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Prediction of post-stroke cognitive impairment using neuroimaging and blood-based markers

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Rong Fang

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Erstes Gutachten:	Prof. Dr. Martin Dichgans
Zweites Gutachten:	Prof. Dr. Nikolaos Koutsouleris
Drittes Gutachten:	Prof. Dr. Thomas Liebig
Viertes Gutachten:	Prof. Dr. Gerhard Ferdinand Hamann

Dekan: Prof. Dr. med. Thomas Gudermann

Tag der mündlichen Prüfung: 17.12.2024

To my husband and our daughter

致我的爱人檩檩和女儿乐乐

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Affidavit

Fang, Rong
Surname, first name

Feodor-Lynen-Straße 17
Street

81377, München, Deutschland
Zip code, town, country

I hereby declare, that the submitted thesis entitled:

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Signature doctoral candidate

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Promotionsbüro Medizinische Fakultät

MMRS

Confirmation of congruency between printed and electronic version of the doctoral thesis

Fang, Rong
Surname, first name

Feodor-Lynen-Straße 17
Street

81377, München, Deutschland
Zip code, town, country

I hereby declare, that the submitted thesis entitled:

Prediction of post-stroke cognitive impairment using neuroimaging and blood-based markers

is congruent with the printed version both in content and format.

München, 29.04.2024
place, date

Rong Fang
Signature doctoral candidate

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List of abbreviations

BBB	blood-brain barrier
BD-tau	brain-derived tau
CBF	cerebral blood flow
CMBs	cerebral microbleeds
CRP	C-reactive protein
CSF	cerebrospinal fluid
DEDEMAS	Determinants of Dementia After Stroke
DEMDAS	DZNE (German Center for Neurodegenerative Disease)-Mechanisms of Dementia After Stroke
DWI	diffusion-weighted imaging
FLAIR	fluid-attenuated inversion recovery
HbA1c	hemoglobin A1c
hs-cTnT	high-sensitivity cardiac troponin T
ICH	intracerebral hemorrhage
IILs	incident ischemic lesions
MMSE	mini-mental state examination
MRI	magnetic resonance imaging
NfL	neurofilament light chain
PSCI	post-stroke cognitive impairment
PSD	post-stroke dementia
PVSs	perivascular spaces
RSSI	recent small subcortical infarct
SVD	small vessel disease
T1w	T1-weighted
WMHs	white matter hyperintensities

List of publications

- Marios K. Georgakis*, **Rong Fang***, Marco Düring, Frank A.Wollenweber, Felix J. Bode, Sebastian Stösser, Christine Kindler, Peter Hermann, Thomas G. Liman, Christian H. Nolte, Lucia Kerti, Benno Ikenberg, Kathleen Bernkopf, Holger Poppert, Wenzel Glanz, Valentina Perosa, Daniel Janowitz, Michael Wagner, Katja Neumann, Oliver Speck, Laura Dobisch, Emrah Düzel, Benno Gesierich, Anna Dewenter, Annika Spottke, Karin Waegemann, Michael Görtler, SilkeWunderlich, Matthias Endres, Inga Zerr, Gabor C. Petzold, Martin Dichgans on behalf of the DEMDAS investigators. Cerebral small vessel disease burden and cognitive and functional outcomes after stroke: a multicenter prospective cohort study. ***Alzheimers Dement.*** 2023;19(4):1152-1163.
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* Authors contribute equally as first authors

1. Your contribution to the publications

1.1 Contribution to paper I

Marios K. Georgakis*, **Rong Fang***, Marco Düring, Frank A.Wollenweber, Felix J. Bode, Sebastian Stösser, Christine Kindler, Peter Hermann, Thomas G. Liman, Christian H. Nolte, Lucia Kerti, Benno Ikenberg, Kathleen Bernkopf, Holger Poppert, Wenzel Glanz, Valentina Perosa, Daniel Janowitz, Michael Wagner, Katja Neumann, Oliver Speck, Laura Dobisch, Emrah Düzel, Benno Gesierich, Anna Dewenter, Annika Spottke, Karin Waegemann, Michael Görtler, SilkeWunderlich, Matthias Endres, Inga Zerr, Gabor C. Petzold, Martin Dichgans on behalf of the DEMDAS investigators. Cerebral small vessel disease burden and cognitive and functional outcomes after stroke: a multicenter prospective cohort study. ***Alzheimers Dement.*** 2023;19(4):1152-1163.

* equally contributed

Contributions: I contributed to the data acquisition of the multicenter prospective hospital-based cohort study (DEMDAS-DEDEMAS, NCT01334749). I also conducted the data quality control for clinical, neuropsychological, and neuroimaging records. During the analysis, I rated conventional MRI markers of cerebral small vessel disease (SVD) and the total SVD score, a well-established marker of total SVD burden. Additionally, I preprocessed neuroimaging data with an in-house pipeline. Subsequently, I performed the statistical analysis and generated the figures for the manuscript. Moreover, I discussed the results with all the co-authors, drafted the manuscript, and drafted the revision after feedback from journal reviewers. I share the first authorship with MG, who contributed to the study design, data acquisition, and supervised me throughout the project in performing the analyses and figure creation, interpretating the data and results, and also significantly contributed to writing and revising the manuscript.

1.2 Contribution to paper II

Regina von Rennenberg, Christian H. Nolte, Thomas G. Liman, Simon Hellwig, Christoph Riegler, Jan F. Scheitz, Marios K. Georgakis, **Rong Fang**, Felix J. Bode, Gabor C. Petzold, Peter Hermann, Inga Zerr, Michael Goertler, Kathleen Bernkopf, Silke Wunderlich, Martin Dichgans, Matthias Endres for the DEMDAS investigators. High-sensitivity cardiac troponin T and cognitive function over 12 months after stroke - results of the DEMDAS study. ***J Am Heart Assoc.*** 2024;13(6):e033439.

Contributions: I participated in the data acquisition of clinical, neuropsychological, and brain MRI data in the DEMDAS-DEDEMAS study. Besides, I was responsible for preprocessing the neuroimaging data and assessing individual SVD lesions. Moreover, I contributed to the interpretation of the data and took part in the critical revision of the manuscript.

1.3 Contribution to paper III (Appendix)

Rong Fang, Marco Duering, Felix J. Bode, Sebastian Stösser, Julius N. Meißner, Peter Hermann, Thomas G. Liman, Christian H. Nolte, Lucia Kerti, Benno Ikenberg, Kathleen Bernkopf, Wenzel Glanz, Daniel Janowitz, Michael Wagner, Katja Neumann, Oliver Speck, Emrah Düzel, Benno Gesierich, Anna Dewenter, Annika Spottke, Karin Waegemann, Michael Görtler, Silke Wunderlich, Inga Zerr, Gabor C. Petzold, Matthias Endres, Marios K. Georgakis*, Martin Dichgans* on behalf of the DEMDAS investigators. Risk factors and clinical significance of post-stroke incident ischemic lesions. ***Alzheimers Dement.*** 2024;20(12):8412-8428.

* equally contributed

Contributions: I participated in the study design, data acquisition, quality control of the clinical, neuropsychological, and brain MRI data, and the interpretation of the results. Specifically, I assessed all incident ischemic lesions (IILs) on longitudinal MRI and then had consensus meetings with MDu on uncertain cases. In addition, I performed the exploration of the characteristics of IILs, statistical analysis, and creating the figures for the manuscript. Moreover, I discussed our results with all co-authors and drafted the manuscript under the supervision of MG and MD.

2. Introductory summary

2.1 Post-stroke cognitive impairment

Over the past thirty years, there has been a global decline in age-standardized mortality rates following a stroke (GBD 2019 Stroke Collaborators, 2021), so long-term outcomes post-stroke have stepped into priorities for current clinical care and research (Hill et al., 2022, Georgakis & **Fang** et al., 2023). Post-stroke cognitive impairment (PSCI) refers to cognitive impairment occurring regardless of cause in the 3 to 6 months following an overt stroke (ischemic, intracerebral hemorrhagic, or subarachnoid hemorrhage) and usually includes two subgroups: (1) PSCI not fulfilling criteria for dementia, which still affects quality of life and is synonymous with mild cognitive impairment (MCI) after stroke, and (2) post-stroke dementia (PSD) (Kalaria et al., 2016, Mijajlović et al., 2017, El Husseini et al., 2023, Rost et al., 2022). Since PSCI is associated with disability (Fride et al., 2015, Melkas et al., 2009), dependency (Nys et al., 2005), and death (Oksala et al., 2009, Ganesh et al., 2017), it results in a high socioeconomic burden globally. Understanding the factors predicting PSCI is crucial for implementing interventions targeting high-risk populations, thereby optimizing prevention strategies.

2.1.1 Epidemiology and clinical features

The estimated prevalence of PSCI varies in different studies due to factors such as the time interval from stroke, demographics (age, ethnicity, education, etc.), the assessment tools, and diagnostic criteria (El Husseini et al., 2023). Around 10% and 20% of stroke patients were reported to develop dementia soon after the first stroke and within 10 years, respectively (Pendlebury and Rothwell, 2009, Ivan et al., 2004). Besides, more than a third have been reported to become demented after a recurrent stroke (Pendlebury and Rothwell, 2009). The prevalence of PSCI not fulfilling criteria for dementia is even higher (with a pooled prevalence of 38%) according to a systematic review that included publications between 1995 and 2017 (Sexton et al., 2019). Overall, up to two thirds of stroke survivors suffer from PSCI within 5 years post-stroke (Lo et al., 2019, El Husseini et al., 2023, Rost et al., 2022).

Global cognitive performance as well as individual cognitive domains were observed to be impaired post-stroke in previous studies, among which, executive ability and attention are the most affected domains in both ischemic and hemorrhagic strokes (Pinter et al., 2019, Banerjee et al., 2018). Acute domain-specific cognitive impairments are usually related to the affected location(s) of the index stroke (e.g., infarcts in the hippocampus may result in memory decline)

(Dichgans and Leys, 2017). In many cases, a transient recovery after stroke is followed by long-term cognitive deterioration. However, it is challenging to predict the diverse cognitive trajectories post-stroke due to the interplay of the acute impairment after stroke, brain resilience, secondary neurodegeneration, and recurrent vascular events (Rost et al., 2022, El Husseini et al., 2023, Mijajlović et al., 2017).

2.1.2 Pathophysiology and mechanisms

Understanding the pathophysiological mechanisms of PSCI is crucial for developing precise prediction models in the era of precision medicine and effective treatments, although the mechanisms are not yet fully understood. Contributors during different stages post-stroke including pre-stroke pathologies, stroke characteristics, post-stroke changes, and brain resilience may have synergistic effects on the development of PSCI (**Fig. 1**).

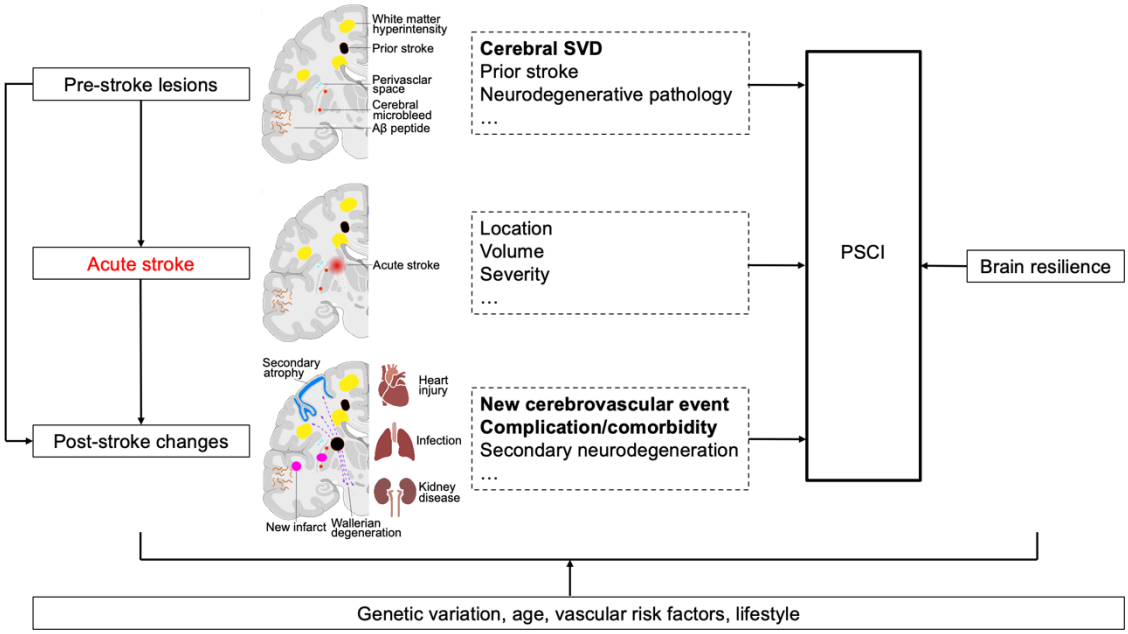

Figure 1. The joint effects of contributors at different stages lead to post-stroke cognitive impairment. Arrows represent the causal relationship between the two entities connected by them. **Bold** contributors were studied in this PhD project. Created with BioRender.com. Abbreviations: SVD = small vessel disease; PSCI = post-stroke cognitive impairment. (El Husseini et al., 2023, Rost et al., 2022, Wardlaw et al., 2019)

First, there is mounting evidence that pre-stroke pathologies, particularly the burden of cerebral small vessel disease (SVD), have a major impact on PSCI. Histopathology studies in postmortem

human brain tissues have revealed endothelial dysfunction and blood-brain barrier (BBB) breakdown in lacunes (Caplan, 2015), as well as pathogenetic mechanisms in white matter hyperintensities (WMHs) including inflammation, BBB leakage, axonal injury, demyelination with or without axonal loss, etc. (Solé-Guardia et al., 2023, Gouw et al., 2011, van Veluw et al., 2022). Another autopsy study showed that the dysfunction of arteriolar dilation in WM was related to WM injury (Bagi et al., 2018), which potentially leads to PSCI through mechanisms such as oxidative damage, gliosis progression, reduced cerebral blood flow (CBF), elevated BBB permeability, and disrupted amyloid-β clearance (Iulita et al., 2018). Moreover, the pathologies caused by SVD were observed not only in the MRI-visible lesions but also in normal-appearing white matter and grey matter (Solé-Guardia et al., 2023). Secondly, there has been considerable investigation into the direct and cascade changes induced by acute stroke. Cell death, BBB leakage, oxidative stress, and immune responses following the acute event exacerbate brain tissue injuries (Zhao et al., 2022). Existing and secondary neurodegenerative pathologies such as beta-amyloid (Aβ) deposition also play a role in PSCI (Kalaria et al., 2016, Goulay et al., 2020). Additionally, individual reactions of brain resilience to compensate for preexisting pathologies or those following stroke, such as vascular remodeling and remapping of brain functions, exert influence, which might mitigate cognitive impairments (Kalaria et al., 2016, Campos et al., 2023). Furthermore, clinical studies have identified that recurrent cerebrovascular events and stroke complications/comorbidities increased risk of PSCI (Lo et al., 2022, Pendlebury and Rothwell, 2009, Rost et al., 2022). However, further research is needed to clarify the causal mechanisms and clinical applications.

2.2 MRI predictors of post-stroke cognitive impairment

Magnetic Resonance Imaging (MRI) is highly sensitive and specific in detecting cerebrovascular lesions including the index stroke and SVD thus offering an opportunity to capture markers of cognitive outcomes in clinical practice. However, there are few reliable MRI-based markers for predicting PSCI.

2.2.1 Characteristics of acute stroke lesions

Stroke itself has a direct impact on patients' cognition, as confirmed by the REGARDS study with 22,875 participants (Levine et al., 2018). The characteristics of the index stroke, such as lesion location, volume, severity, and frequency of stroke, have been reported to be predictors of post-stroke dementia. Lesions located in strategic areas such as left frontotemporal lobes, left

thalamus, and right parietal lobe are highly associated with PSCI within one year after stroke (Weaver et al., 2021b, Weaver et al., 2021a). Another population-based study found that the 1-year occurrence of dementia was 47.3% in severe stroke, while 5.8% in minor stroke (Pendlebury and Rothwell, 2019). Additionally, multiple or recurrent stroke can increase the risk of PSCI (El Husseini et al., 2023, Pendlebury and Rothwell, 2019). It is worth noting that the true proportions of PSCI may be exaggerated if patients have aphasia, unilateral neglect or severe motor deficits caused by the index stroke, as the majority of neuropsychological tests require language and motor abilities.

2.2.2 Cerebral SVD markers

Cerebral SVD refers to a syndrome arising from abnormalities in the small blood vessels of the brain, including perforating arterioles, capillaries, and venules (Wardlaw et al., 2019). It was reported that vascular risk factors, particularly hypertension are related to sporadic SVD, but the underlying mechanisms remain elusive (Wardlaw et al., 2019, Wardlaw et al., 2013). SVD contributes to approximately 25% of stroke cases and is the major factor associated with vascular dementia (Rost et al., 2022, Sudlow and Warlow, 1997, Qureshi et al., 2009, Wardlaw et al., 2019). A meta-analysis published in Neurology in 2019 verified the associations between WMHs, the primary imaging manifestation of cerebral SVD, and cognitive impairment, functional impairment, recurrent stroke, and mortality following ischemic stroke (Georgakis et al., 2019). However, the clinical value and application of SVD markers for predicting PSCI remains to be further substantiated. SVD exhibits as many lesions which can be assessed on conventional MRI (Duering et al., 2023) (**Fig. 2**):

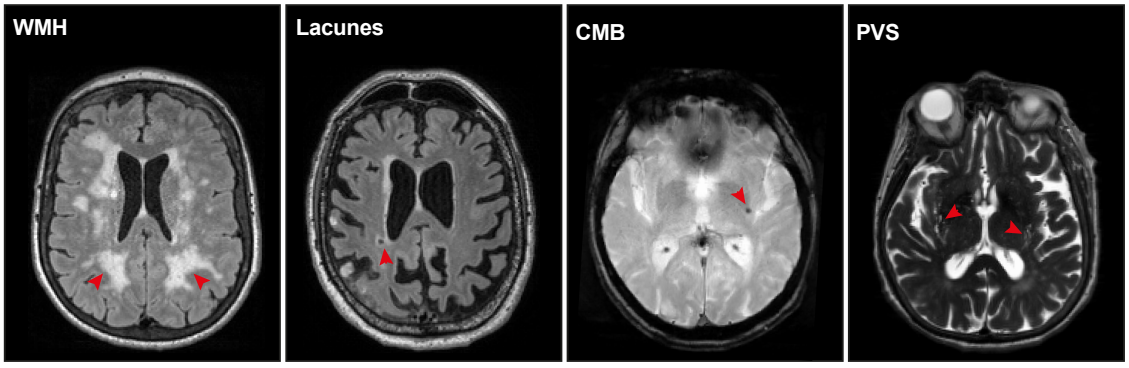

Figure 2. Four types of cerebral small vessel disease markers on brain MRI. Abbreviations: MRI = magnetic resonance imaging; WMH = white matter hyperintensity; CMB = cerebral microbleed; PVS = perivascular space.

White matter hyperintensities (WMHs) are defined as hyperintense lesions in the white matter on T2-weighted (T2w) images and fluid-attenuated inversion recovery (FLAIR) sequences without evidence of a cavity (Duering et al., 2023). WMHs can be quantitatively evaluated through lesion segmentation with fully-automated deep learning pipelines or using rating scales, with the latter being easily applicable in clinical practice (Fazekas et al., 1987).

Lacune is defined as a circular or oval lesion, located in the subcortical region, exhibiting a signal similar to cerebrospinal fluid (CSF) on FLAIR and T1-weighted (T1w) images, with an axial diameter of up to 15 mm (Duering et al., 2023).

Cerebral microbleeds (CMBs) are identified by small, round signal voids typically measuring between 2 to 10 mm on T2*- or susceptibility-weighted imaging (Duering et al., 2023).

Enlarged perivascular spaces (PVSs) are fluid-filled areas appearing as either linear or round/ovoid CSF-like signals on cerebral MRI, with an axial diameter of no more than 2 mm, aligning with the direction of penetrating arterioles (Doubal et al., 2010, Duering et al., 2023).

Summary SVD score integrates SVD markers into a single index as proposed in STRIVE-2 (Duering et al., 2023). One of the most commonly utilized indices is total SVD score, developed in 2014, which encompasses the burden of above four SVD lesions (Staals et al., 2014). It ranges from 0 to 4 based on visual ratings and is convenient for clinical use. Total SVD score has been significantly associated with dementia risk in stroke-free population (Amin Al Olama et al., 2020). However, there is limited evidence regarding its predictive value of PSCI in stroke patients.

2.2.3 Incident ischemic lesions (IILs) at early follow-up post-stroke

Incident ischemic lesions (IILs) are defined as newly appearing lesions and are presumed to originate from infarcts. IILS can be categorized into three main signals on MRI (**Fig. 3**):

(1) Diffusion-weighted imaging (DWI)-positive/FLAIR-positive IILs: new lesions hyperintense on follow-up DWI and hyper- or hypointense (cavities) on follow-up FLAIR; (2) DWI-positive/FLAIR-negative IILs: new hyperintensities on follow-up DWI but isointensities on FLAIR; (3) DWI-negative/FLAIR-positive IILs: new lesions exhibiting hyper- or hypointense (cavities) on follow-up FLAIR. It was reported that up to 30% of patients had IILs following stroke (Kang et al., 2004, Nolte et al., 2012). Additionally, a large cohort study on hemorrhagic stroke showed that DWI lesions at baseline were associated with poor function three months after intracerebral hemorrhage (ICH) (Murthy et al., 2020). Nevertheless, little is known about the clinical

prognostication of IILs detected during an early follow-up visit after stroke for long-term cognitive and functional outcomes.

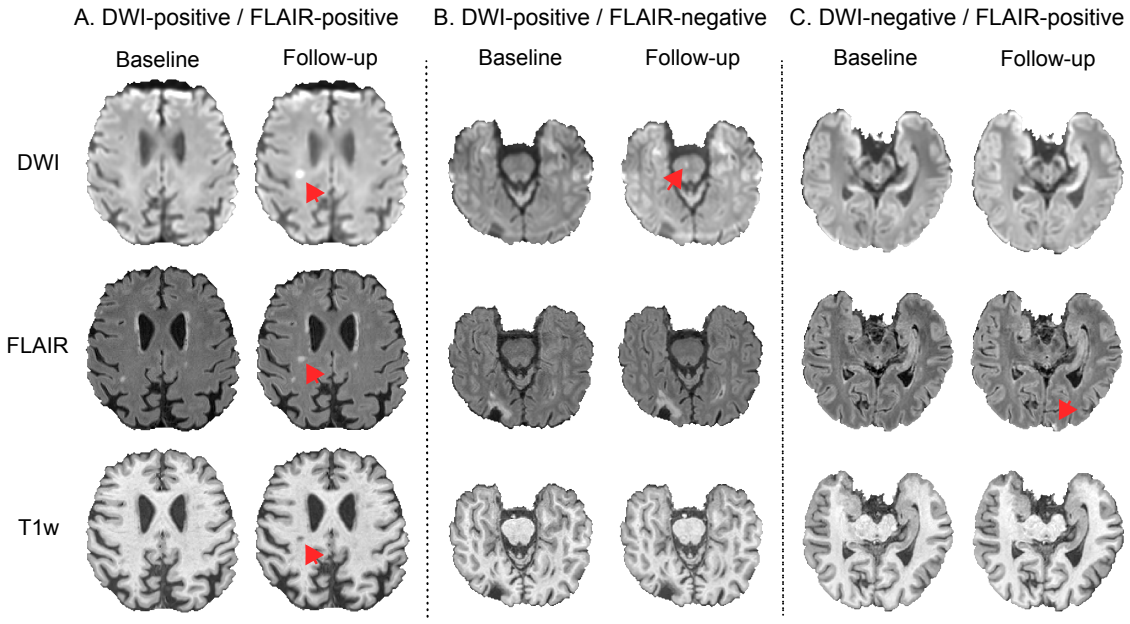

Figure 3. Examples of IILs on brain MRI during follow-up visit. A. a 74-year-old patient with a DWI+/FLAIR+ small subcortical IIL. B. a 75-year-old patient with a DWI+/FLAIR- IIL in the brainstem. C. a 57-year-old patient with a DWI-/FLAIR+ cortical IIL. Abbreviations: IILs = incident ischemic lesions; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; T1w = T1-weighted.

2.3 Blood-based predictors of post-stroke cognitive impairment

There is a growing interest in developing peripheral blood-based markers in stroke care because they can be obtained easily from blood and may serve for disease prediction, treatment targets, as well as tracking pathological processes. For instance, serum neurofilament light chain (NfL) and plasma brain-derived tau (BD-tau) are two novel biomarkers capable of assessing the extent of injury to the central nervous system and have been significantly associated with functional performance post-stroke (Tiedt et al., 2018, Uphaus et al., 2019, Pedersen et al., 2019, Vlegels et al., 2023). However, their implementation in clinical practice is associated with high costs and poses challenges. Apart from the new methods, it is worth considering routine blood tests for evaluating blood function, inflammation and immune response, metabolism, and comorbidities or complications in other systems that are associated with PSCI (Rost et al., 2022, Kim et al., 2022).

Among these, homocysteine, lipid metabolism-related products (such as cholesterol, triglycerides), C-reactive protein (CRP), hemoglobin A1c (HbA1c), and renal function (creatinine levels, creatinine clearance) have been widely studied, but their predictive values for PSCI were not consistent (Casolla et al., 2019, Kim et al., 2022, Sachdev et al., 2006, Narasimhalu et al., 2015, Guo et al., 2018, Auriel et al., 2016, Ben Assayag et al., 2017). Further studies are needed to validate the prognostic values of the blood-based biomarkers which are easily acquired in clinical settings.

2.4 Aims of the thesis

Cognitive impairment affects nearly two thirds of stroke survivors, significantly reducing their quality of life and imposing a substantial burden on both affected families and healthcare systems. An in-depth understanding of factors predicting long-term outcomes post-stroke is crucial for introducing effective interventions to high-risk patients timely. Hence, the overarching goal of the present PhD thesis is to investigate neuroimaging and blood-based predictors of PSCI that are readily applicable in clinical settings.

The three individual studies included in the present PhD thesis focused on the following aims:

(1) SVD is a major contributor to stroke (Sudlow and Warlow, 1997, Qureshi et al., 2009) and individual SVD pathologies have been shown to be significantly associated with cognitive decline (Kandiah et al., 2016, Georgakis et al., 2019, Ball et al., 2023, Arba et al., 2018). Additionally, while a total SVD score integrating global SVD burden is a practical tool, its prognostic value has been limited in stroke patients. We aimed to (i) explore associations between a) the total SVD score and b) individual SVD markers (lacune counts, WMH grade, CMB counts, PVS grade) with cognitive and functional outcomes across 12 months after stroke; (ii) evaluate the predictive performance of the total SVD score for cognitive and functional outcomes at 12 months post-stroke on top of demographic, clinical, and other neuroimaging predictors.

(2) Based on prior evidence indicating that elevated levels of high-sensitivity cardiac troponin T (hs-cTnT), a biomarker of myocardial injury routinely measured in stroke patients, are associated with cognitive impairment (von Rennenberg et al., 2023, Schneider et al., 2014) and WMHs (Dadu et al., 2013) in the general population, our analyses aimed to (i) investigate the association between hs-cTnT levels at baseline and cognitive outcomes in various domains 12 months post-stroke; (ii) examine the relationship between hs-cTnT and SVD burden at baseline in stroke survivors.

(3) Motivated by the frequent occurrence of IIL on follow-up scans and a lack of knowledge regarding their origins and fate at an early phase post-stroke (Kang et al., 2004, Nolte et al., 2012), we set out to (i) describe the characteristics of IILs 6 months after stroke observed on registered DWI, FLAIR, and T1w images at baseline and six months; (ii) explore baseline predictors of IILs 6 months after stroke; and (iii) investigate associations between IILs and outcomes (cognition, function, cardiovascular diseases, and death) across 36 months after stroke.

To address these aims, we used data from DEMDAS (DZNE [German Center for Neurodegenerative Disease]- Mechanisms of Dementia After Stroke)-DEDEMAS ([Determinants of Dementia After Stroke]; NCT01334749) study, a prospective multicenter hospital-based study in Germany with 736 patients who had an acute stroke and no prior dementia.

2.5 Discussion

2.5.1 Main findings

In the present thesis, we observed that both the total SVD score (ranging from 0 to 4) and individual SVD markers, including lacune count, WMH grade, CMB count, and PVS grade, correlated with cognitive and functional decline for up to one-year post-stroke. The severity of individual SVD lesions was significantly associated with poorer performance in executive function, attention, language, and visuospatial domains throughout the 12-month period following stroke. While the total SVD score didn't significantly increase predictive value when controlling for demographic, clinical variables, and the index stroke lesion volume, the inclusion of the four individual SVD markers jointly improved sensitivity, specificity, and calibration to detect PSCI and functional impairment. These findings further imply the need for a more precise tool that integrates SVD burden and is easily applied to predict outcomes post-stroke.

When exploring blood-biomarkers in predicting PSCI, we found a significant correlation between higher hs-cTnT levels and cognitive impairments, specifically in the attention and executive function domains across 12 months after stroke. In addition, hs-cTnT values shortly following stroke showed an association with cerebral SVD burden at baseline, predominantly influenced by the severity of WMHs and lacune count. This indicates potential interactions among subclinical myocardial injury, SVD burden, and cognitive impairment after stroke. Besides, the relationship between hs-cTnT and cognition remained significant after accounting for SVD burden, suggesting

the involvement of additional pathophysiological mechanisms beyond SVD in linking hs-cTnT to cognition post-stroke.

Finally, our data revealed that IILs were common in 15.5% of stroke survivors at 6 months despite receiving secondary prevention. Out of those, more than two-thirds had recent IILs, and the majority showed no corresponding symptoms. Moreover, age and SVD markers at acute phase were associated with IILs, which in turn were associated with worse global cognitive and functional outcomes, as well as recurrent stroke up to 36 months post-stroke. We further verified that the presence of IILs partially mediated the effects of SVD markers on the subsequent global cognitive status at 36 months. These results support the idea that assessing IILs at 6 months post-stroke might aid in predicting long-term cognitive outcomes and monitoring SVD-related progression.

2.5.2 Predictive value of SVD-related markers at baseline post-stroke

In the first project, data from a prospective multicenter study further confirmed that SVD burden at baseline was an independent key risk factor for poor cognitive and functional outcomes post-stroke. Nevertheless, the total SVD score, which is a global measure of the whole SVD burden, did not contribute additional predictive capacity for PSCI and functional impairment within a 12-month period. This observation aligns with findings from a prior investigation focused on outcomes 6 months after stroke (Coutureau et al., 2021). However, a deeper examination of SVD burden uncovered that quantifying rather than merely identifying the presence of individual SVD lesions increases predictive accuracy (Georgakis & **Fang** et al., 2023). This indicates the inadequacy of a simplistic score, where each of the four key hallmarks of SVD is assigned to one point, leading to a loss of valuable details. These results carry implications for the clinical prediction of stroke patients, emphasizing the need to develop more efficient tools for assessing SVD burden at acute phase after stroke. Such tools should be both informative and user-friendly in clinical settings, for instance, by employing an automated approach with machine learning, or a more comprehensive visual-rating scale that incorporates the severity of SVD burden.

In addition to the neuroimaging markers, the second project confirmed a significant association between hs-cTnT levels in blood samples during the baseline visit and SVD burden in stroke patients. Moreover, hs-cTnT may accurately indicate cognitive decline due to vascular pathology rather than being influenced by comorbid neurodegenerative diseases in stroke (von Rennenberg et al., 2024). Hs-cTnT shows promise as an index for identifying patients at risk of cognitive decline, since current guidelines recommend routine testing of hs-cTnT in acute ischemic stroke

management (Hellwig et al., 2021), making hs-cTnT results widely accessible after stroke. However, longitudinal assessment is required to further investigate the predictive value of hs-cTnT and to comprehend underlying mechanisms. Additionally, it is important to mention that hs-cTnT is not specific to SVD but is a sensitive biomarker for myocardial injury which might also result from vascular risk factors and acute stroke (known as “stroke-heart syndrome”). However, further examination of blood biomarkers that extend beyond those related to SVD burden and are easily applicable for predicting post-stroke clinical outcomes is warranted.

2.5.3 Clinical management involving IILs at early follow-up post-stroke

Currently, there are no guidelines for assessing the clinical relevance of IILs found on post-stroke follow-up MRI scans, and the optimal management for patients with these lesions remains uncertain. Our third project revealed that nearly one in six patients had IILs at 6 months post-stroke. The majority of these lesions did not present any associated clinical manifestations, suggesting that the occurrence of IILs may be underestimated when solely relying on clinical symptoms. This project extends our understanding of the long-term prognostic significance of IILs, indicating that individuals with IILs were at a higher risk of cognitive impairment, functional impairment, and stroke recurrence compared to those without across the 36 months after stroke. Our findings support the use of paired MRI scans at 6 months post-stroke for improved prognostication and suggest that follow-up MRI could help identify high-risk patients for inclusion in secondary prevention trials. Given the common practice of conducting follow-up brain MRI scans between six months and one year after stroke (Quinn et al., 2021, Kleindorfer et al., 2021, Santos et al., 2019), our results hold promise for widespread application and verification in other clinical settings.

In addition, this project indicates that IILs are predominantly linked to cerebral SVD. Firstly, SVD burden and all individual SVD markers emerged as the primary baseline predictors for IILs apart from age. Secondly, most IILs were small, consistent with previous data among older individuals with SVD (Ter Telgte et al., 2019) and aligning with the concept proposed in the STRIVE-2 criteria for DWI+ lesions (Duering et al., 2023). Thirdly, the majority of IILs were localized in subcortical and white matter areas, irrespective of the TOAST (Trial of Org 10172 in Acute Stroke Treatment) type of the index stroke. Such subcortical IILs were associated with SVD risk factors observed in the general population (Sigurdsson et al., 2022). Consequently, evaluating IILs at six months post-stroke may also monitor progression triggered by SVD. Therapies targeting both SVD and IILs (e.g., intensive blood pressure control in SPRINT-MIND trial, combining isosorbide mononitrate

and cilostazol in LACI-2 trial) (Nasrallah et al., 2019, Williamson et al., 2019, Wardlaw et al., 2023, Yamano et al., 2015) at an early phase after stroke, in addition to conventional secondary preventions, are promising to protect brain function and preserve cognition.

2.6 Conclusions and future directions

Progress in the development of biomarkers that are sensitive to long-term cognitive outcomes after stroke could aid in identifying high-risk individuals and uncovering underlying mechanisms. This, in turn, may pave the way for more effective strategies for post-stroke care. In the current thesis, I initially confirmed the associations between SVD burden and cognitive and functional declines one-year after stroke, utilizing data from a multicenter prospective cohort. The total SVD score which simply combines the presence of four SVD lesions did not add predictive value. Rather, incorporating individual SVD markers with their severity yields promise in predicting PSCI. Moreover, I discovered significant associations between hs-cTnT, a biomarker for myocardial injury conveniently obtained through routine blood tests post-stroke, and cerebral SVD burden as well as cognitive impairment due to vascular pathology. Nonetheless, further investigation is required to examine the long-term predictive value of hs-cTnT for PSCI and SVD progression, as well as to elucidate the underlying mechanisms. Finally, I explored the origins and outcomes of IILs during an early follow-up visit post-stroke which are commonly observed in clinical practice using conventional MRI (registered DWI, FLAIR, and T1w images). Results revealed that cerebral SVD during the acute phase was the primary risk factor for IILs, which in turn was associated with poorer cognitive and functional performance, along with recurrent stroke over a 3-year period post-stroke. Therefore, evaluating IILs at 6-month after stroke may aid the detection of patients at high risk of cognitive and functional deterioration as well as stroke recurrence.

Our findings hold several implications for future research. Firstly, there is a need for a user-friendly tool in clinical settings, for example, a fully automated approach with machine learning or a more comprehensive visual-rating scale, that captures the severity of individual SVD markers to increase PSCI prediction. Secondly, further investigation is warranted to understand peripheral blood-based biomarkers that are easily applicable for predicting PSCI. Although NfL and BD-tau have emerged as novel biomarkers from blood, showing specificity to brain injury, there is always a trade-off between sensitivity, specificity, and costs in clinical application. Additionally, future longitudinal clinical studies are needed to determine the impacts of IILs on SVD progression, and whether targeting SVD and IILs in the early post-stroke phase could mitigate or prevent PSCI.

3. Paper I

Marios K. Georgakis*, **Rong Fang***, Marco Düring, Frank A.Wollenweber, Felix J. Bode, Sebastian Stösser, Christine Kindler, Peter Hermann, Thomas G. Liman, Christian H. Nolte, Lucia Kerti, Benno Ikenberg, Kathleen Bernkopf, Holger Poppert, Wenzel Glanz, Valentina Perosa, Daniel Janowitz, Michael Wagner, Katja Neumann, Oliver Speck, Laura Dobisch, Emrah Düzel, Benno Gesierich, Anna Dewenter, Annika Spottke, Karin Waegemann, Michael Görtler, SilkeWunderlich, Matthias Endres, Inga Zerr, Gabor C. Petzold, Martin Dichgans on behalf of the DEMDAS investigators. Cerebral small vessel disease burden and cognitive and functional outcomes after stroke: a multicenter prospective cohort study. ***Alzheimers Dement.*** 2023;19(4):1152-1163.

* equally contributed

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RESEARCH ARTICLE

Cerebral small vessel disease burden and cognitive and functional outcomes after stroke: A multicenter prospective cohort study

Marios K. Georgakis[1] | Rong Fang[1] | Marco Düring[1,2] | Frank A. Wollenweber[1] | Felix J. Bode[3,4] | Sebastian Stösser[3,4] | Christine Kindlein[3,4] | Peter Hermann[5] | Thomas G. Liman[6,7] | Christian H. Nolte[6,7,8] | Lucia Kerti[7,9] | Benno Ikenberg[10] | Kathleen Bernkopf[10] | Holger Poppert[11] | Wenzel Glanz[12,13] | Valentina Perosa[12,13] | Daniel Janowitz[1] | Michael Wagner[3] | Katja Neumann[13] | Oliver Speck[13,14,15,16] | Laura Dobisch[13] | Emrah Düzel[13] | Benno Gesierich[1] | Anna Dewenter[1] | Annika Spottke[3,4] | Karin Waegemann[1,17] | Michael Görtler[12,13] | Silke Wunderlich[10] | Matthias Endres[6,7,9,18] | Inga Zerr[5,19] | Gabor Petzold[3,4] | Martin Dichgans[1,17] on behalf of the DEMDAS Investigators*

[1]Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany

[2]Medical Image Analysis Center (MIAC AG) and qbig, Department of Biomedical Engineering, University of Basel, Basel, Switzerland

[3]German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

[4]Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn, Germany

[5]Department of Neurology, University Medical Center Göttingen, Göttingen, Germany

[6]Department of Neurology with Experimental Neurology, Charité - Universitätsmedizin Berlin, Berlin, Germany

[7]German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany

[8]Berlin Institute of Health (BIH), Berlin, Germany

Abstract

Introduction: It remains unknown whether the global small vessel disease (SVD) burden predicts post-stroke outcomes.

Methods: In a prospective multicenter study of 666 ischemic and hemorrhagic stroke patients, we quantified magnetic resonance imaging (MRI)–based SVD markers (lacunes, white matter hyperintensities, microbleeds, perivascular spaces) and explored associations with 6- and 12-month cognitive (battery of 15 neuropsychological tests) and functional (modified Rankin scale) outcomes.

Results: A global SVD score (range 0–4) was associated with cognitive impairment; worse performance in executive function, attention, language, and visuospatial ability; and worse functional outcome across a 12-month follow-up. Although the global SVD score did not improve prediction, individual SVD markers, assessed across their severity range, improved the calibration, discrimination, and reclassification of predictive models including demographic, clinical, and other imaging factors.

Discussion: SVD presence and severity are associated with worse cognitive and functional outcomes 12 months after stroke. Assessing SVD severity may aid prognostication for stroke patients.

Marios K. Georgakis and Rong Fang contributed equally to this work.

*Names and affiliations of DEMDAS investigators are listed in the supplement (Table S23).

[9]Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin, Berlin, Germany

[10]Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany

[11]Department of Neurology, Helios Klinikum München West, Munich, Germany

[12]Department of Neurology, University Hospital, Otto-von-Guericke University Magdeburg, Magdeburg, Germany

[13]German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany

[14]Department of Biomedical Magnetic Resonance, Institute for Physics, Otto-von-Guericke University Magdeburg, Magdeburg, Germany

[15]Leibniz Institute for Neurobiology, Magdeburg, Germany

[16]Center for Behavioral Brain Sciences, Magdeburg, Germany

[17]German Center for Neurodegenerative Diseases (DZNE), Munich, Germany

[18]German Centre for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany

[19]German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany

Correspondence
Martin Dichgans, Institute for Stroke and Dementia Research, University Hospital LMU, Ludwig-Maximilians-University (LMU), Feodor-Lynen-Str. 17, 81377 Munich, Germany.
Email: martin.dichgans@med.uni-muenchen.de

KEYWORDS
cerebral small vessel disease, cognitive impairment, functional outcome, prediction, stroke

Highlights

- In a multi-center cohort, we explored associations of small vessel disease (SVD) burden with stroke outcomes.
- SVD burden associates with post-stroke cognitive and functional outcomes.
- A currently used score of SVD burden does not improve the prediction of poor outcomes.
- Assessing the severity of SVD lesions adds predictive value beyond known predictors.
- To add predictive value in assessing SVD in stroke patients, SVD burden scores should integrate lesion severity.

1 | INTRODUCTION

The ever-growing proportion of stroke survivors worldwide[1] has shifted attention from early complications in the acute phase to long-term consequences after stroke.[2–4] Cognitive and functional deficits are present in up to 80% of stroke survivors, depending on the definition and timepoint of assessment.[3,5–7] These deficits are associated with disability,[8,9] dependency,[10] and morbidity,[11,12] thus posing a major burden to patients, caregivers, and health care systems. A more detailed understanding of the factors that predispose to long-term outcomes is required to counsel patients and to identify high-risk individuals who might benefit from targeted interventions.

Cerebral small vessel disease (SVD) accounts for ~25% of all strokes[13,14] and is the leading cause of vascular dementia.[15] Imaging features of SVD on magnetic resonance imaging (MRI) include lacunes, white matter hyperintensities (WMHs), cerebral microbleeds (CMBs), and enlarged perivascular spaces (PVSs).[16,17] Compared to the general population, stroke patients have a higher burden of SVD.[18,19] Individual SVD markers are associated with worse outcomes including higher risk for dementia, disability, stroke recurrence, and death,[19–21] but their combined predictive value has not been explored systematically. As such, SVD measures have attracted attention both as a traceable risk factor and a predictor of poor outcomes post-stroke.

More recent studies have focused on integrative measures of global SVD burden, which are generated by quantifying the burden of individual lesions (lacunes, WMHs, CMBs, and enlarged PVSs) and combining them into a single score.[22–24] The MRI-based global SVD[25] score ranges from 0 to 4 (one point awarded for presence of each of the four SVD markers) and is strongly associated with cognitive performance[26] and risk of dementia in the general population.[27] Yet its performance for predicting cognitive and functional outcomes in stroke patients remains poorly defined. Previous studies focused on specific patient subgroups, such as patients with lacunar stroke[28] or those receiving thrombolysis,[29] used cognitive screening instruments rather than detailed neuropsychological testing for outcome assessments,[30,31] and had a short follow-up interval of 6 months post-stroke when recovery is still underway.[28,29,31] In addition, the predictive performance of assessing a global SVD score has not been compared to visual rating scores for the severity of individual SVD markers.[30,31]

Here we set out to determine whether the global burden of SVD assessed on baseline MRI predicts cognitive and functional outcomes up to 12 months after stroke. We explored the associations of the global SVD score, as well as individual SVD markers, with cognitive and functional end points. Furthermore, we tested the predictive value of the global SVD score for cognitive and functional impairment beyond known outcome predictors post-stroke and compared it to the predictive value gained by individual SVD markers. To address these aims, we used data from a prospective multicenter study in 736 ischemic and hemorrhagic stroke survivors, which was designed to identify predictors of long-term cognitive outcomes post-stroke.

RESEARCH IN CONTEXT

1. **Systematic review**: Our search in MEDLINE yielded multiple studies that have shown associations between neuroimaging markers of cerebral small vessel disease (SVD) and poor post-stroke outcomes. However, whether a global score of SVD burden that integrates different individual markers is associated with cognitive and functional outcomes after stroke has not been explored systematically.
2. **Interpretation**: Beyond individual lesions, SVD burden is associated with worse cognitive and functional outcomes 12 months after stroke. However, our results indicate that the currently used global SVD score does not improve the prediction of poor outcomes, partly because it does not consider the severity of individual SVD lesions.
3. **Future directions**: To add predictive value in assessing SVD burden in patients with stroke and to improve prognostication of poor cognitive and functional outcomes, future studies should aim to develop a global SVD score that integrates individual lesion severity.

2 | METHODS

2.1 | Study population

Participants for the current study were drawn from the DEMDAS study (DZNE [German Center for Neurodegenerative Disease]-Mechanisms of Dementia After Stroke), a multicenter prospective hospital-based cohort study conducted across seven tertiary stroke centers in Germany. The study began as a single-center pilot study at Ludwig-Maximilians-University (LMU) Munich, Germany (DEDEMAS [Determinants of Dementia After Stroke]; NCT01334749), which enrolled 136 patients between May 2011 and November 2013 and was subsequently expanded to the multicenter study (DEMDAS) with enrollment of an additional 600 patients between January 2014 and January 2019. Details on the study protocol and DEDEMAS have been published previously.[32,33] A detailed description of the clinical and imaging protocols of the two studies is provided in the Supplement (Supplementary methods, Tables S1, S2, Figures S1, S2).

We recruited patients ≥18 years of age who were hospitalized for acute stroke with symptom onset within the last 5 days before admission, as defined by an acute focal neurological deficit in combination with an acute ischemic infarct and as documented by either a diffusion-weighted imaging (DWI)–positive lesion on cranial MRI, a new lesion on a delayed computed tomography (CT), or a hemorrhagic stroke as documented on CT or MRI. Eligible patients needed to have an available informant. Because the target population was patients with acute stroke and no pre-stroke dementia, prior stroke was not an exclusion criterion for this study. Patients were excluded if they had a diagnosis of dementia or if they scored >64 on a screening Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[34] with the informant at recruitment. Furthermore, we excluded patients with shortened life expectancy due to a diagnosis of a malignant disease; patients with contraindications for MRI; and patients with cerebral venous thrombosis, traumatic cerebral hemorrhage, intracerebral hemorrhage because of a vascular malformation, or purely meningeal or intraventricular hemorrhage.

2.2 | Standard protocol approvals, registrations, patient consent, and data availability

The current study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[35] DEDEMAS and DEMDAS were conducted according to the Declaration of Helsinki and were approved by the local ethics committees of all participating sites. All patients or their legal guardians provided written informed consent prior to study inclusion. Anonymized data are available upon reasonable request to the corresponding author.

2.3 | Baseline assessments

Study participants underwent a comprehensive interview using standardized questionnaires as well as clinical, cognitive, and laboratory assessments. Detailed information on sociodemographic data, family and medical history, and prescribed medications were recorded. Assessments further included physiological (e.g., blood pressure and body mass index measurement), clinical (e.g., National Institutes of Health Stroke Scale [NIHSS], Modified Rankin Scale [mRS], Glasgow Coma Scale [GCS]), and cognitive screening tests (Mini-Mental State Examination [MMSE] and Montreal Cognitive Assessment [MoCA]). Peripheral blood was drawn from all enrolled patients within a median of 1 day (interquartile range: 1—2 days) after stroke (>85% of samples were drawn in the morning) and biochemical assessments were performed as part of clinical routine.

2.4 | MRI acquisition, stroke lesion volume, and SVD score

Patients underwent cranial 3-Tesla MRI examinations within 3 (DEDEMAS) or 5 (DEMDAS) days of stroke onset. Details on the imaging protocols are provided in the Supplement (Supplementary methods, Table S2). Acute stroke lesions were segmented on DWI images using a semi-automated procedure detailed in the Supplementary methods. Stroke lesion volume was normalized by total intracranial volume as measured from T1 images. We semi-quantitatively assessed SVD markers on baseline MRI using widely accepted consensus criteria.[17,25] The following individual SVD markers were assessed: (1) lacunes: a lacune was defined as a round or ovoid, subcortical, cerebrospinal fluid (CSF)-like signal lesion with an axial diameter between 3 mm to 15 mm on fluid-attenuated inversion recovery (FLAIR) and T1-weighted images; (2) white matter hyperintensities (or WMHs): periventricular and deep WMH lesions were graded from 0 to 3 according to the Fazekas scale[36] on FLAIR images; (3) cerebral microbleeds (or CMBs): small (2–10 mm), round signal voids on T2*-weighted images; (4) enlarged perivascular spaces (PVSs) in basal ganglia: PVSs are fluid-filled spaces that are visible as either linear or round/ovoid high signals on T2-weighted and low-signals on T1-weighted images (CSF–like signal) of an axial diameter <3 mm that follow the orientation of penetrating arterioles in basal ganglia and centrum semiovale.[37] PVSs were counted bilaterally in the basal ganglia, and the side with the higher number on T2-weighted and T1-weighted images was used for scoring, in line with Staals et al.[25] and according to a method first proposed by MacLullich et al.[38]: 0 = no PVSs, 1 = < 10 PVSs, 2 = 11 to 20 PVSs, 3 = 21 to 40 PVSs, and 4 = > 40 PVSs.[37] Lacunes, WMHs, CMBs, and PVSs within the stroke lesion were not considered when rating the images. All images were rated by an experienced, trained rater (R.F.) without knowledge of the clinical data, and doubtful cases were discussed with a senior imaging specialist (M.Dür.) in regular consensus meetings. To ensure the reproducibility of the ratings, inter-rater reliabilities were assessed by two trained raters (R.F. and A.D.) in a sub-sample of the images: κ for lacunes = 0.720, κ for WMHs = 0.795, κ for CMBs = 0.725, and κ for PVSs = 0.815. For each participant, we quantified the global cerebral SVD burden using a previously validated score ranging from 0 to 4.[25,37] One point was allocated for each of the following lesions (Table S3): (1) presence of lacunes, (2) periventricular WMH Fazekas grade 3 or deep WMH Fazekas grade 2 or 3, (3) presence of CMBs, and (4) PVS grade 2 or higher.

2.5 | Follow-up outcomes

Study participants underwent comprehensive cognitive and functional assessments by face-to-face interviews at 6 and 12 months post-stroke. A comprehensive neuropsychological battery of tests was performed and classified in five domains (executive function, memory, language, attention, and visuospatial function; Table S1, Supplementary methods). The memory domain was a composite of word-learning, recall, recognition, and figure-immediate and delayed recall tests. Missing values for individual tests, along with reasons for missingness are presented in Tables S4–S6. We calculated test-specific *z*-scores based on published norms corrected for age, sex, and education ("Neuropsychological test battery" section in Supplementary methods). We then calculated domain-specific z-scores by averaging the available test-specific *z*-scores per domain, as well as an average global cognitive score by averaging z-scores of five domains.[39] A z-score of < −1.5 in any of five domains was used to define cognitive impairment.[39] Definitions of domain-specific cognitive impairment were likewise based on domain-specific z scores of < −1.5. Functional outcomes were assessed with the modified Rankin scale (or mRS), a global functional scale focused on motor recovery (score range from 0 [no symptoms] to 5 [serious functional impairment]), the Barthel index (BI), which evaluates functional dependence (score range from 0 [fully dependent] to 100 [fully independent]),[40,41] and the instrumental activities of daily living (IADLs), which evaluates independence in eight daily activities (score range from 0 [no independence at any task] to 8 [full independence]).[33] For all tests, information from the patients and their informants was considered. We used two independent definitions of different levels of functional impairment based on two widely applied cutoffs of mRS (>1 and >2).[12,42,43]

2.6 | Statistical analysis

We compared baseline characteristics of study participants using χ^2 or Fisher exact test for categorical variables, a two-tailed *t*-test for variables following a normal distribution (age and body mass index) or Mann–Whitney *U* test for other continuous variables. To account for the repeated assessments of the main outcomes at two follow-up timepoints, we applied generalized estimating equations (GEE) models to explore associations between baseline SVD lesions and cognitive and functional outcomes at 6 and 12 months after stroke. We tested (1) the global SVD score (range 0–4), (2) the four constituent sub-scores (0 or 1 for lacune presence, periventricular WMH grade >2 or deep WMH grade ≥2, CMB presence, PVS grade ≥2), and (3) the five individual SVD markers in their entire range (lacune counts, periventricular WMH grade, deep WMH grade, CMB counts, PVS grade). Using GEE, we fit generalized linear regression models for continuous cognitive and functional outcomes (*z*-scores for global cognitive performance and the five individual domains, mRS, IADL, BI) and logistic regression for binary outcomes (cognitive impairment: z-score < −1.5 in global cognitive performance or individual domains; functional impairment: mRS >1 and mRS >2). To explore the associations between baseline global SVD score and cognitive and functional outcomes at individual timepoints, we applied multiple linear and multivariable logistic regression analyses. We adjusted for age, sex, and educational years (basic model), as well as for cardiovascular risk factors (history of hypertension, diabetes, atrial fibrillation, prior stroke, current smoking, alcohol consumption, body mass index, circulating low-density lipoprotein cholesterol [LDL-C] levels), stroke severity (NIHSS score at baseline), pre-stroke mRS, cognitive impairment in the acute post-stroke phase (MoCA <26 or MMSE <24 if MoCA not available), and

normalized stroke lesion volume at baseline (main model). These factors were selected, as they have previously been reported to be associated with post-stroke outcomes.[6,31,33,44,45] In sensitivity analyses we also adjusted for apolipoprotein E (*APOE*) genotype (0, 1, or 2 ε4 alleles).

To examine the value of assessing the global SVD score for predicting cognitive and functional impairment at 6 and 12 months after stroke,[46] we compared the performance of different logistic regression models: Model 1 included age, sex, education, vascular risk factors, NIHSS, and cognitive impairment in the acute phase; pre-stroke mRS; and normalized stroke lesion volume. Model 2 additionally included the global SVD score. Model 3 included individual SVD markers instead of the global SVD score. We tested model calibration with the Hosmer-Lemeshow test and compared the models with the integrated calibration index (ICI),[47] which is a commonly used method, derived by Loess-based smoothing function between the observed frequency of events and predicted risk from the models.[47] For discrimination, we compared areas under the receiver-operating characteristic (ROC) curves. Finally, we tested changes in reclassification between the models with the Net Reclassification Index (NRI).[48] We considered individuals at high risk for cognitive or functional impairment when their predicted risk was ≥30% and at low risk when their predicted risk was <10%. To account for multiple comparisons, we adjusted *P*-values using the false discovery rate (FDR) method and set statistical significance at an FDR-adjusted $P < .05$. Statistical analyses were performed with R v4.0.4.

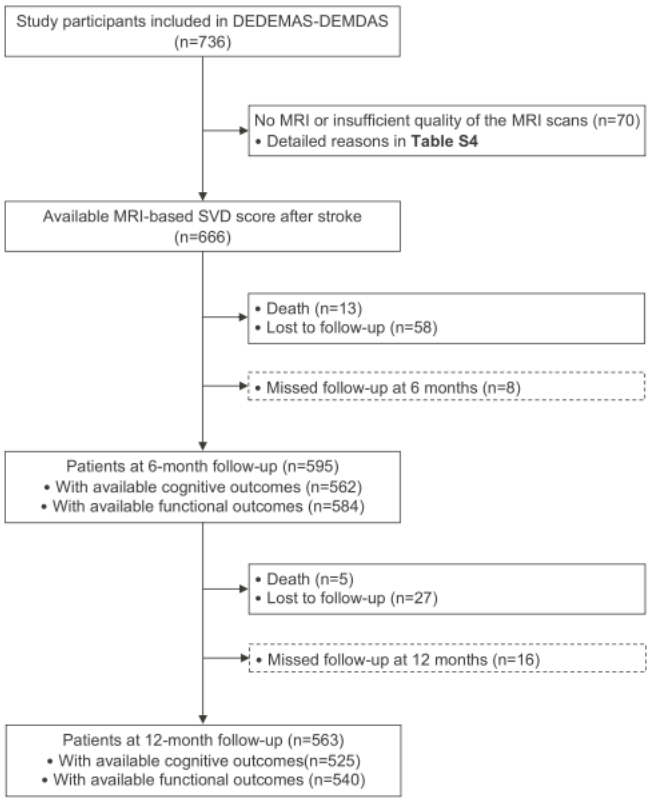

FIGURE 1 Flowchart of study participants and follow-up in the current study. DEDEMAS, Determinants of Dementia After Stroke; DEMDAS, DZNE (German Center for Neurodegenerative Diseases)-Mechanisms of Dementia After Stroke; MRI, magnetic resonance imaging; SVD, small vessel disease.

3 | RESULTS

3.1 | Baseline characteristics and imaging features

A total of 736 participants were recruited at admission (for baseline characteristics see Table S7); 666 of them had baseline MRI scans suitable for a complete assessment of SVD lesions and were thus included in the current analyses (Figure 1). The most common reasons for missing MRI scans were unavailability of the scanner or patient refusal (Table S8). We found no significant differences at baseline between participants with and without a baseline MRI (Table S9).

The baseline characteristics of study participants entering the analyses are presented in Table 1 (mean age 67.9 ± SD 11.4 years, 66.7% men). Of the study participants, 10.7% had a prior history of stroke and their median mRS before the index event was 0 (IQR 0–0). The vast majority of index events represented ischemic strokes (97.3%), with a median NIHSS score at admission of 2 (IQR 1–5). The distribution of stroke lesions across vascular territories and the distribution of normalized lesion volumes are presented in Table S10 and Figure S3, respectively. Differences in demographics and cardiovascular risk profile between male and female study participants are presented in Table S11. Baseline characteristics were largely similar between the run-in DEDEMAS study and the multicenter expansion of DEMDAS, as well as across centers (Table S12), except for higher LDL-C levels in participants recruited to DEDEMAS.

The frequency and burden of individual SVD markers is displayed in Figure 2. The most common SVD marker was WMH (46.8% of study participants had a Fazekas grade of ≥2 for deep lesions or >2 for periventricular lesions) followed by PVS (35.6% had a grade of ≥2 in the basal ganglia), lacunes (12.8%) and CMB (9.8%). When combined into the global SVD score, 38.9% of the participants had an overall score of 0 (no SVD lesions fulfilling the score criteria), 30.2% had a score of 1 (a single lesion type), 20.4% had a score of 2 (two lesion types), and only 8.1% and 2.4% of the participants had scores of 3 and 4, respectively.

3.2 | Association between global SVD score and cognitive and functional outcomes

A total of 595 (89%) and 563 (85%) participants were followed up at 6 or 12 months, respectively, after stroke and were thus included in our analyses (Figure 1, Method S1). Patients who died or were lost to follow-up were older, had a higher systolic blood pressure at baseline, and had a higher rate of cognitive impairment, as defined by their baseline MoCA scores (MoCA <26) (Table S13). At 6 months, 148 (27.6%) of the study participants met the criteria for cognitive impairment, 127 (21.7%) had an mRS score >1, and 50 (8.6%) had an mRS score >2, thus meeting one of the criteria for functional impairment. Cognitive

TABLE 1 Baseline characteristics of patients included in the analysis

Variables	*n* = 666
Demographic variables	
Age, *y*	67.9 ± 11.4
Male, *n* (%)	444 (66.7)
Education, *y*	13 (12–16)
Cardiovascular risk factors	
Hypertension, *n* (%)	515 (77.3)
Diabetes mellitus, *n* (%)	131 (19.7)
Current smoking, *n* (%)	155 (23.3)
Regular alcohol consumption,[a] *n* (%)	498 (74.8)
Atrial fibrillation, *n* (%)	133 (20.0)
Prior history of stroke, *n* (%)	71 (10.7)
BMI, kg/m^2	27.0 ± 4.3
SBP, mm Hg	140 (129–150)
DBP, mm Hg	80 (72–87)
HbA1c, %	5.7 (5.4–6.1)
LDL-C, mg/dL	126 (103, 154)
HDL-C, md/dL	48 (40–58)
Triglycerides, mg/dL	122 (92–170)
APOE genotype (*n* = 529), *n* (%)	
0 ε4 allele	421 (79.6)
1 ε4 allele	107 (20.2)
2 ε4 alleles	6 (1.1)
Index stroke classification, *n* (%)	
Ischemic stroke	648 (97.3)
TOAST subtype, *n* (%)	
Large artery atherosclerosis	172 (26.5)
Cardioembolism	144 (22.2)
Small artery occlusion	77 (11.9)
Other etiology	30 (4.6)
Undefined etiology	224 (34.6)
Hemorrhagic stroke	18 (2.7)
Clinical/cognitive assessment	
NIHSS score	2 (1–5)
mRS before stroke	0 (0–0)
BI score	100 (80–100)
IQCODE score	48 (48–49)
Baseline cognitive impairment,[b] (*n* = 643), *n* (%)	337 (52.4)
MRI variables	
Stroke lesion volume (mm3)	2248 (520, 11760)
Normalized stroke lesion volume[c] (%)	0.15 (0.03–0.77)

Note: Values are expressed as *n* (%), mean ± SD, or median (interquartile range).

Abbreviations: *APOE*, apolipoprotein E; BI, Barthel index; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; LDL-C, low-density lipoprotein cholesterol; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

[a]From a self-reported questionnaire.

[b]MoCA <26 or Mini-Mental Status Examination (MMSE) <24 when MoCA was not available (5.3% of total).

[c]Stroke lesion volume/total intracranial volume.

and functional outcomes both improved between 6 and 12 months after stroke. The proportion of individuals with cognitive impairment, an mRS >1, and an mRS >2 at 12 months, was 19.2% (*N* = 97), 19.8% (*N* = 107), and 5.9% (*N* = 32), respectively. As illustrated in Figure 3, patients with a higher global SVD score at baseline also scored lower in cognitive tests and higher in mRS at both 6 and 12 months after follow-up. Notably, the improvement from 6 to 12 months was evident across patient subgroups stratified by global SVD.

Baseline global SVD score was associated with both a worse cognitive performance and a higher mRS score across the 12 months of follow-up after adjustment for demographic characteristics, vascular risk factors, and index stroke features (beta for cognitive performance: −0.08, 95% confidence interval [CI]: −0.14 to −0.03, *P* = .005; beta for mRS: 0.14, 95% CI: 0.06 to 0.22, *P* = .0006, Figure 3C). Looking at binary outcomes, we likewise found significant associations between the baseline SVD score and global cognitive impairment (odds ratio [OR]: 1.31, 95% CI: 1.09, 1.58; *P* = .005), as well as functional impairment, defined either as mRS >1 (OR: 1.34, 95% CI: 1.13 to 1.60, *P* = .0009) or mRS >2 (OR: 1.42, 95% CI: 1.08 to 1.86, *P* = .01, Figure 3D). The analyses for individual cognitive domains revealed significant associations between the baseline global SVD score and performance in executive function and attention (Figure S4). Looking at binary outcomes, we found the baseline global SVD score to be significantly associated with impairment in all of the examined domains except memory (Figure S5).

The results were largely consistent across sensitivity analyses (Figures S4–S7). Specifically, the significant associations remained stable when adjusting only for age, sex, and education; when adjusting for *APOE* genotype on top of demographic, clinical, and imaging predictors; and when examining associations with the study outcomes at 6 and 12 months separately. The baseline global SVD score was not associated with changes in global cognitive performance or mRS from 6 to 12 months after stroke (*P* = .8183 and *P* = .1969, respectively; Figure S8).

3.3 | Individual SVD markers in association with cognitive and functional outcomes

We next explored the associations between the presence and extent of individual SVD lesions and cognitive and functional outcomes post-stroke (Figure 4). Following correction for multiple testing, no significant associations were noted between any of the four constituent sub-scores of the global SVD score (binary variables for each SVD marker) and any of the continuous or binary cognitive and functional outcomes across the first 12 months of follow-up. In contrast, there were multiple significant associations between individual SVD markers and study outcomes when SVD markers were analyzed in their entire severity range. Overall, lacune count showed the strongest associations, with significant associations for global cognitive score, domain-specific cognitive scores, mRS score, and the corresponding binary outcomes (all except memory). Both deep and periventricular WMH grades showed significant

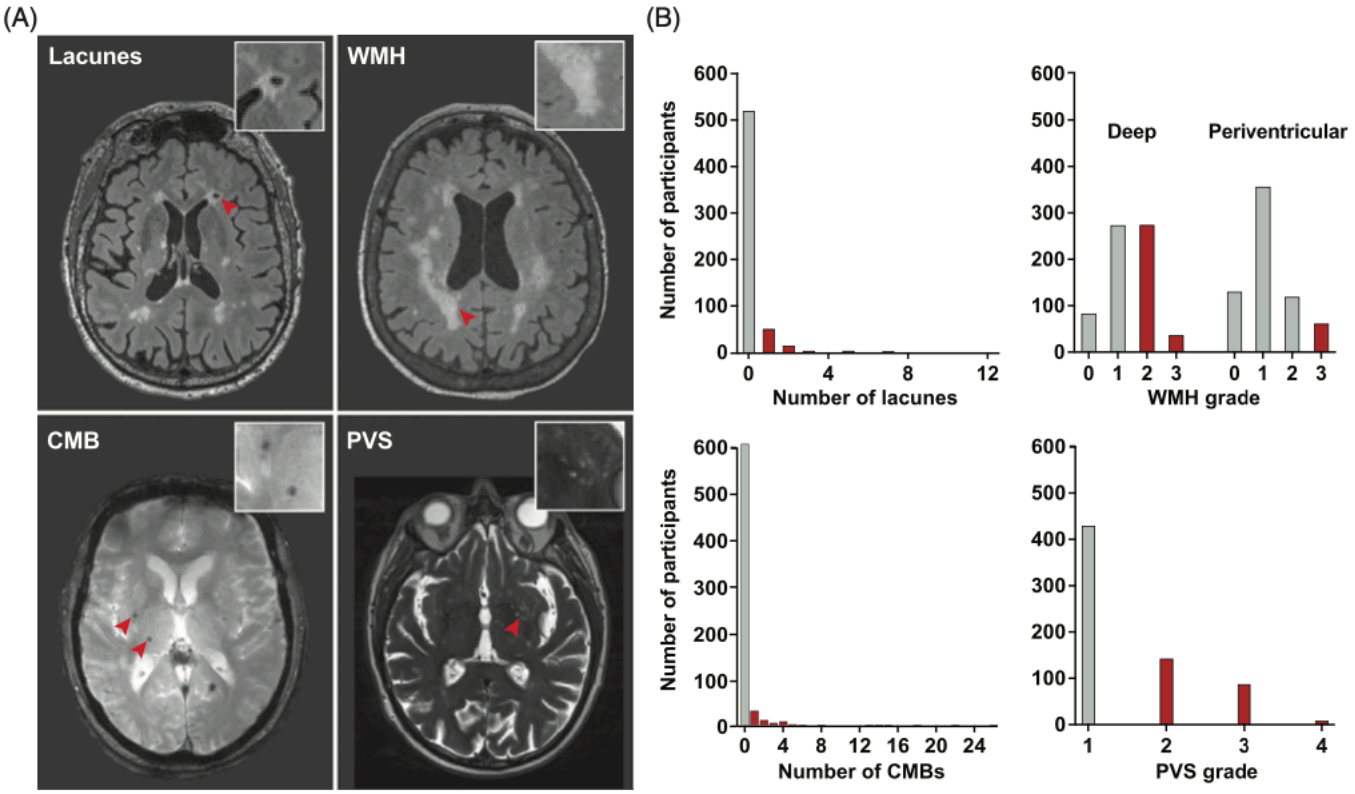

FIGURE 2 Magnetic resonance imaging (MRI) markers of cerebral small vessel disease (SVD) and the distribution of individual lesion types across the study population. (A) Representative images from patients included into the DEDEMAS (Determinants of Dementia After Stroke)-DEMDAS (DZNE [German Center for Neurodegenerative Diseases]-Mechanisms of Dementia After Stroke) study showing a lacune on axial fluid-attenuated inversion recovery (FLAIR) sequences, extensive white matter hyperintensities (WMHs) on FLAIR sequences, cerebral microbleeds (CMBs) on gradient echo T2-weighted (T2*) axial sequences, and enlarged perivascular spaces (PVSs) on T2-weighted images. The lesions are indicated by the arrowheads and also shown in enlargement in the upper corners of the respective images. (B) Distribution of individual lesion types across the study participants. Red bars represent the values that are given a point in the global SVD score (range of total score 0–4). WMHs were rated with the Fazekas scale and PVSs as recommended by Doubal et al.[37]

associations with worse outcomes in global cognition, executive function, attention, visuospatial ability, and functional status. CMB count was associated with a worse score in executive function on a continuous scale, whereas PVS grade was associated with functional impairment (Figure 4).

We further explored associations between SVD and cognitive and functional outcomes separately for strokes in the left and right hemispheres, which showed similar results (Figures S9, S10). When we adjusted additionally for a surrogate lesion location score capturing the impact of strategic stroke locations on risk of post-stroke cognitive impairment,[49] the results were still consistent with those derived from our main models (Figure S11). To explore whether our results are robust to the presence of brain atrophy at the time of the stroke, we also adjusted our models for normalized whole brain volume, which returned highly consistent estimates (Figure S12). Excluding patients with a history of pre-stroke mood, anxiety, or psychotic disorders or further adjusting for depression (the Center for Epidemiological Studies-Depression) and apathy (Starkstein Apathy Scale), scores at 6 and 12 months after stroke also did not materially influence our results (Figures S13—S15). Finally, adjustments for study site did not change our main findings (Figure S16).

Predictive value of SVD burden for cognitive and functional outcomes

As a final step, we explored the value of assessing the global SVD score for predicting binary outcomes beyond well-established predictors, and how predictive models including the global SVD score perform in comparison with models considering the severity of individual SVD lesions. We compared the calibration, discrimination, and classification change between a model of established demographic, clinical, and imaging predictors (model 1), a model also including the global SVD score (model 2), and a model including all individual SVD markers across their severity range instead of the global SVD score (model 3).

Although the overall calibration of all models was good (all Hosmer-Lemeshow–derived goodness-of-fit $P > .05$, Table S19), model 3 that included the individual SVD markers showed a significantly better calibration for the prediction of both cognitive and functional impairment (defined by an mRS >1) at 12 months when compared to both model 1 and model 2 (Figure 5A). Similarly, model 3 improved discrimination significantly for prediction of cognitive impairment at 12 months post-stroke, as demonstrated by areas under the curve when compared to model 1 ($c = 0.72$, 95% CI: 0.66 to 0.78 vs 0.69,

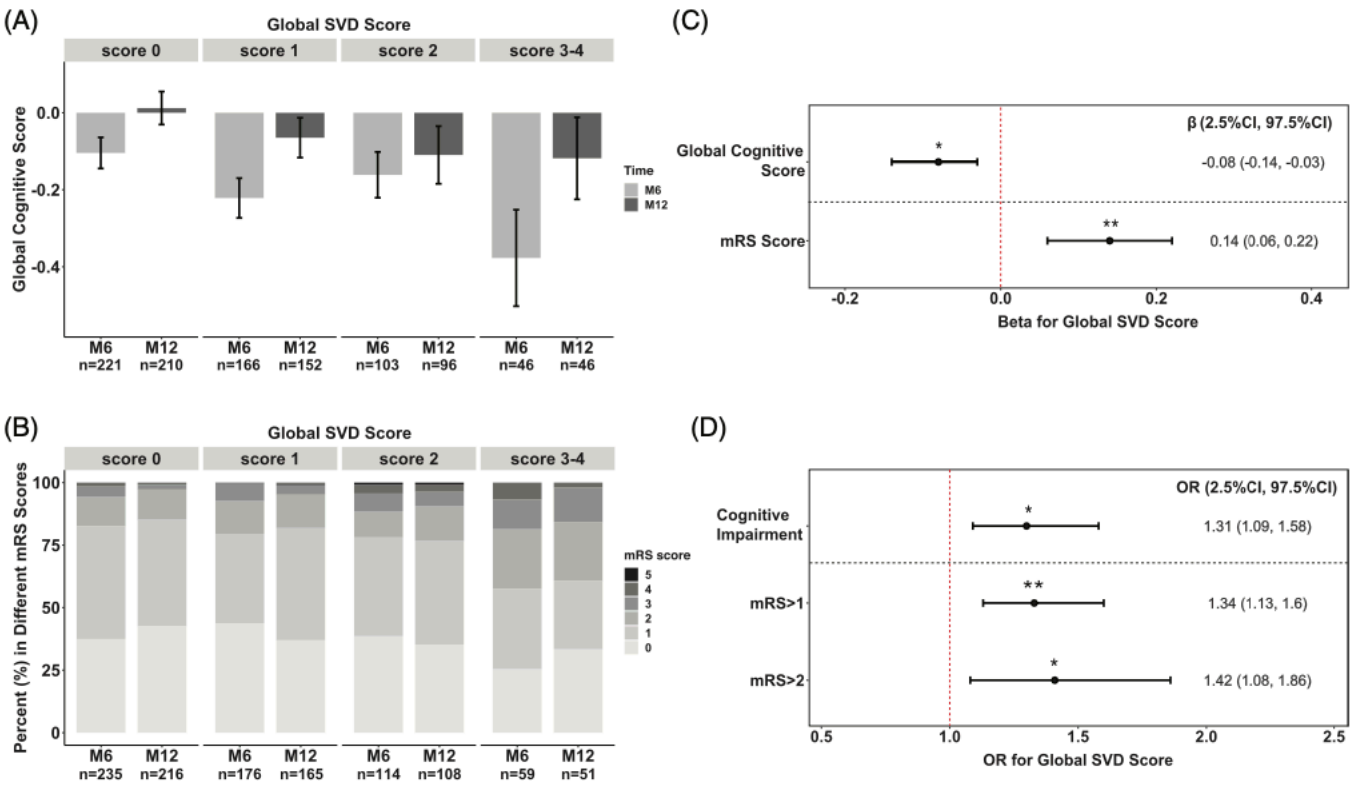

FIGURE 3 Associations between baseline global cerebral small vessel disease (SVD) score (1-point increment, range 0–4) and cognitive and functional outcomes across 12 months of follow-up after stroke. (A) Mean composite z-score of global cognitive performance at 6 (M6) and 12 months (M12) after stroke across categories of the global SVD score as assessed at baseline magnetic resonance imaging (MRI). Error bar represents standard error (SE) of the mean in each bar. (B) Distribution of the modified Rankin scale (mRS) scores across study participants at M6 and M12 across categories of the global SVD score as assessed at baseline MRI. (C) Associations of global SVD scores with global cognitive scores (composite z-score across five cognitive domains) and modified Rankin scale (mRS) scores across 12 months of follow-up incorporating both 6- and 12-month outcomes in linear generalized estimating equation (GEE) models adjusted for age, sex, education, vascular risk factors, National Institutes of Health Stroke Scale (NIHSS), and Montreal Cognitive Assessment (MoCA) in the acute phase, pre-stroke mRS, and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). The association estimates represent betas (β's) and their 95% confidence intervals (CIs). (D) Associations of global SVD scores with cognitive impairment (composite z-score < -1.5 or $z < -1.5$ in any individual cognitive domain) and functional impairment (mRS >1 or mRS >2) across 12 months of follow-up after stroke incorporating both 6- and 12-month outcomes in logistic GEE models adjusted for the abovementioned variables. The association estimates represent odds ratios (ORs) and their 95% CIs. *P*-values are corrected for multiple comparisons with the false discovery rate (FDR) method. **Pcorr.* < .05, ***Pcorr.* < .01

95% CI: 0.63 to 0.75; $P = .036$, Figure 5B). In contrast, we found no evidence of improved calibration or discrimination for cognitive impairment or functional impairment at 6 or 12 months when comparing model 2 that included the global SVD score with model 1 (Figure 5B, Figure S17, Table S20). Finally, we tested the reclassification changes between the three models Tables (S21, S22). Again, model 3 including individual SVD lesions outperformed model 1 and model 2 including the global SVD score in correctly reclassifying patients between low (<10%), intermediate (10% to <30%), and high risk (≥30%) for cognitive and functional impairment at 12 months.

4 | DISCUSSION

In this multicenter cohort of acute stroke patients, we found that the presence and severity of SVD burden on baseline MRI is associated with poor post-stroke cognitive and functional outcomes. Specifically, we found that both a global SVD burden score and individual SVD markers (lacune count, WMH grade, CMB count, PVS grade) are associated with cognitive and functional impairment up to 12 months after stroke. Patients with a higher SVD burden at baseline performed worse in executive function, attention, language, and visuospatial ability across 12 months after stroke. Although the global SVD score did not improve prediction on top of demographic, clinical, and imaging factors, we found that considering individual SVD markers throughout their severity range led to better calibration, discrimination, and reclassification of predictive models for post-stroke cognitive and functional impairment. Collectively, our results provide further evidence for a detrimental role of SVD for post-stroke outcomes, but also highlight the need for a more accurate assessment of global SVD burden to improve prognostication for acute stroke patients.

Our findings extend the previous literature on the prognostic role of SVD markers in stroke patients.[22–24] Specifically, they support an additive effect of individual SVD lesions on post-stroke cognitive and

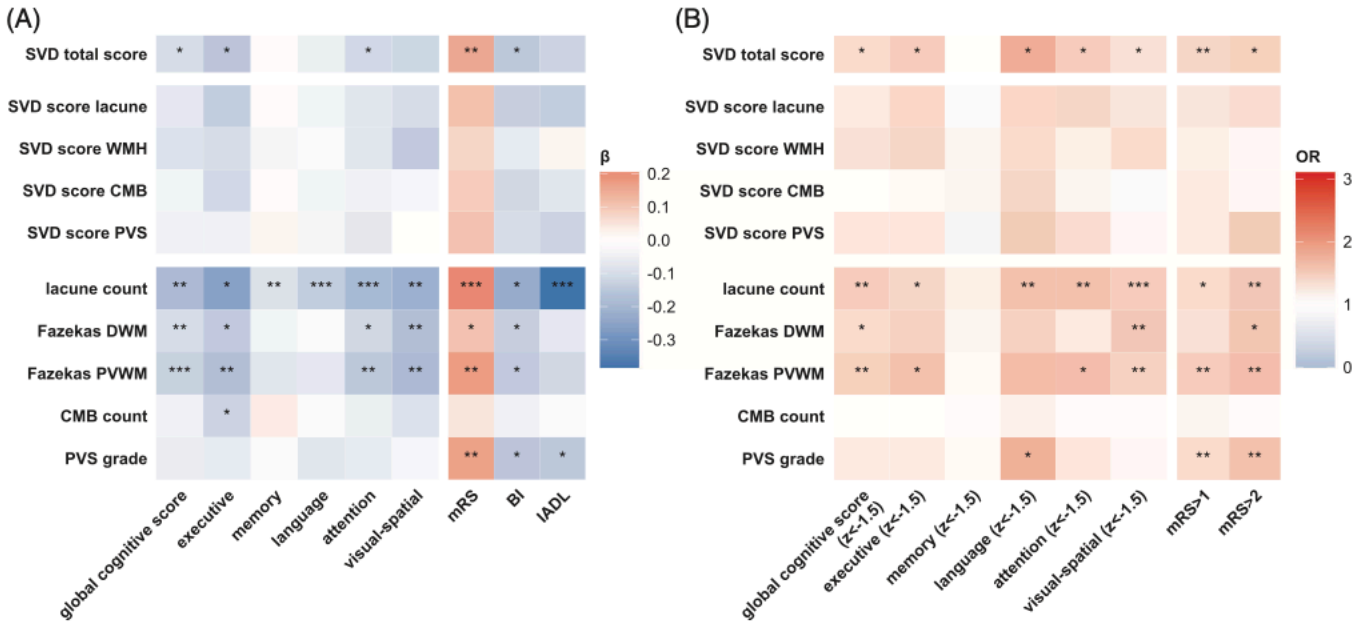

FIGURE 4 Heatmaps of the associations of global cerebral small vessel disease (SVD) score (1-point increment, range 0–4), individual components of the score (presence vs absence), and individual SVD lesion burden with cognitive and functional outcomes over 12 months of follow-up after stroke. (A) Associations with continuous outcomes: global cognitive score (composite *z*-score across five cognitive domains), individual cognitive domain scores, modified Rankin scale (mRS), Barthel index (BI), and instrumental activities of daily living (IADLs) across 12 months of follow-up after stroke. The heatmap includes standardized betas (β's) and their 95% confidence intervals (CIs) derived from generalized linear generalized estimating equation (GEE) models adjusted for age, sex, education, vascular risk factors, National Institutes of Health Stroke Scale (NIHSS), and Montreal Cognitive Assessment (MoCA) in the acute phase, pre-stroke mRS, and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). (B) Associations with binary outcomes: global cognitive impairment (composite *z*-score < -1.5 or $z < -1.5$ in any individual cognitive domain) or cognitive impairment across each individual domains and functional impairment (mRS >1 or mRS >2) across 12 months of follow-up after stroke. The heatmap includes standardized odds ratios (ORs) and their 95% confidence intervals (CIs) derived from logistic GEE models adjusted for the abovementioned variables. *P*-values are corrected for multiple comparisons with the false discovery rate (FDR) method. NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal Cognitive Assessment. $^{*}P_{corr.} < .05$, $^{**}P_{corr.} < .01$, and $^{***}P_{corr.} < .001$

functional outcomes, as captured by a widely used global SVD score.[50] Despite the significant associations, this score did not add value for predicting cognitive and functional outcomes up to 12 months, in line with a previous study examining outcomes at 6 months post-stroke.[31] However, a deeper exploration revealed that a model considering the severity rather than presence of individual SVD lesions improves prediction. This suggests that a simple approach of awarding one point for the presence of each of the four hallmarks of SVD without considering the severity of individual lesion types results in a loss of relevant information. The finding has implications for future research, as it highlights the requirement to develop more efficient tools for SVD burden quantification. Such tools should ideally be both convenient to use in clinical practice and informative, including, for example, accurate and automated segmentation by machine-learning technologies, or a more detailed visual-rating scale that considers lesion severity. Such tools could inform analyses in observational studies that test predictive models for vascular cognitive impairment and the design of clinical trials that target SVD progression to ameliorate poor long-term outcomes.

Beyond clinical predictive purposes, our results provide further support that SVD is an independent risk factor for post-stroke outcomes. Individual lesions contribute independently to poor outcomes and there seems to be a dose-response relationship for all lesion types, with the strongest dose relationship seen for lacune count. Although these results from an observational analysis cannot provide evidence of causality, we believe that the high consistency of these associations with the results from previous studies[19,20] is an indication that targeting SVD progression in stroke patients with SVD lesions at baseline might favorably influence cognitive outcomes. This is not yet part of post-stroke clinical care, but the Systolic Blood Pressure Intervention Trial-Memory and cognition IN Decreased hypertension (SPRINT-MIND) trial demonstrated that intensive blood pressure lowering in hypertensive adults without a history of diabetes or stroke can halt the progression of WMH volume[51] and lower the risk of mild cognitive impairment.[52] Studies incorporating serial imaging are needed to examine the associations between SVD progression and post-stroke cognitive outcomes.

Our study has several methodological strengths. The results were derived from a prospective multicenter study that was designed specifically to identify predictors of post-stroke cognitive impairment and disability. As such, all enrolled patients underwent a 3-Tesla MRI examination using a state-of-the-art, high-quality imaging protocol that

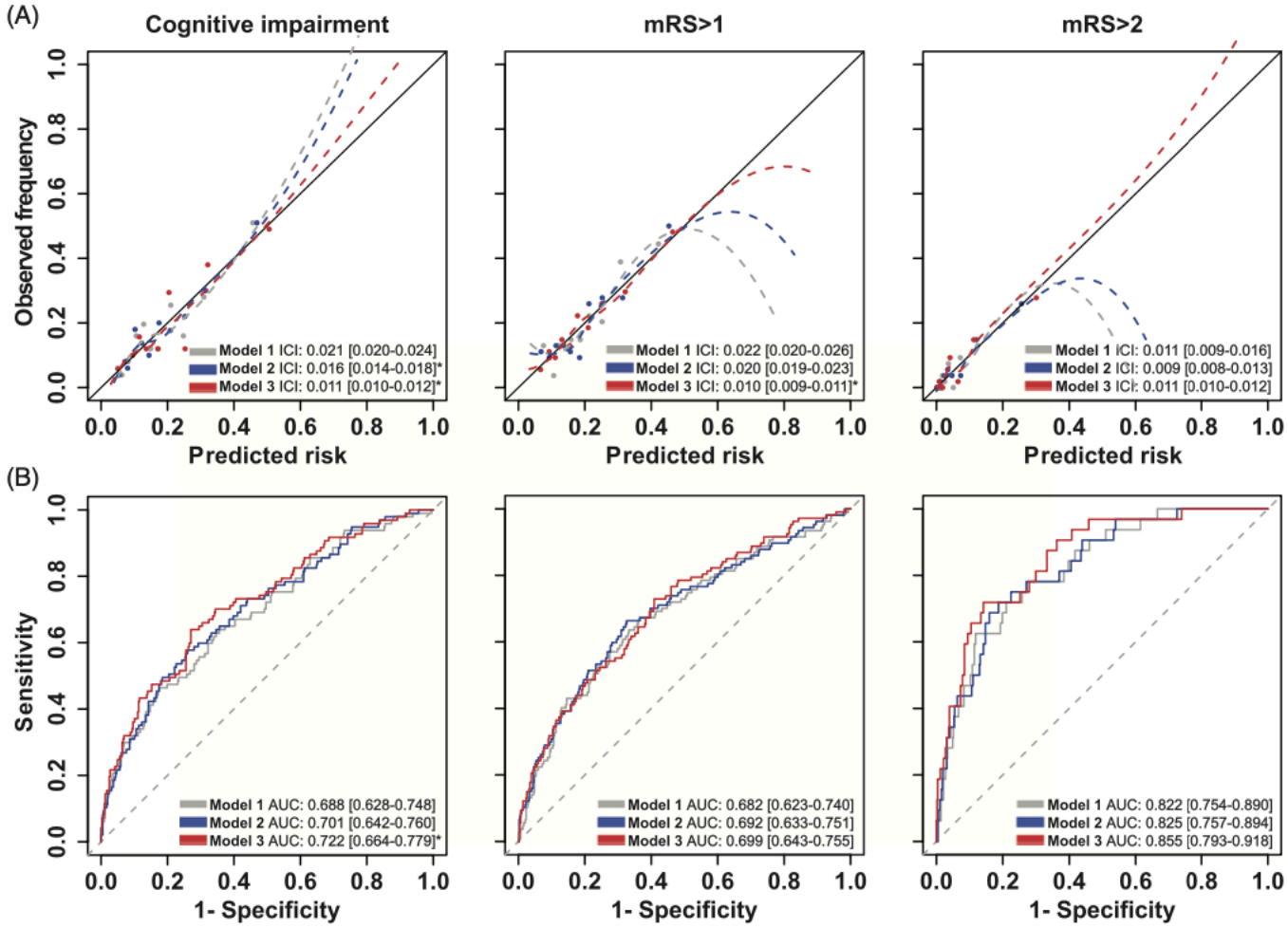

FIGURE 5 Calibration curves and receiver-operating characteristic (ROC) curves for predicting cognitive and functional impairment at 12 months post-stroke derived from models not considering cerebral small vessel disease (SVD), including the global SVD score, and including individual SVD lesions and their burden. The (A) calibration curves and (B) ROC curves were derived from three models predicting cognitive impairment (composite *z*-score < −1.5 or *z* < −1.5 in any individual cognitive domain) (left panel), and functional impairment defined by the modified Rankin scale (mRS) scores <1 (middle panel) and <2 (right panel). Model 1 includes age, sex, education, vascular risk factors, National Institutes of Health Stroke Scale (NIHSS) and Montreal Cognitive Assessment (MoCA) in the acute phase, pre-stroke mRS, and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). Model 2 includes the global SVD score on top of these predictors. Model 3 includes individual SVD markers instead of the global SVD score on top of these predictors (lacune count, deep and periventricular white matter hyperintensity (WMH) Fazekas grades, cerebral microbleed counts, and grade of perivascular spaces). The calibration curves are derived from Loess-based smoothing functions of the observed frequency against the predicted risk. Curves closer to the midline are indicative of better calibration. The integrated calibration index (ICI) indicates the deviation of the curves from the midline and as such lower values are indicative of better calibration. On the contrary, higher area under the ROC curve (AUC) values are indicative of better discrimination. 95% confidence intervals are presented in brackets. AUC, area under the ROC curve; ICI, integrated calibration index; NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal Cognitive Assessment. **P* < .05 when compared to model 1

was standardized across all participating sites, allowing a comprehensive and detailed assessment of both stroke and SVD markers with high reliability. The standardized protocol across centers enabled us to pool data from more than 650 participants at an individual patient level, thereby maximizing statistical power. Furthermore, we examined patients over serial in-person follow-up visits with an extensive neuropsychological battery, which resulted in a comprehensive assessment of cognitive outcomes across multiple domains.

Our study also has limitations. First, because of the extensive imaging and neuropsychological protocol, our cohort consisted primarily of patients with mild stroke (median NIHSS 2), who were more likely to consent to inclusion. This is reflected by the relatively low burden of SVD lesions and favorable cognitive and functional outcomes, when compared to previous studies. Consequently, our study might not be representative of the larger stroke population, where more severe stroke might be associated with challenges in assessing both SVD lesions due to masking by large infarcts and cognitive outcomes due to stroke-related motor and non-motor deficits. It is important to note, however, that it represents a population of less severely affected patients, who might benefit most from preventive interventions. Along

the same lines, the majority of the participants (97%) had an ischemic stroke, possibly as a result of an under-representation of patients with hemorrhagic stroke, who are usually more severely affected. In addition, there was an over-representation of male patients (67%), whereas the average level of education was generally high (median of 13 educational years), thus possibly limiting the generalizability of the study findings to the general stroke population. Second, we had a lost-to-follow-up rate of 15.5% across the first year after stroke, which might introduce attrition bias in our results. Yet, these patients did not significantly differ from the patients ultimately included in the analyses. Third, for 9.5% of the patients it was not possible to obtain MRI imaging at baseline, despite our efforts to be as inclusive as possible. Again, these events were related primarily to technical issues and these patients did not differ with regard to their baseline demographic and clinical characteristics when compared to patients included in the analyses. Fourth, the neuropsychological test battery at 6- and 12-month follow-up visits included identical test material, which may have led to some improvements at 12 months because of practice effects, and thus to an underestimation of the rates of cognitive impairment at 12 months after stroke. Fifth, the available SVD burden scores are surrogate markers of SVD lesions that are visible on MRI and do not capture the real burden of SVD pathology at the level of the microvasculature. Sixth, we acknowledge that we needed to adjust our analyses for a large number of potential confounders, which have been associated previously with both SVD burden and post-stroke outcomes. Although this could theoretically have introduced instability in our main models, the consistency of the association estimates for SVD markers with those derived from models only adjusted for demographic variables (age, sex, education) is reassuring. Finally, the classification of individual neuropsychological tests under specific cognitive domains, although standard in the field, is an inherent limitation because several tests require input from different domains, but also an intact motor output, which might not be the case for patients with a recent stroke.

In conclusion, our results support that both the presence and severity of SVD in patients with acute stroke are associated with poor cognitive and functional outcomes across 12 months after stroke. They further suggest that the development of an aggregate SVD burden score capturing the severity of individual lesion types would be necessary to improve clinical prognostication of stroke patients.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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SUPPLEMENTARY MATERIAL

Cerebral small vessel disease burden and cognitive and functional outcomes after stroke: a multicenter prospective cohort study

Marios K. Georgakis[1]*; Rong Fang[1]*; Marco Düring[1,2]; Frank A. Wollenweber[1]; Felix J. Bode[3,4]; Sebastian Stösser[3,4]; Christine Kindlein[3,4]; Peter Hermann[5]; Thomas G. Liman[6,7]; Christian H. Nolte[6,7,8]; Lucia Kerti[7,9]; Benno Ikenberg[10]; Kathleen Bernkopf[10]; Holger Poppert[11]; Wenzel Glanz[12,13]; Valentina Perosa[12,13]; Daniel Janowitz[1]; Michael Wagner[3]; Katja Neumann[13]; Oliver Speck[13,14,15,16]; Laura Dobisch[13]; Emrah Düzel[13]; Benno Gesierich[1]; Anna Dewenter[1]; Annika Spottke[3,4]; Karin Waegemann[1,17]; Michael Görtler[12,13]; Silke Wunderlich[10]; Matthias Endres[6,7,9,18]; Inga Zerr[5,19]; Gabor Petzold[3,4]; Martin Dichgans[1,17] on behalf of the DEMDAS Investigators[#]

[1] Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany

[2] Medical Image Analysis Center (MIAC AG) and qbig, Department of Biomedical Engineering, University of Basel, Basel, Switzerland

[3] German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

[4] Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn, Germany

[5] Department of Neurology, University Medical Center Göttingen, Göttingen, Germany

[6] Department of Neurology with Experimental Neurology, Charité - Universitätsmedizin Berlin, Berlin, Germany

[7] German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany

[8] Berlin Institute of Health (BIH), Berlin, Germany

[9] Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin, Berlin, Germany

[10] Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany

[11] Neurology Department, Helios Klinikum München West, Munich, Germany

[12] Department of Neurology, University Hospital, Otto-von-Guericke University Magdeburg, Magdeburg, Germany

[13] German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany

[14] Department of Biomedical Magnetic Resonance, Institute for Physics, Otto-von-Guericke University Magdeburg, Magdeburg, Germany

[15] Leibniz Institute for Neurobiology, Magdeburg, Germany

[16] Center for Behavioral Brain Sciences, Magdeburg, Germany

[17] German Center for Neurodegenerative Diseases (DZNE), Munich, Germany

[18] German Centre for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany

[19] German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany

* these authors contributed equally to this study.

[#] Names and affiliations of DEMDAS investigators are listed in the supplement (**Table S23**).

Corresponding author:

Martin Dichgans, MD

Institute for Stroke and Dementia Research, University Hospital LMU

Ludwig-Maximilians-University (LMU), Munich, Germany

Feodor-Lynen-Str. 17, 81377 Munich, Germany

Telephone: +49-89-4400-46018; Fax: +49-89-4400-46040;

e-mail: martin.dichgans@med.uni-muenchen.de

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Supplementary Methods. Summary of the study protocols of DEDEMAS and DEMDAS.

Study population: the DEDEMAS-DEMDAS study

The study started as a single-center run-in phase study at LMU Munich (DEDEMAS, Determinants of Dementia After Stroke) (NCT01334749), which enrolled 136 patients with acute stroke between May 2011 and November 2013, and was subsequently expanded to a multicenter prospective hospital-based cohort study (DEMDAS, DZNE (German Center for Neurodegenerative Diseases)-Mechanisms of Dementia After Stroke), which enrolled an additional 600 patients between Jan 2014 and Jan 2019. The aim of DEDEMAS-DEMDAS is to identify and characterize the determinants of cognitive impairment and dementia post-stroke. Time to post-stroke dementia (PSD) is the primary outcome, while occurrence of post-stroke cognitive impairment-no dementia (PSCI-ND), functional impairment, secondary cognitive improvement after PSD or PSCI-ND, PSD subtyping, occurrence of recurrent stroke, and death are secondary outcomes of the study. DEMDAS was conducted at seven tertiary stroke centers in Germany: the interdisciplinary stroke center including the Institute for Stroke and Dementia Research (coordinating institution) and the Department of Neurology, University Hospital, LMU Munich; the Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich; the Division of Vascular Neurology, Department of Neurology, University Hospital Bonn; the University Medical Center, the Department of Neurology, Göttingen; and the Department of Neurology and Institute of Cognitive Neurology and Dementia Research, Otto von Guericke University Magdeburg; the Center for Stroke Research Berlin and the Department of Neurology of the Charité - Universitätsmedizin Berlin.

We recruited patients ≥ 18 years of age hospitalized for acute stroke with symptom onset within the last three days (DEDEMAS) or last five days (DEMDAS). Stroke was defined by an acute focal neurological deficit in combination with an acute ischemic infarct as documented by either a

diffusion-weighted imaging (DWI)-positive lesion on cranial magnetic resonance imaging (MRI) or a new lesion on a delayed computer tomography (CT) or an intracerebral hemorrhage as documented on CT or MRI. Eligible patients needed to have an available informant. Patients were excluded if they had previously been diagnosed with dementia or if they scored >64 in the screening Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) test with the informant at baseline. We further excluded patients with shortened life expectancy due to malignancy, patients with contraindications for MRI, patients with cerebral venous thrombosis, traumatic cerebral hemorrhage, intracerebral hemorrhage caused by vascular malformation, or purely meningeal or intraventricular hemorrhage, as well as patients participating in an intervention/AMG-study at baseline.[1, 2]

Baseline assessments

Enrolled patients underwent a detailed and comprehensive interview using standardized questionnaires, as well as clinical, biometric, cognitive, and laboratory assessments at baseline (**Table S1**). For each patient, we obtained sociodemographic and family data, a detailed medical history of previous diagnoses, and data about prescribed medications and vascular risk factors. Furthermore, we performed physiological (e.g. blood pressure and body mass index measurement), clinical (e.g. National Institutes of Health Stroke Scale (NIHSS), Modified Rankin Scale (mRS), Glasgow Coma Scale (GCS)), and cognitive assessments (Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA)). Peripheral blood was drawn from all enrolled patients and biochemical assessments were performed as part of the clinical routine. Ischemic stroke subtyping was performed according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification by trained neurologists at each of the participating centers.[3]

Follow-up and assessments

The study participants and their informants were invited for in-person follow-up visits at 6, 12, 36, and 60 months after stroke and underwent comprehensive cognitive and functional assessments by face-to-face interviews with trained neuropsychologists, qualified study nurses, and study physicians. They further participated in telephone interviews including collection of clinical information and cognitive status at 3, 24, and 48 months after stroke (**Table S1**). A comprehensive battery of neuropsychological tests classified in 5 cognitive domains (executive function, memory, language, attention, visuospatial function) and functional tests (modified Rankin Scale (mRS), Barthel Index (BI), and Instrumental Activities of Daily living (IADL)) were administered to participants in face-to-face interviews. Standardized questionnaires were used to assess new clinical events, medical treatment, and cardiovascular risk factors at follow-up visits.

We followed a standardized protocol for contacting patients or informants for follow-up visits in order to minimize attrition rates and missing data (**Figure S1**). As a first step, a trained study nurse contacted the study participants by telephone shortly before the respective follow-up timepoint to arrange an in-person appointment. If the patient could not be reached by telephone, the study nurse called their informant. If neither the study participant nor their informant could be reached by telephone, the study participant and the informant were contacted per mail with an invitation for an in-person appointment. In case of no reply, the data manager contacted the registration office inquiring whether the study participant was alive or had moved to a new address. In case of a new address, the above steps were repeated to establish contact with the patient or informant. For study participants, with whom contact could be established, but were not able or willing to undergo the in-person visits at the respective local sites, two alternative approaches were offered in the following order: first, the study participants and their informants were asked to complete part of the study questionnaires through telephone interviews with the study nurses; second, if the study participants or their informants were not willing to either attend

in-person or have a telephone interview, the study questionnaires were mailed to the participants with a request to complete the questionnaires and return them back to the local study sites.

Neuropsychological test battery

Cognitive performance was assessed by a comprehensive neuropsychological test battery. Specifically, study participants who returned for the in-person follow-up visits (6-, 12-, 36-, and 60-month after index stroke) received a detailed test battery covering five cognitive domains **(Table S1)**:

- Executive function was assessed with the "Trail Making Test Part B" from the "Consortium to Establish a Registry for Alzheimer's Disease Plus (CERAD-Plus)"[4] battery and with the "Stroop Colour-Word-Interference Test"[5]
- Memory was assessed with the "Word List Learning/Recall and Recognition" and "Figure Recall", from CERAD-Plus,[4] and immediate and delayed recall of the "Rey-Osterrieth Complex Figure (ROCF)"[6]
- Language was assessed with the "Semantic and Phonemic Fluency" and "Boston Naming Test", which were sub-tests of the CERAD-Plus[4]
- Attention was assessed with the "Trail Making Test Part A" from CERAD-Plus,[4] and the "Digit-Symbol-Substitution Test of the Wechsler Intelligence Scale"[7]
- Visuospatial function was assessed with the "Figure Drawing Test" from CERAD-Plus,[4] and the copy test of ROCF[6]

We calculated test-specific z-scores based on published norms: (1) Z-scores of CERAD test battery were based on published norms using a standardized program.[8] (2) Z-scores of Rey-Osterrieth complex figure-copy, immediate and delayed recall were calculated based on

published norms corrected for age, sex, and education.[9] (3) Z-scores of Stroop test were calculated based on published norms corrected for age, sex, and education.[10] (4) Z-scores of number symbol test were calculated based on normative scores of Wechsler Adult Intelligence Scale, Third Edition (WAIS-III).[11]

Furthermore, "The Clinical Dementia Rating Score (CDR)"[12] was completed by both the study participant and their informant to assess dementia severity at each in-person follow-up visit starting at 6 months after index stroke. To screen for cognitive impairment, the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) were repeatedly applied at baseline and in-person follow-up visits, whereas the modified German version of the "Telephone Interview for Cognitive Status (TICS)"[13] was applied at the telephone interviews (3-, 24-, and 48-month after index stroke). All tests were performed and rated by centrally trained investigators.

It took on average of about 2 hours for study participants to complete the abovementioned neuropsychological test battery. Based on the investigators experience, this extensive testing was a major reason for attrition. To minimize dropouts of study participants, who were willing to continue participating in the study, but not to undergo the extensive neuropsychological testing, we developed a scaled protocol with different levels of less detailed neuropsychological testing to minimize loss of information regarding the cognitive status of the study participants, as detailed in **Figure S2**.

Follow-up of the current study

The current study is restricted to the 12-month follow-up period, which has been completed for all participants of the DEDEMAS-DEMDAS cohort. The flowchart of the participants for the current analysis is depicted in **Figure 1**. Out of a total of 736 recruited patients 666 had available baseline

MRI scans that qualified for a full assessment of SVD lesions and were thus included in the current analyses. Between baseline and the 6-month visit, 13 patients died and 58 were lost to follow up. Of the remaining 595 patients, six patients skipped the 6-month visit but returned for assessments at 12 months and two patients skipped both the 6- and 12-month visits but were available for the subsequent 24-month telephone interview. Of the patients with available 6-month assessments, five patients received home visits, six patients completed the study questionnaires through mail, and 15 patients were reached through telephone; these patients completed part of the neuropsychological and functional tests and were included only in the respective analyses. Between 6 and 12 months after the index event, five patients died and 27 were lost to follow-up. Of the remaining 563 patients, 16 skipped the 12-month visit but were available for the subsequent 24-month telephone interview. Of the patients with available 12-month assessments, three patients received home visits, three patients completed the study questionnaires through mail, and 15 patients were reached through telephone; these patients completed part of the neuropsychological and functional tests and were included only in the respective analyses.

Data management and quality control

All data (demographic, clinical, and neuropsychological data from both the baseline and follow-up visits and telephone interviews) were initially collected by the participating study sites using Case Report Forms (CRF) that were specifically designed for the current study. All filled CRFs were then mailed to the coordinating center (Institute for Stroke and Dementia Research [ISD], LMU Munich). Next, trained data managers undertook extensive quality controls. As a first quality check, each CRF was manually inspected for completeness and screened for potential outlier values checking for plausibility. In case of missing or implausible values, the study nurses of the respective study sites were contacted to resolve open issues. All data included in the CRFs were

then read (by TeleForm(Electric Paper GmBH, Lüneburg, Germany) into a central access database.

Standardized plausibility check algorithms were regularly applied centrally by data managers at the coordinating center across the database to identify implausible values. At all stages, the study nurses of the respective study site were contacted for feedback regarding the implausible values. Data management and quality control at the central access database were carried out with SAS version 9.4 (SAS Institute Inc, Cary, NC).

Biochemical assessments and biobanking

Peripheral blood assessments (complete blood count, LDL-, HDL-, and total cholesterol, triglycerides, fasting glucose, glycated hemoglobin A1c, electrolytes, transaminases, creatinine, high-sensitivity C-reactive protein, fibrinogen, procalcitonin, homocysteine, thyroid hormones, vitamin B12, folate, total and MB-creatinine kinase, troponin T, and routine coagulation markers) were extracted from the hospital records at baseline and at each in-person follow-up visit. Data were sent to the coordinating center in Munich and subsequently checked independently by two blinded data managers.

All study participants underwent collection of biosamples (serum and plasma) for biobanking. Sampling was done at baseline and at each of the in-person follow-up visits. Additional blood draws included whole blood for the isolation of DNA and a separate sample for preparation of miRNA. All steps were done according to standard operating procedures and all samples were sent to Munich for central storage and subsequent sample processing. The specimens were double-pseudonymized, recorded and administered using a protected data integration system (DIS) developed by Munich Biotech Cluster m4 with maintenance and support by Bitcare GmbH.

Brain MRI acquisition

Patients underwent cranial MRI examinations at baseline within three days (DEDEMAS) or five days (DEMDAS) of stroke onset. All examinations were done on 3-Tesla systems (Siemens Healthineers, Erlangen, Germany). The following imaging sequences were acquired: 3D T1-weighted (T1w) magnetization prepared rapid gradient echo (MPRAGE), 3D fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI) with multiple diffusion directions, T2-weighted (T2w) turbo spin echo, and T2*-weighted (T2*w) fast low angle shot (FLASH) gradient echo. A detailed description of the protocols used per sequence is provided in **Table S2**. There were differences between the imaging protocols used for the run-in phase study (DEDEMAS) and the multicenter DEMDAS study. These differences are minor (not relevant for analyses) due to differences in scanner hardware and software across sites with the exception of the first 18 patients that were recruited in DEDEMAS, who were scanned with a different protocol (as detailed in **Table S2**). There were no major imaging protocol deviations, which led to an exclusion of one or more image series.

Quality control of MRI images

To secure full alignment of the MRI protocol across all participating centers, quality controls (QC) were introduced at multiple levels: (1) a checklist of MRI instructions (e.g. angulation, coverage, scanning position, etc.) with the acquired sequences needed to be completed by the local radiology team and be sent to the coordinating center (ISD, LMU Munich) along with uploading the acquired MRI images to a central PACS server; (2) all MRI images underwent visual QC by qualified researchers of the imaging team at the coordinating center, who visually inspected each sequence for quality, completeness, sequence order, angulations, coverage, new lesions/bleedings, or artifacts; (3) all MRI images were additionally uploaded to XNAT (eXtensibleNeuroimaging Archive Toolkit,[14] DZNE Magdeburg, iNet) and underwent technical

QC, which included automatic screening for completeness, sequence order, protocol parameters, coverage, orientation, and angulation; (4) a combined QC report based on the visual and technical QCs for each participant was compiled and sent back to the respective local radiology team.

Assessment of stroke lesion volume

Acute infarcts (hyperintense on DWI) were segmented using a semi-automated procedure. First, the mean DWI image (mean over all directions) was segmented into two tissue classes using FAST from the FMRIB software library (FSL; v5.0). Then, the tissue class image containing the DWI-hyperintense lesion(s) was segmented further into a high and low intensity component (the former containing mostly infarcted tissue and the latter mainly CSF) using Otsu's method. A trained rater checked the resulting infarct masks and performed manual corrections, when needed. Stroke lesion volume was normalized by total intracranial volume. To this end, T1 images were segmented into tissue probability maps using the Statistical Parametric Mapping (SPM) toolbox (v12; Wellcome Department of Cognitive Neurology, London, UK; https://www.fil.ion.ucl.ac.uk/spm/). Gray matter, white matter and CSF tissue maps were thresholded at 20% probability, binarized and combined to obtain total intracranial volume.

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Supplementary Table 1. Summary of clinical protocols of DEDEMAS and DEMDAS.

	DEDEMAS (NCT01334749)	DEMDAS
Study and status	Single-center-pilot study (completed in Jan 2019)	Multi-center study (ongoing)
Period of enrollment	May 2011 to Nov 2013	Jan 2014 to Jan 2019
Number of enrolled patients	136	600
Baseline interview	demographic variables, living situation and level of independence, vascular risk factors, family history, health history, medication	
Baseline clinical and technical examinations	anthropometry, blood pressure, physical and neurological examination, examination of retinal vascular abnormalities, ankle-brachial index, National Institutes of Health Stroke Scale, Modified Rankin Scale, Barthel score, Delirium Rating Scale, Glasgow Coma scale, intima-media thickness, brain MRI, 12-lead electrocardiogram	
Baseline neuropsychological evaluations	cognitive screening (MMSE, MoCA)	
Baseline laboratory tests	blood draws for biobanking	
Telephone interviews at M3	living situation and level of independence, medication, incident cardiovascular and neurological events/diseases, death situation, Modified Rankin Scale, Barthel score, telephone interview for cognitive status, amyloid- and fluorodeoxyglucose-positron emission tomography (FDG-PET)*, lumbar puncture†	
Detailed in-person assessments at M6 and M12		
Executive function	trail making test B, Stroop test	
Memory	CERAD-word list learning, CERAD-word list recall, CERAD-word list recognition, CERAD-figure recall, Rey-Osterrieth complex figure-immediate and delayed recall	
Language	word fluency test (animal, s-words), CERAD-Boston naming test (15 items)	
Attention	trail making test A, number symbol test	

Visuospatial function	CERAD-figure drawing test, Rey-Osterrieth complex figure-copy test
Functional outcomes	Modified Rankin Scale, Barthel score, Instrumental Activities of Daily living

Abbreviations: MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; M3, 3 months; M6, 6 months; M12, 12 months.

* Amyloid PET examinations were initially part of the protocol for participants developing new-onset cognitive impairment over follow-up and age-matched controls without evidence of cognitive impairment, but were abandoned for logistic reasons following an interim analysis of 56 patients showing no difference in amyloid uptake between participants with cognitive impairment and controls.[15]

† Lumbar puncture was performed in subjects developing new-onset cognitive impairment.

Supplementary Table 2. Summary of cranial MRI protocols of DEDEMAS and DEMDAS.

	DEDEMAS			DEMDAS
Scanner	3T, Siemens Healthineers			3T, Siemens Healthineers
Scanned time	Within 3 days of stroke onset			Within 5 days of stroke onset
T1w	T1w-1 (N=18)		T1w-DEMDAS (N=86)	T1w-DEMDAS (N=567)
Acquisition type	3D		3D	3D
TR (ms)	2400		2500	2500
TI (ms)	900		1100	1100
TE (ms)	3.06		4.37	4.33-4.37
Voxel size (mm^3)	1.00x1.00x1.00		1.00x1.00x1.00	1.00x1.00x1.00
Bandwidth (Hz/Px)	230		140	140
T2w	T2w-1 (N=11)	T2w-2 (N=7)	T2w-DEMDAS (N=85)	T2w-DEMDAS (N=565)
Acquisition type	3D	2D	2D	2D
TR (ms)	3000	6030	6500	6500
TE (ms)	416	91	117	116-117
Voxel size (mm^3)	1.00x1.00x1.00	-	-	-
In-plane resolution (mm^2)	-	0.78x0.78	1.00x1.00	1.00x1.00
Slice thickness (mm)	-	3	3	3
Slice gap (%)	-	10	10	10

Bandwidth (Hz/Px)	751	110	362	362
FLAIR	FLAIR-1 (N=11)	FLAIR-2 (N=7)	FLAIR-DEMDAS (N=85)	FLAIR-DEMDAS (N=567)
Acquisition type	2D	3D	3D	3D
TR (ms)	7000	6000	5000	5000
TI (ms)	2210	2000	1800	1800
TE (ms)	94	351	395	393-398
Voxel size (mm^3)	-	1.00x0.98x0.98	1.00x0.98x0.98	1.00x1.00x1.00
In-plane resolution (mm^2)	1.00x1.00	-	-	-
Slice thickness (mm)	3	-	-	-
Slice gap (%)	10	-	-	-
Bandwidth (Hz/Px)	287	888	781	780-781
DWI/DTI	DWI/DTI-1 (N=16)		DWI/DTI-DEMDAS (N=85)	DWI/DTI-DEMDAS (N=557)
Acquisition type	2D		2D	2D
TR (ms)	9800		12700	12700-13400
TE (ms)	107		81	81-84
In-plane resolution (mm^2)	1.95x1.95		2.00x2.00	2.00x2.00
Slice thickness (mm)	2		2	2
Slice gap (%)	0		0	0
Bandwidth (Hz/Px)	1395		1628	1628
B-values (s/mm^2)	0, 1000		0, 1000	0, 1000

Diffusion Directions	20	30	30
T2*w FLASH	FLASH-DEMDAS (N=103)		FLASH-DEMDAS (N=565)
Acquisition type	2D		2D
TR (ms)	742		742
TE (ms)	19.9		19.9
In-plane resolution (mm^2)	1.00x1.00		1.00x1.00
Slice thickness (mm)	5		5
Slice gap (%)	10		10
Bandwidth (Hz/Px)	199		199-200

Abbreviations: MRI, magnetic resonance imaging; T=Tesla; W=weighted; D=dimension; FLAIR, fluid attenuation inversion recovery; DWI, diffusion-weighted imaging; DTI, diffusion tensor imaging; FLASH, fast low angle shot; TE, echo time; TR, repetition time; TI, inversion time.

Supplementary Table 3. Definition of the global cerebral small vessel disease (SVD) score [16, 17].

SVD feature	Lacunes	White matter hyperintensities (WMH)	Cerebral microbleeds (CMB)	Perivascular spaces (PVS)
Score	1 point	1 point	1 point	1 point
Definition	⩾1 lacunes	Fazekas PVWM=3 or Fazekas DWM⩾2	⩾1 CMB	>10 PVS in the basal ganglia (count one side of the brain slice with the highest number if there is asymmetry between the two sides)[17]

Abbreviations: PVWM, periventricular white matter; DWM, deep white matter.

Supplementary Table 4. Number of missing baseline cognitive and functional assessments per reason of missingness.

Reasons of missingness	Denial	Paresis	Aphasia	Paresis + aphasia	Vision impairment	Other	Total
NIHSS	-	-	-	-	-	-	0
Pre-stroke mRS	-	-	-	-	-	-	0
MoCA	5	12	8	1	13	12	51
MMSE	4	9	6	0	6	9	34

Abbreviations: NIHSS, national institutes of health stroke scale; mRS, modified Rankin scale; MoCA, Montreal cognitive assessment; MMSE, Mini-Mental State Examination.

Supplementary Table 5. Number of missing cognitive and functional assessments by reason of missingness at 6 months after stroke.

Reasons of missing tests at 6 months		Denial	Paresis	Aphasia	Paresis + aphasia	Vision impairment	Paresis + dysarthria	Hearing impairment	No informant or no contact with informant	Other (phone visit, postal survey, healthy condition, etc.)	Total
Executive function	TMT-B	22	3	1	2	7	1	1	0	38	75
	Stroop test	25	1	1	2	2	1	1	0	40	73
Memory	CERAD-word list learning	4	0	0	2	0	0	0	0	25	31
	CERAD-word list recall	4	0	0	2	1	0	1	0	26	34
	CERAD-word list recognition	4	0	0	2	0	0	1	0	26	33
	CERAD-figure recall	5	0	0	1	0	0	1	0	27	34
	Rey-Osterrieth complex figure-immediate recall	28	3	0	1	4	1	1	0	39	77
	Rey-Osterrieth complex figure-delayed recall	26	3	1	1	4	1	1	0	40	77
Language	Word fluency test-animal	5	0	0	2	1	0	1	0	25	34
	Word fluency test-s-words	5	0	0	2	1	0	1	0	26	35
	CERAD-Boston naming test	4	0	0	2	1	0	0	0	25	32

Attention	TMT-A	6	1	1	2	6	1	1	0	30	48
	Number symbol test	8	2	0	1	2	0	0	0	32	45
Visual-spatial function	CERAD-figure drawing test	4	0	0	1	0	0	0	0	25	30
	Rey-Osterrieth complex figure-copy test	20	3	0	1	3	1	1	0	34	64
mRS		0	0	0	0	0	0	0	0	3	3
BI		1	0	0	0	0	0	0	0	5	6
IADL		7	0	0	1	1	0	0	18	24	51
Number of missing any of the evaluations, including neuropsychological and functional tests		62	4	1	2	9	1	1	18	72	170
Number of missing any of the neuropsychological tests, but having all five domain scores		48	2	0	0	6	0	0	0	32	80
Number of missing any of the neuropsychological tests, and lacking of any of the five domain scores		9	2	1	2	3	1	1	0	32	51
Number of missing any of the functional tests		12	0	0	1	1	0	0	18	23	55

Abbreviations: TMT-B, trail making test part B; CERAD, consortium to establish a registry for Alzheimer's Disease; TMT-A, trail making test part A; mRS, modified Rankin scale; BI, Barthel index; IADL, instrumental activities of daily living.

Supplementary Table 6. Number of missing cognitive and functional assessments by reason of missingness at 12 months after stroke.

Reasons of missing tests at 12 months		Denial	Paresis	Aphasia	Paresis + aphasia	Vision impairment	Paresis + dysarthria	Hearing impairment	No informant or no contact with informant	Other (phone visit, postal survey, healthy condition, etc.)	Total
Executive function	TMT-B	20	0	1	1	4	1	0	0	45	72
	Stroop test	17	1	1	1	4	1	0	0	40	65
Memory	CERAD-word list learning	5	0	0	1	1	0	1	0	25	33
	CERAD-word list recall	6	0	0	1	1	0	1	0	26	35
	CERAD-word list recognition	5	0	0	1	1	0	1	0	25	33
	CERAD-figure recall	6	0	0	0	1	1	1	0	25	34
	Rey-Osterrieth complex figure-immediate recall	27	3	0	0	3	1	0	0	47	81
	Rey-Osterrieth complex figure-delayed recall	28	3	1	0	3	1	0	0	47	83
Language	Word fluency test-animal	6	0	0	1	1	0	1	0	25	34
	Word fluency test-s-words	5	0	0	1	1	0	1	0	26	34
	CERAD-Boston naming test	5	0	0	0	1	0	1	0	25	32

Attention	TMT-A	7	0	0	0	3	1	1	0	29	41
	Number symbol test	7	1	0	0	4	0	1	0	28	41
Visual-spatial function	CERAD-figure drawing test	5	0	0	0	1	0	1	0	25	32
	Rey-Osterrieth complex figure-copy test	29	2	0	0	4	1	0	0	48	84
mRS		4	0	0	0	1	0	0	0	2	7
BI		4	0	0	0	1	0	0	0	4	9
IADL		5	0	0	0	1	0	0	26	7	39
Number of missing any of the evaluations, including neuropsychological and functional tests		56	3	1	2	6	1	1	25	72	167
Number of missing any of the neuropsychological tests, but having all five domain scores		50	2	0	2	3	0	0	0	48	105
Number of missing any of the neuropsychological tests, and lacking of any of the five domain scores		6	0	1	0	3	1	1	0	31	43
Number of missing any of the functional tests		6	0	0	0	1	0	0	26	10	43

Abbreviations: TMT-B, trail making test part B; CERAD, consortium to establish a registry for Alzheimer's Disease; TMT-A, trail making test part A; mRS, modified Rankin scale; BI, Barthel index; IADL, instrumental activities of daily living.

Supplementary Table 7. Baseline characteristics and cognitive and functional outcomes at 6 and 12 months after stroke of all patients enrolled in DEDEMAS and DEMDAS.

Variables	**n=736**
Demographic variables	
Age, y	68.0±11.2
Male, n (%)	491 (66.7)
Education, y	13 (12-16)
Cardiovascular risk factors	
Hypertension, n (%)	571 (77.6)
Diabetes mellitus, n (%)	150 (20.4)
Current smoking, n (%)	171 (23.2)
Regular alcohol consumption*, n (%)	557 (75.7)
Atrial fibrillation, n (%)	148 (20.1)
Stroke history, n (%)	79 (10.7)
BMI, kg/m^2	27.0±4.3
SBP, mmHg	140 (129-150)
DBP, mmHg	80 (72-87)
HbA1c, %	5.7 (5.4-6.1)
LDL-C, mg/dL	126 (103, 154)
HDL-C, md/dL	48 (40-58)
Triglycerides, mg/dL	121 (91-170)
APOE genotype (n=594), n (%)	
0 ε4 allele	463 (77.9)
1 ε4 allele	122 (20.5)
2 ε4 alleles	9 (1.5)
Index stroke classification, n (%)	
Ischemic stroke	715 (97.1)

TOAST subtype, n (%)	
Large artery atherosclerosis	186 (26.0)
Cardioembolism	167 (23.4)
Small artery occlusion	84 (11.7)
Other etiology	30 (4.2)
Undefined etiology	248 (34.7)
Hemorrhagic stroke	21 (2.9)
Clinical/cognitive assessment	
NIHSS score	3 (1-5)
mRS before stroke	0 (0-0)
BI score	100 (80-100)
IQCODE score	48 (48-49)
Baseline cognitive impairment[†], (n=709), n (%)	365 (51.5)
Time of cognitive/functional assessment at 6 months, d after stroke	191.0 (182.0-207.0)
Neuropsychological score at 6 months	
Average cognitive score	-0.1263 (-0.5992-0.2564)
Executive function	0.0926 (-0.5418-0.6661)
Memory	-0.0830 (-0.6297-0.3725)
Language	0.0101 (-0.6463-0.4798)
Attention	-0.2347 (-0.7973-0.3777)
Visual-spatial function	-0.1923 (-1.0407-0.3347)
PSCI and PSCI-subtype at 6 months	
PSCI, n (%)	156/584 (26.7)
Executive-PSCI, n (%)	54/587 (9.2)
Memory-PSCI, n (%)	44/612 (7.2)
Language-PSCI, n (%)	28/609 (4.6)
Attention-PSCI, n (%)	63/601 (10.5)

Visual-spatial-PSCI, n (%)	106/611 (17.3)
Functional score at 6 months	
mRS	1 (0-1)
BI	100 (100-100)
IADL	8 (8-8)
Functional impairment at 6 months	
mRS>1, n (%)	143/636 (22.5)
mRS>2, n (%)	57/636 (9.0)
IADL<8, n (%)	97/587 (16.5)
Time of cognitive/functional assessment at 12 months, d after stroke	374.0 (366.0-392.0)
Neuropsychological score at 12 months	
Average cognitive score	0.0564 (-0.3932-0.3841)
Executive function	0.2550 (-0.4304-0.8861)
Memory	0.0507 (-0.4468-0.5092)
Language	0.0901 (-0.4033-0.5313)
Attention	-0.0939 (-0.6592-0.4353)
Visual-spatial function	-0.1230 (-0.8554-0.4198)
PSCI and PSCI-subtype at 12 months	
PSCI, n (%)	103/545 (18.9)
Executive-PSCI, n (%)	29/546 (5.3)
Memory-PSCI, n (%)	30/571 (5.3)
Language-PSCI, n (%)	17/558 (3.0)
Attention-PSCI, n (%)	37/554 (6.7)
Visual-spatial-PSCI, n (%)	79/565 (14.0)
Functional score at 12 months	
mRS	1 (0-1)
BI	100 (100-100)

IADL	8 (8-8)
Functional impairment at 12 months	
mRS>1, n (%)	116/585 (19.8)
mRS>2, n (%)	34/585 (5.8)
IADL<8, n (%)	68/552 (12.3)

Note: Values are expressed as n (%), mean±SD, or median (interquartile range).

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; *APOE*, apolipoprotein E; NIHSS, national institutes of health stroke scale; mRS, modified Rankin scale; BI, Barthel index; IQCODE, informant questionnaire on cognitive decline in the elderly; MoCA, Montreal cognitive assessment.

* from a self-reported questionnaire

† MoCA<26 or MMSE<24 when MoCA was not available (5.1% of total).

Supplementary Table 8. Reasons for exclusion due to unavailability of an MRI allowing a reliable assessment of SVD markers.

Reasons	DEDEMAS	DEMDAS
Patient declined an MRI after recruitment	3	5
Only clinical MRI protocol available	7	2
MRI aborted	1	5
MRI scanner unavailable due to technical reasons	0	8
Critically ill patient	0	4
Patient discharged before MRI	0	3
MRI not feasible due to size/weight limitations of scanner	0	3
Implants non-compatible with MRI	1	1
Insufficient quality of MRI scans	1	0
Claustrophobia	0	1
Reason not documented	21*	4
Total	34	36

* at the beginning of the run-in DEDEMAS study reasons for exclusion were not documented.

Supplementary Table 9. Baseline characteristics and cognitive and functional outcomes at 6 and 12 months after stroke of patients included in the analyses and patients excluded because of no MRI that would allow SVD assessment at baseline.

	Patients included in the analyses (n=666)	Patients without MRI at baseline (n=70)	*P* value
Demographic variables at baseline			
Age, y	67.9±11.4	69.5±9.0	0.4509
Male, n (%)	444 (66.7)	47 (67.1)	0.7193
Education years	13 (12-16)	14 (12- 16)	0.4751
Cardiovascular risk factors at baseline			
Hypertension, n (%)	515 (77.3)	56 (80.0)	0.7193
Diabetes mellitus, n (%)	131 (19.7)	19 (27.1)	0.1867
Current smoking, n (%)	155 (23.3)	16 (22.9)	1.0000
Regular alcohol consumption*, n (%)	498 (74.8)	59 (84.3)	0.1057
Atrial fibrillation, n (%)	133 (20.0)	15 (21.4)	0.8943
Stroke history, n (%)	71 (10.7)	8 (11.4)	0.9999
BMI, kg/m^2	27.0±4.3	26.8±4.2	0.5715
SBP, mmHg	140 (129-150)	135 (128-150)	0.2487
DBP, mmHg	80 (72-87)	79 (71-84)	0.1694
Biochemical results at baseline			
HbA1c, %	5.7 (5.4-6.1)	5.8 (5.5-6.2)	0.0528
LDL-C. mg/dL	126 (103- 154)	129 (99- 150)	0.6086

HDL-C, md/dL	48 (40- 58)	47 (39- 61)	0.9053
Triglycerides, mg/dL	122 (92- 170)	112 (83-171)	0.4435
Stroke classification, n (%)			
Ischemic stroke	648 (97.3)	67 (95.7)	0.4408
TOAST subtype, n (%)			
Large artery atherosclerosis	172 (26.5)	14 (20.9)	0.1030
Cardio-embolic	144 (22.2)	23 (34.3)	
Small artery occlusion	77 (11.9)	7 (10.4)	
Other etiology	30 (4.6)	0 (0.0)	
Undefined etiology	225 (34.7)	23 (34.3)	
Hemorrhagic stroke	18 (2.7)	3 (4.3)	0.4408
Clinical assessment at baseline			
NIHSS score	2 (1-5)	3 (2-6)	0.3163
mRS immediately before stroke	0 (0-0)	0 (0-0)	0.9678
BI score	100 (80-100)	100 (75-100)	0.6879
IQCODE score	48 (48-49)	48 (48-49)	0.4287
Baseline cognitive impairment, n (%)	337/643 (52.4)	28/66 (42.4)	0.1566
Time of cognitive/functional assessment at 6 months, d after stroke	191.0 (182.0-207.0)	194.0 (183.2-206.0)	0.6290
Neuropsychological score at 6 months			
Average cognitive score	-0.1013 (-0.5425-0.2768)	-0.0768 (-0.4682-0.3580)	0.3736
Executive function	0.0926 (-0.5530-0.6661)	0.0715 (-0.3286-0.4984)	0.7068

Memory	-0.0927 (-0.6444-0.3707)	0.0709 (-0.5698-0.4270)	0.5069
Language	0.0101 (-0.6664-0.5057)	-0.0181 (-0.5384-0.3659)	0.6620
Attention	-0.2311 (-0.8005-0.3661)	-0.2762 (-0.7362-0.4716)	0.8052
Visual-spatial function	-0.2078 (-1.0598-0.3127)	0.0887 (-0.7490-0.5354)	0.0672
PSCI and PSCI-subtype at 6 months			
PSCI, n (%)	148/536 (27.6)	8/48 (16.7)	0.1411
Executive-PSCI, n (%)	52/539 (9.6)	2/48 (4.2)	0.2976
Memory-PSCI, n (%)	42/560 (7.5)	2/52 (3.8)	0.5707
Language-PSCI, n (%)	26/557 (4.7)	2/52 (3.8)	0.9999
Attention-PSCI, n (%)	59/550 (10.7)	4/51 (7.8)	0.6860
Visual-spatial-PSCI, n (%)	98/559 (17.5)	8/52 (15.4)	0.8418
Functional score at 6 months			
mRS	1 (0-1)	1 (0-2)	0.3419
BI	100 (100-100)	100 (100-100)	0.9193
IADL	8 (8-8)	8 (8-8)	0.3373
Functional impairment at 6 months			
mRS>1, n (%)	127/584 (21.7)	16/52 (30.8)	0.1868
mRS>2, n (%)	50/584 (8.6)	7/52 (13.5)	0.2131
IADL<8, n (%)	86/536 (16.0)	11/51 (21.6)	0.4135
Time of cognitive/functional assessment in 12 months, d after stroke	374.0 (366.0-392.0)	378.0 (364.0-396.2)	0.5217
Neuropsychological score at 12 months			

Average cognitive score	0.0483 (-0.4119-0.3763)	0.1173 (-0.1713-0.5085)	0.1188
Executive function	0.2558 (-0.4401-0.8769)	0.1009 (-0.3526-0.8991)	0.6995
Memory	0.0609 (-0.4479-0.5061)	0.0026 (-0.4446-0.6190)	0.8089
Language	0.0853 (-0.4155-0.5254)	0.2151 (-0.3065-0.5918)	0.3803
Attention	-0.1082 (-0.6732-0.4280)	0.0307 (-0.2985-0.7082)	0.1050
Visual-spatial function	-0.1406 (-0.8865-0.4088)	0.2758 (-0.4509-0.5900)	0.0193
PSCI and PSCI-subtype at 12 months			
PSCI, n (%)	97/504 (19.2)	6/41 (14.6)	0.6045
Executive-PSCI, n (%)	29/505 (5.7)	0/41 (0.0)	0.1550
Memory-PSCI, n (%)	27/525 (5.1)	3/46 (6.5)	0.7257
Language-PSCI, n (%)	16/515 (3.1)	1/43 (2.3)	1.0000
Attention-PSCI, n (%)	33/512 (6.4)	4/42 (9.5)	0.5131
Visual-spatial-PSCI, n (%)	75/521 (14.4)	4/44 (9.1)	0.4545
Functional score at 12 months			
mRS	1 (0-1)	1 (0-1)	0.4338
BI	100 (100-100)	100 (100-100)	0.8554
IADL	8 (8-8)	8 (8-8)	0.2350
Functional impairment at 12 months			
mRS>1, n (%)	107/540 (19.8)	9/45 (20.0)	1.0000
mRS>2, n (%)	32/540 (5.9)	2/45 (4.4)	1.0000
IADL<8, n (%)	60/508 (11.8)	8/44 (18.2)	0.3200

Note: Values are expressed as number (percent), mean±SD, or median (interquartile range)

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; *APOE*, apolipoprotein E; NIHSS, national institutes of health stroke scale; mRS, modified Rankin scale; BI, Barthel index; IQCODE, informant questionnaire on cognitive decline in the elderly; MoCA, Montreal cognitive assessment; MRI, magnetic resonance imaging; PSCI, post-stroke cognitive impairment; IADL, instrumental activity of daily living scale.

* from a self-reported questionnaire

† MoCA<26 or MMSE<24 when MoCA was not available (5.3% of total).

Supplementary Table 10. Distribution of stroke lesions by vascular territory among patients included in our analyses.

Vascular distribution of the stroke lesions	Number of patients*, n	Proportion of patients (%)
Anterior circulation (ACA or MCA), left	188	28.3
Anterior circulation (ACA or MCA), right	170	25.6
Posterior circulation (PCA), left	46	6.9
Posterior circulation (PCA), right	44	6.6
Posterior circulation, brainstem	61	9.2
Posterior circulation, cerebellum	50	7.5
Multiple territories	106	15.9

Abbreviations: ACA, anterior cerebral artery; PCA, posterior cerebral artery.

*One patient with subarachnoid hemorrhage and no evidence of a localized aneurysm has been excluded.

Supplementary Table 11. Baseline characteristics of patients included in the analysis with sex breakdown.

Variables	Male (n=444)	Female (n=222)	P
Demographic variables			
Age, y	67.1±11.0	69.4±12.0	0.0152
Education, y	13 (12-17)	12 (11-14)	9.759e-11
Cardiovascular risk factors			
Hypertension, n (%)	339 (76.4)	176 (79.3)	0.4517
Diabetes mellitus, n (%)	89 (20.0)	42 (18.9)	0.8094
Current smoking, n (%)	108 (24.3)	47 (21.2)	0.4176
Regular alcohol consumption*, n (%)	355 (80.0)	143 (64.4)	2.058e-05
Atrial fibrillation, n (%)	80 (18.0)	53 (23.9)	0.0931
Prior history of stroke, n (%)	46 (10.4)	25 (11.3)	0.8243
BMI, kg/m^2	27.1±3.9	26.9±4.9	0.2251
SBP, mmHg	141 (130-151)	138 (128-149)	0.1090
DBP, mmHg	81 (74-88)	78 (70-85)	0.0002
HbA1c, %	5.7 (5.4-6.1)	5.7 (5.4-6.1)	0.5158
LDL-C, mg/dL	122 (101-151)	133 (107-157)	0.0086
HDL-C, md/dL	45 (38-53)	56 (46-64)	< 2.2e-16
Triglycerides, mg/dL	120 (91-175)	123 (93-153)	0.6410
APOE genotype, n (%)	359 (80.9)	175 (78.8)	
0 ε4 allele	279 (80.9)	142 (81.1)	0.6704
1 ε4 allele	76 (21.2)	31 (17.7)	
2 ε4 alleles	4 (1.1)	2 (1.1)	
Index stroke classification, n (%)			
Ischemic stroke	431 (97.1)	217 (97.7)	0.7999
TOAST subtype, n (%)			

Large artery atherosclerosis	120 (27.8)	52 (24.0)	0.0541
Cardioembolism	87 (20.2)	57 (26.3)	
Small artery occlusion	48 (11.1)	29 (13.4)	
Other etiology	26 (6.0)	4 (1.8)	
Undefined etiology	150 (34.8)	75 (34.6)	
Hemorrhagic stroke	13 (2.9)	5 (2.3)	0.7999
Clinical/cognitive assessment			
NIHSS score	2 (1-5)	3 (1-5)	0.3997
mRS before stroke	0 (0-0)	0 (0-0)	0.6541
BI score	100 (85-100)	100 (80-100)	0.5593
IQCODE score	48 (48-49)	48 (48-50)	0.2321
Baseline cognitive impairment†, (n=643), n (%)	240/432 (55.6)	97/211 (46.0)	0.0278
MRI variables			
Stroke lesion volume (mm^3)	2268 (526-14786)	2168 (520-7256)	0.0449
Normalized stroke lesion volume‡ (%)	0.15 (0.03-0.95)	0.15 (0.03-0.54)	0.1544

Note: Values are expressed as n (%), mean±SD, or median (interquartile range).

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; *APOE*, apolipoprotein E; NIHSS, national institutes of health stroke scale; mRS, modified Rankin scale; BI, Barthel index; IQCODE, informant questionnaire on cognitive decline in the elderly; MoCA, Montreal cognitive assessment; MRI, magnetic resonance imaging.

* from a self-reported questionnaire

† MoCA<26 or MMSE<24 when MoCA was not available (5.3% of total).

‡ stroke lesion volume/total intracranial volume

Supplementary Table 12. Baseline characteristics of patients in DEDEMAS and DEMDAS by study site.

	DEDEMAS	DEMDAS						
	Munich-LMU[a] (n=102)	Munich-lLMU (n=208)	Munich-TUM[b] (n=58)	Berlin-1[c] (n=35)	Berlin-2[d] (n=33)	Bonn[e] (n=101)	Göttingen[f] (n=76)	Magdeburg[g] (n=53)
Demographic variables at baseline								
Age, y	70.9±8.7	72.2±8.9	64.8±15.9	64.4±13.3	66.7±11.6	62.8±10.5	64.2±11.4	66.4±11.3
Male, n (%)	70 (68.6)	133 (63.9)	36 (62.1)	23 (65.7)	21 (63.6)	70 (69.3)	55 (72.4)	36 (67.9)
Education years	13 (11-17)	13 (11-15)	13 (11-17)	15 (13-19)	14 (13-18)	13 (12-16)	13 (12-14)	14 (12-17)
Cardiovascular risk factors at baseline								
Hypertension, n (%)	80 (78.4)	175 (84.1)	44 (75.9)	24 (68.6)	23 (69.7)	78 (77.2)	56 (73.7)	35 (66.0)
Diabetes mellitus, n (%)	20 (19.6)	45 (21.6)	12 (20.7)	4 (11.4)	5 (15.2)	15 (14.6)	20 (26.3)	10 (18.9)
Current smoking*, n (%)	18 (17.6)	39 (18.8)	11 (19.0)	10 (28.6)	10 (30.3)	34 (33.7)	19 (25.0)	14 (26.4)
Regular alcohol consumption, n (%)	86 (84.3)	164 (78.8)	42 (72.4)	21 (60.0)	19 (57.6)	86 (85.1)	34 (44.7)	46 (86.8)
Atrial fibrillation, n (%)	25 (24.5)	56 (26.9)	8 (13.8)	4 (11.4)	6 (18.2)	14 (13.9)	11 (14.5)	9 (17.0)
Prior history of stroke, n (%)	14 (13.7)	28 (13.5)	7 (12.1)	6 (17.1)	3 (9.1)	5 (5.0)	6 (7.9)	2 (3.8)
BMI, kg/m^2	26.3±3.4	27.0±4.4	26.3±3.9	26.1±4.0	26.9±4.0	27.7±4.4	28.3±4.7	27.3±4.5
SBP, mmHg	141 (134-152)	146 (134-156)	140 (134-149)	138 (129-151)	134 (125-144)	137 (120-150)	132 (125-145)	137 (129-144)
DBP, mmHg	79 (74-85)	82 (73-90)	80 (71-84)	78 (73-84)	80 (75-86)	83 (73-91)	75 (70-85)	79 (67-87)

Biochemical results at baseline								
HbA1c, %	5.7 (5.5-6.1)	5.7 (5.4-6.1)	5.6 (5.3-6.0)	5.6 (5.2-5.9)	5.7 (5.5-6.1)	5.7 (5.4-6.1)	5.7 (5.5-6.5)	5.5 (5.3-5.9)
LDL-C, mg/dL	135 (110-159)	129 (106-155)	119 (89-145)	114 (99-133)	128 (101-153)	130 (102-159)	123 (105-144)	117 (95-141)
HDL-C, md/dL	48 (40-58)	49 (41-61)	49 (44-59)	47 (40-58)	45(38-54)	48 (42-59)	40 (36-50)	54 (38-60)
Triglycerides, mg/dL	120 (93-177)	113 (87-148)	121 (96-147)	104 (81-182)	140 (108-184)	141 (102-195)	125 (94-165)	114 (95-170)
APOE genotype								
0 ε4 allele, n (%)	55 (74.3)	140 (80.9)	28 (73.4)	22 (78.6)	26 (81.3)	65 (74.7)	54 (84.4)	31 (81.6)
1 ε4 allele, n (%)	19 (25.7)	32 (18.5)	9 (23.7)	5 (17.9)	6 (18.8)	20 (23.0)	10 (15.6)	6 (15.8)
2 ε4 alleles, n (%)	0 (0.0)	1 (0.6)	1 (2.6)	1 (3.6)	0 (0.0)	2 (2.3)	0 (0.0)	1 (2.6)
Stroke classification, n (%)								
Ischemic stroke	99 (97.1)	202 (97.1)	55 (94.8)	35 (100.0)	33 (100.0)	99 (98.2)	74 (97.4)	51 (96.2)
TOAST subtype, n (%)								
Large artery atherosclerosis	16 (16.2)	61 (30.2)	12 (21.8)	8 (22.9)	10 (30.3)	32 (32.3)	24 (32.4)	9 (17.6)
Cardio-embolic	26 (26.3)	53 (26.2)	9 (16.4)	6 (17.1)	7 (21.2)	18 (18.2)	12 (16.2)	13 (25.5)
Small artery occlusion	13 (13.1)	16 (7.9)	3 (5.5)	6 (17.1)	8 (24.2)	15 (15.2)	3 (4.1)	13 (25.5)
Other etiology	3 (3.0)	2 (1.0)	5 (9.1)	3 (8.6)	0 (0.0)	7 (7.1)	9 (12.2)	1 (2.0)
Undefined etiology	41 (41.4)	70 (34.7)	26 (47.3)	12 (34.3)	8 (24.2)	27 (27.3)	26 (35.1)	15 (29.4)
Hemorrhagic stroke	3 (2.9)	6 (2.9)	3 (5.2)	0 (0.0)	0 (0.0)	2 (2.0)	2 (2.6)	2 (3.8)

Clinical assessment at baseline								
NIHSS score	2 (1-5)	2 (1-5)	2 (1-5)	2 (1-3)	2 (1-4)	3 (1-6)	3 (2-4)	3 (1-5)
mRS before stroke	0 (0-0)	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-0)
BI score	100 (90-100)	90 (75-100)	93 (66-100)	100 (95-100)	100 (85-100)	100 (85-100)	100 (95-100)	100 (95-100)
IQCODE score	48 (48-49)	48 (48-50)	48 (48-50)	49 (48-51)	48(48-49)	48(48-49)	48(48-49)	48(48-49)
Baseline cognitive impairment†, n (%)	43/98 (43.9)	110/195 (56.4)	33/58 (56.9)	20/35 (57.1)	12/33 (36.4)	52/95 (54.7)	45/76 (59.2)	22/53 (41.5)
MRI at baseline								
Stroke lesion volume (mm^3)	2228 (502-11237)	2104 (512-10408)	2040 (384-11376)	1024 (468-4936)	872 (504-5040)	5944 (1224-15584)	3688 (816-15166)	1344 (464-10264)
Normalized stroke lesion volume‡ (%)	0.15 (0.03-0.75)	0.13 (0.03-0.65)	0.13 (0.02-0.67)	0.07 (0.03-0.30)	0.07(0.03-0.38)	0.39 (0.08-1.01	0.23 (0.05-0.97)	0.09 (0.03-0.69)

Note: Values are expressed as number (percent), mean±SD, or median (interquartile range)

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; *APOE*, apolipoprotein E; NIHSS, national institutes of health stroke scale; mRS, modified Rankin scale; BI, Barthel index; IQCODE, informant questionnaire on cognitive decline in the elderly; MoCA, Montreal cognitive assessment; MRI, magnetic resonance imaging.

* from a self-reported questionnaire

† MoCA<26 or MMSE<24 when MoCA was not available (5.3% of total).

‡ normalized stroke lesion volume: stroke lesion volume/total intracranial volume

[a] Institute for Stroke and Dementia Research, Klinikum der Universität München

[b] Klinik für Neurologie, Klinikum rechts der Isar, Technische Universität München

[c] Center for Stroke Research Berlin, Department of Neurology - Campus Charité Mitte, Charité - Universitätsmedizin Berlin

[d] Center for Stroke Research Berlin, Department of Neurology - Campus Benjamin Franklin, Charité - Universitätsmedizin Berlin

[e] Klinik und Poliklinik für Neurologie, Universitätsklinikum Bonn

[f] Klinik für Neurologie, University Medical Center Göttingen

[g] Universitätsklinikum Magdeburg

Supplementary Table 13. Baseline characteristics of patients with available follow-ups and patients excluded from the analyses because they were lost to follow-up or died.

	Pooled data (n=666)		
	Patients with available follow-up (n=595)	Patients excluded from the analyses because they were lost-to-follow-up or died (n=71)	*P* value
Demographic variables at baseline			
Age, y	67.5±11.3	71.2±11.7	0.0092
Male, n (%)	397 (66.7)	47 (66.2)	1
Education years	13 (12- 16)	13 (12- 15)	0.266
Cardiovascular risk factors at baseline			
Hypertension, n (%)	454 (76.3)	61 (85.9)	0.0932
Diabetes mellitus, n (%)	113 (19.0)	18 (25.4)	0.2642
Current smoking*, n (%)	138 (23.2)	17 (23.9)	1
Drinking regularly, n (%)	451 (75.8)	47 (66.2)	0.1061
Atrial fibrillation, n (%)	113 (19.0)	20 (28.2)	0.0947
Stroke history, n (%)	63 (10.6)	8 (11.3)	1
BMI, kg/m^2	27.0±4.2	27.1±4.6	0.6195
SBP, mmHg	139 (129-150)	143 (135-152)	0.0484
DBP, mmHg	80 (72-87)	80 (74-88)	0.5185
Biochemical results at baseline			
HbA1c, %	5.7 (5.4, 6.1)	5.8 (5.5, 6.2)	0.1485
LDL-C. mg/dL	125 (103- 153)	134 (106-162)	0.2791
HDL-C, md/dL	48 (40- 59)	45 (38- 56)	0.1699
Triglycerides, mg/dL	122 (92- 168)	121 (89- 178)	0.9169
APOE genotype	(n=480)	(n=54)	

0 ε4 allele, n (%)	379 (79.0)	42 (77.8)	0.8535
1 ε4 allele, n (%)	95 (19.8)	12 (22.2)	
2 ε4 allele, n (%)	6 (1.3)	0 (0.0)	
Stroke classification, n (%)			
Ischemic stroke	578 (97.1)	70 (98.6)	0.7095
TOAST subtype, n (%)			
Large artery atherosclerosis	156 (27.0)	16 (22.9)	0.4591
Cardio-embolic	122 (21.1)	22 (31.4)	
Small artery occlusion	70 (12.1)	7 (0.1)	
Other etiology	27 (4.7)	3 (4.3)	
Undefined etiology	203 (35.1)	22 (31.4)	
Hemorrhagic stroke	17 (2.9)	1 (1.4)	0.7095
Clinical assessment at baseline			
NIHSS score	2 (1-5)	3 (1-6)	0.1674
mRS immediately before stroke	0 (0-0)	0 (0-1)	0.0987
BI score	100 (85-100)	95 (70-100)	0.0519
IQCODE score	48 (48-49)	48 (48-50)	0.1329
Baseline cognitive impairment[†], n (%)	287/577 (49.7)	50/66 (75.8)	0.0001

Note: Values are expressed as number (percent), mean±SD, or median (interquartile range)

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; *APOE*, apolipoprotein E; NIHSS, national institutes of health stroke scale; mRS, modified Rankin scale; BI, Barthel index; IQCODE, informant questionnaire on cognitive decline in the elderly; MoCA, Montreal cognitive assessment; MRI=magnetic resonance imaging.

* from a self-reported questionnaire

† MoCA<26 or MMSE<24 when MoCA was not available (5.3% of total).

Supplementary Table 14. Associations of all covariates included in our main models with global cognitive scores (composite z-score across five cognitive domains) across 12 months of follow-up incorporating both 6- and 12-month outcomes in linear generalized estimating equation (GEE) models.

All variables in the model	Coefficients Estimate	95% CI		P
(Intercept)	0.0460	-0.6505	0.7424	0.8971
MoCA<26 or MMSE<24 if MoCA not available	-0.4040	-0.5067	-0.3014	1.2101E-14
Global SVD score	-0.0841	-0.1426	-0.0255	0.0049
Normalized stroke lesion volume/SD	-0.0389	-0.0818	0.0040	0.0756
Days after stroke (d)	0.0007	0.0005	0.0008	<2e-16
Age	0.0051	-0.0007	0.0108	0.0845
Sex (0=male, 1=female)	-0.1244	-0.2385	-0.0103	0.0326
Educational years (y)	-0.0102	-0.0255	0.0051	0.1915
Current smoking	-0.1612	-0.2907	-0.0317	0.0147
Alcohol consumption	0.0607	-0.0668	0.1883	0.3508
History of hypertension	0.0837	-0.0493	0.2167	0.2175
History of diabetes	-0.2047	-0.3416	-0.0677	0.0034
History of atrial fibrillation	-0.2253	-0.3937	-0.0568	0.0088
Prior stroke	-0.0896	-0.2735	0.0943	0.3395
Body mass index/SD	-0.0224	-0.0839	0.0390	0.4716
LDL-C/SD	-0.0114	-0.0609	0.0419	0.6906
NIHSS score at baseline	-0.0043	-0.0128	0.0042	0.3226
Pre-stroke mRS	-0.0596	-0.1411	0.0220	0.1523

Abbreviations: MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; LDL-C, low density lipoprotein-cholesterol; NIHSS, national institutes of health stroke scale; mRS, modified Rankin scale; CI, confidence interval; SD, standard deviation.

Supplementary Table 15. Associations of all covariates included in our main models with modified Rankin scale (mRS) scores across 12 months of follow-up incorporating both 6- and 12-month outcomes in linear generalized estimating equation (GEE) models.

All variables in the model	Coefficients Estimate	95% CI		P
(Intercept)	0.04705	-0.7814	0.8755	0.9114
MoCA<26 or MMSE<24 if MoCA not available	0.1217	-0.0169	0.2603	0.0852
Global SVD score	0.1370	0.0583	0.2158	0.0006
Normalized stroke lesion volume/SD	0.0958	0.0236	0.1680	0.0093
Days after stroke (d)	-9.908E-05	-0.0004	0.0002	0.5606
Age	0.0028	-0.0046	0.0101	0.4610
Sex (0=male, 1=female)	-0.0197	-0.1716	0.1323	0.7996
Educational years (y)	-0.0127	-0.0320	0.0065	0.1954
Current smoking	0.1564	-0.0109	0.3237	0.0668
Alcohol consumption	-0.0535	-0.2148	0.1078	0.5156
History of hypertension	-0.0112	-0.1762	0.1538	0.8942
History of diabetes	0.3050	0.1027	0.5073	0.0031
History of atrial fibrillation	0.1259	-0.0876	0.3394	0.2478
Prior stroke	0.3378	0.0749	0.6007	0.0118
Body mass index/SD	0.0534	-0.0186	0.1250	0.1461
LDL-C/SD	0.0381	-0.0305	0.1100	0.2778
NIHSS score at baseline	0.0197	0.0036	0.0358	0.0167
Pre-stroke mRS	0.0654	-0.0807	0.2114	0.3804

Abbreviations: MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; LDL-C, low density lipoprotein-cholesterol; NIHSS, national institutes of health stroke scale; mRS, modified Rankin scale; CI, confidence interval; SD, standard deviation.

Supplementary Table 16. Associations of all covariates included in our main models with cognitive impairment (composite z-score <-1.5 or z <-1.5 in any individual cognitive domain) across 12 months of follow-up incorporating both 6- and 12-month outcomes in linear generalized estimating equation (GEE) models.

All variables in the model	OR	95% CI		P
(Intercept)	0.6726	0.0558	8.1141	0.7549
MoCA<26 or MMSE<24 if MoCA not available	2.4747	1.7138	3.5732	1.336E-06
Global SVD score	1.3107	1.0851	1.5832	0.0050
Normalized stroke lesion volume/SD	1.1700	0.9970	1.3800	0.0538
Days after stroke (d)	0.9975	0.9963	0.9987	3.8136E-05
Age	0.9890	0.9669	1.01153	0.3349
Sex (0=male, 1=female)	1.5741	1.0477	2.3650	0.0289
Educational years (y)	0.9680	0.9090	1.0308	0.3109
Current smoking	1.2725	0.8291	1.9529	0.2702
Alcohol consumption	0.7404	0.4911	1.1162	0.1513
History of hypertension	0.6967	0.4368	1.1112	0.1292
History of diabetes	1.8298	1.1416	2.9328	0.0121
History of atrial fibrillation	1.7566	1.0796	2.8583	0.0233
Prior stroke	1.1893	0.6671	2.1200	0.5568
Body mass index/SD	0.9870	0.8120	1.200	0.8915
LDL-C/SD	1.0900	0.8950	1.3300	0.3912
NIHSS score at baseline	1.0182	0.9926	1.0445	0.1658
Pre-stroke mRS	1.1852	0.8800	1.5962	0.2633

Abbreviations: MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; LDL-C, low density lipoprotein-cholesterol; NIHSS, national institutes of health stroke scale; mRS, modified Rankin scale; OR, odds ratio; CI, confidence interval; SD, standard deviation.

Supplementary Table 17. Associations of all covariates included in our main models with functional impairment (mRS>1) across 12 months of follow-up incorporating both 6- and 12-month outcomes in linear generalized estimating equation (GEE) models.

All variables in the model	OR	95% CI		P
(Intercept)	0.0267	0.0023	0.3168	0.0041
MoCA<26 or MMSE<24 if MoCA not available	1.1387	0.7893	1.6428	0.4873
Global SVD score	1.3417	1.1276	1.5965	0.0009
Normalized stroke lesion volume/SD	1.1100	0.9310	1.3200	0.2491
Days after stroke (d)	0.9999	0.9988	1.0010	0.8654
Age	1.0127	0.9912	1.0346	0.2485
Sex (0=male, 1=female)	0.9972	0.6555	1.5170	0.9894
Educational years (y)	0.9821	0.9316	1.0353	0.5016
Current smoking	1.2739	0.8065	2.0122	0.2994
Alcohol consumption	0.9451	0.6093	1.4660	0.8010
History of hypertension	0.9984	0.6131	1.6257	0.9948
History of diabetes	2.0585	1.3105	3.2336	0.0017
History of atrial fibrillation	1.3493	0.8414	2.1637	0.2138
Prior stroke	1.7762	1.0452	3.0185	0.0337
Body mass index/SD	1.0800	0.8900	1.3100	0.4376
LDL-C/SD	1.0800	0.9030	1.3000	0.3942
NIHSS score at baseline	1.0379	0.9978	1.0796	0.0643
Pre-stroke mRS	1.2366	0.9326	1.6398	0.1402

Abbreviations: MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; LDL-C, low density lipoprotein-cholesterol; NIHSS, national institutes of health stroke scale; mRS, modified Rankin scale; OR, odds ratio; CI, confidence interval; SD, standard deviation.

Supplementary Table 18. Associations of all covariates included in our main models with functional impairment (mRS>2) across 12 months of follow-up incorporating both 6- and 12-month outcomes in linear generalized estimating equation (GEE) models.

All variables in the model	OR	95% CI		P
(Intercept)	0.0001	2.3395E-06	0.0087	2.3767E-05
MoCA<26 or MMSE<24 if MoCA not available	1.3153	0.7337	2.3578	0.3574
Global SVD score	1.4165	1.0801	1.8577	0.0118
Normalized stroke lesion volume/SD	1.2000	0.9630	1.4900	0.1058
Days after stroke (d)	0.9988	0.9972	1.0004	0.1470
Age	1.0587	1.0165	1.1026	0.0060
Sex (0=male, 1=female)	0.7605	0.3753	1.5407	0.4472
Educational years (y)	0.9509	0.8746	1.0339	0.2385
Current smoking	1.4603	0.6681	3.1922	0.3426
Alcohol consumption	1.0793	0.5058	2.3032	0.8435
History of hypertension	1.0160	0.4580	2.2535	0.9689
History of diabetes	2.3507	1.2426	4.4471	0.0086
History of atrial fibrillation	1.3421	0.6448	2.7937	0.4314
Prior stroke	2.2347	1.1309	4.4157	0.0207
Body mass index/SD	1.1400	0.8360	1.5400	0.4154
LDL-C/SD	1.3400	1.0500	1.7000	0.0202
NIHSS score at baseline	1.0679	1.0197	1.1183	0.0053
Pre-stroke mRS	1.3052	0.8536	1.9958	0.2189

Abbreviations: MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; LDL-C, low density lipoprotein-cholesterol; NIHSS, national institutes of health stroke scale; mRS, modified Rankin scale; OR, odds ratio; CI, confidence interval; SD, standard deviation.

Supplementary Table 19. Calibration performance for predicting cognitive and functional impairment at 6 and 12 months of follow-up after stroke derived from a model not considering cerebral small vessel disease (SVD), a model including the global SVD score and a model including individual SVD lesions and their burden.

	Hosmer-Lemeshow Goodness-of Fit Test		ICI	95%CI
	χ^2 (df=8)	*P* value		
Cognitive impairment at 6 months				
Model 1	13.409	0.0985	0.0258	0.0244 to 0.0272
Model 2	3.7750	0.8768	0.0102	0.0096 to 0.0109
Model 3	6.5536	0.5855	0.0164	0.0152 to 0.0180
Functional impairment (mRS>1) at 6 months				
Model 1	14.936	0.0604	0.0230	0.0204 to 0.0277
Model 2	10.975	0.2031	0.0252	0.0233 to 0.0284
Model 3	3.3418	0.9111	0.0122	0.0116 to 0.0129
Functional impairment (mRS>2) at 6 months				
Model 1	2.8427	0.9438	0.0119	0.0107 to 0.0138
Model 2	4.5299	0.8064	0.0084	0.0076 to 0.0098
Model 3	10.667	0.2213	0.0149	0.0137 to 0.0170
Cognitive impairment at 12 months				
Model 1	8.9063	0.3503	0.0213	0.0197 to 0.0238

Model 2	5.9029	0.6581	0.0155	0.0142 to 0.0175
Model 3	10.0740	0.2599	0.0111	0.0104 to 0.0121
Functional impairment (mRS>1) at 12 months				
Model 1	8.0854	0.4252	0.0215	0.0198 to 0.0255
Model 2	7.2753	0.5072	0.0200	0.0187 to 0.0228
Model 3	2.0715	0.9787	0.0097	0.0088 to 0.0113
Functional impairment (mRS>2) at 12 months				
Model 1	7.7807	0.4552	0.0107	0.0087 to 0.0159
Model 2	4.2968	0.8294	0.0092	0.0077 to 0.0131
Model 3	9.1931	0.3263	0.0111	0.0102 to 0.0123

Note: The results were derived from three models predicting cognitive impairment (composite z-score <-1.5 or z <-1.5 in any individual cognitive domain), and functional impairment defined by the modified Rankin Scale (mRS) scores <1 and <2. The basic model (**model 1**) is adjusted for age, sex, education, vascular risk factors, NIHSS and MoCA in the acute phase, pre-stroke mRS, and normalized stroke lesion volume, whereas the additional models include either the global SVD score (**model 2**), or all individual SVD lesions (lacune count, deep and periventricular white matter hyperintensities Fazekas grades, cerebral microbleed counts, and grade of perivascular spaces) (**model 3**).

Abbreviations: ICI, integrated calibration index. NIHSS, national institutes of health stroke scale; MoCA, Montreal cognitive assessment.

Supplementary Table 20. Area under the curve of ROC (AUC) for predicting cognitive and functional impairment at 6 and 12 months post-stroke derived from models not considering cerebral small vessel disease (SVD), including the global SVD score, and including individual SVD lesions and their burden.

Predicted outcome	**Model 1**		**Model 2**		**Model 3**		**P_{12}***	**P_{13}†**	**P_{23}‡**
	AUC	**95%CI**	**AUC**	**95%CI**	**AUC**	**95%CI**			
Cognitive impairment at M6	0.6730	0.6236 to 0.7224	0.6840	0.6348 to 0.7332	0.6985	0.6501 to 0.7469	0.2402	0.0709	0.1935
mRS>1 at M6	0.6672	0.6130 to 0.7213	0.6715	0.6167 to 0.7263	0.6856	0.6310 to 0.7403	0.7310	0.2666	0.1693
mRS>2 at M6	0.7741	0.7059 to 0.8422	0.7723	0.7024 to 0.8422	0.7850	0.7164 to 0.8537	0.8592	0.5282	0.2400
Cognitive impairment at M12	**0.6882**	**0.6281 to 0.7484**	0.7011	0.6419 to 0.7602	**0.7215**	**0.6638 to 0.7793**	0.2101	**0.0359**	0.0657
mRS>1 at M12	0.6816	0.6227 to 0.7404	0.6916	0.6328 to 0.7505	0.6988	0.6425 to 0.7550	0.3855	0.1897	0.5182
mRS>2 at M12	0.8219	0.7536 to 0.8903	**0.8253**	**0.7565 to 0.8940**	**0.8551**	**0.7925 to 0.9177**	0.7345	0.0633	**0.0267**

Note: Cognitive impairment is defined as a z-score for composite cognitive performance <-1.5 or a z-score <-1.5 in any individual cognitive domain. Functional impairment is defined by the modified Rankin Scale (mRS) scores <1 and <2. The basic model (**model 1**) is adjusted for age, sex, education, vascular risk factors, NIHSS and MoCA in the acute phase, pre-stroke mRS, and normalized stroke lesion volume, whereas the additional models include either the global SVD score (**model 2**), or individual SVD lesions and their burden (lacune count, deep and periventricular white matter hyperintensities Fazekas grades, cerebral microbleed counts, and grade of perivascular spaces – **model 3**). **Bold** indicates statistically significant at $P<.05$.

Abbreviations: M6, 6 months; M12, 12 months.

* P value of AUC difference between Model 1 and Model 2

† P value of AUC difference between Model 1 and Model 3

‡ P value of AUC difference between Model 2 and Model 3.

Supplementary Table 21. Reclassification in prediction of cognitive and functional impairment at 6 and 12 months follow-up after stroke from a model not considering cerebral small vessel disease (SVD), a model including the global SVD score and a model including individual SVD lesions and their burden.

Predicted outcome	Reference model	New model	Event NRI (%)	Nonevent NRI (%)	Categorical NRI		IDI	
					%	95%CI	%	95%CI
Cognitive impairment at M6	Model 1	Model 2	2.03	3.61	5.64	-0.75 to 12.02	**0.95**	**0.09 to 1.82**
	Model 1	Model 3	0.00	11.08	**11.08**	**3.05 to 19.12**	**2.82**	**1.18 to 4.46**
	Model 2	Model 3	-2.03	7.22	5.19	-2.06 to 12.44	**1.87**	**0.56 to 3.18**
mRS>1 at M6	Model 1	Model 2	3.94	0.88	4.81	-2.78 to 12.40	**1.39**	**0.32 to 2.46**
	Model 1	Model 3	2.36	3.28	5.64	-4.05 to 15.34	**3.86**	**1.73 to 5.99**
	Model 2	Model 3	-1.57	2.41	0.83	-7.27 to 8.94	**2.47**	**1.05 to 3.89**
mRS>2 at M6	Model 1	Model 2	0.00	0.00	0.00	-8.29 to 8.29	1.40	-0.05 to 2.84
	Model 1	Model 3	16.00	3.18	**19.18**	**3.82 to 34.54**	**7.33**	**2.04 to 12.61**
	Model 2	Model 3	16.00	3.00	**19.00**	**5.88 to 32.11**	**5.93**	**1.74 to 10.13**
	Model 1	Model 2	-2.06	0.49	-1.57	-9.52 to 6.38	0.75	-0.20 to 1.70

Cognitive impairment at M12	Model 1	Model 3	1.03	6.63	7.66	-1.99 to 17.31	**3.05**	**0.63 to 5.47**
	Model 2	Model 3	3.09	5.90	**8.99**	**0.36 to 17.62**	**2.31**	**0.17 to 4.45**
mRS>1 at M12	Model 1	Model 2	-1.87	5.77	3.90	-4.31 to 12.11	**1.63**	**0.35 to 2.92**
	Model 1	Model 3	2.80	6.70	**9.50**	**0.89 to 18.11**	**2.42**	**0.75 to 4.10**
	Model 2	Model 3	4.67	0.92	5.60	-1.51 to 12.70	0.79	-0.42 to 2.00
mRS>2 at M12	Model 1	Model 2	6.25	0.39	6.64	-8.34 to 21.63	1.39	-0.22 to 3.01
	Model 1	Model 3	18.75	1.77	**20.52**	**4.17 to 36.87**	**7.00**	**2.36 to 11.63**
	Model 2	Model 3	12.50	1.38	**13.88**	**2.09 to 25.66**	**5.60**	**2.03 to 9.17**

Note: Cognitive impairment is defined as a z-score for composite cognitive performance <-1.5 or a z-score <-1.5 in any individual cognitive domain. Functional impairment is defined by the modified Rankin Scale (mRS) scores <1 and <2. Event refers to group of patients with cognitive impairment at M6, mRS>1 at M6, mRS>2 at M12, cognitive impairment at M12, mRS>1 at M12, and mRS>2 at M12 separately in the first column. Nonevent refers to group of patients without cognitive impairment at M6, mRS>1 at M6, mRS>2 at M12, cognitive impairment at M12, mRS>1 at M12, or mRS>2 at M12 separately in the first column. The basic model (**model 1**) is adjusted for age, sex, education, vascular risk factors, NIHSS and MoCA in the acute phase, pre-stroke mRS, and normalized stroke lesion volume, whereas the additional models include either the global SVD score (**model 2**), or individual SVD lesions and their burden (lacune count, deep and periventricular white matter hyperintensities Fazekas grades,

cerebral microbleed counts, and grade of perivascular spaces – **model 3**). The net reclassification improvement (NRI) as well as the integrated discrimination improvement (IDI) are provided for each comparison. Positive values indicate improvement in prediction. **Bold** indicates statistically significant reclassification improvement of the tested model as compared to the reference model at $P<.05$.

Abbreviations: M6, 6 months; M12, 12 months; NIHSS, national institutes of health stroke scale; MoCA, Montreal cognitive assessment.

Supplementary Table 22. Reclassification table stratified by cognitive and functional status at 6 and 12 months of follow-up after stroke with addition of the global SVD score and addition of individual SVD lesions and their burden.

Model 1	**Model 2**			Total
Patients number	<10%	10% to <30%	≥30%	
Cognitive impairment at M6				
<10%	0	0	0	0
10% to <30%	2	57	10	69
≥30%	0	5	74	79
Total	2	62	84	148
Non-cognitive impairment at M6				
<10%	12	4	0	16
10% to <30%	15	219	11	245
≥30%	0	14	113	127
Total	27	237	124	388
Model 1	**Model 3**			Total
Patients number	<10%	10% to <30%	≥30%	
Cognitive impairment at M6				
<10%	0	0	0	0
10% to <30%	2	54	13	69
≥30%	0	11	68	79
Total	2	65	81	148
Non-cognitive impairment at M6				
<10%	13	3	0	16
10% to <30%	30	200	15	245

≥30%	1	30	96	127
Total	44	233	111	388

Model 2	**Model 3**			Total
Patients number	<10%	10% to <30%	≥30%	
Cognitive impairment at M6				
<10%	1	1	0	2
10% to <30%	1	53	8	62
≥30%	0	11	73	84
Total	2	65	81	148
Non-cognitive impairment at M6				
<10%	24	3	0	27
10% to <30%	18	204	15	237
≥30%	2	26	96	124
Total	44	233	111	388

Model 1	**Model 2**			Total
Patients number	<10%	10% to <30%	≥30%	
mRS>1 at M6				
<10%	1	0	0	1
10% to <30%	2	74	13	89
≥30%	0	6	31	37
Total	3	80	44	127
Non-mRS>1 at M6				
<10%	22	3	0	25
10% to <30%	15	343	17	375
≥30%	0	9	48	57

Total	37	355	65	457
Model 1		**Model 3**		Total
Patients number	<10%	10% to <30%	≥30%	
mRS>1 at M6				
<10%	1	0	0	1
10% to <30%	6	65	18	89
≥30%	0	9	28	37
Total	7	74	46	127
Non-mRS>1 at M6				
<10%	14	11	0	25
10% to <30%	30	321	24	375
≥30%	0	20	37	57
Total	44	352	61	457
Model 2		**Model 3**		Total
Patients number	<10%	10% to <30%	≥30%	
mRS>1 at M6				
<10%	2	1	0	3
10% to <30%	5	66	9	80
≥30%	0	7	37	44
Total	7	74	46	127
Non-mRS>1 at M6				
<10%	24	13	0	37
10% to <30%	20	317	18	355
≥30%	0	22	43	65
Total	44	352	61	457

Model 1	**Model 2**			Total
Patients number	<10%	10% to <30%	≥30%	
mRS>2 at M6				
<10%	16	0	0	16
10% to <30%	2	25	2	29
≥30%	0	0	5	5
Total	18	25	7	50
Non-mRS>2 at M6				
<10%	382	23	0	405
10% to <30%	24	88	4	116
≥30%	0	3	10	13
Total	406	114	14	534

Model 1	**Model 3**			Total
Patients number	<10%	10% to <30%	≥30%	
mRS>2 at M6				
<10%	13	3	0	16
10% to <30%	4	16	9	29
≥30%	0	0	5	5
Total	17	19	14	50
Non-mRS>2 at M6				
<10%	382	21	2	405
10% to <30%	38	73	5	116
≥30%	0	7	6	13
Total	420	101	13	534

Model 2	**Model 3**	Total

Patients number	<10%	10% to <30%	≥30%	
mRS>2 at M6				
<10%	15	3	0	18
10% to <30%	2	16	7	25
≥30%	0	0	7	7
Total	17	19	14	50
Non-mRS>2 at M6				
<10%	390	15	1	406
10% to <30%	30	81	3	114
≥30%	0	5	9	14
Total	420	101	13	534

Model 1	**Model 2**			Total
Patients number	<10%	10% to <30%	≥30%	
PSCI at M12				
<10%	5	1	0	6
10% to <30%	5	49	4	58
≥30%	0	2	31	33
Total	10	52	35	97
Non-PSCI at M12				
<10%	89	17	0	106
10% to <30%	21	219	13	253
≥30%	0	11	37	48
Total	110	247	50	407

Model 1	**Model 3**			Total
Patients number	<10%	10% to <30%	≥30%	

PSCI at M12				
<10%	3	3	0	6
10% to <30%	5	46	7	58
≥30%	0	4	29	33
Total	8	53	36	97
Non-PSCI at M12				
<10%	95	10	1	106
10% to <30%	33	210	10	253
≥30%	0	15	33	48
Total	128	235	44	407

Model 2	**Model 3**			Total
Patients number	<10%	10% to <30%	≥30%	
PSCI at M12				
<10%	7	3	0	10
10% to <30%	1	45	6	52
≥30%	0	5	30	35
Total	8	53	36	97
Non-PSCI at M12				
<10%	99	11	0	110
10% to <30%	29	211	7	247
≥30%	0	13	37	50
Total	128	235	44	407

Model 1	**Model 2**			Total
Patients number	<10%	10% to <30%	≥30%	
mRS>1 at M12				

<10%	6	1	0	7
10% to <30%	5	53	6	64
≥30%	0	4	32	36
Total	11	58	38	107
Non-mRS>1 at M12				
<10%	49	9	0	58
10% to <30%	39	274	13	326
≥30%	0	8	41	49
Total	88	291	54	433

Model 1	**Model 3**			Total
Patients number	<10%	10% to <30%	≥30%	
mRS>1 at M12				
<10%	5	2	0	7
10% to <30%	4	52	8	64
≥30%	0	3	33	36
Total	9	57	41	107
Non-mRS>1 at M12				
<10%	50	8	0	58
10% to <30%	44	261	21	326
≥30%	0	14	35	49
Total	94	283	56	433

Model 2	**Model 3**			Total
Patients number	<10%	10% to <30%	≥30%	
mRS>1 at M12				
<10%	8	3	0	11

10% to <30%	1	52	5	58
≥30%	0	2	36	38
Total	9	57	41	107
Non-mRS>1 at M12				
<10%	69	19	0	88
10% to <30%	25	252	14	291
≥30%	0	12	42	54
Total	94	283	56	433

Model 1	**Model 2**			Total
Patients number	<10%	10% to <30%	≥30%	
mRS>2 at M12				
<10%	10	2	0	12
10% to <30%	1	13	2	16
≥30%	0	1	3	4
Total	11	16	5	32
Non-mRS>2 at M12				
<10%	414	13	0	427
10% to <30%	13	58	0	71
≥30%	0	2	8	10
Total	427	73	8	508

Model 1	**Model 3**			Total
Patients number	<10%	10% to <30%	≥30%	
mRS>2 at M12				
<10%	10	2	0	12
10% to <30%	0	11	5	16

≥30%	0	1	3	4
Total	10	14	8	32
Non-mRS>2 at M12				
<10%	406	20	1	427
10% to <30%	33	32	6	71
≥30%	1	2	7	10
Total	440	54	14	508

Model 2	**Model 3**			Total
Patients number	<10%	10% to <30%	≥30%	
mRS>2 at M12				
<10%	10	1	0	11
10% to <30%	0	13	3	16
≥30%	0	0	5	5
Total	10	14	8	32
Non-mRS>2 at M12				
<10%	411	15	1	427
10% to <30%	28	39	6	73
≥30%	1	0	7	8
Total	440	54	14	508

Note: The cognitive & functional impairments were derived from three models predicting cognitive impairment (composite z-score <-1.5 or z <-1.5 in any individual cognitive domain), and functional impairment defined by the modified Rankin Scale (mRS) scores <1 and <2. The basic model (**model 1**) is adjusted for age, sex, education, vascular risk factors, NIHSS and MoCA in the acute phase, pre-stroke mRS, and normalized stroke lesion volume, whereas the additional models include either the global SVD score (**model 2**), or all individual SVD lesions (lacune count, deep

and periventricular white matter hyperintensities Fazekas grades, cerebral microbleed counts, and grade of perivascular spaces) (**model 3**).

Abbreviations: NIHSS, national institutes of health stroke scale; MoCA, Montreal cognitive assessment.

Supplementary Table 23. The banner list of DEMDAS Investigators.

Last name	First name	Email	Affiliation 1	Affiliation 2	Affiliation 3	Affiliation 4
Endres	Matthias	matthias.endres@charite.de	Department of Neurology with Experimental Neurology, Charité - Univeristätsmedizin Berlin, Berlin, Germany	German Center for Neurodegenerative Diseases (DZNE), Berlin 10117, Germany	Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin, Berlin, Germany	German Centre for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany
Liman	Thomas G.	thomas.liman@charite.de	Department of Neurology with Experimental Neurology, Charité - Univeristätsmedizin Berlin	German Center for Neurodegenerative Diseases (DZNE), Berlin 10117, Germany		
Kerti	Lucia	lucia.kerti@charite.de	Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin	German Center for Neurodegenerative Diseases (DZNE), Berlin 10117, Germany		
Nolte	Christian H.	christian.nolte@charite.de	Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin	Department of Neurology with Experimental Neurology, Charité - Univeristätsmedizin Berlin	Berlin Institute of Health (BIH), Germany	
Wittenberg	Tatjana	tatjana.wittenberg@charite.de	Center for Stroke Research Berlin (CSB), Charité -			

			Universitätsmedizin Berlin		
Scheitz	Jan F.	jan.scheitz@charite.de	Department of Neurology with Experimental Neurology, Charité - Univeristätsmedizin Berlin	Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin	
Prüß	Harald	harald.pruess@charite.de	Department of Neurology with Experimental Neurology, Charité - Univeristätsmedizin Berlin	German Center for Neurodegenerative Diseases (DZNE), Berlin 10117, Germany	
Sperber	Pia Sophie	pia.sperber@charite.de	Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin	Department of Neurology with Experimental Neurology, Charité - Univeristätsmedizin Berlin	
Nave	Alexander H.	alexander-heinrich.nave@charite.de	Department of Neurology with Experimental Neurology, Charité - Universitätsmedizin Berlin	Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin	Berlin Institute of Health (BIH), Germany
Kufner Ibaroule	Anna	anna.kufner@charite.de	Department of Neurology with Experimental Neurology, Charité -	Center for Stroke Research Berlin (CSB), Charité -	Berlin Institute of Health (BIH), Germany

			Universitätsmedizin Berlin	Universitätsmedizin Berlin
Petzold	Gabor	Gabor.Petzold@dzne.de	German Center for Neurodegenerative Diseases (DZNE), Bonn 53127, Germany	Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn 53127, Germany
Bode	Felix	felix.bode@ukbonn.de	German Center for Neurodegenerative Diseases (DZNE), Bonn 53127, Germany	Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn 53127, Germany
Stösser	Sebastian	sebastian.stoesser@ukbonn.de	German Center for Neurodegenerative Diseases (DZNE), Bonn 53127, Germany	Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn 53127, Germany
Meissner	Julius	julius.meissner@ukbonn.de	Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn 53127, Germany	

Ebrahimi	Taraneh	taraneh.ebrahimi@ukbonn.de	Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn 53127, Germany	
Nordsiek	Julia	julia.nordsiek@ukbonn.de	German Center for Neurodegenerative Diseases (DZNE), Bonn 53127, Germany	Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn 53127, Germany
Beckonert	Niklas	niklas.beckonert@ukbonn.de	Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn 53127, Germany	
Kindler	Christine	christine.kindler@ukbonn.de	German Center for Neurodegenerative Diseases (DZNE), Bonn 53127, Germany	Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn 53127, Germany
Zerr	Inga	ingazerr@med.uni-goettingen.de	Department of Neurology, University Medical Center	German Center for Neurodegenerative Diseases (DZNE),

			Göttingen, Göttingen 37075, Germany	Göttingen Germany	37075,
Hermann	Peter	peter.hermann@med.uni-goettingen.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		
Schmitz	Matthias	matthias.schmitz@med.uni-goettingen.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		
Goebel	Stefan	stefan.goebel@med.uni-goettingen.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		
Bunck	Timothy	timothy.bunck@med.uni-goettingen.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		
Schütte-Schmidt	Julia	julia.schuette@med.uni-goettingen.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		
Nuhn	Sabine	sabine.nuhn@med.uni-goettingen.de	Department of Neurology, University		

			Medical Center Göttingen, Göttingen 37075, Germany		
Volpers	Corinna	corinna.volpers@med.uni-goettingen.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		
Dechent	Peter	peter.dechent@med.uni-goettingen.de	Department of Cognitive Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		
Bähr	Mathias	mbaehr@gwdg.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany	German Center for Neurodegenerative Diseases (DZNE), Göttingen 37075, Germany	Cluster of Excellence Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB), Göttingen, Germany
Görtler	Michael	Michael.Goertler@med.ovgu.de	Department of Neurology, University Hospital, Otto-von-Guericke University Magdeburg, Magdeburg 39120, Germany	German Center for Neurodegenerative Diseases (DZNE), Magdeburg 39120, Germany	
Glanz	Wenzel	Wenzel.Glanz@dzne.de	Department of Neurology, University Hospital, Otto-von-Guericke University	German Center for Neurodegenerative Diseases (DZNE), Magdeburg 39120, Germany	

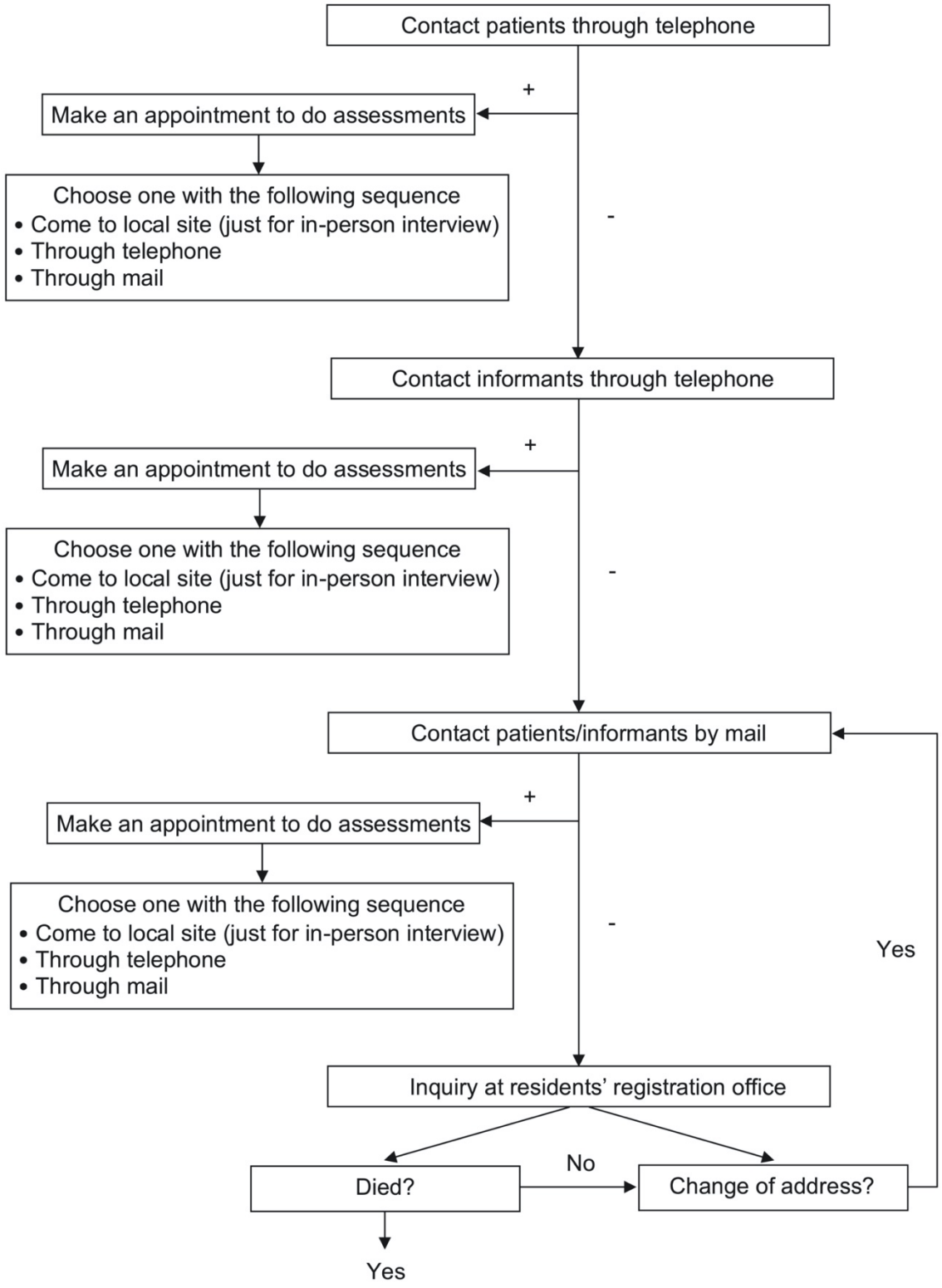
			Magdeburg, Magdeburg 39120, Germany	
Perosa	Valentina	vperosa@mgh.Harvard.edu	Department of Neurology, University Hospital, Otto-von-Guericke University Magdeburg, Magdeburg 39120, Germany	German Center for Neurodegenerative Diseases (DZNE), Magdeburg 39120, Germany
Dichgans	Martin	Martin.Dichgans@med.uni-muenchen.de	Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, 81377 Munich, Germany.	German Center for Neurodegenerative Diseases (DZNE), Munich 81377, Germany
Wollenweber	Frank	frank.wollenweber@med.uni-muenchen.de	Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, 81377 Munich, Germany.	
Georgakis	Marios	marios.georgakis@med.uni-muenchen.de	Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, 81377 Munich, Germany.	
Fang	Rong	Rong.Fang@med.uni-muenchen.de	Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich,	

			81377 Munich, Germany.	
Janowitz	Daniel	daniel.janowitz@med.uni-muenchen.de	Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, 81377 Munich, Germany.	
Waegemann	Karin	karin.waegemann@med.uni-muenchen.de	Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, 81377 Munich, Germany.	German Center for Neurodegenerative Diseases (DZNE), Munich 81377, Germany
Tiedt	Steffen	steffen.tiedt@med.uni-muenchen.de	Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, 81377 Munich, Germany.	
Wunderlich	Silke	Silke.Wunderlich@mri.tum.de	Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany	
Ikenberg	Benno	Benno.Ikenberg@mri.tum.de	Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical	

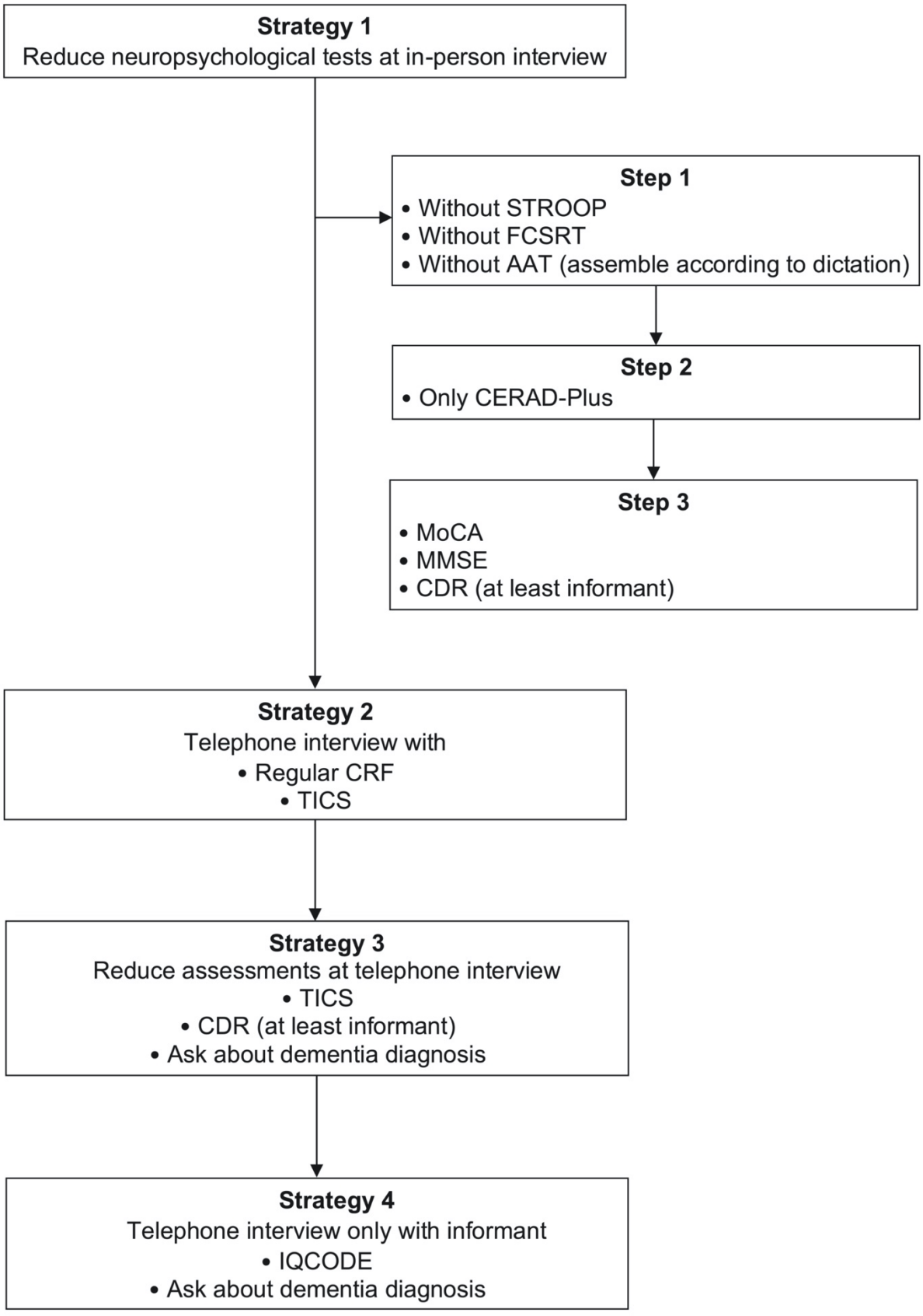
			University of Munich, Munich, Germany	
Bernkopf	Kathleen	Kathleen.Bernkopf@mri.tum.de	Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany	
Huber	Christiane	Christiane.Huber@mri.tum.de	Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany	
Poppert	Holger	Holger.Poppert@helios-gesundheit.de	Neurology Department, Helios Klinikum München West, Munich, Germany	
Düring	Marco	Marco.Duering@med.uni-muenchen.de	Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, 81377 Munich, Germany.	Medical Image Analysis Center (MIAC AG) and qbig, Department of Biomedical Engineering, University of Basel, Basel, Switzerland
Araque Caballero	Miguel Ángel	maaraquecaballero@gmail.com	Institute for Stroke and Dementia Research (ISD), University	German Center for Neurodegenerative Diseases (DZNE),

			Hospital, LMU Munich, 81377 Munich, Germany.	Munich 81377, Germany		
Gesierich	Benno	benno.gesierich@med.uni-muenchen.de	Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, 81377 Munich, Germany.			
Dewenter	Anna	anna.dewenter@med.uni-muenchen.de	Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, 81377 Munich, Germany.			
Dobisch	Laura	Laura.Dobisch@dzne.de	German Center for Neurodegenerative Diseases (DZNE), Magdeburg 39120, Germany			
Neumann	Katja	Katja.Neumann@dzne.de	German Center for Neurodegenerative Diseases (DZNE), Magdeburg 39120, Germany			
Speck	Oliver	oliver.speck@ovgu.de	Department of Biomedical Magnetic Resonance, Institute for Physics, Otto-von-Guericke University	German Center for Neurodegenerative Diseases (DZNE), Magdeburg 39120, Germany	Leibniz Institute for Neurobiology, 39118 Magdeburg, Germany	Center for Behavioral Brain Sciences, 39106 Magdeburg, Germany

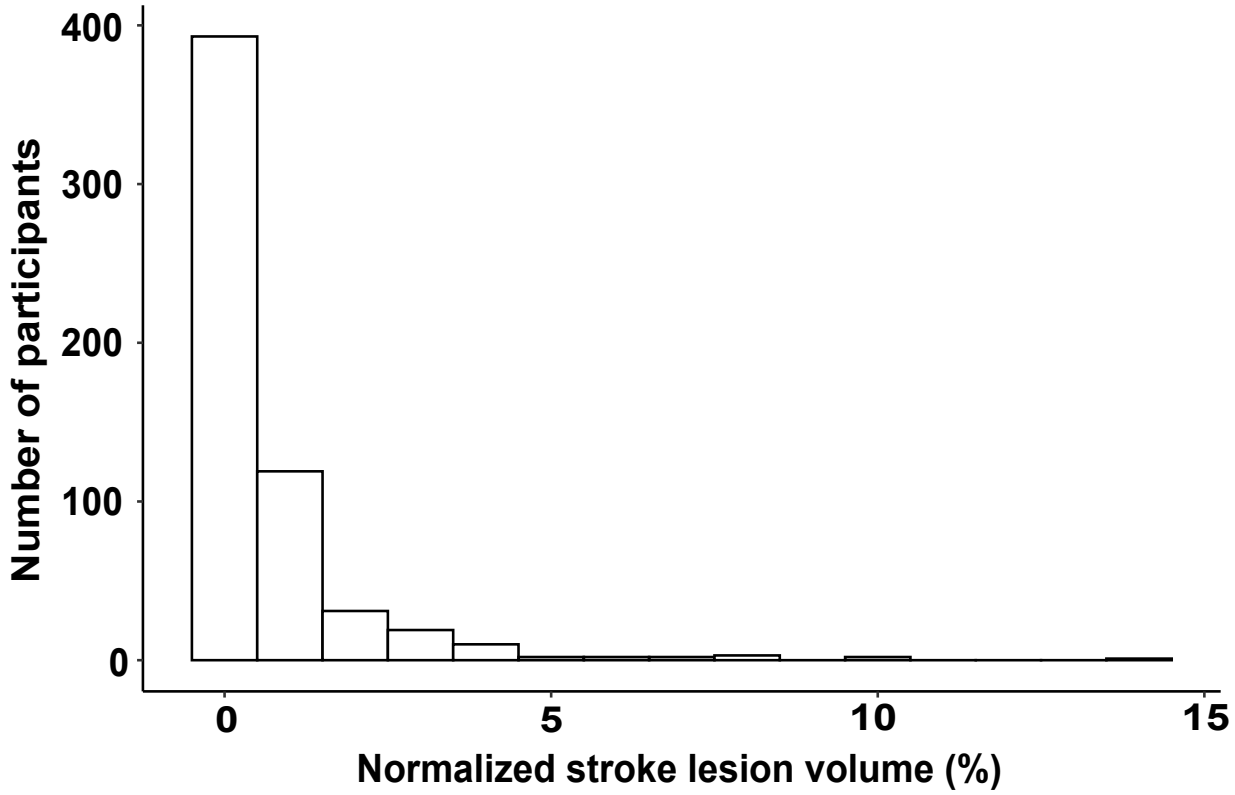
			Magdeburg, Magdeburg 39120, Germany	
Spottke	Annika	Annika.Spottke@dzne.de	German Center for Neurodegenerative Diseases (DZNE), Bonn 53127, Germany	Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn 53127, Germany
Stöcker	Tony	tony.stoecker@dzne.de	German Center for Neurodegenerative Diseases (DZNE), Bonn 53127, Germany	
Bartenstein	Peter	Peter.Bartenstein@med.uni-muenchen.de	Department of Nuclear Medicine, University Hospital, LMU Munich, 81377 Munich, Germany	
Wagner	Michael	michael.wagner@dzne.de	German Center for Neurodegenerative Diseases (DZNE), Bonn 53127, Germany	



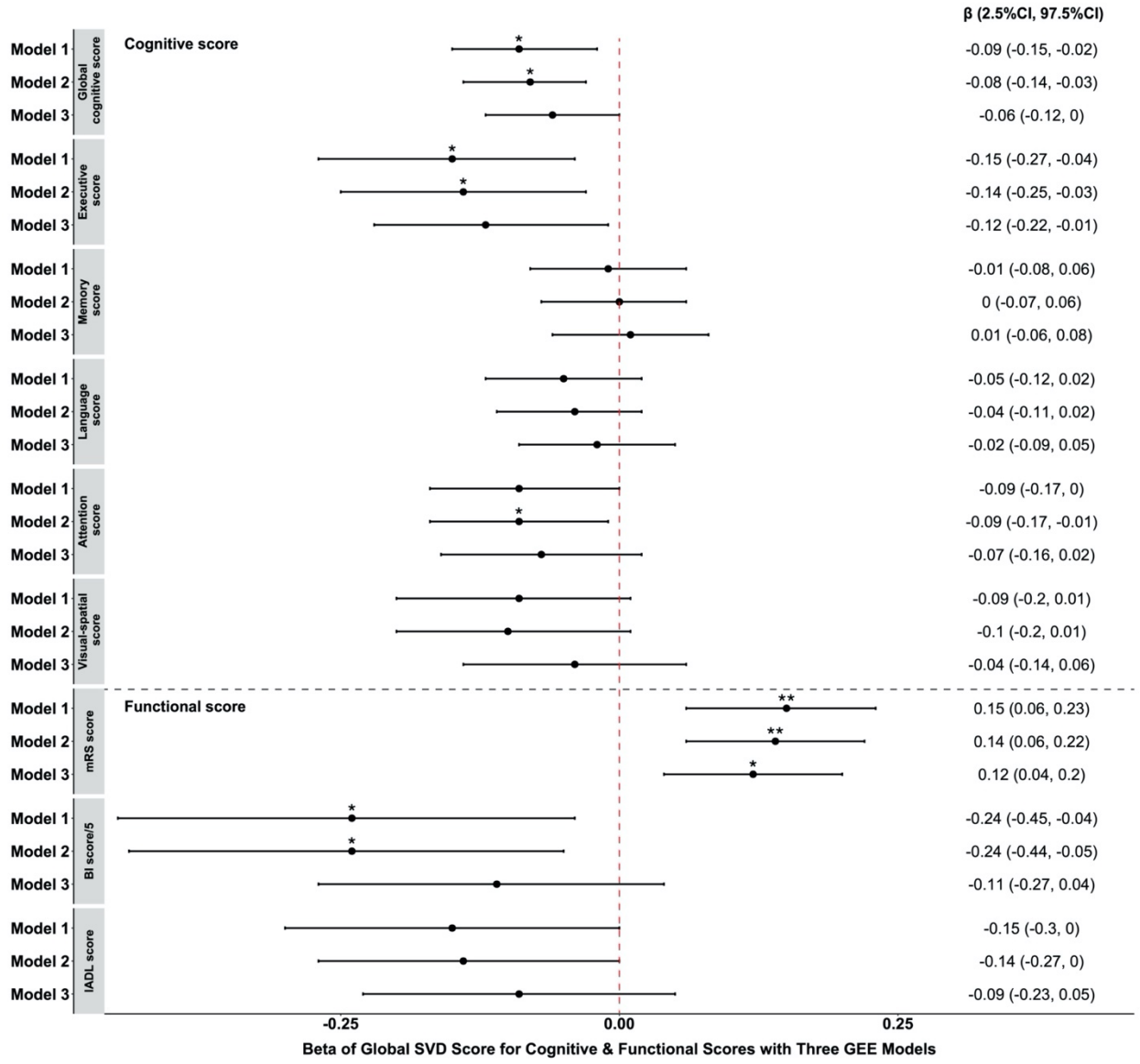
Supplementary Figure 1. Protocol for contacting patients at follow-up visits. (-) indicates no response and (+) indicates successful contact.


Strategy 1
Reduce neuropsychological tests at in-person interview
Step 1
• Without STROOP
• Without FCSRT
• Without AAT (assemble according to dictation)
Step 2
• Only CERAD-Plus
Step 3
• MoCA
• MMSE
• CDR (at least informant)
Strategy 2
Telephone interview with
• Regular CRF
• TICS
Strategy 3
Reduce assessments at telephone interview
• TICS
• CDR (at least informant)
• Ask about dementia diagnosis
Strategy 4
Telephone interview only with informant
• IQCODE
• Ask about dementia diagnosis

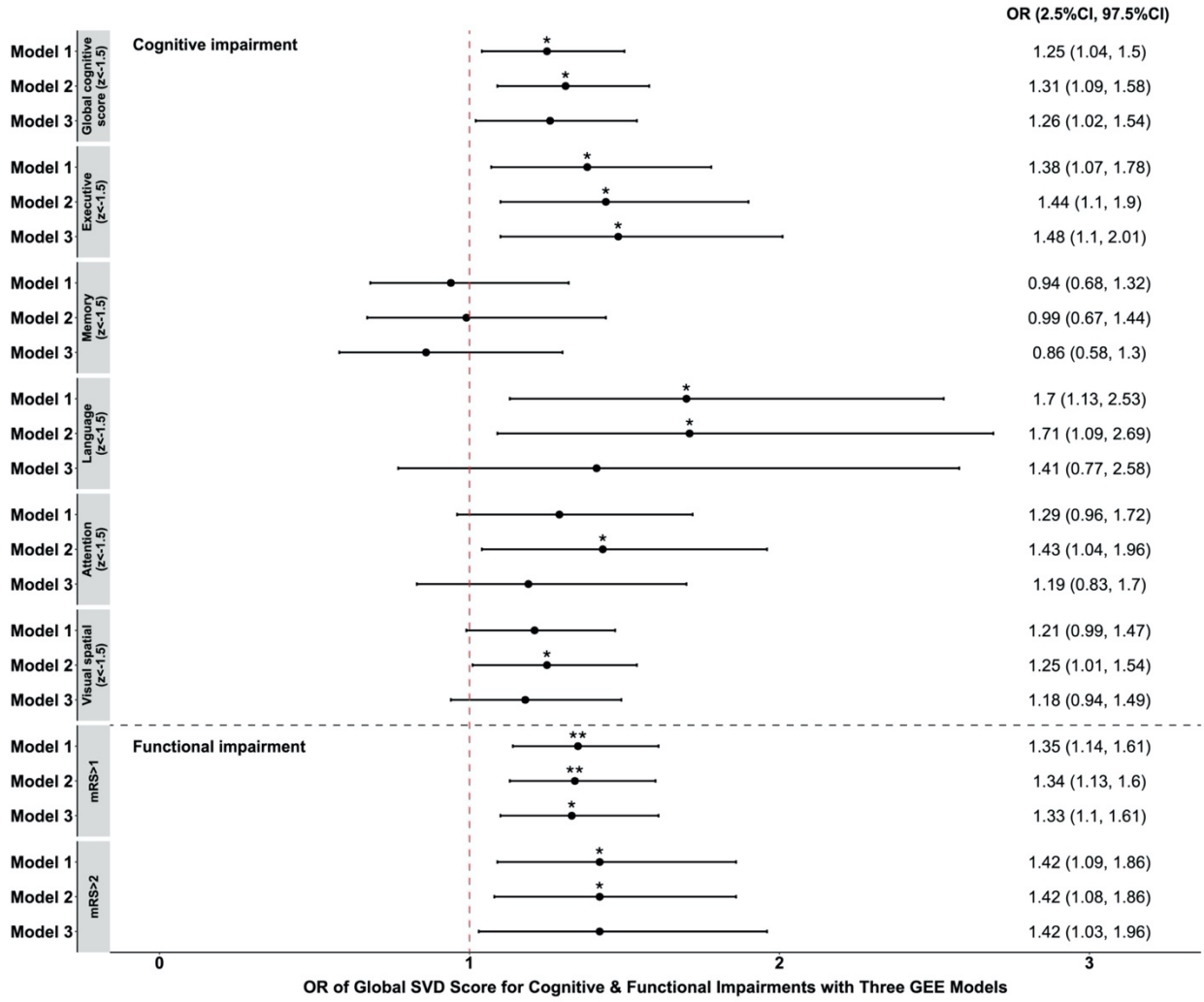
Supplementary Figure 2. Hierarchical procedure to reduce the volume of neuropsychological tests in patients not willing to undergo detailed neuropsychological testing. STROOP, Stroop Colour-Word-Interference Test; FCSRT, Free and Cued Selective Reminding Test; AAT, Aachen Aphasia Test; CERAD-Plus, Consortium to Establish a Registry for Alzheimer's Disease Plus; MoCA, Montreal Cognitive Assessment; MMSE, Mini Mental State Examination; CDR, Clinical Dementia Rating Score; CRF, case report form; TICS, Telephone Interview for Cognitive Status; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly.



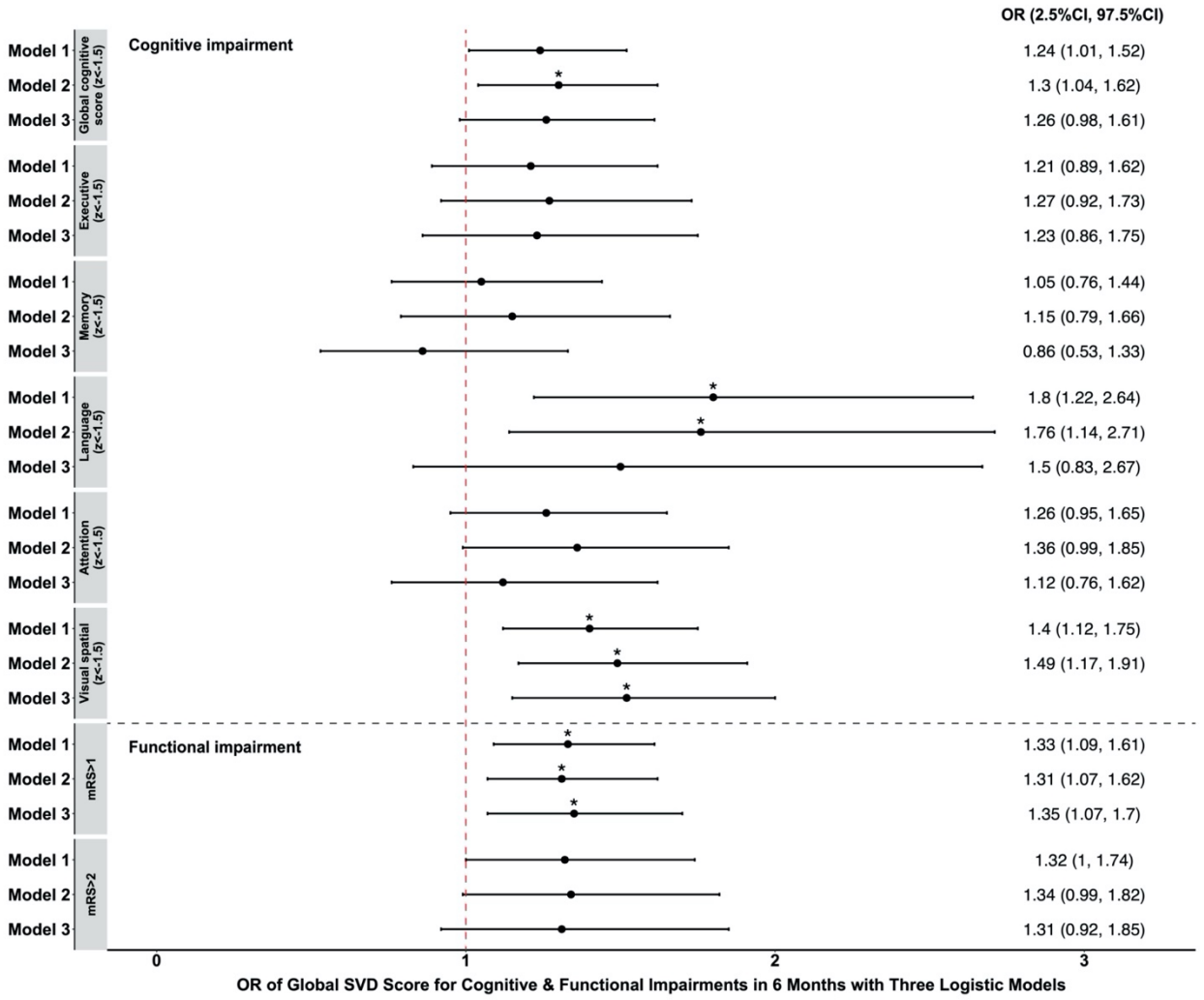
Supplementary Figure 3. Frequency distribution of normalized stroke lesion volume in DEDEMAS and DEMDAS. Stroke lesion includes ischemic and hemorrhagic types.



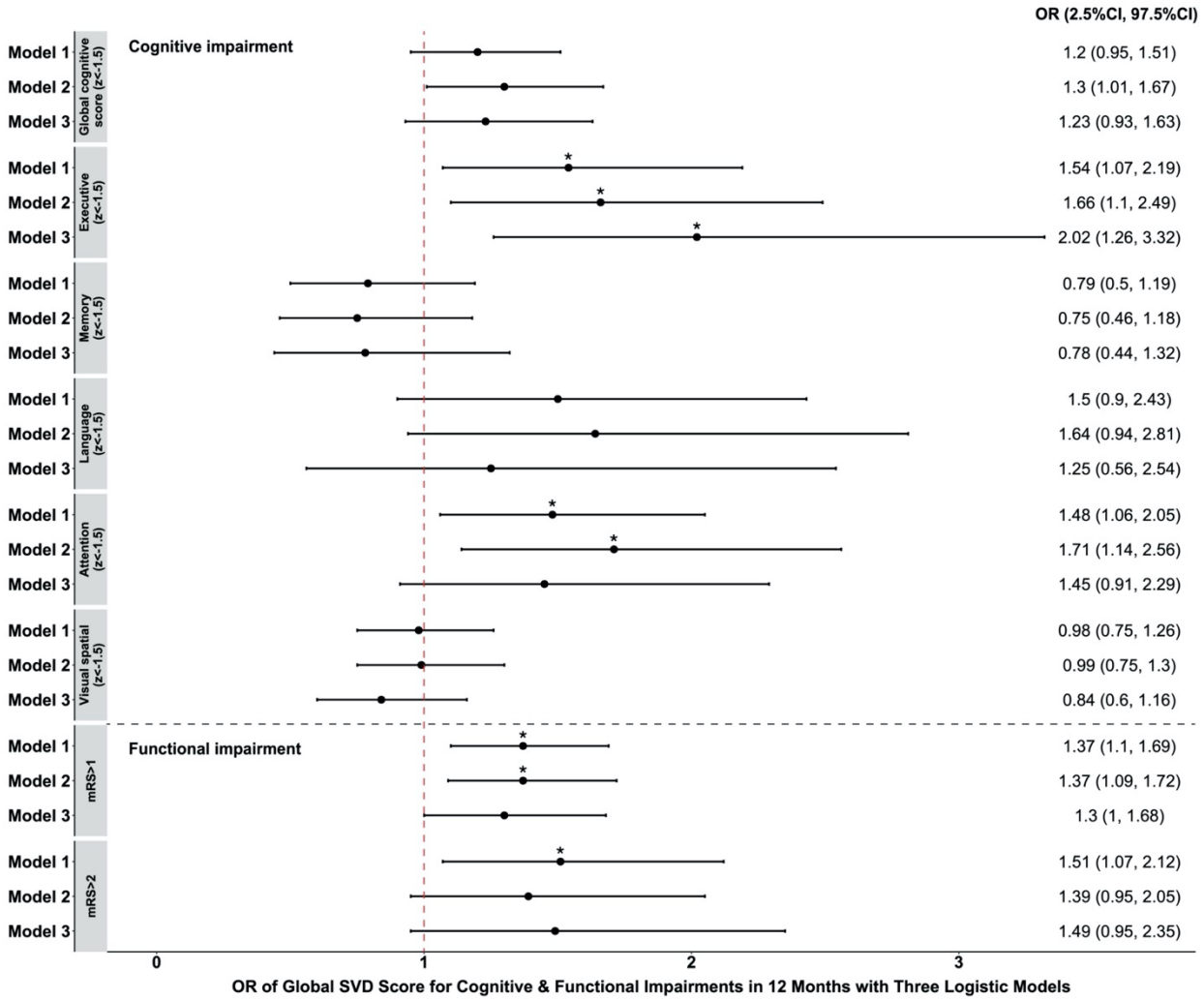
Supplementary Figure 4. Associations of global SVD score with cognitive and functional performance across 12 months of follow-up after stroke, as derived from three GEE models with different levels of adjustments. Model 1 is adjusted for age, sex, and education; model 2 is additionally adjusted for vascular risk factors, NIHSS and MoCA in the acute phase, pre-stroke mRS, and normalized stroke lesion volume (stroke lesion volume/total intracranial volume); model 3 is additionally adjusted for *APOE* genotype. *P* values are corrected for multiple comparisons with the false discovery rate (FDR) method. SVD, small vessel disease; NIHSS, national institutes of health stroke scale; MoCA, Montreal cognitive assessment. * $P_{corr.}$<.05, ** $P_{corr.}$<.01.



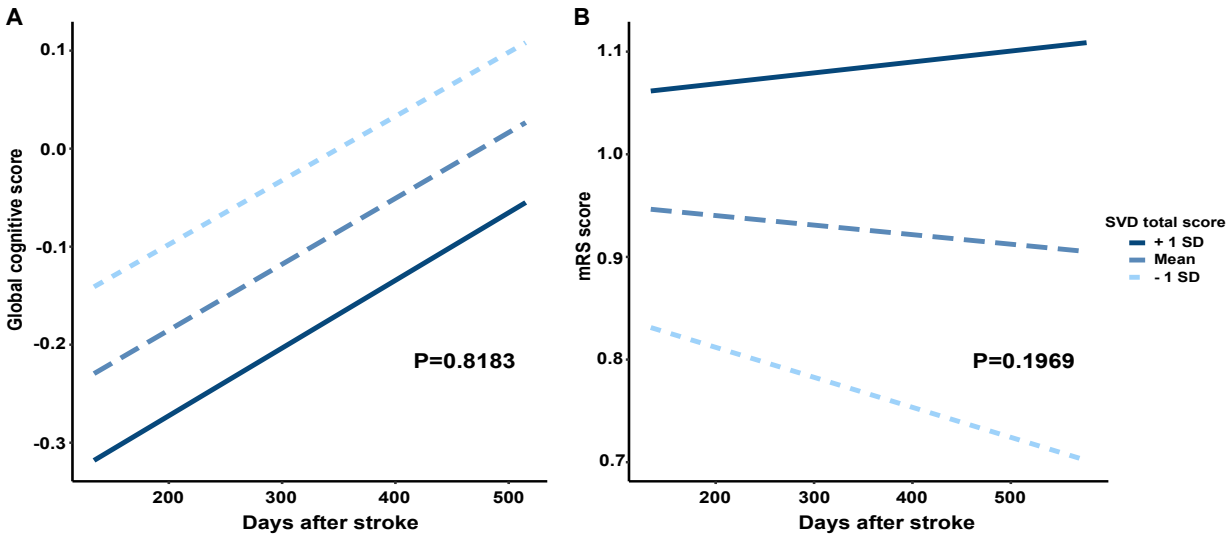
Supplementary Figure 5. Associations of global SVD score with cognitive and functional impairment across 12 months of follow-up after stroke, as derived from three logistic GEE models with different levels of adjustments. Model 1 is adjusted for age, sex, and education; model 2 is additionally adjusted for vascular risk factors, NIHSS and MoCA in the acute phase, pre-stroke mRS, and normalized stroke lesion volume volume (stroke lesion volume/total intracranial volume); model 3 is additionally adjusted for *APOE* genotype. *P* values are corrected for multiple comparisons with the false discovery rate (FDR) method. OR, odds ratios; SVD, small vessel disease; NIHSS, national institutes of health stroke scale; MoCA, Montreal cognitive assessment. * $P_{corr.}$<.05, ** $P_{corr.}$<.01.



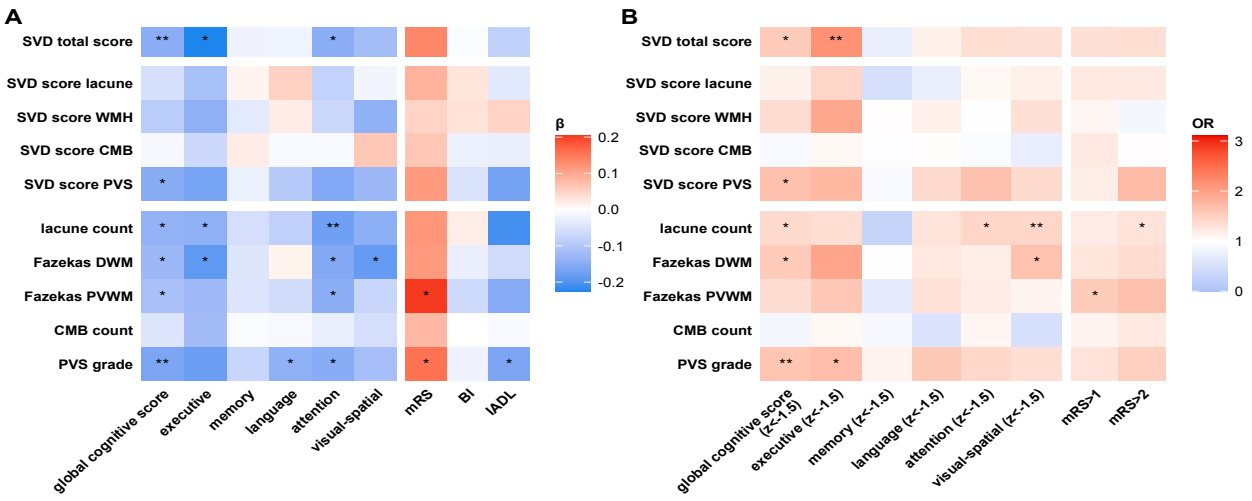
Supplementary Figure 6. Associations of global SVD score with cognitive and functional impairment at 6 months of follow-up after stroke, as derived from three logistic regression models with different levels of adjustments. Model 1 is adjusted for age, sex, and education; model 2 is additionally adjusted for vascular risk factors, NIHSS and MoCA in the acute phase, pre-stroke mRS, and normalized stroke lesion volume volume (stroke lesion volume/total intracranial volume); model 3 is additionally adjusted for *APOE* genotype. *P* values are corrected for multiple comparisons with the false discovery rate (FDR) method. OR, odds ratios; SVD, small vessel disease; NIHSS, national institutes of health stroke scale; MoCA, Montreal cognitive assessment. * $P_{corr.}$<.05, ** $P_{corr.}$<.01.



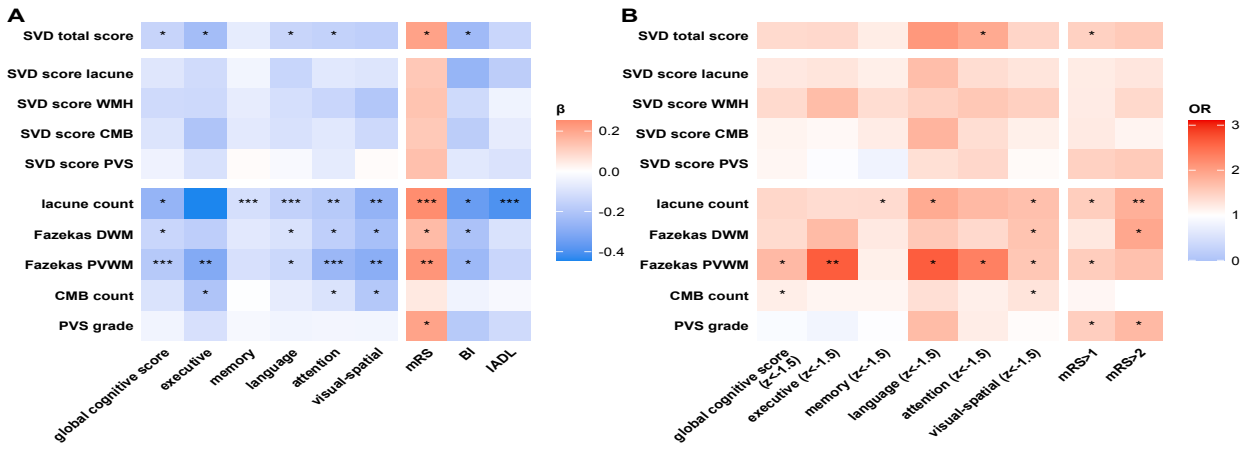
Supplementary Figure 7. Associations of global SVD score with cognitive and functional impairment at 12 months of follow-up after stroke, as derived from three logistic regression models with different levels of adjustments. Model 1 is adjusted for age, sex, and education; model 2 is additionally adjusted for vascular risk factors, NIHSS and MoCA in the acute phase, pre-stroke mRS, and normalized stroke lesion volume volume (stroke lesion volume/total intracranial volume); model 3 is additionally adjusted for *APOE* genotype. *P* values are corrected for multiple comparisons with the false discovery rate (FDR) method. OR, odds ratios; SVD, small vessel disease; NIHSS, national institutes of health stroke scale; MoCA, Montreal cognitive assessment. * $P_{corr.}$<.05, ** $P_{corr.}$<.0



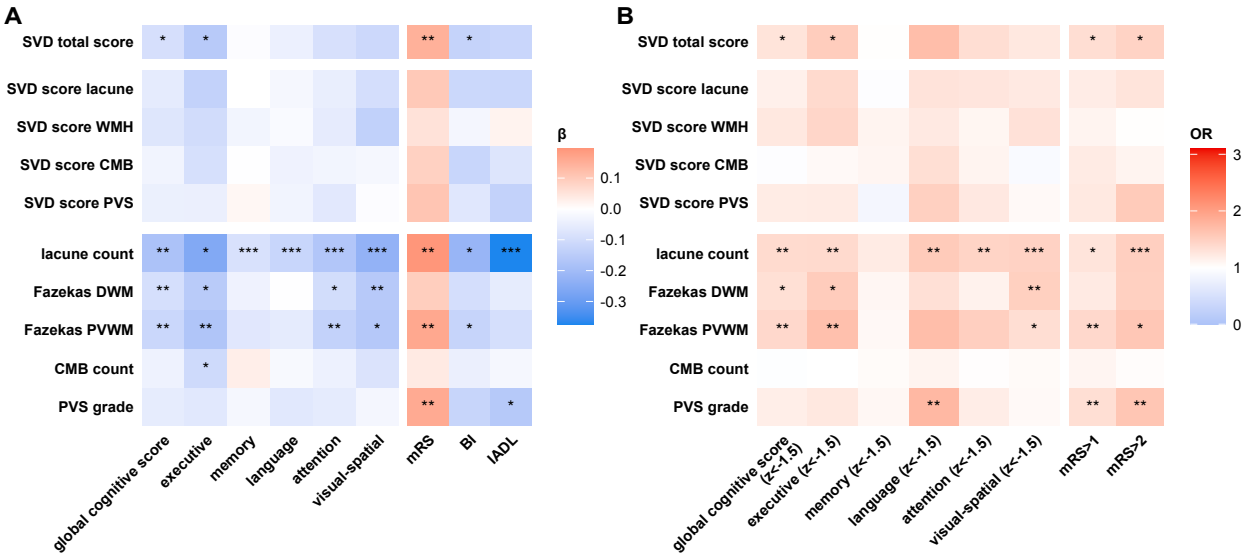
Supplementary Figure 8. Changes of global cognitive and functional scores depending on global small vessel disease (SVD) score at baseline. (A) Global SVD score at baseline did not significantly impact the increase of global cognitive score from 6 months to 12 months after stroke (*P*=0.8183). **(B)** Global SVD score at baseline did not significantly impact the decrease of modified Rankin Scale (mRS) score from 6 months to 12 months after stroke (*P*=0.1969).



Supplementary Figure 9. Heatmaps of the associations of global cerebral small vessel disease (SVD) score (1-point increment, range 0-4), individual components of the score (presence vs. absence), and individual SVD lesion burden with cognitive and functional outcomes over 12 months of follow-up after stroke in the left hemisphere. (A) Associations with continuous outcomes: global cognitive score (composite *z*-score across five cognitive domains), individual cognitive domain scores, modified Rankin scale (mRS), barthel index (BI), and instrumental activities of daily living (IADL) across 12 months of follow-up after stroke. The heatmap includes standardized betas (*β*) and their 95% confidence intervals (CI) derived from generalized linear generalized estimating equation (GEE) models adjusted for age, sex, education, vascular risk factors, NIHSS and MoCA in the acute phase, pre-stroke mRS, and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). **(B)** Associations with binary outcomes: global cognitive impairment (composite *z*-score <-1.5 or *z* <-1.5 in any individual cognitive domain) or cognitive impairment across each individual domains and functional impairment (mRS>1 or mRS>2) across 12 months of follow-up after stroke. The heatmap includes standardized odds ratios (OR) and their 95%CI derived from logistic GEE models adjusted for the abovementioned variables. *P*-values are corrected for multiple comparisons with the false discovery rate (FDR) method. NIHSS, national institutes of health stroke scale; MoCA, Montreal cognitive assessment. *$P_{corr.}$<.05, **$P_{corr.}$<.01, ***$P_{corr.}$<.001.



Supplementary Figure 10. Heatmaps of the associations of global cerebral small vessel disease (SVD) score (1-point increment, range 0-4), individual components of the score (presence vs. absence), and individual SVD lesion burden with cognitive and functional outcomes over 12 months of follow-up after stroke in the right hemisphere. (A) Associations with continuous outcomes: global cognitive score (composite *z*-score across five cognitive domains), individual cognitive domain scores, modified Rankin scale (mRS), barthel index (BI), and instrumental activities of daily living (IADL) across 12 months of follow-up after stroke. The heatmap includes standardized betas (*β*) and their 95% confidence intervals (CI) derived from generalized linear generalized estimating equation (GEE) models adjusted for age, sex, education, vascular risk factors, NIHSS and MoCA in the acute phase, pre-stroke mRS, and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). **(B)** Associations with binary outcomes: global cognitive impairment (composite *z*-score <-1.5 or *z* <-1.5 in any individual cognitive domain) or cognitive impairment across each individual domains and functional impairment (mRS>1 or mRS>2) across 12 months of follow-up after stroke. The heatmap includes standardized odds ratios (OR) and their 95%CI derived from logistic GEE models adjusted for the abovementioned variables. *P*-values are corrected for multiple comparisons with the false discovery rate (FDR) method. NIHSS, national institutes of health stroke scale; MoCA, Montreal cognitive assessment. *$P_{corr.}$<.05, **$P_{corr.}$<.01, ***$P_{corr.}$<.001.



Supplementary Figure 11. Heatmaps of the associations of global cerebral small vessel disease (SVD) score (1-point increment, range 0-4), individual components of the score (presence vs. absence), and individual SVD lesion burden with cognitive and functional outcomes over 12 months of follow-up after stroke when additionally adjusting for lesion location impact score[18] in models. (A) Associations with continuous outcomes: global cognitive score (composite *z*-score across five cognitive domains), individual cognitive domain scores, modified Rankin scale (mRS), barthel index (BI), and instrumental activities of daily living (IADL) across 12 months of follow-up after stroke. The heatmap includes standardized betas (*β*) and their 95% confidence intervals

4. Paper II

Regina von Rennenberg, Christian H. Nolte, Thomas G. Liman, Simon Hellwig, Christoph Riegler, Jan F. Scheitz, Marios K. Georgakis, **Rong Fang**, Felix J. Bode, Gabor C. Petzold, Peter Hermann, Inga Zerr, Michael Goertler, Kathleen Bernkopf, Silke Wunderlich, Martin Dichgans, Matthias Endres for the DEMDAS investigators. High-sensitivity cardiac troponin T and cognitive function over 12 months after stroke - results of the DEMDAS study. ***J Am Heart Assoc.*** 2024;13(6):e033439.

Journal of the American Heart Association

ORIGINAL RESEARCH

High-Sensitivity Cardiac Troponin T and Cognitive Function Over 12 Months After Stroke—Results of the DEMDAS Study

Regina von Rennenberg, MD; Christian H. Nolte, MD; Thomas G. Liman, MD; Simon Hellwig, MD; Christoph Riegler, MD; Jan F. Scheitz, MD; Marios K. Georgakis, MD; Rong Fang, MD; Felix J. Bode, MD; Gabor C. Petzold, MD; Peter Hermann, MD; Inga Zerr, MD; Michael Goertler, MD; Kathleen Bernkopf, MD; Silke Wunderlich, MD; Martin Dichgans, MD; Matthias Endres, MD; for the DEMDAS investigators*

BACKGROUND: Subclinical myocardial injury in form of hs-cTn (high-sensitivity cardiac troponin) levels has been associated with cognitive impairment and imaging markers of cerebral small vessel disease (SVD) in population-based and cardiovascular cohorts. Whether hs-cTn is associated with domain-specific cognitive decline and SVD burden in patients with stroke remains unknown.

METHODS AND RESULTS: We analyzed patients with acute stroke without premorbid dementia from the prospective multicenter DEMDAS (DZNE [German Center for Neurodegenerative Disease]-Mechanisms of Dementia after Stroke) study. Patients underwent neuropsychological testing 6 and 12 months after the index event. Test results were classified into 5 cognitive domains (language, memory, executive function, attention, and visuospatial function). SVD markers (lacunes, cerebral microbleeds, white matter hyperintensities, and enlarged perivascular spaces) were assessed on cranial magnetic resonance imaging to constitute a global SVD score. We examined the association between hs-cTnT (hs-cTn T levels) and cognitive domains as well as the global SVD score and individual SVD markers, respectively. Measurement of cognitive and SVD-marker analyses were performed in 385 and 466 patients with available hs-cTnT levels, respectively. In analyses adjusted for demographic characteristics, cardiovascular risk factors, and cognitive status at baseline, higher hs-cTnT was negatively associated with the cognitive domains "attention" up to 12 months of follow-up (beta-coefficient, −0.273 [95% CI, −0.436 to −0.109]) and "executive function" after 12 months. Higher hs-cTnT was associated with the global SVD score (adjusted odds ratio, 1.95 [95% CI, 1.27–3.00]) and the white matter hyperintensities and lacune subscores.

CONCLUSIONS: In patients with stroke, hs-cTnT is associated with a higher burden of SVD markers and cognitive function in domains linked to vascular cognitive impairment.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01334749.

Key Words: acute stroke ■ cardiac troponin ■ cognitive impairment ■ heart and brain axis

Cognitive impairment and dementia are common complications following stroke and can lead to significant disability.[1] Previous studies have shown an association between heart disease and cognitive decline as well as incident dementia.[2,3] Additionally, data from the general population have provided

Correspondence to: Regina von Rennenberg, MD, Department of Neurology, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Hindenburgdamm 30, 12203 Berlin, Germany. Email: regina-irene.freiin-von-rennenberg@charite.de

This article was sent to Jose R. Romero, MD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

*A complete list of the DEMDAS investigators can be found in the Appendix at the end of the article.

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For Sources of Funding and Disclosures, see page 14.

JAHA is available at: www.ahajournals.org/journal/jaha

RESEARCH PERSPECTIVE

What Is New?

- Higher levels of hs-cTnT (high-sensitivity cardiac troponin T) are associated with cognitive outcome in the domains attention and executive function up to 12 months after acute ischemic stroke, suggesting that hs-cTnT is more closely associated with cognitive domains typically affected by vascular cognitive impairment.
- Higher levels of hs-cTnT are associated with a higher burden of cerebral small vessel disease in acute ischemic stroke, which is mainly driven by an association with higher severity of white matter hyperintensities.

What Question Should Be Addressed Next?

- Future studies should address whether hs-cTnT is linked to progression of small vessel disease and long-term cognitive outcome after stroke.

evidence that (subclinical) myocardial injury, reflected by higher levels of hs-cTnT (high-sensitivity cardiac troponin T), is also associated with poor cognitive performance cross-sectionally as well as incident dementia and cognitive decline even in the absence of manifest cardiac comorbidities.[4,5] Hs-cTnT is a sensitive and specific biomarker of myocardial injury. Routine measurement of hs-cTn is currently not recommended as a screening tool for cognitive impairment in the general population or in a memory clinic setting. However, current guidelines by the American Heart Association recommend routine measurement of hs-cTn in patients with ischemic stroke.[6] This recommendation is based on previous studies that have shown an association between hs-cTn and higher mortality and adverse cardiovascular events after stroke.[7,8] At the same time, there is limited evidence on the association between elevated hs-cTn and cognitive function after stroke. In a study with patients with first-ever ischemic stroke, we have previously demonstrated that hs-cTnT is associated with worse cognitive performance at baseline and during follow-up but not with more severe or faster cognitive decline.[6] However, in the PROSCIS (Prospective Cohort with Incident Stroke) study, longitudinal cognitive data were collected using a screening test via telephone interview, which did not allow for domain-specific assessment. Furthermore, data on prestroke cognitive status were not available.[9] Because hs-cTn indicates myocardial injury, one possible explanation for the link between cognitive outcome and hs-cTn levels is that patients with chronic myocardial injury (reflected in higher levels of cardiac biomarkers such as hs-cTnT) may also have chronic vascular damage in the brain (eg, cerebral small vessel disease [SVD]) due to common underlying cardiac and cerebrovascular risk factors.[5] Indeed, hs-cTnT has been associated with white matter hyperintensities (WMH), a marker of cerebral SVD, both in the general population and in patients with acute ischemic stroke.[10,11] However, previous studies of hs-cTnT and SVD have generally examined individual markers rather than the global burden of SVD. The magnetic resonance imaging (MRI)-based global SVD score,[12] which considers 4 different markers of cerebral SVD, has been linked to cognitive performance both in the general population and in patients with stroke.[13–15]

In this study, we aimed to explore the association of hs-cTnT with longitudinal outcome in different cognitive domains and with SVD burden in patients with stroke without prestroke cognitive impairment or dementia. We assessed data from a prospective multicenter study that was specifically designed to identify predictors of long-term cognitive outcomes in different cognitive domains post stroke.[16]

Nonstandard Abbreviations and Acronyms

CERAD	Consortium to Establish a Registry for Alzheimer's Disease Plus
CMB	cerebral microbleeds
DEMDAS	DZNE [German Center for Neurodegenerative Disease]-Mechanisms of Dementia After Stroke study
NIHSS	National Institutes of Health Stroke Scale
PVS	perivascular spaces
SVD	small vessel disease
WMH	white matter hyperintensities

METHODS

Study Population

The anonymized data that support the findings of this study are available from the principal investigator upon reasonable request.

This study is an exploratory analysis of the ongoing DEMDAS (DZNE [German Center for Neurodegenerative Disease]-Mechanisms of Dementia After Stroke) study (NCT01334749). DEMDAS is an investigator-initiated, prospective, multicenter cohort study. The study protocol has been described in detail before.[16] Between January 2014 and January 2019, 600 patients ≥18 years with acute ischemic or hemorrhagic stroke (onset of

symptoms within 5 days before inclusion) were enrolled in 7 stroke centers across Germany. The diagnosis of stroke was confirmed by neuroimaging (ie, a diffusion-weighted imaging-positive lesion on cranial MRI or a new ischemic lesion on a delayed cranial computed tomography or an intracerebral hemorrhage on cranial computed tomographyor MRI). Due to a low number of patients with hemorrhagic stroke, we included only patients with ischemic stroke into our analyses (see Figure S1). Stroke severity at baseline was measured using the National Institutes of Health Stroke Scale (NIHSS).[17] Prestroke level of function was assessed using the modified Rankin Scale. In order to determine the prestroke modified Rankin Scale level, patients and their informants were questioned about the patient's living situation, need for assistance in activities of daily life, and limited physical abilities before the stroke during the baseline study visit. Patients who were not able to undergo cranial MRI or had a preexisting diagnosis of dementia or an Informant Questionnaire on Cognitive Decline in the Elderly score>64 (indicating preexisting cognitive impairment) at baseline were excluded.[18] For this substudy, we additionally excluded all patients with unavailable hs-cTnT values (n=87). For the analysis of imaging data on SVD, we excluded all patients with incomplete MRI assessment (n=33).

Study participants and their informants were invited for in-person follow-up visits 6 and 12 months after the initial event. At each follow-up visit, patients and their informants underwent comprehensive cognitive assessments; details are in Table S1.

The DEMDAS study was conducted according to the Declaration of Helsinki and was approved by local ethics committees of all participating sites. All patients or their legal guardians provided written informed consent before study inclusion. Reporting of this substudy follows the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Blood Tests

Hs-cTnT was measured from the blood samples collected during the baseline visit using the Elecsys assay (Roche Elecsys Troponin Ths, Mannheim, Germany). This test has a cutoff at 14 ng/L as its upper reference limit (based on the 99th percentile of a healthy population) and a limit of blank at 3 ng/L, a limit of detection at 5 ng/L, and a coefficient of variation of 9% at the upper reference limit.[19]

Neurocognitive Testing

During the follow-up visits, a comprehensive battery of neuropsychological tests classified in 5 cognitive domains (executive function, memory, language, attention, visuospatial function) was performed. Classification of cognitive domains has been published earlier.[20] The Trail Making Test Part B from the Consortium to Establish a Registry for Alzheimer's Disease Plus (CERAD-Plus) battery and the Stroop Colour-Word-Interference Test were used to examine executive function.[21,22] Word List Learning/Recall and Recognition and Figure Recall from CERAD-Plus and immediate and delayed recall of the Rey-Osterrieth Complex Figure were used to examine memory function.[23] Semantic and Phonemic Fluency and Boston Naming Test, which were subtests of the CERAD-Plus as well as language items from the Mini-Mental State Examination were used to examine language.[24] The Trail Making Test Part A from CERAD-Plus and the Digit-Symbol-Substitution Test of the Wechsler Intelligence Scale were used to examine attention.[25] The Figure Drawing Test from CERAD-Plus and the copy test of Rey-Osterrieth Complex Figure were used to examine visual spatial function.[21,23]

First, a *Z* score was calculated for each individual test based on published norms corrected for age, sex, and education.[15] In a second step, the test-specific *Z* scores were averaged for each domain to calculate the 5 domain-specific *Z* scores. Lastly, the 5 domain-specific *Z* scores were averaged to calculate the global cognitive score. Cognitive impairment for any given domain was defined as a domain-specific *Z* score lower than –1.5.

At baseline (ie, during the acute in-hospital stay) we performed the Mini-Mental State Examination and the Montreal Cognitive Assessment to screen for global cognitive impairment in the acute poststroke phase.[22,26]

Neuroimaging

Upon study inclusion 3 Tesla cranial MRI imaging (Siemens, Erlangen, Germany) was performed. Details on the neuroimaging protocol may be found in Data S1. The global SVD burden was examined by assembling the individual SVD markers into a global score from 0 to 4.[9] One point is given for each of the following lesions: (1) presence of lacunes, (2) presence of WMH (periventricular WMH Fazekas grade 3 or deep WMH Fazekas grade≥2), (3) presence of cerebral microbleeds (CMB), and (4) presence of moderate to severe perivascular spaces (PVS) (grade≥2).[12,15] SVD markers that were found within the stroke lesion were not incorporated into imaging analysis.[15]

Statistical Analysis

Data are shown as median with interquartile range (25th and 75th percentile) for continuous and as absolute (N) and relative (%) frequencies for categorical variables. In order to examine the association between hs-cTnT and longitudinal cognitive outcome (ie, cognitive trajectories between 6 and 12 months after stroke), we calculated unadjusted and adjusted generalized linear regression

models for continuous cognitive data (ie *Z* scores for global cognitive performance and the 5 individual domains) and logistic regression for dichotomous outcomes (domain-specific *Z* scores dichotomized at <–1.5) using generalized estimating equations. In addition to longitudinal cognitive outcome, we assessed cross-sectional cognitive data at 6 and 12 months separately by performing linear and penalized logistic regression (using the firthlogit command in STATA) analyses. Both longitudinal and cross-sectional analyses were performed with different levels of adjustment: after running an unadjusted analysis (model 1), we performed our analyses after adjusting for age, sex, and years of education (model 2). In the fully adjusted model (model 3), we additionally adjusted for history of hypertension, diabetes, coronary artery disease, atrial fibrillation, baseline NIHSS score, prestroke modified Rankin Scale score, and cognitive impairment at baseline defined as a Montreal Cognitive Assessment score <26 points or a Mini-Mental State Examination score <24 points if no Montreal Cognitive Assessment was performed in the subacute stroke phase. Because hs-cTnT levels were not normally distributed in our study population, we used log-transformed values for all analyses.

As sensitivity analyses, we reran model 3 with (1) additional adjustment for total SVD score to assess whether the link between hs-cTnT levels and cognitive performance may be mediated by SVD burden, (2) additional adjustment for stroke localization in the left anterior territory, and (3) after exclusion of patients with stroke affecting more than 1 territory.

To investigate the associations between log-transformed hs-cTnT and SVD, we used the following SVD parameters as dependent variables: (1) the global SVD score (range 0–4), (2) the 4 SVD subscores, and (3) the 5 separate SVD markers (lacune counts, periventricular WMH grade, deep WMH grade, CMB counts, PVS grade). For the association with ordinal-scaled variables (ie, global SVD score, periventricular and deep WMH grade as well as with PVS grade), we calculated ordinal logistic regression models. To assess count variables (ie, lacune count and CMB count), we performed negative binomial regression analyses because both lacune count and CMB count data were overdispersed. Finally, to assess the 4 constituent SVD subscores, we used binary logistic regression analyses. All analyses with regard to SVD markers were performed using 3 models with different levels of adjustment: (1) model 1 unadjusted, (2) model 2 adjusted for age and sex, and (3) model 3 with additional adjustment for hypertension, diabetes, hyperlipidemia, coronary artery disease, atrial fibrillation, smoking status and baseline NIHSS score. In a sensitivity analysis, we reran model 3 after exclusion of patients with stroke affecting more than 1 territory.

To account for multiple comparisons, we calculated corrected *P* values for all analyses using false discovery rate according to the Benjamini–Hochberg method. The false discovery rate adjustment of *P* values was based on the sum total of all the tests. We defined statistical significance as a corrected *P* value <0.05. We performed all statistical calculations using SPSS Statistics 26.0 (IBM, Armonk, NY) and STATA 14.0. The corresponding author had full access to all the data from this substudy and takes responsibility for its integrity and the data analysis.

RESULTS

Baseline Characteristics

We included 385 patients in the analysis of cognitive data and 466 patients in the analysis of imaging data (see Figure S1). The study population included in the analysis of cognitive outcome consisted of patients with mostly mild to moderate strokes (median NIHSS score at baseline=2, interquartile range 1–5), the median age was 68 (interquartile range 59–75) years, and 124 (32.3%) of patients were female. Median hs-cTnT levels in our study population were 7 ng/L (interquartile range 4–12 ng/L). Hs-cTnT values were above the upper reference limit of 14 ng/L in 73 (19.0%) of patients. Median time from stroke symptom onset to hs-cTnT measurement was 1 day (interquartile range 1–2 days). Cognitive impairment at baseline was present in 174 (45.2%) patients with available cognitive follow-up data. Detailed patients' baseline characteristics are shown in Table, including differences with respect to patients who were not included in the analysis of cognitive outcome due to missing data. Patients with missing cognitive follow-up data were older, more often had cognitive impairment at baseline, and more often had a history of coronary artery disease or diabetes (see Table). There were no statistically significant differences in baseline characteristics between patients who were included in the analyses of hs-cTnT and SVD markers and those who were excluded from these analyses due to missing data (see Table S2).

Hs-cTnT and Cognitive Outcome

Overall, cognitive outcomes improved in all domains between month 6 and 12 after stroke. The number of individuals with global cognitive impairment was 112 (29.1%) and 90 (23.4%) at 6 and 12 months, respectively. Hs-cTnT was associated with global cognitive performance in the unadjusted longitudinal analysis as well as in the unadjusted cross-sectional analysis at 12 months after stroke. Both associations were no longer statistically significant after full adjustment.

With regard to specific cognitive domains, hs-cTnT was negatively associated with performance in the

Table. Baseline Characteristics of Patients Included in and Excluded From Cognitive Analyses

	Patients included in cognitive analyses (n=385)	Patients excluded from cognitive analyses (n=215)	*P*
Age, y, median (IQR)	68 (59–75)	71 (62–78)	0.010
Female sex, n (%)	124 (32.3%)	76 (35.3%)	0.434
Years of education, median (IQR)	13 (12–17)	13 (11–15)	0.012
History of hypertension, n (%)	208 (54.0%)	128 (59.5%)	0.165
History of diabetes, n (%)	50 (13.0%)	43 (20.0%)	0.021
History of coronary artery disease, n (%)	17 (4.4%)	18 (8.4%)	0.047
History of atrial fibrillation, n (%)	36 (9.4%)	30 (14.0%)	0.067
Cognitive impairment at baseline, n (%)	174 (45.2%)	130 (60.5%)	<0.001
Hs-cTnT, median (IQR)	7 (4–12)		
Hs-cTnT>upper reference limit, n (%)	73 (19.0%)		
Days from symptom onset to blood draw, median (IQR)	1 (1–2)		
Stroke cause			
Large artery atherosclerosis, n (%)	98 (25.5%)	65 (30.2%)	0.066
Cardioembolism, n (%)	80 (20.8%)	53 (24.7%)	0.110
Small artery occlusion, n (%)	50 (13.0%)	16 (7.4%)	0.074
Other cause, n (%)	50 (13.0%)	15 (7.0%)	0.052
Undetermined cause, n (%)	107 (27.8%)	50 (23.3%)	0.491
Informant Questionnaire on Cognitive Decline in the Elderly score, median (IQR)	48 (48–49)	48 (48–50)	0.538
Baseline National Institutes of Health Stroke Scale score, median (IQR)	2 (1–5)	3 (1–5)	0.332
Cognitive impairment at 6 mo, n (%)	112 (29.1%)		
Language	17 (4.4%)		
Memory	26 (6.8%)		
Executive function	30 (7.8%)		
Attention	35 (9.1%)		
Visuospatial function	69 (17.9%)		
Cognitive impairment at 12 mo, n (%)	90 (23.4%)		
Language	15 (3.9%)		
Memory	20 (5.2%)		
Executive function	21 (5.5%)		
Attention	22 (5.7%)		
Visuospatial function	64 (16.6%)		
Stroke localization			
Anterior left	110 (28.6%)	51 (23.7%)	0.199
Anterior right	90 (23.4%)	56 (26.0%)	0.465
Posterior cerebral artery left	29 (7.5%)	13 (6.0%)	0.494
Posterior cerebral artery right	23 (6.0%)	16 (7.4%)	0.484
Brainstem	36 (9.4%)	18 (8.4%)	0.688
Cerebellum	31 (8.1%)	12 (5.6%)	0.261
Multiple	48 (12.5%)	30 (14.0%)	0.604

Baseline characteristics of patients included in cognitive analyses and excluded from cognitive analyses. Univariable comparisons were performed using chi-square test for dichotomous variables and Mann–Whitney *U* test for linear variables. Patients with missing cognitive follow-up data were older, more often had cognitive impairment at baseline and more often had a history of coronary artery disease or diabetes. hs-cTnT indicates high-sensitivity cardiac troponin T; and IQR, interquartile range.

domain "attention" in the longitudinal analysis after adjustment for demographic characteristics, cardiovascular risk factors, and clinical outcome at baseline as well as correction for multiple comparisons (Figure 1). When we examined cognitive outcome at 6 and 12 months separately in cross-sectional analyses, we found an association with the domain "attention" both at 6 and 12 months (Figures 2 and 3) and

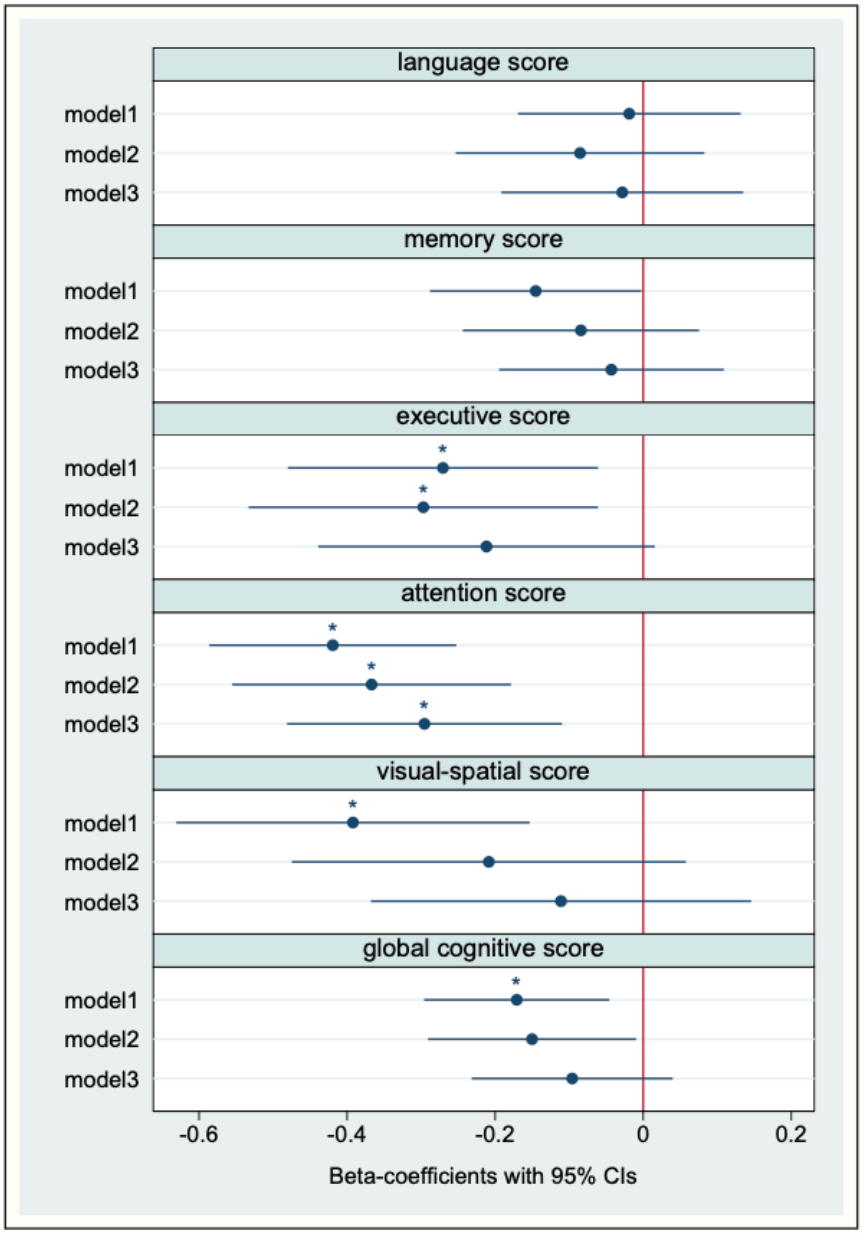

Figure 1. Log-transformed hs-cTnT and cognitive domains (continuous) across 12 months of follow-up according to generalized linear regression models using generalized estimating equations.

The figure displays the respective regression coefficients and 95% CIs. Model 1: unadjusted. Model 2: adjusted for age, sex, and years of education. Model 3: additional adjustment for hypertension, diabetes, coronary artery disease, atrial fibrillation, cognitive impairment at baseline, baseline NIHSS score, and prestroke mRS score. *P_{corr}<0.05. After full adjustment, hs-cTnT was associated with a decline in performance in the cognitive domain "attention" between 6 and 12 months after stroke. Hs-cTnT indicates high-sensitivity cardiac troponin T; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

with executive function at 12 months (Figure 3). The associations we found with the domains "attention" and "executive function" remained significant in the sensitivity analysis after additional adjustment for total SVD burden (see Table S3) and for stroke localization in the left anterior territory (see Table S4). After exclusion of patients with strokes in multiple territories, the association between hs-cTnT and performance in the domain "attention" at 6 months of follow-up was no longer significant (see Table S5). Apart from that, the

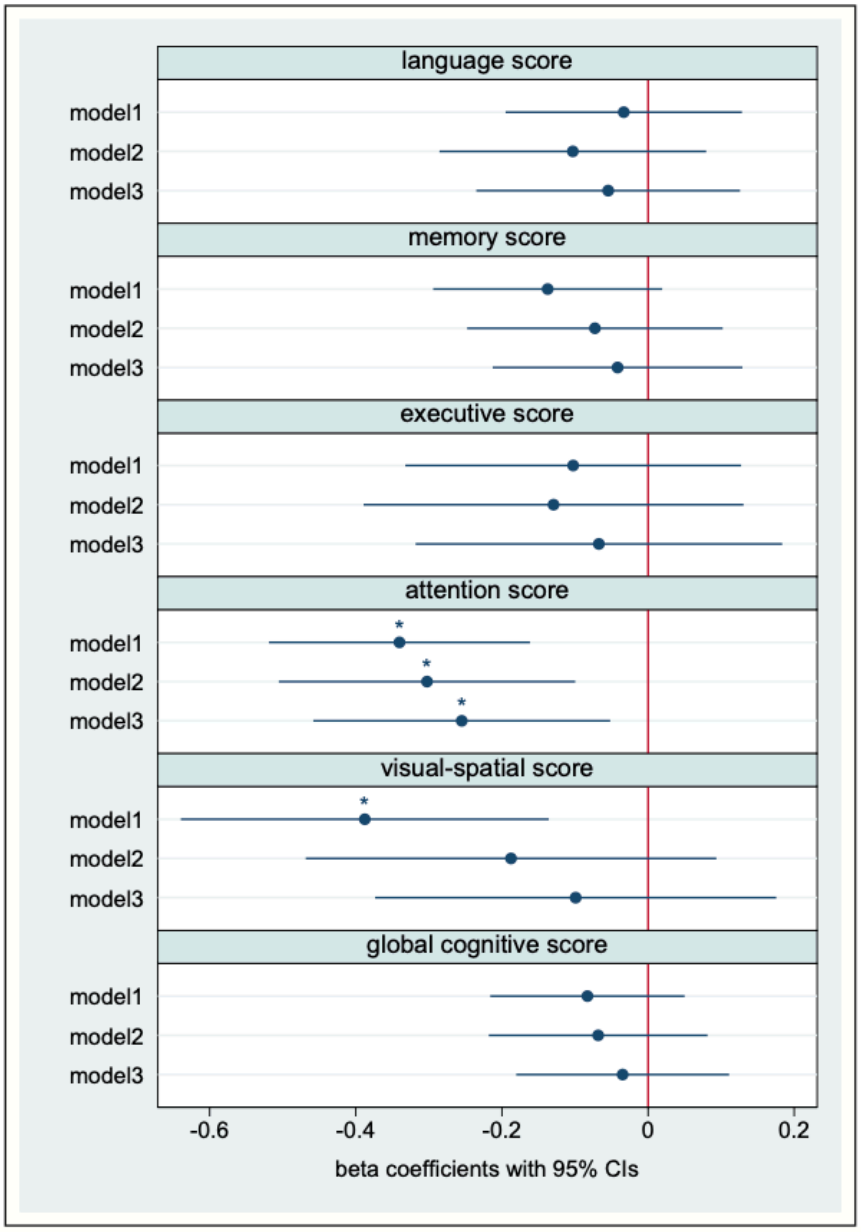

Figure 2. Log-transformed hs-cTnT and cognitive domains (continuous) at 6 months of follow-up according to linear regression models.
The figure displays the respective regression coefficients and 95% CIs. Model 1: unadjusted. Model 2: adjusted for age, sex, and years of education. Model 3: additional adjustment for hypertension, diabetes, coronary artery disease, atrial fibrillation, cognitive impairment at baseline, baseline NIHSS score, and prestroke mRS score. *P_{corr}<0.05. After full adjustment, hs-cTnT was negatively associated with performance in the cognitive domain "attention" in the cross-sectional analyses 6 months after stroke. Hs-cTnT indicates high-sensitivity cardiac troponin T; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

results remained unchanged compared with the main analyses.

There were no statistically significant associations between hs-cTnT and cognitive impairment in any specific domain in the binary outcome models (ie, after dichotomizing cognitive data at a *Z* score of –1.5) both in the longitudinal and in the cross-sectional analyses (see Figures S2 through S4).

Hs-cTnT and SVD Markers

The frequency and burden of SVD markers are displayed in Table S2. Most patients had an SVD score

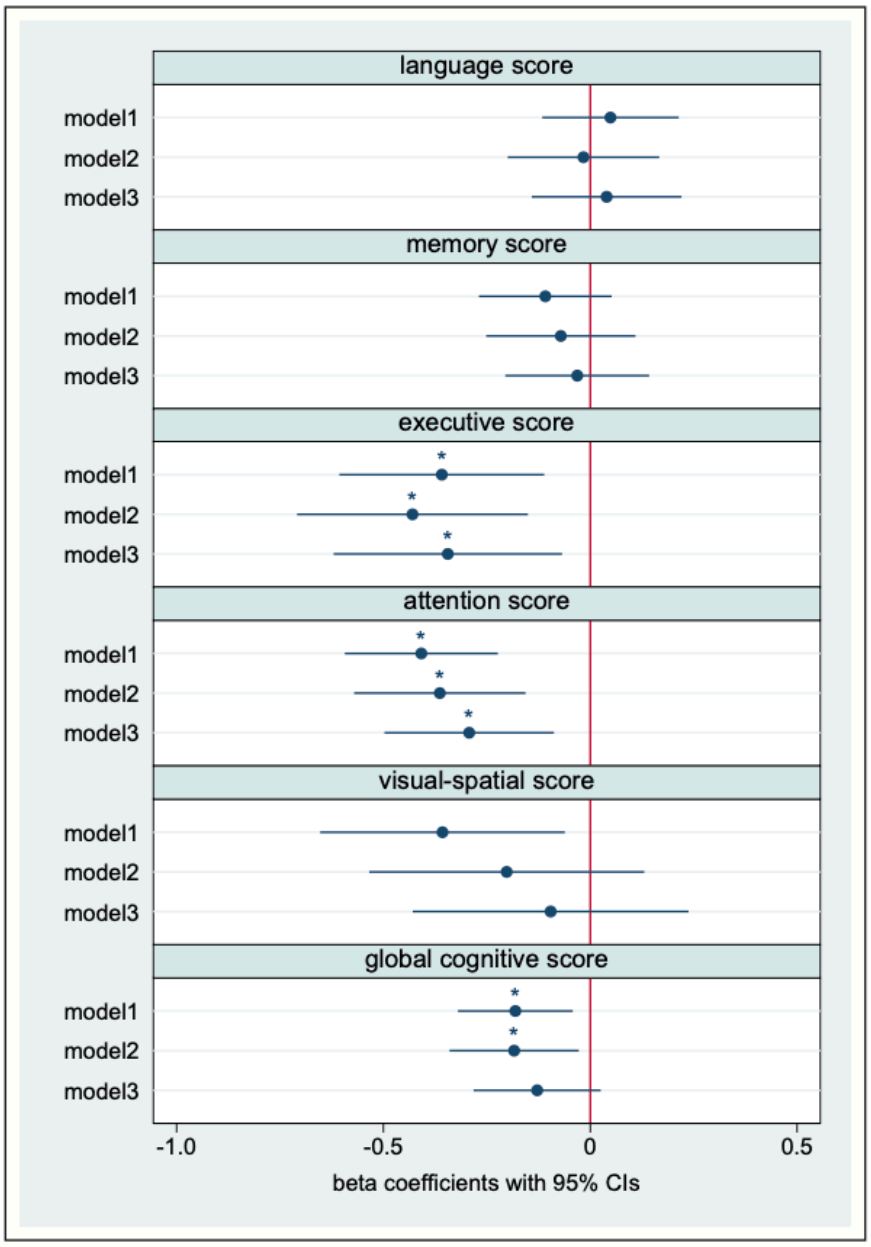

Figure 3. Log-transformed hs-cTnT and cognitive domains (continuous) at 12 months of follow-up according to linear regression models.
The figure displays the respective odds ratios and 95% CIs. Model 1: unadjusted. Model 2: adjusted for age, sex, and years of education. Model 3: additional adjustment for hypertension, diabetes, coronary artery disease, atrial fibrillation, cognitive impairment at baseline, baseline NIHSS score, and prestroke mRS score. *P_{corr}<0.05. After full adjustment, hs-cTnT was negatively associated with performance in the domains "attention" and "executive function" in the cross-sectional analyses 6 months after stroke. Hs-cTnT indicates high-sensitivity cardiac troponin T; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

of either 0 (40.1%, no lesions fulfilling the score criteria) or 1 (29.4%, one lesion type fulfilling the score criteria). The SVD marker most frequently found to fulfill the score criteria was WMH (see Table S2).

Levels of hs-cTnT were associated with the global SVD score (see Figure 4). This association remained statistically significant after full adjustment and correction for multiple testing (adjusted odds ratio for model 3, 1.87 [95% CI, 1.21–2.89], see Figure 4). In the unadjusted models, hs-cTnT was associated with all 4 constituent SVD subscores except for the CMB subscore (see Figure 4). After full adjustment and correction for

multiple testing, the association remained statistically significant for the WMH subscore and the lacune subscore (see Figure 4). However, after exclusion of patients with strokes in multiple territories, the association between hs-cTnT and the lacune subscore was no longer statistically significant (see Table S6). When assessing individual SVD markers in their entire severity range, we found a statistically significant association with deep WMH grade after adjustment for potential confounders and correction for multiple testing (see Figure 5).

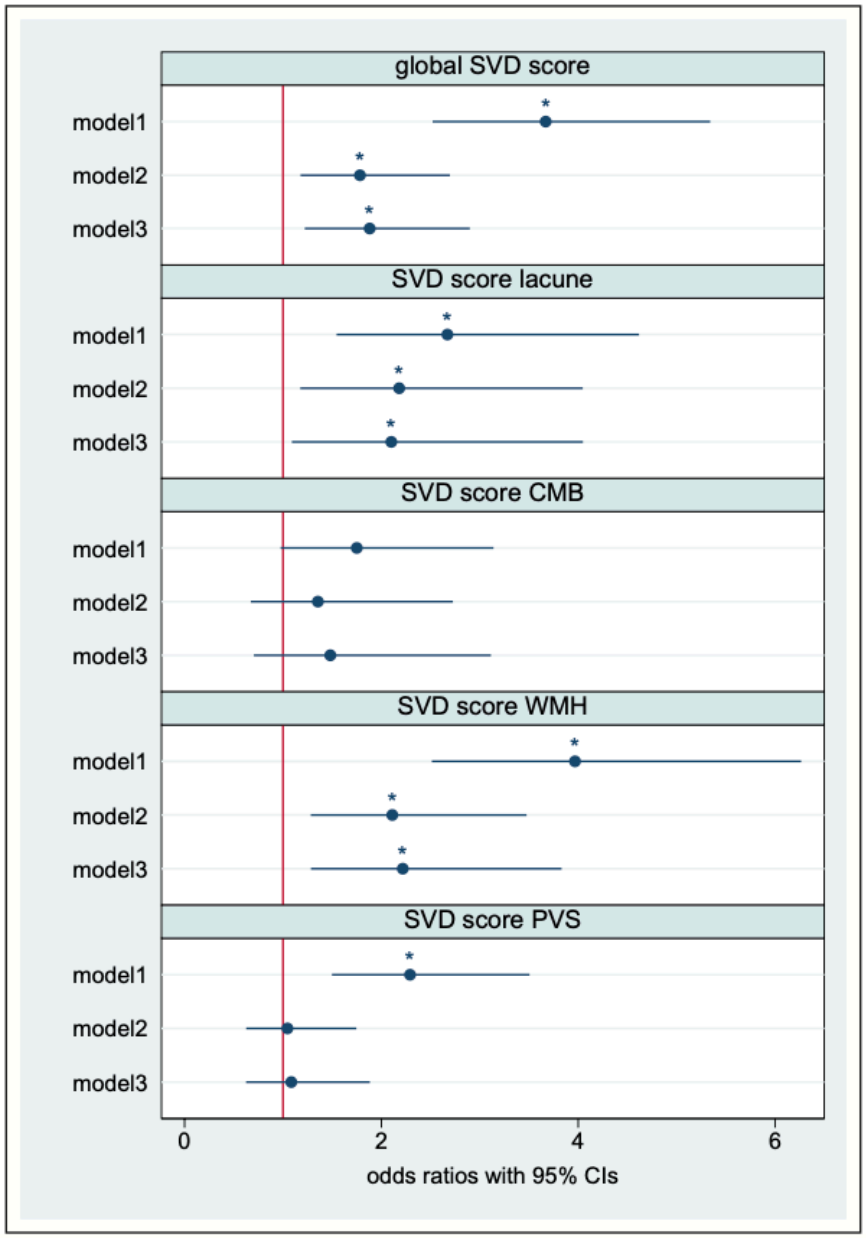

Figure 4. Log-transformed hs-cTnT and global cerebral small vessel disease score as well as 4 constituent SVD subscores.
The figure displays odds ratios and 95% CIs derived from ordinal logistic regression models for the global SVD score and binary logistic regression models for each constituent subscore, respectively. Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: additional adjustment for hypertension, diabetes, hyperlipidemia, coronary artery disease, atrial fibrillation, smoking status, and baseline NIHSS score. After full adjustment, hs-cTnT was associated with higher global SVD scores as well as the WMH and lacune subscores. *P_{corr}<0.05. CMB indicates cerebral microbleeds; hs-cTnT, high-sensitivity cardiac troponin T; NIHSS, National Institutes of Health Stroke Scale; PVS, perivascular spaces; SVD, small vessel disease; and WMH, white matter hyperintensities.

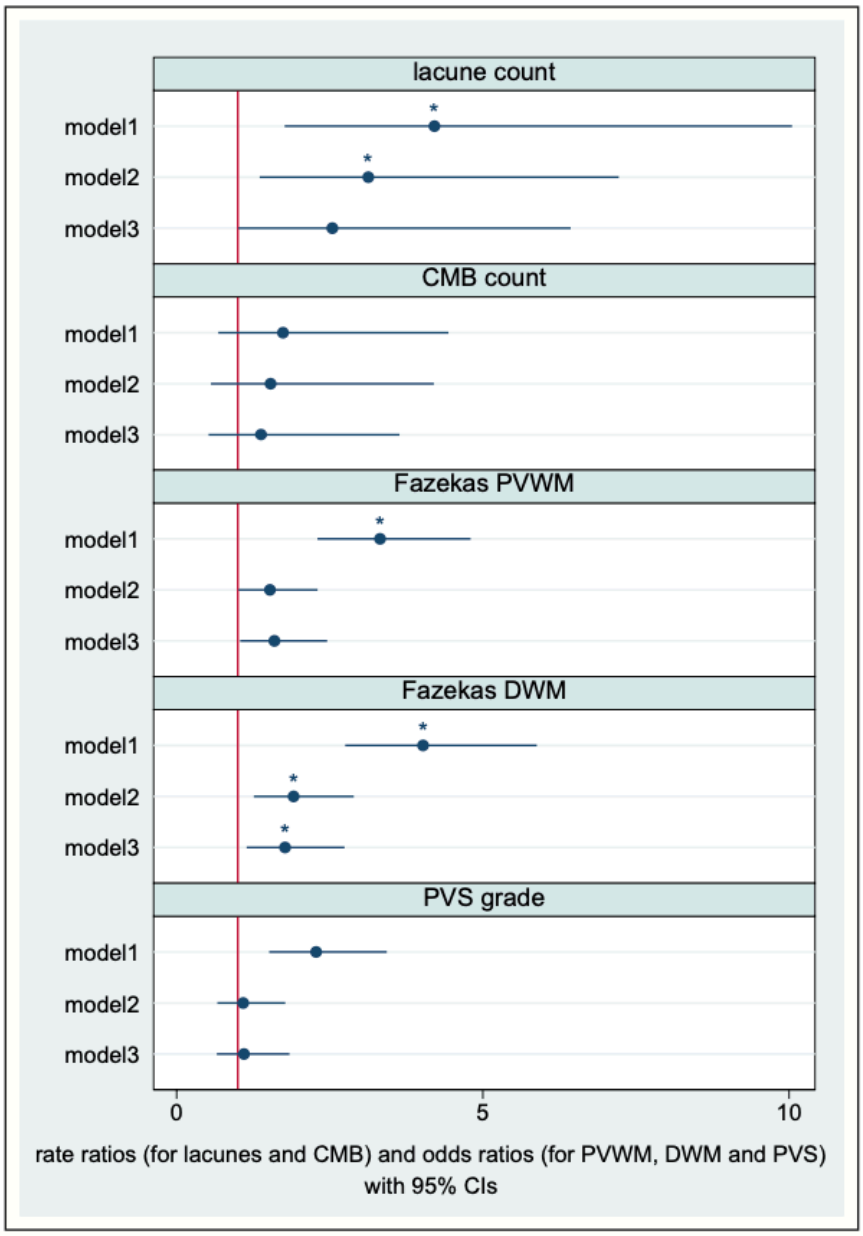

Figure 5. Hs-cTnT and individual cerebral small vessel disease markers in their entire range.
The figure displays odds ratios derived from ordinal regression models for periventricular WMH grade, deep WMH grade, and PVS grade. The figure displays rate ratios calculated using negative binomial regression models for lacune count and CMB count. Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: additional adjustment for hypertension, diabetes, hyperlipidemia, coronary artery disease, atrial fibrillation, smoking status, and baseline NIHSS score. After full adjustment, hs-cTnT remained associated with higher deep WMH grade. *P_{corr}<0.05. CMB indicates cerebral microbleeds; DWM, deep white matter; hs-cTnT, high-sensitivity cardiac troponin T; NIHSS, National Institutes of Health Stroke Scale; PVS, perivascular spaces; PVWM, periventricular white matter; SVD, small vessel disease; and WMH, white matter hyperintensities.

DISCUSSION

This exploratory analysis of the prospective multicenter DEMDAS study contains several important findings. First, hs-cTnT levels were associated with poorer cognitive performance and decline in the domain "attention" up to 12 months of follow-up. Associations were found in both longitudinal and cross-sectional analyses

and remained stable after adjustment for potential confounders, including prevalent cardiovascular risk factors, and after correction for multiple comparisons. Second, hs-cTnT levels were associated with poorer performance in executive function at 12 months after the index stroke. Third, we found that hs-cTnT levels were associated with cerebral SVD burden in patients with stroke, which was driven by the subscores of WMH burden and (to a lesser degree) lacunes. This highlights the potential interplay between subclinical myocardial injury, arteriolosclerotic SVD, and features of vascular dementia. However, because the association between hs-cTnT levels and cognitive function remained statistically significant even after adjustment for SVD burden, the link between hs-cTnT and cognition in patients with stroke seems to also be independently mediated by pathophysiological factors other than SVD.

To our knowledge, our study is the first to examine the association between hs-cTnT levels and different cognitive domains in patients with stroke. Our results are in line with studies from the general population showing an association between hs-cTnT levels and performance in the Digit-Symbol-Substitution Test, which tests mainly attention and processing speed and was also part of the cognitive tests used to assess attention in our study.[4,5,27] Attention and processing speed have typically been attributed to vascular pathology and vascular dementia.[28] Therefore, our results suggest that hs-cTnT is associated with vascular pathology rather than the cognitive domains typically affected in Alzheimer's disease, such as memory or language.[29]

Of note, we did not find a statistically significant association between hs-cTnT levels and cognitive impairment when using the logistic model dichotomizing each score at −1.5. However, only a small percentage of patients (<10% in all cognitive domains except visual spatial function) had cognitive impairment for any given domain. Therefore, we might have missed a statistically significant association due to limited statistical power.

We found that hs-cTnT levels were associated with the global SVD burden measured by the MRI-based SVD score. Our results are in line with 2 previous studies in patients with hypertension and lacunar stroke, respectively, that found an association between NT-proBNP (N-terminal pro–brain natriuretic peptide) and global SVD burden.[30,31] We are, however, not aware of any other studies assessing the link between global SVD burden and hs-cTnT.

When examining the four constituent SVD subscores and the respective SVD markers in their entire severity range, we found that the association with hs-cTnT levels is largely driven by WMH, which was also the most common pathological SVD marker in our study population. Previous studies have also shown a link between hs-cTnT levels and WMH both in the general population and in patients with ischemic stroke.[10,11,32] The association between cardiac biomarkers and other markers of SVD (ie, CMB, PVS, and lacunes) is less well described. We found an association between hs-cTnT levels and the lacune subscore but not with lacune count as a linear variable. A possible explanation is that only a small proportion of our study population had lacunes and that lacune count as a linear variable was highly skewed. This may also be the reason why the association between hs-cTnT and lacune subscore was no longer significant in the sensitivity analysis excluding patients with stroke in more than 1 territory. Concerning the PVS and CMB subscores, we did not find a statistically significant association with hs-cTnT levels after full adjustment and correction for multiple testing. In line with our findings, Gyanwali et al. did not find an association between hs-cTnT and incident CMBs on repeated MRI scans in 343 memory clinic patients.[33]

The pathogenetic mechanisms that explain the association between markers of myocardial injury such as hs-cTnT and cerebral SVD as well as cognitive function have not been fully elucidated. Importantly, it is unlikely that troponin itself causes cognitive impairment or SVD. Hs-cTn is released into the bloodstream as a result of cardiomyocyte injury.[19] Both myocardial injury as well as SVD may result from common underlying vascular risk factors and vascular disease.[34,35] Apart from that, higher levels of hs-cTn may also result from structural heart disease leading to chronic cerebral hypoperfusion.[36,37] Finally, acute stroke has been linked to autonomic cardiac dysfunction and stroke-induced heart injury (so called stroke-heart syndrome) that would explain increased cardiac biomarkers, too.[38] Stroke-heart syndrome typically occurs in the (subacute) stroke phase.[38] It occurs more frequently in patients with higher stroke severity but also depending on stroke localization, for example, in strokes affecting the insular region.[38,39] Because blood draws for hs-cTn measurement were taken relatively early after symptom onset in our study population, both chronic myocardial injury and stroke-induced acute myocardial injury have likely contributed to hs-cTnT levels measured in this study.

Our results suggest that hs-cTnT levels may provide a more accurate determination of the cardiovascular-associated risk for cognitive decline and SVD in patients with stroke than clinical history alone. Indeed, previous research has shown that although a history of cardiovascular comorbidities (such as ischemic heart disease, hypertension, or diabetes) is significantly associated with WMH, cardiovascular risk factors accounted for only a small amount of WMH variability.[40] Hs-cTnT may be a useful parameter to identify patients at risk of cognitive decline because it is a sensitive biomarker for myocardial injury and can be measured in

everyday clinical practice.[41] Moreover, current guidelines for the management of patients with acute ischemic stroke recommend the routine measurement of hs-cTn.[8] Thus, hs-cTn levels are widely available in patients with stroke in particular.

Our study benefits from the multicenter prospective design with the predefined aim to determine factors of cognitive impairment after stroke. To this end, patients underwent repeated face-to-face follow-up examinations including detailed neuropsychological testing that provided an extensive, multidomain, and standardized assessment of cognitive performance. In addition, patients underwent 3T MRI imaging using a standardized protocol in accordance with the Standards for Reporting Vascular Changes on Neuroimaging recommendations for neuroimaging of SVD.[42] Interpretation of MRI was performed centralized and blinded to clinical data.

However, our study also has certain limitations: patients eligible for inclusion in DEMDAS had to be able to give informed consent and be willing and motivated to participate in a study with several years of follow-up including repeated and extensive neuropsychological examinations and cerebral MRI. Therefore, the majority of our study population had mild stroke (median NIHSS score 2). In addition, most of our study population was highly educated (median 13 years of education) and had overall good cognitive outcome resulting in a low number of patients with cognitive impairment for every examined domain. This may have attenuated the association between hs-cTnT levels and cognition, particularly in the dichotomous models and restricts the generalizability to more severely affected patients with stroke. Because hs-cTnT levels were measured only once during the acute phase, we were not able to differentiate between acute and chronic myocardial injury and their respective associations with cognitive performance. Moreover, insular involvement was not systematically recorded in DEMDAS but may also have affected hs-cTn levels in our study population. Stroke localization and the initial neurological deficit may affect the performance in cognitive tests. To account for this, we adjusted our analysis for initial NIHSS score and presence of global cognitive impairment at baseline. In addition, we performed a sensitivity analysis with additional adjustment for stroke located in the left anterior territory, which has been associated with an increased risk of poststroke cognitive impairment.[43] However, we cannot exclude residual confounding of our results due to stroke localization.

In addition, there was a considerable rate of loss to follow-up in our study population. Because patients with poor cognitive function are less likely to take part in repeated follow-up examinations, this might have led to selective attrition bias from loss to follow-up. The analyses we report here were exploratory and not part of the prespecified DEMDAS study protocol. The DEMDAS study was not specifically powered to detect an association between hs-cTnT and cognitive outcome. The long-term follow-up period of the DEMDAS study is still ongoing. Therefore, our current analysis on imaging data is restricted to the MRI at baseline and we were not able to examine the association between hs-cTnT levels and SVD progression. However, the study protocol of DEMDAS includes repeated MRI imaging[16] during the follow-up period so that this question may be addressed in future substudies.

CONCLUSIONS

Our results from this multicenter prospective study with comprehensive neuropsychological assessment show that hs-cTnT levels at baseline is associated with performance in the cognitive domain “attention” and “executive function” in patients with stroke with up to 12 months of follow-up. This suggests that hs-cTnT is associated with vascular pathology and vascular dementia rather than the cognitive domains typically affected in Alzheimer’s disease in patients with stroke. In this cohort, hs-cTnT levels are also associated with the global SVD burden in general and severity of WMH as a marker of arteriolosclerotic atheropathy in particular.

APPENDIX

DEMDAS Investigators

Matthias Endres (Department of Neurology with Experimental Neurology, Charité—Univeristätsmedizin Berlin, Germany; German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany; Center for Stroke Research Berlin (CSB), Charité—Universitätsmedizin Berlin, Germany; German Centre for Cardiovascular Research (DZHK), partner site Berlin, Germany), Thomas G. Liman (Department of Neurology with Experimental Neurology, Charité—Univeristätsmedizin Berlin, Germany; German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany), Lucia Kerti (Center for Stroke Research Berlin (CSB), Charité—Universitätsmedizin Berlin, Germany; German Center for Neurodegenerative Diseases (DZNE), Berlin Germany), Christian H. Nolte (Department of Neurology with Experimental Neurology, Charité—Univeristätsmedizin Berlin, Germany; Center for Stroke Research Berlin (CSB), Charité—Universitätsmedizin Berlin, Germany; Berlin Institute of Health (BIH), Germany), Tatjana Wittenberg (Center for Stroke Research Berlin (CSB), Charité—Universitätsmedizin Berlin, Germany), Jan F. Scheitz (Department of Neurology with Experimental Neurology, Charité—Univeristätsmedizin Berlin, Germany; Center for Stroke Research Berlin (CSB), Charité—Universitätsmedizin

Berlin, Germany; Berlin Institute of Health (BIH), Germany), Harald Prüß (Department of Neurology with Experimental Neurology, Charité—Univeristätsmedizin Berlin, Germany; German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany), Pia Sophie Sperber (Department of Neurology with Experimental Neurology, Charité—Univeristätsmedizin Berlin, Germany; Center for Stroke Research Berlin (CSB), Charité—Universitätsmedizin Berlin, Germany); Alexander H. Nave (Department of Neurology with Experimental Neurology, Charité—Universitätsmedizin Berlin, Germany; Center for Stroke Research Berlin (CSB), Charité—Universitätsmedizin Berlin, Germany; Berlin Institute of Health (BIH), Germany), Anna Kufner Ibaroule (Department of Neurology with Experimental Neurology, Charité—Universitätsmedizin Berlin, Germany; Center for Stroke Research Berlin (CSB), Charité—Universitätsmedizin Berlin, Germany; Berlin Institute of Health (BIH), Germany), Gabor Petzold (Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Germany; German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany), Felix Bode (Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Germany; German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany), Sebastian Stösser (Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Germany; German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany), Julius Meissner (Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Germany), Taraneh Ebrahimi (Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Germany), Julia Nordsiek (Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Germany; German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany), Niklas Beckonert (Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Germany), Christine Kindler (Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Germany; German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany), Inga Zerr (Department of Neurology, University Medical Center Göttingen, Germany; German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany), Peter Hermann (Department of Neurology, University Medical Center Göttingen, Germany), Matthias Schmitz (Department of Neurology, University Medical Center Göttingen, Germany), Stefan Goebel (Department of Neurology, University Medical Center Göttingen, Germany), Timothy Bunck (Department of Neurology, University Medical Center Göttingen, Germany), Julia Schütte-Schmidt (Department of Neurology, University Medical Center Göttingen, Germany), Sabine Nuhn (Department of Neurology, University Medical Center Göttingen, Germany), Corinna Volpers (Department of Neurology, University Medical Center Göttingen, Germany), Peter Dechent (Department of Neurology, University Medical Center Göttingen, Germany), Mathias Bähr (Department of Neurology, University Medical Center Göttingen, Germany; German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany; Cluster of Excellence Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB), Göttingen, Germany), Michael Görtler (Department of Neurology, University Hospital, Otto-von-Guericke University Magdeburg, Germany; German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany), Wenzel Glanz (Department of Neurology, University Hospital, Otto-von-Guericke University Magdeburg, Germany; German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany), Valentina Perosa (Department of Neurology, University Hospital, Otto-von-Guericke University Magdeburg, Germany; German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany), Martin Dichgans (Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany; German Center for Neurodegenerative Diseases (DZNE), Munich, Germany), Frank Wollenweber (Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany), Marios Georgakis (Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany), Rong Fang (Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany), Daniel Janowitz (Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany), Karin Waegemann (Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany; German Center for Neurodegenerative Diseases (DZNE), Munich, Germany), Steffen Tiedt (Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany), Silke Wunderlich (Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Germany), Benno Ikenberg (Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Germany), Kathleen Bernkopf (Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Germany), Christiane Huber (Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Germany), Holger Poppert (Neurology Department, Helios Klinikum München West, Munich, Germany), Marco Düring (Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany; Medical Image Analysis Center (MIAC AG) and Quantitative Biomedical Imaging Group (qbig), Department of

Biomedical Engineering, University of Basel, Switzerland), Miguel Ángel Araque Caballero (Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany; German Center for Neurodegenerative Diseases (DZNE), Munich, Germany), Benno Gieserich (Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany), Anna Dewenter (Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Germany), Laura Dobisch (German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany), Katja Neumann (German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany), Oliver Speck (Department of Biomedical Magnetic Resonance, Institute for Physics, Otto-von-Guericke University Magdeburg, Germany; German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany; Leibniz Institute for Neurobiology, Magdeburg, Germany; Center for Behavioral Brain Sciences, Magdeburg, Germany), Annika Spottke (German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Germany), Tony Stöcker (German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany), Peter Bartenstein (Department of Nuclear Medicine, University Hospital, LMU Munich, Germany), Michael Wagner (German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany).

ARTICLE INFORMATION

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Affiliations

Department of Neurology (Klinik und Hochschulambulanz für Neurologie), Charité—Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany (R.v.R., C.H.N., T.G.L., S.H., C.R., J.F.S., M.E.); Center for Stroke Research Berlin (CSB), Charité—Universitätsmedizin Berlin, Berlin, Germany (R.v.R., C.H.N., T.G.L., S.H., C.R., J.F.S., M.E.); German Center for Neurodegenerative Diseases (Deutsches Zentrum für Neurodegenerative Erkrankungen), partner site Berlin, Berlin, Germany (R.v.R., C.H.N., T.G.L., M.E.); German Center for Cardiovascular Research (Deutsches Zentrum für Herz-Kreislaufforschung), partner site Berlin, Charité-Universitätsmedizin Berlin, Berlin, Germany (C.H.N., J.F.S., M.E.); Berlin Institute of Health at Charité –Universitätsmedizin Berlin, BIH Biomedical Innovation Academy, Berlin, Germany (C.H.N., S.H., J.F.S., M.E.); Department of Neurology, School of Medicine and Health Sciences, Carl von Ossietzky University of Oldenburg, Oldenburg, Germany (T.G.L.); Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany (M.K.G., R.F., M.D.); German Center for Neurodegenerative Diseases (Deutsches Zentrum für Neurodegenerative Erkrankungen), partner site Munich, Munich, Germany (M.K.G., R.F., M.D.); Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn, Germany (F.J.B., G.C.P.); German Center for Neurodegenerative Diseases (Deutsches Zentrum für Neurodegenerative Erkrankungen), partner site Bonn, Bonn, Germany (G.C.P.); German Center for Neurodegenerative Diseases (DZNE) Göttingen, Göttingen, Germany (P.H., I.Z.); Clinical Dementia Center, Department of Neurology, University Medical Center, Göttingen, Germany (P.H., I.Z.); Department of Neurology, Magdeburg University Vascular and Stroke Centre, Magdeburg, Germany (M.G.); German Center for Neurodegenerative Diseases (Deutsches Zentrum für Neurodegenerative Erkrankungen), partner site Magdeburg, Magdeburg, Germany (M.G.); Department of Neurology, School of Medicine, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany (K.B., S.W.); and German Center for Mental Health (DZPG), partner site Berlin, Berlin, Germany (M.E.).

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Neuroimaging

The MRI protocol included 3D T1-weighted (T1w) magnetization prepared rapid gradient echo (MPRAGE), 3D fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI) with multiple diffusion directions, T2-weighted (T2w) turbo spin echo, and T2*-weighted (T2*w) fast low angle shot (FLASH) gradient echo [12]. The following markers of cerebral SVD were assessed: lacune count, periventricular and deep white matter hyperintensities (WMH), cerebral microbleed (CMB) count and perivascular spaces (PVS). Lacune count was examined on FLAIR and T1-weighted images. Lacunes were defined as a round or ovoid, subcortical lesions with a signal similar to CSF and an axial diameter between 3 mm and 15 mm [42]. We evaluated severity of periventricular and deep white matter hyperintensities (WMH) on FLAIR images using the Fazekas scale [44]. Cerebral microbleed (CMB) count was examined on T2*-weighted images. CMB were defined as small (2-10 mm), round areas of signal void [42]. Perivascular spaces (PVS) were defined as fluid-filled, linear or round/ovoid spaces with a signal similar to CSF (i.e. hyperintense on T2-weighted and hypointense on T1-weighted images) and a diameter <3 mm that follow the typical course of penetrating vessels in the basal ganglia and centrum semiovale [42]. PVS were graded from 0 to 4 according to MacLullich et al [45]. All images were analyzed by experienced raters in a centralized core laboratory and blinded to clinical information. SVD markers were evaluated for both hemispheres collectively.

Table S1. Neuropsychological tests included in each cognitive domain

Domain	Included tests
Language	word fluency test (animal, s-words), CERAD-Boston naming test (15 items), MMSE-language items
Memory	CERAD-word list learning, CERAD-word list recall, CERAD-word list recognition, CERAD-figure recall, Rey-Osterrieth complex figure-immediate and delayed recall
Executive function	trail making test B, Stroop test
Attention	trail making test A, number symbol test
Visuospatial function	CERAD-figure drawing test, Rey-Osterrieth complex figure-copy test

Neuropsychological testing was performed six and twelve months after the index stroke. Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease, MMSE = mini-mental status examination

Table S2. Baseline characteristics of patients included in and of SVD excluded from analyses markers

	Patients included in analyses of SVD markers (n=466)	Patients excluded from analyses of SVD markers (n=134)	p
Age, years, median (IQR)	68 (60-76)	70 (57-76)	0.551
Female sex, n (%)	156 (33.5%)	44 (32.8%)	0.890
Years of education, median (IQR)	13 (12-16)	13 (12-16)	0.766
History of hypertension, n (%)	259 (55.6%)	77 (57.5%)	0.639
History of diabetes, n (%)	67 (14.4%)	26 (19.4%)	0.146
History of coronary artery disease, n (%)	26 (5.6%)	9 (6.7%)	0.611
History of atrial fibrillation, n (%)	46 (9.9%)	20 (14.9%)	0.106
Cognitive impairment at baseline, n (%)	232 (49.8%)	72 (53.7%)	0.398
Hs-cTnT, median (IQR)	7 (4-13)		
Hs-cTnT > URL, n (%)	100 (21.5%)		
Stroke etiology			
Large artery atherosclerosis, n (%)	131 (28.1%)	32 (23.9%)	0.830
Cardioembolism, n (%)	98 (21.0%)	35 (26.1%)	0.054
Small artery occlusion, n (%)	57 (12.2%)	9 (6.7%)	0.158

Other etiology, n (%)	52 (11.2%)	13 (9.7%)	0.965
Undetermined etiology, n (%)	128 (27.5%)	29 (21.6%)	0.527
IQCODE score, median (IQR)	48 (48-50)	48 (48-50)	0.942
Baseline NIHSS score, median (IQR)	2 (1-5)	3 (1-5)	0.431
SVD total score, n (%)			
0	187 (40.1%)		
1	137 (29.4%)		
2	94 (20.2%)		
3	36 (7.7%)		
4	12 (2.6%)		
Lacune count, median (IQR)	0 (0-0)		
SVD score lacunes, n (%)	58 (12.4%)		
CMB count, median (IQR)	0 (0-0)		
SVD score CMB, n (%)	48 (10.3%)		
PVS grade, n (%)			
1	321 (68.9%)		
2	76 (16.3%)		
3	64 (13.7%)		
4	5 (1.1%)		
SVD score PVS, n (%)	145 (31.1%)		
Fazekas periventricular white matter, n (%)			
0	93 (20.0%)		
1	249 (53.4%)		
2	81 (17.4%)		

3	43 (9.2%)		
Fazekas deep white matter, n (%)			
0	63 (13.5%)		
1	174 (37.3%)		
2	201 (43.1%)		
3	28 (6.0%)		
SVD score WMH, n (%)	230 (49.4%)		
Stroke localization			
Anterior left	133 (28.5%)	28 (20.9%)	0.078
Anterior right	117 (25.1%)	29 (21.6%)	0.410
Posterior cerebral artery left	36 (7.7%)	6 (4.5%)	0.194
Posterior cerebral artery right	34 (7.3%)	5 (3.7%)	0.140
Brainstem	46 (9.9%)	8 (6.0%)	0.164
Cerebellum	35 (7.5%)	8 (6.0%)	0.542
Multiple	64 (13.7%)	14 (10.4%)	0.319

There were no statistically significant differences in baseline characteristics between patients that were included in the analyses of hs-cTnT and SVD markers and those that were excluded from these analyses due to missing data.

Abbreviations: SVD = small vessel disease, IQR = interquartile range, hs-cTnT = high-sensitivity cardiac troponin T, IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly, NIHSS = National Institutes of Health Stroke Scale, CMB = cerebral microbleeds, PVS = perivascular spaces, WMH = white matter hyperintensities

Table S3. Association between hs-cTnT and cognitive adjustment domains after additional for total SVD score

	Language score	Memory score	Executive score	Attention score	Visual-spatial score	Global cognitive score
Longitudinal	-0.01 (-0.18-0.16), p=0.884	-0.04 (-0.18-0.09), p=0.513	-0.19 (-0.42-0.06), p=0.130	***-0.26 (-0.43 - -0.09), p=0.003***	-0.06 (-0.29-0.18), p=0.625	-0.07 (-0.20-0.06), p=0.303
At 6 months	-0.06 (-0.25 – 0.13), p=0.527	-0.06 (-0.24-0.11), p=0.486	-0.05 (-0.31-0.22), p=0.725	***-0.23 (-0.44 - -0.02), p=0.030***	-0.05 (-0.33-0.23), p=0.719	-0.02 (-0.17-0.13), p=0.783
At 12 months	0.04 (-0.15-0.23), p=0.672	-0.02 (-0.20-0.16), p=0.798	***-0.33 (-0.62 - -0.04), p=0.027***	***-0.29 (-0.51 - -0.08), p=0.009***	-0.07 (-0.40-0.27), p=0.703	-0.12 (-0.28-0.04), p=0.149

Log-transformed Hs-cTnT and cognitive domains (continuous) across 12 months of follow-up according to generalized linear regression models using GEE. Log-transformed Hs-cTnT and cognitive domains (continuous) at 6 and 12 months of follow-up according to linear regression models. The table displays the respective regression coefficients and 95% confidence intervals. Adjustment was made for age, sex, years of education, hypertension, diabetes, coronary artery disease, atrial fibrillation, cognitive impairment at baseline, baseline NIHSS, pre-stroke mRS and total SVD score. The results remained unchanged compared to the main analyses: after additional adjustment for the total SVD score, hs-cTnT remained negatively associated with performance in the domain 'attention' in the longitudinal and cross-sectional analyses. Hs-cTnT remained negatively associated with performance in the domain 'executive function' after twelve months of follow-up.

Table S4. Association between hs-cTnT and cognitive adjustment domains after additional for stroke localization (left anterior territory)

	Language score	Memory score	Executive score	Attention score	Visual-spatial score	Global cognitive score
Longitudinal	-0.01 (-0.17-0.15), p=0.922	-0.03 (-0.15-0.10), p=0.670	-0.20 (-0.43-0.02), p=0.077	***-0.26 (-0.43 - -0.10), p=0.002***	-0.08 (-0.30-0.14), p=0.473	-0.08 (-0.20-0.05), p=0.218
At 6 months	-0.05 (-0.23-0.13), p=0.564	-0.03 (-0.20-0.14), p=0.735	-0.07 (-0.32-0.19), p=0.610	***-0.24 (-0.44 - -0.04), p=0.019***	-0.08 (-0.36-0.19), p=0.546	-0.03 (-0.18-0.11), p=0.675
At 12 months	0.04 (-0.14-0.22), p=0.654	-0.02 (-0.20-0.15), p=0.739	***-0.35 (-0.62 - -0.07), p=0.015***	***-0.29 (-0.49 - -0.08), p=0.006***	-0.08 (-0.41-0.25), p=0.646	-0.13 (-0.28-0.03), p=0.109

Log-transformed Hs-cTnT and cognitive domains (continuous) across 12 months of follow-up according to generalized linear regression models using GEE. Log-transformed Hs-cTnT and cognitive domains (continuous) at 6 and 12 months of follow-up according to linear regression models. The table displays the respective regression coefficients and 95% confidence intervals. Adjustment was made for age, sex, years of education, hypertension, diabetes, coronary artery disease, atrial fibrillation, cognitive impairment at baseline, baseline NIHSS, pre-stroke mRS and localization in the left anterior territory. The results remained unchanged compared to the main analyses: after additional adjustment for stroke localization in the left anterior territory, hs-cTnT remained negatively associated with performance in the domain 'attention' in the longitudinal and cross-sectional analyses. Hs-cTnT remained negatively associated with performance in the domain 'executive function' after twelve months of follow-up.

Table S5. Association between hs-cTnT and cognitive patients with domains after exclusion of stroke in multiple territories

	Language score	Memory score	Executive score	Attention score	Visual-spatial score	Global cognitive score
Longitudinal	-0.022 (-0.198-0.154), p=0.806	0.012 (-0.129-0.153), p=0.868	-0.249 (-0.512-0.015), p=0.064	***-0.235 (-0.431 - -0.040), p=0.018***	-0.053 (-0.319-0.214), p=0.699	-0.057 (-0.200-0.086), p=0.434
At 6 months	-0.084 (-0.287-0.119), p=0.417	0.004 (-0.186-0.194), p=0.967	-0.125 (-0.412-0.163), p=0.394	-0.224 (-0.453-0.004), p=0.054	-0.088 (-0.405-0.229), p=0.585	-0.026 (-0.190-0.137), p=0.752
At 12 months	0.048 (-0.161-0.257), p=0.652	0.024 (-0.175-0.222), p=0.815	***-0.379 (-0.678 - -0.080), p=0.013***	***-0.245 (-0.477- -0.013), p=0.039***	-0.015 (-0.401 – 0.372), p=0.941	-0.088 (-0.256 – 0.079), p=0.301

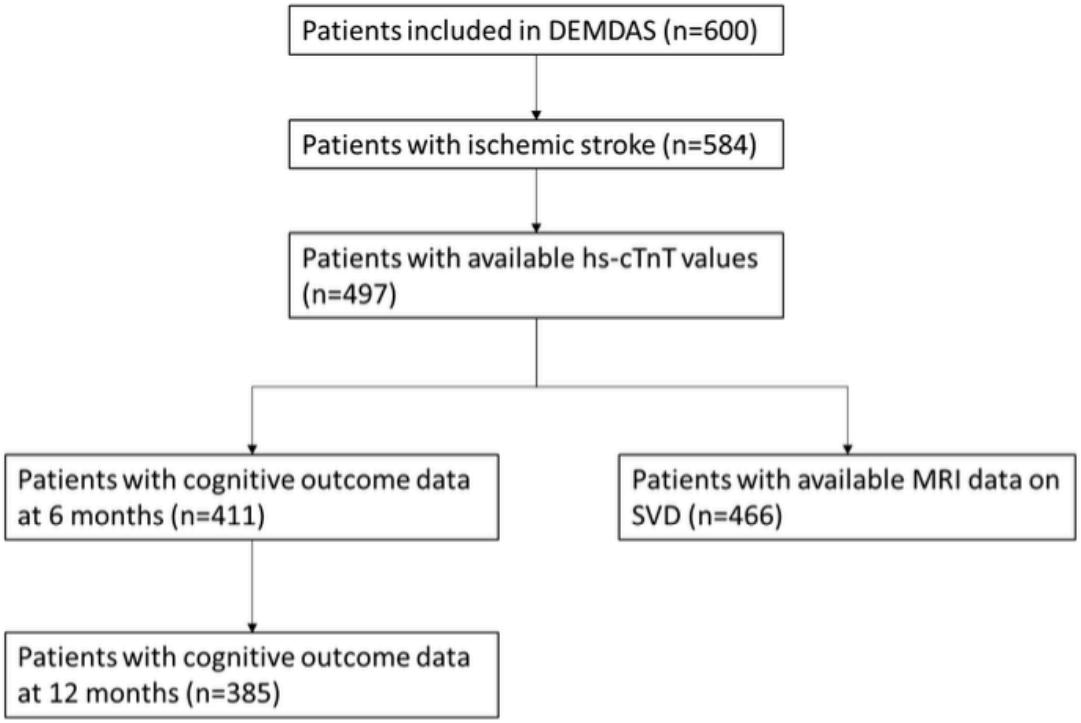
Log-transformed Hs-cTnT and cognitive domains (continuous) across 12 months of follow-up according to generalized linear regression models using GEE. Log-transformed Hs-cTnT and cognitive domains (continuous) at 6 and 12 months of follow-up according to linear regression models. The table displays the respective regression coefficients and 95% confidence intervals. Adjustment was made for age, sex, years of education, hypertension, diabetes, coronary artery disease, atrial fibrillation, cognitive impairment at baseline, baseline NIHSS and pre-stroke mRS. After exclusion of patients with strokes in multiple territories, the association between hs-cTnT and performance in the domain 'attention' at six months of follow-up was no longer significant. Apart from that, the results remained unchanged compared to the main analyses.

Table S6. Association between hs-cTnT and markers patients with of SVD after exclusion of stroke in multiple territories

	Global SVD score	SVD score lacune	SVD score CMB	SVD score PVS	SVD score WMH
Hs-cTnT	***1.741 (1.060-2.860), p=0.029***	2.149 (0.993-4.652), p=0.052	1.695 (0.733-3.921), p=0.218	0.947 (0.502-1.787), p=0.867	***2.109 (1.108-4.013), p=0.023***
	Lacune count	**CMB count**	**PVS grade**	**Fazekas PVWM**	**Fazekas DWM**
Hs-cTnT	***2.292 (1.226-4.386), p=0.009***	1.561 (0.871-2.798), p=0.135	1.016 (0.560-1.844), p=0.959	1.494 (0.903-2.472), p=0.118	***1.750 (1.042-2.940), p=0.035***

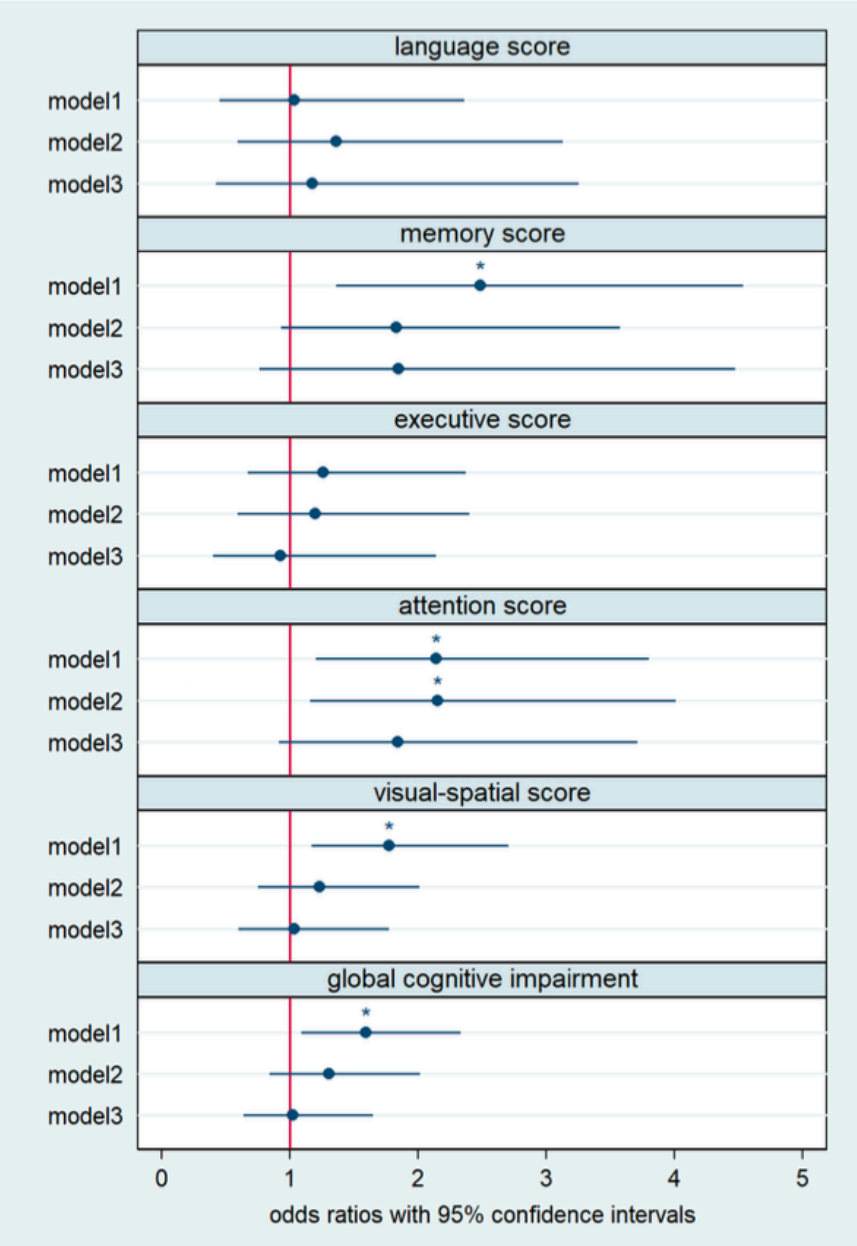
Log-transformed hs-cTnT and global cerebral small vessel disease (SVD) score, the four constituent SVD subscores and individual SVD markers in their entire range. Odds ratios and 95% confidence intervals were derived from ordinal logistic regression models for the global SVD score and binary logistic regression models for each constituent subscore, respectively. Odds ratios were derived from ordinal regression models for periventricular white matter hyperintensities (PVWMH) grade, deep WMH (DWM) grade and perivascular spaces (PVS) grade and from negative binomial regression models for lacune count and cerebral microbleed (CMB) count. Adjustment was made for age, sex, hypertension, diabetes, hyperlipidemia, coronary artery disease, atrial fibrillation, smoking status and baseline NIHSS. Abbreviations: SVD = small vessel disease, CMB = cerebral microbleeds, WMH = white matter hyperintensities, PVS = perivascular spaces. After exclusion of patients with strokes in multiple territories, the association between hs-cTnT and the lacune sub-score was no longer statistically significant. Apart from that, the results remained unchanged compared to the main analyses.

Figure S1. Flow chart for inclusion/exclusion of patients.



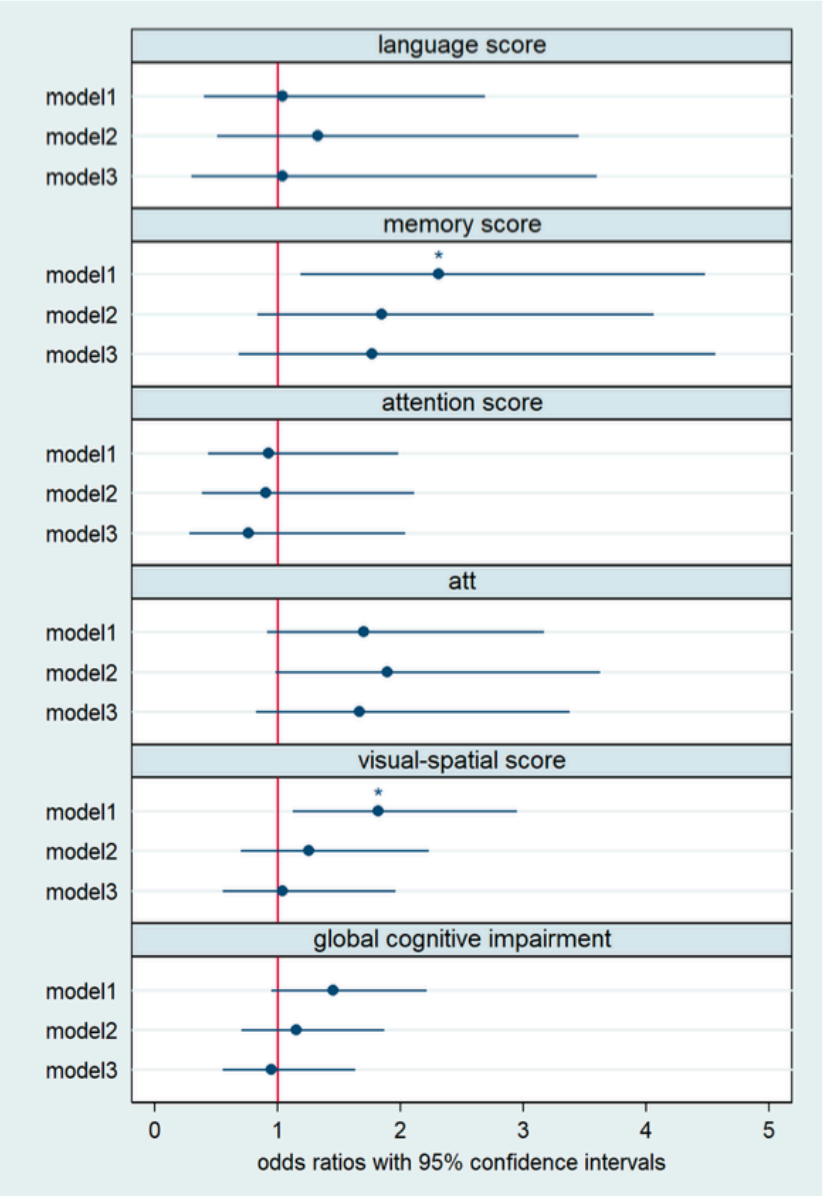
hs-cTnT = high-sensitivity cardiac troponin T. SVD = small vessel disease

Figure S2. Association between hs-cTnT and cognitive impairment across 12 months of follow-up after stroke, as derived from three logistic GEE models with different levels of adjustments.



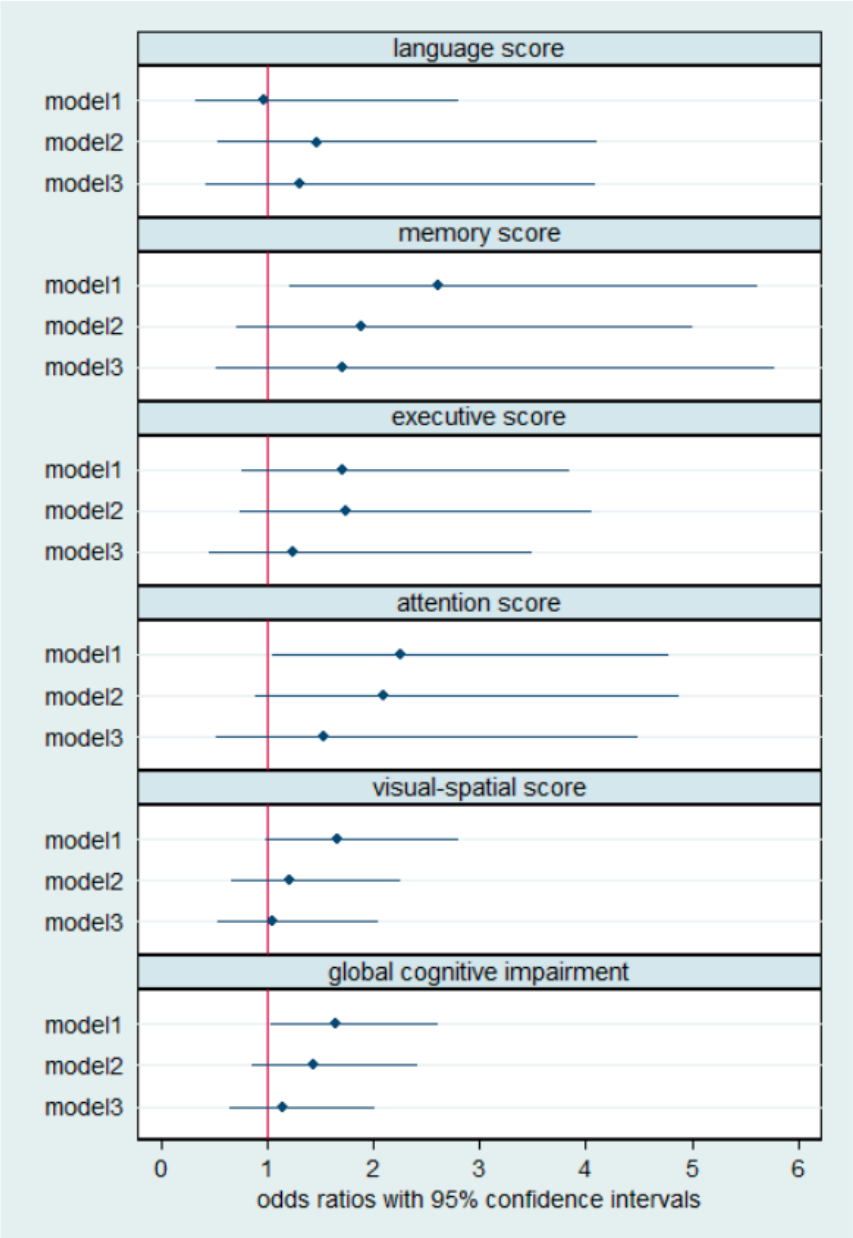
Model 1: unadjusted. Model 2: adjusted for age, sex and years of education. Model 3: additional adjustment for hypertension, diabetes, coronary artery disease, atrial fibrillation, cognitive impairment at baseline, baseline NIHSS and pre-stroke mRS. After full adjustment, there was no significant association between hs-cTnT and impairment in any cognitive domain in the longitudinal analyses. *$P_{corr} < 0.05$

Figure S3. Association between hs-cTnT and cognitive impairment at 6 months of follow-up after stroke, as derived from three penalized logistic regression models with different levels of adjustments.



Model 1: unadjusted. Model 2: adjusted for age, sex and years of education. Model 3: additional adjustment for hypertension, diabetes, coronary artery disease, atrial fibrillation, cognitive impairment at baseline, baseline NIHSS and pre-stroke mRS. After full adjustment, there was no significant association between hs-cTnT and impairment in any cognitive domain at 6 months of follow-up. *$P_{corr} < 0.05$

Figure S4. Association between hs-cTnT and cognitive impairment at 12 months of follow-up after stroke, as derived from three penalized logistic regression models with different levels of adjustments.



Model 1: unadjusted. Model 2: adjusted for age, sex and years of education. Model 3: additional adjustment for hypertension, diabetes, coronary artery disease, atrial fibrillation, cognitive impairment at baseline, baseline NIHSS and pre-stroke mRS. After full adjustment, there was no significant association between hs-cTnT and impairment in any cognitive domain at 12 months of follow-up. *$P_{corr} < 0.05$

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Appendix A: Paper III

Rong Fang, Marco Duering, Felix J. Bode, Sebastian Stösser, Julius N. Meißner, Peter Hermann, Thomas G. Liman, Christian H. Nolte, Lucia Kerti, Benno Ikenberg, Kathleen Bernkopf, Wenzel Glanz, Daniel Janowitz, Michael Wagner, Katja Neumann, Oliver Speck, Emrah Düzel, Benno Gesierich, Anna Dewenter, Annika Spottke, Karin Waegemann, Michael Görtler, Silke Wunderlich, Inga Zerr, Gabor C. Petzold, Matthias Endres, Marios K. Georgakis*, Martin Dichgans* on behalf of the DEMDAS investigators. Risk factors and clinical significance of post-stroke incident ischemic lesions. ***Alzheimers Dement.*** 2024;20(12):8412-8428.
* equally contributed

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RESEARCH ARTICLE

Risk factors and clinical significance of post-stroke incident ischemic lesions

Rong Fang[1] | Marco Duering[1,2] | Felix J. Bode[3,4] | Sebastian Stösser[3,4] | Julius N. Meißner[3,4] | Peter Hermann[5,6] | Thomas G. Liman[7,8,9] | Christian H. Nolte[8,10,11] | Lucia Kerti[7,8] | Benno Ikenberg[12] | Kathleen Bernkopf[12] | Wenzel Glanz[13,14] | Daniel Janowitz[1] | Michael Wagner[3,15] | Katja Neumann[13] | Oliver Speck[14,16,17,18] | Emrah Düzel[14] | Benno Gesierich[1,2] | Anna Dewenter[1] | Annika Spottke[3,4] | Karin Waegemann[1,19] | Michael Görtler[13,14] | Silke Wunderlich[20] | Inga Zerr[5,6] | Gabor C. Petzold[3,4] | Matthias Endres[7,8,21,22,23] | Marios K. Georgakis[1,24] | Martin Dichgans[1,19,25,26] | on behalf of the DEMDAS investigators

[1]Institute for Stroke and Dementia Research (ISD), LMU University Hospital, LMU Munich, Munich, Germany
[2]Medical Image Analysis Center (MIAC AG) and Department of Biomedical Engineering, University of Basel, Basel, Switzerland
[3]German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany
[4]Department of Vascular Neurology, University Hospital Bonn, Bonn, Germany
[5]Universitätsmedizin Göttingen, Klinik für Neurologie, Göttingen, Germany
[6]German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany
[7]Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin, Berlin, Germany
[8]German Center for Neurodegenerative Diseases (DZNE, Berlin), Berlin, Germany
[9]Department of Neurology, Carl Von Ossietzky University, Oldenburg, Germany
[10]Department of Neurology with Experimental Neurology, Charité - Universitätsmedizin Berlin, Berlin, Germany
[11]Berlin Institute of Health (BIH), Berlin, Germany
[12]Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany
[13]Department of Neurology, University Hospital, Otto-von-Guericke University Magdeburg, Magdeburg, Germany
[14]German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany
[15]Department of Old Age Psychiatry and Cognitive Disorders, University Hospital Bonn, Bonn, Germany
[16]Department of Biomedical Magnetic Resonance, Institute for Physics, Otto-von-Guericke University Magdeburg, Magdeburg, Germany
[17]Leibniz Institute for Neurobiology, Magdeburg, Germany
[18]Center for Behavioral Brain Sciences, Magdeburg, Germany
[19]German Center for Neurodegenerative Diseases (DZNE, Munich), Munich, Germany
[20]Department of Neurology, TUM School of Medicine, Technical University of Munich, Munich, Germany
[21]German Centre for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany
[22]German Center for Mental Health (DZPG), partner site Berlin, Berlin, Germany
[23]Klinik und Hochschulambulanz für Neurologie, Charité - Universitätsmedizin Berlin, Berlin, Germany
[24]Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA
[25]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany
[26]German Centre for Cardiovascular Research (DZHK, Munich), Munich, Germany

Marios K. Georgakis and Martin Dichgans have contributed equally to this study.

Correspondence
Martin Dichgans, Director, Institute for Stroke and Dementia Research, LMU Hospital, Ludwig-Maximilians-University (LMU), Munich, Germany, Feodor-Lynen-Street 17, 81377 Munich, Germany.
Email: martin.dichgans@med.uni-muenchen.de

Names and affiliations of collaborators for the DEMDAS study are listed in the Appendix.

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Abstract

INTRODUCTION: While incident ischemic lesions (IILs) are not unusual on follow-up magnetic resonance imaging (MRI) following stroke, their risk factors and prognostic significance remain unknown.

METHODS: In a prospective multicenter study of 503 acute stroke patients, we assessed IILs on registered MRI images at baseline and 6 months, analyzing risk factors and clinical outcomes across 36 months.

RESULTS: At 6 months, 78 patients (15.5%) had IILs, mostly diffusion-weighted imaging-positive (72%) and clinically covert (91%). Older age and small vessel disease (SVD) lesions were baseline risk factors for IILs. IILs were associated with worse cognitive (beta for global cognition: −0.31, 95% confidence interval [CI]: −0.48 to −0.14) and functional outcomes (beta for modified Rankin scale [mRS]: 0.36, 95% CI: 0.14 to 0.58), and higher recurrent stroke risk (hazard ratio: 3.81, 95% CI: 1.35 to 10.69). IILs partially explained the relationship between SVD and poor cognition.

DISCUSSION: IILs are common and are associated with worse cognitive and functional outcomes and stroke recurrence risk. Assessing IILs following stroke might aid prognostication.

KEYWORDS
cerebral small vessel disease, cognitive impairment, functional outcome, incident ischemic lesions, recurrent stroke, stroke

Highlights

- Incident ischemic lesions (IILs) were assessed with registered baseline and 6-month magnetic resonance imaging (MRI) scans in a stroke cohort.
- IILs 6 months after stroke are present in one-sixth of patients and are mostly clinically silent.
- Small vessel disease burden is the main baseline risk factor for IILs.
- IILs are associated with cognitive and functional impairment and stroke recurrence.
- Assessing IILs by follow-up MRI aids long-term prognostication for stroke patients.

1 | BACKGROUND

Stroke mortality rates have declined worldwide over the past 30 years,[1] drawing attention to the long-term outcomes following stroke.[2–5] Cognitive and functional impairment affect up to 80% of stroke survivors[5–8] and are associated with disability,[9–11] dependency,[12,13] and death,[14–17] placing a major socioeconomic burden on healthcare systems. An understanding of the factors determining long-term outcomes after stroke is needed to identify high-risk patients and optimize strategies for prevention.

Up to 30% of stroke survivors are found to have incident (new) ischemic lesions (IILs) on follow-up magnetic resonance imaging (MRI) scans,[18,19] but few studies have assessed IILs weeks or months after stroke,[20–26] which is when patients typically return for a follow-up visit. Even less is known about the association between such lesions and long-term clinical outcomes. In a study of 270 stroke survivors, IILs at 30 days after stroke were associated with an increased rate of recurrent stroke and vascular events over a 4-year follow-up period.[22] However, data from large prospective studies are lacking, and the impact of IILs detected weeks or months after the index event on post-stroke cognitive and functional outcomes remains unknown.

The current study aimed to define the characteristics, baseline predictors, and clinical significance of IILs detected on MRI scans 6 months after stroke. Using paired (baseline and 6 months) MRI data from a multicenter, prospective cohort of 736 stroke patients, we (i) determined the frequency and imaging as well as clinical features of IILs 6 months after stroke, (ii) explored risk factors for IILs, and (iii) tested the associations of IILs with cognitive and functional outcomes, recurrent stroke, and mortality across a 36-month follow-up period.

RESEARCH IN CONTEXT

1. **Systematic review**: Our MEDLINE search yielded cross-sectional studies showing a prevalence of up to 30% of new incident ischemic lesions (IILs) on follow-up magnetic resonance imaging (MRI) after stroke. However, the characteristics, risk factors, and associated long-term cognitive, functional, and clinical outcomes of IILs have not been systematically explored.
2. **Interpretation**: IILs, although mostly clinically silent, are common at 6 months after stroke and are associated with small vessel disease (SVD) lesions at baseline. IILs are associated with worse cognitive and functional outcomes and a higher risk of stroke recurrence over 36 months. IILs partially mediated the relationship between SVD and poorer cognition.
3. **Future directions**: Future studies should explore whether assessing IILs on MRI as part of post-stroke follow-up care could aid risk stratification and patient selection for inclusion in future clinical trials.

2 | METHODS

2.1 | Study design and baseline assessments

Participants were from the DEMDAS (DZNE [German Center for Neurodegenerative Disease]-Mechanisms of Dementia After Stroke)-DEDEMAS ([Determinants of Dementia After Stroke]; NCT01334749) study, a multicenter prospective hospital-based cohort study in Germany. Details of the study rationale, protocol, and baseline characteristics have been published elsewhere.[3,27] We recruited consecutive patients ≥18 years old who had experienced an acute stroke of any stroke severity, with symptom onset within the last 5 days and no pre-stroke dementia and provided informed consent for the study. Stroke was defined by an acute focal neurological deficit combined with an acute ischemic infarct as documented on cranial MRI scans, a new lesion on a delayed computed tomography (CT) scan, or an intracerebral hemorrhage as documented on CT or MRI scans. Eligible patients needed to have an available informant. The key exclusion criteria were as follows: patients who had previously been diagnosed with dementia or patients who scored >64 in the screening Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) test with the informant at baseline, patients with cerebral venous thrombosis, traumatic cerebral hemorrhage, intracerebral hemorrhage because of a vascular malformation, purely meningeal or intraventricular hemorrhage, shortened life expectancy due to a malignant disease, and patients with contraindications for MRI. The enrollment started as a single-center pilot study at the Ludwig-Maximilians-University (LMU) University Hospital in Munich (DEDEMAS), which enrolled 136 patients between May 2011 and November 2013. It was subsequently expanded to a multicenter study (DEMDAS) conducted at seven tertiary stroke centers in Germany, which enrolled an additional 600 patients between January 2014 and January 2019. Participants in the current study attended face-to-face follow-ups at 6, 12, and 36 months. Brain MRI examinations were conducted at baseline and 6 months. The study was performed according to the Declaration of Helsinki and was approved by the local ethics committees of all participating sites. All participants or their legal caregivers provided written informed consent. The study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[28]

2.2 | MRI scan acquisition and image processing

Participants underwent 3 Tesla MRI (all scanners Siemens Healthineers, Erlangen, Germany) examinations within 5 days of stroke onset and at 6 months (median 190 days [interquartile range {IQR}: 183 to 207 days]) using a standardized imaging protocol. The details on the neuroimaging parameters and the preprocessing steps are in the Supplement (Supplementary Methods).

To assist in the identification of IILs at 6 months, we used difference images between baseline and 6 months for diffusion-weighted imaging (DWI and trace image), fluid-attenuated inversion recovery (FLAIR), and T1-weighted (T1w) images. For registration and intensity bias correction, we used tools from the Advanced Normalization Tools (ANTs version 2.3.2).[29] The difference images were calculated by subtracting the intensity-normalized images at baseline from the registered 6-month follow-up images. All images were evaluated in a standardized reading setup (Figure 1A, Video S1, and Figure S1).

2.3 | Neuroimaging markers at baseline

Index acute stroke lesions were segmented on the preprocessed trace images using Otsu's method.[3] Baseline markers of small vessel disease (SVD), including lacunes, white matter hyperintensities (WMHs), cerebral microbleeds (CMBs), and perivascular spaces (PVSs), were further assessed following widely accepted standards[30,31] and as previously reported.[3] Three types of indices were used to determine SVD burden (Supplementary Methods): (1) presence of SVD marker; (2) summary SVD score[3,31,32] (the score ranges from 0 to 4, with one point awarded for (i) the presence of lacunes, (ii) a Fazekas score[33] of 3 for periventricular WMHs or a Fazekas score of 2 or 3 for deep WMHs, (iii) the presence of CMBs, and (iv) a PVS grade of 2 or higher, respectively); and (3) individual SVD markers.[3] An experienced, trained rater (R.F., board-certified neurologist) assessed all images blinded to the clinical data including various clinical outcomes, and doubtful cases were discussed with a senior neuroimaging specialist (M.Due.) in regular consensus meetings. To guarantee the reproducibility of the ratings, inter-rater reliabilities were evaluated by two trained raters (R.F. and A.D., PhD in neuroimaging) in a subset of the images, resulting in κ values of 0.720 for lacunes, 0.795 for WMHs, 0.725 for CMBs, and 0.815 for PVSs.

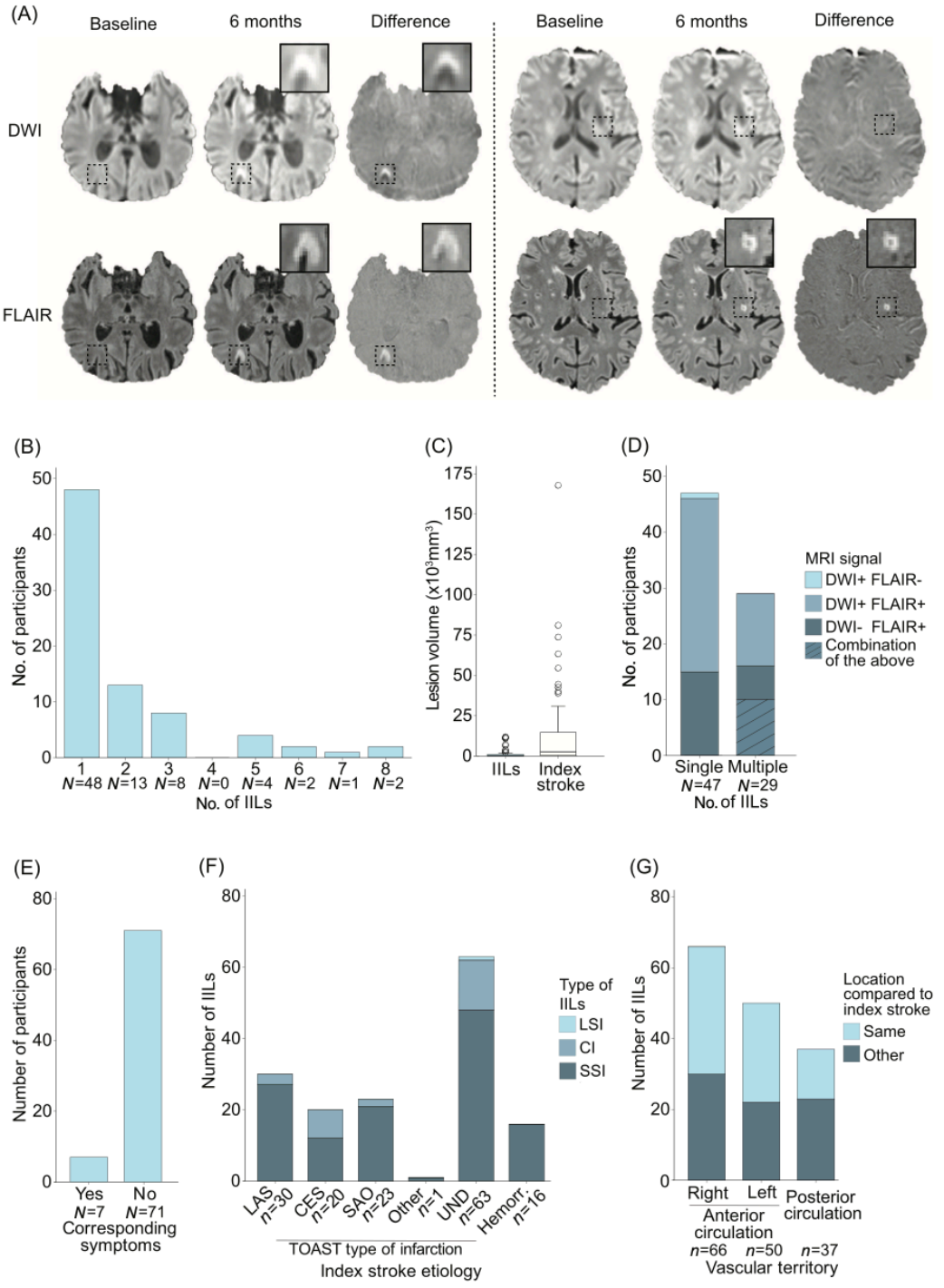

FIGURE 1 Characteristics of IILs at 6 months after stroke. (A) Examples of IILs on brain MRI scans at 6 months. Left: 77-year-old patient with incident DWI+/FLAIR+ cortical infarct; right: 59-year-old patient with incident DWI−/FLAIR+ small subcortical infarct. For more details see *Methods* and Figure S1 in Supplement. (B) Distribution of IIL counts among participants who had IILs ($N = 78$). (C) Boxplot of volume of IILs and index stroke in participants with IILs. (D) Number of participants with different MRI signals of IILs. (E) Number of participants with and without symptoms corresponding to IILs. (F) Number of IILs with different types of IILs stratified by index stroke. Fisher's exact tests were applied to

2.4 | IILs at 6 months after stroke

IILs were detected visually by comparing images at baseline and 6 months using three image contrasts (DWI, FLAIR, and T1w) and their respective different images to increase the sensitivity of the visual rating. Lesions were classified into three categories[34]: (1) DWI+/FLAIR− IILs: new lesions appearing hyperintense on 6-month DWI but isointense on FLAIR, primarily representing the early hyperacute phase (0 to 6 h) after stroke; (2) DWI+/FLAIR+ IILs: new lesions appearing hyperintense on 6-month DWI and hyper- or hypointense (cavitated) on 6-month FLAIR, typically present in the late hyperacute, acute, or subacute phases (6 h to 3 weeks). These two categories were further combined into one overarching DWI+ category: (3) DWI−/FLAIR+ IILs: new lesions appearing hyper- or hypointense (cavitated) on FLAIR at 6 months but isointense on DWI, indicating chronic lesions. Signals of IILs on T1w could be isointense or hypointense. One experienced rater (R.F.) visually screened all images for IILs while being blinded to clinical information. When uncertain, consensus meetings were held with a senior neuroimaging specialist (M.Due.).

IILs were manually segmented using ITK-SNAP (version 3.8.0, www.itksnap.org)[35] and further classified into three types based on their size and location: (1) small subcortical infarct (SSI), which refers to a lesion up to 20 mm in diameter on the axial plane in the territory of penetrating arteries, following the criterion adopted by STRIVE;[30] (2) large (>20 mm in diameter) subcortical infarct (LSI); and (3) cortical infarct (CI). The clinical manifestations of IILs were also extracted. Data on ischemic stroke symptoms after the index stroke were collected at the 6-month in-person follow-up visit by a physician. All recurrent stroke reports were confirmed through medical records, including clinical manifestations and neuroimaging information, as documented by the treating physicians. Symptomatic IILs referred to confirmed recurrent infarcts that were associated with acute clinical manifestations. Asymptomatic IILs were not associated with clinical symptoms.

2.5 | Follow-up outcomes across 36 months after stroke

2.5.1 | Cognitive and functional outcomes

Participants underwent detailed in-person cognitive and functional evaluations at 6, 12, and 36 months. The evaluations included a comprehensive neuropsychological test battery (15 tests) covering five domains: executive function, memory, language, attention, and visuospatial function.[3] Domain-specific *z*-scores were obtained by averaging the scale-specific *z*-scores[36–39] within each domain, and an average global cognitive score was derived by averaging the *z*-scores from all five domains. Cognitive impairment was defined as a *z*-score of < -1.5 in any of the five domains, and domain-specific cognitive impairments were defined according to domain-specific *z*-scores of < -1.5.[40] Functional outcomes were assessed using the modified Rankin scale (mRS), the Barthel index (BI),[41,42] and the instrumental activities of daily living (IADLs).[43] Functional impairment was defined based on two widely adopted cutoffs of mRS (>1 and >2).[17,44]

2.5.2 | Recurrent stroke and mortality

Information on recurrent stroke between 6 and 36 months, which was defined as the occurrence of neurological deficits caused by a newly diagnosed stroke, was obtained from reports from the patients or informants during annual follow-ups and an inspection of their medical records complying with the published procedure.[3] For participants who did not attend the scheduled follow-up visits, we followed a standardized protocol for establishing contact with them or their informants.[3] In short, a trained study nurse initially contacted participants by telephone and, if unsuccessful, called their informant or sent a mail questionnaire. In case of no response, the data manager checked with the local registration office for the participant's information related to mortality or new address, and the contact process was repeated if a new address was found.

2.6 | Statistical analysis

Baseline risk factors of IILs at 6 months were explored by applying logistic regression analysis for IIL presence and quasi-Poisson regression analysis for IIL number to obtain more accurate standard errors (SEs) adjusting the overdispersed data. We applied a main model adjusting for age, sex, and the National Institutes of Health Stroke Scale (NIHSS), as well as an additional model further adjusting for history of hypertension, diabetes, prior stroke, atrial fibrillation, current smoking, body mass index (BMI), low-density lipoprotein-cholesterol (LDL-C) levels, large artery disease (defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of ≥50% on ultrasound or computed tomography angiography [CTA], if ultrasound not available), and normalized index stroke volume.

compare categorical differences across all six groups and between any pair of groups. The results showed a significant difference across all six groups; CES had a higher proportion of CI-IILs than LAS, SAO, and Hemorr. Strokes, with all *p*-values being <.05. SSI refers to a lesion up to 20 mm in diameter on the axial plane in the territory of penetrating arteries, following STRIVE criteria.[30] LSI refers to a lesion located in the subcortex with an axial diameter above 20 mm. CI refers to a lesion located in the cortex of any size. (G) Number of IILs in locations compared to the vascular territories of the index stroke. *N* represents the number of participants; *n* represents the number of IILs. CES, cardioembolic stroke; CI: cortical infarct; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; Hemorr., hemorrhagic stroke; IIL, incident ischemic lesion; LAS, large artery stroke; LSI, large subcortical infarct; MRI, magnetic resonance imaging; SAO, small artery occlusion; SSI, small subcortical infarct; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Associations between IIL presence and number at 6 months and clinical outcomes were assessed across 36 months after stroke using the cognitive and functional evaluations at 6-, 12-, and 36-month follow-ups. Generalized estimating equations (GEEs) with a first-order autoregressive working correlation structure and robust SEs were used to account for repeated outcomes. Linear GEE analyses were fitted for continuous outcomes, and logistic GEE analyses were fitted for binary outcomes. For stability and interpretability,[45] we chose five covariables in the main model: age, sex, NIHSS, educational years, and cognitive impairment in the acute phase (MoCA < 26 or MMSE < 24 if MoCA is not available), considering that these variables are strong predictors of poststroke cognitive/functional outcomes in the previous literature.[3,43,46–48] In sensitivity analysis, we utilized two additional models: (1) the main model plus history of hypertension, diabetes, prior stroke, atrial fibrillation, current smoking, BMI, LDL-C, large artery disease, and normalized index stroke volume and (2) a model adjusting for apolipoprotein E (*APOE*) genotype (0, 1, or 2 ε4 alleles) on top of all covariates. The aforementioned models showed no multicollinearity, as indicated by variance inflation factors (VIF) <2 for all included variables.[49,50] We assumed the missingness of the adjusted covariates was at random and used multiple imputation methods to replace missing data.[51] All missing ratios were below 4% with missing data on cognitive impairment in the acute phase, LDL-C, and normalized index stroke volume. Linear, ordinal logistic and logistic regressions were further applied to examine the relationship of IIL presence and number with outcomes at 6, 12, and 36 months, separately.

Because non-stroke death is a competing risk for recurrent stroke, we calculated the cumulative incidence of recurrent stroke using the cumulative incidence function, and the difference between the presence and absence of IIL groups was estimated by Gray's test.[52] Associations of IILs (presence and number) and recurrent stroke between 6 and 36 months were assessed by competing-risk regression models (cause-specific and Fine-Gray subdistribution hazard models), with non-stroke death representing the competing risk.[53,54] Data from patients who were lost to follow-up or who did not experience recurrent strokes between 6 and 36 months were censored at the last visit, at which the patients were present or at the last contact. Considering stroke history as a consistent risk factor for recurrent stroke,[55,56] the main model was adjusted for age, sex, NIHSS, and whether there was a recurrent clinical stroke between the index stroke and 6 months. An additional model further adjusted for hypertension, diabetes, prior stroke, atrial fibrillation, current smoking, BMI, LDL-C, large artery disease, and normalized index stroke volume. Further sensitivity analyses were conducted in patients after excluding those who had recurrent clinical strokes between the index stroke and 6 months. Associations of IILs (presence and number) and mortality between 6 and 36 months were calculated using Cox proportional hazard models. The main model was adjusted for age, sex, and NIHSS, and a second model included further adjustments for hypertension, diabetes, prior stroke, atrial fibrillation, current smoking, BMI, LDL-C, large artery disease, and normalized index stroke volume.

We further performed mediation analysis[57–59] with the R package mediation version 4.5.0 to test whether IILs explain the associations between baseline SVD burden and cognitive outcomes at 36 months that we previously reported.[3] SVD presence (dichotomous) was treated as the exposure (X), IIL presence (dichotomous) was treated as the mediator (M), and the global cognitive score (continuous) or cognitive impairment (dichotomous) was regarded as the outcome (Y). Confidence intervals were estimated by bootstrapping 10,000 times. In the main analysis, no covariates were adjusted, whereas sensitivity analyses were adjusted for age, sex, and NIHSS score. Additional sensitivity analyses set the summary SVD score, an ordinal (0 to 4) variable, as the exposure in the aforementioned mediation models.

In all analyses, we adjusted for multiple comparisons setting as a statistical significance threshold a false discovery rate (FDR)-derived p-value < .05. Statistical analyses were performed using R version 4.3.0 (R Foundation).

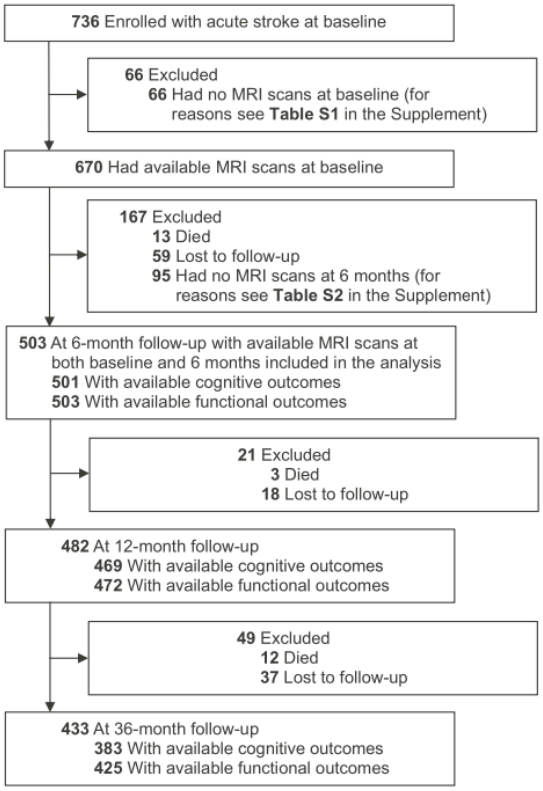

FIGURE 2 Study profile. MRI, magnetic resonance imaging.

3 | RESULTS

3.1 | Frequency and characteristics of IILs

Among 736 recruited participants, 503 had paired MRI scans (baseline and 6 months after the index stroke) and were included in current analyses (Figure 2). Reasons for missing MRIs at each time point are

listed in Tables S1,S2. Compared with the 233 participants who were excluded from the analyses, the included participants were younger, had a higher educational level, had lower HbA_{1c} and triglyceride levels, less frequently had a history of atrial fibrillation, large artery disease, and cardio-embolic stroke, more frequently had stroke related to other etiology, had less prestroke disability, less cognitive impairment, and a lower SVD burden at baseline (Table S3).

We detected a total of 153 IILs in 78 out of 503 (15.5%) participants at 6 months. The baseline characteristics of the 503 participants (mean age 66.7 ± SD 11.1 years, 32.0% female) and a comparison of participants with and without IILs are presented in Table 1. Compared to participants without IILs, participants with IILs were older, more frequently had a history of hypertension, had a lower BI, a higher proportion of cognitive impairment, and a greater SVD burden.

Among participants with IILs: (1) 48 (62%) had only one IIL and the median number of IILs was one (IQR: 1 to 2) (Figure 1B); (2) the overall volume of IILs per patient (median: 302 mm^3, IQR: 100 to 902 mm^3) was an order of magnitude smaller than the index stroke lesion volume (median volume in participants with IILs: 2656 mm^3, IQR: 344 to 14,672 mm^3) (Figure 1C); (3) among participants with informative DWI and FLAIR images at both time points ($N = 76$, Table S4), 45 (59%) had DWI+ IILs ($N = 1$ with DWI+/FLAIR−; $N = 44$ with DWI+/FLAIR+), 21 (28%) had DWI−/FLAIR+ IILs, and 10 (13%) had both DWI+ and DWI−/FLAIR+ IILs (Figure 1D); (4) only 7 (9%) had corresponding clinical symptoms (Figure 1E, Table S5); (5) the majority ($n = 125$, 81.7%) had SSI-IILs, whereas few had CI-IILs ($n = 27$, 17.6%) or LSI ($n = 1$, 0.7%)-IILs, regardless of the index stroke etiology (although CI-IILs were proportionally more common in cardioembolic stroke, as to be expected) (Figure 1F); (6) about half of the IILs (78/153, 51.0%) occurred in the same vascular territory as the index stroke (Figure 1G); (7) IILs were observed throughout the brain, most frequently in the white matter (100 IILs, 65.4%), followed by cortex (27, 17.6%), subcortical gray matter (12, 7.8%), brainstem (7, 4.6%), and cerebellum (7, 4.6%) (Figure S2).

3.2 | Associations between baseline characteristics and IILs at 6 months

In age-, sex-, and NIHSS-adjusted logistic regression analyses of potential risk factors at baseline, the following variables associated with IIL presence 6 months after stroke: age (odds ratio [OR]: 1.05, 95% confidence interval: 1.02 to 1.08, $p < .001$), SVD burden including the presence of SVD marker (OR: 3.47, 95% confidence interval: 1.81 to 7.08, $p < .001$), summary SVD score (OR: 1.68, 95% confidence interval: 1.33 to 2.14, $p < .001$), and all individual SVD markers (OR for lacune count: 1.46, 95% confidence interval: 1.13 to 2.04, $p = .01$; deep white matter [DWM] Fazekas score: 1.93, 95% confidence interval: 1.32 to 2.86, $p < .001$; periventricular white matter [PVWM] Fazekas score: 1.66, 95% confidence interval: 1.20 to 2.31, $p = .002$; CMB count: 1.11, 95% CI: 1.002 to 1.23, $p = 0.04$; PVS grade: 1.62, 95% CI: 1.16 to 2.27, $p = 0.005$). In analyses further adjusting for vascular risk factors and normalized index stroke volume for IIL presence, as well as exploring risk factors for the IIL number, associations with SVD burden remained stable (Table 2).

3.3 | Associations between IILs and long-term clinical outcomes

3.3.1 | Cognitive and functional outcomes

Among the 503 participants included, 503 (100%), 482 (95.8%), and 433 (86.1%) attended the follow-up visits at 6, 12, and 36 months, respectively (Figure 2). At 6 months, 151 (30.3%), 96 (19.1%), and 30 (6.0%) participants had cognitive impairment, mRS > 1, and mRS > 2, respectively. Corresponding numbers at 12 months were 100 (21.6%), 83 (17.6%), and 21 (4.5%) and at 36 months 66 (17.4%), 70 (16.5%), and 22 (5.2%).

Participants with IILs at 6 months had a lower composite global cognitive score and a higher mRS at 6, 12, and 36 months compared to those without IILs (Figure 3A,B). Accordingly, patients with IILs exhibited a higher occurrence of cognitive impairment, mRS > 1, and mRS > 2 at each follow-up visit (all $p < .05$) (Figure S3). After adjusting for age, sex, NIHSS, educational status, and cognitive impairment at baseline, IILs presence was significantly associated with a lower global cognitive score and a higher mRS score across the 36-month follow-up (beta for global cognitive score: −0.31, 95% confidence interval: −0.48 to −0.14, $p < .001$; beta for mRS: 0.36, 95% confidence interval: 0.14 to 0.58, $p = .001$; Figure 3C). Looking at binary outcomes, significant associations were likewise observed in both cognitive (OR: 2.86, 95% confidence interval: 1.82 to 4.49, $p < .001$) and functional impairment (OR for mRS > 1: 2.41, 95% confidence interval: 1.56 to 3.71, $p < .001$; OR for mRS > 2: 2.81, 95% confidence interval: 1.46 to 5.38, $p = .002$; Figure S4). The IIL presence was further associated with all individual cognitive domains and functional tests when considering both continuous and binary outcomes (Figure 3C, Figures S4,S5). Sensitivity analyses showed that significant associations between IIL presence/number and cognitive and functional outcomes remained consistent when additionally accounting for vascular risk factors and normalized index stroke volume, when additionally accounting for *APOE* genotype (Figures S4–S7), and when exploring associations at 6, 12, and 36 months, respectively (Figures S8 to S11).

3.3.2 | Recurrent stroke and mortality

Between 6 and 36 months, 7/78 (9.0%) of participants with IILs and 10/425 (2.4%) without IILs experienced a (clinically overt) recurrent stroke ($p = .009$), and 5/78 (6.4%) with IILs and 11/425 (2.6%) without IILs died ($p = .09$). In competing-risk regression analyses, the IIL presence was associated with a significantly higher risk of stroke recurrence from 6 to 36 months after stroke (Table S6) (1) when adjusting for age, sex, NIHSS, and recurrent clinical stroke between baseline and 6 months (cause-specific hazard ratio [csHR]: 3.81, 95% confidence

TABLE 1 Baseline characteristics of all participants.

Baseline characteristics	No. (%) All (*N* = 503)	With IILs (*N* = 78)	No IILs (*N* = 425)	*p*-value, with versus no IILs[a]
Age, mean (SD), years	66.7 (11.1)	70.9 (9.8)	65.9 (11.2)	**<0.001**
Sex[b]				
Male	342 (68.0)	56 (71.8)	286 (67.3)	0.51
Female	161 (32.0)	22 (28.2)	139 (32.7)	
Education, median (IQR), years	13 (12 to 17)	13 (11 to 16)	13 (12 to 17)	0.27
Cardiovascular risk factors				
Hypertension	380 (75.5)	67 (85.9)	313 (73.6)	**0.03**
Diabetes mellitus	94 (18.7)	17 (21.8)	77 (18.1)	0.54
Current smoking	118 (23.5)	17 (21.8)	101 (23.8)	0.82
Atrial fibrillation	87 (17.3)	13 (16.7)	74 (17.4)	>0.99
Prior history of stroke	49 (9.7)	11 (14.1)	38 (8.9)	0.23
Large artery disease[c]	157 (31.2)	28 (35.9)	129 (30.4)	0.40
BMI, mean (SD), kg/m^2	27.0 (4.2)	26.5 (4.1)	27.1 (4.2)	0.23
SBP, median (IQR), mmHg	139 (128 to 150)	144 (132 to 151)	138 (128 to 150)	0.14
DBP, median (IQR), mmHg	80 (72 to 87)	80 (73 to 87)	80 (72 to 87)	0.70
HbA_{1c}, median (IQR), %	5.7 (5.4 to 6.1)	5.7 (5.3 to 6.2)	5.7 (5.4 to 6.0)	0.49
LDL-C, median (IQR), mg/dL	124 (103 to 153)	126 (107 to 160)	124 (103 to 150)	0.41
HDL-C, median (IQR), mg/dL	48 (40 to 58)	46 (38 to 56)	48 (40 to 59)	0.26
Triglycerides, median (IQR), mg/dL	124 (94 to 172)	135 (94 to 173)	123 (94 to 168)	0.39
APOE genotype (*n* = 410)				
0 ε4 allele	318 (77.6)	52 (81.3)	266 (76.9)	0.27
1 ε4 allele	85 (20.7)	10 (15.6)	75 (21.7)	
2 ε4 allele	7 (1.7)	2 (3.1)	5 (1.4)	
Stroke classification				
Ischemic stroke	490 (97.4)	75 (96.2)	415 (97.6)	0.44
TOAST subtype				
Large artery atherosclerosis	122 (24.3)	21 (28.0)	101 (24.3)	0.33
Cardioembolism	99 (19.7)	11 (14.7)	88 (21.2)	
Small artery occlusion	63 (12.5)	11 (14.7)	52 (12.5)	
Other etiology	24 (4.8)	1 (1.3)	23 (5.5)	
Undefined etiology	182 (36.2)	31 (41.3)	151 (36.4)	
Hemorrhagic stroke	13 (2.6)	3 (3.8)	10 (2.4)	0.44
Clinical/cognitive assessment				
NIHSS score, median (IQR)	2 (1 to 5)	3 (1 to 5)	2 (1 to 5)	0.42
mRS[d] before stroke				
0	426 (84.7)	62 (79.5)	364 (85.6)	0.30
1	53 (10.5)	10 (12.8)	43 (10.1)	
2	11 (2.2)	2 (2.6)	9 (2.1)	
3	13 (2.6)	4 (5.1)	9 (2.1)	
BI score, median (IQR)	100 (85 to 100)	95 (80 to 100)	100 (90 to 100)	**0.01**
IQCODE score, median (IQR)	48 (48 to 49)	48 (48 to 49)	48 (48 to 49)	0.51
Baseline cognitive impairment[e]	236/490 (48.2)	48/74 (64.9)	188/416 (45.2)	**0.003**
MRI variables				
Primary stroke lesion volume, median (IQR), mm^3	2168 (452 to 12,262)	2656 (344 to 14,672)	2152 (480 to 11,544)	0.94
Total intracranial volume, median (IQR), $\times 10^6$ mm^3	1.56 (1.44 to 1.65)	1.58 (1.44 to 1.65)	1.56 (1.44 to 1.65)	0.65

(Continues)

TABLE 1 (Continued)

Baseline characteristics	No. (%) All (*N* = 503)	With IILs (*N* = 78)	No IILs (*N* = 425)	*p*-value, with versus no IILs[a]
Presence of SVD marker[f]	293/502 (58.4)	65/78 (83.3)	228/424 (53.8)	**<0.001**
Summary SVD score[g]				
0	209/502 (41.6)	13/78 (16.7)	196/424 (46.2)	**<0.001**
1	155/502 (30.9)	30/78 (38.5)	125/424 (29.5)	
2	90/502 (17.9)	15/78 (19.2)	75/424 (17.7)	
3 to 4	48/502 (9.6)	20/78 (25.6)	28/424 (6.6)	
Lacune count				
0	445 (88.5)	57 (73.1)	388 (91.3)	**<0.001**
1	41 (8.2)	14 (17.9)	27 (6.4)	
2	11 (2.2)	3 (3.8)	8 (1.9)	
≥3	6 (1.2)	4 (5.1)	2 (0.5)	
Fazekas DWM score				
0	71 (14.1)	4 (5.1)	67 (15.8)	**<0.001**
1	213 (42.3)	23 (29.5)	190 (44.7)	
2	200 (39.8)	44 (56.4)	156 (36.7)	
3	19 (3.8)	7 (9.0)	12 (2.8)	
Fazekas PVWM score				
0	112 (22.3)	9 (11.5)	103 (24.2)	**<0.001**
1	269 (53.5)	35 (44.9)	234 (55.1)	
2	89 (17.7)	23 (29.5)	66 (15.5)	
3	33 (6.6)	11 (14.1)	22 (5.2)	
CMB count				
0	454/502 (90.4)	65/78 (83.3)	389/424 (91.7)	**0.01**
1	22/502 (4.4)	3/78 (3.8)	19/424 (4.5)	
2	8/502 (1.6)	4/78 (5.1)	4/424 (0.9)	
≥3	18/502 (3.6)	6/78 (7.7)	12/424 (2.8)	
PVS grade[h]				
1	335 (66.6)	38 (48.7)	297 (69.9)	**<0.001**
2	110 (21.9)	21 (26.9)	89 (20.9)	
3	56 (11.1)	18 (23.1)	38 (8.9)	
4	2 (0.4)	1 (1.3)	1 (0.2)	
IILs volume, median (IQR), mm^3	NA	302 (100 to 902)	NA	NA

Note: SI conversion factors: to convert a percentage of total HbA_{1c} to the proportion of total HbA_{1c}, multiply by 0.01; LDL-C and HDL-C to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113. Bold indicates statistically significant at $p < .05$.

Abbreviations: BI, Barthel index; BMI, body mass index; CMB, cerebral microbleed; DBP, diastolic blood pressure; DWM, deep white matter; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein-cholesterol; IIL, incident ischemic lesion; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; IQR, interquartile range; LDL-C, low-density lipoprotein-cholesterol; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NA, not applicable.; NIHSS, National Institutes of Health Stroke Scale; PVS, perivascular space; PVWM, periventricular white matter; SBP, systolic blood pressure; SD, standard deviation; SVD, small vessel disease; TOAST, Trial of Org 10172 in Acute Stroke Treatment; WMH, white matter hyperintensity.

[a]Categorical variables were analyzed using the χ^2 or Fisher's exact test, a two-tailed *t* test was employed for continuous variables with a normal distribution, and the Mann–Whitney U test was used for other continuous variables.

[b]Self-reported.

[c]Large artery disease is defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of >50% on ultrasound or computed tomography angiography (CTA) if ultrasound is not available.

[d]A global functional scale ranges from 0 (no symptoms) to 5 (serious functional impairment).

[e]Montreal Cognitive Assessment (MoCA) <26 or Mini-Mental State Examination (MMSE) <24 when MoCA was not available (2.6% of total).

[f]Summary SVD score is equal to or greater than 1.

[g]Summary SVD score ranges from 0 to 4, with 1 point awarded for (i) the presence of lacunes, (ii) a Fazekas score of 3 for periventricular WMHs or a Fazekas score of 2 or 3 for deep WMHs, (iii) the presence of CMBs, and (iv) a PVS grade of 2 or higher, respectively.

[h]PVSs were counted bilaterally in the basal ganglia, and the side with the higher number was used for scoring: 0 = no PVSs, 1 = < 10 PVSs, 2 = 11 to 20 PVSs, 3 = 21 to 40 PVSs, and 4 = > 40 PVSs.[3,31,32]

TABLE 2 Relationship between baseline risk factors and IILs at 6 months after stroke.

	Presence of IILs at 6 months after stroke[a]		Number of IILs at 6 months after stroke[b]	
Potential risk factor at baseline	OR (95% CI)[c]	OR (95% CI)[d]	RR (95% CI)[c]	RR (95% CI)[d]
Demographic factor				
Age (years)	**1.05 (1.02 to 1.08)**	**1.05 (1.02 to 1.09)**	1.02 (0.998 to 1.05)	1.02 (0.99 to 1.06)
Sex (0 = male vs 1 = female)	0.73 (0.42 to 1.25)	0.73 (0.41 to 1.26)	0.63 (0.31 to 1.17)	0.65 (0.31 to 1.24)
NIHSS score	1.00 (0.94 to 1.04)	0.99 (0.93 to 1.05)	1.00 (0.93 to 1.04)	0.98 (0.90 to 1.05)
Cardiovascular risk profile				
History of hypertension	1.67 (0.87 to 3.51)	1.71 (0.86 to 3.68)	1.45 (0.70 to 3.38)	1.45 (0.68 to 3.52)
History of diabetes (yes vs no)	1.16 (0.62 to 2.08)	1.20 (0.62 to 2.25)	1.19 (0.58 to 2.30)	1.26 (0.59 to 2.51)
Current smoking (yes vs no)	1.26 (0.66 to 2.29)	1.22 (0.63 to 2.28)	1.24 (0.60 to 2.38)	1.21 (0.58 to 2.38)
Prior stroke history (yes vs no)	1.40 (0.65 to 2.84)	1.72 (0.77 to 3.59)	1.63 (0.71 to 3.30)	1.86 (0.78 to 3.90)
History of atrial fibrillation (yes vs no)	0.66 (0.32 to 1.26)	0.72 (0.34 to 1.44)	0.82 (0.36 to 1.69)	0.83 (0.34 to 1.81)
BMI/SD	0.94 (0.71 to 1.22)	0.92 (0.68 to 1.22)	0.92 (0.66 to 1.25)	0.90 (0.63 to 1.24)
LDL-C/SD	1.24 (0.97 to 1.58)	1.32 (1.03 to 1.70)	1.06 (0.79 to 1.40)	1.15 (0.86 to 1.54)
Large artery disease[e] (yes vs no)	1.28 (0.76 to 2.13)	1.08 (0.63 to 1.84)	0.997 (0.53 to 1.79)	0.88 (0.46 to 1.62)
Normalized primary stroke lesion volume[f]/SD	1.17 (0.91 to 1.46)	1.27 (0.99 to 1.59)	1.19 (0.93 to 1.46)	1.23 (0.95 to 1.52)
SVD lesion burden				
Presence of SVD marker[g]	**3.47 (1.81 to 7.08)**	**3.33 (1.68 to 7.04)**	**4.19 (1.93 to 10.25)**	**4.17 (1.78 to 11.18)**
Summary SVD score[h]	**1.68 (1.33 to 2.14)**	**1.71 (1.33 to 2.21)**	**1.93 (1.55 to 2.39)**	**2.01 (1.57 to 2.58)**
Lacune count	**1.46 (1.13 to 2.04)**	**1.48 (1.14 to 2.09)**	**1.31 (1.17 to 1.42)**	**1.35 (1.19 to 1.51)**
DWM Fazekas score	**1.93 (1.32 to 2.86)**	**1.91 (1.29 to 2.90)**	**2.66 (1.78 to 4.03)**	**2.71 (1.76 to 4.25)**
PVWM Fazekas score	**1.66 (1.20 to 2.31)**	**1.66 (1.19 to 2.34)**	**2.20 (1.61 to 3.00)**	**2.22 (1.60 to 3.07)**
CMB count	1.11 (1.002 to 1.23)	1.11 (1.001 to 1.24)	**1.13 (1.08 to 1.18)**	**1.14 (1.08 to 1.20)**
PVS grade[i]	**1.62 (1.16 to 2.27)**	**1.65 (1.17 to 2.33)**	**1.93 (1.37 to 2.69)**	**1.95 (1.37 to 2.74)**

Note: Bold indicates statistically significant ORs/RRs at $p < .05$, corrected for multiple comparisons with false discovery rate (FDR) method.
Abbreviations: BMI, body mass index; CI, confidence interval; CMB, cerebral microbleed; DWM, deep white matter; IIL, incident ischemic lesion; LDL-C, low-density lipoprotein-cholesterol; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PVS, perivascular space.; PVWM, periventricular white matter; RR, rate ratio; SD, standard deviation; SVD, small vessel disease; WMH, white matter hyperintensity.
[a]Logistic regression analysis was applied to explore the baseline risk factors of the presence of IILs at 6 months.
[b]Quasi-Poisson regression analysis was applied to explore the baseline risk factors of the number of IILs at 6 months.
[c]Adjusted for age, sex, and NIHSS score at baseline.
[d]Adjusted for age, sex, NIHSS score, hypertension history, diabetes history, current smoking, prior stroke history, atrial fibrillation history, BMI, LDL-C, stenosis of brain vessels, and normalized primary stroke lesion volume at baseline.
[e]Large artery disease is defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of >50% on ultrasound or computed tomography angiography (CTA) if ultrasound is not available.
[f]Primary stroke lesion volume/total intracranial volume.
[g]Summary SVD score is equal to or greater than 1.
[h]Summary SVD score ranges from 0 to 4, with 1 point awarded for (i) the presence of lacunes, (ii) a Fazekas score of 3 for periventricular WMHs or a Fazekas score of 2 or 3 for deep WMHs, (iii) the presence of CMBs, and (iv) a PVS grade of 2 or higher, respectively.
[i]PVSs were counted bilaterally in the basal ganglia, and the side with the higher number was used for scoring: 0 = no PVSs, 1 = < 10 PVSs, 2 = 11 to 20 PVSs, 3 = 21 to 40 PVSs, and 4 = >40 PVSs.[3,31,32]

interval: 1.35 to 10.69, $p = .01$; subdistribution HR [sdHR]: 3.77, 95% confidence interval: 1.31 to 10.83, $p = .01$; Figure 3D), (2) when additionally adjusting for vascular risk factors and normalized index stroke volume (csHR: 3.43, 95% confidence interval: 1.24 to 9.49, $p = .02$; sdHR: 3.37, 95% confidence interval: 1.24 to 9.12, $p = .02$), and (3) when excluding those who had recurrent clinical strokes between baseline and 6 months. No significant association was found between IILs and mortality (Figure S12).

3.4 | Mediating effects of IILs at 6 months in relationships between baseline SVD burden and cognitive outcomes at 36 months

Finally, given that SVD is associated with cognitive impairment after stroke,[3] we tested the hypothesis that IILs at 6 months partly mediate the relationship between baseline SVD burden and cognitive outcome at 36 months. A mediation analysis showed a significant

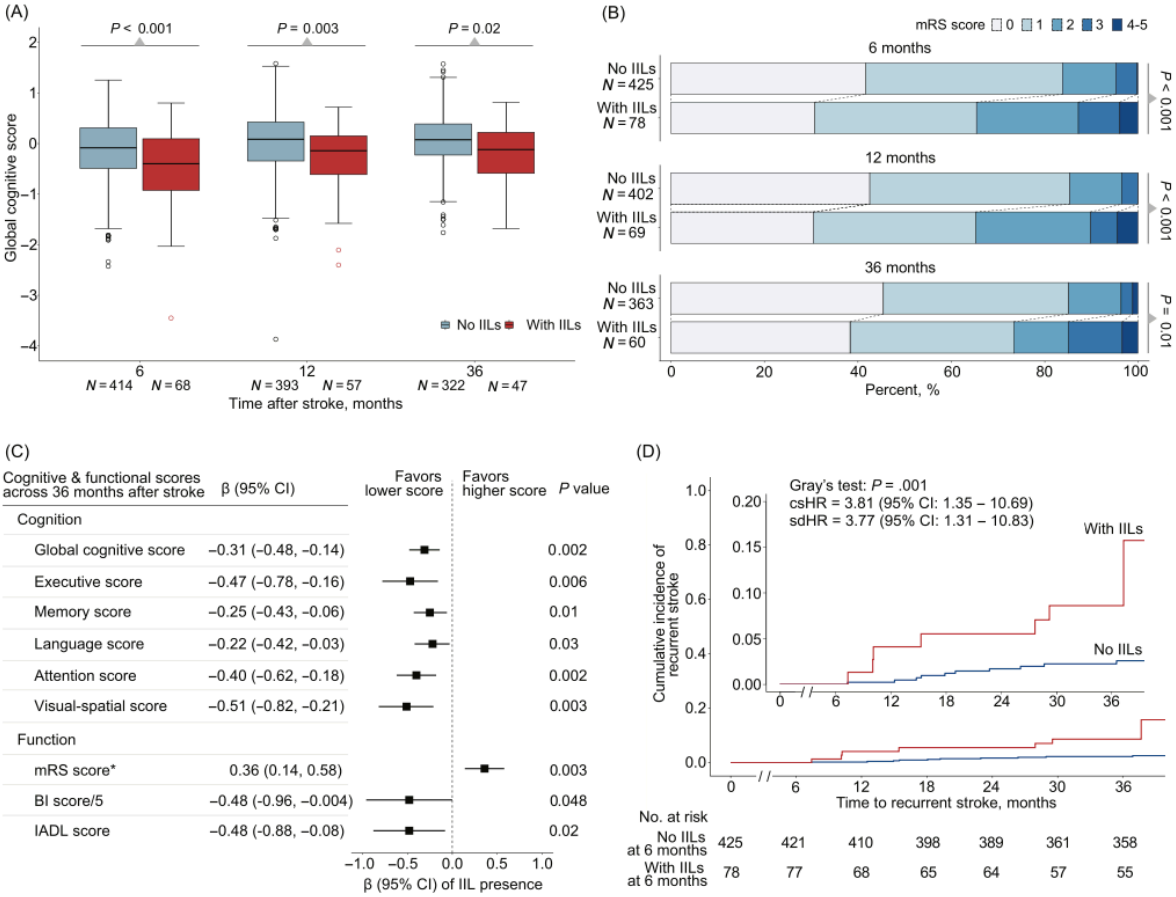

FIGURE 3 Associations between IILs at 6 months and cognitive and functional outcomes, as well as recurrent stroke over 36 months after the index stroke. (A) Median and interquartile range of *z*-scores of global cognitive performance at 6, 12, and 36 months stratified by IIL status. (B) Distributions of mRS score at 6, 12, and 36 months stratified by IIL status. (C) Associations of presence of IILs with cognitive and functional scores across 36 months using linear GEEs. The models in C adjusted for age, sex, NIHSS score, educational years, and cognitive impairment (MoCA<26 or MMSE<24 if MoCA is not available) at baseline. *p*-values were corrected for multiple comparisons with the FDR method. (D) Cumulative incidence curve of recurrent stroke stratified by presence and absence of IILs based on the competing-risk model. Hazard ratios associated with the presence of IILs for recurrent stroke between 6 and 36 months after the index stroke were calculated using competing-risk regression models (cause-specific and subdistribution hazard models) incorporating the competing risk of non-stroke death. The two models adjusted for age, sex, and NIHSS score at baseline and recurrent clinical stroke between baseline and 6 months. BI, Barthel index; CI, confidence interval; csHR, cause-specific hazard ratio; FDR, false discovery rate; IILs, incident ischemic lesions; GEE, generalized estimating equation; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; sdHR, subdistribution hazard ratio.*mRS assesses functional outcome, with a score ranging from 0 (no symptoms) to 5 (serious functional impairment)

indirect effect of SVD marker presence at baseline on global cognitive performance at 36 months through IIL presence (beta: −0.02, 95% confidence interval: −0.06 to −0.002, p = .02) representing 14.3% of the total effect. Similar results were obtained for the binary outcome (OR for cognitive impairment: 1.03, 95% confidence interval: 1.01 to 1.07, p = .002; mediation effect: 26.7%) (Figure S13). The results remained significant after adjusting for age, sex, and NIHSS, as well as when using the summary SVD score as the exposure (Table S7).

4 | DISCUSSION

The main finding from this study is that IILs detected on MRI scan 6 months after stroke were associated with both worse cognitive and functional outcomes and with a higher risk of stroke recurrence. Compared to study participants without IILs, those with IILs had about three-fold higher odds of cognitive impairment, 2.5-fold higher odds of functional impairment, and a four-fold increased risk of stroke recurrence across the 3-year follow-up.

Almost one out of six patients had IILs. Several observations suggest that IILs in the current cohort mostly related to cerebral SVD: first, apart from age, SVD burden was the main baseline predictor for IILs, with all individual SVD markers predicting IILs. Second, the majority of lesions were small, which is consistent with data on IILs in older people with SVD[60] and in line with the definition of DWI+ lesions in the updated STRIVE-2 criteria.[30] Third, the majority of lesions affected the white matter and were localized in subcortical brain structures regardless of index stroke etiology. IILs in subcortical regions are associated with a risk factor profile of SVD in the general population.[61] Additionally, the statistical finding of a mediation effect of IILs on the relationship between SVD and worse cognitive and functional outcomes provides key mechanistic insights. SVD neuroimaging markers are surrogates of SVD pathologies, the commonest of which is arteriolosclerosis.[62,63] Our results suggest that existing SVD pathology in stroke patients contributes to the emergence of IILs, which then influence cognitive and functional performance. However, we cannot rule out mechanisms other than SVD, such as cardioembolism or hypoperfusion due to stenotic atherosclerotic lesions.

Most of the IILs were positive on DWI scans and were not associated with clinical manifestations, which is consistent with the observation in a sporadic SVD cohort,[60] where DWI+ lesions were common and silent. DWI+ is widely seen in acute ischemic stroke, with cytotoxic edema being the most common underlying pathophysiology, resulting from ion and water shifts.[64] Diffusion restriction may also occur in other brain diseases, such as demyelination, infection, and metabolic disorders, each with different clinical presentations and anatomical distributions.[65] Nevertheless, the nature and pathophysiology of SVD-related DWI+ lesions remain undefined. Acute IILs might have been overestimated since FLAIR+ largely coexisted with DWI+ in this study, and DWI+ might occur due to T2 shine-through. However, with a diffusion weighting of $b = 1000$ s/mm^2 as used in the current study, T2 shine-through is mostly absent.[66–68] Hence, DWI hyperintensities at 6 months indicate that the lesions occurred within the recent 10 to 20 days.[34] This may suggest that we missed many IILs without clinical symptoms by scanning at only one time point, with some of them eventually disappearing. Considering the evidence that transient DWI+ lesions do not necessarily indicate complete recovery from injury,[69] exploring the dynamics and determinants of IILs after stroke remains an interesting and important topic.

There is currently no guidance for assessing the clinical relevance of IILs on MRI scans performed as part of follow-up care after a stroke. It is also unclear how patients with IILs on follow-up scans should be managed. Our results suggest that the availability of paired MRI scans 6 months after stroke aids prognostication. Our results further imply that follow-up MRI might be suited to select high-risk patients even months after stroke for inclusion in secondary prevention trials. Such trials seem warranted given the substantial increase in stroke recurrence rate and both cognitive and functional decline in study participants with IILs. The four clinical studies (dose-finding trials of PACIFIC-STROKE[23,70] and AXIOMATIC-SSP,[24] DATAS II trial,[25] and ATTUNE[26]) show it is possible to integrate follow-up MRI for the assessment of covert infarcts as an endpoint in secondary stroke prevention trials. Selecting patients based on IILs for intensified preventive treatment would be a different approach, targeting a different population and time interval after stroke but should be equally feasible. On the other hand, although there is limited evidence from randomized trials, the European Stroke Organisation (ESO) guidelines have recommended securing blood pressure control, as well as smoking cessation, healthy diet, good sleep habits, and avoiding obesity and stress in patients with covert cerebral SVD, specifically WMHs and lacunes, to prevent adverse clinical outcomes.[71] Stroke patients with SVD-related covert IILs fall within these recommendations. Several clinical trials have shown that anticoagulation[23–25,70] did not prevent incident MRI-detected brain infarcts after stroke, which is to be expected given the predominant role of SVD in IILs that we demonstrated in our study. However, a post hoc analysis of the PACIFIC stroke trial further revealed that FXIa inhibition was associated with numerically fewer incident cortical covert infarcts, which highlights the importance of IIL subtyping in defining underlying mechanisms and predicting responses to different preventive strategies.[70]

Our study is limited by the preferential recruitment of patients with mild stroke, which in part relates to the requirement for comprehensive imaging and neuropsychological assessment. Related to this, there was an overrepresentation of patients with ischemic stroke. Despite our efforts to be as inclusive as possible, the requirement for paired baseline and follow-up MRI scans resulted in a high attrition rate, a common issue in real-world neuroimaging research,[22,72] and the selection for less severely affected patients could have led to an underestimation of IILs and adverse outcomes after stroke. Although our findings may not be fully representative of an unselected stroke population, they likely reflect patients who can follow up with MRI and would benefit from personalized approaches. As one of the technical limitations, the use of identical neuropsychological tests at follow-up visits might have led to learning effects and an underestimation of cognitive impairment rates at 12 and 36 months. Surveillance for symptomatic IILs or recurrent strokes, originally derived from patients' or caregivers' reports, may introduce recall bias. In neuroimaging, it is indeed challenging to differentiate old small subcortical infarcts from non-specific WMHs, and this cannot be fully resolved with MRI. To address this issue, we used the STRIVE-2[30] guidelines as guidance, taking other imaging features into account, such as small cavitations, which are more indicative of small subcortical infarcts than newly formed WMHs, and held consensus meetings with a senior neuroimaging expert. Strengths include the standardized 3T MRI protocol enabling advanced image processing and image reading on registered scans in a standardized reading environment. Also, follow-up MRI scans were conducted at an interval compatible with clinical practice.[73–75] As such, our data could aid clinical prognostication.

In conclusion, IILs are common on MRI scans 6 months after stroke and are associated with adverse outcomes. Assessing IILs on follow-up MRI aids prognostication and might help in selecting high-risk patients suited for inclusion in secondary prevention trials.

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CONFLICT OF INTEREST STATEMENT

Dr. Duering reports consulting for Roche, serving on the scientific advisory board for Biogen, and receiving speaker honoraria from Sanofi Genzyme, all outside of the submitted work. Dr. Nolte reports speaker honoraria and/or lecture fees from Abbott, Alexion, AstraZeneca, BMS, Daiichi Sankyo, Novartis, Pfizer, and Takeda, all outside the submitted work. Dr. Endres reported receiving grants from Bayer and fees paid to the Charité – Universitätsmedizin Berlin from Amgen, AstraZeneca, Bayer Healthcare, Boehringer Ingelheim, BMS, Daiichi Sankyo, Sanofi, and Pfizer, all outside the submitted work. Other (Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid): European Academy of Neurology (Board of directors, unpaid), German Society of Neurology (Member, unpaid), International Society of Cerebral Blood Flow Metabolism (Member, unpaid), American Heart Association/American Stroke Association (Member, unpaid), World Stroke Organization (Member, unpaid), European Stroke Organisation (Fellow, unpaid), German Center of Neurodegenerative Diseases (personal contract, paid). All other authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants or their legal caregivers provided written informed consent, and the study was approved by the local ethics committees of all participating sites.

ORCID

Rong Fang https://orcid.org/0000-0002-5663-9407
Christian H. Nolte https://orcid.org/0000-0001-5577-1775
Matthias Endres https://orcid.org/0000-0001-6520-3720
Martin Dichgans https://orcid.org/0000-0002-0654-387X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX

Collaborators for the DEMDAS study

Last name	First name	Email	Affiliation 1	Affiliation 2	Affiliation 3
Wittenberg	Tatjana	tatjana.wittenberg@charite.de	Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin		
Scheitz	Jan F.	jan.scheitz@charite.de	Department of Neurology with Experimental Neurology, Charité - Univeristätsmedizin Berlin	Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin	
Prüß	Harald	harald.pruess@charite.de	Department of Neurology with Experimental Neurology, Charité - Univeristätsmedizin Berlin	German Center for Neurodegenerative Diseases (DZNE), Berlin 10117, Germany	
Sperber	Pia Sophie	pia.sperber@charite.de	Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin	Department of Neurology with Experimental Neurology, Charité - Univeristätsmedizin Berlin	
Nave	Alexander H.	alexander-heinrich.nave@charite.de	Department of Neurology with Experimental Neurology, Charité - Universitätsmedizin Berlin	Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin	Berlin Institute of Health (BIH), Germany
Kufner Ibaroule	Anna	anna.kufner@charite.de	Department of Neurology with Experimental Neurology, Charité - Universitätsmedizin Berlin	Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin	Berlin Institute of Health (BIH), Germany
Ebrahimi	Taraneh	taraneh.ebrahimi@ukbonn.de	Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn 53127, Germany		
Nordsiek	Julia	julia.nordsiek@ukbonn.de	German Center for Neurodegenerative Diseases (DZNE), Bonn 53127, Germany	Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn 53127, Germany	
Beckonert	Niklas	niklas.beckonert@ukbonn.de	Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Bonn 53127, Germany		
Schmitz	Matthias	matthias.schmitz@med.uni-goettingen.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		
Goebel	Stefan	stefan.goebel@med.uni-goettingen.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		
Schütte-Schmidt	Julia	julia.schuette@med.uni-goettingen.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		

Last name	First name	Email	Affiliation 1	Affiliation 2	Affiliation 3
Nuhn	Sabine	sabine.nuhn@med.uni-goettingen.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		
Volpers	Corinna	corinna.volpers@med.uni-goettingen.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		
Dechent	Peter	peter.dechent@med.uni-goettingen.de	Department of Cognitive Neurology, University Medical Center Göttingen, Göttingen 37075, Germany		
Bähr	Mathias	mbaehr@gwdg.de	Department of Neurology, University Medical Center Göttingen, Göttingen 37075, Germany	German Center for Neurodegenerative Diseases (DZNE), Göttingen 37075, Germany	Cluster of Excellence Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB), Göttingen, Germany
Tiedt	Steffen	steffen.tiedt@med.uni-muenchen.de	Institute for Stroke and Dementia Research (ISD), LMU University Hospital, LMU Munich, 81377 Munich, Germany.		
Huber	Christiane	Christiane.Huber@mri.tum.de	Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany		
Stöcker	Tony	tony.stoecker@dzne.de	German Center for Neurodegenerative Diseases (DZNE), Bonn 53127, Germany		
Kellert	Lars	Lars.kellert.@med.uni-muenchen.de	Department of Neurology, University Hospital, LMU Munich, 81377 Munich, Germany		
Bartenstein	Peter	Peter.Bartenstein@med.uni-muenchen.de	Department of Nuclear Medicine, University Hospital, LMU Munich, 81377 Munich, Germany		

SUPPLEMENTARY MATERIAL

Risk factors and clinical significance of post-stroke incident ischemic lesions

Rong Fang[1]; Marco Duering[1,2]; Felix J. Bode[3,4]; Sebastian Stösser[3,4]; Julius N. Meißner[3,4]; Peter Hermann[5]; Thomas G. Liman[6,7,8]; Christian H. Nolte[7,9,10]; Lucia Kerti[6,7]; Benno Ikenberg[11]; Kathleen Bernkopf[11]; Wenzel Glanz[12,13]; Daniel Janowitz[1]; Michael Wagner[14,15]; Katja Neumann[12]; Oliver Speck[13,16,17,18]; Emrah Düzel[13]; Benno Gesierich[1,2]; Anna Dewenter[1]; Annika Spottke[3,4]; Karin Waegemann[1,19]; Michael Görtler[12,13]; Silke Wunderlich[11]; Inga Zerr[5,20]; Gabor C. Petzold[3,4]; Matthias Endres[6,7,9,21,22]; Marios K. Georgakis*[1,23]; Martin Dichgans*[1,19] on behalf of the DEMDAS investigators[#]

[1] Institute for Stroke and Dementia Research (ISD), LMU University Hospital, LMU Munich, Feodor-Lynen-Str. 17, 81377 Munich, Germany

[2] Medical Image Analysis Center (MIAC AG) and Department of Biomedical Engineering, University of Basel, Marktgasse 8, 4051 Basel, Switzerland

[3] German Center for Neurodegenerative Diseases (DZNE), Venusberg Campus 1/99, 53127 Bonn, Germany

[4] Division of Vascular Neurology, Department of Neurology, University Hospital Bonn, Venusberg Campus 1, 53127 Bonn, Germany

[5] Department of Neurology, University Medical Center Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany

[6] Center for Stroke Research Berlin (CSB), Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

[7] German Center for Neurodegenerative Diseases (DZNE), Charitéplatz 1, 10117 Berlin, Germany

[8] Department of Neurology, Carl Von Ossietzky University, Ammerländer Heerstrasse 114-118, 26129 Oldenburg, Germany

[9] Department of Neurology with Experimental Neurology, Charité - Universitätsmedizin Berlin, Hindenburgdamm 30, 12203 Berlin, Germany

[10] Berlin Institute of Health (BIH), Anna-Louisa-Karsch-Str. 2, 10178 Berlin, Germany

[11] Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Ismaninger Str. 22, 81675 Munich, Germany

[12] Department of Neurology, University Hospital, Otto-von-Guericke University Magdeburg, Leipziger Straße 44, 39120 Magdeburg, Germany

[13] German Center for Neurodegenerative Diseases (DZNE), Leipziger Straße 44, 39120 Magdeburg, Germany

[14] German Center for Neurodegenerative Diseases (DZNE), Venusberg Campus 1/80, 53127 Bonn, Germany

[15] Department of Neurodegenerative Diseases and Geriatric Psychiatry, University Hospital Bonn, Venusberg Campus 1/80, 53127 Bonn, Germany

[16] Department of Biomedical Magnetic Resonance, Institute for Physics, Otto-von-Guericke University Magdeburg, Leipziger Str. 44, 39120 Magdeburg, Germany

[17] Leibniz Institute for Neurobiology, Brenneckestraße 6, 39118 Magdeburg, Germany

[18] Center for Behavioral Brain Sciences, Universitätsplatz 2, 39106 Magdeburg, Germany

[19] German Center for Neurodegenerative Diseases (DZNE), Feodor-Lynen-Str. 17, 81377 Munich, Germany

[20] German Center for Neurodegenerative Diseases (DZNE), Robert-Koch-Str. 40, 37075 Göttingen, Germany

[21] German Centre for Cardiovascular Research (DZHK), partner site Berlin, Potsdamer Str. 58, 10785 Berlin, Germany

[22] German Center for Mental Health (DZPG), partner site Berlin, Charitéplatz 1, 10117 Berlin, Germany

[23] Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, 415 Main St., Cambridge, 02142 MA, USA

* Georgakis and Dichgans contributed equally to this work.

[#] Names and affiliations of collaborators for the DEMDAS study are listed in the **Appendix**.

Corresponding author:

Martin Dichgans, MD

Director, Institute for Stroke and Dementia Research, LMU Hospital,

Ludwig-Maximilians-University (LMU), Munich, Germany

Feodor-Lynen-Str. 17, 81377 Munich, Germany

Telephone: +49-89-4400-46019; Fax: +49-89-4400-46040;

e-mail: martin.dichgans@med.uni-muenchen.de

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Supplementary Methods. MRI parameters, image preprocessing, and SVD indices at baseline.

MRI parameters

The imaging protocol at baseline and 6 months after stroke included the following sequences: (1) 3D T1-weighted (T1w) magnetization prepared rapid gradient echo (MPRAGE): TR=2500ms, TI=1100ms, TE=4.33-4.37ms, voxel size=1.00x1.00x1.00mm^3, bandwidth=140Hz/Px; (2) T2-weighted (T2w) turbo spin echo: TR=6500ms, TE=116-117ms, in-plane resolution=1.00x1.00mm^2, slice thickness=3mm, slice gap=10%, bandwidth=362Hz/Px; (3) 3D fluid-attenuated inversion recovery (FLAIR): TR=5000ms, TI=1800ms, TE=393-398ms, voxel size=1.00x1.00x1.00 or 1.00x0.98x0.98mm^3, bandwidth=780-781Hz/Px; (4) Diffusion-weighted imaging (DWI): TR=12700-13400ms, TE=81-84ms, in-plane resolution=2.00x2.00mm^2, slice thickness=2mm, slice gap=0%, bandwidth=1628Hz/Px, b-values=[0, 1000s/mm^2], 30 diffusion directions; (5) T2*-weighted (T2*w) fast low angle shot (FLASH) gradient echo: TR=742ms, TE=19.9ms, in-plane resolution=1.00x1.00mm^2, slice thickness=5mm, slice gap=10%, bandwidth=199-200Hz/Px. The first 18 patients recruited in the run-in phase study of DEDEMAS followed a slightly different protocol,[1] but there were no major differences in the imaging protocol that would compromise data pooling.

Diffusion MRI preprocessing

Diffusion MRI data were pre-processed using tools from MRtrix3 (https://www.mrtrix.org/)[2] and the FMRIB Software Library (FSL, v5.0.11).[3] Specifically, the “dwidenoise”,[4] “mrdegibbs”,[5] and “eddy_correct”,[6] tools were employed for denoising, Gibbs artefact correction, and correction of head motion and eddy current induced distortions. The diffusion tensor was estimated using “dtifit” from FSL. Diffusion-weighted trace images were generated by averaging preprocessed b=1000 images from all diffusion directions used for visual ratings.

SVD indices at baseline

Three types of indices were utilized to evaluate the intracranial cerebral small vessel disease (SVD) burden in each participant: (1) Presence of SVD marker: This index was derived from a summary SVD score (described below). A score of 0 was assigned if the summary SVD score was 0, while a score of 1 was assigned if the summary SVD score ranged between 1 and 4; (2) Summary SVD score: This index is a widely used visual score that summarizes SVD burden (lacunes, white matter hyperintensities [WMHs], cerebral microbleeds [CMBs], and perivascular spaces [PVSs]) in the brain. It ranges from 0 to 4,[1, 7, 8] with one point awarded for i) the presence of lacunes, ii) a Fazekas score[9] of 3 for periventricular WMHs or a Fazekas score of 2 or 3 for deep WMHs, iii) the presence of CMBs, and iv) a PVS grade of 2 or higher, respectively; (3) Individual SVD markers:[1] These are quantitative indices that include lacune count, Fazekas scores for periventricular (PVWM) and deep WMHs (DWM), CMB count, and PVS grade.

Supplementary Table 1. Reasons for exclusion due to unavailability of MRI scans at baseline.

Reasons	DEDEMAS	DEMDAS
Patient declined an MRI after recruitment	3	5
Only clinical MRI protocol available	7	2
MRI canceled	1	2
MRI scanner unavailable due to technical reasons	0	8
Critically ill patient	0	4
Patient discharged before MRI	0	3
MRI not feasible due to size/weight limitations of scanner	0	3
Implants non-compatible with MRI	1	1
Claustrophobia	0	1
Reason not documented	21*	4
Total	33	33

Abbreviation: MRI, magnetic resonance imaging

* at the beginning of the run-in DEDEMAS study reasons for exclusion were not documented.

Supplementary Table 2. Reasons for exclusion due to unavailability of MRI scans at 6 months.

Reasons	DEDEMAS	DEMDAS
Patient declined an MRI	1	15
MRI canceled	0	11
MRI scanner unavailable due to technical reasons	0	6
Critically ill patient	0	5
Implants non-compatible with MRI	3	12
Claustrophobia	0	2
Unavailable MRI scans due to a not on-site visit	9	19
Missed follow-up at 6 months	1	4
Reason not documented	0	7
Total	14	81

Abbreviation: MRI, magnetic resonance imaging

Supplementary Table 3. Baseline characteristics of patients included in the analyses and excluded because of no difference images between baseline and six months after stroke.

	Patients included in the analyses (n=503)	**Patients without difference images (n=233)**	***P* value***
Demographic variables at baseline			
Age, mean (SD), y	66.7 (11.1)	70.9 (10.8)	**<0.001**
Sex[†]			
Male, n (%)	342 (68.0)	149 (63.9)	0.32
Female, n (%)	161 (32.0)	84 (36.1)	
Education years, median (IQR), y	13 (12 to 17)	13 (11 to 15)	**0.03**
Cardiovascular risk factors at baseline			
Hypertension, n (%)	380 (75.5)	191 (82.0)	0.06
Diabetes mellitus, n (%)	94 (18.7)	56 (24.0)	0.11
Current smoking, n (%)	118 (23.5)	53 (22.7)	0.91
Atrial fibrillation, n (%)	87 (17.3)	61 (26.2)	**0.007**
Stroke history, n (%)	49 (9.7)	30 (12.9)	0.25
Large artery disease[‡], n (%)	157 (31.2)	100 (42.9)	**0.003**
BMI, mean (SD), kg/m^2	27.0 (4.2)	27.0 (4.4)	0.98
SBP, median (IQR), mmHg	139 (128 to 150)	141 (130 to 151)	0.13
DBP, median (IQR), mmHg	80 (72 to 87)	80 (73 to 86)	0.88
HbA_{1c}, median (IQR), %	5.7 (5.4 to 6.1)	5.8 (5.5 to 6.2)	**0.03**
LDL-C, median (IQR), mg/dL	124 (103 to 153)	129 (102 to 156)	0.64
HDL-C, median (IQR), mg/dL	48 (40 to 58)	48 (40 to 59)	0.99
Triglycerides, median (IQR), mg/dL	124 (94 to 172)	112 (84 to 166)	**0.03**
APOE genotype (n=594)			
0 ε4 allele, n (%)	318/410 (77.6)	145/184 (78.8)	0.88
1 ε4 allele, n (%)	85/410 (20.7)	37/184 (20.1)	
2 ε4 allele, n (%)	7/410 (1.7)	2/184 (1.1)	
Stroke classification, n (%)			
Ischemic stroke	490 (97.4)	225 (96.6)	0.69
TOAST subtype, n (%)			**0.009**
Large artery atherosclerosis	122 (24.9)	64 (28.4)	0.36
Cardio-embolic	99 (20.2)	68 (30.2)	**0.004**
Small artery occlusion	63 (12.9)	21 (9.3)	0.22

	Patients included in the analyses (n=503)	Patients without difference images (n=233)	*P* value*
Other etiology	24 (4.9)	6 (2.7)	**0.008**
Undefined etiology	182 (37.1)	66 (29.3)	0.05
Hemorrhagic stroke	13 (2.6)	8 (3.4)	0.69
Clinical assessment at baseline			
NIHSS score, median (IQR)	2 (1 to 5)	3 (1 to 5)	0.07
mRS[§] before stroke			
0	426 (84.7)	175 (75.1)	**0.006**
1	53 (10.5)	39 (16.7)	
2	11 (2.2)	13 (5.6)	
3	13 (2.6)	6 (2.6)	
BI score, median (IQR)	100 (85 to 100)	95 (65 to 100)	**<0.001**
IQCODE score, median (IQR)	48 (48 to 49)	48 (48 to 50)	0.35
Baseline cognitive impairment[¶], n (%)	236/490 (48.2)	129/219 (58.9)	**0.01**
MRI variables			
Primary stroke lesion volume, median (IQR), mm^3	2168 (452 to 12262)	2864 (720 to 12334)	0.16
Total intracranial volume, median (IQR), $\times 10^6 mm^3$	1.56 (1.44 to 1.65)	1.53 (1.42 to 1.64)	0.12
Presence of SVD marker[#], n (%)	293/502 (58.4)	114/164 (69.5)	**0.01**
Summary SVD score[**]			
0	209/502 (41.6)	50/164 (30.5)	**0.007**
1	155/502 (30.9)	46/164 (28.0)	
2	90/502 (17.9)	46/164 (28.0)	
3-4	48/502 (9.6)	22/164 (13.4)	
Lacune count			
0	445/503 (88.5)	141/168 (83.9)	0.14
1	41/503 (8.2)	15/168 (8.9)	
2	11/503 (2.2)	6/168 (3.6)	
≥3	6/503 (1.2)	6/168 (3.6)	
Fazekas DWM score			
0	71/503 (14.1)	12/168 (7.1)	**<0.001**
1	213/503 (42.3)	61/168 (36.3)	
2	200/503 (39.8)	78/168 (46.4)	
3	19/503 (3.8)	17/168 (10.1)	

	Patients included in the analyses (n=503)	Patients without difference images (n=233)	*P* value*
Fazekas PVWM score			
0	112/503 (22.3)	18/168 (10.7)	**<0.001**
1	269/503 (53.5)	88/168 (52.4)	
2	89/503 (17.7)	32/168 (19.0)	
3	33/503 (6.6)	30/168 (17.9)	
CMB count			
0	454/502 (90.4)	147/164 (89.6)	0.9
1	22/502 (4.4)	9/164 (5.5)	
2	8/502 (1.6)	3/164 (1.8)	
≥3	18/502 (3.6)	5/164 (3.0)	
PVS grade††			
1	335/503 (66.6)	95/167 (56.9)	**<0.001**
2	110/503 (21.9)	34/167 (20.4)	
3	5/503 (11.1)	32/167 (19.2)	
4	2/503 (0.4)	6/167 (3.6)	

Note: SI conversion factors: To convert percentage of total HbA_{1c} to proportion of total HbA_{1c}, multiply by 0.01; LDL-C and HDL-C to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113. **Bold** indicates statistically significant at *P* value<.05.

Abbreviations: FLAIR, fluid-attenuated inversion recovery; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA_{1c}, hemoglobin A_{1c}; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; TOAST, Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin scale; BI, Barthel index; IQCODE, informant questionnaire on cognitive decline in the elderly; MRI, magnetic resonance imaging; SVD, small vessel disease; PVWM, periventricular white matter; DWM, deep white matter; PVS, perivascular space; CMB, cerebral microbleed; SD, standard deviation; IQR, interquartile range.

***** Categorical variables were analyzed using the χ^2 or Fisher exact test, a two-tailed t-test was employed for continuous variables with a normal distribution, and the Mann-Whitney U test was used for other continuous variables.

† Self-reported.

‡ Large artery disease is defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of >50% on ultrasound or computed tomography angiography (CTA), if ultrasound not available.

§ A global functional scale ranges from 0 (no symptoms) to 5 (serious functional impairment).

[¶] Montreal cognitive assessment (MoCA) <26 or mini-mental state examination (MMSE) <24 when MoCA was not available (5.3% of total).

[#] Summary SVD score is equal to or greater than 1.

[**] Summary SVD score ranges from 0 to 4, with one point awarded for i) the presence of lacunes, ii) a Fazekas score of 3 for periventricular WMHs or a Fazekas score of 2 or 3 for deep WMHs, iii) the presence of CMBs, and iv) a PVS grade of 2 or higher, respectively.

[††] PVSs were counted bilaterally in the basal ganglia, and the side with the higher number was used for scoring: 0 = no PVSs, 1 = < 10 PVSs, 2 = 11 to 20 PVSs, 3 = 21 to 40 PVSs, and 4 = > 40 PVSs.[1,7,8]

Supplementary Table 4. Availability of three MRI sequences at baseline and six months after the index stroke in current study.

	Baseline			**6 months**			**Difference images between baseline and 6 months**			**Number of patients**
	DWI	**FLAIR**	**T1**	**DWI**	**FLAIR**	**T1**	**DWI**	**FLAIR**	**T1**	
DEDEMAS	√	√	√	√	√	√	√	√	√	81
	√	√	√	X	√	√	X	√	√	2
DEMDAS	√	√	√	√	√	√	√	√	√	411
	X	√	√	√	√	√	X	√	√	5
	√	√	√	X	√	√	X	√	√	3
	√	√	√	X	√	X	X	√	X	1

Abbreviations: MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery.

Supplementary Table 5. Demographic and imaging characteristics of participants with corresponding clinical symptoms to their incident ischemic lesions.

No.	Age	Sex	NIHSS at baseline	Number of IILs	Location of each IIL	Vascular area of IIL	Type of IILs*	Main symptoms corresponding to IILs
1	72	male	2	5	occipital lobe (right)	posterior cerebral artery (right)	CI	Speech problem, hemiparesis (left), double vision
					occipital lobe (right)	posterior cerebral artery (right)	SSI	
					brain stem	right superior cerebellar artery	SSI	
					brain stem	right superior cerebellar artery	SSI	
					cerebellum	artery basilar	SSI	
2	80	male	2	1	frontal lobe (left)	anterior cerebral artery (left)	SSI	A general decrease in muscle strength on both sides
3	45	male	3	2	frontal lobe (right)	middle cerebral artery (right)	CI	Speech problem, dizziness
					periventricular white matter (left)	anterior cerebral artery (left)	SSI	
4	59	male	14	1	temporal lobe (right)	middle cerebral artery (right)	CI	Tingling paresthesia (left)
5	79	male	5	8	periventricular white matter (right)	middle cerebral artery (right)	SSI	Hemiparesis (left)
					periventricular white matter (right)	middle cerebral artery (right)	SSI	
					temporal lobe (right)	middle cerebral artery (right)	SSI	
					deep white matter (left)	anterior cerebral artery (left)	SSI	
					parietal lobe (right)	anterior cerebral artery (right)	SSI	
					globus pallidus (left)	middle cerebral artery (left)	SSI	
					deep white matter (right)	middle cerebral artery (right)	SSI	
					deep white matter (right)	middle cerebral artery (right)	SSI	
6	74	male	12	2	brain stem	artery basilar	SSI	Speech problem, dizziness
					thalamus (right)	posterior cerebral artery (right)	SSI	
7	57	male	2	7	parietal lobe (left)	anterior cerebral artery (left)	SSI	Speech problem, impairment of fine motor skills (right)
					parietal lobe (left)	anterior cerebral artery (left)	SSI	

					frontal lobe (left)	anterior cerebral artery (left)	SSI	
					corpus callosum (right)	anterior cerebral artery (right)	SSI	
					corpus callosum (left)	posterior cerebral artery (left)	SSI	
					occipital lobe (left)	posterior cerebral artery (left)	CI	
					occipital lobe (left)	posterior cerebral artery (left)	CI	

Abbreviations: IILs, incident ischemic lesions; NIHSS, National Institutes of Health Stroke Scale; CI, cortical infarct; SSI, small subcortical infarct.

* SSI refers to a lesion up to 20mm in diameter on the axial plane in the territory of penetrating arteries, following the criterion adopted by STRIVE.[10]
CI refers to a lesion located in the cortex of any size.

Supplementary Table 6. Hazard ratios associated with the presence and number of IILs from subdistribution and cause-specific hazard models for recurrent stroke between 6 and 36 months after the index stroke.

Independent variable	Group	Model	Cause-Specific HR (95% CI)		Subdistribution HR (95% CI)	
			Recurrent stroke	Non-stroke death	Recurrent stroke	Non-stroke death
The presence of IILs	All included participants (N=503)	Model 1a	**3.81 (1.35-10.69)**	2.11 (0.69-6.45)	**3.77 (1.31-10.83)**	1.88 (0.73-4.82)
		Model 2a	**3.43 (1.24-9.49)**	1.57 (0.45-5.50)	**3.37 (1.24-9.12)**	1.44 (0.41-5.09)
	Participants without recurrent stroke between baseline and 6 months (N=486)	Model 1b	**4.41 (1.54-12.65)**	2.07 (0.65-6.60)	**4.39 (1.58-12.17)**	1.80 (0.64-5.12)
		Model 2b	**4.01 (1.40-11.48)**	1.58 (0.44-5.69)	**3.96 (1.39-11.30)**	1.42 (0.35-5.75)
The number of IILs	All included participants (N=503)	Model 1a	1.10 (0.76-1.60)	1.28 (0.84-1.95)	1.10 (0.81-1.48)	1.27 (0.89-1.80)
		Model 2a	1.14 (0.79-1.65)	1.29 (0.81-2.07)	1.14 (0.87-1.48)	1.29 (0.87-1.90)
	Participants without recurrent stroke between baseline and 6 months (N=486)	Model 1b	1.35 (0.93-1.96)	1.49 (0.90-2.46)	**1.35 (1.06-1.71)**	1.46 (0.93-2.28)
		Model 2b	1.27 (0.86-1.87)	1.33 (0.72-2.43)	1.27 (0.96-1.68)	1.31 (0.69-2.46)

Note: **Model 1a** adjusted for age, sex, NIHSS score, and *the presence of recurrent clinical stroke between baseline and 6 months*. **Model 2a** additionally adjusted for hypertension history, diabetes history, current smoking, prior stroke history, arterial fibrillation history, BMI, LDL value, large artery disease (defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of ≥50% on ultrasound or CTA, if ultrasound not available), and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). **Model 1b** adjusted for age, sex, and NIHSS score in the acute phase. **Model 2b** additionally adjusted for hypertension history, diabetes history, current smoking, prior stroke history, arterial fibrillation history, BMI, LDL value, large artery disease (defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of ≥50% on ultrasound or CTA, if ultrasound not available), and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). **Bold** indicates statistically significant at *P* value<.05.

Abbreviations: IILs, incident ischemic lesions; HR, hazard ratios; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; BMI, body mass index; LDL, low density lipoprotein; CTA, computed tomography angiography.

Supplementary Table 7. Mediation analysis for presence of incident ischemic lesions at six months after stroke as a mediator in the relationship between cerebral small vessel disease burden at baseline and cognitive performance at 36 months after stroke.

Path a: the effect of the exposure (SVD burden at baseline) on the mediator (presence of IILs at six months); Path b: the effect of the mediator (presence of IILs at six months) on the outcome (cognitive performance at 36 months) controlling for the exposure (presence of SVD marker at baseline); Path c: the total effect of the exposure (SVD burden at baseline) on the outcome (cognitive performance at 36 months); Path c': the direct effect of the exposure (SVD burden at baseline) on the outcome (cognitive performance at 36 months) controlling for the mediator (presence of IILs at six months). Logistic regression analysis was applied to regress IIL presence on SVD variables; linear or logistic regression analyses were applied to regress the cognitive score or cognitive impairment at 36 months, respectively on SVD variables and IIL presence. Confidence intervals were estimated by bootstrapping 10,000 times.

Exposure at baseline	**Outcome at 36 months**	**a**		**b**		**Average total effect (c)**		**Average direct effect (c')**		**Average indirect effect**		**Average proportion mediated**	
		OR (95% CI)	***P* value**	**β (95% CI)**	***P* value**	**β (95% CI)**	***P* value**	**β (95% CI)**	***P* value**	**β (95% CI)**	***P* value**	**Percent, %**	***P* value**
Presence of SVD marker*	Global cognitive score‡	3.64 (1.78 to 8.24)	<.001	-0.20 (-0.37 to -0.03)	.02	-0.17 (-0.28 to -0.05)	.004	-0.15 (-0.26 to -0.03)	.01	-0.02 (-0.06 to -0.002)	.02	14.3	.03
Summary SVD score†		1.81 (1.36 to 2.42)	<.001	-0.21 (-0.38 to -0.03)	.02	-0.06 (-0.12 to -0.01)	.03	-0.05 (-0.12 to 0.004)	.07	-0.01 (-0.03 to 0.0002)	.06	12.8	.09
Presence of SVD marker*	Global cognitive score§	3.50 (1.61 to 8.36)	.003	-0.21 (-0.38 to -0.04)	.02	-0.20 (-0.33 to -0.07)	.002	-0.17 (-0.31 to -0.04)	.009	-0.02 (-0.06 to -0.003)	.02	11.5	.02
Summary SVD score†		1.74 (1.28 to 2.37)	<.001	-0.21 (-0.39 to -0.04)	.02	-0.07 (-0.14 to -0.01)	.02	-0.06 (-0.13 to -0.004)	.04	-0.01 (-0.03 to 0.001)	.07	11.1	.08

		OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	Percent, %	*P* value
Presence of SVD marker*	Cognitive impairment‡	3.64 (1.84 to 7.90)	<.001	4.50 (2.35 to 8.59)	<.001	1.11 (1.04 to 1.21)	.005	1.08 (1.003 to 1.17)	.04	1.03 (1.01 to 1.07)	.002	26.7	.007
Summary SVD score†		1.76 (1.34 to 2.33)	<.001	4.65 (2.41 to 8.91)	<.001	1.03 (1.004 to 1.07)	.03	1.02 (0.99 to 1.05)	.15	1.01 (1.001 to 1.03)	.04	32.3	.06
Presence of SVD marker*	Cognitive impairment§	3.14 (1.50 to 7.16)	.004	4.73 (2.44 to 9.15)	<.001	1.12 (1.03 to 1.22)	.009	1.09 (0.998 to 1.18)	.06	1.03 (1.01 to 1.06)	.009	25.2	.02
Summary SVD score†		1.63 (1.22 to 2.19)	.001	4.83 (2.49 to 9.38)	<.001	1.03 (0.999 to 1.07)	.05	1.02 (0.99 to 1.06)	.18	1.01 (0.998 to 1.03)	.08	22.4	.11

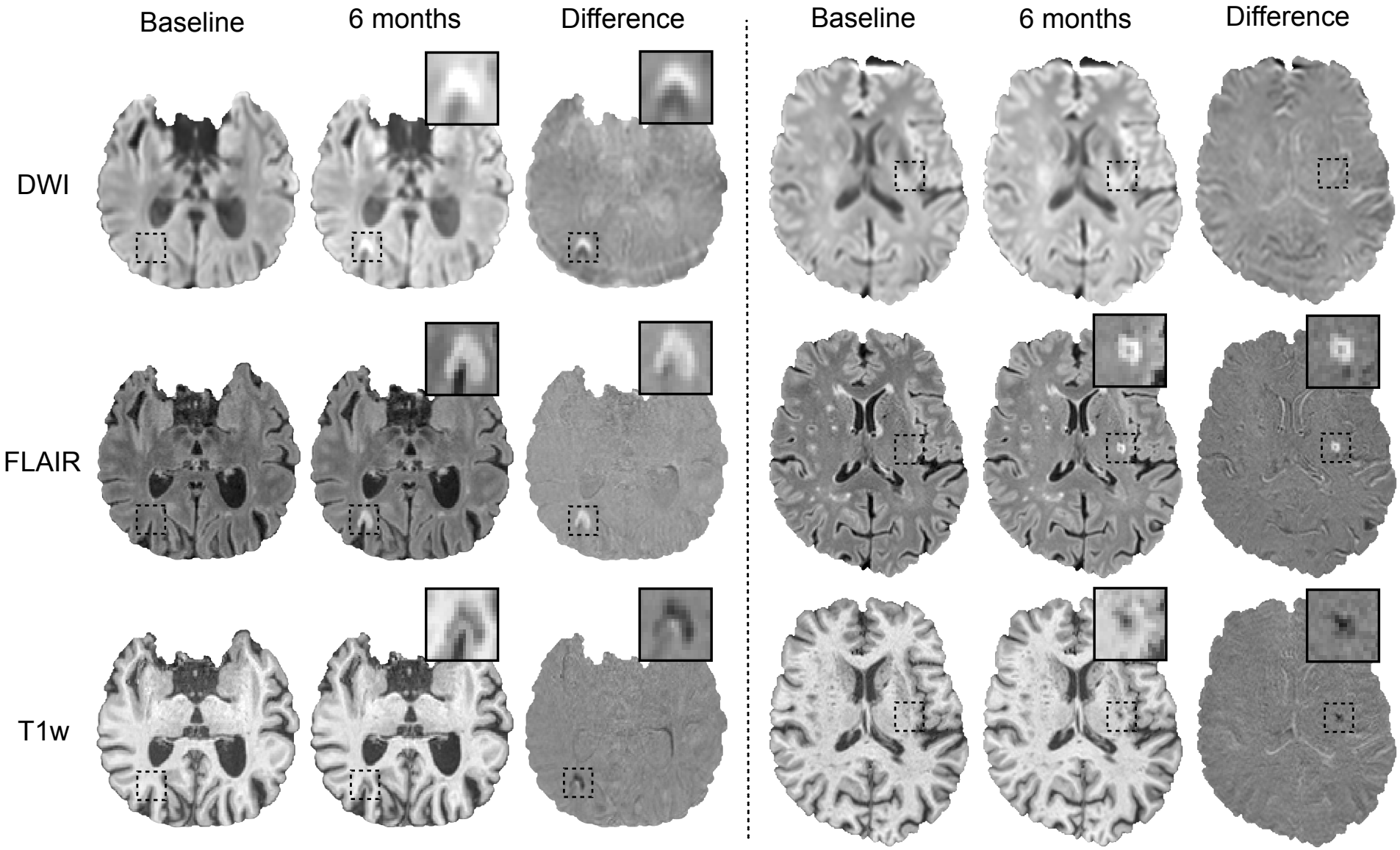
Abbreviations: OR, odds ratio; SVD, small vessel disease; IILs, incident ischemic lesions; CI, confidence interval.

Summary SVD total score is equal to or greater than 1.

Summary SVD score ranges from 0 to 4, with one point awarded for i) the presence of lacunes, ii) a Fazekas score of 3 for periventricular white matter hyperintensities (WMHs) or a Fazekas score of 2 or 3 for deep WMHs, iii) the presence of cerebral microbleeds (CMBs), and iv) a perivascular space (PVS) grade of 2 or higher, respectively.

Adjusted for no covariates.

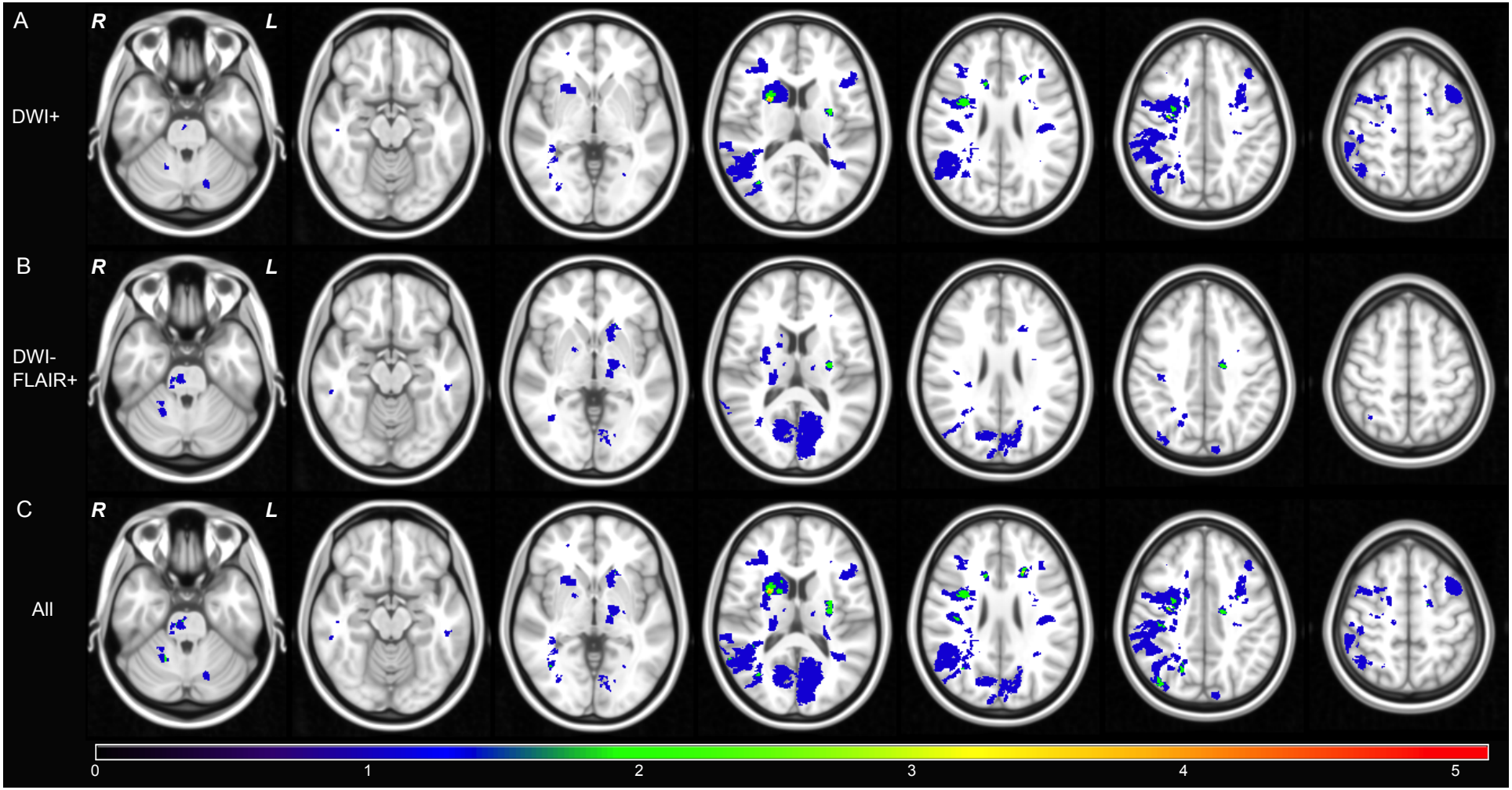
Adjusted for age, sex, and National Institutes of Health Stroke Scale (NIHSS) score at baseline.



Supplementary Figure 1. Examples of incident ischemic lesions on brain MRI scans at 6 months including T1-weighted images.

Shown are two exemplary cases as in Figure 1A (main manuscript). **Left:** a 77-year-old patient with an incident DWI+/FLAIR+ cortical infarct. **Right:** a 59-year-old patient with an incident DWI-/FLAIR+ small subcortical infarct. For methods see the main manuscript.

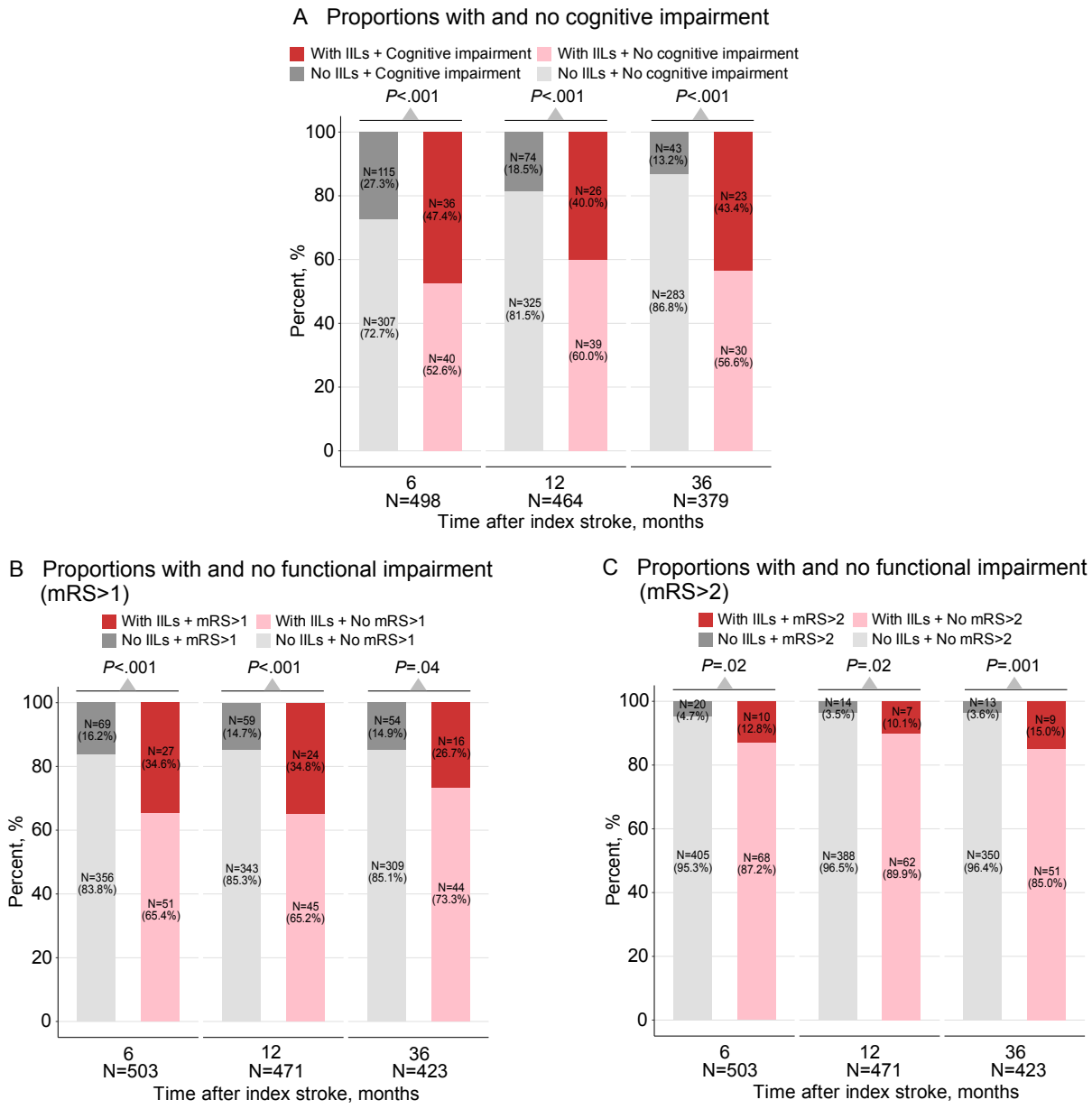
MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; T1w, T1-weighted.



Supplementary Figure 2. Lesion prevalence map showing the frequency of incident ischemic lesions across brain locations.

Shown are lesion prevalence maps for IILs stratified by signal characteristics **(A)** DWI+; **(B)** DWI-FLAIR+, and **(C)** all (either DWI+ or DWI-FLAIR+). Colors represent the number of participants with IILs in the respective brain region. The images were generated with MRIcron (http://www.nitrc.org/projects/mricron).

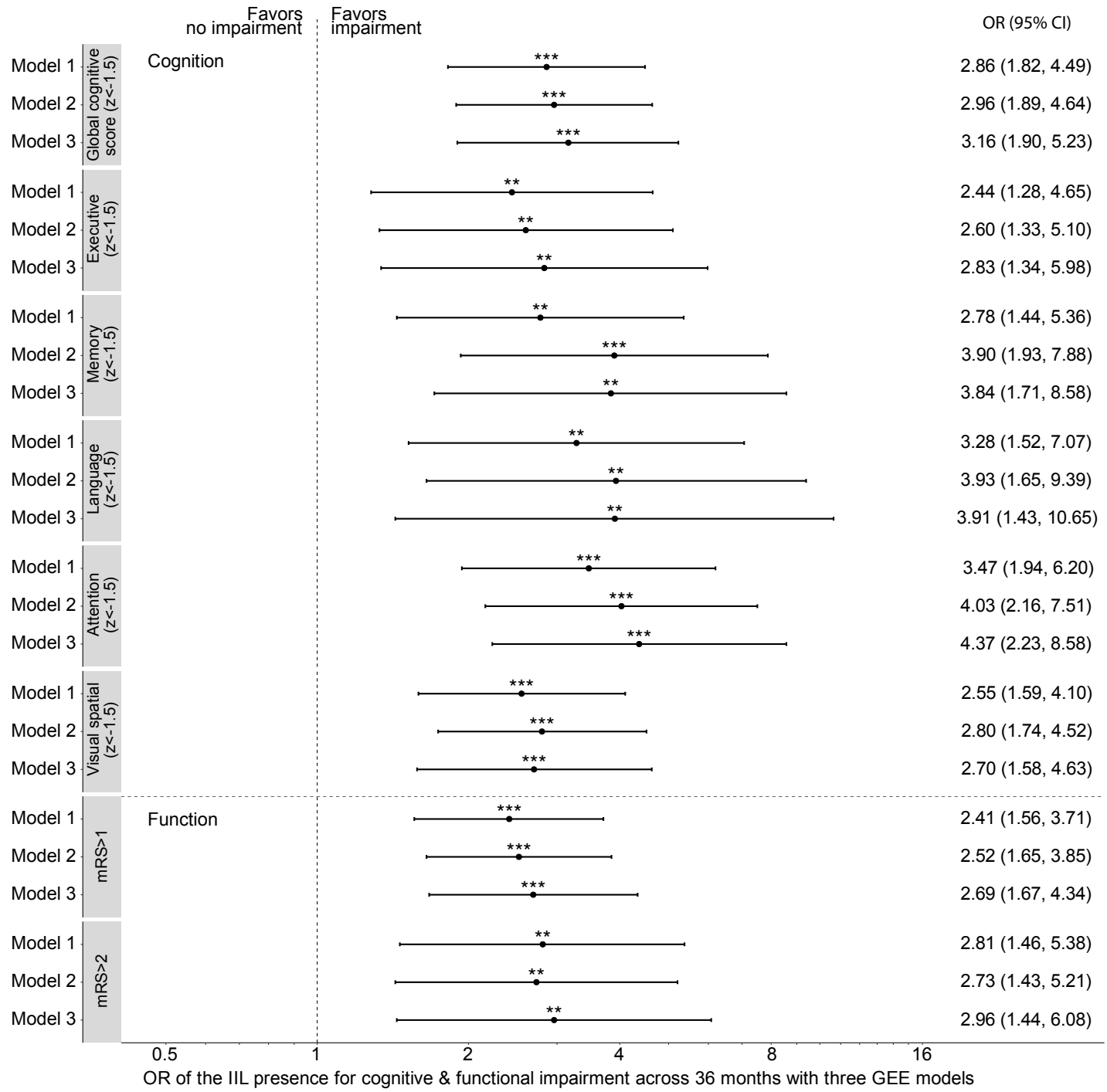
Ls, incident ischemic lesions; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; R, right; L, left



Supplementary Figure 3. Proportions of participants with and without cognitive & functional impairment across 36 months after the index stroke.

(A) Proportions of participants with and without cognitive impairment at 6, 12, and 36 months stratified by IILs status. **(B)** Proportions of participants with and without functional impairment (mRS>1) at 6, 12, and 36 months stratified by IILs status. **(C)** Proportions of participants with and without functional impairment (mRS>2) at 6, 12, and 36 months stratified by IILs status.

IILs, incident ischemic lesions; mRS, modified Rankin scale.



Supplementary Figure 4. Associations between the presence of incident ischemic lesions and cognitive and functional impairment across 36 months after the index stroke using logistic generalized estimating equation (GEE).

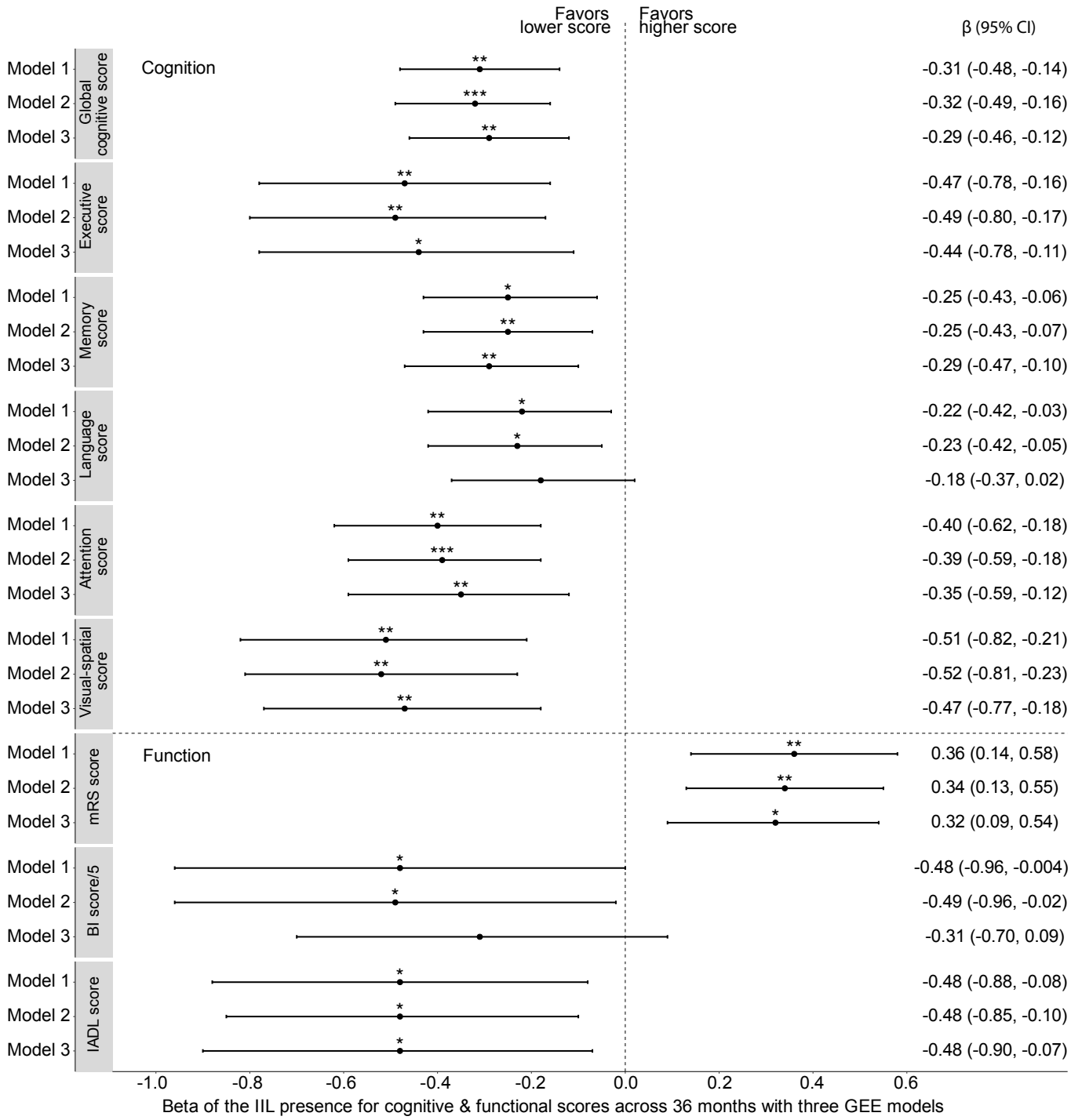
Model 1 adjusted for age, sex, education, NIHSS score, and cognitive impairment (MoCA<26 or MMSE<24 if MoCA not available) in the acute phase. **Model 2** additionally adjusted for hypertension history, diabetes history, current smoking, prior stroke history, arterial fibrillation history, BMI, LDL value, large artery disease (defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of ≥50% on ultrasound or CTA, if ultrasound not

available), and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). **Model 3** additionally adjusted for *APOE* genotype on top of model 2. Values are expressed as OR (95% confidence interval).

P values are corrected for multiple comparisons with the false discovery rate (FDR) method.

IILs, incident ischemic lesions; OR, odds ratios; CI, confidence interval; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; BMI, body mass index; LDL, low density lipoprotein; CTA, computed tomography angiography; *APOE*, apolipoprotein-E.

* *P* value<.05, ** *P* value<.01, *** *P* value<.001



Supplementary Figure 5. Associations between the presence of incident ischemic lesions and cognitive and functional scores across 36 months after the index stroke using linear generalized estimating equation (GEE).

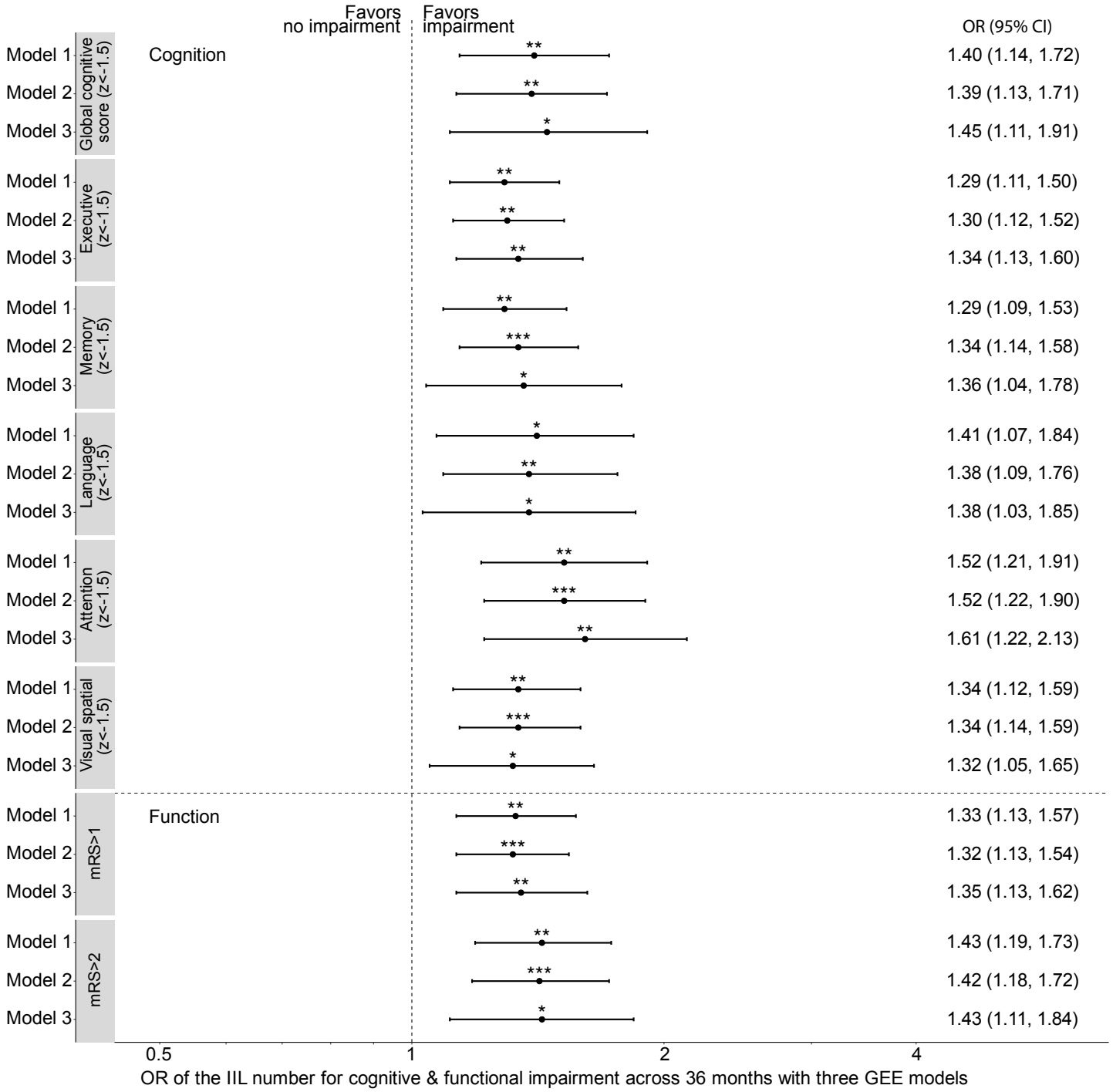
Model 1 adjusted for age, sex, education, NIHSS score, and cognitive impairment (MoCA<26 or MMSE<24 if MoCA not available) in the acute phase. **Model 2** additionally adjusted for hypertension history, diabetes history, current smoking, prior stroke history, arterial fibrillation history, BMI, LDL value, large artery disease (defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of ≥50% on ultrasound or CTA, if ultrasound not

available), and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). **Model 3** additionally adjusted for *APOE* genotype on top of model 2. Values are expressed as beta value (95% confidence interval).

P values are corrected for multiple comparisons with the false discovery rate (FDR) method.

IILs, incident ischemic lesions; CI, confidence interval; mRS, modified Rankin scale; BI, Barthel index; IADL, instrumental activities of daily living; NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; BMI, body mass index; LDL, low density lipoprotein; CTA, computed tomography angiography; *APOE*, apolipoprotein-E.

* *P* value<.05, ** *P* value<.01, *** *P* value<.001



Supplementary Figure 6. Associations between the number of incident ischemic lesions with cognitive and functional impairment across 36 months after the index stroke using logistic generalized estimating equation (GEE).

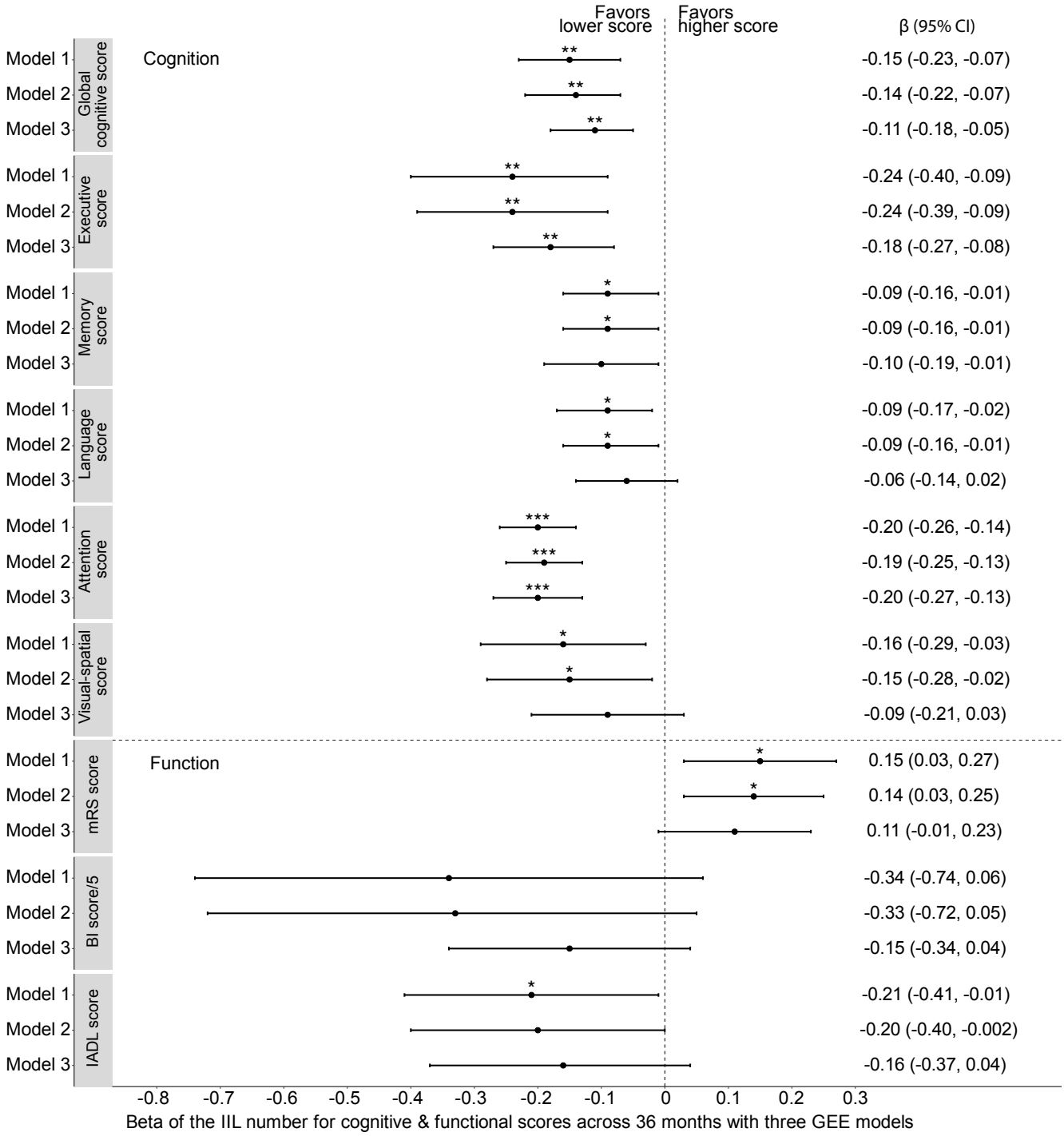
Model 1 adjusted for age, sex, education, NIHSS score, and cognitive impairment (MoCA<26 or MMSE<24 if MoCA not available) in the acute phase. **Model 2** additionally adjusted for hypertension history, diabetes history, current smoking, prior stroke history, arterial fibrillation history, BMI, LDL value, large artery disease (defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of ≥50% on ultrasound or CTA, if ultrasound not

available), and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). **Model 3** additionally adjusted for *APOE* genotype on top of model 2. Values are expressed as OR (95% confidence interval).

P values are corrected for multiple comparisons with the false discovery rate (FDR) method.

IILs, incident ischemic lesions; OR, odds ratios; CI, confidence interval; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; BMI, body mass index; LDL, low density lipoprotein; CTA, computed tomography angiography; *APOE*, apolipoprotein-E.

* *P* value<.05, ** *P* value<.01, *** *P* value<.001



Supplementary Figure 7. Associations between the number of incident ischemic lesions and cognitive and functional scores across 36 months after stroke using linear generalized estimating equation (GEE).

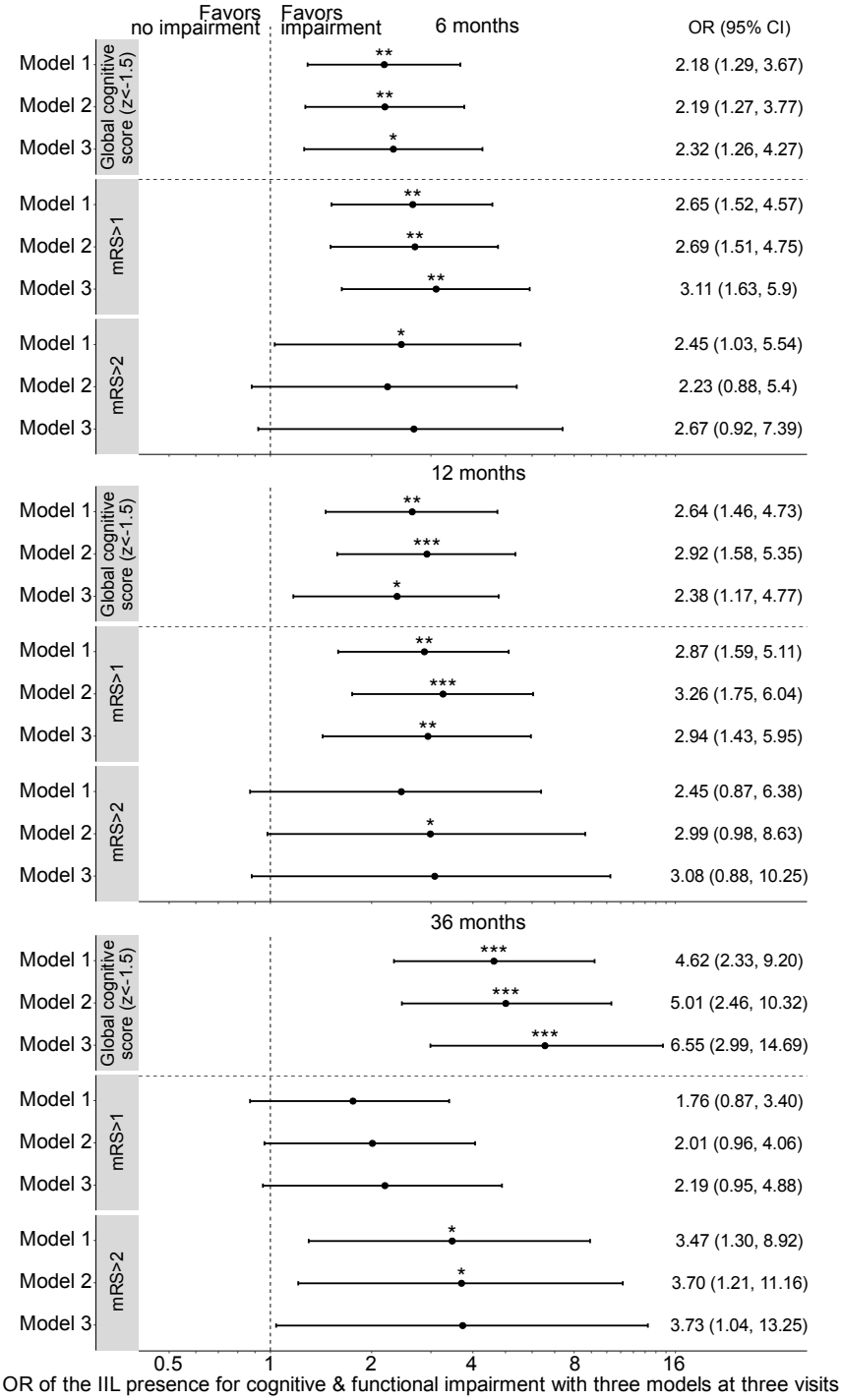
Model 1 adjusted for age, sex, education, NIHSS score, and cognitive impairment (MoCA<26 or MMSE<24 if MoCA not available) in the acute phase. **Model 2** additionally adjusted for hypertension history, diabetes history, current smoking, prior stroke history, arterial fibrillation history, BMI, LDL value, large artery disease (defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of ≥50% on ultrasound or CTA, if ultrasound not

available), and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). **Model 3** additionally adjusted for *APOE* genotype on top of model 2. Values are expressed as beta value (95% confidence interval).

P values are corrected for multiple comparisons with the false discovery rate (FDR) method.

IILs, incident ischemic lesions; CI indicates confidence interval; mRS, modified Rankin scale; BI, Barthel index; IADL, instrumental activities of daily living; NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; BMI, body mass index; LDL, low density lipoprotein; CTA, computed tomography angiography; *APOE*, apolipoprotein-E.

* *P* value<.05, ** *P* value<.01, *** *P* value<.001



Supplementary Figure 8. Associations between the presence of incident ischemic lesions and cognitive and functional impairment after the index stroke using three logistic regression models at 6-, 12-, and 36-month, separately.

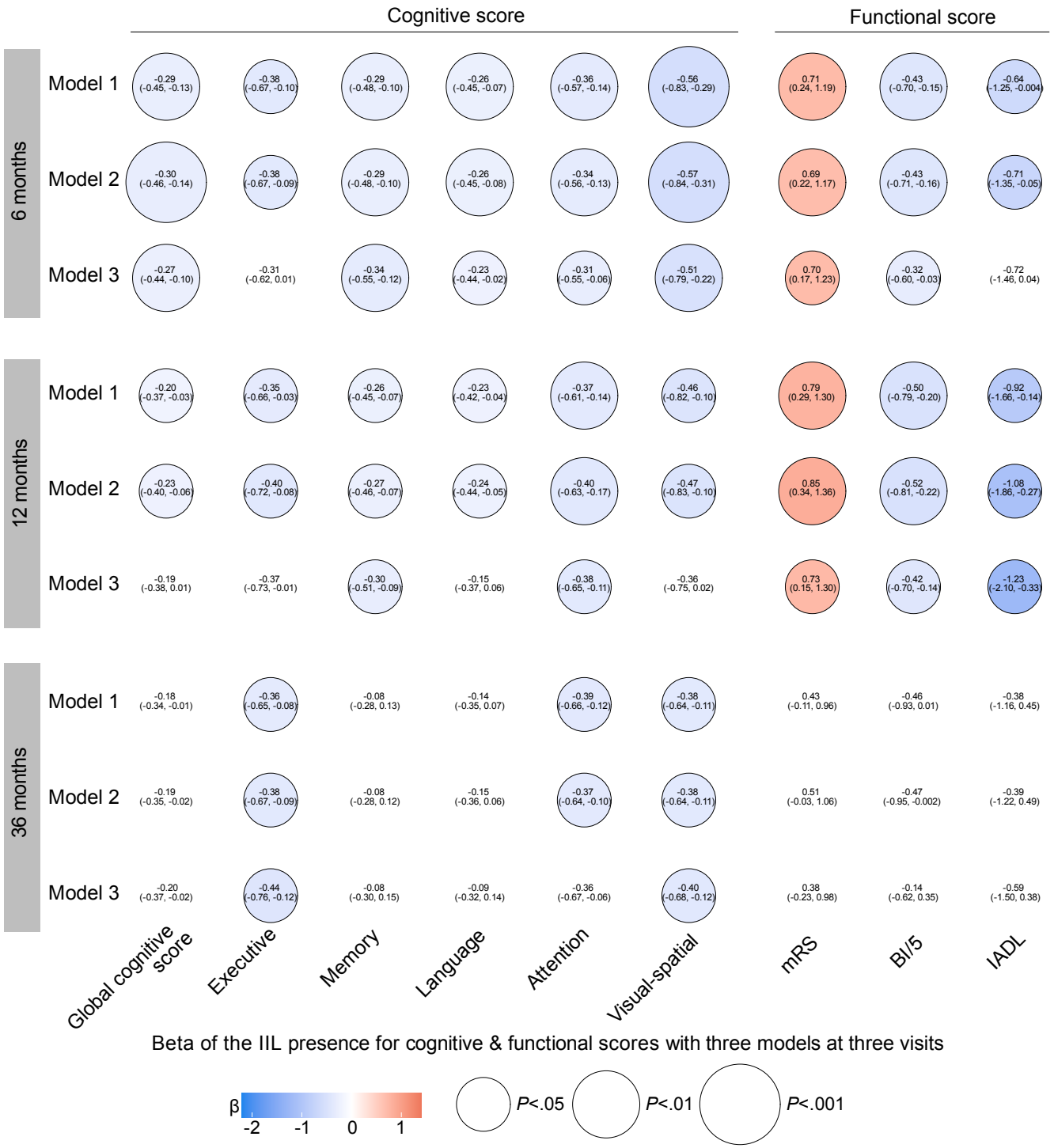
Model 1 adjusted for age, sex, education, NIHSS score, and cognitive impairment (MoCA<26 or MMSE<24 if MoCA not available) in the acute phase. **Model 2** additionally adjusted for hypertension history, diabetes history, current smoking, prior stroke history, arterial fibrillation history, BMI, LDL value, large artery disease (defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of ≥50% on ultrasound or CTA, if ultrasound not

available), and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). **Model 3** additionally adjusted for *APOE* genotype on top of model 2. Values are expressed as OR (95% confidence interval).

P values are corrected for multiple comparisons with the false discovery rate (FDR) method.

IILs, incident ischemic lesions; OR, odds ratios; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; BMI, body mass index; LDL, low density lipoprotein; CTA, computed tomography angiography; *APOE*, apolipoprotein-E.

* *P* value<.05, ** *P* value<.01, *** *P* value<.001



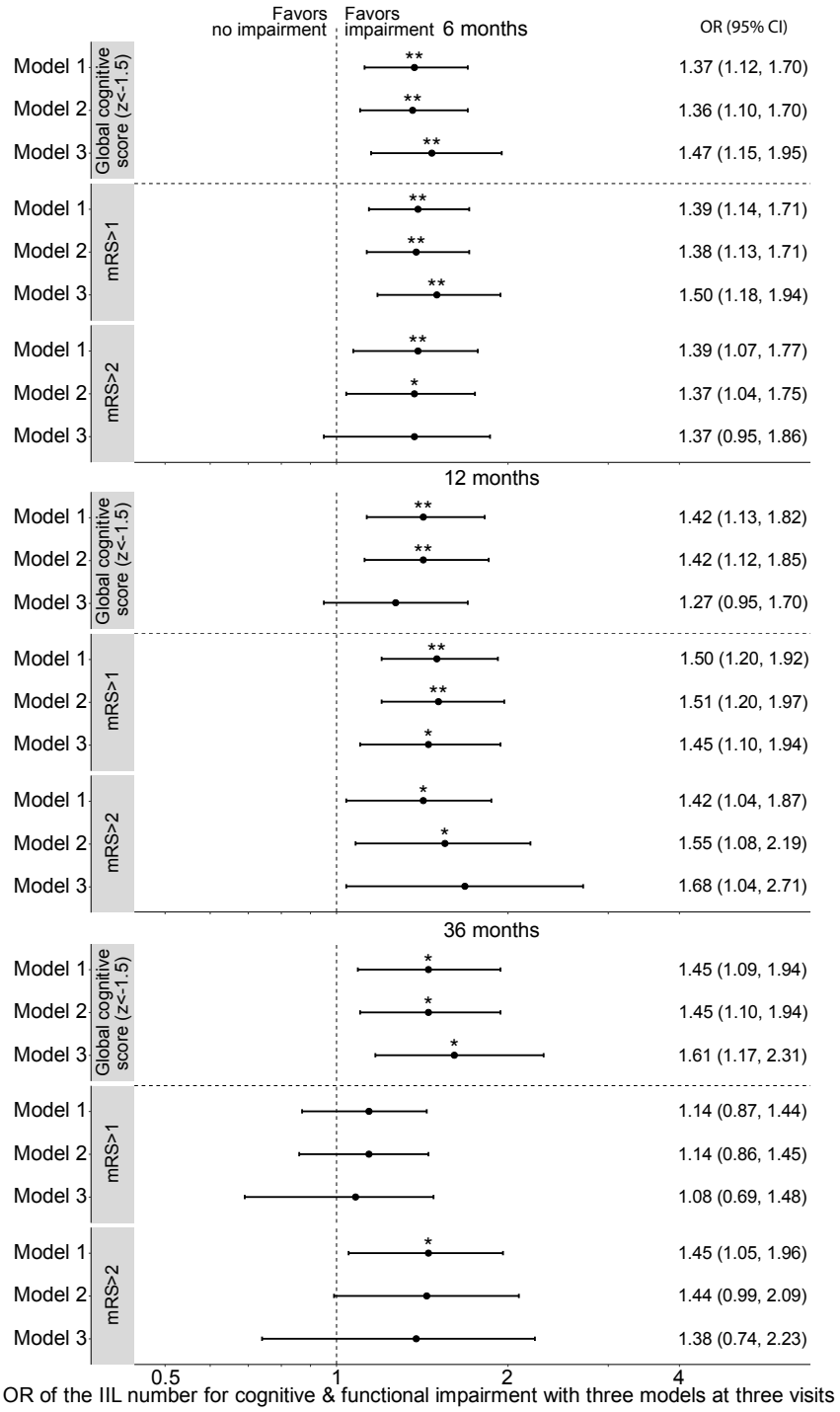
Supplementary Figure 9. Associations between the presence of incident ischemic lesions and cognitive and functional scores after the index stroke at 6-, 12-, and 36-month, separately.

Linear regression models were used in global cognitive score, five individual cognitive scores, and BI/5 score at each time point; Ordinal logistic regression models were applied in mRS and IADL scores at each time point. **Model 1** adjusted for age, sex, education, NIHSS score, and cognitive impairment (MoCA<26 or MMSE<24 if MoCA not available) in the acute

phase. **Model 2** additionally adjusted for hypertension history, diabetes history, current smoking, prior stroke history, arterial fibrillation history, BMI, LDL value, large artery disease (defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of ≥50% on ultrasound or CTA, if ultrasound not available), and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). **Model 3** additionally adjusted for *APOE* genotype on top of model 2. Values are expressed as beta value (95% confidence interval).

P values are corrected for multiple comparisons with the false discovery rate (FDR) method.

IILs, incident ischemic lesions; mRS, modified Rankin scale; BI, Barthel index; IADL, instrumental activities of daily living; NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; BMI, body mass index; LDL, low density lipoprotein; CTA, computed tomography angiography; *APOE*, apolipoprotein-E.



Supplementary Figure 10. Associations between the number of incident ischemic lesions and cognitive and functional impairment after the index stroke using three logistic regression models at 6-, 12-, and 36-month, separately.

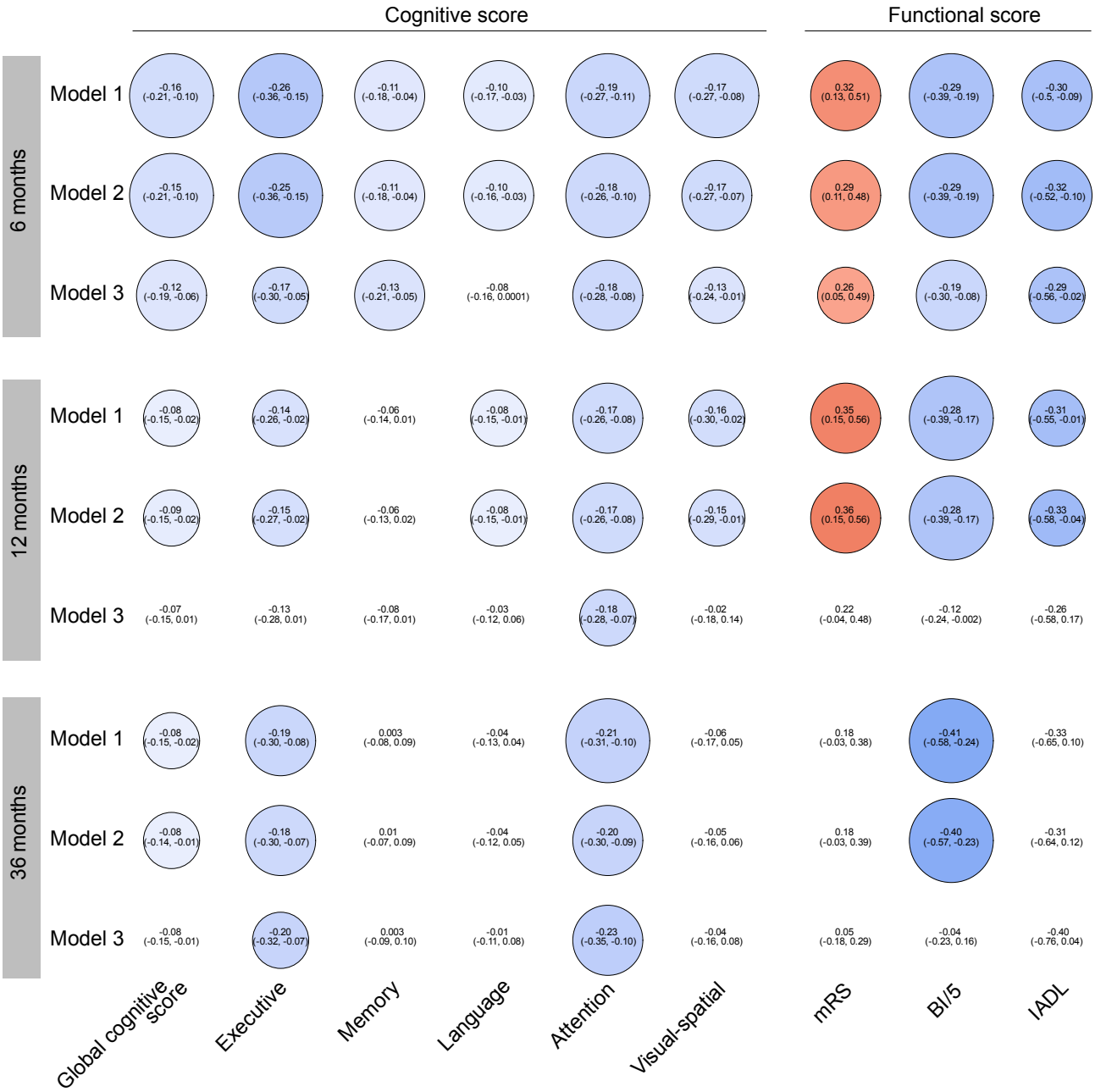
Model 1 adjusted for age, sex, education, NIHSS score, and cognitive impairment (MoCA<26 or MMSE<24 if MoCA not available) in the acute phase. **Model 2** additionally adjusted for hypertension history, diabetes history, current smoking, prior stroke history, arterial fibrillation history, BMI, LDL value, large artery disease (defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of ≥50% on ultrasound or CTA, if ultrasound not

available), and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). **Model 3** additionally adjusted for *APOE* genotype on top of model 2. Values are expressed as OR (95% confidence interval).

P values are corrected for multiple comparisons with the false discovery rate (FDR) method.

IILs, incident ischemic lesions; OR, odds ratios; mRS, modified Rankin scale; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; BMI, body mass index; LDL, low density lipoprotein; CTA, computed tomography angiography; *APOE*, apolipoprotein-E.

* *P* value<.05, ** *P* value<.01



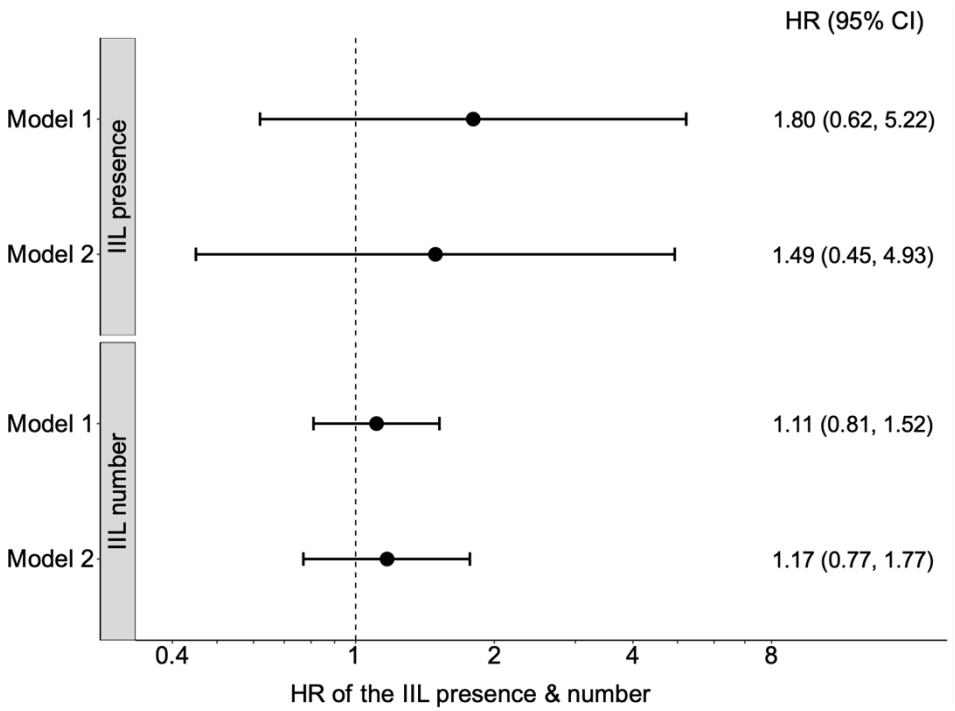
Supplementary Figure 11. Associations between the number of incident ischemic lesions and cognitive and functional scores after the index stroke at 6-, 12-, and 36-month, separately.

Linear regression models were used in global cognitive score, five individual cognitive scores, and BI/5 score at each time point; Ordinal logistic regression models were applied in mRS and IADL scores at each

time point. **Model 1** adjusted for age, sex, education, NIHSS score, and cognitive impairment (MoCA<26 or MMSE<24 if MoCA not available) in the acute phase. **Model 2** additionally adjusted for hypertension history, diabetes history, current smoking, prior stroke history, arterial fibrillation history, BMI, LDL value, large artery disease (defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of ≥50% on ultrasound or CTA, if ultrasound not available), and normalized stroke lesion volume (stroke lesion volume/total intracranial volume). **Model 3** additionally adjusted for *APOE* genotype on top of model 2. Values are expressed as beta value (95% confidence interval).

P values are corrected for multiple comparisons with the false discovery rate (FDR) method.

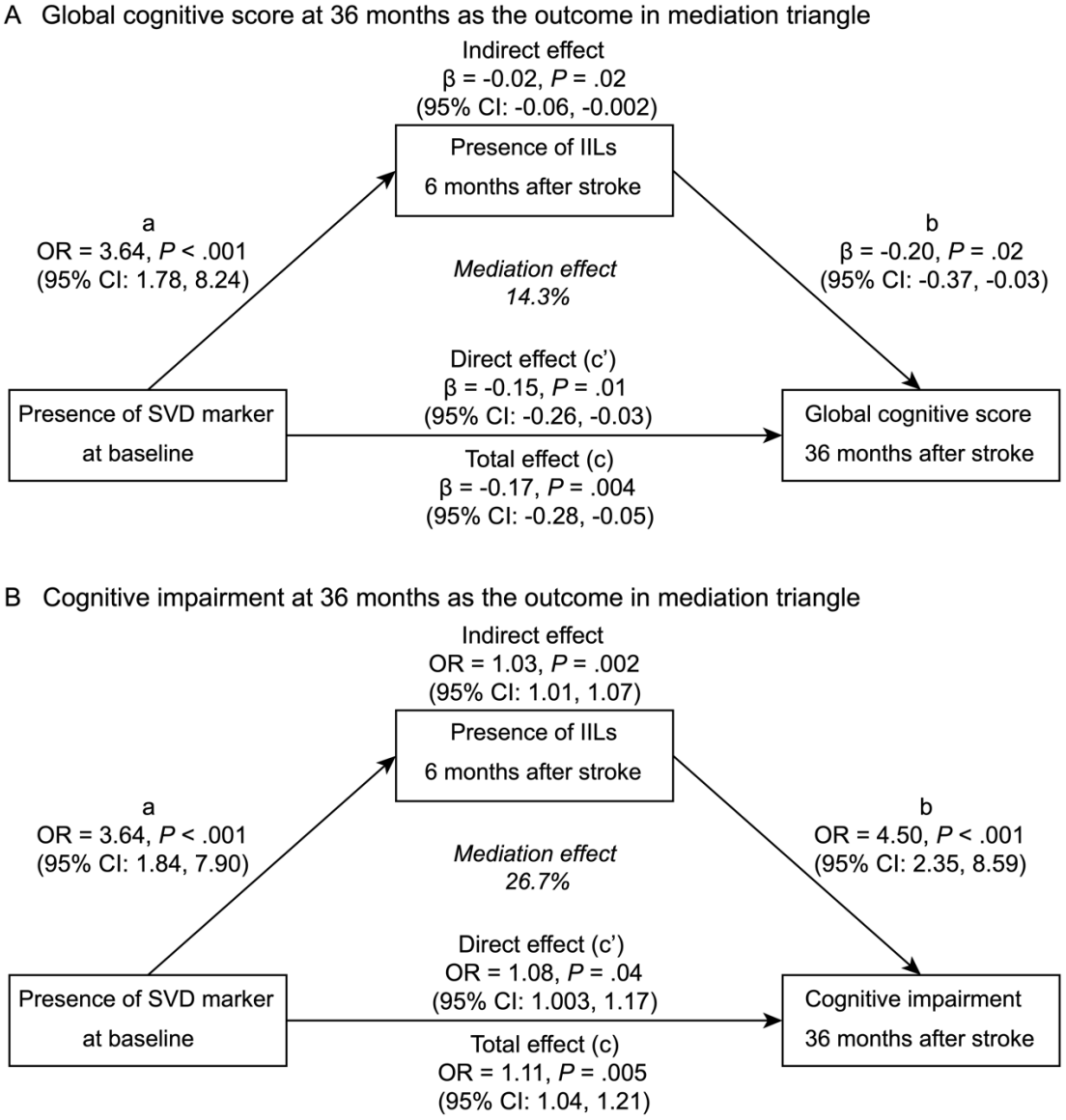
IILs, incident ischemic lesions; mRS, modified Rankin scale; BI, Barthel index; IADL, instrumental activities of daily living; NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; BMI, body mass index; LDL, low density lipoprotein; CTA, computed tomography angiography; *APOE*, apolipoprotein-E.



Supplementary Figure 12. Hazard ratios associated with the presence and number of incident ischemic lesions for death between 6 and 36 months after the index stroke using COX proportional hazards survival regression.

Model 1 adjusted for age, sex, and NIHSS score. **Model 2** adjusted for age, sex, NIHSS score, hypertension history, diabetes history, current smoking, prior stroke history, arterial fibrillation history, BMI, LDL value, large artery disease (defined as large artery atherosclerosis stroke or stenosis of any intra- or extracranial brain-supplying artery of ≥50% on ultrasound or CTA, if ultrasound not available), and normalized stroke lesion volume (stroke lesion volume/total intracranial volume).

IILs, incident ischemic lesions; HR, hazard ratios; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; BMI, body mass index; LDL, low density lipoprotein.



Supplementary Figure 13. The presence of small vessel disease marker at baseline in relation to the presence of incident ischemic lesions at six months and cognitive performance at 36 months after the index stroke.

(A) Mediation analysis for IILs at 6 months as a mediator in the relationship between the presence of SVD marker (summary SVD score≥1) at baseline and global cognitive score at 36 months. **(B)** Mediation analysis for IILs at 6 months as a mediator in the relationship between the presence of SVD marker (summary SVD score≥1) at baseline and cognitive impairment (yes/no) at 36 months. Path a: the effect of the exposure (presence of SVD marker at baseline) on the mediator (presence of IILs at six months); Path b: the effect of the mediator (presence of IILs at six months) on the outcome (cognitive performance at 36 months) controlling for the exposure (presence of SVD marker at baseline); Path c: the total effect of the exposure (presence of SVD marker at baseline) on the outcome (cognitive performance at 36 months); Path c': the direct effect of the exposure (presence of SVD marker at baseline) on the outcome (cognitive performance at 36 months)

controlling for the mediator (presence of IILs at six months). Logistic regression analysis was applied to regress IIL presence on SVD variables; linear or logistic regression analyses were applied to regress the global cognitive score or cognitive impairment at 36 months, respectively on SVD variables and IIL presence. Confidence intervals were estimated by bootstrapping 10,000 times.

SVD, small vessel disease; IILs, incident ischemic lesions; OR, odds ratio; CI, confidence interval.

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