Supplementary Online Content

eMethods. Search terms and variables definition

eResults. Additional results regarding cerebral microbleeds locations

eTable 1. Quality criteria of included studies

eTable 2. Assessment of quality of included studies using the Newcastle-Ottawa scale

eTable 3. Summary of meta-analysis results for the association of magnetic resonance imaging (MRI) markers of vascular brain injury (VBI) with incident stroke, dementia, and death in the general population and in high-risk populations

eTable 4. Studies testing the association of burden of white matter hyperintensity (WMH) of presumed vascular origin with incident stroke

eTable 5. Studies testing the association of burden of white matter hyperintensity (WMH) of presumed vascular origin with incident dementia

eTable 6. Studies testing the association of burden of white matter hyperintensity (WMH) of presumed vascular origin with mortality

eTable 7. Studies testing the association of magnetic resonance imaging (MRI)–defined covert brain infarcts (BI) with incident stroke

eTable 8. Studies testing the association of magnetic resonance imaging (MRI)–defined covert brain infarcts (BI) with incident dementia

eTable 9. Studies testing the association of magnetic resonance imaging (MRI)–defined covert brain infarcts (BI) with mortality

eTable 10. Studies testing the association of cerebral microbleed (CMB) with incident stroke

eTable 11. Studies testing the association of cerebral microbleed (CMB) with incident dementia

eTable 12. Studies testing the association of cerebral microbleed (CMB) with mortality

eTable 13. Studies testing the association of perivascular spaces (PVS) with incident stroke

eTable 14. Studies testing the association of perivascular spaces (PVS) with incident dementia

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Search terms and variables definition

Search terms

(("white matter" or "periventricular" or "subcortical" or ("Leukoaraiosis"[Mesh] or "Leukoaraiosis/pathology"[Mesh])) or ("silent brain infarct" or "silent cerebral infarct" or "silent cerebral infarction" or "silent brain infarction" or "SBI" or "SLI" or "silent lacunar infarct" or "silent lacunar infarction" or "lacunes" or "lacunae") or ("cerebral microbleed" or "CMB" or "microhemorrhage" or "microhaemorrhage) or ("Virchow-Robin Spaces" or "VR" or "VRs" or "dilated perivascular spaces" or "enlarged perivascular spaces")) and ("Dementia" or "Alzheimer disease" or "Vascular dementia" or "Stroke" or "Brain Infarction" or "Cerebral Hemorrhage" or "Cerebral Haemorrhage" or "Death" or "Mortality" or "cognitive" or ("Stroke"[Mesh] or "Stroke/epidemiology"[Mesh]) or ("Dementia"[Mesh] or "Dementia/epidemiology"[Mesh])) and ("Magnetic Resonance Imaging"[Mesh]) and ("Risk Factors"[Mesh] or "Longitudinal Studies"[Mesh] or "Cohort Studies"[Mesh] or Prospective Studies[Mesh]).

Variable definitions

The population type was defined as "general population" when the study was carried out in a community-based setting or on participants described as "healthy", and "high-risk population" for studies carried out on individuals selected for the presence of a particular prevalent disease such as stroke, symptomatic atherosclerotic disease, mild cognitive impairment, depression, gait disorder, or in individuals at high risk for cardiovascular disease.

WMH burden was studied as a dichotomous variable (extensive vs low WMH burden) whenever possible, or as a continuous variable (volume from automated quantification or grade from a semi-quantitative visual scale) when dichotomous measures were not available. In a few studies, periventricular WMH and deep WMH were available but not the measure of total WMH. In this case we used the relative risk estimate related to periventricular WMH, which is highly correlated with total WMH.[e1] MRI-defined BI, CMB and PVS were studied as dichotomous variables, either presence versus absence or one grade or number of lesions versus others (for the latter we used the result comparing the highest category to absence whenever possible); studies analysing these variables (BI or CMB count) in a continuous manner were not included in the meta-analysis; and so were studies exploring the clinical significance of deep and lobar CMB separately only.

Stroke was defined as an acute onset focal neurological deficit of presumed vascular cause lasting at least 24 hours or causing death within 24 hours. Strokes were divided into ischemic and haemorrhagic stroke, depending on appearances on brain imaging. As the vast majority of strokes are ischemic (>80% in European populations), we also included studies with association data on ischemic stroke but no association data on all stroke in the meta-analysis of all stroke. Unless specified differently dementia was defined according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, third or fourth editions disorders,[e2,e3] and AD based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association for definite, probable, or possible AD.[e4] We did not examine the association with vascular or mixed dementia because only very few studies explored association with these dementia subtypes, with wide variations in their definition.

eResults. Additional results regarding cerebral microbleeds locations

- Association with incident stroke of *non-strictly lobar CMB*: HR=2.82 (95%CI: 1.60-5.01), p=3.53x10^{-4}; 2 studies, N=745

- Association with incident dementia of *strictly lobar CMB*: HR=1.57 (95%CI: 0.87-2.83), p=0.13; 2 studies, N=1,690

- Association with incident dementia of *strictly nonlobar CMB*: HR=1.91 (95%CI: 0.81-4.51), p=0.14; 2 studies, N=1,628

- Association with incident dementia of *non-strictly nonlobar CMB*: HR=2.33 (95%CI: 0.96-5.66), p=0.06; 2 studies, N=4,510

- Association with mortality of *strictly lobar CMB*: HR=1.12 (95%CI: 0.81-1.54), p=0.49; 2 studies, N=5,543

- Association with mortality of *non-strictly nonlobar CMB*: HR=1.54 (95%CI: 1.11-2.15), p=0.01; 2 studies, N=5,287

eTable 1. Quality criteria of included studies

Paper	Loss to follow-up	Surveillance for diagnosis of incident events	Definition used for outcome events	Information on event subtypes	Effect estimate available	Analysis taking into account time to event
Akoudad, 2016 [e5]	none reported	Home interviews and physical and laboratory examinations every 4 years	DSM-III-R, NINCDS-ADRDA	yes (dementia type)	yes	yes
Akoudad, 2015 [e6]	5.1% of potential person-years	Automated linkage of general practitioners' medical records with the study database, contact with nursing homes or treating physicians for individuals who moved outside the study district or lived in nursing homes	WHO criteria	yes (ischemic stroke and hemorrhagic stroke)	yes	yes
Akoudad 2013 [e7]	0%	Municipal health authorities (monthly basis) and general practitioners in the study area (continuous basis)	death	yes (cause of death)	yes	yes
Andersen, 2017 [e8]	none reported	identification in the registries	ICD-10 codes I63, I64	yes (all ischemic stroke) / no for mortality	yes	yes
Appelros, 2005 [e9]	none reported	medical visit	WHO criteria for stroke, death	yes (ischemic stroke, lacunar stroke), death	yes	yes
Altmann-Schneider, 2011 [e10]	none reported	continuous follow-up after end of study	death	yes (cause of death)	yes	yes
Benedictus, 2015 [e11]	9.6%	Information on mortality was obtained from from the Dutch Municipal Population Register, and cause of death from Statistics Netherlands. Information on stroke was obtained by sending questionnaires to patients' general practioners	Not specified for stroke; death	yes (ischemic stroke, intracerebral hemorrhage) / yes for death (cause of death)	yes	yes
Bernick, 2001 [e12]	0%	yearly examinations and interim 6-month phone contacts + hospital records review	Stroke definitions were derived from the criteria used for the Systolic Hypertension in the Elderly Program (SHEP)	no	yes	yes
Bokura, 2011 [e13]	none reported	Questionnaire, telephone interview + confirmation with attending physician	Not detailed	yes (cerebral infarctions, intracerebral hemorrhage, subarachnoid hemorrhage, transient ischemic attack)	yes and no (some calculated by authors)	yes and no (for those calculated by authors)
Bokura, 2006 [e14]	none reported	self-reported questionnaire + telephone	not detailed + death	yes (ischemic, hemorrhagic stroke) / no for death	yes	no
Bombois, 2008 [e15]	none reported	medical visit	DSM-IV, NINCDS-ADRDA, NINDS-AIREN	yes (dementia type)	yes	yes

Boulanger, 2006 [e16]	2.5%	Phone questionnaire (Questionnaire for Verifying Stroke Free Status) every 6 months	Recurrent stroke / death	yes (ischemic stroke, hemorrhagic stroke, cause of death)	yes	yes
Boulouis, 2017 [e17]	none reported	follow-up phone calls at 3 months after enrollment and every 6 months thereafter, and systematic chart review using standardized forms	symptomatic stroke syndrome associated with neuroimaging evidence of a corresponding ICH and death of any cause	yes (hemorrhagic stroke only)	yes	yes
Charidimou, 2016 [e18]	0%	regular patients visits + systematic review of prospective database + medical and hospital records review	Recurrent stroke, not specified	yes (ischemic stroke, hemorrhagic stroke)	yes (except for associations between CMB [dichotomized] and stroke and stroke subtypes, which were calculated by authors)	yes (no for mixed + vascular dementia, no for CMB [dichotomized] and strokes and stroke subtypes)
Conijn, 2011 [e19]	0.3%	Questionnaire every 6 months	Stroke: described in supplement which is not accessible /death	yes (ischemic stroke only) / yes (cause of death)	yes	yes
CROMIS-1 (Wilson, 2016 [e20])	>10%	NA	standardised	yes (ischemic stroke only)	yes	no
Debette, 2010 [e21]	none reported	medical visit + continuous monitoring	WHO criteria, DSMIV, NINCDS-ADRDA + death	yes (ischemic, hemorrhagic stroke; dementia type; cause of death)	yes	yes
DeCarli, 2004 [e22]	0%	medical visit	CDR>1.0	yes (dementia type)	yes	yes
Ding, 2017 [e23]	none reported	follow-up examination	DSM-IV, NINCDS-ADRDA, ADDTC	yes (dementia type)	yes	no
Ding, 2017 [e109]	Participants selected on availabilyt of follow up cognitive measures	follow-up examination	DSM-IV, NINCDS-ADRDA, ADDTC	yes (dementia type)	no	no
Di Tullio, 2013 [e24]	2% at 5 years, 2.7% at 10 years	Annual telephone call	TOAST	yes (ischemic stroke)	yes (provided by Gupta et al)	yes (provided by Gupta et al)
Eckerström, 2015 [e25]	none reported	follow up visits	Global Deterioration Scale, NINCDS-ADRDA, Erkinjuntti criteria	yes (dementia type)	yes (calculated by authors for mixed + vascular dementia)	yes (no for mixed + vascular dementia)

Study						
Fan, 2003 [e26]	3.3%	telephone interview	Recurrent stroke: acute onset of focal neurological deficit lasting 24 hours presumably of vascular origin after investigation to exclude other causes /death	yes (ischemic stroke, intracerebral hemorrhage) / no for death	no (calculated by authors)	no
Firbank, 2007 [e27]	0% (only patients with 2 year assessment included)	medical visit	DSM-IV, CAMCOG	no	yes	yes
Fluri, 2012 [e28]	none reported	no details	Criteria of the Oxfordshire Community Stroke Project + TOAST	yes (ischemic stroke only)	yes	no
Folsom 2012 [e29]	0%	Yearly phone interview + reported deaths + relevant hospital records (ARIC); semi-annual phone interview + reported death + relevant hospital records (CHS)	National Survey of Stroke criteria	yes (intraparenchymal hemorrhage only)	yes	yes
Fu, 2005 [e30]	4.8%	medical visit or telephone	WHO criteria / death	yes (ischemic, hemorrhagic stroke) / death	yes	yes
Gerdes 2006 [e31]	none reported	self-reported questionnaire + telephone	Ischemic stroke defined as acute neurologic deficit persisting >= 1week and hemorrhage ruled out by early CT scan	yes (ischemic stroke only)	yes	yes
Geroldi 2006 [e32]	none reported	medical visit	DSM-IV, NINCDS-ADRDA	yes (dementia type)	yes	no
Gutierrez 2017 [e33]	negligible	Annual telephone interviews and/or in-person visits if the participant screens positive for a predefined outcome	WHO criteria / death (causes of vascular death include ischemic stroke, myocardial infarction, heart failure, pulmonary embolus, cardiac arrhythmia and other vascular causes)	no for strokes; yes for death (vascular or non vascular death)	yes	yes
Heidelberg (Wilson, 2016 [e20])	<10%	NA	standardised	yes (ischemic stroke only)	yes	no
Henneman, 2009 [e34]	none reported	Questionnaires sent to patients' general practioners	death	no	yes	yes
Huang, 2008 [e35]	12.6%	no details	no details	yes (ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage)	yes (risk ratio provided by Wilson et al, Neurology 2016, for intracerebral hemorrhage)	no

Ikram, 2009 [e36]	1.6%	Municipal health authorities (biweekly basis) + continuous report by general practioners	WHO criteria, DSM-III	yes (cause of death)	yes	yes
Imaizumi, 2014 [e37]	none reported	Readmission or retreatment	Recurrent stroke type diagnosed based on radiological findings	yes (ischemic stroke, intracerebral hemorrhage)	yes (except for associations between CMB and stroke subtypes, which were provided by Wilson et al, Neurology 2016)	no
Jeon, 2007 [e38]	none reported	follow up GRE MRI	newly appeared dark signal with a diameter >5 mm on follow-up GRE with or without corresponding symptoms	yes (recurrent intracerebral hemorrhage only)	no (calculated by authors)	no
Jokinen, 2009 [e39]	11.4%	medical visit	DSM-IV	no	yes	no
Kaffashian, 2016 [e40]	only individuals with fu for stroke and dementia and at least one fu visit were included	Regular examinations	WHO criteria /DSM-IV, NINCDS-ADRDA	yes (fatal) / yes (dementia type)	yes	yes
Kaffashian, 2016 [e41]	only individuals with fu for stroke and dementia and at least one fu visit were included	no details	New focal neurological deficit of sudden or rapid onset, of presumed vascular origin, that persisted for >24 hours, or leading to death, subtyping done by expert panel	yes (ischemic stroke [+subtypes]; hemorrhagic stroke)	yes	yes
Kang, 2012 [e42]	none reported	patient interview in outpatient clinic every 3 months, telephone (every 3 months for the first year and then every 6 months)	Confirmed by CT or MRI	yes	yes (provided by Charidimou et al)	no
Kantarci, 2009 [e43]	none reported	medical visit	DSM-III-R	yes (dementia type)	yes	yes

Study	Loss to follow-up	Follow-up method	Outcome definition	Outcome subtypes		
Kario, 2001 [e44]	2.0%	intermittent review of patients' medical records + telephone interviews	Documented in medical records or confirmed by general practitioner	yes (ischemic, hemorrhagic stroke)	yes	yes
Kerber 2006 [e45]	5.5%	medical visit, death certificates	death	yes (cause of death)	yes	yes
Kim, 2015 [e46]	only individuals with relevant fu were included	Follow-up evaluations	DSM-IV, NINDS-ADRDA, NINDS-AIREN, Erkinjuntti	yes (dementia type)	yes	yes
Korf, 2004 [e47]	7.4%	medical visit	DSM-IV	yes (dementia type)	yes	yes
Kuller, 2007 [e48]	none reported	medical visit, death certificates	death	yes (cause of death)	yes	yes
Kuller, 2004 [e49]	none reported	medical visit + surveillance phone call	WHO criteria	yes (ischemic, hemorrhagic stroke; ischemic stroke subtype)	yes	yes
Kuller, 2003 [e50]	none reported	medical visit or self-reported questionnaire + telephone	not specified	yes (dementia type)	yes	yes
Kwa, 2013 [e51]	1.0%	Telephone interview every 6 months	Imaging data to classify as ischemic or hemorrhagic stroke, Oxford classification for ischemic stroke subtyping	yes (ischemic stroke, intracerebral hemorrhage)	yes	yes
Lau, 2017 [e52]	none reported	OXVASC: follow up by a research nurse or physician after 1, 3, 6, 12, 24, 60, and 120 months after the index event. HKU: follow up by a clinician every 3 to 6 months, or more frequently if clinically indicated.	recurrent stroke : sudden new neurological deficit fitting the definition of ischaemic stroke, or intracerebral haemorrhage, occurring after a period of unequivocal neurological stability and not attributable to cerebral oedema, mass effect, or haemorrhagic transformation of the incident cerebral infarction. Vascular death : death due to lethal cardiac arrhythmias, acute coronary syndrome, congestive heart failure, fatal stroke, pulmonary embolism, aortic dissection or unexplained sudden death	yes (ischemic stroke, intracerebral hemorrhage) / yes (vascular and non vascular mortality)	yes	yes

Levy, 2003 [e53]	none reported	medical visit, Social Security death index, obituary newspaper	death	no	yes	yes
Lim, 2015 [e54]	0%	outpatient clinic or telephone interview with a structured questionnaire	no details	yes (ischemic strokes)	yes	yes
Melkas, 2012 [e55]	0%	extensive national registers kept by the National Institute for Health and Welfare + ICD codes obtained from National Care Register	ICD codes	yes (recurrent ischemic or hemorrhagic stroke)	yes	yes
Miwa, 2015 [e56]	0%	Regular examinations	DSM-III-R, NINCDS-ADRDA, NINDS-AIREN	yes (dementia type)	yes	yes
Miwa, 2014 [e57]	0%	Regular examinations + medical records + interviews	DSM-III-R, NINCDS-ADRDA, NINDS-AIREN	yes (dementia type)	yes	yes
Miwa, 2010 [e58]	none reported	medical records review + clinic visit + telephone interview	sudden onset of a neurologic deficit that persisted for 24 hours + confirmation by CT / MRI, TOAST	yes (ischemic stroke, hemorrhagic stroke, subarachnoid hemorrhage)	yes	yes
Mok, 2009 [e59]	0%	Follow-up visits every 6 months	no details	yes (intracerebral hemorrhage; lacunar infarction; cardioembolic infarction; undefined)	yes and no (Risk ratio for CMB-ICH or IS, provided by Wilson et al, Neurology 2016)	yes and no (for CMB-ICH or IS)
Naka, 2006 [e60]	1.1%	no details	NINDS classification	yes (ischemic, hemorrhagic stroke; ischemic stroke subtype)	yes	yes
Nam, 2017 [e61]	none reported [a]	no details	TOAST	yes (ischemic stroke and subtypes)	yes	yes
Nishikawa, 2009 [e62]	49.0%	outpatient visits	For stroke: based on neurological findings and neuroradiological examination. For cerebral infarction: criteria of the National Institute of Neurologic disorders and stroke.	yes (ischemic stroke; intracerebral hemorrhage)	yes	yes
Oksala, 2009 [e63]	0.5%	Statistics Finland, death certificates	death, ICD9 and ICD10 causes	yes (cause of death)	yes	yes
Orken, 2013 [e64]	none reported	Follow-up MRI	no details	yes (hemorrhagic stroke)	yes (provided by Charidimou et al)	no
OXVASC (Wilson, 2016 [e20])	<10%	NA	standardised	yes (ischemic stroke, hemorrhagic stroke)	yes	no

Pasquini, 2016 [e65]	n.a	patient follow-up visit (at 6 months and then every year)	WHO criteria	yes (hemorrhagic stroke)	yes (provided by Charidimou et al)	no
Poels, 2012 [e66]	3.1%	review of medical records + continuous monitoring through linkage of study database with files from general practioners (for about half of the participants) + regular review of nursing home doctors' and general practitioners' files	no details	yes (ischemic, hemorrhagic stroke)	yes	yes
Prasad, 2011 [e67]	0% (inclusion criteria comprised availability of follow-up cognitive evaluations for a minimum of 18 months)	no details (clinical follow-up)	DSM-IV, NINCDS-ADRDA	yes (dementia type)	yes	no
Prins, 2013 [e68]	0%	CDR assessment at 3, 6, 9, 12, 18, 21 and 24 months	CDR >=1.0	no	yes	yes
Prins 2004 [e69]	none reported	medical visit + continuous monitoring	DSM-IIIR, NINCDS-ADRDA, NINDS-AIREN	yes (dementia type)	yes	yes
Putaala, 2011 [e70]	1%	structured telephone interview + letters (if not reachable by phone) + patients records from hospital and primary care / mortality data obtained from Statistics Finland	episode of focal neurologic deficits with acute onset and lasting 24 hours or if lasting 24 hours, with imaging evidence of stroke corresponding with current symptoms; TOAST and Bamford criteria for stroke subtyping / death	yes (ischemic stroke, hemorrhagic stroke) - ischemic stroke only for WMH / yes (cause of death)	yes	yes
Romero, 2017 [e72]	participants with lack of follow-up information were not included in the study sample	clinic evaluation, biennal questionnaires, annual telephone health history update, report by participant or relative or care provider	DSM-IV, NINCDS-ADRDA, NINDS-AIREN	yes (dementia type)	yes	yes
Romero, 2017 [e73]	participants with lack of follow-up information were not included in the study sample	no details	death	yes (cause of death)	yes	yes

Samarasekera, 2015 [e74]	n.a.	multiple sources	ICD-10	yes (hemorrhagic stroke)	yes (provided by Charidimou et al)	no
Shoamanesh, 2017 [e75]	none reported	Visit at least every 3 months	Ischemic stroke was clinically defined as a focal neurologic deficit of sudden onset persisting for >24 hours, and without evidence of hemorrhage on neuroimaging. Intracranial hemorrhages included those in intracerebral, subdural, epidural, and subarachnoid locations as documented on neuroimaging / all cause mortality	yes (ischemic stroke, intracerebral hemorrhage)	yes	yes
Sigurdsson, 2017 [e76]	0%	Follow-up exams + vital statistics and hospital records (using nursing and home-based Resident Assessment Instrument)	DSM-IV	no	yes	no
Smith, 2008 [e77]	none reported	medical visit	DSM-IV, NINCDS-ADRDA, NINDS-AIREN	yes (dementia type)	yes	yes
Smith, 2004 [e78]	none reported	telephone interview + review of medical records	recurrent intracerebral hemorrhage	yes (intracerebral hemorrhage)	yes	yes
Song, 2013 [e79]	none reported	medical chart review, telephone interview, and death certificates from the Korean National Statistical Office	no details	yes (intracerebral hemorrhage, ischemic stroke data provided by Wilson et al, Neurology 2016)	yes for intracerebral hemorrhage; provided by Wilson et al, Neurology 2016, for ischemic stroke	yes for intracerebral hemorrhage, no for ischemic stroke

Soo, 2008 [e80]	2.3%	clinical interviews at maximum 6 months intervals	Stroke diagnosis based on symptoms, physical examination and CT findings; ischemic stroke: acute onset of neurological symptoms, physical findings and radiological features /death	yes (recurrent ischemic stroke, intracerebral hemorrhage) / yes (cause of death)	yes for intracerebral hemorrhage (provided by Wilson et al, Neurology 2016, for ischemic stroke); yes for death from subsequent intracerebral hemorrhage - CMB	yes for ICH, no for ischemic stroke; no for death from subsequent intracerebral hemorrhage - CMB
Staekenborg, 2009 [e81]	none reported	medical visit	NINCDS-ADRDA, NINDS-AIREN, Neary and Snowden, McKeith	yes (dementia type)	yes	yes
Tapiola, 2008 [e82]	none reported	medical visit	DSM-IV, NINCDS-ADRDA	yes (dementia type)	yes	yes
Thijs, 2010 [e83]	1.6%	follow-up examination 3-6 months after hospital admission + phone interview every 6 months	A recurrent ischemic stroke was defined as the sudden onset of a new focal neurological deficit lasting either 24 hours or leading to death with absence of hemorrhage on acute CT or with a new ischemic lesion on diffusion-weighted imaging. Intracerebral hemorrhage was defined as the sudden onset of a new neurological deficit with hemorrhage within the brain parenchyma. Unclassified stroke was defined as the sudden onset of a new focal neurological deficit lasting 24 hours or leading to death in which cerebral imaging or autopsy was not obtained.	yes (ischemic stroke, intracerebral hemorrhage)	yes for all strokes, no for stroke subtypes (calculated by authors)	yes for all strokes, no for stroke subtypes
Tsushima, 2003 [e84]	29.4%	no details	spontaneous intracerebral bleeding confirmed by CT without evidence of any kind of vascular	yes (recurrent intracerebral hemorrhage only, no	no	no

			malformation, cavernous angioma, brain tumor, surgical intervention, or trauma as the source of the hematoma	patient had subsequent ischemic stroke)		
Umemura, 2011 e85	11.1%	NA	no details	yes (ischemic stroke, hemorrhagic stroke)	no (calculated by authors based on informations provided by Gupta et al., Stroke 2016)	no
van der Holst, 2016 e86	none reported	data on mortality obtained from Dutch Municipal Personal Records database + cause of death obtained from general practitioner or treating physician	Cause of death classified according to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)	yes (cause of death)	yes	yes
van Straaten, 2008 e87	none reported	medical visit	NINCDS-ADRDA	yes (dementia type)	yes	yes
Van Uden, 2016 e110	0.6%	Follow-up assessment or medical records if follow-up asessment not possible	DSM-IV, NIA-AA, NINDS-AIREN	Yes (dementia type)	Yes and no (for subtypes, calculated by authors)	Yes and no for calculations performed by authors
Weber 2012 e88	none reported	no details	no details	yes (ischemic stroke, hemorrhagic stroke) / no for death	yes and no (for stroke subtypes, calculated by authors)	no
Weinstein, 2013 e89	participants with lack of follow-up information were not included in the study sample	biennal examinations / biennal MMSE screening (poor performance leading to further evaluation)	stroke was defined as an acuteonset focal neurological deficit of presumed vascular pathogenesis lasting ≥24 hours. Ischemic stroke was diagnosed if a focal neurological deficit was documented, imaging showed an infarct that correlated with the clinical deficit, or an infarct was documented at autopsy. Hemorrhagic stroke was defined on the basis of brain imaging, lumbar puncture, or autopsy/ NINCDS-ADRDA	no for strokes; yes for dementia (Alzheimer disease only)	yes	yes

Vermeer, 2003 [e90]	0%[†]	medical visit + continuous monitoring	WHO criteria	yes (ischemic, hemorrhagic stroke)	yes	yes
Vermeer, 2003 [e104]	0%[†]	Follow-up visit + medical records reviews	DSM-III-R, NINCDS-ADRDA, NINDS-AIREN	no (all dementia)	yes	yes
Windham, 2015 [e91]	none reported	yearly phone interviews + hospital record reviews and medical chart abstraction / death information was obtained by contacts with next of kin, hospital records, state death records, and the National Death Index	National Survey of Stroke criteria; Symptoms plus acute infarctions or absence of hemorrhage on imaging defined ischemic strokes; Hemorrhagic strokes met 1 of the following criteria: (1) CT or MRI with intraparenchymal hematoma; (2) demonstration at autopsy or surgery; or (3) at least 1 major or 2 minor neurological deficits; a bloody spinal fluid on lumbar puncture; and no CT or MRI, with or without cerebral angiography demonstrating an avascular mass effect and no evidence of aneurysm or arteriovenous malformation /death	yes (ischemic stroke; hemorrhagic stroke); yes (cause of death)	yes	yes
Yamauchi, 2002 [e92]	none reported	medical visit	non specified / death	yes (ischemic, hemorrhagic stroke) / no for death	yes	yes
Yamashita, 2010 [e93]	none reported	review of patients' clinical charts + detailed questioning by email	DSM-IV/death	no for dementia /no for death	no (calculated by authors)	no
Zhu, 2010 [e94]	0%	interviews every 2 years	DSM-IV, NINCDS-ADRDA, NINDS-AIREN	no	yes	yes

GRE: gradient-echo T2*-weighted image: fu: follow-up; [a] specified in article: about 69% of patients had completed a 2-year follow-up (80% of them had completed a 1-year follow-up); [†] individuals did not attend follow-up visits but medical records review of all included participants was performed for incident event

eTable 2. Assessment of quality of included studies using the Newcastle-Ottawa scale

Paper	Selection				Comparability	Outcome			SCORE
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis [a]	Assessment of outcome	Was follow-up long enough for outcomes to occur [b]	Adequacy of follow up of cohorts [c]	
Akoudad, 2016 e5	*	*	*	*	**	*	*	*	9
Akoudad, 2015 e6	*	*	*	*	**	*	*	*	9
Akoudad 2013 e7	*	*	*	*	**	*	*	*	9
Andersen, 2017 e8	*	*	*	*	**	*	*	*	9
Appelros, 2005 e9	*	*	*	*	**	*	*	*	9
Altmann-Schneider, 2011 e10	*	*	*	*	**	*	*	*	9
Benedictus, 2015 e11	*	*	*	*	**	*	*		8
Bernick, 2001 e12	*	*	*	*	**	*	*	*	9
Bokura, 2011 e13	*	*	*	*	*		*	*	7
Bokura, 2006 e14	*	*	*	*	**		*	*	8
Bombois, 2008 e15	*	*	*	*	**	*	*	*	9
Boulanger, 2006 e16	*	*	*	*		*	*	*	7
Boulouis, 2017 e17	*	*	*	*		*	*	*	7

Charidimou, 2016 [e18]	*	*	*	*		*	*	*	7
Conijn, 2011 [e19]	*	*	*	*	**		*	*	8
CROMIS-1 (Wilson, 2016 [e20])	*	*	*	*	NA		*	NA	5
Debette, 2010 [e21]	*	*	*	*	**	*	*	*	9
DeCarli, 2004 [e22]	*	*	*	*	**	*	*	*	9
Ding, 2017 [e23]	*	*	*	*	**	*	*	*	9
Ding, 2017 [e109]	*	*	*	*		*	*	*	7
Di Tullio, 2013 [e24]	*	*	*	*	**	*	*	*	9
Eckerström, 2015 [e25]	*	*	*	*		*	*	*	7
Fan, 2003 [e26]	*	*	*	*			*	*	6
Firbank, 2007 [e27]	*	*	*	NA		*	*	*	6
Fluri, 2012 [e28]	*	*	*	*		*		*	6
Folsom 2012 [e29]	*	*	*	*	**	*	*	*	9
Fu, 2005 [e30]	*	*	*	*	**	NA	*	*	8
Gerdes 2006 [e31]	*	*	*			*	*	*	6
Geroldi 2006 [e32]	*	NA	*	*		*	*	*	6
Gutierrez 2017 [e33]	*	*	*	*	**	*	*	*	9

Study								Score
Heidelberg (Wilson, 2016 e20)	*	*	*	*	NA		*	NA	5
Henneman, 2009 e34	*	*	*	*	**	*	*	*	9
Huang, 2008 e35	*	*	*	*			*		5
Ikram, 2009 e36	*	*	*	*	*	*	*	*	8
Imaizumi, 2014 e37	*	*	*	*	**	*	*	*	9
Jeon, 2007 e38	*	*	*	*		*	*	*	7
Jokinen, 2009 e39	*	*	*		**	*	*		7
Kaffashian, 2016 e40	*	*	*	*	*	*	*	*	8
Kaffashian, 2016 e41	*	*	*	*	**	*	*	*	9
Kang, 2012 e42	*	*	*	*	NA	*	*	*	7
Kantarci, 2009 e43	*	*	*	*	**	*	*	*	9
Kario, 2001 e44	*	*	*	*		*	*	*	7
Kerber 2006 e45	*	*	*	*	**	*	*		8
Kim, 2015 e46	*	*	*	*	**	*	*	*	9
Korf, 2004 e47	*	*	*	*		*	*	*	7
Kuller, 2007 e48	*	*	*	*	**	*	*	*	9
Kuller, 2004 e49	*	*	*	*	**		*	*	8
Kuller, 2003 e50	*	*	*	*	**		*	*	8

Kwa, 2013 [e51]	*	*	*	*	*		*	*	7
Lau, 2017 [e52]	*	*	*	*	**	*	*		8
Levy, 2003 [e53]	*	*	*	*	*	*	*		7
Lim, 2015 [e54]	*	*	*	*	*	*		*	7
Melkas, 2012 [e55]	*	*	*	*	*	*	*	*	8
Miwa, 2015 [e56]	*	*	*	*	**	*	*	*	9
Miwa, 2014 [e57]	*	*	*	*	**	*	*	*	9
Miwa, 2010 [e58]	*	*	*	*	**	*	*		8
Mok, 2009 [e59]	*	*	*	*		*	*	*	7
Naka, 2006 [e60]	*	*	*	*	**		*	*	8
Nam, 2017 [e61]	*	*	*	*			*		5
Nishikawa, 2009 [e62]	*	*	*	*	**	*	*		8
Oksala, 2009 [e63]	*	*	*	*	**	*	*	*	9
Orken, 2013 [e64]	*	*	*	*		*	*		6
OXVASC (Wilson, 2016 [e20])	*	*	*	*	NA		*	NA	5
Pasquini, 2016 [e65]	*	*	*	*	NA	*	NA		5
Poels, 2012 [e66]	*	*	*	*	**	*	*	*	9

Study									
Prasad, 2011 e67	*	*	*	*	-	*	*	*	7
Prins, 2013 e68	*	*	*	*	*	*	*	*	8
Prins 2004 e69	*	*	*	*	*	*	*		7
Putaala, 2011 e70	*	*	*	*	**	*	*	*	9
Romero, 2017 e72	*	*	*	*	**	*	*	*	9
Romero, 2017 e73	*	*	*	*	**		*	*	8
Samarasekera, 2015 e74	*	*	*	*	NA	*			5
Shoamanesh, 2017 e75	*	*	*	*	**	*	*		8
Sigurdsson, 2017 e76	*	*	*	*	**	*	*	*	9
Smith, 2008 e77	*	*	*	*		*	*		6
Smith, 2004 e78	*	*	*	*		*	*		6
Song, 2013 e79	*	*	*	*	*	*	*		7
Soo, 2008 e80	*	*	*	*		*	*	*	7
Staekenborg, 2009 e81	*	*	*	*	*	*	*		7
Tapiola, 2008 e82	*	*	*	*		*	*		6
Thijs, 2010 e83	*	*	*	*		*	*	*	7
Umemura, 2011 e85	*	*	*	*			*		5
van der Holst, 2016 e86	*	*	*	*	**	*	*		8

Study									Score
van Straaten, 2008 [e87]	*	*	*	*	*	*	*		7
Van Uden, 2016, [e110]	*	*	*	*	**	*	*	*	9
Weber, 2012 [e88]	*	*	*	*	*		*		6
Weinstein, 2013 [e89]	*	*	*	*	**	*	*	*	9
Vermeer, 2003 [e90]	*	*	*	*	**	*	*	*	9
Vermeer, 2003 [e104]	*	*	*	*	**	*	*	*	9
Windham, 2015 [e91]	*	*	*	*	**	*	*		8
Yamauchi, 2002 [e92]	*	*	*	*		*	*		6
Yamashita, 2010 [e93]	*	*	*	NA		*	*		5
Zhu, 2010 [e94]	*	*	*	*		*	*	*	7

[a] please see the eTables below for adjustment variables for each study in each category; The study is assigned one star if the HR is adjusted for age and sex (sex adjustment is only needed if both men and women are included in the study). Two stars if further adjusted for education when the outcome is dementia/AD or for at least one more risk factors (e.g., smoking, hypertension, or diabetes) if the outcome is stroke or death. [b] The study was assigned a star if follow-up was 1 year or longer ; [c] Loss to follow-up threshold was defined as <5% ; NA : information not available, therefore we have not granted a star

Newcastle-Ottawa scale for cohort studies : Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability
Selection
1) Representativeness of the exposed cohort
a) truly representative of the average _____ (describe) in the community *
b) somewhat representative of the average _____ in the community *
c) selected group of users eg nurses, volunteers
d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
a) drawn from the same community as the exposed cohort *

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

<u>3) Ascertainment of exposure</u>

a) secure record (eg surgical records) *

b) structured interview *

c) written self report

d) no description

<u>4) Demonstration that outcome of interest was not present at start of study</u>

a) yes *

b) no

Comparability

<u>1) Comparability of cohorts on the basis of the design or analysis</u>

a) study controls for _____ (select the most important factor) *

b) study controls for any additional factor * (This criteria could be modified to indicate specific   control for a second important factor.)

Outcome

<u>1) Assessment of outcome</u>

a) independent blind assessment *

b) record linkage *

c) self report

d) no description

<u>2) Was follow-up long enough for outcomes to occur</u>

a) yes (select an adequate follow up period for outcome of interest) *

b) no

<u>3) Adequacy of follow up of cohorts</u>

a) complete follow up - all subjects accounted for *

b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an   adequate %) follow up, or description provided of those lost) *

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement

eTable 3. Summary of meta-analysis results for the association of magnetic resonance imaging (MRI) markers of vascular brain injury (VBI) with incident stroke, dementia, and death in the general population and in high-risk populations

Incident event	Subgroup	MRI-marker of covert VBI		
		Extensive WMH burden	BI presence	CMB presence
Stroke	General population	HR=2.43 [1.96-3.01], p=4.93x10^{-16}	HR=2.30 [1.80-2.93], p=2.06x10^{-11}	HR=2.62 [1.08-6.36], p=3.32x10^{-2}
		6 studies, N=9,731, 511 events	*7 studies, N=13,886, 688 events*	*2 studies, N=6,861, 137 events*
	High-risk population	HR=2.55 [1.73-3.77], p=2.47x10^{-6}	HR=2.86 [1.49-5.49], p=1.59x10^{-3}	HR=1.92 [1.47-2.50], p=1.47x10^{-6}
		11 studies, N=4,798, 538 events	*5 studies, N=2,126, 193 events*	*20 studies, N=8,832, 694 events*
Ischemic stroke	General population	HR=2.16 [1.60-2.93], p=6.04x10^{-7}	HR=2.27 [1.62-3.18], p=1.89x10^{-6}	HR=2.38 [0.76-7.39], p=0.14
		3 studies, N=4,993, 420 events	*3 studies, N=5,664, 216 events*	*2 studies, N=6,861, 94 events*
	High-risk population	HR=2.78 [1.43-5.40], p=2.56x10^{-3}	HR=2.04 [1.32-3.16], p=1.37x10^{-3}	HR=1.87 [1.32-2.64], p=4.00x10^{-4}
		6 studies, N=2,327, 276 events	*3 studies, N=1,209, 117 events*	*18 studies, N=6,264, 365 events*
Intracerebral hemorrhage	General population	HR=4.73 [2.67-8.40], p=1.07x10^{-7}	HR=5.39 [2.56-11.35], p=9.24x10^{-6}	HR=16·77 [1.89-148.79], p=1.13x10^{-2}
		3 studies, N=6,592, 58 events	*3 studies, N=7,778, 74 events*	*2 studies, N=6,861, 21 events*
	High-risk population	HR=1.92 [0.58-6.37], p=0.29	HR=1.17 [0.30-4.57], p=0.82	HR=2.73 [1.71-4.38], p=2.84x10^{-5}
		4 studies, N=1,384, 90 events	*2 studies, N=1,069, 14 events*	*21 studies, N=7,419, 197 events*
Dementia	General population	HR=2.39 [1.49-3.84], p=3.09x10^{-4}	HR=1.37 [0.99-1.89], p=5.63x10^{-2} *	HR=1.40 [0.95-2.06], p=0.09
		4 studies, N=7,444, 642 events	*5 studies, N=9,711, 879 events*	*3 studies, N=7,713, 251 events*
	High-risk population	HR=1.55 [1.08-2.24], p=1.85x10^{-2}	HR=1.20 [0.76-1.87], p=0.44	HR=1.30 [0.30-5.62], p=0.72
		8 studies, N=1,894, 485 events	*4 studies, N=1,061, 150 events*	*2 study, N=1,023, 87 events*
Alzheimer's disease	General population	HR=1.49 [1.16-1.92] p=1.92x10^{-3}	HR=1.10 [0.86-1.45]	HR= 1.43 [0.76-2.70], p=0.27
		2 studies, N=4,221, 358 events	*1 study, N=2807 , 330 events*	*3 studies, N=7,713, 186 events*
	High-risk population	HR=1.51[1.08-2.12], p=1.66x10^{-2}	HR=0.76 [0.35-1.67], p=0.50	HR= 0.78 [0.37-1.64], p=0.52
		4 studies, N=985, 214 events	*2 studies, N=622, 84 events*	*3 studies, N=1,162, 104 events*
Death	General population	HR=2.10 [1.76-2.51], p=2.54x10^{-16}	HR=1.63 [1.31-2.03], p=1.23x10^{-5}	HR=1.28 [1.00-1.64], p=5.04x10^{-2}
		5 studies, N=10,266, 1,062 events	*4 studies, N=7,213, 957 events*	*2 studies, N=5,797, 468 events*
	High-risk population	HR=1.89 [1.42-2.50], p=1.03x10^{-5}	HR=1.54 [1.02-2.31], p=3.84x10^{-2}	HR=1.75 [1.42-2.17], p=2.30x10^{-7}
		8 studies, N=2,872, 638 events	*4 studies, N=2,794, 255 events*	*8 studies, N=4,145, 666 events*

BI: covert brain infarcts; CMB: cerebral microbleeds; HR: hazard ratio; VBI: vascular brain injury; WMH: white matter hyperintensities of presumed vascular origin* Of note, one population-based study provided only effect estimates either comparing participants with at least one prevalent but no incident MRI-defined BI to participants with neither prevalent nor

incident MRI-defined BI, or comparing participants with at least one prevalent and one incident MRI-defined BI to participants with neither prevalent nor incident MRI-defined BI, with respect to dementia risk:5 by default the effect estimates of the first comparison were included, but meta-analysis results in the general population were strengthened when using effect estimates from the second comparison (HR=1.59 [1.12, 2.24], p=8.73x10^{-3})

eTable 4. Studies testing the association of burden of white matter hyperintensity (WMH) of presumed vascular origin with incident stroke

Author, y	Mean age	Population	N	Fu (y)	MRI characteristics	WMH measure	Incident event	Result
General population								
Vermeer, 2003 [e90]	72	Rotterdam study	1077 (1015 for analyses)	4.2	1.5T ; T1, T2, PD	SQ (0-9) for PVH, quantitative for DWMH *, studied in tertiles and continuously	57 (42 IS, 6 ICH, 9 unspecified)	**HR=4.7(2.0-11.2) ‡ for 3rd vs. 1st PVH tertile (N=677)** HR=1.36(1.20-1.54) ‡ per grade increase of PVH HR=3.6(1.4-9.2) ‡ for 3rd vs. 1st DWMH tertile (N=677) Risk of stroke did not increase linearly with DWMH
Kuller, 2004 [e49]	75	CHS	3293	7	1.5T †; T1, T2, PD	SQ (0-9), 6 classes: 0, 1, 2, 3, 4, ≥5 (reference = 0-1)	278 (226 IS)	HR=3.0(1.9-4.7) [aa] for grade ≥5 vs 0-1, for all strokes (N=1395, of which 82 strokes) HR=2.9(1.7-4.8) for grade ≥5 vs 0-1, for IS (N=1395)
Bokura, 2006 [e14]	57.8	Shimane Study	2684	6.3	0.15T, 0.2T, 1.5T; T1, T2, ±PD, ±Flair	SQ (0-4 for PVH, 0-3 for DWMH), dichotomized (PVH: ≥3 vs. <3, DWMH: ≥2 vs. <2)	102 (56 IS, 21 ICH, 11 SAH, 11 TIA, 3 unspecified)	**OR=2.08(1.04-4.17) ‡ for PVH ≥3 vs. <3** OR=2.73(1.32-5.63) ‡ for DWMH ≥2 vs. <2
Bokura, 2011 [e13]	62.1	Healthy volunteers / Shimane institute of health sciences	2102	3.6	1.5T ; T1, T2, T2*GRE, FLAIR	Presence or absence of periventricular hyperintensities	44 strokes (22 cerebral infarctions, 10 ICH, 4 SAH, 8 TIA)	Crude OR=8.36(2.13-32.81), p=0.0023 for ICH, as calculated by authors based on raw data provided in the article
Folsom, 2012 [e29]	NA	ARIC + CHS	4872	13 (median)	T1, T2	SQ (0-9), groups for analysis: 0- 1, 2, 3, 4-9	71 intraparenchymal hemorrhage	HR=1.68(0.86–3.30) [c] for grade 2 vs 0-1 HR=3.52(1.80–6.89) [c] for grade 3 vs 0-1 **HR=3.96(1.90–8.27) [c] for grade 4-9 vs 0-1** (N=2759, of which 33 intraparenchymal hemorrhages) P for trend<0.0001 HR=1.60(0.81–3.14) [d] HR=3.19(1.61, 6.28) [d] HR=3.28(1.53, 7.04) [d] P for trend=0.0003 Crude OR=2.71(1.57-4.69) for grade ≥2 vs 0-1 (computed from table)
Weinstein, 2013 [e89]	65.7	Framingham Offspring study	1679	7.4	1.0T, 1.5T ; T1, T2, PD	Quantitative (automated), continuous,	55 (not detailed)	HR=2.73(1.48–5.02), p=0.001 [w] for top quintile vs others (45/1414 for analyses)

						dichotomized (5th quintile vs rest)		
Windham, 2015 [e91]	63 (median)	ARIC	1884	14.5	1.5T; T1, T2, PD	SQ (0-9), dichotomized for analysis ≥3 vs <3)	157 (140 IS; 15 hemorrhagic strokes)	high grade vs low (≥3 vs <3): HR=2.14(1.45, 3.16), p<0.001 [e] for all strokes HR=2.12(1.41, 3.20), p<0.001 [e] for IS HR=7.14(1.63, 31.34), p=0.009 [e] for hemorrhagic stroke (Overlap with Folsom 2012 for hemorrhagic stroke, not included in meta-analysis for this outcome)
Kaffashian, 2016 [e40]	74	3C-Dijon study	1677	9.5	1.5T; T1, T2, PD	Quantitative (automated) and dichotomous (top quartile vs rest)	68 (10 fatal)	Continuous variable: HR=1.72(1.24-2.40) [v] Top quartile vs rest: **HR=1.88(1.16-3.07) [v]**
Kaffashian, 2016 [e41]	72	3C-Dijon Study	1731	9.5	1.5T; T1, T2, PD	Quantitative (automated) and dichotomous (top quartile vs rest)	54 IS (11 lacunar; 15 cardioembolic) and 15 ICH	Continuous variable: HR=1.50(1.03-2.20) [z] for all IS HR=1.15(0.45-2.92) [z] for lacunar IS HR=1.82(0.91-3.63) [z] for cardioembolic IS HR=3.54(1.65-7.60) [z] for ICH Top quartile vs rest: **HR=1.60(0.91-2.80) [z] for all IS** HR=0.66(0.14-3.09) [z] for lacunar IS HR=1.91(0.67-5.38) [z] for cardioembolic IS **HR=4.92(1.43-16.88) [z] for ICH**
High-risk populations								
Yamauchi, 2002 [e92]	66.0	patients with lacunar stroke, headache or dizziness	89	4.3	0.5T ; T1, T2, PD	SQ [g] studied continuously and dichotomous (severe vs. Mild or absent)	7 (5 IS, 2 ICH)	HR=1.60(1.02-2.54) [i] **OR=20.5(3.6-118.0) [j]**
Smith, 2004 [e78]	76.3 [b]	lobar ICH patients	82 [f]	2.7 [f]	NA ; Flair	SQ (0-9) for PVH, quantitative for DWMH, dichotomized (middle or high vs. Low tertile)	NA (recurrent ICH)	**HR=9.0(1.2-67.2) for PVH** NS for DWMH (no HR)
Appelros, 2005 [e9]	66.4	lacunar stroke patients	81	5.0	1.0T ; T2	SQ [h], studied continuously	24 (21 IS, 2 ICH, 1 unspecified)	HR=1.7(1.2-2.7) [h]
Fu, 2005 [e30]	68.3	stroke patients	228	1.9	1.5T ; T1, T2, Flair, DWI	SQ (0-3) ; studied continuously	29 (23 IS, 6 ICH)	HR=4.18(2.04-8.56) [‡]
Gerdes, 2006 [e31]	62	patients with recent IS,	230	3.5	1.5T ; T1, T2, PD	SQ (PVH+/-, DWMH+/-	21 (IS)	HR=4.4(1.8-11.0) for PVH+/- **HR=3.2(1.3-8.4) [i] for PVH+/-**

Study	Age	Population	N	Follow-up	MRI	WMH assessment	Events	Results
		myocardial infarction or peripheral artery disease				and for total WMH: none, <50%, >50% of total white matter)		HR=1.5(0.6–3.8) for DWMH+/-
Naka, 2006 [e60]	67.2	stroke patients	266	1.5	1T ; T2, T2*	SQ (0-3) ; dichotomized (≥2 vs. <2)	26 (16 IS, 10 ICH) recurrent strokes	HR=10.7(2.6-43.7) [m] for IS HR=0.016(0.001-0.258) [m] for ICH
Mok, 2009 [e59]	70.7	Patients with lacunar infarct	75	5.0	1.5T ; T1, T2, GRE, DWI	WMH volume	12 (5 ICH, 5 lacunar infarction, 1 cardioembolic, 1 undefined)	Crude HR=1.97(1.47-2.62), p<0.001 for all strokes
Conijn, 2011 [e19]	58.6	SMART-MR study, patients with symptomatic atherosclerotic disease	1228	4.5 (median)	1.5T; T1, T2, FLAIR, and IR	Q (volume in mL) ; dichotomized 5th quintile vs 1st	46 IS	Per mL increase in WML volume HR=1.04(1.01-1.07), p=0.003 [n] HR=1.04(1.01-1.06), p=0.010 [o] HR=1.02(0.99-1.05), p=0.191 [p] 5th WML quintile vs 1st (N=492, 22 IS) HR=3.9(2.1-7.6), p<0.001 [n] **HR=3.6(1.9-6.9), p<0.001 [o]** HR=2.6(1.3-4.9), p=0.004 [p]
Putaala, 2011 [e70]	40	First-ever IS patients; Helsinki Young Stroke Registry	655	8.7	1.0T or 1.5T; T1, T2, FLAIR	Grade of LA (none; mild, moderate to severe), compared moderate to severe vs none for analyses	72 IS	HR=1.07(0.40-2.85), p=0.90 [bb] (N=634, of which 69 IS)
Melkas, 2012 [e55]	70.8	Helsinki Stroke Aging Memory (SAM) cohort, 1st ever IS patients	320	5.0 and 12.0	1.0T; T1, T2, PD	SQ (absente to mild, moderate, severe); dichotomized in absent to moderate WMCs vs severe WMCs	76 recurrent IS (fatal or non fatal) at 5 years	HR=1.63(1.00-2.66), p=0.048 [q] HR=1.80(1.11-2.95), p=0.018 [r]
							127 recurrent IS (fatal or non fatal) at 12 years	**HR=1.23(0.85-1.80), p=0.272 [q]**
Imaizumi, 2014 [e37]	69.8	Stroke patients	807	2.63	FLAIR, T2*GRE	SQ s ; dichotomized for analyses	111 recurrent strokes (24 ICHs, 21 lacunar infarctions, 27 cardioembolic infarctions, 38 atherothrombotic infarctions, and 1 infarction of unknown origin).	OR=1.61(1.02-2.55), p=0.04 [t] for all strokes, grade 2-3 vs grade 1 or 0 OR=3.32(1.38-7.99), p=0.008 [u] for ICH, grade 2-3 vs grade 1 or 0
Lim, 2015 [e54]	64.0	TIA patients	500	0.25	T2, T2*GRE, FLAIR	SQ (modified Fazekas scale); dichotomized for analyses	25 (early recurrent strokes)	HR=1.78(0.78-4.09) [x]

Study	Age	Population	N	Fu	MRI	WMH assessment	Outcome	Result
Charidimou, 2016 [e18]	76 (median)	Patients with cardioembolic stroke due to atrial fibrillation	119	1.42	1.5T; T2*GRE, FLAIR, DWI	Dichotomized: no/mild WMH vs moderate/severe WMH	17 (14 IS and 3 hemorrhagic stroke)	HR=2.99(1.01-8.30), p=0.036 [y]
Andersen, 2017 [e8]	59.6	Danish stroke registry and Danish national registry (IS patients)	832	3.3 (mean)	1.5T ; T2 ; FLAIR, DWI	SQ (Fazekas scale)	55 recurrent IS	HR=5.28(1.98-14.07) for Fazekas score = 6 vs 1 (N=385, 21 recurrent IS, 78 individuals with Fazekas score=6) [cc]
Boulouis 2017 [e17]	73	CAA-related ICH patients	229	2.8 (median)	1.5T; T1, T2*GRE or SWI, FLAIR	SQ (Fazekas scale); dichotomized: qualifying WMH = scoring 3 for periventricular and/or scoring >2 for deepWMH	56 ICH	HR=1.39(0.78-2.60), p=0.256 [dd]
Nam, 2017 [e61]	66	First ever LAA IS patients	956	2.8 y (duration)	1.5T or 3T; T1, T2, DWI, T2 gradient echo, FLAIR	Severe vs non severe WMH	92 recurrent strokes	OR=2.23(1.35-3.70), p=0.002 [ee]

DWI: diffusion-weighted imaging; DWMH: deep white matter hyperintensities; FLAIR: fluid-attenuated inversion recovery; Fu: follow-up; HR: hazard ratio; ICH: intracerebral hemorrhage; IS: ischemic stroke; LA: leukoaraiosis; LAA: large-artery atherosclerosis; NA: not available; NS: non significant; OR: odds ratio; PD: proton density; PVH: periventricular hyperintensities; SAH: subarachnoid hemorrhage; SQ: semi-quantitative; TIA: transient ischemic attack; WMH: white matter hyperintensities of presumed vascular origin; WMC: white matter changes; * approximation (based on number and size of lesions); † +0.35 in one of the 4 centers; ‡ adjusted for age, sex, vascular risk factors; § adjusted for clinic, age, sex, vascular risk factors; [a] extensive WMH: > age-group specific mean[logWMH]+1SD; [b] Adjusted for age, sex, time between scans, and vascular risk factors; [c] Adjusted for age, study, race, systolic blood pressure, current smoking, triglycerides, low-density lipoprotein cholesterol, fibrinogen, carotid intima-media thickness, and carotid plaque; [d] Adjusted for age, study, race, systolic blood pressure, current smoking, triglycerides, low-density lipoprotein cholesterol, fibrinogen, carotid intima-media thickness, carotid plaque, and MRI infarct (yes, no); [e] Adjusted for age, sex, race-site, education, BMI, smoking, alcohol, diabetes, systolic and diastolic blood pressures, hypertension medication use, heart disease, HDL, LDL, TG, statin use; [f] with MRI (182 patients overall, 100 had computed tomography only), mean follow-up and age are for overall group; [g] van Swieten[e95]; [h] Wahlund scale[e96]; [i] adjusted for age, sex, vascular risk factors, multiple lacunar infarcts; [j] computed by authors of meta-analysis from published raw numbers, for severe vs. mild or no WMH; [k] adjusted for age, ischemic heart disease, impairment score, MMSE, basal ganglia score; [l] adjusted for age, hypertension, type of atherosclerotic disease at entry; [m] adjusted for age, sex, vascular risk factors, stroke type, days from stroke onset, microbleeds; [n] adjusted for age and sex; [o] adjusted for age, sex, hypertension, diabetes mellitus, body mass index, smoking, alcohol consumption, and hyperlipidemia; [p] age, sex, hypertension, diabetes mellitus, body mass index, smoking, alcohol consumption, hyperlipidemia, nonlacunar infarcts on MRI or clinical history of stroke and WML and WML ; [q] adjusted for age, sex and education; [r] adjusted for age, sex, education, past medical history and variables associated with stroke recurrence in Kaplan-Meier analysis; [s] Fazekas scale[e97]; [t] adjusted for MBs of 5 or more, female gender, age 65 years or older, body mass index of 26 kg/m2 or more, hypertension, and a history of cerebral infarction and ICH; [u] adjusted for female gender, 65 years or older, hypertension, diabetes mellitus, and low-density lipoprotein cholesterol more than 150 mg/dL; [v] adjusted for sex; [w] adjusted for age, sex, education, hypertension, current smoking, history of diabetes mellitus, body mass index, and ApoEε4 status; [x] adjustment for ABCD-I score 8-13, cerebral microbleeds; [y] Adjusted for CHADS-2; [z] adjusted for sex, education and number of cardiovascular risk factors; [aa] Adjusted for clinic, age, gender, race, systolic blood pressure, diabetes (ADA definition), CVD (angina,MI, claudication, or CHF), and atrial fibrillation (by ECG); [bb] Adjusted for age, gender, hypertension, history of TIA, diabetes mellitus type 1 and 2, stroke etiology, silent brain infarcts, and leukoaraiosis; [cc] adjusted for the components of the CHA_2DS_2VASc score; [dd] adjusted for age at event, hypertension, diabetes mellitus, cortical superficial siderosis, enlarged centrum-semiovale perivascular spaces, cerebral microbleeds count; [ee] adjusted for age, old lacunar infarction, asymptomatic territorial infarction, cerebral microbleeds, and severe stenosis of relevant artery

eTable 5. Studies testing the association of burden of white matter hyperintensity (WMH) of presumed vascular origin with incident dementia

Author, y	Mean age	Population	N	Fu (y)	MRI characteristics	WMH measure	Incident event	Dementia type	Result
General population									
Kuller, 2003 [e50]	≥65	CHS	3375	NA	1.5T ; T1, T2, PD	SQ (0-9), dichotomized (≥3 vs. <3)	480 (criteria not specified): 52 VaD, 76 MD, 330 AD	All dem	HR=1.7(95%CI:1.36-2.10) [†] for WMH≥3 (N=2939)
								AD	HR=1.5(1.17-1.99) [†] for WMH≥3 (N=2807)
								VaD/MD	HR=2.1(1.36-3.11) [†] for WMH≥3 (N=2659)
Prins, 2004 [e69]	72.2	Rotterdam study	1077	5.2	1.5T ; T1, T2, PD	SQ (0-9) for PVH, quantitative for DWMH *, continuous (per SD increment) and dichotomized	45 (DSM-IIIR): 34 AD, 6 VaD, 5 other types	All dem	HR=1.67(1.25-2.24) [‡] for PVH (NS for DWMH) HR=2.2(1.0-4.8) [a] for DWMH >6 **HR=4.4(1.9-5.0) [a] for PVH >6** (N=815 of which 27 dementias)
								AD	HR=1.41(1.01-1.98) [‡] for PVH (NS for DWMH) (N=1066)
Meguro, 2007 [e111]	≥65	Osaki–Tajiri project	257	5	1.5T ; T1, T2	SQ : PVH (4 grades), DWMH (4 grades), continuous	27 (DSM-IV and CDR1+): 17 AD (NINCDS-ADRDA), 5 VaD (NINDSAIREN)	AD	OR=0.78(NS) for increasing PVH OR=1.07, 1.02(NS) for DWMH right and left
								VaD	OR=4.14(p<0.005) for PVH OR=4.04, 3.27(p<0.05) for DWVH right and left
Debette, 2010 [e21]	62	Framingham Offspring study	2013	5.9	1.0T, 1.5T ; T1, T2, PD	quantitative (automated), continuous and dichotomized [b]	11 (DSM-IV): 7 AD, 3 VaD, 1 other	All dem	HR=2.22(1.32-3.72) [§] for increasing WMH **HR=3.97(1.10-14.30) [§] for extensive WMH**
Weinstein, 2013 [e89]	65.7	Framingham Offspring study	1679	7.4	1.0T, 1.5T ; T1, T2, PD	Quantitative (automated), continuous, dichotomized (5th quintile vs rest)	31 AD (NINCDS-ADRDA)	AD	HR=1.43(0.61–3.36) [r] for top quintile vs others (28/1414 for analyses)

Kaffashian, 2016 [e40]	74	3C-Dijon study	1677	8.2	1.5T ; T1, T2, PD	quantitative (automated) and dichotomous (top quartile vs rest)	124 (DSM-IV): 89 AD (NINCDS-ADRDA)	All dem	Continuous variable: HR=1.41(1.08-1.83) [q] Top quartile vs rest: **HR=1.73(1.24-2.59) [q]**
High-risk populations									
Steffens, 2000 [e112]	>60	depression	182	1 to 5	1.5T ; T2	quantitative (automated)	26 (criteria not specified), type unspecified	All dem	No association
Korf, 2004 [e47]	62.9	MCI	75	2.8	1.5T ; T2, PD	SQ [c], continuous	37 (DSM-IV): 34 AD, 3 VaD	All dem	HR=1.01(0.94-1.08)
DeCarli, 2004 [e22]	72.8	MCI	52	3.1	1.5T ; T1, T2, PD	quantitative (automated), continuous	17 (CDR>1.0): 10 AD, 4 MD, 2 VaD, 1 other	All dem	HR=0.73(0.35-1.54) [h]
Geroldi, 2006 [e32]	70.0	MCI	52	1.3	1.0T ; gradient echo	SQ [c], dichotomized [e]	11 (DSM-IV): 7 AD, 1 VaD, 1 DLB	All dem	OR=2.9(0.7-11.4)
Firbank, 2007 [e27]	80.1	stroke	79	2	1.5T ; T1, Flair	quantitative (automated), continuous and dichotomized (> vs. < 1/4 of white matter)	14 (DSM-IV): type not available	All dem	OR=1.0(0.2-4.1) [j]
Steffens, 2007 [e113]	69.2	depression	161	5.4	1.5T; T2	Quantitative (automated)	20 (DSM-IV): 10 AD, 3 VaD, 7 undertermined	All dem	No association [v]
Smith, 2008 [e77]	72.3	MCI	156	6.4	1.5T ; T2, PD	quantitative (automated), dichotomized [f]	54 (DSM-IV): 45 AD	All dem	HR=1.26(0.61-2.59)
Tapiola, 2008 [e82]	72.7	MCI	60	2.8	1.5T ; T2, Flair, PD	SQ [c], continuous	13 (DSM-IV): 9 AD, 3 VaD, 1 MD	All dem	HR=1.01(0.89-1.14)
Bombois, 2008 [e15]	68.1	MCI	170	3.8	1.5T ; T1, T2, PD	SQ [g], continuous, and also dichotomized for total WMH (> vs. <median)	67 (DSM-IV): 29 AD (NINCDS-ADRDA), 19 DLB, 8 MD, 7 VaD (NINDS-AIREN)	All dem	HR=1.01(0.97-1.05) [k] per unit WMH **HR=1.32(0.77-2.24) [k,l] for WMH >6**
								AD	HR=1.02(0.96-1.09) [k,l] per unit WMH **HR=1.67(0.73-3.81) [k,l] for WMH >6**
								VaD/MD	HR=1.14(1.06-1.24) [k] per unit WMH HR=10.00(1.55-64.39) [k] for WMH >6

Author, Year	Age	Population	N	Follow-up (y)	MRI (field strength; sequences)	WMH measure	Outcome (criteria)	Dementia type	Result
									HR=2.71(1.60-4.58) [k] per unit PVH
Van Straaten, 2008 [e87]	72.4	amnestic MCI	152	3	NA ; T1, T2, PD	SQ [g], continuous	55 (NINCDS-ADRDA): 55 AD	AD	HR=1.03(0.99–1.06) [m] for total WMH HR=1.02(0.97–1.08) [m] for DWMH HR=1.59(1.24–2.05) [m] for PVH
Kantarci, 2009 [e43]	77	MCI	151	2.1	1.5T ; T1, Flair	quantitative (visual scale), dichotomized (>mean+1SD)	75 (DSM-III): 57 AD, 15 DLB, 3 FTLD	All dem	HR=0.75(0.42-1.35) [n] (N=103)
Jokinen, 2009 [e39]	73.5	with WMH and minor neurological problems (LADIS study)	639	3	0.5T, 1.5T ; T1, T2, Flair	SQ [d], dichotomized into presence (or absence of SIVD)	91 (DSM-IV)	All dem	OR=3.01(1.64-5.55) [o]
Staekenborg, 2009 [e81]	69.9	MCI patients	152	2.0	1.0T ; T1, Flair, T2*	SQ [g], dichotomized into < vs. ≥6 for WMH, < vs. ≥3 for PVH, < vs. ≥4 for DWMH	72: 56 AD (NINCDSADRDA), 16 non-AD (7 VaD, 5 FTLD, 2 DLB, 1 PD, 1 alcohol dementia)	AD	(N=136) **HR=1.2(0.7-2.2) ‡ for WMH ≥6** HR=1.3(0.8-2.3) ‡ for DWMH ≥4 HR=1.1(0.7-2.0) ‡ for PVH ≥3
								Non-AD	(N=96) HR=5.8(1.2-26.6) ‡ for WMH ≥6 HR=5.7(1.2-26.7) ‡ for DWMH ≥4 HR=6.5(1.4-29.8) ‡ for PVH ≥3
Prasad, 2011 [e67]	68.4 for converters / 60.2 for MCI stable	MCI patients	79	≥1.5	T2	SQ (Scheltens scale and modified Fazekas scale: from 0 to 6 for PVH and deep subcortical WMH)	23 dementia DSM-IV (all 23 are AD using NINDS-ADRDA)	AD	OR=2.38(0.57-10), p=0.234 [t] for PVH OR=7.69(1.22-50), p=0.03 [t] for deep subcortical WMH
Prins, 2013 [e68]	71	MCI patients	426	2.0	1.5T ; T1, FLAIR	SQ (ARWMC, range 0–30) continuous	81 dementia (CDR score from 0.5 to ≥1.0)	All dementia	HR=0.98(0.94-1.03) ‡
Eckerström, 2015 [e25]	40-79	Gothenburg MCI Study ;	73	10 (maximum)	0.5T or 1.5T ; T2 2D TSE	SQ (modified Scheltens	34 dementia (18 AD, 10 VaD or mixed)	All dementia	HR=1.4(0.6-3.2)

Study	Age	Cohort	N	Fu	MRI	WMH assessment	Dementia diagnosis	Dementia type	Result
		MCI patients				scale : graded 1, 2 or 3); dichotomized for analyses 2 or 3 vs 1		AD	HR=0.5(0.06-3.8) (N=57)
								VaD + mixed	OR=8.75(1.74-43.97) [j] (N=49)
Kim, 2015 [e46]	72	CREDOS study (MCI participants)	622	1.2 (median); maximum 3 years	1.5T; T1, T2, FLAIR, GRE	SQ (visual grading of PVH and DWMH, 3 grades); dichotomized for analyses (≥10mm vs <10mm)	139 dementia using DSM-IV (AD: 111 using NINDS-ADRDA; subcortical vascular dementia: 25 using NINDS-AIREN)	All dementia	**HR=2.22(1.43-3.43), p<0.001 [s] for PVH** HR=0.70(0.44-1.11) [s] for DWMH
								AD	**HR=1.86(1.12-3.07), p<0.05 [s] for PVH** HR=0.35(0.19-0.63), p<0.01 [s] for DWMH
								Subcortical vascular dementia	HR=16.14(1.97-132.06), p<0.01 [s] for PVH HR=8.77(1.77-43.49), p<0.01 [s] for DWMH
Miwa, 2015 [e56]	67.2	OSACA2	643	7.3	T1, T2, FLAIR, T2*GRE	SQ (modified Scheltens' scale : range 0-30, 0-24 for DWMH and 0-6 for PVH)	47 dementia using DSM-III-R (AD: 24; vascular dementia: 18; mixed-type: 3; other: 2).	All dementia	RR=1.06(1.01-1.11), p<0.05 [p] for WMH RR=1.15(0.95-1.41) [p] for PVH RR=1.08(1.02-1.14) [p] for DWMH
								AD	(N=620) RR=1.03(0.96-1.09) [p] for WMH RR=1.02(0.77-1.30) [p] for PVH RR=0.98(0.90-1.10) [p] for DWMH
								VaD + mixed	(N=617) RR=1.11(1.04-1.17), p<0.01 [p] for WMH RR=1.48(1.08-2.09), p<0.01 [p] for PVH RR=1.14(1.06-1.22), p<0.01 [p] for DWMH
Van Uden, 2016 [e110]	65.6	patients with SVD	500	5.2	1.5T; T1, FLAIR, T2*, DTI	Quantitave, volume	43 dementia (DSM-IV) (28 AD [NIA-AA], 11 VaD [NINDS-AIREN])	All dementia	HR=1.78(0.79-4.01), p=0.167, N=499 [u]

AD: Alzheimer's disease; All dem: all types of dementia; ARWMC: age-related white matter changes; CDR: Clinical Dementia Rating scale Morris[e98]; DLB: dementia with Lewy bodies; DSM-III: Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition American[e99]; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition american[e100]; DWMH: deep white matter hyperintensities; FLAIR: fluid-attenuated inversion recovery; FTLD; frontotemporal lobe dementia; Fu: follow-up; HR: hazard ratio; MCI: mild cognitive impairment; MD: mixed dementia; NA: not available; NIA-AA: The National Institute on Aging and the Alzheimer's Association [e71]; NINCDS-ADRDA: criteria for AD from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association[e4]; NINDS-AIREN: National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences[e101]; NS: non significant; OR: odds ratio; PD: proton density; PVH: periventricular hyperintensities; SIVD: subcortical ischemic vascular disease, defined by either severe WMH (Fazekas scale[e97]) plus >1 lacune or moderate WMH[e97] plus >5 lacunes; SQ: semi-quantitative; VaD: vascular dementia; WMH: white matter hyperintensities of presumed vascular origin; * approximation (based on number and size of lesions); † adjusted for age, sex, race, education, baseline cognition, ApoE_4, ventricular grade, infarcts on MRI, vascular risk factors, stroke, subclinical disease; ‡ adjusted for age, sex; §

adjusted for age, sex, vascular risk factors; [a] numbers computed from graph; [b] extensive WMHV: >age-group specific mean[logWMH]+1SD; [c] Wahlund scale[e96]; [d] grade 1 to 3 from Fazekas scale[e37]; [e] extensive WMH if total score>6 or any regional score>2; [f] extensive WMH if log-transformed >mean+1SD; [g] Scheltens scale[e102]; [h] adjusted for age, sex, education, cortical gray matter, hippocampal volume, lacunes; [i] adjusted for age, sex, baseline cognition, education; [j] OR computed by authors of meta-analysis from the raw data; [k] adjusted for age, sex, education, medial temporal lobe atrophy, vascular risk factors, baseline cognition; [l] unpublished data; [m] adjusted for age, education; [n] adjusted for age, sex, education; [o] adjusted for age, sex, education, medial temporal lobe atrophy; [p] adjusted for age, gender, educational level, and APOEε4 carrier status; [q] adjusted for sex; [r] adjusted for age, sex, education, hypertension, current smoking, history of diabetes mellitus, body mass index, and ApoEε4 status; [s] adjusted for age, sex, education, Korean Mini-Mental State Examination, Clinical Dementia Rating scale sum of boxes, Korean version of the Geriatric Depression Scale short form, Hachinski Ischemic Score, vascular risk factors, and WMH severity (DWMH and PVH simultaneously entered in the model); [t] adjusted for medial temporal atrophy, age, hyperlipidemia; [u] adjusted for age, gender, education, baseline MMSE, and territorial infarcts; [v] adjusted for age, sex, baseline cognition, education

eTable 6. Studies testing the association of burden of white matter hyperintensity (WMH) of presumed vascular origin with mortality

Author	Mean age	Population	N	Fu (yrs)	MRI characteristics	WMH measure	Incident deaths (N)	Results
General population								
Bokura, 2006 [e14]	57.8	Shimane Study	2684	6.3	0.15T, 0.2T, 1.5T; T1, T2, ±PD, ±Flair	SQ (0-4 for PVH, 0-3 for DWMH), dichotomized (PVH: ≥3 vs. <3) and 3 classes (DWMH: 0, 1, >1)	93	**OR=4.01(95%CI:1.91-8.45) [†] for PVH ≥3 vs. <3** OR=0.63(0.32–1.25) [†] for 1 vs. 0 DWMH OR=1.06(0.45–2.53) [†] for >1 vs. 0 DWMH
Kuller, 2007 [e48]	74.8	CHS	3245	10 to 12	1.5T; T1, T2, PD	SQ (0-9); 5 classes: 0-1, 2, 3, 4, ≥5 (reference = 0-1)	1056	HR=2.22(1.75-2.82) [‡] for grade ≥ 5 vs. 0-1 (p for trend <0.0001 across grades) (N for analysis: NA, 105 deaths)
Ikram, 2009 [e36]	73.4	Rotterdam study	490	8.4	1.5T; T1, T2, PD, HASTE	quantitative (automated), continuous and in quartiles	191 (49 cardiovascular)	All-cause death: HR=1.38(1.16-1.65) [§] per SD increase in WMH volume **HR=2.05(1.32–3.20) [§] for 4th vs. 1st quartile (N=245)** Cardiovascular death: HR=2.52(1.65, 3.84) [a] per SD increase in WMH volume
Debette, 2010 [e21]	62	Framingham Offspring study	2208	5.2	1.0T, 1.5T; T1, T2, PD	quantitative (automated), continuous and dichotomized *	97	HR=1.38(1.13-1.69) [†] for increasing WMH volume **HR=2.27(1.41-3.65) [†] for extensive WMH [a]**
Windham, 2015 [e91]	63 (median)	ARIC	1884	14.5	1.5T; T1, T2, PD	SQ (0-9), dichotomized for analysis ≥3 vs <3)	576 all-cause deaths (50 stroke related death)	All-cause death HR=1.20(1.12-1.29) [f] per unit **HR=1.78(1.42-2.23) [f] for grade ≥3 vs <3** Stroke-related death HR=1.35(1.10-1.66) [f] per unit HR=2.47(1.25-4.87) [f] for grade ≥3 vs <3
High-risk populations								
Yamauchi, 2002 [e92]	66.0	Lacunar stroke, headache, or dizziness	89	4.3	0.5T; T1, T2, PD	SQ [b], dichotomized (presence vs. absence)	4	0R=0.26(0.03-2.59) [g]
Levy, 2003 [e53]	70	depression	259	5.5	1.5T; T1, T2	SQ [c]: PVH (0-3), DWMH (0-3), SGMH (0-3), studied as binary variable (2-3 vs. 0-1)	30	HR=3.43(1.29-9.08) [h] for DWMH **OR=2.36(1.07-5.21) [i] for PVH** association with PVH non-significant in Cox regression including DWMH
Appelros, 2005 [e9]	66.4	Lacunar stroke	81	5.0	1.0T; T2	SQ [d], studied continuously	15	HR=1.6(1.2-2.2) [j]
Fu, 2005 [e30]	68.3	stroke	228	1.9	1.5T; T1, T2, Flair, DWI	SQ (0-3), studied continuously	25	HR=2.02(1.03-3.96) [†]

Author, Year								
Kerber, 2006 [e45]	>75	Mild imbalance	108	11.8	1.5T; T1, T2	SQ (0-2), grade 0 = reference	62	HR=1.98(1.06-3.7) **HR=2.31(1.21-4.40) [k] for grade 2 vs. 0 (N=72, 40 deaths)**
Henneman, 2009 [e34]	66	Memory clinic patients	1138	2.6	1.0T (N=998) or 1.5T (N=140); T1, T2, T2*, FLAIR	WMH grade (0-3); dichotomized (severe vs grade 0; grade 1 vs grade 0 and grade 2 vs grade 0)	153	HR=1.2(1.0-1.4), p<0.10 [l] for WMH grade (N=1117) HR=1.2(1.0-1.4), p<0.10 [m] for WMH grade (N=1117) **HR=1.7(1.0-2.8), p=0.06 [l] for severe WMH vs none (N=545)** HR=1.0(0.6-1.6), p=0.94 [l] for grade 1 vs 0 (N=861) HR=1.0(0.6-1.8), p=0.90 [l] for grade 2 vs 0 (N=603)
Oksala, 2009 [e63]	70.8	stroke	396	7.5	1.0T; T1, T2, PD	SQ [d], dichotomized: severe vs. mild to moderate	277 (91 brain-associated)	**HR=1.31(1.00-1.71) [n] for all-cause death** HR=1.76(1.05-2.95) for brain-associated causes of death [n]
Conijn, 2011 [e19]	58.6	SMART-MR study, patients with symptomatic atherosclerotic disease	1228	4.5 (median)	1.5T; T1, T2, FLAIR, and IR	Q (volume in mL) ; dichotomized 5th quintile vs 1st	106 (57 vascular; 48 nonvascular)	All-cause mortality HR=1.03(1.01-1.05) [o] for WMH volume **HR=2.0(1.3-3.0) [o] for 5th quintile vs 1st (N=492, 48 deaths)** Vascular death HR=1.04(1.02-1.06) [o] for WMH volume HR=2.8(1.6-5.0) [o] for 5th quintile vs 1st (N=492, 30 deaths) Nonvascular death HR=1.02(0.99-1.05) [o] for WMH volume HR=1.2(0.6-2.4) [o] for 5th quintile vs 1st (N=492, 17 deaths)
Putaala, 2011 [e70]	40	First-ever IS patients; Helsinki Young Stroke Registry	655	8.7	1.0T or 1.5T; T1, T2, FLAIR	Grade of LA (none; mild, moderate to severe); compared moderate to severe LA vs none for analyses	57	HR=3.43(1.58-7.42), p=0.002 [s] (N=634, of which 53 deaths)
Van der Holst, 2016 [e86]	65.7	The Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort (RUN DMC) Study ; patients with cerebral SVD	503 (492 for analyses)	8 y	1.5 T; T1, FLAIR, T2*, DTI	Q (manually segmented)	80 (78 for analyses)	HR per 1 SD increase in WMH volume (mL): 1.65(1.28-2.15), p<0.001 [q] HR=1.62(1.24-2.11), p<0.001 [r]
Andersen, 2017 [e8]	59.6	Danish stroke registry and Danish national	832	3.3 (mean)	1.5T ; T2 ; FLAIR, DWI	SQ (Fazekas scale)	80	HR=2.54(1.10-5.83) for Fazekas score = 6 vs 1 (N=385, 33 deaths, 78 individuals with Fazekas score=6) [s]

		registry (IS patients)						

DTI: diffusion tensor imaging; DWMH: deep white matter hyperintensities; DWI: diffusion-weighted imaging; FLAIR: fluid-attenuated inversion recovery; Fu: follow-up; HASTE: 3D half-Fourier acquisition single-shot turbo spin echo sequence; HR: hazard ratio; LA: leukoaraiosis; OR: odds ratio; NA: not available; PD: proton density; PVH: periventricular hyperintensities; Q: quantitative; SD: standard deviation; SGMH: subcortical grey matter hyperintensities; SQ: semi-quantitative; SVD: small vessel disease; SWI: susceptibility-weighted images; WMH: white matter hyperintensities of presumed vascular origin; * extensive WMHV: > age-group specific mean[logWMH]+1SD; [†] adjusted for age, sex, vascular risk factors; [‡] adjusted for age, sex and race (still significant when adjusting for vascular risk factors, incident dementia, infarct on MRI); [§] adjusted for age and sex (unchanged after adjustment for vascular risk factors and after censoring for incident dementia or stroke); [a] adjusted for age, sex, systolic blood pressure, diastolic blood pressure, body mass index, current smoking, former smoking, intima-media thickness, diabetes mellitus; [b] Wahlund scale[e96]; [c] none to mild, moderate, severe (modified Fazekas scale[e97]); [d] van Swieten[e95]; [e]: Adjusted for age, sex, time between scans, and vascular risk factors; [f] Adjusted for age, sex, race-site, education, BMI, smoking, alcohol, diabetes, systolic and diastolic blood pressures, hypertension medication use, heart disease, HDL, LDL, TG, statin use; [g] OR computed by authors of meta-analysis from published raw numbers; [h] adjusted for age, sex, race, measure of comorbidity, MMSE; [i] OR computed by authors of meta-analysis using raw numbers; [j] non-significant in multivariable model; [k] age- and sex-matched and adjusted for vascular risk factors and coronary heart disease; [l] adjusted for age, sex, diagnosis; [m] adjusted for age, sex, diagnosis, and history of hypertension, diabetes mellitus, hypercholesterolemia, and myocardial infarction; [n] stepwise model including age, sex, vascular risk factors, vascular disease and poor modified Rankin score; [o] adjusted for age, sex, hypertension, diabetes mellitus, body mass index, smoking, alcohol consumption and hyperlipidemia; [p] Adjusted for age, sex, education, body mass index, smoking, serum cholesterol, systolic blood pressure, antihypertensive medication, diabetes mellitus, statin treatment, history vascular diseases, and baseline periventricular white matter hyperintensities; [q] Adjusted for age and sex; [r] Adjusted for age, sex, vascular risk factors (smoking, diabetes mellitus, hypertension); [s] adjusted for the components of the CHA_2DS_2VASc score

eTable 7. Studies testing the association of magnetic resonance imaging (MRI)–defined covert brain infarcts (BI) with incident stroke

Author, y	Mean age	Population	N	Fu (y)	MRI characteristics	BI measure	Incident event	Result
General population								
Bernick, 2001 [e12]	NA	CHS	3324	4.0	T1, T2, spin density	Number of silent infarcts and lacunes, location of silent infarcts ; all analyses vs no silent infarct	159 (not detailed)	**HR=1.52(1.10-2.10) * for any infarct vs none (N=3275)** HR=1.52(1.08-2.13) * for subcortical infarcts only HR=1.00(0.37-2.80) * for cortical infarcts only HR=2.20(1.00-4.86) * for subcortical + cortical infarcts HR=1.30(0.88-1.94) * for 1 silent infarct HR=1.85(1.23-2.80) * for multiple silent infarcts HR=1.44(0.96-2.16) * for single lacune only HR=1.75(1.09-2.81) * for multiple lacune only
Bokura, 2006 [e14]	57.8	Shimane Study	2684	6.3	0.15T, 0.2T, 1.5T ; T1, T2, ±PD, ±Flair	Presence or absence of silent brain lesions	102 (56 IS, 21 ICH, 11 SAH, 11 TIA, 3 unspecified)	OR=3.66(2.28-5.89), p<0.0001 ‡
Debette, 2010 [e21]	62	Framingham Offspring study	2013	5.9	1.0T, 1.5T ; T1, T2, PD	Present or absence of brain infarcts	32 (26 IS, 5 ICH, 1 unspecified)	HR=2.84(1.32–6.10), p=0.008 §
Bokura, 2011 [e13]	62.1	Healthy volunteers / Shimane institute of health sciences	2102	3.6	1.5T ; T1, T2, T2*GRE, FLAIR	Presence or absence of silent brain infarction	44 strokes (22 cerebral infarctions, 10 ICH, 4 SAH, 8 TIA)	HR= 2.94(1.26-6.82), p=0.012 for IS (N for analysis: NA) HR NA for ICH [a] Crude OR=10.76(3.01-38.38), p=0.0003 for ICH as calculated by authors based on raw data provided in the article
Folsom, 2012 [e29]	NA	CHS+ARIC	4872	13 (median)	T1, T2	Number of brain infarcts on MRI, groups for analysis: 0, 1, 2, ≥3	71 intraparenchymal hemorrhage	HR=1.97(1.10-3.54) [c] for 1 vs 0 HR=2.00(0.83-4.78) [c] for 2 vs 0 **HR=3.12(1.31-7.43) [c] for ≥3 vs 0 (N=3945, of which 49 intraparenchymal hemorrhages)** P for trend=0.002 HR=1.72(0.95-3.11) [d] for 1 vs 0 HR=1.49(0.61-3.60) [d] for 2 vs 0 HR=2.11(0.87-5.14) [d] for ≥3 vs 0 P for trend=0.049
Poels, 2012 [e66]	72	Rotterdam Study	1007	10	1.5T; T1, T2, PD	Presence vs absence of	99 (59 ischaemic, 12 haemorrhagic, 28 unspecified)	HR=2.50(1.70-3.90) †

Author, year	Age	Study	N	Follow-up (y)	MRI	Outcome measure	Strokes	Results
						silent brain infarcts		
Di Tullio, 2013 [e24]	71	NOMAS study	1287	7.1	1.5T; T2, FLAIR	Presence vs absence of silent brain infarcts	71	HR=1.9(1.1-3.3), p=0.014 [k] N=1235
Windham, 2015 [e91]	63 (median)	ARIC	1884	14.5	1.5T; T1, T2, PD	Presence vs absence of any lesion ≥3mm; presence vs absence of lacunes; count of lacunes	157 strokes (140 IS; 15 hemorrhagic strokes)	Any lesion ≥3 mm (SBI): **HR=2.54(1.70-3.79), p<0.001 [e] for all strokes (N=1831)** **HR=2.35(1.54-3.60), p<0.001 [e] for IS** HR=6.42(1.68-24.44), p=0.006 [e] for hemorrhagic strokes Any lacunes: HR=2.30(1.49-3.55), p<0.001 [e] for all strokes HR=2.04(1.28-3.25), p=0.003 [e] for IS HR=7.14(1.63-31.34), p=0.009 [e] for hemorrhagic stroke 1-2 lacunes vs none: HR=1.81(1.06-3.08), p=0.029 [e] for all strokes HR=1.83(1.05-3.16), p=0.032 [e] for IS HR=2.46(0.26-23.71), p=0.436 [e] for hemorrhagic strokes >2 lacunes vs none: HR=3.64(1.98-6.69), p<0.001 [e] for all strokes HR=2.58(1.26-5.28), p=0.009 [e] for IS HR=23.24(3.96-136.48), p<0.001 [e] for hemorrhagic strokes
Kaffashian, 2016 [e40]	74	3C-Dijon study	1677	9.4	1.5T; T1, T2, PD	Presence or absence of brain infarcts	68 (10 fatal)	HR=2.15(1.18-3.93) [j]
Kaffashian, 2016 [e41]	72	3C-Dijon Study	1731	9.5	1.5T; T1, T2, PD	Presence or absence of brain infarcts	54 IS (11 lacunar; 15 cardioembolic); 15 ICH	**HR=1.70(0.82-3.52) [m] for all IS** HR=3.64(0.94-14.11) [m] for lacunar IS HR=0.55(0.07-4.31) [m] for cardioembolic IS **HR=6.78(2.00-23.04) [m] for ICH**
High-risk populations								
Kario, 2001 [e44]	68 (normotensive) / 72 (white coat HTN) / 73 (sustained HTN)	ABPM study, hypertensive patients	958	3.5	1.5T; T1, T2	Presence or absence of SCI	62 (40 IS; 12 hemorrhagic strokes; 12 unknown)	RR=5.9 Unadjusted Risk Ratio=5.83(2.65-12.85) [f] (N=585, of which 45 strokes)

Miwa, 2010 [e58]	66.9	Patients with >1 atherosclerotic risk factor	282	4.1	1.5T; T1, T2, FLAIR	Presence of silent cerebral infarction	8 stroke or TIA	HR=9.01(1.81-44.88) [g]
Putaala, 2011 [e70]	40	First-ever IS patients; Helsinki Young Stroke Registery	655	8.7	1.0T or 1.5T; T1, T2, FLAIR	Grade of SBI (none; single, multiple), compared multiple SBI vs none for analyses; Presence or absence of SBI	81 (72 IS and 9 hemorrhagic stroke)	HR=1.62(0.93-2.82), p=0.087 [n] for all strokes, as provided by Gupta et al (N=655)

HR=2.48(1.24-4.94), p=0.010 [o] for IS (multiple SBI vs none: N=605, of which 64 IS; of note 40 patients in multiple SBI group)

Crude OR= 0.82(0.10-6.68), p=0.86 for hemorrhagic stroke, calculated by authors based on information provided by Gupta [e103] et al (N=655) |
| Umemura, 2011 [e85] | 62.7 | Type 2 diabetes | 190 | 6 | 1.5T; T1; T2, FLAIR | Presence or absence of SBI | 13 (12 IS; 1 hemorrhagic) | Unadjusted Risk ratio= 3.65(1.29-10.32) for all strokes
Unadjusted Risk ratio=3.13(1.06-9.23) for IS
Calculated by authors based on information provided by Gupta [e103] et al |
| Weber, 2012 [e88] | 66.1 | PRoFESS (IS patients) | 1014 | 2.5 | T1, T2, FLAIR | Presence or absence of silent cerebral infarction | 46 recurrent strokes | OR=1.42(0.79-2.56), p=0.24 [h] (N=414)
OR=1.72(1.06-2.78) [i] (N=995)
Crude OR=1.47(0.76-2.82), for IS (N=414, of which 41 IS), calculated by authors based on raw data provided in the article
Crude OR=1.51(0.25-9.12), for hemorrhagic stroke (N=414, of which 5 hemorrhagic strokes), calculated by authors based on raw data provided in the article |

BI: covert brain infarct; FLAIR: fluid-attenuated inversion recovery; Fu: follow-up; HR: hazard ratio; HTN: hypertension; ICH: intracerebral hemorrhage; IS: ischemic stroke; NA: not available; OR: odds ratio; PFO: patent foramen ovale; PD: proton density; SAH: subarachnoid hemorrhage; SBI: silent brain infarction; SCI: silent cerebral infarction; TIA: transient ischemic attack; * Adjusted for diastolic blood pressure, systolic blood pressure, EKG-AFIB, EKG-left ventricular hypertrophy, fasting insulin, common carotid artery wall thickness, internal carotid artery wall thickness, and myocardial infarction status at MRI; [†] adjusted for age, sex (if applicable), smoking (never/former/ current), systolic blood pressure, antihypertensive treatment, systolic blood pressure x antihypertensive treatment, diabetes mellitus, atrial fibrillation, left ventricular hypertrophy and coronary heart disease; [‡] adjusted for age, sex, family history of stroke, hypertension, diabetes mellitus, smoking, alcohol consumption habits, and dyslipidemia; [§] age, gender, systolic blood pressure, current smoking, diabetes, and history of cerebrovascular disease; [a] adjusted for age and sex; [b] adjusted for age, sex, time between scans, and vascular risk factors; [c] adjusted for age, study, race, systolic blood pressure, current smoking, triglycerides, low-density lipoprotein cholesterol, fibrinogen, carotid intima-media thickness, and carotid plaque; [d] adjusted for age, study, race, systolic blood pressure, current smoking, triglycerides, low-density lipoprotein cholesterol, fibrinogen, carotid intima-media thickness, carotid plaque and WM grade ≥3 (yes, no); [e] adjusted for age, sex, race-site, education, BMI, smoking, alcohol, diabetes, systolic and diastolic blood pressures, hypertension medication use, heart disease, HDL, LDL, TG, statin use; [f] unadjusted relative risk calculated by authors based on the information provided in the article; [g] adjusted for age, sex, smoking, hypertension, diabetes mellitus and dyslipidemia; [h] comparing 207 individuals with SBI on MRI with 207 age- and sex-matched controls without SBI; [i] comparing 207 individuals with SBI on MRI with the 788 individuals from the

PRoFESS imaging substudy with no evidence of SBI on MRI; [j] adjusted for sex; [k] 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; [l] adjusted for age, duration, sex, ischemic heart disease, hypertension, diabetes, dyslipidemia, smoking habits, serum albumin, body mass index; [m] adjusted for sex, education and number of cardiovascular risk factors; [n] adjusted for age, sex, hypertension, history of transient ischemic attack, diabetes, stroke etiology, SBI and leukoaraiosis; [o] adjusted for age, gender, risk factors, stroke etiology and leukoaraiosis

eTable 8. Studies testing the association of magnetic resonance imaging (MRI)–defined covert brain infarcts (BI) with incident dementia

Author, y	Mean age	Population	N	Fu (y)	MRI characteristics	BI measure	Incident event	Dementia type	Result
General population									
Kuller, 2003 [e50]	≥65	CHS / history of stroke not excluded	3375	NA	1.5T ; T1, T2, PD	Presence or absence of large infarcts (>3mm)	480 (criteria not specified): 52 VaD, 76 MD, 330 AD	All dementia	HR=1.2(1.00-1.54) * (N=2939)
								AD	HR=1.1(0.86-1.45) * (N=2807)
								VaD/MD	HR=1.8(1.18-2.66) *
Vermeer, 2003 [e104]	72.1	Rotterdam study	1015	3.6	1.5T, T1, T2, PD	Presence or absence of silent brain infarcts	30 (DSM-III-R ; NINCDS-ADRDA; NINDS-AIREN): 26 AD, 2 VaD, 1 multisystem atrophy	All dementia	HR=2.26(1.09-4.70) [†]
Debette, 2010 [e21]	62	Framingham Offspring study	2013	5.9	1.0T ; 1.5T ; T1, T2, PD	Present or absence of brain infarcts	11 (DSM-IV): 7 AD, 3 VaD, 1 other	All dementia	HR=6.12(1.82–20.54), p=0.003 [‡]
Kaffashian, 2016 [e40]	72	3C Study	1677	8.2	1.5T ; T1, T2, PD	Presence or absence of brain infarcts	124 (DSM-IV) : 89 AD (NINCDS-ADRDA)	All dementia	HR=1.07(0.60-1.92), p=0.79 [§]
Sigurdsson, 2017 [e76]	74.6	AGES-Reykjavik study	2612	5.2 (mean)	1.5T; T2 FSE, PD, FLAIR, T2*	Presence or absence of prevalent and incident infarcts	358 (DSM-IV)	All dementia	RR=1.1(0.8-1.4) [c] comparing individuals with ≥1 prevalent infarct and no incident infarct vs individuals with no prevalent and no incident infarct (N=2067, of which 234 incident dementia cases; 803 individuals with prevalent infarcts) For sensitivity analyses: RR=1.7(1.3-2.2) [c] comparing individuals with ≥1 prevalent infarct and ≥1 incident infarct vs individuals with no prevalent and no incident infarct (N=1609, of which 241 incident dementia cases; 803 individuals with prevalent infarcts)
High-risk populations									
DeCarli, 2004 [e22]	72.8	MCI patients	52	3.1	1.5T ; T1, T2, PD	Presence or absence of lacunes	17 (CDR ≥1): 10 AD, 4 MD, 2 VaD, 1 other	All dementia	HR=1.11(0.36-3.42) [a]

Staekenborg, 2009 [e81]	69.9	MCI patients	152	2.0	1.0T ; T1, Flair, T2*	Presence or absence of lacunes / infarcts	72: 56 AD (NINCDS-ADRDA), 16 non-AD (7 VaD, 5 FTLD, 2 DLB, 1 PaD, 1 alcohol dementia)	AD	HR=1.1(0.5-2.2) [b] for lacunes HR=1.2(0.6-2.6) [b] for lacunes in basal ganglia **HR=1.1(0.3-3.8) [b] for infarcts**
								Non-AD	HR=2.1(0.7-6.4) [b] for lacunes HR=2.4(0.8-7.5) [b] for lacunes in basal ganglia HR=1.4(0.2-12.1) [b] for infarcts
Yamashita, 2010 [e93]	60.2 (SCI-) ; 63.0 (SCI+)	Unipolar depression	84	5.0	1.5T or 0.5T ; T1, T2	Presence of ≥4 silent cerebral infarctions (SCI+) vs <4 (SCI-)	9 (DSM-IV)	All dementia	Dementia rate significantly higher in SCI+ group (19% vs 4%), p=0.04 Crude OR=5.25(1.02-27.01), p=0.047, as calculated by authors based on raw data provided in the article
Prins, 2013 [e68]	71	MCI patients	426	2.0	1.5T ; T1, FLAIR	Presence vs absence of lacunes	81 dementia (CDR score from 0.5 to ≥1.0)	All dementia	HR=1.19 (0.75-1.88) [d]
Van Uden, 2015 [e110]	65.6	patients with SVD	500	5.2	1.5T; T1, FLAIR, T2*, DTI	Presence vs absence of lacunes	43 dementia (DSM-IV) (28 AD [NIA-AA], 11 VaD [NINDS-AIREN])	All dementia	HR=0.88(0.44-1.76), p=0.714, N=499 [e]
								AD	Crude OR=0.61(0.23-1.67), N=486, as calculated by authors based on raw data provided in the article

AD : Alzheimer's disease ; APOE: apolipoprotein E; BI: covert brain infarct; CDR: Clinical Dementia Rating scale Morris[e98]; DLB: dementia with Lewy bodies; DSM-III: Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition American[e99]; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition american[e100]; FLAIR: fluid-attenuated inversion recovery; FSE: fast spin echo; Fu: follow-up; FTLD: frontotemporal lobar degeneration; HR=hazard ratio; MCI: mild cognitive impairment; MD: mixed dementia; NA: not available; NIA-AA: The National Institute on Aging and the Alzheimer's Association [e71]; NINCDS-ADRDA: criteria for AD from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association[e4]; NINDS-AIREN: National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences[e101]; PD: proton density; PaD: Parkinson dementia; RR: risk ratio; SCI: silent cerebral infarction; SVD: small vessel disease; VaD: vascular dementia; * adjusted for age, race, gender, education, 3MSE, APOEε4, WM grade ≥3, ventricular grade ≥5, any subclinical disease, diabetes, hypertension, MI prior MRI, angina prior to MRI, stroke prior to MRI; † adjusted for age, sex and level of education; ‡ age, gender, systolic blood pressure, current smoking, diabetes, and history of cerebrovascular disease; § adjusted for sex ; [a] adjusted for age, sex, education, cortical gray matter, hippocampal volume; [b] adjusted for age and sex; [c] adjusted for baseline age, sex, time interval between magnetic resonance imaging scans, vascular risk factors, education; [d] adjusted for age and gender; e adjusted for age, gender, education, baseline MMSE, and territorial infarcts

eTable 9. Studies testing the association of magnetic resonance imaging (MRI)–defined covert brain infarcts (BI) with mortality

Author, y	Mean age	Population	N	Fu (y)	MRI characteristics	BI measure	Incident deaths	Result
General population								
Bokura, 2006 [e14]	57.8	Shimane Study	2684	6.3	0.15T, 0.2T, 1.5T ; T1, T2, ±PD, ±Flair	Presence or absence of silent brain lesions	93	HR=1.87(1.23-3.10), p=0.015 * **HR=1.95(1.16-3.29), p=0.012 †**
Ikram, 2009 [e36]	73.4	Rotterdam Scan Study	490	8.4	1.5T ; T1, T2, PF, HASTE	Presence or absence of brain infarcts	191 (of which 49 cardiovascular)	**HR=1.25(0.90-1.73) * for all-cause deaths** HR=1.70(0.90-3.21) * for cardiovascular deaths HR=1.88(0.98-3.60) ‡ for cardiovascular deaths
Debette, 2010 [e21]	62	Framingham Offspring study	2208	5.9	1.0T, 1.5T ; T1, T2, PD	Presence or absence of brain infarcts	97 (of which 21 vascular)	**HR=1.53(0.94-2.48), p=0.087 § for all deaths** HR=3.42(1.40-8.34) ª for vascular deaths HR=2.76(1.02-7.44) ª for cardiovascular deaths
Windham, 2015 [e91]	63 (median)	ARIC	1884	14.5	1.5T; T1, T2, PD	Presence vs absence of any lesion ≥3mm; presence vs absence of lacunes; count of lacunes	576 (of which 50 stroke related)	Any lesion ≥3 mm (SBI): **HR=1.88(1.48-2.37), p<0.001 ᶜ for all-cause deaths (N=1831)** HR=2.63(1.25-5.52), p=0.011 ᶜ for stroke mortality Any lacunes: HR=1.49(1.04-2.13),p=0.031 ᶜ for all-cause deaths (N=1696) HR=5.14(2.08-12.73), p<0.001 ᶜ for stroke mortality 1-2 lacunes vs none: HR=1.39(0.94-2.06), p=0.095 ᶜ for all-cause deaths (N=1684) HR=5.87(2.33-14.78), p<0.001 ᶜ for stroke mortality >2 lacunes vs none: HR=2.13(0.98-4.66), p=0.058 ᶜ for all-cause deaths (N=1623) NA for stroke mortality
High-risk populations								
Henneman, 2009 [e34]	66	Memory clinic patients	1138	2.6	1.0T (N=998) or 1.5T (N=140); T1, T2, T2*, FLAIR	Presence or absence of infarct	153	HR=1.2(0.6-2.4) ᵈ HR=1.2(0.6-2.4) ᵉ
Yamashita, 2010 [e93]	60.2 (SCI-) ; 63.0 (SCI+)	Unipolar depression	84	5.0	1.5T or 0.5T ; T1, T2	Presence of ≥4 silent cerebral infarctions	13 (6 in SCI negative group and 7 in SCI positive group)	No difference between SCI positive and negative groups in terms of mortality (p=0.44)

						(SCI+) vs <4 (SCI-)		Crude OR=1.59(0.49-5.23), p=0.44, calculated by authors based on raw data provided in the article
Putaala, 2011 [e70]	40	First-ever IS patients; Helsinki Young Stroke Registry	655	8.7	1.0T or 1.5T; T1, T2, FLAIR	Grade of SBI (none; single, multiple); compared multiple SBI vs none for analyses	57	HR=1.15(0.43-3.04), p=0.778 [g] (N=605, of which 50 deaths)
Weber, 2012 [e88]	66.1	PRoFESS (IS patients)	1014	2.5	T1, T2, FLAIR	Presence or absence of silent cerebral infarction	39 (for N=995)	OR=2.22(1.12-4.35), p=0.02 (N=995) [f]

BI: covert brain infarct; FLAIR: fluid-attenuated inversion recovery; Fu: follow-up; HR: hazard ratio; HASTE: high-resolution, inversion recovery double contrast, 3D half-Fourier acquisition single-shot turbo spin echo; IS: ischemic stroke; NA: not available; OR: odds ratio; PD: proton density; SBI: silent brain infarction; SCI: silent cerebral infarction; * adjusted for age and gender; [†] adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol habits, and family history of stroke; [‡] adjusted for age, sex, systolic blood pressure, diastolic blood pressure, body-mass index, current smoking, former smoking, intima-media thickness and diabetes mellitus; [§] adjusted for age, gender, systolic blood pressure, current smoking, diabetes, and history of cerebrovascular disease; [a] becomes non-significant after adjustment for vascular risk factors; [b] Adjusted for age, sex, time between scans, current smoking, weight, histories of coronary artery disease, heart failure, claudication, hypertension and diabetes, all at time of follow-up scan; [c] Adjusted for age, sex, race-site, education, BMI, smoking, alcohol, diabetes, systolic and diastolic blood pressures, hypertension medication use, heart disease, HDL, LDL, triglycerides, statin use; [d] adjusted for age, sex, diagnosis; [e] adjusted for age, sex, diagnosis, and history of hypertension, diabetes mellitus, hypercholesterolemia, and myocardial infarction; [f] comparing 207 individuals with SBI on MRI with the 788 individuals from the PRoFESS imaging substudy with no evidence of SBI on MRI; [g] Adjusted for age, gender, hypertension, obesity, cardiovascular disease, history of TIA, diabetes mellitus type 1, heavy drinking, stroke severity, stroke etiology, Bamford subtype, silent brain infarcts, and leukoaraiosis.

eTable 10. Studies testing the association of cerebral microbleed (CMB) with incident stroke

Author, y	Mean age	Population	N	Fu (y)	MRI characteristics	CMB measure	Incident event	Result
General populations								
Bokura, 2011 [e13]	62.1	Healthy volunteers / Shimane institute of health sciences	2102	3.6	1.5T ; T1, T2, T2*GRE, FLAIR	Presence or absence of CMB	44 strokes (22 cerebral infarctions, 10 ICH, 4 SAH, 8 TIA)	HR=4.48(2.20-12.2), p<0.0001 * for IS HR=50.2(16.7-150.9), p<0.0001 * for ICH (N for analyses: NA)
Akoudad, 2015 [e6]	63.8	Rotterdam study	4759	4.9	1.5T ; T1, T2, T2* ; FLAIR	Presence or absence or CMB	93 strokes (72 IS, 11 hemorrhagic, and 10 unspecified).	All strokes: HR=1.93(1.25–2.99), p=0.004 [†] HR=1.87(1.20–2.90), p=0.007 [‡] **HR=1.79(1.16–2.78), p=0.010 [§]** HR=1.68(1.07–2.65), p=0.025 [a] IS: HR=1.52(0.91–2.53), p=0.124 [†] HR=1.49(0.89–2.49), p=0.145 [‡] **HR=1.40(0.84–2.34), p=0.213 [§]** HR=1.28(0.75–2.17), p=0.371 [a] Hemorrhagic stroke HR=5.64(1.66–19.13), p=0.006 [†] HR=5.34(1.56–18.32), p=0.009 [‡] **HR=5.41(1.58–18.46), p=0.008 [§]** HR=4.64(1.33–16.19), p=0.017 [a]
High-risk populations								
Fan, 2003 [e26]	67.96	IS patients	121	2.26	1.5T ; T1, T2, T2* GRE	Presence or absence of CMB	16 recurrent stroke (11 IS, 5 ICH)	No difference according to CMB presence for recurrent IS (p=0.84) 4 patients with CMB had ICH during fu vs 1 without CMB, p=0.053 Crude OR=7.90(0.85-73.07), p=0.069, for IS, calculated by authors based on raw data provided in the article Crude OR=1.58(0.45-5.51), p=0.47, for ICH, calculated by authors based on raw data provided in the article
Tsushima, 2003 [e84]	67.2	Stroke patients with CMB	197	1.12 (median)	1.0T ; T1, T2, T2* GRE	Presence or absence of CMB	4 recurrent ICH	Out of the 139 patients with CMB who were followed up, 4 had new hemorrhagic stroke, no IS was observed.
Boulanger, 2006 [e16]	NA	IS/TIA patients (VISION study)	236	1.17 (median)	3T ; T1, T2, FLAIR, DWI, T2*GRE or PWEPI	Presence or absence of microhemorrhages	24 (22 IS, 2 cerebral hemorrhage)	Crude HR=2.6(1.1-6.0), p=0.023 for all strokes **Adjusted HR=1.5(0.7-3.6), p=0.322 [d] for all strokes** Crude HR=4.4(1.8-11.2), p=0.002 for disabling or fatal stroke

								HR=2.8(1.1-7.3), p=0.036 [d] for disabling or fatal strokes OR=1.68(0.62-4.58) for the association between presence of CMB and IS, calculated by authors from the raw data provided in the article OR=4.32(0.26-70.38) for the association between presence of CMB and cerebral hemorrhage, calculated by authors from the raw data provided in the article
Naka, 2006 [e60]	67.2	stroke patients	266	1.5	1T ; T2, T2*	Presence or absence of CMB	26 (16 IS, 10 ICH) recurrent strokes	HR=0.609(0.174-2.132), p=0.4378 [e] for IS HR=85.626(6.344-1155.649), p=0.0008 [e] for ICH
Jeon, 2007 [e38]	58.3	ICH patients	63	1.9	1.5T ; T2*GRE	Number of CMB	7 recurrent ICH	The number of CMB on MRI was associated with recurrent ICH (p< 0.0001) Crude OR=3.08(0.34-27.48), p=0.31 as calculated by authors based on raw data provided in the article
Huang, 2008 [e35]	60.0 [e20]	IS patients	636 [e20]	1.2 (mean) [e20]	1.5T ; T1, T2, DWI, FLAIR, T2*GRE	Presence or absence of CMB	21 IS, 6 ICH [e20]	Risk Ratio=2.51(1.06-5.97) for IS Risk Ratio=20.04(1.13-354.24) for the association between presence of CMB and ICH (N=6/636) as provided by Wilson et al [e20]
Soo, 2008 [e80]	NA	IS patients	908	2.2	1.5T ; T1, T2, T2*GRE, FLAIR	Number, location of CMB ; presence vs absence	111 (96 recurrent IS and 15 recurrent ICH)	HR for recurrent ICH HR=5.99(1.90-18.86), p=0.002 for presence of CMB [h] HR=8.87(3.208-24.520), p<0.0001 for presence of mixed Cortical subcortical CMB HR=2.75(0.50-14.99), p=0.244 for 1 CMB HR=6.08(1.35-27.42), p=0.019 for 2-4 CMB HR=9.81(2.76-34.83), p<0.001 for ≥5 CMB RR=1.30(0.87-1.94) for the association between presence of CMB recurrent IS (N=96/908), as provided by Wilson et al [e20]
Mok, 2009 [e59]	70.7	Patients with lacunar infarct	75	5.0	1.5T ; T1, T2, GRE, DWI	Presence or absence of CMB	12 (5 ICH, 5 lacunar infarction, 1 cardioembolic, 1 undefined)	Crude HR=5.95(1.42-24.95), p=0.015 for all strokes Crude Risk ratio=13.65(1.63-114.10) for ICH [j] RR=0.85(0.10-7.13) for the association between presence of

Study	Age	Population	N	Follow-up (years)	MRI	CMB assessment	Events	Results
								CMB and IS (N=5/75), as provided by Wilson et al [e20]
Nishikawa, 2009 [e62]	68.5 (CMB+) / 64.8 (CMB-)	Subjects who underwent MRI for screening of cerebrovascular diseases, headache, vertigo, screening of brain tumors or degenerative diseases, and head injury	698	3.5	T2*GRE	Presence vs absence of CMB	36 (10 cerebral infarction and 26 ICH)	HR=2.64(1.34-5.19), p = 0.005 [f] for any stroke HR=11.77(2.95-46.82), p<0.001 [f] for cerebral infarction HR=1.48(0.63-3.45), p=0.36 [f] for ICH
Thijs, 2010 [e83]	72	TIA or IS patients	487	2.2 (median)	1.0T (N=139), 1.5T (N=244) or 3T (N=104) ; T1, T2, FLAIR, T2*GRE + DWI	Number and location of microbleeds	37 (32 IS, 2 ICH, 3 unclassified)	HR=2.4(1.2-5.0), p=0.03 [g] for lobar or mixed CMB HR=2.3(1.02-5.19), p=0.04 [g] for lobar CMB HR=2.7(1.2-6.4), p=0.02 [g] for mixed CMB **HR=1.6(0.8-3.1) [g] for any CMB** Crude OR=2.00(0.96-4.17), for the association between CMB presence and IS, calculated by authors with the raw data provided in the article Crude OR=2.79(0.17-44.92), for the association between CMB presence and ICH, calculated by authors with the raw data provided in the article
Fluri, 2012 [e28]	63 (incident stroke) / 69 (no incident stroke)	TIA patients	176	0.25	T2*GRE, DWI	Number, size and location of CMB; dichotomized into presence or absence of CMB	7 (all IS)	Crude OR=8.91(1.87-42.51), p<0.001
Kang, 2012 [e42]	59 [e105]	ICH patients	97	3.5 (mean)	1.5T; T2*, DWI	Presence or absence of microbleeds [e105]	1 ICH	OR=0.96(0.04-24.35) as provided by Charidimou et al [e105]
Kwa, 2013 [e51]	65.3	TIA or minor IS patients	397	3.8 (mean)	0.5T, 1.0T, 1.5T ; T2* FFE GRE	Presence of microbleeds	28 (23 IS, 5 ICH)	HR=2.3(1.0-5.3) [k] for all strokes HR=2.3(0.9-5.8) [k] for IS HR=2.6(0.3-27) [k] for ICH
Orken, 2013 [e64]	67	IS stroke patients	204	2.06 (mean)	1.5T ; T1, T2 fast spin echo, T2 gradient echo, FLAIR	Presence or absence of microbleeds	4 ICH	OR=1.63(0.16-16.12), as provided by Charidimou et al [e106]

Study	Age	Population	N	Follow-up (years)	MRI	CMB assessment	Outcome events	Results
Song, 2013 [e79]	70.4	IS patients with non-valvular atrial fibrillation	550	3.1 (median)	3.0T ; T2*GRE, FLAIR	Number and location of CMB; dichotomized into presence or absence of microbleeds	11 ICH (2 fatal)	HR=3.785(1.090-13.148), p=0.036 [l] RR=0.59(0.25-1.44) for the association between presence of CMB and IS (N=28/550), as provided by Wilson et al [e20]
Imaizumi, 2014 [e37]	69.8	Stroke patients	807	2.63	T2*GRE, FLAIR	Dichotomized (≥5 vs <5)	111 recurrent strokes (24 ICHs, 21 lacunar infarctions, 27 cardioembolic infarctions, 38 atherothrombotic infarctions, and 1 infarction of unknown origin).	OR=1.59(0.97-2.63), p=0.068 [l] for CMB≥5 RR=1.50(0.26-8.70) for the association between CMB presence and recurrent IS (N=5/138) as provided by Wilson et al [e20] RR=17.00(1.00-288.90) for the association between presence of CMB and recurrent ICH (N=8/138), as provided by Wilson et al e20
Benedictus, 2015 [e11]	71.2	AD patients from the MISTRAL study (from the Amsterdam Dementia Cohort)	333 (111 with CMB; 222 without CMB, matched for age, sex and MRI)	>3.0	1T (n = 171), 1.5T (n = 57), or 3T (n = 105); T1, T2, FLAIR, T2*	Presence or absence of CMB and location	23 (12 IS; 5 ICH)	N=301 All strokes: **HR=3.3(1.3-8.4), for any CMB vs none [n]** HR=1.3(0.2-11.5) for strictly nonlobar CMB [n] HR=3.8(1.5-10.1) for any lobar CMB [n] IS Crude OR=0.99(0.29-3.37), as calculated by authors based on raw data provided in the article (12 incident IS, 101 participants with CMB) ICH Crude OR=22.85(1.25-417.54), as calculated by authors based on raw data provided in the article (5 incident ICH, 101 participants with CMB)
Lim, 2015 [e54]	64.0	TIA patients	500	0.25	T2, T2*, FLAIR	Number of CMB; dichotomized in presence or absence of microbleeds	25 (all IS) early recurrent strokes	HR=3.66(1.47-9.09), p=0.005 [m]

Study	Age	Population	N	Follow-up	MRI	Comparison	Events	Results
Samarasekera, 2015 [e74]	66 in CAA-unrelated ICH; 74 in CAA-related ICH [e105]	ICH patients	76 [e105]	48.47 person-years in CAA-unrelated ICH; 28.38 person-years in CAA-related ICH [e105]	1.5T [e105]	Presence vs absence of CMB [e105]	2 ICH [e105]	OR for CAA-unrelated ICH=2.05(0.08-53.05), as provided by Charidimou et al [e105] OR for CAA-related ICH=0.65(0.02-17.51), as provided by Charidimou et al [e105]
Charidimou, 2016 [e18]	76 (median)	Patients with cardioembolic stroke due to atrial fibrillation	119	1.4	1.5T; T2*GRE, FLAIR, DWI	Presence vs absence of CMB	17 (14 IS and 3 hemorrhagic stroke)	HR=1.05(0.99-1.11), p=0.137, per each additional CMB increase [o] Crude OR=0.74(0.19-2.78) for all strokes Crude OR=0.56(0.12-2.69 for IS Crude OR=1.82(0.16-20.90) for ICH Crude ORs calculated by authors based on raw data provided in the article.
Pasquini 2016 [e65]	65 in CAA-unrelated ICH; 74 in CAA-related ICH [e105]	ICH patients	249 [e105]	506 person-years in CAA-unrelated ICH; 900 person-years in CAA-related ICH [e105]	1.5T ; T1, T2 GRE, FLAIR	Presence vs absence of CMB [e105]	7 ICH	OR for CAA-unrelated ICH=1.98(0.20-19.41), as provided by Charidimou et al [e105] OR for CAA-related ICH=2.18(0.18-25.77), as provided by Charidimou et al [e105]
Boulouis 2017 [e17]	73	CAA-related ICH patients	229	2.8 (median)	1.5T; T1, T2*GRE or SWI, FLAIR	≥5 CMB vs 0-1 or vs 2-4 CMB	56 ICH	HR=0.84(0.39-1.67), p=0.640 for ≥5 CMB vs 0-1 CMB [b] (N for analyses = 197, of which 44 individuals with ≥5 CMB, exact number of incident ICH unknown) HR=0.69(0.29-1.65), p=0.397 for ≥5 CMB vs 2-4 CMB [b] (N for analyses = 76, of which 44 individuals with ≥5 CMB, exact number of incident ICH unknown)
Nam, 2017 [e61]	66	First ever LAA IS patients	956	2.8 y (duration)	1.5T or 3T; T1, T2, DWI, T2 gradient echo, FLAIR	Presence vs absence of CMB	92 recurrent strokes	OR=1.14(0.71-1.84), p=0.585 [q]

Shoamanesh, 2017 [e75]	63	SPS3 trial (patients with recent, symptomatic, MRI-confirmed lacunar infarcts)	1278	3.3	T1, FLAIR, T2*	CMB count + comparison of 1-2; 3-10; >10 vs none	100	All strokes: HR=4.0(1.8-8.7) for >10 CMB vs none (N=943, 62 incident strokes, 45 participants with >10 CMB) [p] ICH: Crude OR=1.07(0.37-3.12) as calculated by authors based on raw data provided in the article (N=1278, 16 incident ICH, 380 participants with CMB)
CROMIS-1 (unpublished, from Wilson 2016 [e20])	66 [e20]	IS/TIA patients [e20]	68 [e20]	2 [e20]	1.5T; T2* [e20]	Presence vs absence of CMB [e20]	12 IS [e20]	RR=2.68(0.99-7.31) as provided by Wilson et al [e20]
Heidelberg (unpublished, from Wilson 2016 [e20])	65 [e20]	IS patients [e20]	265 [e20]	1 [e20]	1.5T; SWI [e20]	Presence vs absence of CMB [e20]	8 IS [e20]	RR=1.30(0.27-6.27) as provided by Wilson et al [e20]
OXVASC (unpublished, from Wilson 2016 [e20])	72 [e20]	IS/TIA patients [e20]	323 [e20]	2.92 [e20]	1.5T; T2* [e20]	Presence vs absence of CMB [e20]	18 IS and 1 hemorrhagic stroke [e20]	RR=2.58(1.04-6.38), for IS as provided by Wilson et al [e20] RR=12.00(0.49-291.18), for hemorrhagic stroke, as provided by Wilson et al [e20]

AD: Alzheimer Disease; CAA: cerebral amyloid angiopathy; CMB: cerebral microbleed; DWI: diffusion-weighted imaging; FLAIR: fluid-attenuated inversion recovery; Fu: follow-up; GRE: gradient-recalled echo; HR: hazard ratio; ICH: intracerebral hemorrhage; NA: not available; PWEPI: gadolinium bolus-tracking perfusion-weighted echo-planar imaging; RR: Risk Ratio; IS: ischemic stroke; SAH; subarachnoid hemorrhage; SWI: susceptibility weighted imaging; TIA: transient ischemic attack; * adjusted for age and sex; † adjusted for age-squared, sex, and Rotterdam Study subcohort; ‡ adjusted for age-squared, sex, Rotterdam Study subcohort, and APOE ε4 carriership; § adjusted for age-squared, sex, Rotterdam Study subcohort, and for propensity score. (The propensity score included hypertension, total and high-density lipoprotein cholesterol, smoking, diabetes mellitus, lipid-lowering medication, and antithrombotic medication use.); ª adjusted for age-squared, sex, Rotterdam Study subcohort, lacunes, white matter lesion volume, and intracranial volume; ᵇadjusted for age at event, hypertension, diabetes mellitus, cortical superficial siderosis, enlarged centrum-semiovale perivascular spaces and qualifying white matter hyperintensities ᶜ adjusted for interval between MRI scans, APOE genotype and history of prior ICH; ᵈ adjusted for age and presence of confluent white matter disease; ᵉ adjusted for age, gender, stroke type, advanced leukoaraiosis, hypertension, diabetes, hypercholesterolemia, antiplatelet therapy, days from stroke onset; ᶠ adjusted for age, gender, hypertension, anti-thrombotic treatment; ᵍ corrected for baseline imbalances in white matter disease and prestroke history; ʰ adjusted for age; ⁱ adjusted for WMH grade 2-3, female gender, age 65 years or older, body mass index of 26 kg/m2 or more, hypertension, and a history of cerebral infarction and ICH; ʲcalculated by the authors based on raw data provided in the article; ᵏ adjusted for age and sex; ˡ adjusted for age, gender, previous hemorrhagic stroke; ᵐ adjustment for ABCD-I score 8-13, WMH; ⁿ Adjusted for age, sex, Mini-Mental State Examination score, vascular risk factors, white matter hyperintensities, and lacunes.; ᵒ Adjusted for CHADS-2; ᵖ adjusted for assigned treatments and clinical risk factors male sex, black race, diabetes, and prior symptomatic lacunar stroke or transient ischemic attack; �q adjusted for age, severe white matter hyperintensity, old lacunar infarction, asymptomatic territorial infarction,and severe stenosis of relevant artery

eTable 11. Studies testing the association of cerebral microbleed (CMB) with incident dementia

Author, y	Mean age	Population	N	Fu (y)	MRI characteristics	CMB measure	Incident event	Dementia type	Result
General population									
Akoudad, 2016 [e5]	62.4 (CMB -, N=3911) / 69.8 (CMB +, N=930)	Rotterdam Study	4841	4.8 (mean)	1.5T; T1, PD, FLAIR, T2	Presence or absence of CMB; location;	72 (53 AD)	All dementia	Any microbleed (vs none) HR=2.02(1.25-3.24) (N=4841) [b] **HR=1.59(0.88-2.89) (N=3816, of which 47 incident dementias) [c]** HR=1.73(1.03-2.90) (N=4611) [d] Lobar (with or without cerebellar MB, vs none) HR=1.81(1.05-3.11) (N=4559) [b] HR=1.65(0.86-3.17) (N=3600) [c] HR=1.55(0.86-2.81) (N=4346) [d] Deep or infratentorial (with or without lobar MB, vs none) HR=2.39(1.23-4.61) (N=4193) [b] **HR=1.40(0.55-3.52) (N=3304) [c]** HR=2.42(1.18-4.96) (N=4008) [d]
								AD	Any microbleed (vs none) HR=2.10(1.21-3.64) [b] **HR=1.67(0.83-3.36) (N=3816, of which 34 incident AD) [c]** HR=1.83(1.00-3.33) [d] Lobar (with or without cerebellar MB, vs none) HR=2.00(1.08-3.71) [b] HR=1.66(0.77-3.59) [c] HR=1.70(0.87-3.32) [d] Deep or infratentorial (with or without lobar MB, vs none) HR=2.15(0.97-4.78) [b] HR=1.58(0.56-4.45) [c] HR=2.34(0.98-5.63) [d]
Ding, 2017 [e109]	74.6	AGES– Reykjavik Study	2602	5.2 (mean)	1.5T; T2* gradient echo, PD/T2 FSE	Presence or absence of microbleeds	119 (86 AD, 21 VaD)	All dementia	Crude OR=1.00 (0.61-1.64), (N=2,601, 119 dementia, 437 individuals with CMB) as calculated by authors based on raw data provided in the article
								AD	Crude OR=0.80(0.43-1.48), (N=2,601, 86 AD, 437 individuals with CMB), as calculated by

								authors based on raw dara provided in the article
							VaD	Crude OR=1.99(0.77-5.17), (N=2,601, 21 VaD, 437 individuals with CMB) as calculated by authors based on raw dara provided in the article
Romero, 2017 [e72]	72	FHS (dementia free)	1296	6.7 (mean)	1.5T; T1, T2, T2* gradient echo	Presence or absence of CMB (overall and according to location)	85 (63 AD and 21 VaD)	All dementia	Any CMB : HR=1.74(1.00-3.01), p=0.049 [e] HR=1.44(0.82-2.54), p=ns [f] **HR=1.89(1.04-3.44), p=0.038 [g]** Lobar CMB only HR=1.01(0.46-2.23), p=ns [e] HR=0.85(0.38-1.90), p=ns [f] HR=0.89(0.35-2.27), p=ns [g] Lobar + mixed CMB HR=1.48(0.79-2.78), p=ns [e] HR=1.21(0.63-2.31), p=ns [f] **HR=1.51(0.75-3.05), p=ns [g]** Deep only HR=2.50(1.00-6.30), p=0.05 [e] HR=2.16(0.85-5.48), p=ns [f] **HR=2.85(1.10-7.36), p=0.03 [g]** Deep + mixed HR=2.99(1.52-5.90), p=0.002 [e] HR=2.44(1.22-4.88), p=0.01 [f] **HR=3.49(1.72-7.10), p<0.001 [g]**

								AD	Any CMB : HR=1.92(1.02-3.61), p=0.044 [e] HR=1.69(0.88-3.25), p=ns [f] **HR=2.30(1.16-4.55), p=0.017 [g]** Lobar CMB only HR=1.07(0.42-2.73), p=ns [e] HR=0.95(0.37-2.47), p=ns [f] HR=1.10(0.38-3.15), p=ns [g] Lobar + mixed CMB HR=1.65(0.79-3.44), p=ns [e] HR=1.43(0.67-3.03), p=ns [f] HR=1.90(0.86-4.22), p=ns [g] Deep only HR=2.68(0.95-7.52), p=ns [e] HR=2.55(0.89-7.17), p=ns [f] HR=3.27(1.12-9.59), p=0.03 [g] Deep + mixed HR=3.29(1.54-7.06), p=0.002 [e] HR=2.95(1.36-6.42), p=0.006 [f] HR=4.15(2.23-7.73), p<0.001 [g]
High-risk populations									
Staekenborg, 2009 [e81]	69.9	MCI patients	152	2.0	1.0T ; T1, FLAIR, T2*	Presence or absence of CMB	72: 56 AD (NINCDS-ADRDA), 16 non-AD (7 VaD, 5 FTLD, 2 DLB, 1 PaD, 1 alcohol dementia)	AD	HR=0.8(0.2-2.2) [‡]
								Non-AD	HR=2.6(0.9-7.5) [‡]
Miwa, 2014 [e57]	67.7	OSACA2	524	7.5 (median)	T1, T2, FLAIR, T2* GRE	Number of CMB; location of CMB; categories: 0 CMB (ref), 1 CMB, ≥2 CMB; presence or absence	44 using DSM-III-R (20 AD, 18 VaD, 3 mixed-type, and 3 other type).	All dementia	**HR=2.67(1.38-5.14), p<0.01 [§] for presence vs absence of CMB** HR=1.09(0.26-3.14) [§] for 1CMB vs 0 HR= 2.43(1.17-4.83), p<0.01 [§] for ≥2 CMB vs 0 **HR=1.18(0.33-2.89) [§] for strictly deep CMB** HR=2.54(1.07-5.57) [§] for mixed CMB **HR=1.73(0.51-4.42) [§] for strictly lobar CMB**
								AD	**HR=1.22(0.32-3.72) [§] for presence vs absence**

								VaD + mixed	HR=0.66(0.03–3.77) § for 1CMB vs 0 HR=1.62(0.36-5.30) § for ≥2CMB vs 0 HR NA for strictly deep CMB HR=2.23(0.34-8.42) § for mixed CMB HR=1.04(0.15-3.99) § for strictly lobar CMB
								VaD + mixed	HR=3.36(1.25-8.88) § for presence vs absence HR=1.86(0.28-7.41) § for 1 CMB vs 0 HR=4.57(1.51-12.8) § for ≥2 CMB vs 0 HR=2.26(0.51-7.19) § for strictly deep CMB HR=5.37(1.47-15.8), p<0.05 § for mixed CMB HR=0.87(0.05-4.40) § for strictly lobar CMB
Van Uden, 2016 [e110]	65.6	patients with SVD	500	5.2	1.5T; T1, FLAIR, T2*, DTI	Presence vs absence of CMB	43 dementia (DSM-IV) (28 AD [NIA-AA], 11 VaD [NINDS-AIREN])	All dementia	HR=0.60(0.25-1.43), p=0.252, N=499 [h]
								AD	Crude OR=0.41(0.09-1.75), N=486 (28 AD, 75 participants with CMB), as calculated by authors based on raw data provided in the article
								VaD	Crude OR=4.39(1.31-14.78), N=469 (11 VaD, 78 participants with CMB), as calculated by authors based on raw data provided in the article

AD: Alzheimer's disease; CMB: cerebral microbleed; DLB: dementia with Lewy bodies; DSM-III: Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition American[e99]; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition american[e100]; Fu: follow-up; FLAIR: fluid-attenuated inversion recovery; FSE: fast spin echo; FTLD: frontotemporal lobar degeneration; HR: hazard ratio; MCI: mild cognitive impairment; ; NIA-AA: The National Institute on Aging and the Alzheimer's Association [e71] ; NINCDS-ADRDA: criteria for AD from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association[e4]; NINDS-AIREN: National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences[e101] ; PaD: Parkinson dementia; PD: proton density; RR: risk ratio; VaD: vascular dementia;* adjusted for age, sex, and education; † adjusted for age, sex, education, depressive symptomology, visual acuity, smoking, hypertension, diabetes, body mass index, use of anticoagulants, brain infarcts, load of subcortical and periventricular white matter hyperintensities, and if applicable, for retinopathy or CMBs; ‡ analyses adjusted for age and sex; § analyses adjusted for age, sex, education level, and APOE e4 status; a adjusted for age, gender, educational level, and APOEε4 carrier status; b Adjusted for age, sex, and educational level; c adjusted for age, sex, educational level, APOE ε4 allele and a propensity score of cardiovascular risk factors that included hypertension, total and high-density lipoporotein cholesterol levels, smoking status, diabetes, and use of lipid level–lowering medication and antithrombotics ; d adjusted for age, sex, educational level, lacunes, intracranial volume, and white matter lesion volume ; e adjusted for age, sex, education and APOE4 ; f adjusted for age, sex, education, APOE4, ischemic MRI markers: log-white matter hyperintensity volume, covert brain infarcts ; g adjusted for age, sex, education, APOE4, hypertension, diabetes, and prevalent cardiovascular disease; h adjusted for age, gender, education, baseline MMSE, and territorial infarcts,

eTable 12. Studies testing the association of cerebral microbleed (CMB) with mortality

Author, y	Mean age	Population	N	Fu (y)	MRI characteristics	CMB measure	Incident deaths	Result
General population								
Akoudad, 2013 [e7]	64.5 (CMB +) / 59.5 (CMB -)	Rotterdam Scan Study	3979	5.2	1.5T; T1, T2*GRE, FLAIR, PD	Presence or absence or CMB ; number and location of CMB	172 (36 cardiovascular deaths and 11 stroke-related deaths)	CMB ≥1 vs none (N=3979): HR=1.56(1.12-2.17) * for all-cause mortality **HR=1.37(0.96-1.94) [†] for all-cause mortality** HR=2.37(1.19-4.70) * for cardiovascular mortality HR=1.98(0.59-6.70) * for stroke mortality HR=1.30(0.81-2.09) * for non-cardiovascular mortality CMB deep or infratentorial (N=3566): HR=2.27(1.50-3.45) * for all-cause mortality **HR=1.87(1.20-2.92) [†] for all-cause mortality** HR=4.08(1.78-9.39) * for cardiovascular mortality HR=5.02(1.33-18.91) * for stroke mortality HR=1.81(0.99-3.29) * for non-cardiovascular mortality CMB strictly lobar (N=3783): HR=1.16(0.76-1.79) * for all-cause mortality **HR=1.04(0.65-1.66) [†] for all-cause mortality** HR=1.73(0.71-4.19) * for cardiovascular mortality HR=1.00(0.10-10.32) * for stroke mortality HR=0.96(0.51-1.80) * for non-cardiovascular mortality
Romero, 2017 [e73]	67	FHS	1963	7.2 (mean)	1.5 T; T1, T2, T2* gradient echo	Presence vs absence of CMB (also in locations)	296 (60 CVD deaths)	Any CMB vs none: HR=1.39(1.03–1.88), for all-cause mortality (N=1963) [d] **HR=1.20(0.85-1.70), for all-cause mortality (N=1818) [e]** HR=1.15(0.82–1.63), for all-cause mortality (N=1818) [f] HR=1.65(0.88-3.10), for CVD mortality (N=1963) [d]

								HR=1.58(0.75-3.35), for CVD mortality (N=1818) [e] HR=1.71(0.80-3.67), for CVD mortality (N=1818) [f] Lobar CMB only vs no CMB: HR=1.41(0.97-2.04), for all-cause mortality (N=1899) [d] **HR=1.19(0.77-1.84), for all-cause mortality (N=1760) [e]** HR=1.14(0.74-1.77), for all-cause mortality (N=1760) [f] HR=1.95(0.94-4.03), for CVD mortality (N=1899) [d] HR=1.63(0.65-4.08), for CVD mortality (N=1760) [e] HR=1.77(0.69-4.53), for CVD mortality (N=1760) [f] Deep + mixed CMB vs no CMB HR=1.33(0.85-2.08), for all-cause mortality (N=1854) [d] **HR=1.21(0.73-1.99), for all-cause mortality (N=1721) [e]** HR=1.17(0.71-1.94), for all-cause mortality [f] NA for CVD mortality
High-risk populations								
Fan, 2003 [e26]	67.96	IS patients	121	2.26	1.5T ; T1, T2, T2* GRE	Presence or absence of CMB	14 (5 in CMB positive group and 9 in CMB negative group)	No difference between the CMB positive group and the CMB negative group (p=1.0) Crude OR=1.01(0.31-3.21), p=0.99, calculated by authors based on raw information provided in the article
Boulanger, 2006 [e16]	NA	IS/TIA patients (VISION study)	236	1.17 (median)	3T ; T1, T2, FLAIR, DWI, T2*GRE or PWEPI	Presence or absence of microhemorrhages	20	HR=4.4(1.9-10.7), p<0.001 (crude) **HR=3.1(1.2-7.8), p=0.015 ‡**
Soo, 2008 [e80]	NA	IS patients	908	2.2	1.5T ; T1, T2, T2*GRE, FLAIR	Number, location of CMB ; presence vs absence	107 (of which 30 from subsequent ICH, recurrent IS, or MI)	OR=2.04(0.98-4.27), p=0.057 § for mortality from subsequent ICH, recurrent IS, or MI
Henneman, 2009 [e34]	66	Memory clinic patients	1138	2.6	1.0T (N=998) or 1.5T (N=140); T1, T2, T2*, FLAIR	Number of CMB and categories (0, 1-2 ; ≥3)	153	HR=1.01(1.00-1.03), p<0.05 [a] for number of CMB (N=938) HR=1.01(1.00-1.03), p<0.05 [b] for number of CMB HR=1.4(1.1-1.9), p<0.05 [a] for categorical CMB HR=1.6(1.2-2.1), p<0.01 [b] for categorical CMB

								HR=2.4(1.4-4.3), p<0.05 [a] for ≥3 CMB vs none (N=836) HR=0.8(0.4-1.6), p=0.60 [a] for 1-2 CMB vs none (N=882)
Altmann-Schneider, 2011 [e10]	75	PROSPER study (Nested MRI substudy)	435	7.0	1.5T; FSE, FLAIR, T2*	Number and location of CMB	153 (of which 57 cardiovascular deaths)	Overall mortality: HR=0.70(0.38-1.28), p=0.24 [c] (N=367) for 1 CMB vs 0 **HR=1.41(0.87-2.27), p=0.16 [c] (N=371, of which 131 deaths) for >1 CMB vs 0** Cardiovascular mortality: HR=0.60(0.21-1.71), p=0.34 [c] (N=366) for 1 CMB vs 0 HR=1.78(0.86-3.70), p=0.12 [c] (N=370, of which 49 deaths) for >1CMB vs 0 Stroke-related mortality: NA for 1 CMB vs 0 [c] HR=5.97(1.60-22.26), p=0.01 [c] (N=370, of which 13 deaths) for >1 CMB vs 0
Kwa, 2013 [e51]	65.3	TIA or minor IS patients	397	3.8 (mean)	0.5T, 1.0T, 1.5T ; T2* FFE GRE	Presence of microbleeds	40	HR=1.6(0.8-3.3) [i]
Benedictus, 2015 [e11]	71.2	AD patients from the MISTRAL study (from the Amsterdam Dementia Cohort)	333 (111 with CMB; 222 without CMB, matched for age, sex and MRI)	>3.0	1-T (n = 171), 1.5-T (n = 57), or 3-T (n = 105); T1, T2, FLAIR, T2*GRE	Presence or absence of CMB and location	147 (of which 11 cardiovascular deaths and 7 stroke-related deaths)	N=301 for analyses All-cause mortality **HR=1.7(1.2-2.4), for any CMB vs none [g]** HR=1.6(0.7-3.4) for strictly nonlobar CMB [g] HR=1.7(1.2-2.5) for any lobar CMB [g] Stroke-related mortality HR=14.6(1.6-132.7) for any CMB [g] HR=33.9(2.5-461.7) for any lobar CMB [g] NA for strictly nonlobar CMB [g] Cardiovascular death HR=2.1(0.8-5.7) for any CMB [g] HR=12.0(3.2-44.7) for strictly nonlobar CMB [g] HR=1.0(0.3-3.5) for any lobar CMB [g]
Shoamanesh, 2017 [e75]	63	SPS3 trial (patients with recent, symptomatic, MRI-confirmed lacunar infarcts)	1278	3.3	T1, FLAIR, T2*	CMB count + comparison of 1-2; 3-10; >10 vs none	78	HR=1.4(0.4-4.4) for >10 CMB vs none (N=943, 54 deaths, 45 participants with >10 CMB) [h]

CMB: cerebral microbleed; CVD: cardiovascular disease; DWI: diffusion-weighted imaging; FLAIR: fluid-attenuated inversion recovery; Fu: follow-up; GRE: gradient-recalled echo; HR: hazard ratio; PD: proton density; PWEPI: gadolinium bolus-tracking perfusion-weighted echo-planar imaging; IS: ischemic stroke; OR: odds ratio; TIA: transient ischemic attack; y: years; * Adjusted for age, sex, subcohort; † Adjusted for age, sex, subcohort, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein, antihypertensive

medication, diabetes, smoking; ‡ Adjusted for age and presence of confluent white matter disease; § crude OR computed by authors from figures provided in the article; [a] adjusted for age, sex and diagnosis; [b] adjusted for age, sex, diagnosis, and history of hypertension, diabetes mellitus, hypercholesterolemia, and myocardial infarction; [c] adjusted for age, sex, use of statins and cardiovascular risk factors ; [d] Adjusted for age at MRI and sex ; [e] Adjusted for age at MRI, sex, systolic blood pressure, hypertension treatment, current smoking, diabetes mellitus, total cholesterol, cholesterol treatment, aspirin use, antiplatelet use, anticoagulant use, prevalent CVD, apoE4, and time between covariate assessment and MRI ; [f] Adjusted for age at MRI, sex, systolic blood pressure, hypertension treatment, current smoking, diabetes mellitus, total cholesterol, cholesterol treatment, aspirin use, antiplatelet use, anticoagulant use, prevalent CVD, apoE4, and time between covariate assessment and MRI, covert brain infarcts and ln-transformed WMH volume ; [g] Adjusted for age, sex, Mini-Mental State Examination score, vascular risk factors, white matter hyperintensities, and lacunes; [h] adjusted for assigned treatments; [i] adjusted for age and sex;

eTable 13. Studies testing the association of perivascular spaces (PVS) with incident stroke

Author, y	Mean age	Population	N	Fu (y)	MRI characteristics	PVS measure	Incident event	Result
General population								
Gutierrez, 2017 [e33]	71	NOMAS	1228	9 (mean)	1.5T; FLAIR	Highest tertile	Any stroke	HR=1.51(0.88-2.57) [*]
High-risk populations								
Boulouis 2017 [e17]	73	CAA-related ICH patients	229	2.8 (median)	1.5T; T1, T2*GRE or SWI, FLAIR	≥20	56 ICH	HR=3.50(1.04-21), p=0.042 [‡]
Lau, 2017 [e52]	68 (OXVASC); 69 (HKU)	OXVASC and HKU, IS or TIA patients	2156 (1080 from OXVASC + 1076 from HKU)	3.5 (mean)	3T (N=1076 from HKU + 450 from OXVASC), 1.5T (630 from OXVASC); T1, T2, FLAIR	11-20 and >20 compared to <11	199 (170 IS; 29 ICH)	N=2002 for analyses (1028 from OXVASC and 974 from HKU) Recurrent all strokes PVS in basal ganglia HR=1.13(0.79-1.61) [†] for 11-20 vs <11 HR=1.94(1.31-2.89) [†] for >20 vs <11 PVS in centrum semiovale HR=0.92(0.66-1.28) [†] for 11-20 vs <11 HR=0.89(0.60-1.33) [†] for >20 vs <11 Recurrent IS PVS in basal ganglia HR=1.15(0.78-1.68) [†] for 11-20 vs <11 HR=1.82(1.18-2.80) [†] for >20 vs <11 PVS in centrum semiovale HR=0.96(0.67-1.37) [†] for 11-20 vs <11 HR=0.83(0.54-1.28) [†] for >20 vs <11 Recurrent ICH PVS in basal ganglia HR=0.95(0.37-2.46) [†] for 11-20 vs <11 HR=2.58(0.97-6.89) [†] for >20 vs <11 PVS in centrum semiovale HR=0.69(0.28-1.67) [†] for 11-20 vs <11 HR=1.36(0.51-3.59) [†] for >20 vs <11

CAA: cerebral amyloid angiopathy; FLAIR: fluid-attenuated inversion recovery; GRE: gradient-recalled echo; HR: hazard ratio; ICH: intracerebral hemorrhage; IS: ischemic stroke; TIA: transient ischemic attack; RR: relative rate; SWI: susceptibility-weighted imaging; [*] adjusted for age, sex, vascular risk factors, and ethnic origin, intracranial volume; [†] adjusted for age, sex, hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, smoking history, MRI scanner strength, center; [‡] adjusted for age at event, hypertension, diabetes mellitus, cortical superficial siderosis, qualifying white matter hyperintensities and cerebral microbleeds

eTable 14. Studies testing the association of perivascular spaces (PVS) with incident dementia

Author, y	Mean age	Population	N	Fu (y)	MRI characteristics	PVS measure	Incident event	Dementia subtype	Result
General population									
Zhu, 2010 [e94]	72.4	3C-Dijon study	1778	3.5 (median)	1.5T; T1, T2, PD	Degree of PVS and location	27 (DSM-IV)	All dementia	PVS in basal ganglia HR=1.8(0.7-4.5), p=0.19 * for degree 2 vs 1 HR=0.9(0.2-4.3), p=0.90 * for degree 3 vs 1 HR=5.8(1.2-28.4), p=0.03 * for degree 4 vs 1 PVS in white matter HR=3.1(0.7-13.9), p=0.13 * for degree 2 vs 1 HR=2.6(0.5-14.4), p=0.26 * for degree 3 vs 1 HR=9.8(1.7-55.3), p=0.01 * for degree 4 vs 1
Ding, 2017 [e23]	74.6	AGES-Reykjavik Study	2612	5.2 (mean)	1.5T; T1, T2, PD/FSE, T2*	trichotomous variable (none, 1 single and multiple [≥ 2]); by location ; presence versus absence for analyses	119 all dementia using DSM-IV: (86 AD (NINCDS-ADRDA) and 21 vascular dementia (ADDTC)	All dementia	N=5,591 for analyses RR=1.32(0.89-1.97)[†]
								AD	RR=1.16(0.66-2.05) [†]
								Vascular dementia	RR=3.34(1.41-7.93) [†]

AD: Alzheimer's disease; ADDTC: Alzheimer's disease Diagnostic and Treatment Centers[e107,e108]; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition american[e100]; fu: follow-up; FLAIR: fluid-attenuated inversion recovery; HR: hazard ratio; NINCDS-ADRDA: criteria for AD from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association[e4]; PD: proton density; PVS: dilated perivascular spaces; y: year; RR: risk ratio; * adjusted for age, apolipoprotein E4 and total intracranial volume; † adjusted for age, sex, brain scan interval, coil type, body mass index, education, depression scores at follow-up, current smoking, hypertension, total cholesterol, microbleeds, relative measure of white matter hyperintensities, Apolipoprotein E genotype;

eTable 15. Studies testing the association of perivascular spaces (PVS) with mortality

Author, y	Mean age	Population	N	Fu (y)	MRI characteristics	PVS measure	Incident event	Result
General population								
Gutierrez, 2017 [e33]	71	NOMAS	1228	9 (mean)	1.5T; FLAIR	Highest tertile	Death	HR=1.34(0.80-2.23) *
High-risk populations								
Lau, 2017 [e52]	68 (OXVASC); 69 (HKU)	OXVASC and HKU, IS or TIA patients	2156 (1080 from OXVASC + 1076 from HKU)	3.5 (mean)	3T (N=1076 from HKU + 450 from OXVASC), 1.5T (630 from OXVASC); T1, T2, FLAIR	11-20 and >20 compared to <11	266 (92 vascular deaths)	N=2002 for analyses (1028 from OXVASC and 974 from HKU) Death PVS in basal ganglia HR=0.89(0.66-1.20) [†] for 11-20 vs <11 HR=1.33(0.96-1.85) [†] for >20 vs <11 PVS in centrum semiovale HR=0.70(0.52-0.94) [†] for 11-20 vs <11 HR=0.74(0.53-1.03) [†] for >20 vs <11 Vascular deaths PVS in basal ganglia HR=0.93(0.57-1.54) [†] for 11-20 vs <11 HR=1.31(0.74-2.31) [†] for >20 vs <11 PVS in centrum semiovale HR=0.80(0.49-1.30) [†] for 11-20 vs <11 HR=0.81(0.45-1.45) [†] for >20 vs <11 Nonvascular deaths PVS in basal ganglia HR=0.86(0.58-1.27) [†] for 11-20 vs <11 HR=1.32(0.87-2.00) [†] for >20 vs <11 PVS in centrum semiovale HR=0.61(0.42-0.90) [†] for 11-20 vs <11 HR=0.68(0.44-1.03) [†] for >20 vs <11

FLAIR: fluid-attenuated inversion recovery; HR: hazard ratio; ICH: intracerebral hemorrhage; IS: ischemic stroke; TIA: transient ischemic attack; *adjusted for age, sex, vascular risk factors, and ethnic origin, intracranial volume; [†] adjusted for age, sex, hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, smoking history, MRI scanner strength, center

eTable 16. Sensitivity analyses after exclusion of studies with medium-quality to low-quality scores on the Newcastle-Ottawa Scale (NOS) or studies reporting odds ratios only

Event	MRI-marker of covert VBI		
Studies	**Extensive WMH burden**	**BI presence**	**CMB presence**
Stroke			
All	HR= 2.45 (1.93-3.12), p=2.61x10^{-13}	HR= 2.38 (1.87-3.04), p=2.65x10^{-12}	HR= 1.98 (1.55-2.53), p=4.62x10^{-8}
	17 studies; N=14,529; 1,049 events	*12 studies; N=16,012; 881 events*	*22 studies; N=15,693;831 events*
NOS < 7 excluded	HR= 2.31 (1.83-2.91), p=1.49x10^{-12}	HR= 2.46 (1.89-3.19), p=1.57x10^{-11}	HR= 1.82 (1.39-2.39), p=1.48x10^{-5}
	15 studies; N=14,210; 1,021events	*10 studies; N=15,408; 822 events*	*16 studies; N=14,104; 749 events*
ORs excluded	HR= 2.52 (1.90-3.34), p=1.34x10^{-10}	HR= 2.36 (1.83-3.05), p=4.42x10^{-11}	HR= 2.08 (1.59-2.71), p=7.28x10^{-8}
	13 studies; N=9,993; 737 events	*10 studies; N=12,914; 733 events*	*17 studies; N=13,514; 588 events*
IS			
All	HR= 2.39 (1.65-3.47), p=4.34x10^{-6}	HR= 2.18 (1.67-2.85), p=1.09x10^{-8}	HR= 1.92 (1.40-2.63), p=5.00x10^{-5}
	9 studies; N=7,320; 696 events	*6 studies; N=6,873; 333 events*	*20 studies; N=13,125; 459 events*
NOS < 7 excluded	HR= 2.34 (1.57-3.48), p=2.83x10^{-5}	HR= 2.31 (1.71-3.13), p=5.67x10^{-8}	HR=1.66 (1.14-2.40), p=7.61x10^{-3}
	8 studies; N events	*4 studies; N=6,269; 280 events*	*14 studies; N=11,536; 377 events*
ORs excluded	HR= 2.39 (1.65-3.47), p=4.34x10^{-6}	HR= 2.36 (1.77-3.16), p=6.34x10^{-9}	HR= 1.92 (1.33-2.78), p=5.24x10^{-4}
	9 studies; N=7,320; 696 events	*5 studies; N=6,459; 292 events*	*14 studies; N=11,685; 297 events*
ICH			
All	HR= 3.17 (1.54-6.52), p=1.72x10^{-3}	HR= 3.81 (1.75-8.27), p=7.35x10^{-4}	HR= 3.82 (2.15-6.80), p=5.05x10^{-6}
	7 studies; N=7,976; 148 events	*5 studies; N=8,847; 88 events*	*23 studies; N=14,280; 218 events*
NOS < 7 excluded	HR= 2.87 (1.34-6.14), p=6.62x10^{-3}	HR= 4.40 (1.88-10.31), p=6.43x10^{-4}	HR= 4.48 (2.16-9.31), p=5.73x10^{-5}
	6 studies; N=7,894; 148 events	*4 studies; N=8,433; 83 events*	*19 studies; N=12,671; 193 events*
ORs excluded	HR= 2.54 (0.95-6.82), p=0.06	HR= 4.06 (1.98-8.35), p=1.35x10^{-4}	HR= 6.73 (2.67-17.00), p=5.40x10^{-5}
	5 studies; N=5,067; 114 events	*2 studies; N=5,676; 64 events*	*14 studies; N=11,049; 164 events*
Dementia			
All	HR= 1.84 (1.40-2.43), p=1.46x10^{-5}	HR= 1.29 (1.02-1.65), p=3.79x10$^{-2\ a}$	HR= 1.41 (0.90-2.21), p=0.13
	12 studies; N=9,338; 1,127 events	*9 studies; N=10,772; 1,029 events*	*5 studies; N=8,736; 338 events*
NOS < 7 excluded	HR= 1.91 (1.40-2.61), p=4.65x10^{-5}	HR= 1.24 (1.00-1.55), p=0.05	HR= 1.41 (0.90-2.21), p=0.13
	9 studies; N=9,051; 1,048 events	*8 studies; N=10,688; 1,020 events*	*5 studies; N=8,736; 338 events*
ORs excluded	HR= 1.76 (1.29-2.38), p=2.97x10^{-4}	HR= 1.24 (1.00-1.55), p=0.05	HR= 1.57 (0.93-2.66), p=0.09
	9 studies; N=8,568; 1,011 events	*8 studies; N=10,688; 1,020 events*	*4 studies; N=6,135; 269 events*
AD			
All	HR= 1.50 (1.22-1.84), p=1.10x10^{-4}	HR= 1.06 (0.83-1.36), p=0.64	HR= 1.18 (0.73-1.89), p=0.49
	6 studies; N=5,206; 572 events	*3 studies; N=3,429; 414 events*	*6 studies; N=8,875; 290 events*
NOS < 7 excluded	HR= 1.50 (1.22-1.84), p=1.10x10^{-4}	HR= 1.06 (0.83-1.36), p=0.64	HR= 1.18 (0.73-1.89), p=0.49
	6 studies; N=5,206; 572 events	*3 studies; N=3,429; 414 events*	*6 studies; N=8,875; 290 events*
ORs excluded	HR= 1.50 (1.22-1.84), p=1.10x10^{-4}	HR= 1.10 (0.85-1.42), p=0.47	HR= 1.66 (1.09-2.54), p=1.88x10^{-2}
	6 studies; N=5,206; 572 events	*2 studies; N=2,943; 386 events*	*4 studies; N=5,788; 176 events*
Death			
All	HR= 2.00 (1.69-2.36), p=4.06x10^{-16}	HR= 1.64 (1.40-1.91), p=4.30x10^{-10}	HR= 1.53 (1.31-1.80), p=1.55x10^{-7}
	13 studies; N=13,138; 1,700 events	*8 studies; N=10,007; 1,212 events*	*10 studies; N=9,942; 1,134 events*
NOS < 7 excluded	HR= 2.00 (1.71-2.35), p=1.27x10^{-17}	HR= 1.59 (1.32-1.90), p=6.01x10^{-7}	HR= 1.55 (1.31-1.82), p=1.74x10^{-7}
	12 studies; N=13,049; 1,696 events	*6 studies; N=8,928; 1,160 events*	*9 studies; N=9,821; 1,120 events*
ORs excluded	HR= 1.92 (1.65-2.24), p=6.02x10^{-17}	HR= 1.59 (1.32-1.90), p=6.01x10^{-7}	HR= 1.53 (1.29-1.82), p=1.28x10^{-6}
	10 studies; N=10,106; 1,573 events	*6 studies; N=8,928; 1,160 events*	*8 studies; N=8,913; 1,013 events*

BI : covert brain infarcts ; CMB : cerebral microbleeds ; HR : hazard ratio ; NOS : Newcastle-Ottawa Scale ; OR : odds ratio ; WMH : white matter hyperintensities of presumed vascular origin ;

eTable 17. Meta-regression showing the *P* value for the regression coefficient

| Incident event | Subgroup | Moderator variable | MRI-marker of covert vascular brain injury | | |
			WMH	BI presence	CMB presence
Stroke	**General population**	Length of follow-up	0.25	0.47	−†
		Adjusted for age	−*	−*	−†
		Adjusted for smoking	0.91	0.04	−†
		Adjusted for hypertension	0.32	−*	−†
		Adjusted for diabetes	0.32	−*	−†
	High-risk population	Length of follow-up	0.17	0.69	0.76
		Adjusted for age	0.07	0.98	0.83
		Adjusted for smoking	0.26	0.98	0.18
		Adjusted for hypertension	0.65	0.98	0.69
		Adjusted for diabetes	0.51	0.98	0.23
	Total	Length of follow-up	0.13	0.97	0.69
		Adjusted for age	0.05	0.60	0.99
		Adjusted for smoking	0.25	0.61	0.34
		Adjusted for hypertension	0.19	0.60	0.91
		Adjusted for diabetes	0.12	0.60	0.48
Dementia	**General population**	Length of follow-up	0.12	0.50	−†
		Adjusted for age	−*	−*	−†
		Adjusted for education	0.48	0.09	−†
	High-risk population	Length of follow-up	0.66	0.81	−†
		Adjusted for age	0.80	0.21	−†
		Adjusted for education	0.80	0.21	−†
	Total	Length of follow-up	0.93	0.81	−†
		Adjusted for age	0.44	0.21	−†
		Adjusted for education	0.45	0.02	−†
Death	**General population**	Length of follow-up	0.12	0.56	−†
		Adjusted for age	−*	−*	−†
		Adjusted for smoking	0.93	−*	−†
		Adjusted for hypertension	0.93	−*	−†
		Adjusted for diabetes	0.93	−*	−†
	High-risk population	Length of follow-up	0.71	0.60	0.24
		Adjusted for age	0.86	−*	0.76
		Adjusted for smoking	0.42	0.59	0.66
		Adjusted for hypertension	0.70	0.32	0.67
		Adjusted for diabetes	0.70	0.32	0.77
	Total	Length of follow-up	0.93	0.56	0.05
		Adjusted for age	0.81	0.46	0.89
		Adjusted for smoking	0.70	0.94	0.24
		Adjusted for hypertension	0.71	0.46	0.86
		Adjusted for diabetes	0.71	0.46	0.80

BI: covert brain infarcts; CMB: cerebral microbleeds; WMH, white matter hyperintensities.

* All studies adjusted for this variable. †Insufficient data.

eFigure 1. Flow chart of article selection for the systematic review and meta-analyses
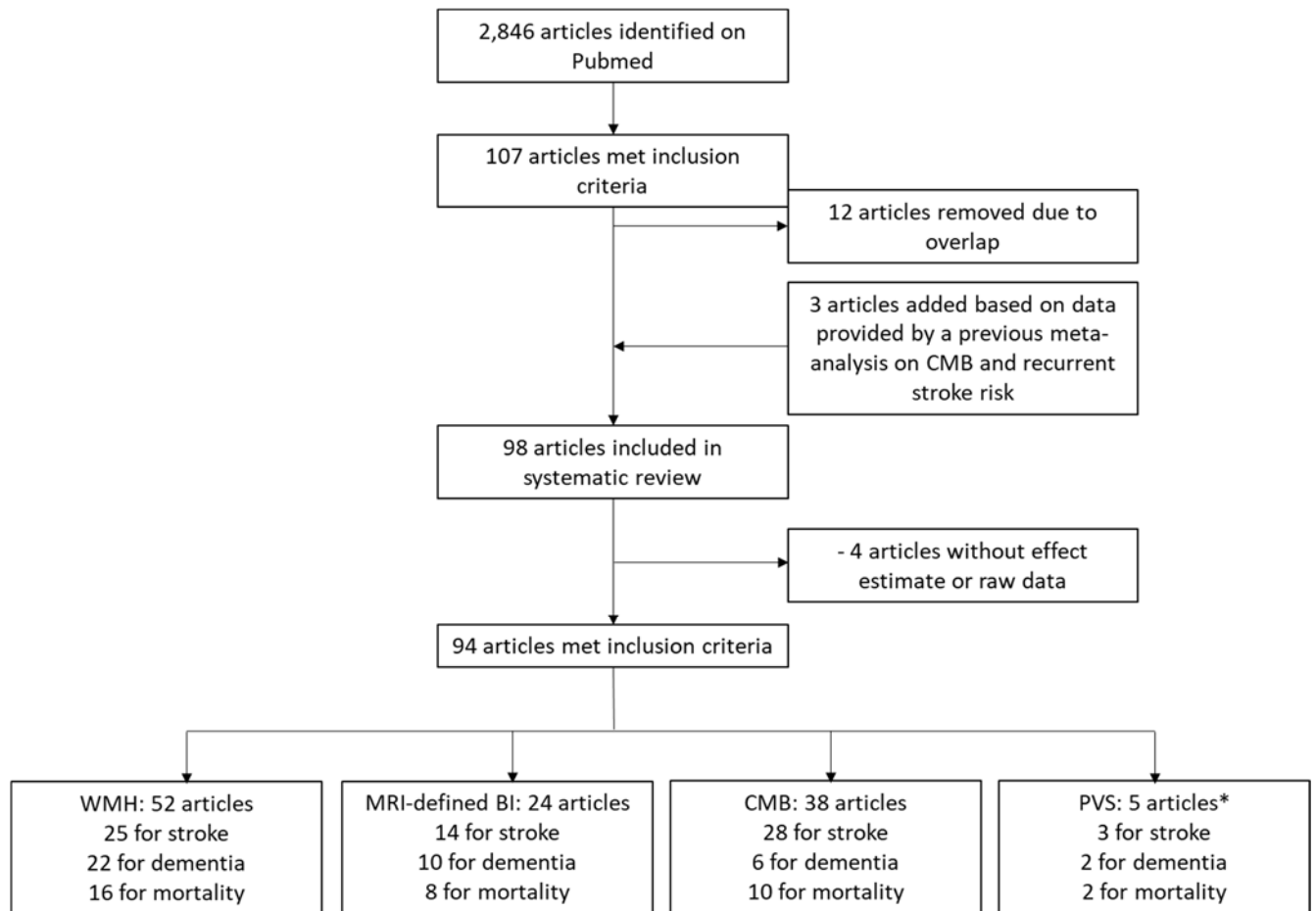
BI: covert brain infarcts; CMB: cerebral microbleeds; PVS: perivascular spaces; WMH: white matter hyperintensities of presumed vascular origin; * number of studies per outcome was insufficient to run a meta-analysis

eFigure 2. Association of extensive white matter hyperintensity (WMH) of presumed vascular origin with incident stroke and dementia subtypes

Association between WMH and incident ischemic stroke

Author	n/N	weight	risk
Kuller 2004	226/1395	13.8%	2.90 (1.70-4.80)
Windham 2015	140/1867	15.3%	2.12 (1.41-3.20)
Kaffashian 2016	54/1731	13.2%	1.60 (0.91-2.80)
GP	**420/4993**	**42.3%**	**2.16 (1.60-2.93)**
Gerdes 2006	21/230	8.6%	3.20 (1.30-8.40)
Naka 2006	16/266	5.1%	10.70 (2.60-43.70)
Conijn 2011	22/492	12.0%	3.60 (1.90-6.90)
Putaala 2011	69/634	8.2%	1.07 (0.40-2.85)
Melkas 2012	127/320	15.8%	1.23 (0.85-1.80)
Andersen 2017	21/385	8.2%	5.28 (1.98-14.07)
HRP	**276/2327**	**57.9%**	**2.78 (1.43-5.40)**
Total	**696/7320**	**100.0%**	**2.39 (1.65-3.47)**

HR scale: 0.8 2.0 3.0 5.0 10.0 20.0 45.0

Association between WMH and incident hemorrhagic stroke

Author	n/N	weight	risk
Bokura 2011	10/2102	13.3%	8.36 (2.13-32.81)
Folsom 2012	33/2759	20.2%	3.96 (1.90-8.27)
Kaffashian 2016	15/1731	14.6%	4.92 (1.43-16.88)
GP	**58/6592**	**48.1%**	**4.73 (2.67-8.40)**
Smith 2004	NA/82	8.6%	9.00 (1.20-67.20)
Naka 2006	10/266	3.0%	0.02 (0.00-0.26)
Imaizumi 2014	24/807	18.6%	3.32 (1.38-7.99)
Boulouis 2017	56/229	21.7%	1.39 (0.78-2.60)
HRP	**90/1384**	**51.9%**	**1.92 (0.58-6.37)**
Total	**148/7976**	**100.0%**	**3.17 (1.54-6.52)**

HR scale: 0.001 0.200 2.000 15.000

Association between WMH and incident Alzheimer's Disease

Author	n/N	weight	risk
Kuller 2003	330/2807	58.5%	1.50 (1.17-1.99)
Weinstein 2013	28/1414	5.7%	1.43 (0.61-3.36)
GP	**358/4221**	**64.2%**	**1.49 (1.16-1.92)**
Bombois 2008	29/170	6.0%	1.67 (0.73-3.81)
Staekenborg 2009	56/136	12.6%	1.20 (0.70-2.20)
Eckerström 2015	18/57	1.0%	0.50 (0.06-3.80)
Kim 2015	111/622	16.2%	1.86 (1.12-3.07)
HRP	**214/985**	**35.8%**	**1.51 (1.08-2.12)**
Total	**572/5206**	**100.0%**	**1.50 (1.22-1.84)**

HR scale: 0.06 0.10 0.20 0.50 1.00 2.00 4.00

GP: general population; HR: High Risk populations; WMH: white matter hyperintensities of presumed vascular origin; results correspond to hazard ratios (the size of blue boxes is proportional to sample size) with 95% confidence interval (horizontal line) for reach study; the meta-analysis results (inverse variance weighted meta-analysis with random effects) are shown in red diamonds; n/N corresponds to the number of individuals with the outcome of interest / the total sample size; Statistics for heterogeneity across studies: WMH-incident ischemic stroke: I²=67%, p=0.002; WMH-incident hemorrhagic stroke: I²=65%, p=0.008; WMH-incident Alzheimer's Disease: I²=0%, p=0.79

eFigure 3. Association of magnetic resonance imaging (MRI)–defined covert brain infarcts (BI) with incident stroke subtypes
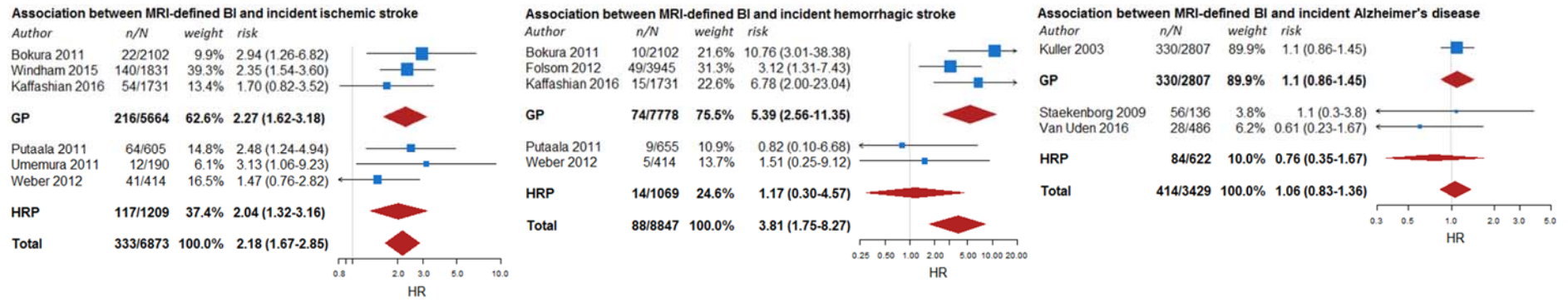
BI: covert brain infarcts; GP: general population; HR: High Risk populations; WMH: white matter hyperintensities of presumed vascular origin; results correspond to hazard ratios (the size of blue boxes is proportional to sample size) with 95% confidence interval (horizontal line) for reach study; the meta-analysis results (inverse variance weighted meta-analysis with random effects) are shown in red diamonds; n/N corresponds to the number of individuals with the outcome of interest / the total sample size; Statistics for heterogeneity across studies: MRI-defined BI-incident ischemic stroke: I²=0%, p=0.70; MRI-defined BI-incident hemorrhagic stroke: I²=40%, p=0.15; MRI-defined BI – incident Alzheimer's disease: I²=0%, p=0.53

eFigure 4. Association of cerebral microbleeds with incident stroke and dementia subtypes

Association between CMB and incident ischemic stroke

Author	n/N	weight	risk
Bokura 2011	22/2102	6.3%	4.48 (1.90-10.55)
Akoudad 2015	72/4759	9.0%	1.40 (0.84-2.34)
GP	**94/6861**	**15.3%**	**2.38 (0.76-7.39)**
Fan 2003	11/121	1.7%	7.90 (0.85-73.24)
Boulanger 2006	22/236	5.4%	1.68 (0.62-4.57)
Naka 2006	16/266	4.1%	0.61 (0.17-2.14)
Huang 2008	21/636	6.2%	2.51 (1.06-5.96)
Soo 2008	96/908	9.9%	1.30 (0.87-1.94)
Mok 2009	5/75	1.8%	0.85 (0.10-7.18)
Nishikawa 2009	10/698	3.6%	11.77 (2.95-46.89)
Thijs 2010	32/487	7.2%	2.00 (0.96-4.17)
Fluri 2012	7/176	3.0%	8.91 (1.87-42.48)
Kwa 2013	23/397	5.8%	2.30 (0.91-5.84)
Song 2013	28/550	6.1%	0.59 (0.25-1.42)
Imaizumi 2014	5/138	2.5%	1.50 (0.26-8.68)
Benedictus 2015	12/301	4.2%	0.99 (0.29-3.37)
Lim 2015	25/500	5.9%	3.66 (1.47-9.10)
Charidimou 2016	14/119	3.0%	0.56 (0.12-2.65)
CROMIS-1 (Wilson et al)	12/68	5.4%	2.68 (0.99-7.28)
Heidelberg (Wilson et al)	8/265	3.0%	1.30 (0.27-6.26)
OXVASC (Wilson et al)	18/323	5.9%	2.58 (1.04-6.39)
HRP	**365/6264**	**84.7%**	**1.87 (1.32-2.64)**
Total	**459/13125**	**100.0%**	**1.92 (1.40-2.63)**

Association between CMB and incident hemorrhagic stroke

Author	n/N	weight	risk
Bokura 2011	10/2102	6.2%	50.20 (16.70-150.90)
Akoudad 2015	11/4759	5.8%	5.41 (1.58-18.46)
GP	**21/6861**	**12.0%**	**16.77 (1.89-148.79)**
Fan 2003	5/121	5.8%	1.58 (0.45-5.51)
Boulanger 2006	2/236	2.8%	4.32 (0.26-70.38)
Naka 2006	10/266	3.0%	85.63 (6.34-1155.65)
Jeon 2007	7/63	3.7%	3.08 (0.34-27.48)
Huang 2008	6/636	2.7%	20.04 (1.13-354.24)
Soo 2008	15/908	6.1%	5.99 (1.90-18.86)
Mok 2009	5/75	3.8%	13.65 (1.63-114.10)
Nishikawa 2009	26/698	6.8%	1.48 (0.63-3.45)
Thijs 2010	2/487	2.8%	2.79 (0.17-44.92)
Kang 2012	1/97	2.3%	0.96 (0.04-24.35)
Kwa 2013	5/397	3.6%	2.60 (0.30-27.00)
Orken 2013	4/204	3.5%	1.63 (0.16-16.12)
Song 2013	11/550	5.8%	3.79 (1.09-13.15)
Imaizumi 2014	8/138	2.7%	17.00 (1.00-288.90)
Benedictus 2015	5/301	2.6%	22.85 (1.25-417.54)
Samarasekera 2015 CAA- ICH	1/48	2.3%	2.05 (0.08-53.05)
Samarasekera 2015 CAA+ ICH	1/28	2.1%	0.65 (0.02-17.51)
Charidimou 2016	3/119	3.3%	1.82 (0.16-20.90)
Pasquini 2016 CAA- ICH	4/200	3.5%	1.98 (0.20-19.41)
Pasquini 2016 CAA+ ICH	3/49	3.2%	2.18 (0.18-25.77)
Boulouis 2017	56/197	7.1%	0.84 (0.39-1.67)
Shoamanesh 2017	16/1278	6.3%	1.07 (0.37-3.12)
OXVASC (Wilson et al)	1/323	2.3%	12.00 (0.49-291.18)
HRP	**197/7419**	**88.1%**	**2.73 (1.71-4.38)**
Total	**218/14280**	**100.0%**	**3.82 (2.15-6.80)**

Association between CMB and incident Alzheimer's Disease

Author	n/N	weight	risk
Akoudad 2016	34/3816	22.0%	1.67 (0.83-3.36)
Ding 2017	86/2601	24.6%	0.80 (0.43-1.48)
Romero 2017	69/1296	22.5%	2.3 (1.16-4.55)
GP	**186/7713**	**69.1%**	**1.43 (0.76-2.70)**
Staekenborg 2009	56/152	11.4%	0.80 (0.20-2.20)
Miwa 2014	20/524	11.0%	1.22 (0.32-3.72)
Van Uden 2016	28/486	8.4%	0.41 (0.09-1.75)
HRP	**104/1162**	**30.8%**	**0.78 (0.37-1.64)**
Total	**290/8875**	**100%**	**1.18 (0.73-1.89)**

CAA: cerebral amyloid angiopathy; CMB: cerebral microbleeds; GP: general population; HR: High Risk populations; ICH: intracerebral hemorrhage; results correspond to hazard ratios (the size of blue boxes is proportional to sample size) with 95% confidence interval (horizontal line) for reach study; the meta-analysis results (inverse variance weighted meta-analysis with random effects) are shown in red diamonds; n/N corresponds to the number of individuals with the outcome of interest / the total sample size;; Statistics for heterogeneity across studies: CMB-incident ischemic stroke: I²=50%, p=0.006; CMB-incident hemorrhagic stroke: I²=60%, p<0.0001; CMB-incident Alzheimer's disease: I²=42%, p=0.13

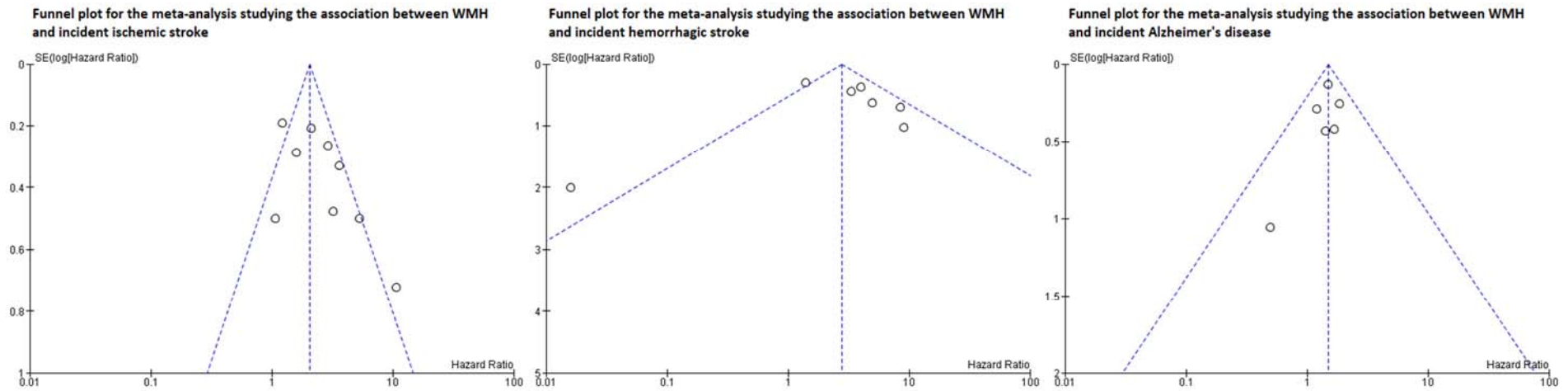**eFigure 5.** Funnels plots of the association of extensive white matter hyperintensity (WMH) burden with incident stroke, dementia, and mortality

Funnel plot for the meta-analysis studying the association between WMH and incident stroke

Funnel plot for the meta-analysis studying the association between WMH and incident dementia

Funnel plot for the meta-analysis studying the association between WMH and mortality
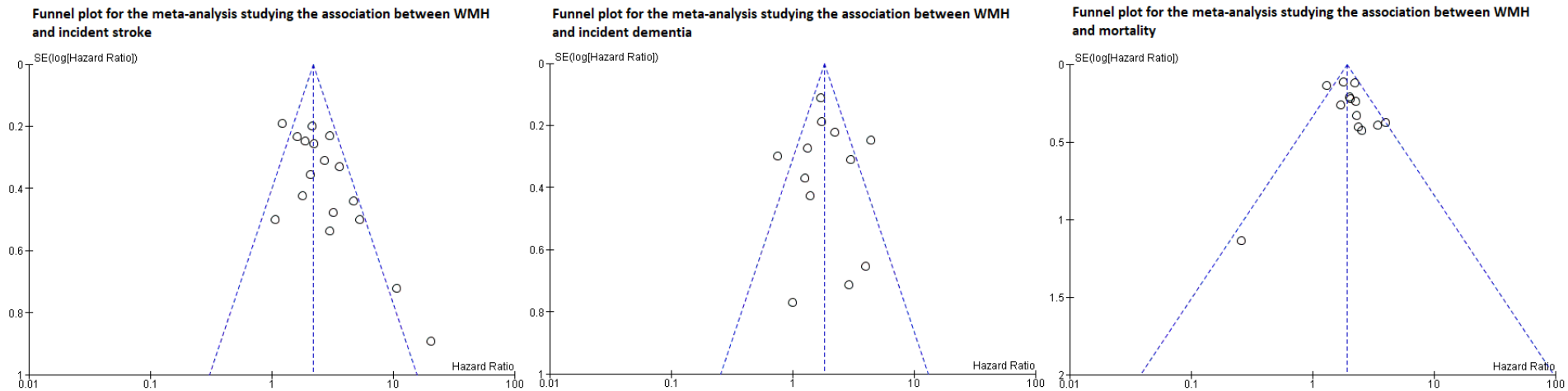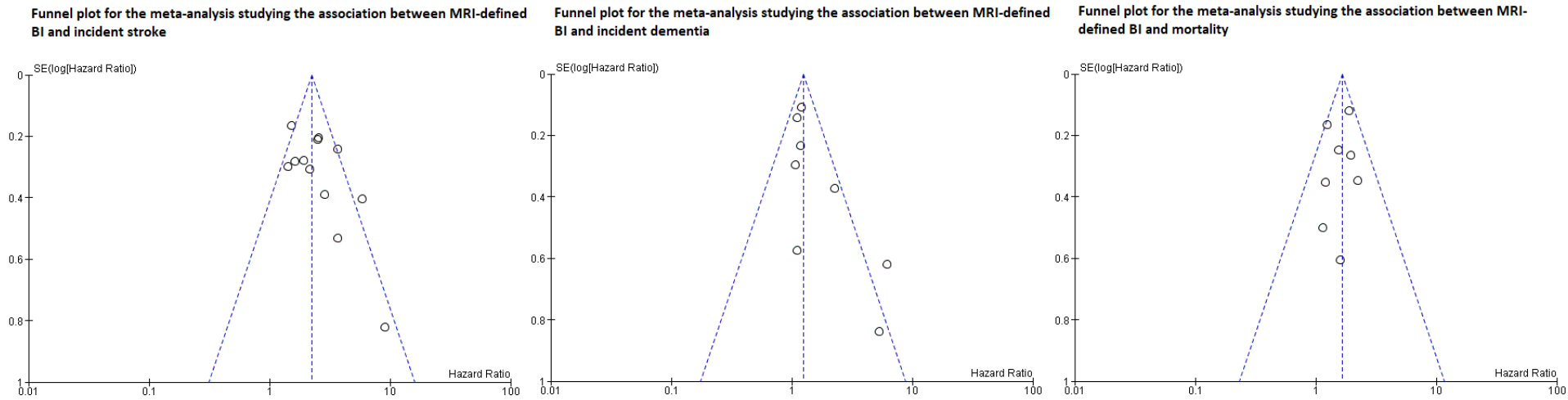
WMH: white matter hyperintensities of presumed vascular origin

eFigure 6. Funnels plots of the association of extensive white matter hyperintensity (WMH) burden with incident stroke and dementia subtypes
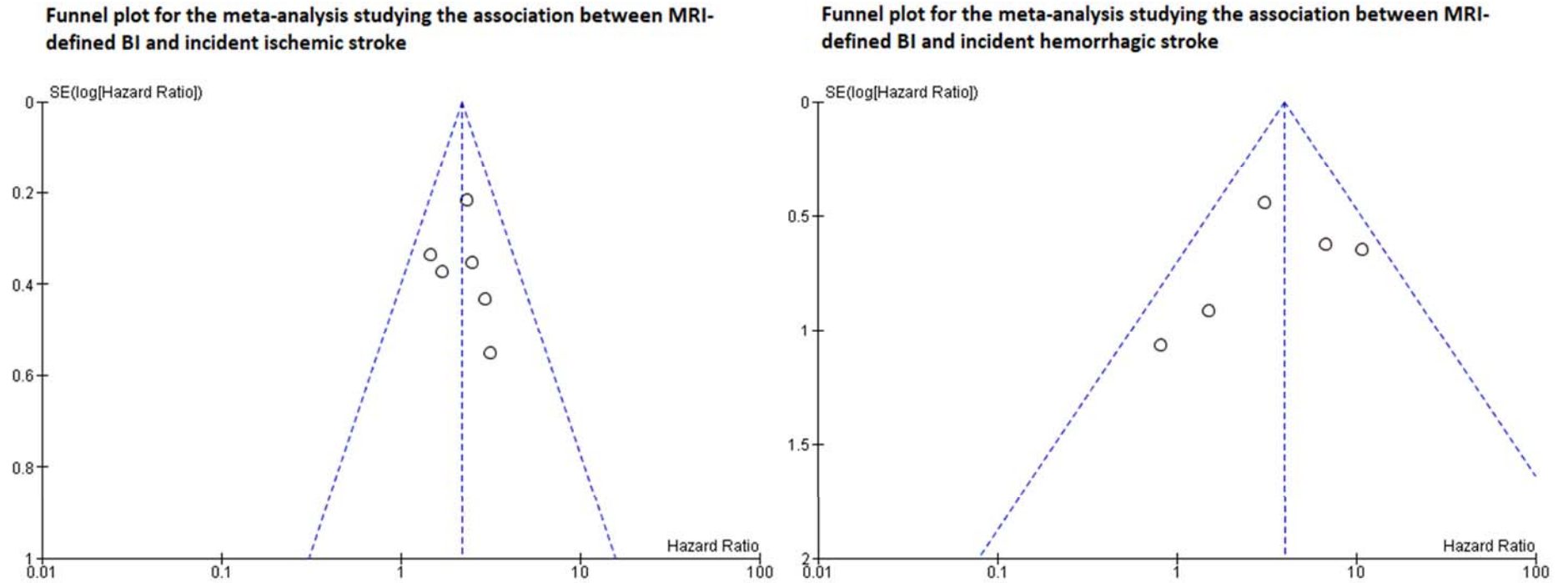

Funnel plot for the meta-analysis studying the association between WMH and incident ischemic stroke

Funnel plot for the meta-analysis studying the association between WMH and incident hemorrhagic stroke

Funnel plot for the meta-analysis studying the association between WMH and incident Alzheimer's disease

WMH: white matter hyperintensities of presumed vascular origin

eFigure 7. Funnels plots of the association of magnetic resonance imaging (MRI)–defined brain infarct (BI) with incident stroke, dementia, and mortality
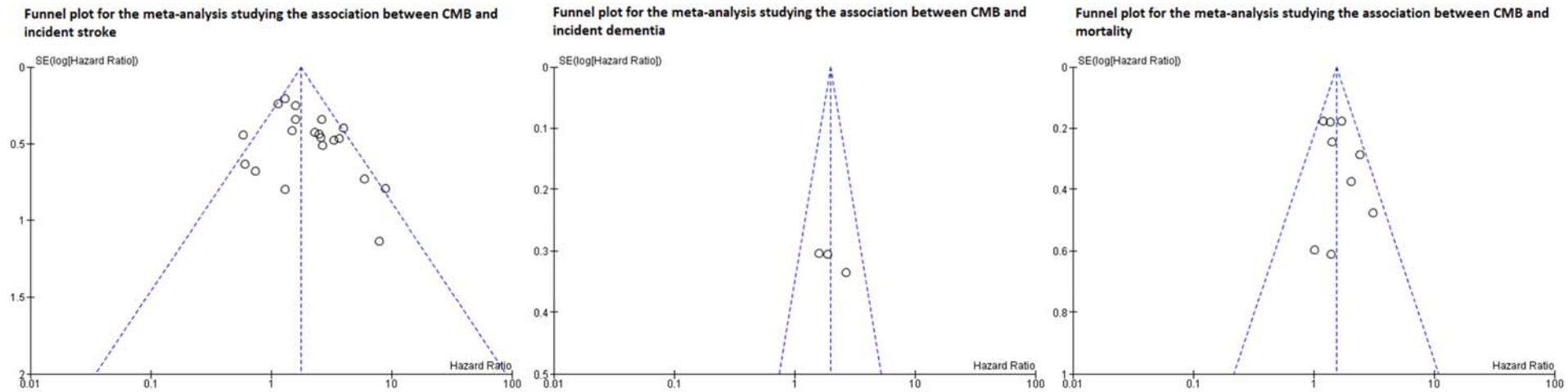

Funnel plot for the meta-analysis studying the association between MRI-defined BI and incident stroke

Funnel plot for the meta-analysis studying the association between MRI-defined BI and incident dementia

Funnel plot for the meta-analysis studying the association between MRI-defined BI and mortality

BI: covert brain infarct

eFigure 8. Funnels plots of the association of magnetic resonance imaging (MRI)–defined brain infarct (BI) with incident stroke subtypes
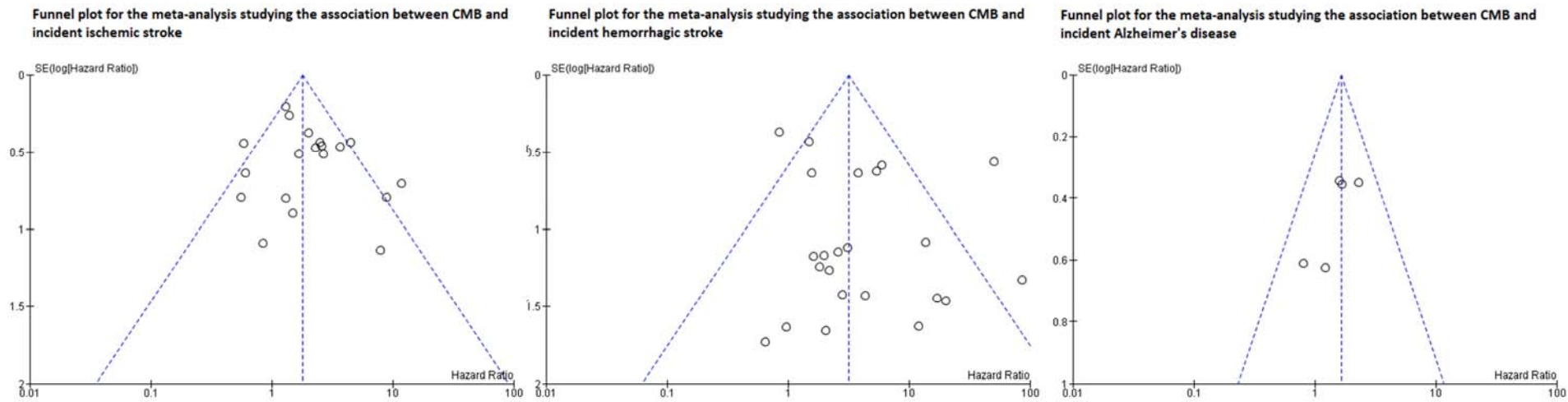
Funnel plot for the meta-analysis studying the association between MRI-defined BI and incident ischemic stroke

Funnel plot for the meta-analysis studying the association between MRI-defined BI and incident hemorrhagic stroke

BI: covert brain infarct

eFigure 9. Funnels plots of the association of cerebral microbleeds (CMB) with incident stroke, dementia, and mortality

Funnel plot for the meta-analysis studying the association between CMB and incident stroke

Funnel plot for the meta-analysis studying the association between CMB and incident dementia

Funnel plot for the meta-analysis studying the association between CMB and mortality

CMB: cerebral microbleeds

eFigure 10. Funnels plots of the association of cerebral microbleeds (CMB) with incident stroke and dementia subtypes

Funnel plot for the meta-analysis studying the association between CMB and incident ischemic stroke

Funnel plot for the meta-analysis studying the association between CMB and incident hemorrhagic stroke

Funnel plot for the meta-analysis studying the association between CMB and incident Alzheimer's disease

CMB: cerebral microbleeds

eReferences.

e1.   DeCarli C, Fletcher E, Ramey V, Harvey D, Jagust WJ. Anatomical mapping of white matter hyperintensities (WMH): exploring the relationships between periventricular WMH, deep WMH, and total WMH burden. Stroke. 2005;36(1):50-55.

e2.   First MB. Diagnostic and statistical manual of mental disorders. DSM IV-4th edition. APA. 1994:1994.

e3.   Association AP. Diagnostic and statistical manual of mental disorders (revised). 3rd Ed. Washington, DC. 1987.

e4.   McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984;34(7):939-944.

e5.   Akoudad S, Wolters FJ, Viswanathan A, et al. Association of Cerebral Microbleeds With Cognitive Decline and Dementia. JAMA Neurol. 2016;73(8):934-943.

e6.   Akoudad S, Portegies ML, Koudstaal PJ, et al. Cerebral Microbleeds Are Associated With an Increased Risk of Stroke: The Rotterdam Study. Circulation. 2015;132(6):509-516.

e7.   Akoudad S, Ikram MA, Koudstaal PJ, Hofman A, van der Lugt A, Vernooij MW. Cerebral microbleeds and the risk of mortality in the general population. Eur J Epidemiol. 2013;28(10):815-821.

e8.   Andersen SD, Larsen TB, Gorst-Rasmussen A, Yavarian Y, Lip GY, Bach FW. White Matter Hyperintensities Improve Ischemic Stroke Recurrence Prediction. Cerebrovasc Dis. 2017;43(1-2):17-24.

e9.   Appelros P, Samuelsson M, Lindell D. Lacunar infarcts: functional and cognitive outcomes at five years in relation to MRI findings. Cerebrovasc Dis. 2005;20(1):34-40.

e10.   Altmann-Schneider I, Trompet S, de Craen AJ, et al. Cerebral microbleeds are predictive of mortality in the elderly. Stroke. 2011;42(3):638-644.

e11.   Benedictus MR, Prins ND, Goos JD, Scheltens P, Barkhof F, van der Flier WM. Microbleeds, Mortality, and Stroke in Alzheimer Disease: The MISTRAL Study. JAMA Neurol. 2015;72(5):539-545.

e12.   Bernick C, Kuller L, Dulberg C, et al. Silent MRI infarcts and the risk of future stroke: the cardiovascular health study. Neurology. 2001;57(7):1222-1229.

e13.   Bokura H, Saika R, Yamaguchi T, et al. Microbleeds are associated with subsequent hemorrhagic and ischemic stroke in healthy elderly individuals. Stroke. 2011;42(7):1867-1871.

e14.   Bokura H, Kobayashi S, Yamaguchi S, et al. Silent brain infarction and subcortical white matter lesions increase the risk of stroke and mortality: a prospective cohort study. J Stroke Cerebrovasc Dis. 2006;15(2):57-63.

e15.   Bombois S, Debette S, Bruandet A, et al. Vascular subcortical hyperintensities predict conversion to vascular and mixed dementia in MCI patients. Stroke. 2008;39(7):2046-2051.

e16.   Boulanger JM, Coutts SB, Eliasziw M, et al. Cerebral microhemorrhages predict new disabling or fatal strokes in patients with acute ischemic stroke or transient ischemic attack. Stroke. 2006;37(3):911-914.

e17.   Boulouis G, Charidimou A, Pasi M, et al. Hemorrhage recurrence risk factors in cerebral amyloid angiopathy: Comparative analysis of the overall small vessel disease severity score versus individual neuroimaging markers. J Neurol Sci. 2017;380:64-67.

e18.   Charidimou A, Inamura S, Nomura T, Kanno A, Kim SN, Imaizumi T. Cerebral microbleeds and white matter hyperintensities in cardioembolic stroke patients due to atrial fibrillation: single-centre longitudinal study. J Neurol Sci. 2016;369:263-267.

e19.   Conijn MM, Kloppenborg RP, Algra A, et al. Cerebral small vessel disease and risk of death, ischemic stroke, and cardiac complications in patients with atherosclerotic disease: the Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study. Stroke. 2011;42(11):3105-3109.

e20.   Wilson D, Charidimou A, Ambler G, et al. Recurrent stroke risk and cerebral microbleed burden in ischemic stroke and TIA A meta-analysis. Neurology. 2016;87(14):1501-1510.

e21.   Debette S, Beiser A, DeCarli C, et al. Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: the Framingham Offspring Study. Stroke. 2010;41(4):600-606.

e22.   DeCarli C, Mungas D, Harvey D, et al. Memory impairment, but not cerebrovascular disease, predicts progression of MCI to dementia. Neurology. 2004;63(2):220-227.

e23.   Ding J, Sigurethsson S, Jonsson PV, et al. Large Perivascular Spaces Visible on Magnetic Resonance Imaging, Cerebral Small Vessel Disease Progression, and Risk of Dementia: The Age, Gene/Environment Susceptibility-Reykjavik Study. JAMA Neurol. 2017;74(9):1105-1112.

e24.   Di Tullio MR, Jin Z, Russo C, et al. Patent foramen ovale, subclinical cerebrovascular disease, and ischemic stroke in a population-based cohort. Journal of the American College of Cardiology. 2013;62(1):35-41.

e25.   Eckerstrom C, Olsson E, Klasson N, et al. Multimodal prediction of dementia with up to 10 years follow up: the Gothenburg MCI study. J Alzheimers Dis. 2015;44(1):205-214.

e26.   Fan YH, Zhang L, Lam WW, Mok VC, Wong KS. Cerebral microbleeds as a risk factor for subsequent intracerebral hemorrhages among patients with acute ischemic stroke. Stroke. 2003;34(10):2459-2462.

e27.   Firbank MJ, Burton EJ, Barber R, et al. Medial temporal atrophy rather than white matter hyperintensities predict cognitive decline in stroke survivors. Neurobiol Aging. 2007;28(11):1664-1669.

e28.   Fluri F, Jax F, Amort M, et al. Significance of microbleeds in patients with transient ischaemic attack. Eur J Neurol. 2012;19(3):522-524.

e29.   Folsom AR, Yatsuya H, Mosley TH, Jr., Psaty BM, Longstreth WT, Jr. Risk of intraparenchymal hemorrhage with magnetic resonance imaging-defined leukoaraiosis and brain infarcts. Ann Neurol. 2012;71(4):552-559.

e30.   Fu JH, Lu CZ, Hong Z, Dong Q, Luo Y, Wong KS. Extent of white matter lesions is related to acute subcortical infarcts and predicts further stroke risk in patients with first ever ischaemic stroke. J Neurol Neurosurg Psychiatry. 2005;76(6):793-796.

e31.   Gerdes VE, Kwa VI, ten Cate H, Brandjes DP, Buller HR, Stam J. Cerebral white matter lesions predict both ischemic strokes and myocardial infarctions in patients with established atherosclerotic disease. Atherosclerosis. 2006;186(1):166-172.

e32.   Geroldi C, Rossi R, Calvagna C, et al. Medial temporal atrophy but not memory deficit predicts progression to dementia in patients with mild cognitive impairment. J Neurol Neurosurg Psychiatry. 2006;77(11):1219-1222.

e33.   Gutierrez J, Elkind MSV, Dong C, et al. Brain Perivascular Spaces as Biomarkers of Vascular Risk: Results from the Northern Manhattan Study. AJNR Am J Neuroradiol. 2017;38(5):862-867.

e34.   Henneman WJ, Sluimer JD, Cordonnier C, et al. MRI biomarkers of vascular damage and atrophy predicting mortality in a memory clinic population. Stroke. 2009;40(2):492-498.

e35.   Huang Y, Cheng Y, Wu J, et al. Cilostazol as an alternative to aspirin after ischaemic stroke: a randomised, double-blind, pilot study. Lancet Neurol. 2008;7(6):494-499.

e36.   Ikram MA, Vernooij MW, Vrooman HA, Hofman A, Breteler MM. Brain tissue volumes and small vessel disease in relation to the risk of mortality. Neurobiol Aging. 2009;30(3):450-456.

e37.   Imaizumi T, Inamura S, Nomura T. The severities of white matter lesions possibly influence the recurrences of several stroke types. J Stroke Cerebrovasc Dis. 2014;23(7):1897-1902.

e38.   Jeon SB, Kang DW, Cho AH, et al. Initial microbleeds at MR imaging can predict recurrent intracerebral hemorrhage. J Neurol. 2007;254(4):508-512.

e39.   Jokinen H, Kalska H, Ylikoski R, et al. Longitudinal cognitive decline in subcortical ischemic vascular disease--the LADIS Study. Cerebrovasc Dis. 2009;27(4):384-391.

e40.   Kaffashian S, Soumare A, Zhu YC, Mazoyer B, Debette S, Tzourio C. Long-Term Clinical Impact of Vascular Brain Lesions on Magnetic Resonance Imaging in Older Adults in the Population. Stroke. 2016;47:2865-2869.

e41.   Kaffashian S, Tzourio C, Zhu YC, Mazoyer B, Debette S. Differential Effect of White-Matter Lesions and Covert Brain Infarcts on the Risk of Ischemic Stroke and Intracerebral Hemorrhage. Stroke. 2016;47(7):1923-1925.

e42.   Kang DW, Han MK, Kim HJ, et al. New ischemic lesions coexisting with acute intracerebral hemorrhage. Neurology. 2012;79(9):848-855.

e43.   Kantarci K, Weigand SD, Przybelski SA, et al. Risk of dementia in MCI: combined effect of cerebrovascular disease, volumetric MRI, and 1H MRS. Neurology. 2009;72(17):1519-1525.

e44.   Kario K, Shimada K, Schwartz JE, Matsuo T, Hoshide S, Pickering TG. Silent and clinically overt stroke in older Japanese subjects with white-coat and sustained hypertension. J Am Coll Cardiol. 2001;38(1):238-245.

e45.   Kerber KA, Whitman GT, Brown DL, Baloh RW. Increased risk of death in community-dwelling older people with white matter hyperintensities on MRI. J Neurol Sci. 2006;250(1-2):33-38.

e46.   Kim S, Choi SH, Lee YM, et al. Periventricular white matter hyperintensities and the risk of dementia: a CREDOS study. Int Psychogeriatr. 2015;27(12):2069-2077.

e47.   Korf ES, Wahlund LO, Visser PJ, Scheltens P. Medial temporal lobe atrophy on MRI predicts dementia in patients with mild cognitive impairment. Neurology. 2004;63(1):94-100.

e48.   Kuller LH, Arnold AM, Longstreth WT, Jr., et al. White matter grade and ventricular volume on brain MRI as markers of longevity in the cardiovascular health study. Neurobiol Aging. 2007;28(9):1307-1315.

e49.   Kuller LH, Longstreth WT, Jr., Arnold AM, Bernick C, Bryan RN, Beauchamp NJ, Jr. White matter hyperintensity on cranial magnetic resonance imaging: a predictor of stroke. Stroke. 2004;35(8):1821-1825.

e50.   Kuller LH, Lopez OL, Newman A, et al. Risk factors for dementia in the cardiovascular health cognition study. Neuroepidemiology. 2003;22(1):13-22.

e51.   Kwa VI, Algra A, Brundel M, Bouvy W, Kappelle LJ. Microbleeds as a predictor of intracerebral haemorrhage and ischaemic stroke after a TIA or minor ischaemic stroke: a cohort study. BMJ Open. 2013;3(5).

e52.   Lau KK, Li L, Lovelock CE, et al. Clinical Correlates, Ethnic Differences, and Prognostic Implications of Perivascular Spaces in Transient Ischemic Attack and Ischemic Stroke. Stroke. 2017;48(6):1470-1477.

e53.   Levy RM, Steffens DC, McQuoid DR, Provenzale JM, MacFall JR, Krishnan KR. MRI lesion severity and mortality in geriatric depression. Am J Geriatr Psychiatry. 2003;11(6):678-682.

e54.   Lim JS, Hong KS, Kim GM, et al. Cerebral microbleeds and early recurrent stroke after transient ischemic attack: results from the Korean Transient Ischemic Attack Expression Registry. JAMA Neurol. 2015;72(3):301-308.

e55.   Melkas S, Sibolt G, Oksala NK, et al. Extensive white matter changes predict stroke recurrence up to 5 years after a first-ever ischemic stroke. Cerebrovasc Dis. 2012;34(3):191-198.

e56.   Miwa K, Tanaka M, Okazaki S, et al. Increased Total Homocysteine Levels Predict the Risk of Incident Dementia Independent of Cerebral Small-Vessel Diseases and Vascular Risk Factors. J Alzheimers Dis. 2015;49(2):503-513.

e57.   Miwa K, Tanaka M, Okazaki S, et al. Multiple or mixed cerebral microbleeds and dementia in patients with vascular risk factors. Neurology. 2014;83(7):646-653.

e58.   Miwa K, Hoshi T, Hougaku H, et al. Silent cerebral infarction is associated with incident stroke and TIA independent of carotid intima-media thickness. Intern Med. 2010;49(9):817-822.

e59.   Mok VC, Lau AY, Wong A, et al. Long-term prognosis of Chinese patients with a lacunar infarct associated with small vessel disease: a five-year longitudinal study. Int J Stroke. 2009;4(2):81-88.

e60.   Naka H, Nomura E, Takahashi T, et al. Combinations of the presence or absence of cerebral microbleeds and advanced white matter hyperintensity as predictors of subsequent stroke types. AJNR Am J Neuroradiol. 2006;27(4):830-835.

e61.   Nam KW, Kwon HM, Lim JS, Han MK, Nam H, Lee YS. The presence and severity of cerebral small vessel disease increases the frequency of stroke in a cohort of patients with large artery occlusive disease. PLoS One. 2017;12(10):e0184944.

e62.   Nishikawa T, Ueba T, Kajiwara M, Fujisawa I, Miyamatsu N, Yamashita K. Cerebral microbleeds predict first-ever symptomatic cerebrovascular events. Clin Neurol Neurosurg. 2009;111(10):825-828.

e63.   Oksala NK, Oksala A, Pohjasvaara T, et al. Age related white matter changes predict stroke death in long term follow-up. J Neurol Neurosurg Psychiatry. 2009;80(7):762-766.

e64.   Orken DN, Uysal E, Timer E, Kuloglu-Pazarci N, Mumcu S, Forta H. New cerebral microbleeds in ischemic stroke patients on warfarin treatment: two-year follow-up. Clin Neurol Neurosurg. 2013;115(9):1682-1685.

e65.   Pasquini M, Benedictus MR, Boulouis G, Rossi C, Dequatre-Ponchelle N, Cordonnier C. Incident Cerebral Microbleeds in a Cohort of Intracerebral Hemorrhage. Stroke. 2016;47(3):689-694.

e66.   Poels MM, Steyerberg EW, Wieberdink RG, et al. Assessment of cerebral small vessel disease predicts individual stroke risk. J Neurol Neurosurg Psychiatry. 2012;83(12):1174-1179.

e67.   Prasad K, Wiryasaputra L, Ng A, Kandiah N. White matter disease independently predicts progression from mild cognitive impairment to Alzheimer's disease in a clinic cohort. Dement Geriatr Cogn Disord. 2011;31(6):431-434.

e68.   Prins ND, van der Flier WM, Brashear HR, et al. Predictors of progression from mild cognitive impairment to dementia in the placebo-arm of a clinical trial population. J Alzheimers Dis. 2013;36(1):79-85.

e69.   Prins ND, van Dijk EJ, den Heijer T, et al. Cerebral white matter lesions and the risk of dementia. Arch Neurol. 2004;61(10):1531-1534.

e70.   Putaala J, Haapaniemi E, Kurkinen M, Salonen O, Kaste M, Tatlisumak T. Silent brain infarcts, leukoaraiosis, and long-term prognosis in young ischemic stroke patients. Neurology. 2011;76(20):1742-1749.

e71.   McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to alzheimer's disease: Recommendations from the national institute on aging-alzheimer's association workgroups on diagnostic guidelines for alzheimer's disease. *Alzheimers Dement*. 2011;7:263-269

e72.   Romero JR, Beiser A, Himali JJ, Shoamanesh A, DeCarli C, Seshadri S. Cerebral Microbleeds and risk of Incident Dementia: The Framingham Heart Study. Neurobiology of aging. 2017;54:94-99.

e73.   Romero JR, Preis SR, Beiser A, et al. Cerebral Microbleeds as Predictors of Mortality: The Framingham Heart Study. Stroke. 2017;48(3):781-783.

e74.   Samarasekera N, Fonville A, Lerpiniere C, et al. Influence of intracerebral hemorrhage location on incidence, characteristics, and outcome: population-based study. Stroke. 2015;46(2):361-368.

e75.   Shoamanesh A, Pearce LA, Bazan C, et al. Microbleeds in the Secondary Prevention of Small Subcortical Strokes Trial: Stroke, mortality, and treatment interactions. Ann Neurol. 2017;82(2):196-207.

e76.   Sigurdsson S, Aspelund T, Kjartansson O, et al. Incidence of Brain Infarcts, Cognitive Change, and Risk of Dementia in the General Population: The AGES-Reykjavik Study (Age Gene/Environment Susceptibility-Reykjavik Study). Stroke. 2017;48(9):2353-2360.

e77.   Smith EE, Egorova S, Blacker D, et al. Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia. Arch Neurol. 2008;65(1):94-100.

e78.   Smith EE, Gurol ME, Eng JA, et al. White matter lesions, cognition, and recurrent hemorrhage in lobar intracerebral hemorrhage. Neurology. 2004;63(9):1606-1612.

e79.   Song TJ, Kim J, Lee H, et al. The frequency of cerebral microbleeds increases with CHADS2 scores in stroke patients with non   valvular atrial fibrillation. European journal of neurology. 2013;20(3):502-508.

e80.   Soo YO, Yang SR, Lam WW, et al. Risk vs benefit of anti-thrombotic therapy in ischaemic stroke patients with cerebral microbleeds. J Neurol. 2008;255(11):1679-1686.

e81.   Staekenborg SS, Koedam EL, Henneman WJ, et al. Progression of mild cognitive impairment to dementia: contribution of cerebrovascular disease compared with medial temporal lobe atrophy. Stroke. 2009;40(4):1269-1274.

e82.   Tapiola T, Pennanen C, Tapiola M, et al. MRI of hippocampus and entorhinal cortex in mild cognitive impairment: a follow-up study. Neurobiol Aging. 2008;29(1):31-38.

e83.   Thijs V, Lemmens R, Schoofs C, et al. Microbleeds and the risk of recurrent stroke. Stroke. 2010;41(9):2005-2009.

e84.   Tsushima Y, Aoki J, Endo K. Brain microhemorrhages detected on T2*-weighted gradient-echo MR images. AJNR Am J Neuroradiol. 2003;24(1):88-96.

e85.   Umemura T, Kawamura T, Umegaki H, et al. Endothelial and inflammatory markers in relation to progression of ischaemic cerebral small-vessel disease and cognitive impairment: a 6-year longitudinal study in patients with type 2 diabetes mellitus. J Neurol Neurosurg Psychiatry. 2011;82(11):1186-1194.

e86.   van der Holst HM, van Uden IW, Tuladhar AM, et al. Factors Associated With 8-Year Mortality in Older Patients With Cerebral Small Vessel Disease: The Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort (RUN DMC) Study. JAMA Neurol. 2016;73(4):402-409.

e87.   van Straaten EC, Harvey D, Scheltens P, et al. Periventricular white matter hyperintensities increase the likelihood of progression from amnestic mild cognitive impairment to dementia. J Neurol. 2008;255(9):1302-1308.

e88.   Weber R, Weimar C, Wanke I, et al. Risk of recurrent stroke in patients with silent brain infarction in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) imaging substudy. Stroke. 2012;43(2):350-355.

e89.   Weinstein G, Wolf PA, Beiser AS, Au R, Seshadri S. Risk estimations, risk factors, and genetic variants associated with Alzheimer's disease in selected publications from the Framingham Heart Study. J Alzheimers Dis. 2013;33 Suppl 1:S439-445.

e90.   Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. Stroke. 2003;34(5):1126-1129.

e91.   Windham BG, Deere B, Griswold ME, et al. Small Brain Lesions and Incident Stroke and Mortality: A Cohort Study. Ann Intern Med. 2015;163(1):22-31.

e92.   Yamauchi H, Fukuda H, Oyanagi C. Significance of white matter high intensity lesions as a predictor of stroke from arteriolosclerosis. J Neurol Neurosurg Psychiatry. 2002;72(5):576-582.

e93.   Yamashita H, Fujikawa T, Takami H, et al. Long-term prognosis of patients with major depression and silent cerebral infarction. Neuropsychobiology. 2010;62(3):177-181.

e94.   Zhu YC, Dufouil C, Soumare A, Mazoyer B, Chabriat H, Tzourio C. High degree of dilated Virchow-Robin spaces on MRI is associated with increased risk of dementia. J Alzheimers Dis. 2010;22(2):663-672.

e95.   van Swieten JC, Hijdra A, Koudstaal PJ, van Gijn J. Grading white matter lesions on CT and MRI: a simple scale. J Neurol Neurosurg Psychiatry. 1990;53(12):1080-1083.

e96.   Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke. 2001;32(6):1318-1322.

e97.   Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol. 1987;149(2):351-356.

e98.   Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993;43(11):2412-2414.

e99.   Association AP. Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition: Washington DC: American Psychiatric Association; 1987.

e100.   Association AP. Diagnostic and statistical manual of Mental Disorders. 4th ed.: Washington, DC: American Psychiatric Association; 1994.

e101.   Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. 1993;43(2):250-260.

e102.   Scheltens P, Barkhof F, Leys D, et al. A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. J Neurol Sci. 1993;114(1):7-12.

e103.   Gupta A, Giambrone AE, Gialdini G, et al. Silent Brain Infarction and Risk of Future Stroke A Systematic Review and Meta-Analysis. Stroke. 2016;47(3):719-725.

e104.   Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med. 2003;348(13):1215-1222.

e105.   Charidimou A, Imaizumi T, Moulin S, et al. Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: A meta-analysis. Neurology. 2017;89(8):820-829.

e106.   Charidimou A, Karayiannis C, Song TJ, et al. Brain microbleeds, anticoagulation, and hemorrhage risk: Meta-analysis in stroke patients with AF. Neurology. 2017;89(23):2317-2326.

e107.   Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology. 1992;42(3 Pt 1):473-480.

e108.   Lopez OL, Kuller LH, Becker JT, et al. Classification of vascular dementia in the Cardiovascular Health Study Cognition Study. Neurology. 2005;64(9):1539-1547.

e109.   Ding J, Sigurethsson S, Jonsson PV, et al. Space and location of cerebral microbleeds, cognitive decline, and dementia in the community. *Neurology*. 2017;88:2089-2097

e110.   van Uden IW, van der Holst HM, Tuladhar AM, et al. White matter and hippocampal volume predict the risk of dementia in patients with cerebral small vessel disease: The run dmc study. *J Alzheimers Dis*. 2016;49:863-873

e111.   Meguro K, Ishii H, Kasuya M, et al. Incidence of dementia and associated risk factors in japan: The osaki-tajiri project. *J Neurol Sci*. 2007;260:175-182

e112.   Steffens DC, MacFall JR, Payne ME, Welsh-Bohmer KA, Krishnan KR. Grey-matter lesions and dementia. *Lancet*. 2000;356:1686-1687

e113.   Steffens DC, Potter GG, McQuoid DR, et al. Longitudinal magnetic resonance imaging vascular changes, apolipoprotein e genotype, and development of dementia in the neurocognitive outcomes of depression in the elderly study. *The American Journal of Geriatric Psychiatry*. 2007;15:839-849