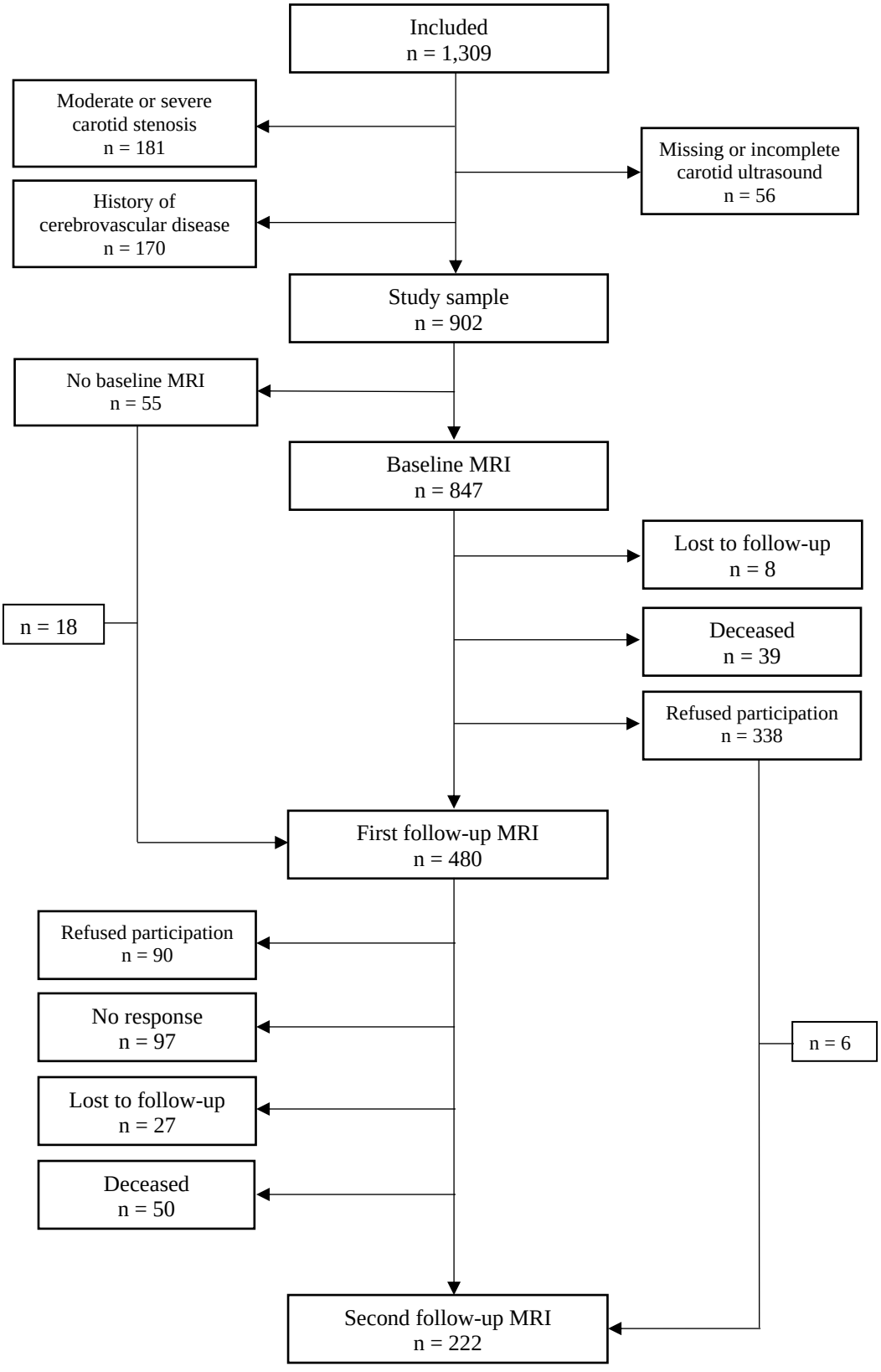
Supplementary Material

Supplementary Figure 1:

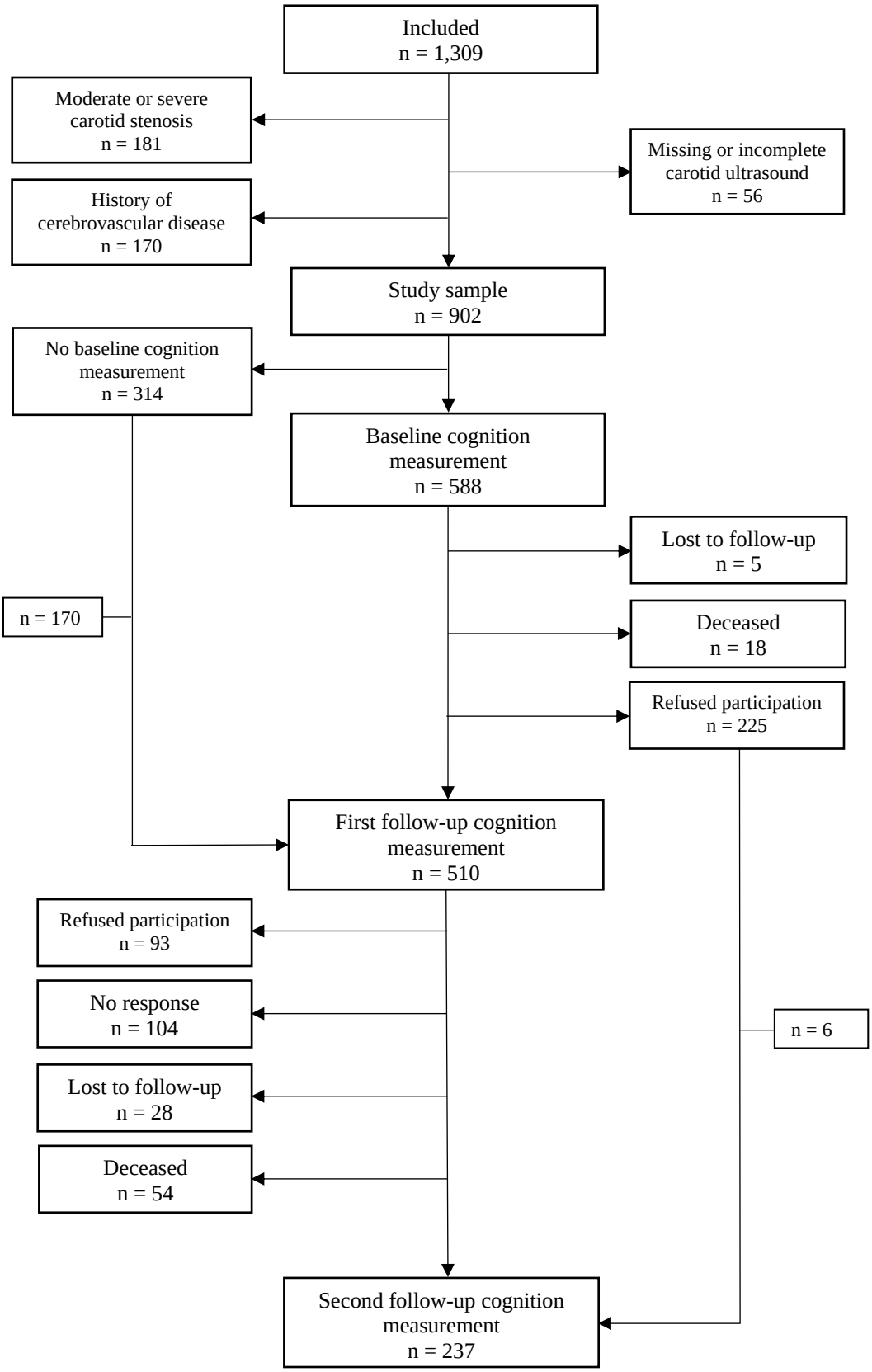


Supplementary Figure 1.

Title: Neuroimaging analysis flow diagram

Legend: Participation flow diagram of the 902 patients included in this study for neuroimaging analysis. The neuroimaging analysis included patients with consecutive and non-consecutive MRI measurements.

Supplementary Figure 2:



Supplementary Figure 2.

Title: Cognitive analysis flow diagram

Legend: Participation flow diagram of the 902 patients included in this study for cognitive analysis. The cognitive analysis included patients with consecutive and non-consecutive cognitive functioning assessment.

Supplementary Table 1

Output of the linear mixed-effects models with age of patients at each visit as the time variable, neuroimaging outcomes as dependent variables and low-grade carotid stenosis as independent variable.

	BPF		CSFF		VF		WMH [b]	
	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value
Intercept	79.6 (78.5 to 80.8)	<0.001	18.4 (17.5 to 19.5)	<0.001	1.99 (1.54 to 2.43)	<0.001	-3.34 (-3.94 to -2.74)	<0.001
Time	-0.25 (-0.28 to -0.22)	<0.001	0.19 (0.16 to 0.22)	<0.001	0.06 (0.05 to 0.07)	<0.001	0.08 (0.07 to 0.10)	<0.001
LGCS [a]	0.07 (-0.30 to 0.40)	0.717	0.07 (-0.23 to 0.37)	0.661	-0.10 (-0.24 to 0.03)	0.134	0.00 (-0.18 to 0.17)	0.987
LGCS x Time	-0.03 (-0.06 to -0.01)	0.002	0.03 (0.01 to 0.05)	0.011	0.01 (0.002 to 0.02)	0.019	0.01 (-0.03 to 0.02)	0.162
Sex [c]	0.93 (0.58 to 1.30)	<0.001	-0.57 (-0.88 to -0.25)	0.001	-0.36 (-0.49 to -0.22)	<0.001	0.29 (0.11 to 0.48)	0.002
Large infarcts on MRI	-0.44 (-1.25 to 0.36)	0.283	0.20 (-0.52 to 0.92)	0.581	0.11 (-0.23 to 0.45)	0.524	0.20 (-0.23 to 0.62)	0.371
Lacunes on MRI	-0.61 (-1.09 to -0.13)	0.013	0.19 (-0.24 to 0.61)	0.396	0.41 (0.21 to 0.61)	<0.001	0.76 (0.50 to 1.01)	<0.001
Hypertension	-0.08 (-0.36 to 0.20)	0.584	0.01 (-0.24 to 0.26)	0.920	0.09 (-0.02 to 0.20)	0.108	0.11 (-0.03 to 0.26)	0.125
Diabetes mellitus	-1.15 (-1.52 to -0.78)	<0.001	0.94 (0.62 to 1.27)	<0.001	0.17 (0.03 to 0.32)	0.019	0.17 (-0.02 to 0.37)	0.075
Body mass index	0.01 (-0.02 to 0.05)	0.483	-0.01 (-0.04 to 0.02)	0.493	-0.00 (-0.02 to 0.01)	0.684	0.01 (-0.01 to 0.01)	0.428
Smoking pack years	-0.01 (-0.02 to -0.01)	<0.001	0.01 (0.01 to 0.02)	<0.001	-0.00 (-0.00 to 0.00)	0.659	0.00 (-0.00 to 0.01)	0.435
Alcohol use								
Current	0 (reference)		0 (reference)		0 (reference)		0 (reference)	
Former	-0.50 (-0.98 to -0.02)	0.041	0.40 (-0.02 to 0.83)	0.064	0.14 (-0.04 to 0.32)	0.118	0.15 (-0.10 to 0.39)	0.243

Abstinent	-0.00 (-0.40 to 0.40)	0.99	-0.12 (-0.48 to 0.24)	0.504	0.10 (-0.06 to 0.25)	0.224	-0.04 (-0.25 to -0.17)	0.692

Results adjusted for sex, large infarcts on MRI, lacunes on MRI, hypertension, diabetes mellitus, body mass index, smoking pack years and alcohol use at baseline.

[a] No LGCS as the reference category.

[b] Natural log-transformed and standardized for total intracranial volume.

[c] Males as the reference category.

CI: confidence interval, LGCS: low-grade carotid stenosis, BPF: brain parenchymal fraction, CSFF: sulcal cerebrospinal fluid fraction, VF: ventricular fraction, WMH: white matter hyperintensity volume.

Supplementary Table 2

Output of the linear mixed-effects models with age of patients at each visit as the time variable, cognition domain-specific z-scores as dependent variables and low-grade carotid stenosis as independent variable.

	Executive functioning		Memory	
	Estimate (95% CI)	*p*-value	Estimate (95% CI	*p*-value
Intercept	-0.84 (-1.37 to -0.32)	0.002	-0.29 (-0.84 to 0.27)	0.311
Time	-0.06 (-0.08 to -0.05)	<0.001	-0.06 (-0.04 to -0.08)	<0.001
LGCS [a]	-0.06 (-0.20 to 0.09)	0.403	0.05 (-0.10 to 0.20)	0.496
LGCS x Time	-0.020 (-0.031 to -0.01)	<0.001	-0.012 (-0.02 to -0.001)	0.032
Sex [b]	0.00 (-0.15 to 0.16)	0.976	0.33 (0.17 to 0.50)	<0.001
Education level	0.19 (0.16 to 0.22)	<0.001	0.15 (0.12 to 0.19)	<0.001
Large infarcts on MRI	-0.05 (0.41 to 0.30)	0.778	-0.08 (-0.45 to 0.29)	0.677
Lacunes on MRI	-0.11 (-0.33 to 0.11)	0.330	-0.22 (-0.44 to 0.01)	0.062
Hypertension	0.09 (-0.03 to 0.21)	0.160	0.08 (-0.05 to 0.20)	0.237
Diabetes mellitus	-0.06 (-0.22 to 0.10)	0.481	-0.06 (-0.23 to 0.11)	0.502
Body mass index	-0.00 (-0.02 to 0.01)	0.837	-0.01 (-0.03 to 0.00)	0.126
Smoking pack years	0.00 (-0.00 to 0.01)	0.119	-0.00 (-0.00 to 0.00)	0.706

Alcohol use				
Current	0 (reference)		0 (reference)	
Former	0.06 (-0.15 to 0.27)	0.600	-0.09 (-0.31 to 0.13)	0.415
Abstinent	-0.19 (-0.37 to -0.02)	0.028	-0.19 (-0.38 to -0.01)	0.043

Results adjusted for sex, education level, practice effect, large infarcts on MRI, lacunes on MRI, hypertension, diabetes mellitus, body mass index, smoking pack years and alcohol use at baseline.

[a] No LGCS as the reference category.

[b] Males as the reference category.

CI: confidence interval, LGCS: low-grade carotid stenosis.

Supplementary Table 3

Joint Model Analysis with brain volumes and cognitive domains as dependent variables

	Joint Models		Association parameter	
	Estimate (SE)	p values	Estimate	p values
BPF				
Intercept	92.7 (0.46)	<0.001	-0.0374	0.0631
Time	-0.21 (0.006)	<0.001		
LGCS [a]	2.18 (0.66)	0.001		
LGCS x Time	-0.036 (0.01)	0.0013		
CSFF				
Intercept	8.52 (0.41)	<0.001	0.0485	0.0356
Time	0.16 (0.006)	<0.001		
LGCS [a]	-1.55 (0.59)	0.0081		
LGCS x Time	0.0278 (0.01)	0.0057		
VF				
Intercept	-1.02 (0.16)	<0.001	0.1428	0.0021
Time	0.05 (0.002)	<0.001		
LGCS [a]	-0.67 (0.21)	0.0013		
LGCS x Time	0.0097 (0.004)	0.0124		
WMH				
Intercept	-7.60 (0.23)	<0.001	-0.0117	0.772
Time	0.076 (0.003)	<0.001		
LGCS [a]	-0.42 (0.31)	0.1727		
LGCS x Time	0.0073 (0.005)	0.1786		
Executive functioning				
Intercept	2.69 (0.22)	<0.001	-1.340	<0.001
Time	-0.06 (0.003)	<0.001		
LGCS [a]	1.04 (0.256)	<0.001		
LGCS x Time	-0.0174 (0.005)	<0.001		
Memory				
Intercept	2.59 (0.14)	<0.001	-0.546	<0.001
Time	-0.06 (0.002)	<0.001		
LGCS [a]	0.68 (0.20)	<0.001		
LGCS x Time	-0.011 (0.003)	0.002		

The longitudinal submodel was adjusted for sex, large infarcts on MRI, lacunes on MRI, hypertension, diabetes mellitus, body mass index, smoking pack years and alcohol use at baseline. Models that estimated cognitive change in addition included education level and practice effect as covariates.
The survival submodel included LGCS, baseline age and sex as predictors.

Note that the time variable (i.e., age of patients at each visit) was not centered as negative values for the time variable are not compatible with the JM package.

[a] No LGCS as the reference category.

SE: standard error, LGCS: low-grade carotid stenosis, BPF: brain parenchymal fraction, CSFF: sulcal cerebrospinal fluid fraction, VF: ventricular fraction, WMH: white matter hyperintensity volume.

The estimates of the association parameters in the joint models for CSFF, VF, executive functioning and memory were statistically significant, indicating that death/dropout impacted change in CSFF, VF, executive functioning and memory throughout the follow-up period. This was not however the case for BPF and WMH.