Supplemental Material

Supplemental Methodology

Literature Search Details

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present - Search ran 04/03/2015

1. exp Brain Infarction/
2. ((brain or cerebral or circulation or covert or lacunar or subcortical or venous) adj3 infarct*).tw.
3. 1 or 2
4. silent.tw.
5. 3 and 4
6. (SBI or SLI or SSBI).tw.
7. 5 or 6
8. exp Magnetic Resonance Imaging/
9. magnetic resonance.tw.
10. (MR or MRA or MRDTI or MRI or MRIs or NMR).tw.
11. or/8-10
12. exp stroke/
13. stroke*.tw.
14. Cerebrovascular.tw.
15. ((brain or cerebral or isch?emic or lacunar or vascular or venous) adj2 (accident* or attack* or event* or infarct*)).tw.
16. (cva or cvas).tw.
17. or/14-16
18. 7 and 11 and 17

The English language filter was not applied. The first search was conducted in Ovid MEDLINE. Subject headings and key words were adapted for the other databases.

Supplemental Table I: Risk of Bias Questions to Assess the Quality of Included Studies

Type of Bias	Question	Answers
Selection	Was the study sample randomly selected or a community-dwelling population to minimize the risk of selection bias?	Yes (+) or no (-)
	Were the inclusion and exclusion criteria adequately described?	Yes (+) or no (-)
	Was the study's primary objective to assess whether SBI is predictive of clinically overt stroke?	Yes (+) or no (-)
Detection	Was the study prospective in nature?	Yes (+) or no (-)
	Were the investigators blinded to the clinical history of patients during ascertainment of SBI?	Yes (+) or no (-)
	Did more than one investigator assess for the presence of SBI?	Yes (+) or no (-)
	Were investigators blinded to SBI status when determining stroke outcomes?	Yes (+) or no (-)
Misclassification	Did the investigators describe a method by which SBI was differentiated from dilated perivascular spaces?	Yes (+) or no (-)
Reporting	Did more than one investigator assess for stroke outcomes?	Yes (+) or no (-)
Attrition	Were losses to follow up systematically recorded and reported?	Yes (+) or no (-)
Confounding	Were data adjusted for covariate risk factors to minimize the risk of confounding bias?	Minimal (+) if studies controlled for 4 of the following 6 potential stroke risk factors which are potential confounders: age, sex, hypertension, diabetes mellitus, coronary artery disease, and smoking history and hyperlipidemia by including these variables in the multivariate model or by ensuring that patients with and without SBI were similar or matched on these variables. Relatively higher risk (-) if studies did not provide adjusted risk metric demonstrating strength of association between SBI and incident stroke.

Note if data not provided or not specified, recorded as no (-).

Supplemental Table II. Overview of Patient Characteristics in Studies Evaluating Risk of Stroke in Patients with MRI defined Silent Brain Infarct

Study Number	Study First Author and Year	Study Design	Major Inclusion Criteria	Study Name	Country	Mean Follow-Up (Mo)	SBI status at baseline	Number of Subjects	Mean Age (+/- SD)	Women, no. (% female)	Hypertension (%)	Diabetes Mellitus (%)	Chronic Kidney Disease (%)	Atrial Fibrillation (%)	Coronary Artery Disease (%)	Hyperlipidemia (%)	Smoking History (%)
1	Bernick 2001[1]	prospective cohort	stroke-free subjects, randomly sampled, population-based cohort	Cardiovascular Health Study	United States	50.4	SBI positive	923	76*	543 (58.8)	526 (57)	123 (13.3)	No data	22 (2.4)	216 (23.4)	208.4†	1.2‡
							SBI negative	2401	73.1*	1437 (59.9)	1118 (46.6)	317 (13.2)	No data	65 (2.7)	411 (17.1)	207.1†	0.5‡
2	Kario 2001§[2]	prospective cohort	stroke-free, ambulatory subjects with hypertension	/	Japan	42	Total sample with SBI status known	585	72.0 +/- 9.9	592 (61.8)	811 (84.6)	111 (11.6)	No data	No data	No data	187 (19.5)	197 (20.6)
3	Naganuma 2005[3]	prospective cohort	stroke-free, ambulatory subjects on hemodialysis	/	Japan	40.2	SBI positive	59	62.9+/-8.1	18(30.5)	51 (86.4)	24 (40.6)	59 (100)	No data	17 (28.8)	11 (18.6)	22 (37.2)
							SBI negative	60	49.2+/-12.8	17(28.3)	51 (85)	10 (16.7)	60 (100)	No data	3 (5)	4 (6.6)	8 (13.3)
4	Bokura 2006[4]	prospective cohort	stroke-free subjects, healthy volunteers	/	Japan	75.6	SBI positive	380	62 +/- 7.2	142 (37.4)	248 (65.3)	42 (11.1)	No data	6 (1.6)	No data	124 (32.6)	142 (37.4)
							SBI negative	2304	57.1 +/- 7.1	1069 (46.4)	894 (38.8)	221 (9.6)	No data	14 (0.6)	No data	733 (31.8)	740 (32.1)
5	Debette 2010[5]	prospective cohort	community-based, prospective study, offspring of original Framingham Heart Study participants	Framingham Offspring Cohort Study	United States	67.2	SBI positive	253	65+/-9	126 (49.8)	146 (57.7)	40 (15.8)	No data	No data	No data	No data	33 (13.0)
							SBI negative	1975	62 +/- 9	923 (46.7)	770 (39.0)	215 (10.9)	No data	No data	No data	No data	234 (12.0)
6	Putaala 2011§[6]	prospective cohort	subjects with history of any ischemic stroke	/	Finland	104.4	Total sample with SBI status known	655	40+/-8.0	270 (41.2)	244 (37.3)	66(10.1)	No data	19 (2.9)	46 (7.0)	368 (56.2)	264 (40.3)
7	Umemura 2011[7]	prospective cohort	stroke-free, ambulatory subjects with DM	/	Japan	72	SBI positive	46	62.7 +/-8.1	102 (53.7)	96 (50.5)	46 (100)	No data	No data	No data	95 (50)	38 (20.0)
							SBI negative	144	62.7 +/-8.1	102 (53.7)	96 (50.5)	144 (100)	No data	No data	No data	95 (50)	38 (20.0)
8	Gioia 2012[8]	retrospective cohort	subjects with history of any ischemic stroke	/	Canada	25.7	SBI positive	48	42.5+/-7.0	27(56.2)	20 (41.7)	10 (20.8)	No data	No data	6 (12.5)	36 (75)	24 (50)
							SBI negative	122	38.2+/-8.7	54(43.8)	32 (26.2)	12 (9.8)	No data	No data	5 (4.1)	74 (60.7)	56 (45.9)
9	Poels 2012§[9]	prospective cohort	stroke-free subjects, randomly sampled, population-based cohort	The Rotterdam Scan Study	Netherlands	120	Total sample with SBI status known	210 ‖	72+/-7.4	522 (51.8)	332 (33.0)	66 (6.6)	No data	28 (2.8)	96 (9.5)	No data	176 (17.5)
10	Weber 2012[10]	prospective cohort data from a randomized controlled trial	subjects with recent ischemic stroke within 120 days of study, SBI positive and negative patients matched by age and sex	Prevention Regimen for Effectively Avoiding Second Strokes trial	Multicenter trial (35 countries or regions)	30	SBI positive	207	66.2 +/-8.5	57 (27.5)	162 (78.2)	67 (32.3)	No data	8 (3.8)	No data	99 (47.8)	135
							SBI negative	207	66.2 +/-8.5	57 (27.5)	155 (74.7)	63 (30.4)	No data	6 (2.9)	No data	111 (53.8)	130

11	Di Tullio 2013 ||, §[11]	prospective cohort	stroke-free subjects, population-based cohort	Northern Manhattan Study	United States	85.2	Total sample with SBI status known	1287	71+/-9	779 (61)	934 (73)	291 (23)	No data	31 (2.4)	160 (12.4)	504 (39)	119 (9)
12	Miwa 2013[12]	prospective cohort	stroke-free, ambulatory subjects with >1 cardiovascular risk factor	Osaka Follow-up Study for Carotid Atherosclerosis, part 2	Japan	57.6	SBI positive	130	68.8+/-8.6	237 (51)	315(68)	79 (17)	No data	No data	No data	246(53)	70 (15)
							SBI negative	334	68.8+/-8.6	237 (51)	315(68)	79 (17)	No data	No data	No data	246(53)	70 (15)
13	Windham 2015¶[13]	prospective cohort	stroke-free subjects, population-based cohort	The Atherosclerosis Risk in Communities Study	United States	174	SBI positive	220	64.0+/-4.5	134 (61)	143 (65)	50 (23)	No data	No data	17 (8)	No data	57 (26)
							SBI negative	1611	62.1+/-4.5	972 (60)	722 (45)	264 (17)	No data	No data	82 (5)	No data	277 (17)

* weighted median value

†Weighted median value, total cholesterol (mg/dL)

‡Weighted median value, pack-years of smoking

§cohort characteristics refer to entire patient sample as data stratified by SBI status is not available

|| Di Tullio et al. presented SBI results and stroke outcomes for a subset of those subjects enrolled in the MRI substudy of the Northern Manhattan Study. The study characteristics in this table for this study were obtained after direct correspondence with study authors who were preparing a study focused on SBI and incident stroke risk at the time of data extraction.

¶Windham et al. studied small brain lesions less than 3 mm as putative vascular lesions, in addition to lesions greater than 3 mm which were considered to be SBI. The data extracted from this study, including clinical characteristics, are focused on SBI defined>3mm versus no lesions.

Supplemental Table III: Silent Brain Infarction Definitions

Study Number	Study First Author and Year	Magnet Field Strength	Section Thickness (mm)	Section Gap (mm)	Size classification	SBI MRI Signal Characteristics	Means of differentiating SBI from perivascular spaces	Means of detecting SBI in patients with documented prior stroke
1	Bernick 2001[1]	0.35 and 1.5 Tesla	5 mm	0	3 mm or greater	brighter lesions on spin density and T2 sequences than normal gray matter (for cortical and deep grey matter); brighter at spin density and T1 hypointense (for white matter)	spin density brigthness used to distinguish SBI from perivascular spaces	NA
2	Kario 2001[2]	1.5 Tesla	7.8 to 8.0 mm	not specified	3 to 15 mm	low signal intensity area on T1-weighted images that was also visible as a hyperintense lesion on T2-weighted images	not specified	NA
3	Naganuma 2005[3]	1.5 Tesla	10 mm	not specified	>3 mm	focal area on both T1 and T2-weighted images that was visible as low-intensity areas on T1 weighted image and as high signal intensity area on T2 weighted images.	not specified	NA
4	Bokura 2006[4]	0.15, 0.2 and 1.5 Tesla	10 mm, 7 mm	not specified	>3 mm	focal hyperintensity lesion on T2WI corresponding to a hypointensity lesion on T1WI	proton density weighted or FLAIR images used to distinguish infarcts from dilated perivascular spaces	NA
5	Debette 2010[5]	1 or 1.5 Tesla	4 mm	not specified	>3 mm	area of abnormal signal intensity in a vascular distribution, at least 3 mm in size with a cerebrospinal fluid density on the subtraction image and, for lesions in the basal ganglia area, distinct separation from the circle of Willis vessels	size, location, shape, and tissue contrast to distinguish SBI from dilated perivascular spaces	NA
6	Putaala 2011[6]	1.0 to 1.5 Tesla	not specified	not specified	≥ 3 mm	focal hyperintensity on T2-weighted images without a corresponding history of neurologic symptoms or signs	simultaneous hyperintensity on T2-weighted images and hypointensity on FLAIR images for perivascular spaces as opposed to SBI	MRI of the brain studies acquired at the initial presentation for acute ischemic stroke were reinterpreted by study stroke neurologists and a senior neuroradiologist. SBI classification required appropriate imaging criteria as well as no corresponding history of neurologic symptoms or signs.
7	Umemura 2011[7]	1.5 Tesla	5 mm	2 mm	>3 mm	areas of focal hyperintensity larger than 3 mm in diameter detected on T2-weighted images, hypointensity areas on T1-weighted images and areas of hypointensity surrounded by hyperintense rim on FLAIR images.	lesions less than 3 mm in diameter or with a signal intensity similar to that of cerebrospinal fluid on FLAIR images excluded because of the high possibility of enlarged perivascular spaces, even if hyperintensity on T2-weighted images and hypointensity on T1-weighted images	NA
8	Gioia 2012[8]	1.5 T or 3 Tesla	not specified	not specified	≥ 3 mm	focal hyperintensities on T2-weighted and FLAIR-weighted sequences, 3 mm in diameter, without corresponding neurologic symptoms; leukoaraiosis defined as multifocal or confluent hyperintensities located in periventicular or subcortical regions or in the pontine white matter on T2-weighted or FLAIR sequences. Differentiated from SBIs based on lesion morphology and localization	hyperintensity of T2-FLAIR images used to distinguish SBI from dilated perivascular space	SBI determined on imaging performed during the patient's initial workup for acute ischemic stroke; consensus of 2 neurologists needed to establish a lesion as an asymptomatic brain infarction using all available clinical data
9	Poels 2012[9]	1.5 Tesla	5 or 6 mm	1 or 2 mm	at least 3 mm	evidence of one or more infarcts on MRI, without a history of (corresponding) stroke or TIA (focal hyperintensities on T2 weighted images); white matter lesions (rather than SBIs) were considered to be present if hyperintensities were visible on proton-density and T2-weighted images, without prominent hypointensities on T1-weighted scans	proton density scans were used to distinguish infarcts from dilated perivascular spaces	NA
10	Weber 2012[10]	Not specified	not specified	not specified	≥ 3 mm	focal hyperintense lesion on T2-weighted images and/or fluid-attenuated inversion recovery with no corresponding symptoms in the clinical history of the patient that could be attributed to the lesion; SBI were distinguished from nonspecific subcortical and periventricular white matter lesions by the presence of a corresponding hypointense lesion on T1-weighted images	hyperintensity of T2-FLAIR images used to distinguish SBI from dilated perivascular space	Two study investigators defined SBI on the baseline imaging performed for acute ischemic stroke as chronic lesions with no corresponding symptoms in the clinical history of the patient that could be attributed the presumed SBI; Information about symptoms of the qualifying ischemic stroke was collected using baseline case report forms
11	Di Tullio 2013[11]	1.5 Tesla	FLAIR=3 mm; T1=1.3 mm	0 mm	≥ 3 mm	(1) CSF density on the subtraction image and (2) if the stroke was in the basal ganglia area, distinct separation from the circle of Willis vessels and perivascular spaces.	lesion morphology used to distinguish SBI from perivascular spaces	NA
12	Miwa 2013[12]	Not specified	Not specified	not specified	>3 and <15 mm	hypointense lesion and hyperintense rim on FLAIR images when located supratentorially, according to the corresponding hyperintensity and hypointensity on T2- and T1-weighted images, respectively, without stroke history.	hyperintensity of T2-FLAIR images used to distinguish SBI from dilated perivascular space	NA
13	Windham 2015[13]	1.5 Tesla	5 mm	0	≥ 3 mm	lesions 3 mm in size and visible on both T1- and proton-density/T2-weighted images were classified as infarcts; an additional analysis was performed on putative vascular lesions <3 mm which were too small to definitely characterize as SBI	spin density brigthness used to distinguish SBI from perivascular spaces	NA

MRI = magnetic resonance imaging; SBI = silent brain infarction; FLAIR = fluid attenuated inversion recovery; NA = not applicable

Supplemental Table IV: Definitions of stroke

Study First Author and Year	Ischemic Stroke Definition	Hemorrhagic Stroke Definition	Stroke Outcome Adjudication Process
Bernick 2001[1]	clinical event of rapid onset consisting of neurological deficit lasting more than 24 hours or if less than 24 hours, associated with an appropriate brain lesion not due to hemorrhage	clinical event of rapid onset consisting of neurological deficit lasting more than 24 hours or if less than 24 hours, with evidence of blood in the subarachnoid space, ventricles, or brain parenchyma	follow up yearly examinations and at interim 6 months phone contacts; additional review from all non stroke hospitalizations for ICD codes 403 through 438 identifying cerebrovascular disease; events adjudicated by stroke adjudication committee made up of study neurologists, neuroradiologist, and a clinician from the Coordinating Center
Kario 2001[2]	evidence of brain infarction or embolism with neurological deficit lasting more than 24 hours	parenchymal or subarachnoid hemorrhage at brain imaging	intermittent review of medical records and telephone interviews confirmed by physician caring for the patient at the time of the event
Naganuma 2005[3]	standard clinical criteria, not further specified	standard clinical criteria, not further specified	review of medical records with diagnosis made by attending physician blinded to study purpose; family telephone interview in events that happened out of hospital
Bokura 2006[4]	not specified	not specified	annual questionnaire sent to the patient's home and, if needed, telephone interview and interview of attending physician
Debette 2010[5]	acute-onset focal neurological deficit of presumed vascular etiology lasting ≥24 hours with imaging showing no hemorrhage and an infarct correlating with the clinical deficit, or an infarct documented at autopsy	acute-onset focal neurological deficit of presumed vascular etiology lasting ≥24 hours with imaging showing intracranial hemorrhage	panel adjudication of Framingham investigators reviewing all relevant medical records and clinical data
Putaala 2011[6]	an episode of focal neurologic deficits with acute onset and lasting more than 24 hours or if lasting less than 24 hours, with imaging evidence of stroke corresponding with current symptoms plus corresponding ischemic lesion on MRI	not specified	telephone interview or letter sent to the patient and all patient records available from hospitals and primary care; outcome events were classified by study stroke neurologists blinded to other clinical data with consensus agreement
Umemura 2011[7]	not specified	not specified	not specified
Gioia 2012[8]	sudden onset of a persistent neurologic deficit or a transient neurologic deficit associated with a new infarct on brain imaging	not specified, obtained from database and chart review	patient follow-up was performed by outpatient hospital visits with stroke neurologists; clinical outcomes were obtained from the database and confirmed by retrospective chart review
Poels 2012[9]	rapidly developing clinical signs of focal disturbance of cerebral function with no apparent cause other than a vascular origin, with a duration of more than 24 hours	not specified	review of medical records of all participants at the general practitioner's office and additional information from hospital records and municipal health authorities; to verify all diagnoses, investigators discussed information on all potential strokes and TIA with an experienced stroke neurologist
Weber 2012[10]	focal neurological deficit of vascular origin lasting more than 24 h, or where there is evidence of a new brain infarct upon brain imaging; brain imaging must rule out hemorrhagic stroke, but it does not need to confirm the presence of a brain infarct if clinical symptomatology is sufficient to diagnose stroke	not studied	all strokes are reviewed by at least 2 Prevention Regimen for Effectively Avoiding Second Strokes Trial study adjudicators
Di Tullio 2013[11]	stroke defined by Trial of Org 10172 in Acute Stroke Treatment criteria. Diagnosis of ischemic stroke was determined by two neurologists independently, and Northern Manhattan Study principal investigators adjudicated disagreements	not studied	follow-up annually by telephone; any vascular event or neurological or cardiac symptoms triggered an in-person assessment; active hospital surveillance of admission and discharge) codes was performed.
Miwa 2013[12]	an acute disturbance of focal neurological dysfunction with symptoms lasting >24 hours (or resulting in earlier death) and thought to be a result of either cerebral infarction	an acute disturbance of focal neurological dysfunction with symptoms lasting >24 hours (or resulting in earlier death) and thought to be a result of either cerebral hemorrhage.	outpatient periodic visits and, in case of missed appointment follow-up, telephone interview; original medical records were also reviewed to determine the occurrence of stroke; all possible events were audited independently by 3 physicians.
Windham 2015[13]	evidence of sudden or rapid onset of neurologic symptoms that persisted for more than 24 hours or led to death with no other apparent cause, such as trauma, tumor, infection, or anticoagulation	any one of the following criteria: CT or MRI with intraparenchymal hematoma; demonstration at autopsy or surgery; or at least 1 major or 2 minor neurologic deficits, bloody spinal fluid on lumbar puncture, no CT or MRI with or without cerebral angiography demonstrating an avascular mass effect, and no evidence of aneurysm or arteriovenous malformation	annual follow-up interviews and community surveillance, including medical record reviews; cases were reviewed separately using a computerized algorithm and a physician reviewer

CT = computed tomography; MRI = magnetic resonance imaging

Supplemental Table V: Silent Brain Infarction MRI Test Results and Stroke Outcomes

Study Number	Study First Author and Year	Mean Follow-Up (Mo)	Number of Subjects with MRI evidence of SBI at baseline	Number of Subjects without MRI evidence of SBI at baseline	All Strokes in SBI Positive Test Group	Ischemic Strokes in SBI Group	Hemorrhagic Strokes in SBI Group	Unknown or Unclassifed Stroke Subtype in SBI Group	All Strokes in no SBI Group	Ischemic Strokes in no SBI Group	Hemorrhagic Strokes in no SBI Group	Unknown or Unclassifed Stroke Subtype in no SBI Group	Adjusted All Stroke risk metric	Adjustments for which covariates	Magnitude of Adjusted All Stroke Risk Metric (HR or OR) in presence of SBI at baseline	Adjusted All Stroke 95% CI	Adjusted All Stroke p-value
1	Bernick 2001[1]	50.4	923	2401	67	57	10		92	74	13	5	HR	age, sex, systolic blood pressure, diastolic blood pressure, atrial fibrillation, left ventricular hypertrophy, fasting insulin, common carotid artery wall thickness, myocardial infarction history	1.52	1.10-2.10	0.051
2	Kario 2001[2]	42	282	303	38	not available	not available		7	not available	not available		RR	not specified, adjusted relative risks and 95% CI were calculated using Cox regression analysis	4.63	2.04-10.5	0.003
3	Naganuma 2005[3]	40.2	59	60	10	6	4		0	0	0		HR	not specified, adjusted HR obtained with a multivariate Cox proportional hazards taking into account 11 clinical variables	7.33	1.27-42.25	0.026
4	Bokura 2006[4]	75.6	380	2304	48	32	15	1	43	24	17	2	OR	age, sex hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol use, family history of stroke	3.66	2.28-5.89	<0.0001
5	Debette 2010[5]	110.4*	224*	1862*	16*	15*	not available		51	42	not available		HR	age, sex, systolic blood pressure, current smoking, diabetes, history of cerebrovascular disease	2.3*	1.30-4.06*	0.004*
6	Putaala 2011[6]	104.4	86	569	19*	18	1*		62*	54	8*		HR*	age, sex, hypertension, history of transient ischemic attack, diabetes, stroke etiology, silent brain infarcts, and leukoaraiosis	1.62*	0.93-2.82*	0.087*
7	Umemura 2011[7]	72	46	144	7*	6*	1		6*	6*	0*		not provided	not applicable	not applicable	not applicable	not applicable
8	Gioia 2012[8]	25.7	48	122	11	11	0		8	8	0		HR	age, sex, hypertension, diabetes, dyslipidemia, coronary artery disease, tobacco use, alcohol use, and chronic renal failure	3.2	1.2-8.7	0.02
9	Poels 2012[9]	120	210	797	42	25*	5*	12*	57	34*	7*	16*	HR	age, sex, smoking, systolic blood pressure, antihypertensive treatment, systolic blood pressure X antihypertensive treatment, diabetes, atrial fibrillation, left ventricular hypertrophy, and coronary heart disease	2.5	1.7-3.9	not provided
10	Weber 2012[10]	30	207	207	27	24	3		19	17	2		OR	patients with and without SBI were matched on age and sex	1.42	0.79-2.56	0.24
11	Di Tullio 2013 (Northern Manhattan Study)[11]	85.2	192*	1043*	22*	not available	not available		49*	not available	not available		HR	age, sex, race-ethnicity, education, medical insurance status, body mass index, smoking, physical activity, moderate alcohol drinking, hypertension, diabetes, hypercholesterolemia, history of atrial fibrillation, coronary artery disease, and myocardial infarction	1.9	1.1-3.3	0.014
12	Miwa 2013[12]	57.6	130*	334*	12*	9*	3*		9*	7*	2*		not provided	not applicable	not applicable	not applicable	not applicable
13	Windham 2015[13]	174	220	1611	40	not available	not available		95	not available	not available		HR	age, sex, race–center, education level, body mass index, smoking, alcohol use, diabetes, systolic and diastolic blood pressures, antihypertensive medication use, heart disease, statin use, high- and low-density lipoprotein cholesterol levels, and triglyceride level.	2.54	1.70-3.79	<.001

*data obtained via direct correspondence with study authors

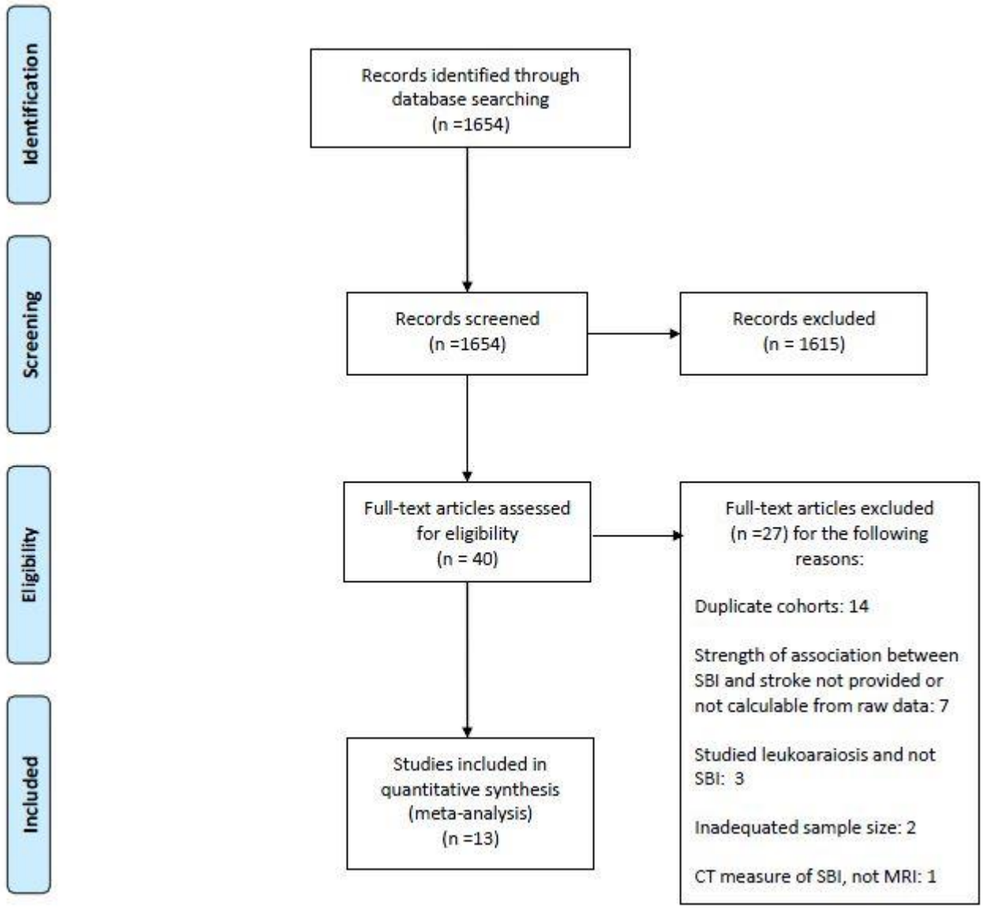
MRI = magnetic resonance imaging; SBI = silent brain infarction; CI = confidence interval; HR = hazard ratio; OR = odds ratio;

Supplemental Table VI: Results of Risk of Bias Questions to Assess the Quality of Included Studies

Type of Bias:	**Selection**			**Detection**				**Misclassification**	**Reporting**	**Attrition**	**Confounding**
Question:	Was the study sample randomly selected or a community-dwelling population to minimize the risk of selection bias?	Were the inclusion and exclusion criteria adequately described?	Was the study's primary objective to assess whether SBI is predictive of clinically overt stroke?	Was the study prospective in nature?	Were the investigators blinded to the clinical history of patients during ascertainment of SBI?	Did more than one investigator assess for the presence of SBI?	Were investigators blinded to SBI status when determining stroke outcomes?	Did the investigators describe a method by which SBI was differentiated from dilated perivascular spaces?	Did more than one investigator assess for stroke outcomes?	Were losses to follow up systematically recorded and reported?	Were data adjusted for covariate risk factors to minimize the risk of confounding bias?
Answer:	Yes (+) or no (-)	Yes (+) or no (-)	Yes (+) or no (-)	Yes (+) or no (-)	Yes (+) or no (-)	Yes (+) or no (-)	Yes (+) or no (-)	Yes (+) or no (-)	Yes (+) or no (-)*	Yes (+) or no (-)	Yes (+) or no (-)*
Bernick 2001[1]	+	+	+	+	+	+	+	+	+	-	+
Kario 2001[2]	-	+	-	+	+	+	-	-	+	+	+
Naganuma 2005[3]	-	+	+	+	+	+	-	-	+	+	+
Bokura 2006[4]	-	-	+	+	-	+	-	+	-	+	+
Debette 2010[5]	+	+	+	+	+	+	+	+	+	-	+
Putaala 2011[6]	-	+	+	+	-	+	+	+	+	+	+
Umemura 2011[7]	-	+	-	+	+	+	-	+	-	+	-
Gioia 2012[8]	-	+	+	-	+	+	+	+	-	+	+
Poels 2012[9]	+	+	+	+	+	+	-	+	+	+	+
Weber 2012[10]	-	+	-	+	+	+	+	+	+	+	+
Di Tullio 2013[11]	+	+	-	+	+	+	+	+	+	+	+
Miwa 2013[12]	-	-	-	+	+	+	-	+	+	-	-
Windham 2015[13]	+	+	+	+	+	+	-	+	+	+	+

*Minimal (+) if studies controlled for 4 of the following 6 potential stroke risk factors which are potential confounders: age, sex, hypertension, diabetes mellitus, coronary artery disease, and smoking history and hyperlipidemia by including these variables in the multivariate model or by ensuring that patients with and without SBI were similar or matched on these variables. Relatively higher risk (-) if studies did not provide adjusted risk metric demonstrating strength of association between SBI and incident stroke.

Supplemental Figure I. Study selection flow diagram.



SBI = silent brain infarction

Supplemental References

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