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Prevalence and Predictors of Vascular Cognitive Impairment in Patients With CADASIL

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Abstract

Background and Objective

CADASIL is the most common monogenic form of stroke and early onset dementia. We determined the prevalence of vascular cognitive impairment (VCI) in a cohort of CADASIL patients, and investigated which factors were associated with VCI risk, including clinical, genetic and MRI parameters.

Methods

Cognition was assessed in genetically confirmed CADASIL patients (n = 176) and healthy controls (n = 265) (mean(SD) age 50.95(11.35) v 52.37(7.93) years), using the Brief Memory and Executive Test (BMET) and the Montreal Cognitive Assessment (MoCA). VCI was defined according to previously validated cut-offs. We determined the prevalence of VCI and its associations with clinical risk factors, mutation location (EGFr 1-6 versus EGFr 7-34), and MRI markers of small vessel disease.

Results

VCI was more common in CADASIL than controls; 39.8 v 10.2% on BMET 47.7% v 19.6% of MOCA. CADASIL patients had worse performance across all cognitive domains. History of stroke was associated with VCI on the BMET (OR 2.12, 95% CI [1.05, 4.27] p = 0.04) and on the MoCA (OR 2.55 [1.21, 5.41] p = 0.01), after controlling for age and sex. There was no association of VCI with mutation site. Lacune count was the only MRI parameter independently associated with VCI on the BMET (OR: 1.63, 95% CI [1.10, 2.41], p = 0.014), after controlling for other MRI parameters. These associations persisted after controlling for education in the sensitivity analyses.

Conclusions

VCI is present in almost half of CADASIL patients with a mean age of 50. Stroke and lacune count on MRI were both independent predictors of VCI on the BMET.

Keywords: CADASIL, Cognition, Vascular Cognitive Impairment, NOTCH3, BMET

Nonstandard Abbreviations and Acronyms

BMET: Brief Memory and Executive Test

CMB: Cerebral Microbleeds

MoCA: Montreal Cognitive Assessment

NBV: Normalised Brain Volume

SVD: Cerebral Small Vessel Disease

VCI: Vascular Cognitive Impairment

WMH: White Matter Hyperintensities

Introduction

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is the most common inherited form of stroke[1]. Mutations in the *NOTCH3* gene result in a small vessel arteriopathy, characterized clinically by early onset stroke, vascular cognitive impairment and dementia.[1-4] Although most symptomatic patients will exhibit some cognitive impairment in later years[3-6], the disease course and severity are very variable between individuals and even within families.[1,3] The reason for this is uncertain

although vascular risk factors have been associated with more rapid progression[1,2,7], and recently the mutation site has been associated with severity, with more proximal mutations resulting in earlier stroke onset.[8] Previous studies have shown that early features of cognitive impairment in CADASIL include executive dysfunction and slowing of information processing speed.[1, 9-14] Early effects on working memory and episodic long-term memory have been less consistently associated. [5,9,12,13] Most previous studies of cognition in CADASIL have been small or moderate in size.

In a large cohort of patients with CADASIL we determined the pattern, and prevalence, of cognitive impairment. We then determined which factors, including mutation location, were associated with the cognitive impairment, and how cognitive impairment related to MRI markers of the disease including lacunar infarcts, white matter hyperintensities (WMH), and brain atrophy.

Methods

Study Population

CADASIL patients

CADASIL patients in this analysis were collected from a national CADASIL clinic in Cambridge UK and as part of the UK Familial Cerebral Small Vessel Disease (SVD) study, which recruits patients with monogenic SVD from 6 neurological centres in the UK (see acknowledgements). Information is collected prospectively on clinical presentation, vascular risk factors and family history, and original clinical brain MRI images are obtained. We included the first 265 CADASIL patients recruited to the study. Of these, 176 had cognitive assessments available and were included in the current analysis. All patients had typical cysteine changing mutations.

Control Subjects

Healthy controls were previously collected as part of the Brief Memory and Executive Test (BMET) validation study by Brookes et al.[14] This consists of 502 healthy volunteers with no history of stroke, for whom vascular risk factors and demographic information was collected and neuropsychological testing administered. 265 were selected to roughly match the age and sex distribution of the patients, as seen on histogram.

Neuroimaging Features

Original brain MRIs of CADASIL patients, acquired as part of routine clinical assessment, were reviewed by a neurologist (SN). FLAIR and T1 sequences were reviewed to determine the presence and number of old cavitated lacunar infarcts, and Diffusion Weighted Imaging (DWI) sequences to identify recent lacunar infarcts. A lacunar infarction was defined as a subcortical infarct between 3 and 15 mm in diameter.[15] Cerebral microbleeds (CMBs) were graded on Gradient Echo (GE) or Susceptibility Weighted Imaging (SWI) sequences using the Brain Observer Microbleed Rating Scale (BOMBS)[16]. Brain volume, whilst adjusting for skull size, was estimated using SIENAX (from FSL software, fsl.fmrib.ox.ac.uk[17]) with T1 sequences. SIENAX first extracts brain tissue, then estimates brain volume.[18] White Matter Hyperintensities (WMH) were defined as areas of increased signal on FLAIR images and were quantified by trained raters, using a semi-automated contouring tool in the Jim image analysis Software, version 8 (Xinapse Systems, http://www.xinapse.com/j-im-8-software/). Inter-rater agreement for WMH lesion volume was calculated in a subset of data (n=10) and showed good agreement (ICC = 0.96).

Neuropsychological Testing

Brief Memory and Executive Test (BMET)

The BMET is a cognitive screening tool designed and previously validated to be sensitive to the cognitive deficit seen in sporadic SVD, and also shown to be sensitive to the cognitive deficit in CADASIL.[14,19,20] The test comprises 8 tasks (domains) which provide measures that form two subscales and an overall score. The first subscale, Executive Functioning and Processing Speed, is calculated using the tasks Letter-Number Matching, Motor Sequencing, Letter Sequencing and Number-Letter Sequencing.[20] The second subscale, Orientation and Memory, is made up of the Orientation, 5-item Repetition, 5-item Recall and 5-item Recognition tasks.[20] The measures from each task are transformed into scales that have a maximum of 2, giving a maximum total of 8 on each subscale and 16, overall.[20] These scorings are age-adjusted, with each measure adjusted for the age of the participant.[20] The BMET is freely available to download (www.bmet.info).

Montreal Cognitive Assessment (MoCA) [21]

The Montreal Cognitive Assessment is a brief cognitive screening tool, for detecting mild cognitive impairments.[21] The MoCA has 8 domains: Visuospatial, naming, memory, attention, language, abstraction, delayed recall and orientation, aimed overall at measuring global cognition.[21]

Standard Protocol Approvals, Registrations, and Patient Consents

All participants gave written informed consent. For those without capacity, a consultee gave written informed consent. UK Familial SVD study was approved by East of England Cambridge Central Research Ethics Committee (16/EE/0118). Control data collection study was approved by the London Bridge Research Ethics Committee (11/LO/0636).

Statistical Analyses

Comparison of demographics and vascular risk factors between CADASIL patients with and without stroke were assessed using independent *t*-tests, Chi-square tests and logistic regression, where appropriate.

Means and standard deviations on BMET and MoCA and it's measures and scales were calculated. To examine the cognitive profile of the groups, means and standard deviations of the control group were used to calculate Z-scores for the overall CADASIL group, and those with and without stroke in the CADASIL group.[11] Z-scores for the control group were by definition set at zero.[11] VCI on the BMET was defined using a previously validated cut-off of ≤13 on the overall score.[20] On the MoCA, patients were classified as having VCI when scoring ≤25 out of 30 for the total score, as previously defined.[21]

Performance on the BMET was compared between CADASIL patients and controls, and between CADASIL patients subdivided into those with and without a history of stroke, using Mann-Whitney U. Comparison of performance on MoCA was determined using Analysis of Covariance to assess performance on the MoCA and its subscales, with age as a covariate as MoCA is not age-adjusted. Binary logistic regression was used to determine whether clinical features and risk factors predicted VCI on BMET and on MoCA.

Due to their non-normal distribution MRI parameters were normalised. Normalised white matter hyperintensity lesion volume (WMH) (accounting for skull size) and lacune count were normalised using square root transformation. Normalised total brain volume (NBV) (again, accounting for skull size) was normalised using a square transformation. Microbleed count (CMB) was normalised with logarithm transformation. Binary logistic regression was

run within the CADASIL cohort to determine whether MRI parameters predicted VCI on BMET and MoCA. As only a subgroup had sequences to allow quantification of CMB, microbleeds were excluded from this analysis and assessed separately. Mutation site was categorised as a binary variable by dividing the NOTCH3 protein's 34 Epidermal Growth Factor-like repeats (EGFr) into two groupings: EGFr 1-6 and EGFr 7-34, as previously described.[8] Binary logistic regression was run within the CADASIL cohort to determine whether mutation site predicted VCI on the BMET and the MoCA.

Education was assessed as a binary variable, with ≤12 years of education as a cut-off, in line with the MoCA.[21] Due to some of CADASIL group having missing years of education data (n = 61), analyses were initially run without education as a covariate. An additional sensitivity analysis including education as a covariate was then carried out on all analyses, separately. Missing values were coded as such using '-99', in order to retain sample size.

Data Availability

Upon reasonable request, data from this study are available from the corresponding author.

Results

Demographics for CADASIL patients and controls are shown in Table 1. Hypertension and hypercholesterolaemia were more common in CADASIL patients than controls. More than 12 years education was more common in controls.

Cognition performance between groups

On the BMET, CADASIL patients had significantly worse performance than controls on total BMET score (Mann Whitney, $p < 0.0001$), Orientation and Memory subscale score (Mann

Whitney, $p < 0.0001$) and Executive Functioning and Processing Speed subscale score (Mann Whitney, $p < 0.0001$) (Table 1). They also performed worse on total MoCA score in age adjusted analysis ($p < 0.0001$) (Table 1). Z-score plots show the pattern of impairment across all BMET individual measures (Figure 1) and on the BMET subscales and total score (Figure 2); CADASIL patients had lower performance across all domains, with the greatest impairment on the Letter Sequencing task (Figure 1)

VCI, defined using the BMET, was present in 39.8% of the CADASIL group and 10.2% of controls. VCI, defined using the MoCA, was present in 47.7% of CADASIL group and 19.6% of controls. On multivariate analysis, controlling for age and sex, the VCI was more common in CADASIL patients when VCI was defined on both on the BMET (OR= 6.39, 95% CI [3.85, 10.62], $p < 0.001$) and on the MoCA (OR= 4.23, 95% CI [2.69, 6.65], $p < 0.001$). Sensitivity analysis controlling for education showed the relationship remained significant on the BMET ($p < 0.001$) and on the MoCA ($p< 0.001$).

CADASIL patients with stroke were more likely to be male, older and have hypertension, hypercholesterolaemia and diabetes compared with CADASIL patients without stroke (Table 1). CADASIL patients with stroke had worse performance on total BMET score ($p = 0.007$), Executive Functioning and Processing subscale score ($p = 0.04$) and Orientation and Memory subscale score ($p = 0.005$) than stroke free CADASIL patients (Table 1). This impairment was seen across all cognitive domains (Figures 1 and 2). There was also a significant difference in total MoCA between the two CADASIL groups ($p = 0.002$) (Table 1).

Risk factors for the presence of VCI

Factors associated with VCI as determined on either BMET or MoCA are shown in Table 2. Age was associated with VCI on the MoCA but not on the BMET, which uses age-adjusted

norms. On age and sex adjusted analysis smoking was associated with decreased VCI on the MoCA and stroke was associated with increased VCI on both the BMET and the MoCA (Table 2).

While controlling for age and sex, only stroke (OR 2.12, 95% CI [1.05, 4.27] $p = 0.04$) was associated with increased VCI on BMET. On multivariate analyses, looking at history of stroke and history of migraine with aura, age (OR 1.04, 95% CI [1.01, 1.08] $p = 0.01$) and history of stroke (OR 2.55, 95% CI [1.21, 5.41] $p = 0.01$) were associated with increased VCI on MoCA, whilst controlling for age, and sex. These relationships remained significant when controlling for education in the sensitivity analyses: MoCA (Stroke, $p = 0.02$; Age, $p = 0.008$), BMET (Stroke, $p = 0.03$).

Whilst controlling for age and sex there was no relationship between mutation site (EGFr 1-6 versus EGFr 7-34) and VCI on BMET or MoCA ($p = 0.83$, and $p = 0.58$, respectively).

Relationship between MRI Parameters, cognition and presence of VCI

Within the CADASIL group, while controlling for age and sex, lacune count was significantly and negatively correlated to total BMET score ($r_s = -.266$, $p = 0.001$), and both Executive Functioning and Processing Speed ($r_s = -.224$, $p = 0.007$) and Orientation and Memory subscales ($r_s = -.218$, $p = 0.009$). In the sensitivity analysis these remained significant when controlling for education: $p < 0.001$, $p = 0.005$ and $p = 0.007$, respectively.

In contrast there was no difference in WMH lesion volume, CMB count and normalised brain volume between those with and without VCI on either the BMET or MoCA, after controlling for age and sex (Table 3). Lacune count was significantly higher in those with VCI as defined

by the BMET, and by the MoCA (Table 3). This remained significant in the sensitivity analysis (BMET: $p = 0.003$, MoCA: $p = 0.03$).

On logistic regression, including WMH lesion volume, lacunes, and brain volume as well as age and sex controlling, only lacune count (OR: 1.63, 95% CI [1.10, 2.41], $p = 0.014$) was a significant predictor of VCI on the BMET (Table 4). This remained significant on the sensitivity analysis: $p = 0.01$. Similarly, on multivariate analysis, only lacune count was a significant predictor of total BMET score (Beta= -0.27, 95% CI [-1.36, -0.19], $p = 0.01$). On multivariate analysis, only lacune count (Beta= -0.28, 95% CI [-0.78, -0.12], $p = 0.008$) predicted performance on the Orientation and Memory subscale of the BMET. These relationships remaining significant on the sensitivity analyses: $p = 0.009$ and $p = 0.008$. On multivariate analysis, there were no significant MRI predictors associated to the Executive Functioning and Processing Speed Scale, total MoCA score or increased VCI on the MoCA.

Only a subgroup of CADASIL patients had GE/SWI sequences allowing CMB identification (n= 105) and, therefore, CMB were not included in the multivariate analysis. However, when controlling for age and sex in a separate analysis, CMB were not associated with VCI on either BMET ($p = 0.91$) or on MoCA ($p = 0.07$). Only age predicted VCI on the MoCA (OR 1.10, 95% CI [1.02, 1.20] $p = 0.02$).

Discussion

In our cohort of symptomatic CADASIL patients, with a mean age of 50 years, we found VCI was present in almost a half. Consistent with previous reports in sporadic cerebral small vessel disease and CADASIL, the most prominent deficits were found in executive function and processing speed,[9-14] although impairment was seen across all aspects of cognition. The

most important factor determining cognition was the presence of strokes, both symptomatic and asymptomatic MRI determined lacunar infarcts.

Most previous studies of cognition and VCI in CADASIL have been in small cohorts. Consistent with our study, the most common and earliest deficits have been reported in executive function and processing speed.[9-14] There have been conflicting reports as to whether memory is also affected particularly early in the disease.[5,9,12,13] Our results demonstrate that it is not spared, with CADASIL patients performing below controls on memory tasks.[16] Z-scores of the 5-item memory repetition task on the BMET were higher than on the 5-item memory recall task. Since the repetition task requires initial encoding of material in memory, including use of working memory, this is consistent with this ability being spared later into the progression of CADASIL, while long term memory recall is not.[5,13]

By studying a larger cohort than in previous publications we were able to investigate factors underlying cognitive impairment and VCI. Although vascular risk factors were more common in CADASIL patients compared with controls, there was no association between them and risk of VCI. The major clinical determinant of VCI was the presence of a previous stroke, with stroke being associated with an approximately doubling of VCI prevalence as determined on the BMET, after controlling for age and sex. This finding was consistent with a strong association between the presence, and number, of lacunes with both VCI and the degree of cognitive impairment. [14, 22, 23]. Such associations with stroke and lacune count remained significant in the sensitivity analyses. This was in contrast to other radiological features of SVD, NBV, WMH and CMB, none of which were associated with cognitive impairment. The extent of WMH has been associated with cognitive impairment in some[24],

but not all studies in SVD.[22, 23,25] The lack of association in the CADASIL cohort may reflect the fact that almost all patients had relatively severe WMH. Nevertheless, the clinical and radiological results emphasize the key role of stroke and asymptomatic lacunar infarction, in precipitating VCI in patients with CADASIL. Therefore, any strategies that could reduce the impact of stroke would have an impact on reducing VCI in such patients.

Recently NOTCH3 mutation site has been associated with severity of CADASIL, particularly age of onset of stroke.[8] Mutations in the more proximal part of the gene in EGFr 1-6 have been found to be associated with more severe disease.[8] However we found no association between EGFr and VCI. It is possible that the lack of a relationship was observed due to a large majority of our sample falling in the EGFr 1-6 grouping (73.3%); future research should investigate the relationship in a more diverse range of mutations.

We assessed cognition with both the BMET and the MoCA, and although the overall prevalence of VCI was broadly similar when defined by the two cognitive scales, the associations with MRI parameters varied. When defined by the BMET the number of lacunes was a strong predictor of VCI, but other MRI parameters were not predictors. When defined by MoCA, lacunes did not predict VCI. This is likely to reflect the differing cognitive domains assessed by each test. BMET has been designed to be particularly sensitive to impairment in executive function and processing speed seen in SVD[14,15,19], while MoCA was developed as a global cognitive score primarily to assess cortical dementias.[21] It has been demonstrated that lacunes impair cognition by disrupting white matter tracts involved in domains such as executive function and processing speed[24-25], and therefore the BMET would be expected to be more sensitive to detecting this association.[14,15,19] These differences emphasise the complexity of determining associations between brain structure and cognition,

and that differing results may be obtained with cognitive batteries tapping into different cognitive domains

In addition, we saw the prevalence of VCI on the MoCA was higher than on the BMET. Given the body of research suggesting that the MoCA cut-offs should be lower[26] we conducted additional analyses that showed, when using cut offs of ≤24 and ≤23, VCI on the MoCA to be 37.5%, and 28.24%, respectively. This difference in prevalence of VCI, on one test alone, again emphasises the importance of using several cognitive tests in order to sensitively measure cognitive impairment.

Our study has a number of strengths. It was conducted in a relatively large, prospectively recruited, cohort of CADASIL patients all of whom had standardised cognitive testing at the time of recruitment. Original MRI scans were centrally reviewed to determine the presence of WMH, lacunes, CMB and brain atrophy. Two cognitive assessments, BMET and MoCA, were performed. However it also has limitations. Clinical MRI scans were used and performed on different scanners which may have reduced our sensitivity to detect associations with MRI markers of CADASIL. Education was only partially recorded in the CADASIL population and therefore was included as a sensitivity analysis. Education is a protective factor against cognitive decline and VCI in other populations, [27,28] thus, future research should aim to include education as a covariate in the main analyses.

Our study found VCI to be present in 40-50% of CADASIL patients with a mean age of 50 years. Reductions in cognitive performance were seen across all cognitive domains, including memory. Stroke and lacune count on MRI were both independent predictors of VCI on the BMET. We found no association of VCI with mutation site.

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Table 1. Demographics comparison between CADASIL group and the control group and between CADASIL patients with and without stroke.

	CADASIL (n= 176)	Control (n= 265)	Comparison	CADASIL (No Stroke) (*n*= 110)	CADASIL (Stroke) (*n*= 66)	Comparison
Age at BMET (Mean, SD, Min-Max)	50.95, 11.35, 28-74	52.37, 7.93, 36-74	$p = 0.12$	48.32, 11.37, 28-74	56.32, 9.50, 37-75	$p < 0.001$**
Sex (% Male)	73 (41.5%)	118 (44.5%)	$p = 0.49$	39 (35.5%)	34 (51.5%)	$p = 0.036$*
History of hypertension (% yes)	42 (23.9%)	37 (14%)	$p = 0.008$**	20 (18.2%)	22 (33.3%)	$p = 0.02$*
History of Hypercholesterolaemia (% yes)	57 (32.4%)	24 (9.1%)	$p < 0.0001$**	28 (25.5%)	29 (43.9%)	$p = 0.01$*
Diabetes Mellitus (% yes)	10 (5.7%)	9 (3.4%)	$p = 0.34$	2 (1.8%)	8 (12.1%)	$p = 0.006$**
History of Ever Smoking (% yes)	72 (40.9%)	107 (40.4%)	$p = 0.91$	44 (40%)	28 (42.2%)	$p = 0.75$
12+ Years of Education (% yes) †	70 (39.8%)	196 (74%)	$p < 0.0001$**	45 (40.9%)	26 (39.4%)	$p = 0.78$
Total BMET Score (Median, IQR, Min- Max)	14, 5, 0-16	16, 1, 10-16	$p < 0.0001$**	14, 4, 0-16	12.5, 5, 1-16	$p = 0.007$**
Orientation and Memory Subscale Score (Median, IQR, Min- Max)	7, 3, 0-8	8, 1, 2-8	$p < 0.0001$**	7, 2, 0-8	6, 4, 0-8	$p = 0.005$*
Executive Functioning/Processing Speed Subscale Score (Median, IQR, Min- Max)	7.5, 2, 0-8	8, 0, 4-8	$p < 0.0001$**	8, 2, 0-8	7, 3, 0-8	$p = 0.04$**
MoCA Total Score (Median, IQR, Min- Max)	25, 5, 9-31	27, 3, 15-30	$p < 0.0001$**	26, 4.25, 10-31	24, 5, 9-30	$p = 0.002$*

Note: * $p < .05$, ** $p < .01$. Diabetes Mellitus assessed using Fisher's Exact to account for small cell size. † indicates missing data, see eTable 1 available in the supplement.

BMET = Brief Memory and Executive Test, MoCA = Montreal Cognitive Assessment

Table 2. Demographics and clinical features comparison of those with/without VCI on BMET and on MoCA

	BMET			MoCA		
	No VCI (*n*= 97) †	VCI (*n*= 70) †	Comparison	No VCI (*n*= 77) †	VCI (*n*= 84) †	Comparison
Age at Clinic (Mean, SD, Min-Max)	49.95, 12.14, 28-74	52.59, 9.93, 31-74	$p = 0.14$	48.13, 11.34, 28-74	54.60, 10.42 29-75	$p < 0.001$**
Sex (% Male)	35 (36.1%)	34 (48.6%)	$p = 0.11$	30 (39.0%)	33 (39.3%)	$p = 0.94$
History of hypertension (% yes)	21 (21.6%)	18 (25.7%)	$p = 0.98$	14 (18.2%)	24 (28.6%)	$p = 0.51$
History of Hypercholesterolaemia (% yes)	33 (34.0%)	22 (31.4%)	$p = 0.21$	24 (31.2%)	28 (33.3%)	$p = 0.24$
Diabetes Mellitus (% yes)	0 (0%)	8 (11.4%)	$p = 0.99$	0 (0%)	7 (8.3%)	$p = 0.99$
History of Ever Smoking (% yes)	40 (41.2%)	30 (42.9%)	$p = 0.71$	40 (51.9%)	27 (32.1%)	$p = 0.02$*
History of Migraine (% yes)	74 (76.3%)	48 (68.6%)	$p = 0.53$	59 (76.6%)	58 (69.0%)	$p = 0.41$
History of Migraine with Aura (% yes)	72 (74.2%)	43 (61.4%)	$p = 0.20$	55 (71.4%)	53 (63.1%)	$p = 0.32$
History of Stroke (% yes)	27 (27.8%)	34 (48.6%)	$p = 0.03$*	19 (24.7%)	43 (52.4%)	$p = 0.01$*
EGFr Grouping (Median, IQR, Min-Max)	4, 5, 2-31	4, 5.25, 1-31	$p = 0.96$	4, 5, 2-28	4, 5, 1-31	$p = 0.33$
EGFr Grouping 1-6 (%)	71 (73.2%)	51 (72.9%)	$p = 0.83$	55 (71.4%)	61 (74.4%)	$p = 0.16$
12+ Years of Education (% yes) †	40 (41.2%)	28 (40%)	$p = 0.12$	33 (42.9%)	33 (39.3%)	$p = 0.38$

Note: * $p < .05$, ** $p < .01$. † indicates missing data, see eTable 1 available in the supplement.. Excluding age and sex, all *p* values are adjusted for age and sex.

BMET = Brief Memory and Executive Test, MoCA= Montreal Cognitive Assessment, VCI= Vascular Cognitive Impairment, EGFr = Epidermal Growth Factor-like repeats

Table 3. MRI parameter comparison of those with/without VCI on BMET and on MoCA

	BMET			MoCA		
	No VCI (*n*= 97) †	VCI (*n*= 70) †	Comparison	No VCI (*n*= 77) †	VCI (*n*= 84) †	Comparison
Normalised Brain Volume (Mean, SD) †	1585249.68 (139445.34)	1572628.76 (117538.01)	$p = 0.84$	1576459.13 (125100.55)	1579871.64 (1277115.30)	$p = 0.26$
WMH Lesion Volume (Mean, SD) †	64071.12 (48987.10)	72626.31 (54476.03)	$p = 0.59$	54097.71 (45278.72)	82895.98 (51337.13)	$p = 0.11$
Normalised WMH Lesion Volume (Mean, SD) †	86008.41 (66435.08)	97196.48 (74449.77)	$p = 0.61$	73076.97 (60920.45)	113644.73) (72388.36)	$p = 0.07$
Lacune Count (Mean, SD) †	2.08 (2.72)	4.33 (4.89)	$p = 0.005$**	1.95 (3.16)	4.36 (4.44)	$p = 0.02$*
Microbleed Count (Mean, SD) †	5.87 (24.83)	9.29 (30.72)	$p = 0.84$	8.44 (31.41)	6.65 (25.18)	$p = 0.31$

Note: * $p < .05$, ** $p < .01$. † indicates missing data, see eTable 1 available in the supplement. All *p* values are adjusted for age and sex.

BMET = Brief Memory and Executive Test, MoCA= Montreal Cognitive Assessment, VCI= Vascular Cognitive Impairment, WMH= White Matter Hyperintensities

Table 4. Logistic regression for the influence of MRI parameters (minus microbleeds) on BMET VCI and MoCA VCI in CADASIL patients while controlling for age and sex.

BMET						
					95% CI for OR	
	Wald	df	Sig	OR	Lower	Upper
Age	.149	1	.700	.991	.948	1.037
Sex	.015	1	.901	1.048	.500	2.198
Lacune Count*	6.017	1	.014	1.629	1.103	2.407
Normalised WMH Lesion Volume	.024	1	.876	1.000	.996	1.004
Normalised Brain Volume	.241	1	.624	1.000	1.000	1.000
Constant	.002	1	.967	1.073		
MoCA						
					95% CI for OR	
	Wald	df	Sig	OR	Lower	Upper
Age	.366	1	.545	1.015	.968	1.065
Sex	.070	1	.792	1.114	.502	2.472
Lacune Count	3.670	1	.055	1.484	.991	2.222
Normalised WMH Lesion Volume	2.056	1	.152	1.003	.999	1.008
Normalised Brain Volume	1.550	1	.213	1.000	1.000	1.000
Constant	3.955	1	.047	.024		

Note: * $p < .05$, ** $p < .01$.

BMET = Brief Memory and Executive Test, MoCA= Montreal Cognitive Assessment, OR = Odds Ratio, VCI= Vascular Cognitive Impairment, WMH= White Matter Hyperintensities

Figure 1. Z-scores of CADASIL patients overall, with and without stroke and controls on the individual BMET tasks.

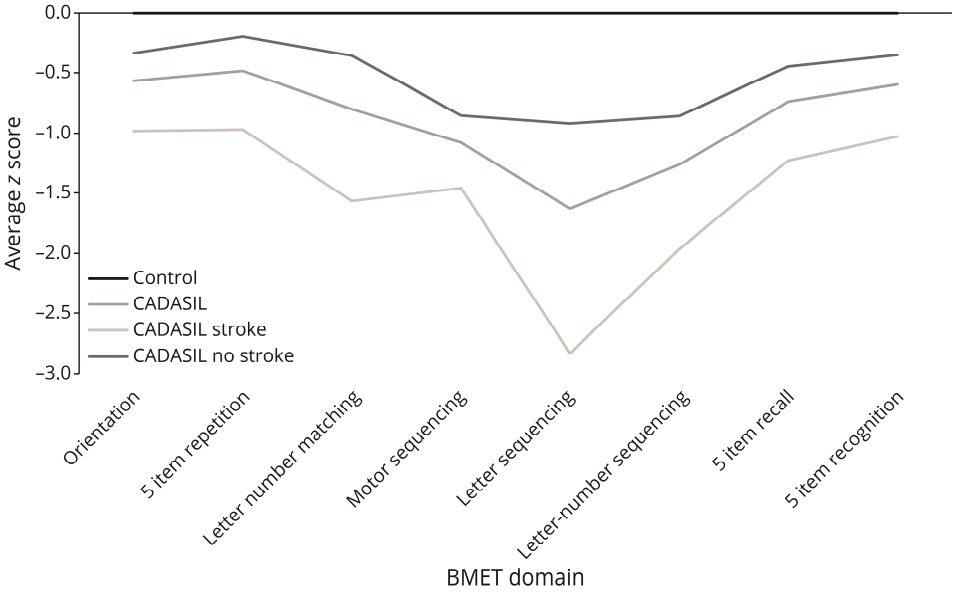
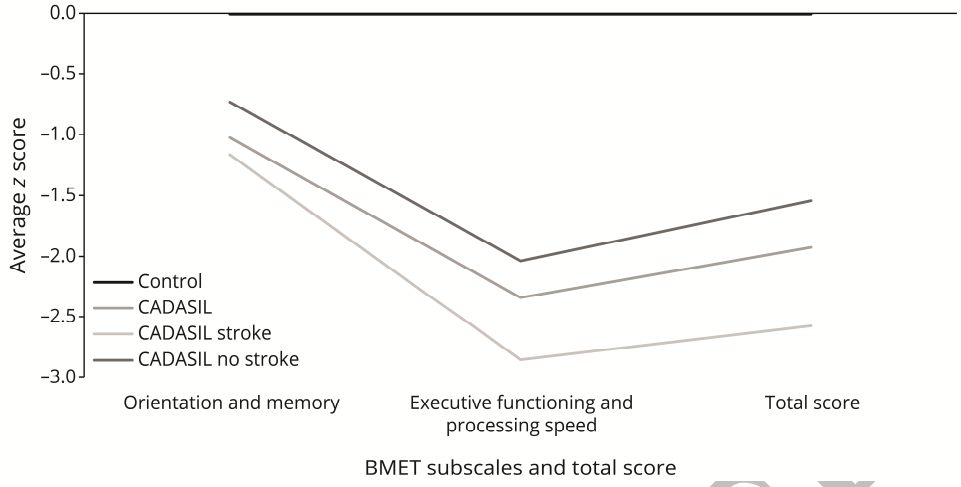


Figure 2. Z-scores of CADASIL patients overall, with and without stroke and controls on the BMET subscales and total BMET score.



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