NIHSS Median [IQR]	1 [0-2]	1 [0-1]	1 [0-2]
mRS Median [IQR]	1 [1-2]	1 [1-2]	1 [1-2]
Lacunar stroke	118 (100%)	0 (0%)	118 (44.7%)
Cortical stroke	0 (0%)	146 (100%)	146 (55.3%)
ACE-R score Median [IQR]	90 [82.5, 94]	90 [83, 95]	90 [83, 94]
WMH volume (ml) Median [IQR]	13.9 [4.49-35.5]	12.9 [4.57-33.7]	13.1 [4.5-34.0]
WMH ml as % ICV Median [IQR]	0.93 [0.29-2.46]	0.86 [0.32-2.32]	0.89 [0.31-2.38]

Table 2. Multivariate mixed-effects model of associations with co-varying change in ACE-R and mRS scores at baseline and one year

	<i>Coefficients</i>	<i>95%CI</i>	<i>Scaled coefficients</i>	<i>95%CI scaled</i>	<i>Z ratio</i>	<i>F-inc (ACE-R:mRS)</i>	<i>p (ACE-R:mRS)</i>
ACE-R:Vascular risk factors	0.92	-0.21-2.05	0.11	-0.03-0.25	1.56	1.6	0.21
mRS:Vascular risk factors	0.03	-0.04-0.10	0.02	-0.06-0.10	0.66		
ACE-R:NIHSS	-0.67	-1.31 to -0.02	-0.08	-0.16-0.00	-2.01	72.0	<0.001
mRS:NIHSS	0.51	0.43-0.58	0.48	0.40-0.55	11.91		
ACE-R:ICV ($ICV = scaled \div 1000$)	8.76	0.92-16.6	1.08	0.11-2.04	2.19	5.1	0.03
mRS:ICV	-0.48	-1.06-0.10	-0.45	-1.01-0.11	-1.57		
ACE-R:Normalised WMH volume ($WMH = cube\ root\ of\ ICV$)	-8.05	-25.41-9.31	-0.99	-3.13-1.15	-0.90	9.3	0.03
mRS:Normalised WMH	1.92	0.39-3.44	1.81	0.35-3.26	2.45		
ACE-R:Cortical subtype	-0.55	-2.88-1.78	-0.06	-0.35-0.23	-0.46	0.0	0.11
mRS:Cortical subtype	0.19	0.01-0.36	0.17	0.00-0.33	2.08		
ACE-R:One-year visit	-0.06	-0.96-0.84	-0.007	-0.11-0.10	-0.12	2.2	0.03
mRS:One-year visit	0.22	0.06-0.37	0.21	0.04-0.37	2.59		
ACE-R:Age	-0.22	-0.31 to -0.13	-0.02	-0.03 to 0.00	-4.03	9.9	<0.001
mRS:Age	0.004	-0.003-0.012	0.0004	-0.00-0.00	0.10		

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