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

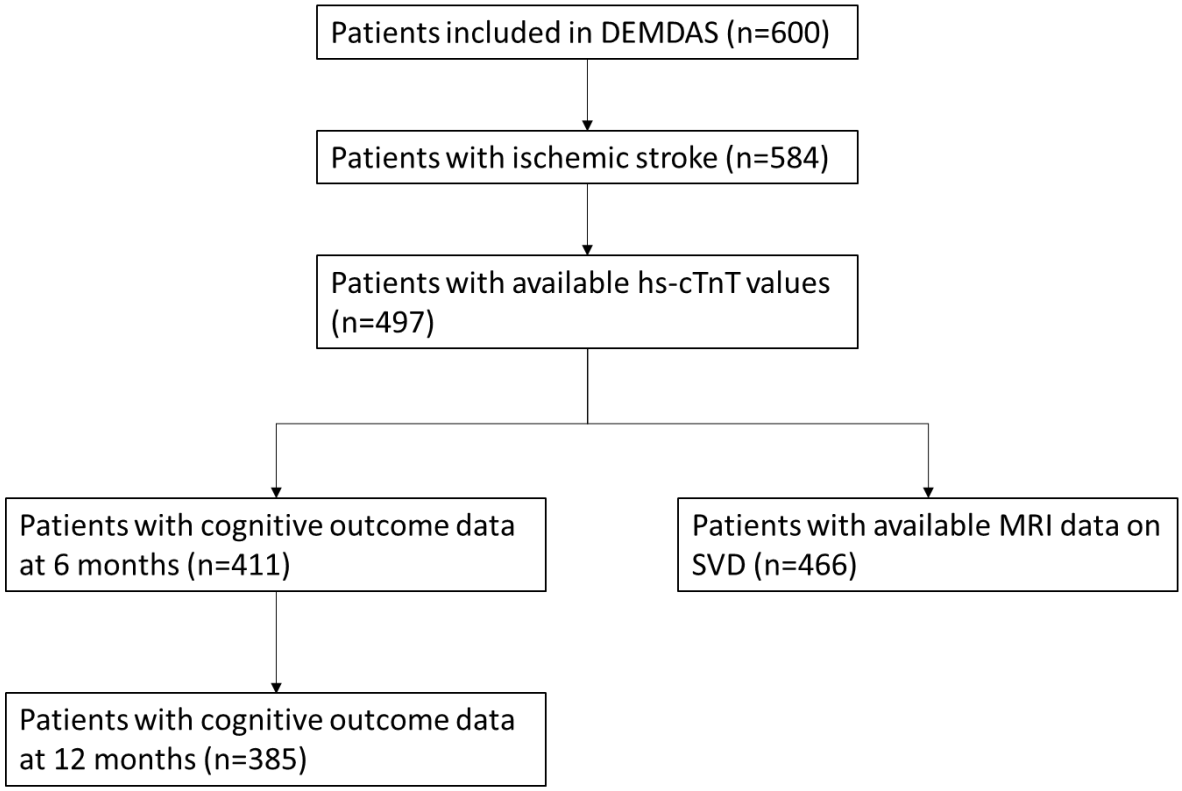
Log-transformed Hs-cTnT and cognitive domains (continuous) across 12 months of follow-up according to generalized linear regression models using GEE. Log-transformed Hs-cTnT and cognitive domains (continuous) at 6 and 12 months of follow-up according to linear regression models. The table displays the 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***

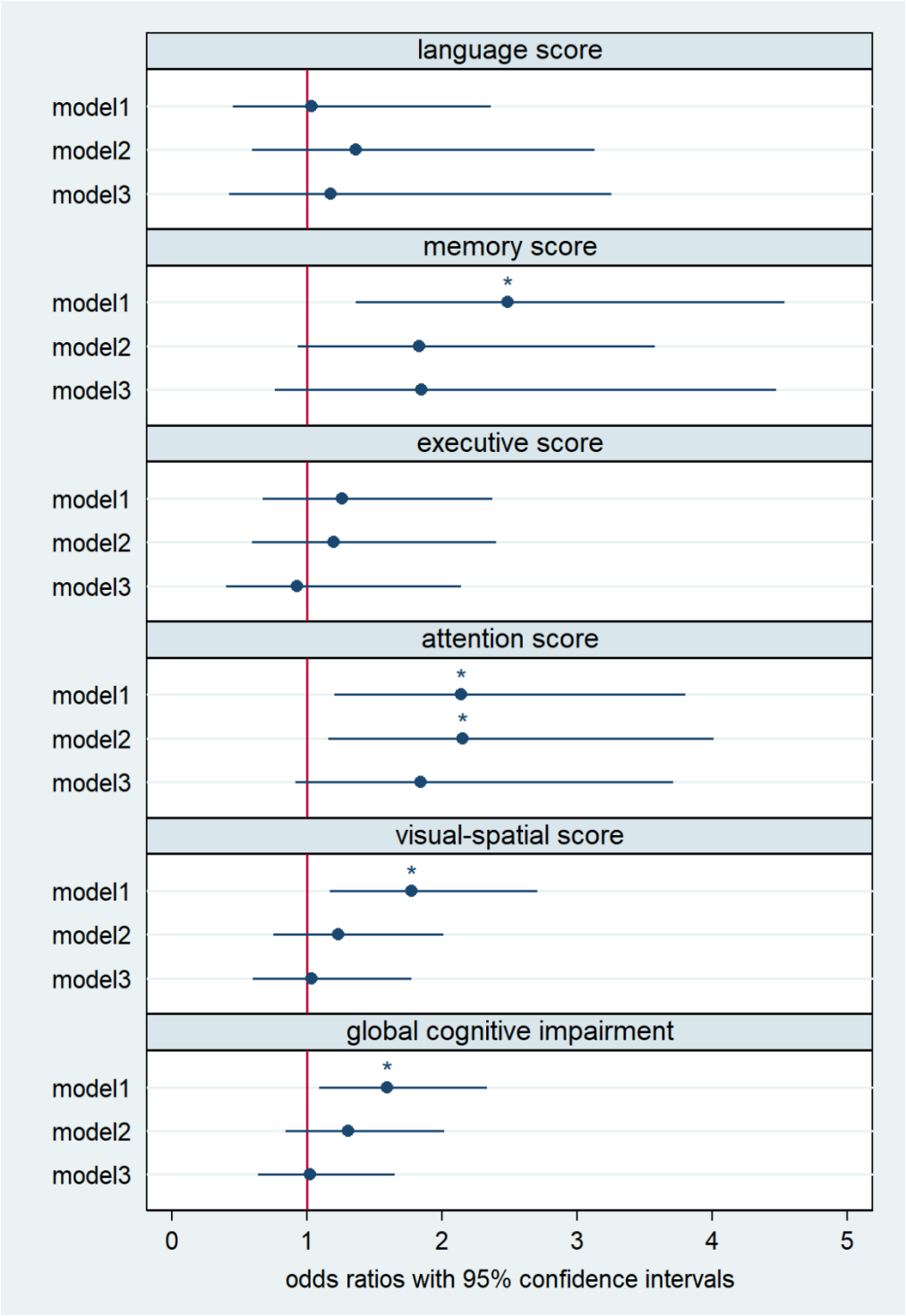
Log-transformed hs-cTnT and global cerebral small vessel disease (SVD) score, the four constituent SVD subscores and individual SVD markers in their entire range. Odds ratios and 95% confidence intervals were derived from ordinal logistic regression models for the global SVD score and binary logistic 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.



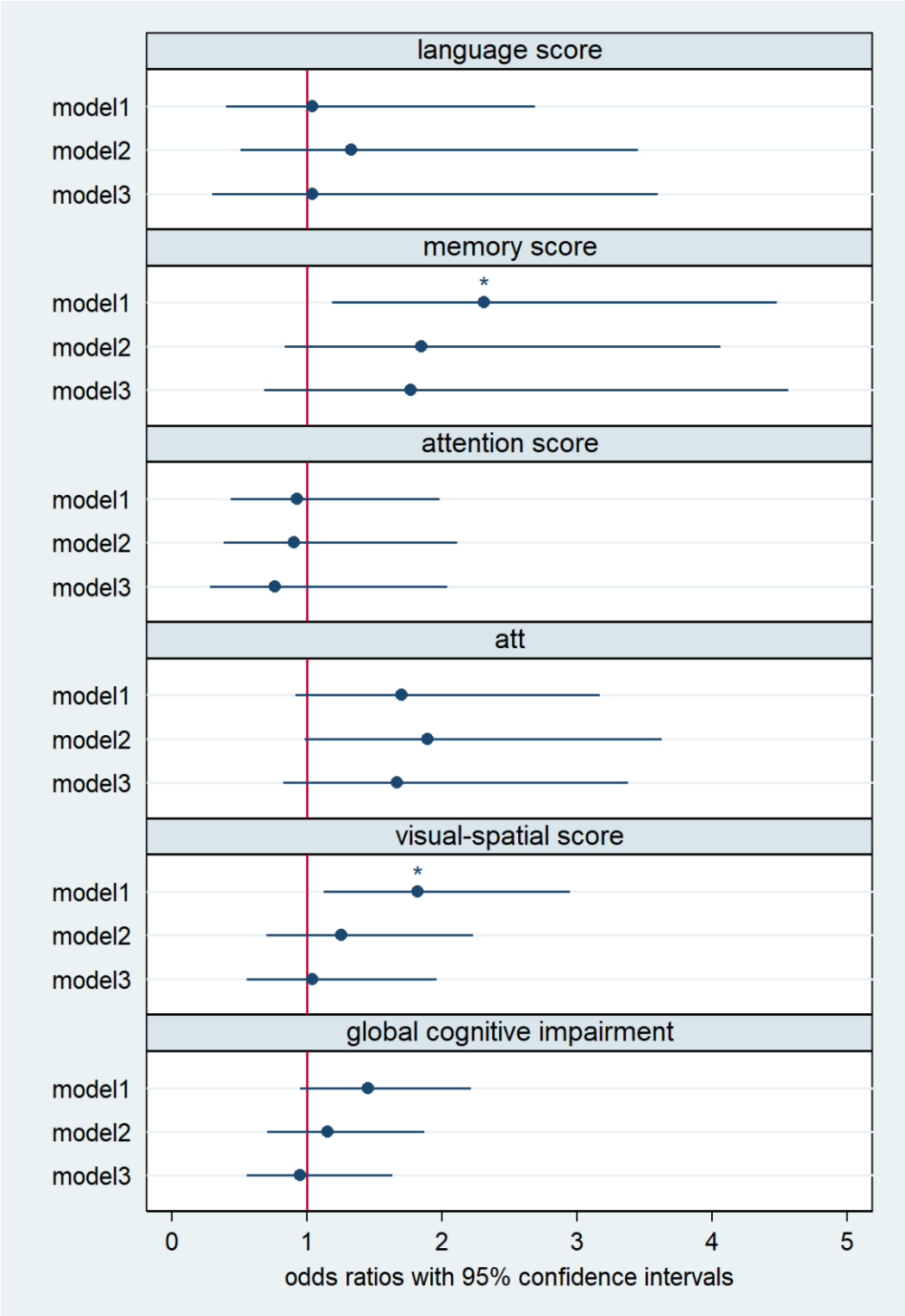
hs-cTnT = high-sensitivity cardiac troponin T. SVD = small vessel disease

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.



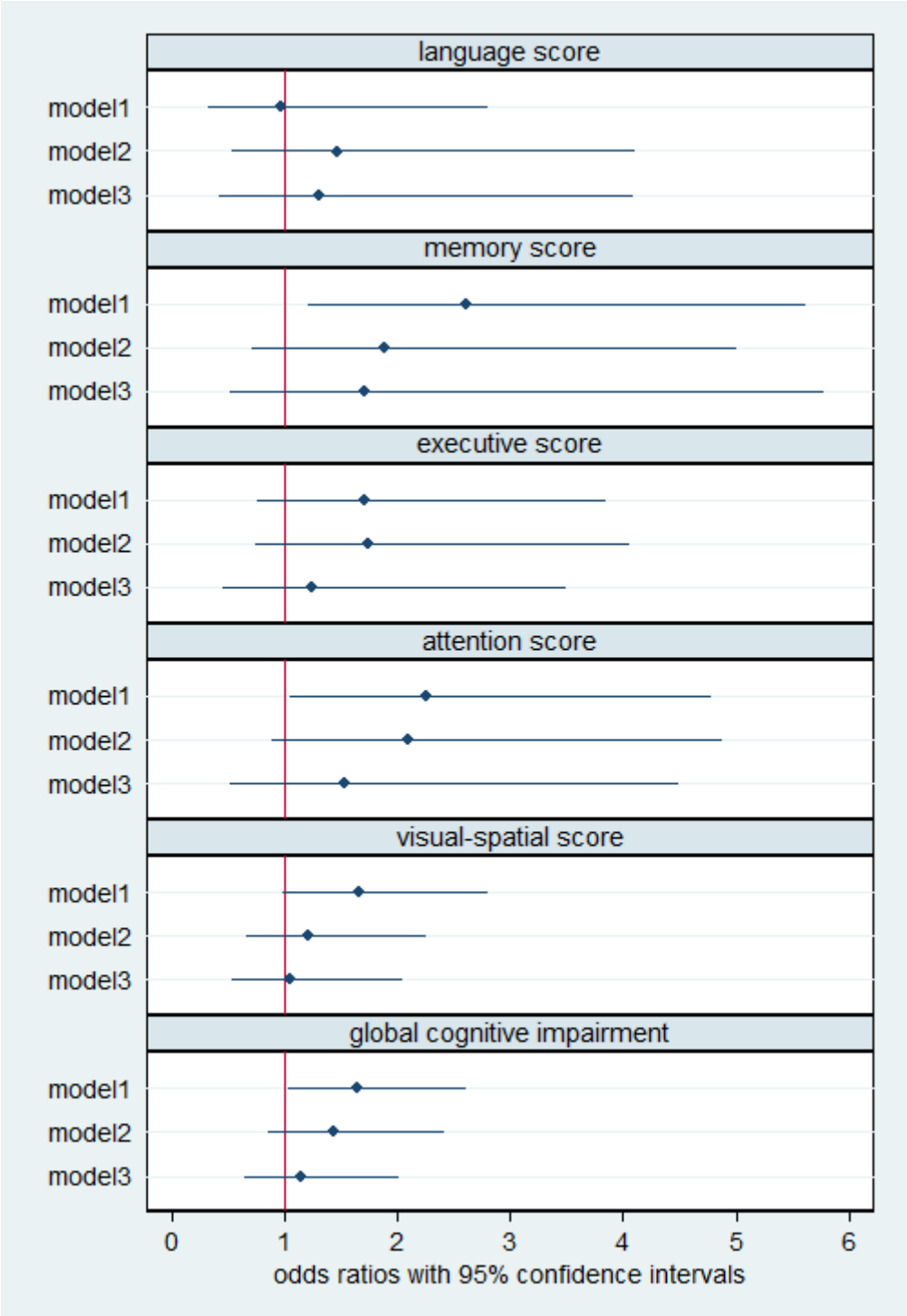
Model 1: unadjusted. Model 2: adjusted for age, sex and years of education. Model 3: additional adjustment for hypertension, diabetes, coronary artery disease, atrial fibrillation, cognitive impairment at baseline, baseline NIHSS and pre-stroke mRS. After full adjustment, there was no significant association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