

Supplementary Table 1. Details of MRI parameters and definition of lacunes.

Reference Number	1st Author Year	Study Name	Term for Lacunes	MR Field Strength	Thickness/ Gap (mm)	Matrix	Size (mm)	Signal Characteristics	Differential Diagnosis of Perivascular Spaces	Location of Incident Lacunes	Reproducibility
Population-Based Cohorts											
55	Nylander 2018	PIVUS	Lacunar infarcts	1.5T	1.2-3/0	NS	3-15	Hypointense on T1, hyperintense on T2 and isointense proton density	Location	No	NS
56	Nylander 2018	PIVUS	Lacunar infarcts	1.5T	1.2-3/0	NS	3-15	Hypointense on T1, hyperintense on T2 and isointense proton density	Location	No	NS
17	Sigurdsson 2017	AGES	Infarcts	1.5T	3/NS	NS	≥4	CSF intensity on FLAIR and T2	Hyperintense rim on FLAIR and size	Yes	intra κ 0.89 and 0.93. inter κ 0.76
28	Dearborn 2015	ARIC	Lacunes	1.5T	5/0	256*192	3-20	Hyperintense on T2 and proton density, hypointense on T1	NS	No	NS
29	Haring 2015	ARIC	Silent cerebral infarcts	1.5T	5/0	256*192	≥3	Hyperintense on T2 and proton density, hypointense on T1	NS	No	NS
30	Windham 2012	ARIC	Lacunar infarcts	1.5T	5/0	256*192	≥3	Hyperintense on T2/proton density, hypointense on T1	NS	No	NS
31	Knopman 2011	ARIC	Silent brain infarcts	1.5T	5/0	256*192	≥3	Hyperintense on T2 and proton density, hypointense on T1	NS	No	interrater agreement 89%.
32	Cheung 2010	ARIC	Infarcts	1.5T	5/0	256*192	3-20	Hyperintense on T2 and proton density, hypointense on T1	Using proton density	No	NS
33	Virtanen 2013	CHS	Subclinical infarcts	1.5T/0.35 T	5/0	NS	≥3	In GM: hyperintense on T2 and proton density, In WM, hypointense on T1	Using spin-density	No	NS
18	Longstreth 2011	CHS	Infarcts	1.5T/0.35 T	5/0	NS	≥3	In GM: hyperintense on T2 and proton density, In WM, hypointense on T1	NS	No	NS
19	Longstreth 2002	CHS	Lacunes	1.5T/0.35 T	5/0	NS	3-20	In GM: hyperintense on T2 and proton density, In WM, hypointense on T1	Using spin-density	Yes	NS
34	Satizabal 2012	3C	Silent brain infarcts	1.5T	3.5/0.5	256*192	≥3	CSF intensity in T1, T2 and proton density	Shape, size and location	No	NS
36	Chen 2009	PTLS	Lacunar infarcts	1.5T	1.5-2/0-1	256*256	3-20	Hypointense on T1 and FLAIR, hyperintense rim on FLAIR	NS	Yes	NS
37	van Dijk 2008	RSS	Lacunar infarcts	1.5T	5-6/1-1.2	256*192	3-20	In GM: hyperintense on T2, In WM: hypointense on T1	NS	No	NS
38	Ikram 2006	RSS	Lacunar infarcts	1.5T	5-6/1-1.2	256*192	3-20	In GM: hyperintense on T2, In WM: hypointense on T1	NS	No	NS
39	van Dijk 2005	RSS	Lacunar infarcts	1.5T	5-6/1-1.2	256*192	3-20	In GM: hyperintense on T2, In WM: hypointense on T1	NS	No	NS
40	Schmidt 2006	ASPS	Lacunes	1.5T	5/NS	128*256	<10	CSF intensity in T1, T2 and FLAIR	NS	No	NS
Patients with Cerebrovascular Disease											
59	van Leijsen 2018	RUN DMC	Lacunes	1.5T	1/0	NS	3-15	Hypointense on FLAIR and T1	Size and location	No	intra κ 0.87 inter κ 0.95
60	Staszewsk 2018	SHEF-CSVD	Lacunar infarcts	1.5T	5/0	NS	3-15	Hyperintense on T2, hypointense on T1, and hyperintense rim on FLAIR	Hyperintense rim on FLAIR and size	No	NS
42	Benjamin 2016	SCANS study	Lacunes	1.5T	1.1/NS	256*192	3-15	CSF intensity in T1, T2 and FLAIR	Size	No	NS

49	Xiong 2014	VITATOPS MRI	Lacunes	1.5T	5/0.5	256*256	<15	CSF intensity in T1, T2 and FLAIR	NS	No	NS
50	Cavalieri 2012	VITATOPS MRI	Lacunes	1.5T	5/0.5	256*256	<15	CSF intensity in T1, T2 and FLAIR	NS	No	NS
26	Jokinen 2011	LADIS	Lacunes	1.5T/0.5T	5/NS	NS	3-10	CSF intensity in T1, T2 and FLAIR	Hyperintense rim on FLAIR and size	Yes	ICC 0.84
35	Gouw 2008	LADIS	Lacunes	1.5T/0.5T	5/NS	NS	3-10	CSF intensity in T1, T2 and FLAIR	Hyperintense rim on FLAIR and size	No	NS
54	Walters 2003	St Mary's Hospital	Silent ischemic lesions	1.5T	NS/NS	256*192	NS	Using proton density and T2	NS	No	NS
Patients with Vascular Risk Factors											
41	van Dalen 2017	preDIVA trial	Lacunar infarcts	3T	1.12/0.56	NS	3-15	Hypointense on FLAIR	NS	No	NS
58	Uiterwijk 2017	HYBRID	Lacunes	1.5T	5/0.5	T2: 512*512, FLAIR: 512*512	3-15	Hyperintense on T2, hypointense with a hyperintense rim on FLAIR.	NS	No	inter κ 0.62
57	Kloppenborg 2017	SMART-MR	Lacunar infarcts	1.5T	4/0	180*256	3-15	Hyperintense on T2, hypointense on T1 and FLAIR	Location, form, and gliosis	Yes	NS
43	van der Veen 2015	SMART-MR	Lacunes	1.5T	4/0	180*256	3-15	Hyperintense on T2, hypointense on T1 and FLAIR	Location, form, and gliosis	No	NS
44	van der Veen 2015	SMART-MR	Lacunar infarcts	1.5T	4/0	180*256	3-15	Hyperintense on T2, hypointense on T1 and FLAIR	Location, form, and gliosis	No	NS
45	Jochemsen 2015	SMART-MR	Lacunar infarcts	1.5T	4/0	180*256	3-15	Hyperintense on T2, hypointense on T1 and FLAIR	Location, form, and gliosis	No	NS
46	van der Veen 2014	SMART-MR	Infarcts	1.5T	4/0	180*256	3-15	Hyperintense on T2, hypointense on T1 and FLAIR	Location, form, and gliosis	No	NS
47	Kloppenborg 2014	SMART-MR	Lacunar infarcts	1.5T	4/0	180*256	3-15	Hyperintense on T2, hypointense on T1 and FLAIR	Location, form, and gliosis	No	NS
48	Jochemsen 2012	SMART-MR	Lacunar infarcts	1.5T	4/0	180*256	3-15	Hyperintense on T2, hypointense on T1 and FLAIR	Location, form, and gliosis	No	NS
51	Saito 2014	Asahikawa Hospital	Asymptomatic cerebral infarctions	1.5T	5.5/1	256*256	NS	Hyperintense on T2, hypointense on T1	NS	No	NS
52	Umamura 2011	Chubu Rosai Hospital	Silent brain infarcts	1.5T	5/2	T1: 320*224, T2:156*256, FLAIR:256*192	>3	Hyperintense on T2, hypointense on T1 and FLAIR	Hyperintense rim on FLAIR and size	No	Cohen κ 0.75-0.86
53	Imamine 2011	Chubu Rosai Hospital	Silent brain infarcts	1.5T	5/2	T1: 320*224, T2:156*256, FLAIR:256*192	>3	Hyperintense on T2, hypointense on T1 and FLAIR	Hyperintense rim on FLAIR and size	No	NS

Abbreviations: MR: Magnetic Resonance, PIVUS: Prospective Investigation of the Vasculature in Uppsala Seniors study, AGES: Age Gene/Environment Susceptibility-Reykjavik study, ARIC: Atherosclerosis Risk in Communities study, CHS: CardioVascular Health Study, 3C: Three-City-Dijon Study, PTLs: PATH Through Life Study, RSS: Rotterdam Scan Study, ASPs: Austrian Stroke Prevention Study, RUN DMC: Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort, SHEF-CSVD: Significance of Haemodynamic and Haemostatic Factors in the Course of Different Manifestations of Cerebral Small Vessel Disease Study, SCANS: St George's Cognition and Neuroimaging in Stroke study, VITATOPS: VITamins TO Prevent Stroke MRI-Substudy, LADIS : Leukoaraiosis and Disability study, preDIVA : Prevention of Dementia by Intensive Vascular Care study, SMART-MR: Second Manifestations of Arterial Disease-Magnetic Resonance study, HYBRID: Hypertension and brain damage study, CSVD: cerebral small vessel diseases, CSF: cerebral spinal fluid , FLAIR: fluid-attenuated inversion recovery, GM: gray matter, WM: white matter, NS: not specified, ICC: intraclass correlation coefficient

Supplementary Table 2. Predictors of incident lacunes in patients with cerebrovascular disease

BASELINE PREDICTORS	REFERENCES OF STUDIES WITH A SIGNIFICANT ASSOCIATION	REFERENCES OF STUDIES WITH NO SIGNIFICANT ASSOCIATION
Age		35
Sex		
Female		35
Blood pressure		
Hypertension		35
Systolic blood pressure	35	
Diastolic blood pressure	35*	
Dyslipidemia		
Total cholesterol		35
Triglycerides		35
High-density lipoprotein	35*	
Low-density lipoprotein	35*	
Diabetes		
Diabetes		35
Glucose		35
Metabolic syndrome and Obesity		
Body mass index		35
Smoking		35
Atrial fibrillation		35
Previous stroke		35, 49
Myocardial infarction		35
MRI markers		
Lacunes	35	
White matter hyperintensities	35	
Others		
Plasma A β 38	59	
Plasma A β 40		59
Plasma A β 42		59
CRP		60
Z-score of systematic inflammation	60	
Hyperhomocysteinemia	60	
IL-6		60
IL-1 α		60
TNF- α		60
B-vitamin supplementation		50

Abbreviations: CRP: C-reactive protein, IL-6: interleukin-6, IL-1 α : interleukin-1 α , TNF- α : Tumor necrosis factor- α

* These predictors with a significant adjusted OR < 1.0

Supplementary Table 3. Predictors of incident lacunes in patients with vascular risk factors

BASELINE PREDICTORS	REFERENCES OF STUDIES WITH A SIGNIFICANT ASSOCIATION	REFERENCES OF STUDIES WITH NO SIGNIFICANT ASSOCIATION
Age	46	
Sex		
Male	46	
Blood pressure		
Hypertension	47 ^b	
Systolic blood pressure		
Diastolic blood pressure		
Hypertensive Target Organ Damage		44
Diabetes		
sICAM-1	52	
Peripheral arterial disease		46
Abdominal aortic aneurysm	46	
Cerebrovascular disease	46	
Vascular markers		
Stiffening of carotid arteries		45
MRI markers		
Parenchymal CBF		43
White matter hyperintensities	47 ^b	
Others		
Serum ACE		48
CRP	52	
Hyperhomocysteinemia	47 ^a	
Multidomain intensive vascular care		41

Abbreviations: sICAM-1: soluble intercellular adhesion molecule-1, CBF: cerebral blood flow, ACE: angiotensin-converting-enzyme, CRP: C-reactive protein

^a Independently associated with incident lacunes in all location and the basal ganglia.

^b Independently associated with incident lacunes in the deep white matter.

Supplementary Figure 1. Study selection flow diagram.

