

Supplementary Table 1: Frailty Index variables

Variable	Deficit coding	n (%)	
Self-reported medical history:			
Hypertension	no =0, yes = 1	193/385	50.1
Angina pectoris	no =0, yes = 1	53/384	13.8
Myocardial infarction	no =0, yes = 1	47/385	12.2
Dyslipidemia	no =0, yes = 1	164/385	42.6
Diabetes Mellitus	no =0, yes = 1	45/385	11.7
Stroke	no =0, yes = 1	29/385	7.5
Migraine	no =0, yes = 1	59/385	15.3
History of falls	no =0, yes = 1	65/384	16.9
Arthritis	no =0, yes = 1	215/381	56.4
Sensorimotor function:			
Postural Sway eyes open (mm)	<27 = 0, >27 = 1	79/383	20.6
Postural Sway eyes closed (mm)	<54.2 = 0, >54.2 = 1	71/382	18.4
Lower Limb Strength (kg)		84/380	22.1
Male	>27 = 0, <27 = 1		
Female	>18 = 0, <18 = 1		
Visual contrast (dB units)	<19 = 0, >19 = 1	111/385	28.8
Proprioception (degrees)	<2.4 = 0, >2.4 = 1	81/384	21.1
Reaction Time (ms)	<255.1 = 0, >255.1 = 1	74/384	19.3
Other measures			
Geriatric Depression Scale	<6 = 0, ≥6 = 1	9/374	2.3
Steps per day (no.)	>3219 = 0, <3219 = 1	68/357	19.1
Activities of daily living	>21 = 0, <21 = 1	20/384	5.2
Gait speed (cm/s)	>80 = 0, <80 = 1	23/375	6.1
Grip strength (psi)		78/38	20.3
Male	>8 = 0, <8 = 1		
Female	>5.5 = 0, <5.5 = 1		
BMI (kg/m ²)	18.5-35 = 0, <18.5 or >35 = 1	25/384	6.5
15-item AQoL*	1 = 0, 2 = 0.5, 3 and 4 = 1	3.71	2.19

*AQoL, Adjusted Quality of Life 15-item questionnaire; presented as mean, *SD*, as scored for the frailty index

Supplementary table 2: MRI measures at baseline and cognitive domains over time

Cerebral small vessel disease (n)							
		Model 1			Model 2		
		Beta	95% CI	p value	Beta	95% CI	p value
Global cognition							
	Time	-0.04	-0.06, -0.03	<0.001	0.004	-0.018, 0.026	0.71
	cSVD	-0.19	-0.28, -0.1	<0.001	-0.053	-0.140, 0.035	0.24
	cSVD × Time	-0.018	-0.03, -0.005	0.004	-0.019	-0.031, -0.007	0.003
Attention and processing speed							
	Time	-0.005	-0.02, 0.01	0.59	0.049	0.028, 0.071	<0.001
	cSVD	-0.19	-0.28, -0.1	<0.001	-0.042	-0.126, 0.043	0.034
	cSVD × Time	-0.02	-0.03, -0.004	0.011	-0.017	-0.030, -0.005	0.007
Visuospatial ability							
	Time	-0.31	-0.35, -0.27	<0.001	-0.277	-0.322, -0.231	<0.001
	cSVD	-0.18	-0.28, -0.08	<0.001	-0.088	-0.189, 0.012	0.08
	cSVD × Time	-0.03	-0.07, -0.003	0.03	-0.036	-0.067, -0.006	0.02
Executive function							
	Time	-0.001	-0.04, 0.24	0.58	0.015	-0.020, 0.051	0.67
	cSVD	-0.15	-0.23, -0.06	0.001	-0.076	-0.163, 0.012	0.09
	cSVD × Time	0.007	-0.017, 0.03	0.59	0.005	-0.019, 0.029	0.67
Verbal fluency							
	Time	0.02	0.002, 0.047	0.04	0.052	0.026, 0.078	<0.001
	cSVD	-0.14	-0.23, -0.05	0.002	-0.050	-0.141, 0.042	0.29
	cSVD × Time	-0.013	-0.029, 0.003	0.10	-0.014	-0.029, 0.002	0.09
Working memory							
	Time	0.02	-0.004, 0.05	0.1	0.034	0.006, 0.063	0.02
	cSVD	-0.07	-0.16, 0.017	0.11	-0.023	-0.117, 0.070	0.62
	cSVD × Time	0.001	-0.017, 0.018	0.94	-0.001	-0.018, 0.017	0.97
Verbal memory							
	Time	0.057	0.03, 0.08	<0.001	0.095	0.066, 0.124	<0.001
	cSVD	-0.13	-0.22, -0.04	0.006	-0.005	-0.089, 0.079	0.91
	cSVD × Time	-0.01	-0.03, 0.007	0.25	-0.012	-0.030, 0.007	0.22
Visual memory							
	Time	-0.15	-0.17, -0.12	<0.001	-0.112	-0.142, -0.083	<0.001
	cSVD	-0.13	-0.21, 0.04	0.004	-0.040	-0.126, 0.045	0.36
	cSVD × Time	-0.009	-0.028, 0.01	0.33	-0.011	-0.030, 0.008	0.25
Grey matter volume (mL)							
		Model 1			Model 2		
		Beta	95% CI	p value	Beta	95% CI	p value
Global cognition							
	Time	-0.142	-0.259, -0.025	0.02	-0.107	-0.223, 0.009	0.07

	GMV	0.005	0.003, 0.007	<0.001	0.006	0.003, 0.009	<0.001
	GMV × Time	0.0002	-0.001, 0.0003	0.18	0.0001	-0.0001, 0.0003	0.18
Attention and processing speed							
	Time	-0.080	-0.201, 0.041	0.19	-0.041	-0.161, 0.078	0.50
	GMV	0.005	0.004, 0.007	<0.001	0.006	0.003, 0.009	<0.001
	GMV × Time	0.0001	-0.0001, 0.0003	0.34	0.0002	-0.0001, 0.0003	0.32
Visuospatial ability							
	Time	-0.352	-0.653, -0.051	0.02	-0.327	-0.625, -0.028	0.03
	GMV	0.005	0.003, 0.007	<0.001	0.004	0.001, 0.007	0.03
	GMV × Time	0.0001	-0.0005, 0.0005	0.96	0.0001	-0.0005, 0.0005	0.96
Executive function							
	Time	-0.048	-0.271, 0.174	0.67	-0.035	-0.258, 0.188	0.76
	GMV	0.002	0.001, 0.004	0.01	0.003	0.001, 0.006	0.03
	GMV × Time	0.0001	-0.0003, 0.0005	0.68	0.0001	-0.0003, 0.0005	0.66
Verbal fluency							
	Time	0.054	-0.097, 0.204	0.48	0.061	-0.089, 0.211	0.42
	GMV	0.004	0.003, 0.006	<0.001	0.008	0.004, 0.011	<0.001
	GMV × Time	-0.0001	-0.0004, 0.0001	0.58	-0.0001	-0.0003, 0.0002	0.59
Working memory							
	Time	0.005	-0.163, 0.173	0.96	0.012	-0.156, 0.181	0.89
	GMV	0.004	0.002, 0.005	<0.001	0.003	-0.001, 0.006	0.08
	GMV × Time	0.0001	-0.0003, 0.0003	0.84	0.0001	-0.0003, 0.0003	0.98
Verbal memory							
	Time	-0.027	-0.202, 0.148	0.76	0.001	-0.174, 0.175	0.99
	GMV	0.002	0.001, 0.004	0.02	0.004	0.001, 0.007	0.005
	GMV × Time	0.0001	-0.0002, 0.0005	0.41	0.0001	-0.0002, 0.0005	0.42
Visual memory							
	Time	-0.147	-0.327, 0.033	0.11	-0.130	-0.310, 0.051	0.16
	GMV	0.005	0.003, 0.007	<0.001	0.004	0.001, 0.007	0.02
	GMV × Time	-0.0001	-0.0003, 0.0003	0.93	-0.0001	-0.0003, 0.0003	0.99

Model 1: unadjusted model

Model 2: adjusted for age, sex, level of education, additionally adjusted for total intracranial volume in GMV models

Abbreviations: 95% CI, 95% confidence intervals; cSVD, cerebral small vessel disease; GMV gray matter volume

Supplementary table 3: associations between MRI measures and cognitive domains over time stratified by baseline frailty status, adjusting for age, sex and years of formal education and additionally adjusting for total intracranial volume in grey matter models

	Low frailty (<0.26)			High frailty (>0.26)		
	Beta	95% CI	p value	Beta	95% CI	p value
Cerebral small vessel disease (n)						
Attention and processing speed						
Time	0.053	0.030, 0.077	<0.001	0.011	-0.041, 0.063	0.68
cSVD	0.026	-0.069, 0.122	0.59	-0.044	-0.208, 0.120	0.60
cSVD × Time	-0.022	-0.037, -0.007	0.004	-0.008	-0.033, 0.017	0.53
Visuospatial ability						
Time	-0.279	-0.334, -0.224	<0.001	-0.318	-0.419, -0.217	0.39
cSVD	-0.099	-0.206, 0.009	0.07	0.001	-0.199, 0.201	0.99
cSVD × Time	-0.040	-0.082, 0.002	0.06	-0.023	-0.075, 0.029	0.39
Executive function						
Time	0.011	-0.033, 0.056	0.62	-0.018	-0.104, 0.069	0.69
cSVD	0.021	-0.050, 0.092	0.56	-0.110	-0.330, 0.110	0.33
cSVD × Time	-0.015	-0.050, 0.019	0.39	0.027	-0.017, 0.070	0.24
Verbal fluency						
Time	0.061	0.031, 0.091	<0.001	-0.003	-0.058, 0.053	0.93
cSVD	-0.019	-0.131, 0.094	0.74	-0.048	-0.216, 0.120	0.58
cSVD × Time	-0.011	-0.031, 0.009	0.30	-0.008	-0.035, 0.019	0.56
Working memory						
Time	0.042	0.008, 0.077	0.015	0.004	-0.051, 0.059	0.89
cSVD	-0.021	-0.145, 0.104	0.75	0.025	-0.120, 0.171	0.73
cSVD × Time	-0.005	-0.028, 0.019	0.70	0.008	-0.020, 0.035	0.58
Verbal memory						
Time	0.081	0.050, 0.112	<0.001	0.126	0.055, 0.196	<0.001
cSVD	-0.045	-0.147, 0.058	0.39	0.112	-0.047, 0.271	0.17
cSVD × Time	0.004	-0.019, 0.026	0.76	-0.037	-0.074, -0.001	0.05
Visual memory						
Time	-0.111	-0.146, -0.077	<0.001	-0.126	-0.186, -0.065	<0.001
cSVD	-0.63	-0.177, 0.051	0.28	0.039	-0.097, 0.175	0.57
cSVD × Time	-0.014	-0.039, 0.011	0.28	-0.007	-0.037, 0.024	0.67
Gray matter volume (mL)						
Attention and processing speed						
Time	-0.046	-0.193, 0.102	0.55	-0.024	-0.247, 0.200	0.84
GMV	0.004	0.001, 0.007	0.02	0.005	-0.001, 0.011	0.07
GMV × Time	0.0001	-0.0001, 0.0004	0.36	0.0001	-0.0004, 0.0005	0.90
Visuospatial ability						

	Time	-0.387	-0.800, 0.027	0.07	-0.203	-0.668, 0.263	0.40
	GMV	-0.001	-0.004, 0.003	0.81	0.008	0.001, 0.015	0.02
	GMV × Time	0.0002	-0.0006, 0.0009	0.71	-0.0003	-0.001, 0.0006	0.49
Executive function							
	Time	-0.190	-0.527, 0.146	0.27	0.109	-0.282, 0.500	0.58
	GMV	0.001	-0.002, 0.003	0.73	0.007	-0.001, 0.014	0.10
	GMV × Time	0.0003	-0.0003, 0.0009	0.29	-0.0002	-0.0009, 0.0006	0.62
Verbal fluency							
	Time	0.095	-0.103, 0.292	0.35	0.100	-0.139, 0.339	0.41
	GMV	0.006	0.002, 0.010	0.35	0.010	0.004, 0.015	0.001
	GMV × Time	-0.0001	-0.0005, 0.0003	0.56	-0.0003	-0.0007, 0.0002	0.27
Working memory							
	Time	-0.030	-0.260, 0.200	0.80	0.069	-0.178, 0.315	0.59
	GMV	0.002	-0.002, 0.007	0.25	0.003	-0.002, 0.008	0.30
	GMV × Time	0.0001	-0.0003, 0.0005	0.60	-0.0001	-0.0006, 0.0003	0.62
Verbal memory							
	Time	0.024	-0.194, 0.241	0.83	-0.024	-0.351, 0.303	0.89
	GMV	0.003	-0.001, 0.007	0.07	0.004	-0.001, 0.010	0.13
	GMV × Time	0.0001	-0.0003, 0.0005	0.64	0.0002	-0.0005, 0.0008	0.62
Visual memory							
	Time	-0.081	-0.325, 0.163	0.51	-0.215	-0.489, 0.060	0.13
	GMV	0.002	-0.002, 0.006	0.28	0.005	0.001, 0.010	0.04
	GMV × Time	-0.0001	-0.005, 0.0004	0.71	0.0001	-0.0004, 0.0007	0.64

Abbreviations: 95% CI, 95% confidence intervals; cSVD, cerebral small vessel disease; GMV, gray matter volume.