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Vascular Cognitive Impairment and cognitive decline; a longitudinal study comparing different types of vascular brain injury - The TRACE-VCI study

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ABSTRACT

Background: Little is known about the trajectories of cognitive decline in relation to different types of vascular brain injury in patients presenting at a memory clinic with Vascular Cognitive Impairment (VCI).
Methods: We included 472 memory clinic patients (age 68 (±8.2) years, 44% female, MMSE 25.9 (±2.8), 210 (44.5%) dementia) from the prospective TRACE-VCI cohort study with possible VCI, defined as cognitive complaints and vascular brain injury on MRI and at least 1 follow-up cognitive assessment (follow-up time 2.5 (±1.4) years, $n = 1172$ assessments). Types of vascular brain injury considered lacune(s) (≥1; $n = 108$ patients (23%)), non-lacunar infarct(s) (≥1; $n = 54$ (11%)), white matter hyperintensities (WMH) (none/mild versus moderate/severe ($n = 211$ patients (45%)) and microbleed(s) (≥1; $n = 202$ patients (43%)). We assessed cognitive functioning at baseline and follow-up, including the Rey Auditory Verbal Learning Test (RAVLT), Trail Making Test (TMT) A and B, category naming task and MMSE. The association of different types of vascular brain injury with cognitive decline was evaluated with linear mixed models, including one type of vascular brain injury (dichotomized), time and vascular brain injury*time, adjusted for sex, age, dementia status (yes/no), education (Verhage scale) and medial temporal lobe atrophy (MTA) score (dichotomized as ≥ 1.5).
Results: Across the population, performance declined over time on all tests. Linear mixed models showed that lacune(s) were associated with worse baseline TMTA (Beta(SE)) (8.3 (3.8), $p = .03$) and TMTB (25.6 (10.3), $p = .01$), albeit with a slower rate of decline on MMSE, RAVLT and category naming. By contrast, patients with non-lacunar infarct(s) showed a steeper rate of decline on TMTB (29.6 (7.7), $p = .00$), mainly attributable to patients with dementia (62.9 (15.5), $p = .00$).
Conclusion: Although different types of vascular brain injury have different etiologies and different patterns, they show little differences in cognitive trajectories depending on type of vascular brain injury.

1. Introduction

Patients presenting at a memory clinic often show different types of vascular brain injury on magnetic resonance imaging (MRI) scan of the brain. The clinical significance of these types of vascular brain injury often remains unknown. Yet, different types of vascular brain injury might contribute to different trajectories of cognitive decline.

In general, cerebral small vessel disease is considered to affect attention and executive dysfunction, memory and visuomotor speed deficits and is assumed to show a progressive course over time [1–3].

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However, this has mostly been evaluated in population-based studies and not in a memory clinic setting. The latter is important, as apart from different types of vascular brain injury, memory clinic patients often have co-occurring neurodegenerative pathology, in particular Alzheimer's disease. Yet, patients referred to a memory clinic all experience some form of cognitive impairment, compared to population based studies in which most patients show no cognitive complaints. One of our previous studies showed that memory clinic patients show a remarkably similar cognitive profile across all different types of vascular brain injury [4]. However, it is unknown if different types of vascular brain injury are related to different trajectories of cognitive decline over time, which could provide memory clinic patients more prognostic information about the future. This is clinical relevant from patient's perspective and doctors' point of view.

Therefore, in this current study we compared cognitive decline over time between patients with different types of vascular brain injury including lacune(s), non-lacunar infarct(s), severe/moderate white matter hyperintensities (WMH) and microbleed(s) in a memory clinic cohort. Secondly, we assessed the influence of dementia status on the relation between vascular brain injury and cognitive decline. We aimed to provide a better insight in the trajectories of cognitive decline over time in different types of vascular brain injury in a memory clinic population with Vascular Cognitive Impairment (VCI).

2. Materials and methods

2.1. Study population

Patients were included from the TRACE-VCI study population [5]. In short, the aim of the TRACE-VCI study was to investigate the clinical features and prognosis of patients with possible VCI in a memory clinic setting. The TRACE-VCI study included 860 consecutive patient with evidence of vascular brain injury from the outpatient clinic of the VU University Medical Center (VUMC), registered in the Amsterdam Dementia Cohort (N = 664) and from two outpatient memory clinics of the University Medical Center Utrecht (UMCU) (N = 196) [5]. Follow-up was collected from 707 (82%) patients without advanced dementia (MMSE score of $\geq$ 20 and/or a clinical dementia rating (CDR) of $\leq$ 1 at baseline visit) [6]. For the current study, only patients with at least 1 neuropsychological follow-up test were included (n = 472).

All patients presented at a memory clinic for evaluation of cognitive complaints and showed evidence of vascular brain injury (i.e. possible VCI) on MRI (WMH, also known as Fazekas scale 1 [7] and an increased vascular risk defined as the presence of $\geq$ 2 vascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, obesity, current smoking or a reported history of a vascular event other than stroke: full definitions in design paper [5]) or Fazekas scale 2 or 3, $\geq$ 1 non-lacunar infarct(s), $\geq$ 1 lacune(s), $\geq$ 1 microbleed(s), $\geq$ 1 intracerebral hemorrhage(s) (ICH) /macrobleed(s)). Patients were included regardless of objective cognitive severity including patients with dementia and no dementia (no objective cognitive impairment (NOCI)) and mild cognitive impairment (MCI). Dementia was diagnosed if there was a clear decline in cognitive function, defined as a deficit in $\geq$ 2 cognitive domains at neuropsychological testing and interference in daily living [2].

Each patient underwent a standardized extensive one-day memory clinic evaluation including an interview, physical and (cognitive) neurological examination, laboratory testing, standardized neuropsychological testing and a MRI-scan of the brain. Lumbar puncture was performed in a subset of the study population [5]. All patients provided informed consent prior to research related procedures.

2.2. Cognitive assessment

We used the Dutch version of the MMSE (maximum score of 30) for global cognitive functioning [8]. The Dutch version of the Rey Auditory Verbal Learning Test (RAVLT) and both the total number of words remembered in five learning trials (RAVLT trials 1-5; immediate recall) and delayed recall (RAVLT delayed recall) were used to evaluate memory [9]. For the RAVLT, the total number of words remembered in five learning trials was recorded and the delayed recall task was used. The Trail Making Test (TMT) part A and B were used to examine attention and executive functioning [10]. The total time to complete the TMT part A and part B was used. Category naming task (animal naming, 1 minute) measured executive functioning and language [11]. The same versions of neuropsychological tests were used for follow-up. The 472 included patients had 1172 test moments, with a mean of 2.2 (standard deviation (SD) 1.3) tests per patient in 2.5 (SD 1.4) years. Baseline cognitive assessment were available in all patients, follow-up tests were available in $\geq$ 86% of patients. More information about the tests is provided in the design article of the TRACE-VCI study [5] and our manuscript studying baseline cognition in different types of vascular brain injury in the TRACE-VCI study population [4].

2.3. Brain MRI

Details on MRI scanners and protocol were described in detail previously [4,5]. In short, WMH were rated using the Fazekas scale (deep WMH grade 0-3) on FLAIR images [7]. WMH were dichotomized as none or mild WMH (Fazekas 0 or 1) versus moderate or severe WMH (Fazekas 2 or 3). Lacune(s), non-lacunar infarct(s) and microbleed(s) were all rated in line with the STRIVE (standards for reporting vascular changes on neuroimaging) criteria [12] and were dichotomized as the presence or absence of $\geq$ 1 lacune, non-lacunar infarct or microbleed. There were 3 patients with no microbleed rating because of missing or unreadable T2*-weighted scans, therefore in 469 of 472 patients (99%) microbleeds were scored. Ratings were performed by or under the supervision of a neuroradiologist. Medial temporal lobe atrophy (MTA) was visually rated (possible range of scores for each site, 0-4) on reconstructions of the 3D T1-weighted images [13]. In 466 (99%) of 472 patients MTA scores were available. MTA score was dichotomized into a mean MTA score of $\geq$ 1.5 or $<$ 1.5.

2.4. CSF biomarkers

CSF concentrations of amyloid-β_{42} ($A\beta_{42}$), tau and/or total tau phosphorylated at threonine 181 (p-tau) were measured at the neurochemistry laboratory at the Department of Clinical Chemistry of Amsterdam UMC [14]. CSF samples were stored at -20℃ until biomarker analysis (within 2 months). $A\beta_{42}$, total tau, and p-tau were measured with commercially available ELISAs (Innotest β-amyloid($_{1-42}$), Innotest hTAU-Ag and Innotest Phosphotau($_{181Q}$), respectively; Innogenetics, Ghent, Belgium) on a routine basis [14]. In 293 (62%) of 472 patients CSF biomarkers were available. A ratio of total tau/amyloid-β_{42} $>$ 0.52 was considered a positive CSF Alzheimer biomarker profile, which we observed in 168 (57%) patients with available CSF [15].

2.5. Statistical analysis

We used linear mixed models to evaluate cognitive decline and the association between different types of vascular brain injury and cognitive decline. These models included dichotomized terms per type of vascular brain injury, time (years) and the interaction-term vascular brain injury*time. Model 1 represents one type of vascular brain injury per model and model 2 included all types of vascular brain injury simultaneously. Both models were adjusted for sex, age, dementia status (yes/no), level of education and MTA score. Data are presented as unstandardized beta (ß) (± standard error (SE)) for different types of vascular brain injury representing the association between this type of vascular brain injury and baseline neuropsychological test performance, whereas the interaction term between the different types of vascular brain injury and time represented the annual decline of neuropsychological test performance over time in relation to presence versus absence

of that type of vascular brain injury. Additional models were run stratified by dementia status and for patients with a positive and negative Alzheimer biomarker profile. A p-value of less than 0.05 was considered significant. Statistical analyses were performed using SPSS (version 22; SPSS, Chicago, IL, USA).

3. RESULTS

Table 1 summarizes the baseline characteristics of the total study population. Mean age at baseline was 68 (± 8) years, 206 (44%) patients were female and 210 (44%) patients were diagnosed with dementia. Dementia was further classified due to its main etiology, based on internationally established diagnostic criteria without knowledge of CSF biomarkers or APOE genotyping results, in a vascular [16], neurodegenerative [17–19], or unknown origin.

Table 2 is showing the baseline test results and annual cognitive change in the total study population and in patient with and without dementia. All tests showed decline over time.

Fig. 1 shows two examples to visualize the trajectory of decline, presenting the association between type of vascular brain injury and decline on the MMSE and TMTB. These lines show the presence and absence of each type of vascular brain injury, showing raw data.

Linear mixed models were used to evaluate associations between type of vascular brain injury and cognitive decline, adjusted for sex, age, diagnosis, education, follow-up time and MTA ≥ 1.5 (Table 3). Overall, all patients showed cognitive decline over time, independent of type of vascular brain injury. Little differences were found in patients with lacune(s) and non-lacunar infarct(s). Lacune(s) were associated with worse baseline TMTA and TMTB performances compared to patients without lacune(s). In addition, patients with lacune(s) showed a slower rate of decline on various tests including the MMSE, RAVLT immediate recall, RAVLT delayed recall and category naming. By contrast, non-lacunar infarct(s) were associated with worse baseline performance on the RAVLT immediate recall, TMTA and category naming in comparison with no non-lacunar infarct(s). In addition, patients with non-lacunar infarct(s) had a faster rate of cognitive decline on the TMTB and a slower rate of decline on the category naming. We found no associations between WMH or microbleed(s) and baseline cognitive performance, nor (rate of) cognitive decline. When we entered all types of vascular brain injury simultaneously (model 2), associations between type of vascular brain injury and rate of cognitive decline remained similar. Although three baseline associations lost statistical significance, the effect sizes remained largely similar.

In an additional set of analyses, we stratified for dementia status (Table 4). We found that the observed association between worse baseline TMTB performance and lacune(s) was attributable to patients with dementia. The faster rate of cognitive decline on the TMTB in patients with non-lacunar infarct(s) was also restricted to the dementia group. In addition, we found that moderate/severe WMH were associated with worse performance on baseline TMTB in patients with dementia, albeit better performance on baseline TMTA in the no dementia group.

Finally, we stratified for CSF Alzheimer biomarker profile in a subset of 293 (62%) patients with available CSF data. Data are shown in supplementary area, Table 1. Our results of worse baseline performance on TMTB in patients with lacune(s) and faster rate of decline on TMTB in non-lacunar infarct(s) was attributable to patients with a negative CSF Alzheimer biomarker profile. In patients with a positive CSF Alzheimer biomarker profile, non-lacunar infarct(s) showed a worse baseline performance on the TMTA, no other associations were found.

Table 1
baseline characteristics of the total study population.

	Number of patients (N = 472)	
Female, n (%)	206 (44%)	
Age in years, mean (SD)	68 (8)	
Level of education (n = 469), median (IQR)[1]	5 (4-6)	
Dementia, n (%)	210 (44%)	
Vascular [10], n (%)	19 (9%)	
Neurodegenerative, n (%)	177 (84%)	
Alzheimer's disease [18], n (%)		134 (76%)
Frontotemporal dementia [19], n (%)		12 (7%)
Lewy body dementia [9], n (%)		12 (7%)
Others[2], n (%)		19 (11%)
Unknown etiology[3], n (%)	14 (7%)	
Positive CSF Alzheimer biomarker profile (n = 293), n (%)	166 (57%)	
MRI characteristics		
Lacune(s), n (%)	108 (23%)	
Non-lacunar infarct(s), n (%)	54 (11%)	
Fazekas 2-3, n (%)	211 (45%)	
Microbleed(s) (n = 469), n (%)	202 (43%)	
Number of types of vascular brain injury (n = 469), n		
Fazekas 1 and VRF[4]	115	
1[4]	202	
2[4]	94	
3[4]	52	
4[4]	6	
MTA score ≥ 1.5 (n = 464), n (%)	164 (35%)	

Abbreviations: n; number, SD; standard deviation, IQR; interquartile range, CSF; cerebrospinal fluid, VRF; vascular risk factors, MTA; medial temporal lobe atrophy.
If there were missing data the number (n) is specifically mentioned.
[1] Verhage scale [20].
[2] Such as Primary Progressive Aphasia [21], Cortical Basal Syndrome [22] and Progressive Supranuclear Palsy [23].
[3] Dementia of unknown origin; further examination needed to state diagnosis.
[4] Number of patients with Fazekas scale 1 [7] and the presence of ≥ 2 vascular risk factors [5], patients with 1, 2, 3 or all 4 types of vascular brain injury (lacune (s), non-lacunar infarct(s), fazekas 2-3 and microbleed(s)).

4. Discussion

This study demonstrated that memory clinic patients with VCI and different types of vascular brain injury on MRI showed little difference in cognitive trajectories depending on type of vascular brain injury. Independent of type of vascular brain injury, VCI patients showed cognitive decline over time on global cognitive functioning, memory, attention and executive functioning and language. We found some minor associations of lacune(s) and non-lacunar infarct(s), as lacune(s) were associated with a lower baseline performance in a few tests assessing attention and executive functioning, yet less steep cognitive decline over time. By contrast, non-lacunar infarct(s) were associated with a faster rate of cognitive decline on the TMTB, a test assessing attention and executive functioning. For both lacune(s) and non-lacunar infarct(s), the subtle associations we found were largely attributable to patients with dementia. At memory clinics neuropsychological tests in combination with patterns of vascular and non-vascular brain injury on MRI scans guide clinical diagnoses at baseline visit and prognosis of cognitive decline in time. Our results showed that, in this setting, different types of vascular brain injury showed only little difference in cognitive trajectories over time. Cross-sectional studies evaluating the relationship between vascular brain injury on MRI and cognitive profile show that vascular brain injury has a significant influence on the cognitive profile, mostly showing worse performance on attention and executive function [24–27]. This conclusion is based on numerous studies that examined one type of vascular brain injury only or including all types of vascular brain injury as one disorder, in comparison to the absence of vascular brain injury [2]. However, among memory clinic patients with vascular brain injury, we previously found that baseline cognitive performance was remarkably similar across all different types of vascular brain injury [4]. Focusing on the trajectories of cognitive decline, these are also

Table 2
baseline cognitive performance and annual change of cognitive decline in the total study population and in patients with and without dementia.

Cognitive performance	Total study population *N* = 472		Dementia *N* = 210		No dementia *N* = 262	
	Baseline[1] B (SE)	Slope[1] B(SE)	Baseline[1] B(SE)	Slope[1] B(SE)	Baseline[1] B(SE)	Slope[1] B(SE)
MMSE, (n = 469)	26.2 (.1)	-.9 (.1)*	24.6 (.2)	-1.8 (.2)*	27.4 (.1)	-.3 (.1)*
RAVLT immediate recall	30.3 (.5)	-.8 (.2)*	24.4 (.6)	-1.3 (.2)*	35.1 (.6)	-.4 (.2)*
RAVLT delayed recall (n = 465)	4.4 (.2)	-.2 (.1)*	2.7 (.2)	-.3 (.1)*	5.8 (.2)	-.1 (.1)
TMTA (n = 448)[2]	57.5 (1.7)	8 (.9)*	70.8 (3.2)	13.8 (1.8)*	46.7 (1.3)	4.0 (.9)*
TMTB (n = 407)[2]	160.2 (4.9)	18 (2)*	210 (9.1)	29.2 (4.5)*	124.9 (4.3)	12.0 (2.2)*
Category naming task (animals) (n = 463)	16.6 (.3)	-.6 (.1)*	13.3 (.4)	-1.1 (.1)*	19.0 (.4)	-.4 (.1)*

Abbreviations: n; number, B; unstandardized beta, SE; standardized error, IQR; interquartile range, MMSE; mini-mental state examination, RAVLT; Rey Auditory Verbal Learning Test, TMTA; Trail Making Test A, TMTB; Trail Making Test B.
If there were missing data the number (n) is specifically mentioned.
[1] linear mixed model analysis: using time as sole determinant and cognitive test as outcome. Data are unstandardized beta (B) and standardized error (SE) for intercept (performance at baseline) and time (estimated annual change).
[2] Positive and higher scores indicate a worse performance.
* $p < 0.05$.

studied in different study populations and none of them deliberately focused on a memory clinic study population. The LADIS study evaluated cognitive decline in subcortical ischemic vascular disease (SIVD) in a mixed, initially non-disabled, study population; patients were included from stroke clinic, memory clinic and population-based settings. Patient with SIVD showed steeper decline during follow-up in information processing speed, executive function and global cognitive function (MMSE) compared to patients without SIVD [28]. In contrast, in 680 participants from a longitudinal Scottish community-dwelling older-age cohort no association was found between total MRI load of cerebral small vessel disease (derived from visual rating scales of individual MRI markers of vascular brain injury) and a composite score of information processing speed in time [29]. These studies compared patients with vascular brain injury to patients without vascular brain injury. Our study includes a unique and large number of memory clinic patients with VCI. This inclusion procedure has clinical relevance, as these patients presented at a memory clinic worrying about their cognitive function. It furthermore supports generalizability of our findings to patients who attend a memory clinic with any type of vascular brain injury and allow an unbiased assessment of the potential impact of vascular brain injury on the trajectory of cognitive decline in this clinical setting.

We showed that patients with lacune(s) and non-lacunar infarct(s) have little different trajectories of cognitive decline. This association should be interpreted with caution. The numbers of patients with lacune (s) and non-lacunar infarct(s) were relatively small, 23% versus 11%. Also, it is important to realize that all patients were included in this study population due to vascular brain injury. We did not compare the presence or absence of vascular brain injury and did not measure the total burden of vascular brain injury. Previous studies on the association between non-lacunar infarct(s) and lacune(s) and the cognitive profile largely focus on acute post-stroke deficits. A recent meta-analysis showed that patients after stroke showed a decline in global cognition and executive function from 1 to 3 years after stroke compared to stroke-free controls [30]. Patients with lacune(s) have been reported to have poorer performance in multiple cognitive domains and steeper decline in global cognitive function in post-stroke cohorts and population-based studies such as the Cardiovascular Health Study, the Rotterdam Study and the Epidemiology of Dementia in Singapore study [31–34]. Our results might add to this, that in memory clinic patients the presence of lacune(s) might be associated with cognitive deficits at baseline visit, but with a slower subsequent rate of cognitive decline. This is in apparent contradiction to previous studies, however our memory clinic population markedly differs from these previously studied cohorts in that the inclusion procedure of our study already included vascular brain injury. Our study also included stroke patients, in fact 45 (9.5%) patients suffered from stroke in the past based on their medical history. However, the TRACE-VCI study population includes a memory clinic population and our findings might not be generalizable to VCI in other settings; such as for example post-stroke cognitive impairment. Also, in post-stroke cohorts, a recent systematic review and meta-analysis showed a prevalence of post-stroke dementia in 22% [35]. While in this current study, all patients visited the memory clinic due to cognitive complaints and 44% of patients were diagnosed with dementia.

Stratification for dementia status also showed little differences in cognitive trajectories. The association between non-lacunar infarct(s) and faster rate of cognitive decline on the TMTB was only found in the dementia group, just as the worse baseline performance on the TMTB in patients with lacune(s). In addition, we found that moderate/severe WMH were associated with worse performance on baseline TMTB in patients with dementia. This might indicate that the little different trajectories of cognitive decline we found, were mostly due to patient with dementia. It might indicate that patients with dementia and lacune(s), non-lacunar infarct(s) or moderate/severe WMH show a lower threshold for worse baseline performance on attention and executive functioning or steeper decline over time on attention and executive functioning.

The strength of our study include its large, unique and detailed cohort of memory clinic patients with possible VCI with different levels of cognitive impairment, vascular brain injury and clinical diagnosis, with an extensive clinical and MRI evaluation. This inclusion procedure supports generalizability of our findings to patients who attend a memory clinic with any type of vascular injury and neuropsychological assessment. The mean follow-up time is quite long compared to other studies, which gives a good reflection of cognitive decline in time. The evaluated neuropsychological tests are common, uniform tests included in mostly every neuropsychological test battery.

There are several limitations to our study. Our study population included a subset of patients of the total study population of the TRACE-VCI study. In our previous manuscript evaluating the 2-year risk of poor clinical outcome in the TRACE-VCI study population, 707 out of 860 patients were eligible for follow-up [6]. In 472 (67%) patients, one or more neuropsychological follow-up test was performed. However, the general demographics among the total TRACE-VCI study population and this subset of 472 patients was more or less the same (types of vascular brain injury, mean age, cognitive impairment), supporting generalizability of our findings to patients who attend a memory clinic with any form of vascular brain injury. Secondly, there were some differences in

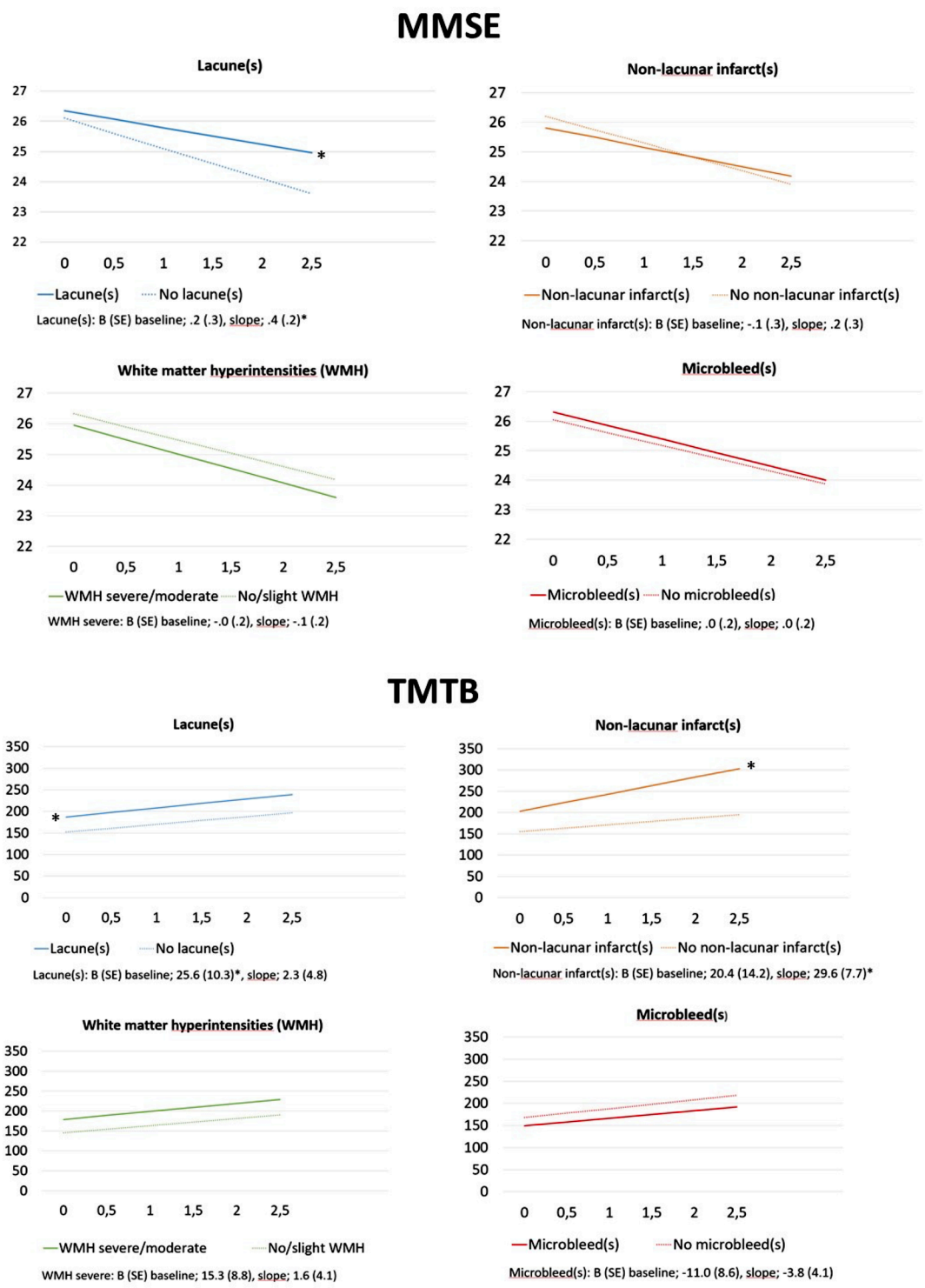

Fig. 1. the association between type of vascular brain injury and MMSE and TMTB (time in seconds) performance (raw data).
Abbreviations: B; unstandardized beta, SE; standard error, MMSE; mini-mental state examination, WMH; white matter hyperintensities, Raw data are visualized, showing the association of the type of vascular brain injury on the MMSE and TMTB performance at baseline visit and in time. Two lines are shown; one with this type of vascular brain injury and one without. The x-axis is showing time in years. The y-axis is showing MMSE in total points out of 30 and the TMTB is showing time in seconds. Note, higher TMTB scores indicated worse performance. Lacune(s) were defined as the presence of 1 or more lacune(s) on MRI. Non-lacunar infarct(s) were defined as the presence of 1 or more infarct(s) on MRI. WMH were categorized as severe (Fazekas 2 and 3) and non-severe (Fazekas 0 and 1) white matter hyperintensities on MRI. Microbleed(s) were defined as the presence of 1 or more microbleed(s) on MRI. Statistical analysis show the results of Table 3, model 1, evaluating linear mixed models including dichotomized terms per type of vascular brain injury, time (years) and interaction-term vascular brain injury*time, adjusted for sex, age, diagnosis, education, follow-up time, MTA score $\geq$ 1.5. Data are presented as unstandardized beta (B) ($\pm$ standardized error (SE)) for different types of vascular brain injury representing the association between this type of vascular brain injury and baseline neuropsychological test performance, whereas the interaction term between the different types of vascular brain injury and time represents the annual decline of neuropsychological test performance in time. * $p < 0.05$.

Table 3
associations between type of vascular brain injury and cognitive test performance.

Neuropsychological tests	Baseline association		Slope association	
	Model 1B (SE)	Model 2B (SE)	Model 1B (SE)	Model 2B (SE)
MMSE				
Lacune(s)	.2 (.3)	.2 (.3)	**.4 (.2)** p = **.047**	**.5 (.2)** p = **.039**
Non-lacunar infarct(s)	-.1 (.3)	-.2 (.4)	.2 (.3)	.1 (.3)
WMH	-.0 (.2)	-.1 (.2)	-.1 (.2)	-.1 (.2)
Microbleed(s)	.0 (.2)	.0 (.2)	.0 (.2)	.0 (.2)
RAVLT immediate recall				
Lacune(s)	-1.4 (.9)	-.9 (.9)	**1.6 (.4)** p = **<.001**	**1.6 (.4)** p = **<.001**
Non-lacunar infarct(s)	**-2.8 (1.2)** p = **.016**	-2.3 (1.2)	.9 (.6)	.3 (.6)
WMH	-.5 (.8)	-.3 (.8)	.1 (.3)	-.2 (.3)
Microbleed(s)	1.1 (.7)	1.0 (.7)	-.5 (.3)	-.6 (.3)
RAVLT delayed recall				
Lacune(s)	-.3 (.3)	-.3 (.3)	**.3 (.1)** p = **.007**	**.3 (.1)** p = **.009**
Non-lacunar infarct(s)	-.5 (.4)	-.4 (.4)	.2 (.2)	.1 (.2)
WMH	-.1 (.3)	-.1 (.3)	.0 (.1)	-.1 (.1)
Microbleed(s)	.2 (.3)	.2 (.3)	-.1 (.1)	-.1 (.1)
TMTA[1]				
Lacune(s)	**8.3 (3.8)** p = **.027**	5.7 (3.9)	-2.7 (2.1)	-2.4 (2.2)
Non-lacunar infarct(s)	**20.4 (5.1)** p = **<.001**	**18.0 (5.3)** p = **<.001**	-3.1 (3.3)	-1.9 (3.5)
WMH	-.9 (3.2)	-1.8 (3.2)	-1.8 (1.7)	-1.4 (1.8)
Microbleed(s)	-2.1 (3.1)	-1.4 (3.1)	.8 (1.7)	.9 (1.8)
TMTB[1]				
Lacune(s)	**25.6 (10.3)** p = **.013**	20.5 (10.9)	2.3 (4.8)	-2.6 (5.0)
Non-lacunar infarct(s)	20.4 (14.2)	11.6 (14.8)	**29.6 (7.7)** p = **<.001**	**30.2 (8.1)** p = **<.001**
WMH	15.3 (8.8)	12.8 (8.9)	1.6 (4.1)	.7 (4.1)
Microbleed(s)	-11.0 (8.6)	-10.6 (8.6)	-3.8 (4.1)	-2.1 (4.1)
Category naming task (animals)				
Lacune(s)	-.9 (.6)	-.4 (.7)	**.6 (.2)** p = **.006**	**.4 (.2)** p = **.047**
Non-lacunar infarct(s)	**-2.5 (.8)** p = **.003**	**-2.4 (.9)** p = **.006**	**1.1 (.4)** p = **.001**	**1.0 (.4)** p = **.010**
WMH	.1 (.5)	.2 (.5)	.2 (.2)	.1 (.2)
Microbleed(s)	-.2 (.5)	-.3 (.5)	-.1 (.2)	-.1 (.2)

Abbreviations: B; unstandardized beta, SE; standard error, MMSE; mini-mental state examination, WMH; white matter hyperintensities, RAVLT; Rey Auditory Verbal Learning Test, TMTA; Trail Making Test A, TMTB; Trail Making Test B.
Lacune(s) were defined as the presence of 1 or more lacune(s) on MRI.
Non-lacunar infarct(s) were defined as the presence of 1 or more infarct(s) on MRI.
WMH were categorized as severe (Fazekas 2 and 3) and non-severe (Fazekas 0 and 1) white matter hyperintensities on MRI.
Microbleed(s) were defined as the presence of 1 or more microbleed(s) on MRI.
We used linear mixed models including dichotomized terms per type of vascular brain injury, time (years) and interaction-term vascular brain injury*time. Model 1 included the presence or absence of one type of vascular brain injury and model 2 included all types of vascular brain injury simultaneously. Both models were adjusted for sex, age, diagnosis, education, follow-up time, MTA score $\geq$ 1.5. Data are presented as unstandardized beta (B) ($\pm$ standardized error (SE)) for different types of vascular brain injury representing the association between this type of vascular brain injury and baseline neuropsychological test performance, whereas the interaction term between the different types of vascular brain injury and time represents the annual decline of neuropsychological test performance in time.
[1] Positive and higher scores indicate a worse performance. Results are expressed in bold if they indicate a $p < 0.05$. The p-value is specifically mentioned.

neuropsychological test battery between centers. We decided not to impute or recode missing variables, since available raw data was still relatively complete (all available neuropsychological follow-up tests above the 86%). The included neuropsychological tests did not cover all key cognitive domains. However, the most important cognitive domains in vascular cognitive impairment, including memory, attention and executive functioning were included. Another limitation might be that CSF Alzheimer biomarker profile was only available in a subset of patients (62%). The CSF biomarker analysis was different by center; either it was a standard procedure or at the discretion of the doctor and the patient. However, also here, there was no difference in demographics and cognitive impairment between patients with and without CSF biomarker analysis. Lastly, by design, our primary aim was to compare the different cognitive trajectories in different types of vascular brain injury rather than comparing the cognitive trajectories of patients with vascular brain injury to patients without any type of vascular brain injury. Due to this design, the association of vascular burden might be underestimated. However, this inclusion procedure supports generalizability of our findings to patients who attend a memory clinic with any form of vascular brain injury and allow an unbiased assessment of the potential impact of vascular brain injury in this clinical setting. The use of a categorical measure of vascular brain injury (none versus $\geq$ 1) for analytical purposes may have underestimated the impact of this type of vascular brain injury in a (small) subgroup of patients with very high counts. Such rare cases will have little impact on the overall results of a large cohort study such as ours, but could still be clinically relevant. Also, our study protocol did not include standardized guidance on treatment and we did not follow-up risk factor control over time, which could be potential confounders. However, vascular risk factors are generally well controlled in Dutch patients [36]. .

5. Conclusions

In this memory clinic population with VCI, little differences were found in trajectories of cognitive decline over time depending on type of vascular brain injury. Although types of vascular brain injury explain little of the differences in trajectories of cognitive decline, MRI can still provide important leads on the underlying etiology and direct patient management. Since all patients showed cognitive decline, vascular risk management might be important for all memory clinic patients with VCI, independent on type of vascular brain injury.

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Table 4
mixed model analysis; univariate analysis (model 1) in patients with (n = 210 (45%)) and without (n = 262 (56%)) dementia.

Neuropsychological tests	Dementia (n = 210) Baseline association B (SE)[1]	Slope association B (SE)[1]	No dementia (n = 262) Baseline association B (SE)[1]	Slope association B (SE)[1]
MMSE				
Lacune(s)	.0 (.5)	.5 (.4)	.2 (.3)	**.4 (.2)** p = $^{.018}$
Non-lacunar infarct(s)	-.1 (.6)	.7 (.5)	-.2 (.4)	.2 (.3)
WMH	-.5 (.4)	-.2 (.3)	.2 (.3)	.0 (.1)
Microbleed(s)	-.3 (.4)	.3 (.4)	.1 (.2)	-.1 (.1)
RAVLT trials 1-5				
Lacune(s)	-1.0 (1.3)	**1.8 (.5)** p = $^{<.001}$	-1.7 (1.3)	**1.3 (.5)** p = $^{.010}$
Non-lacunar infarct(s)	-2.5 (1.7)	1.1 (.9)	-3.1 (1.9)	.9 (.9)
WMH	-1.7 (1.1)	.3 (.4)	.3 (1.2)	-.2 (.4)
Microbleed(s)	-.3 (1.1)	-.2 (.4)	2.0 (1.1)	-.7 (.4)
RAVLT delayed recall				
Lacune(s)	-.4 (.5)	.3 (.1)	-.2 (.5)	.3 (.2)
Non-lacunar infarct(s)	-.5 (.6)	.2 (.2)	-.5 (.7)	.3 (.3)
WMH	-.3 (.4)	.1 (.1)	-.0 (.4)	-.1 (.1)
Microbleed(s)	-.6 (.4)	.0 (.1)	.7 (.4)	-.2 (.1)
TMTA[2]				
Lacune(s)	14.8 (7.6)	-3.0 (4.4)	5.4 (3.0)	-2.2 (1.5)
Non-lacunar infarct(s)	**22.6 (9.4)** p = $^{.017}$	-9.0 (6.5)	**18.9 (4.3)** p = $^{<.001}$	.1 (2.6)
WMH	5.3 (6.2)	-5.4 (3.6)	**-5.6 (2.6)** p = $^{.031}$	-.6 (1.2)
Microbleed(s)	-4.9 (6.3)	.1 (3.7)	.2 (2.5)	1.5 (1.2)
TMTB[2]				
Lacune(s)	**56.1 (21.2)** p = $^{.009}$	12.4 (11.1)	11.2 (9.6)	-1.1 (4.8)
Non-lacunar infarct(s)	8.9 (26.4)	**62.9 (15.5)** p = $^{<.001}$	28.3 (14.3)	9.9 (8.1)
WMH	**35.3 (17.1)** p = $^{.041}$	13.0 (9.0)	5.4 (8.5)	-4.4 (4.1)
Microbleed(s)	-19.5 (17.7)	.7 (9.4)	-3.4 (8.1)	-4.8 (4.1)
Category naming task (animals)				
Lacune(s)	-.9 (1.0)	**.8 (.3)** p = $^{.013}$	-1.0 (.8)	.5 (.3)
Non-lacunar infarct(s)	-2.0 (1.2)	.9 (.5)	**-2.7 (1.2))**p = $^{.025}$	**1.3 (.5)** p = $^{.007}$
WMH	-1.4 (.8)	.3 (.3)	1.1 (.7)	.2 (.2)
Microbleed(s)	-.2 (.8)	.2 (.3)	-.2 (.7)	-.4 (.2)

Abbreviations: B; unstandardized beta, SE; standard error MMSE; mini-mental state examination, WMH; white matter hyperintensities, RAVLT; Rey Auditory Verbal Learning Test, TMTA; Trail Making Test A, TMTB; Trail Making Test B.
Lacune(s) were defined as the presence of 1 or more lacune(s) on MRI.
Non-lacunar infarct(s) were defined as the presence of 1 or more infarct(s) on MRI.
WMH were categorized as severe (Fazekas 2 and 3) and non-severe (Fazekas 0 and 1) white matter hyperintensities on MRI.
Micobleed(s) were defined as the presence of 1 or more microbleed(s) on MRI.
[1] Univariate model: one type of vascular brain injury, interaction-term of one type of vascular brain injury and follow-up time (years), adjusted for sex, age, education, follow-up time, MTA score $\geq$ 1.5.
[2] Positive and higher scores indicate a worse performance. Results are expressed in bold if they indicate a $p < 0.05$. The p-value is specifically mentioned.

Declarations of interest

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Supplementary materials

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