The Clinical Significance of Brain MRI White Matter Hyperintensities: a Systematic Review and Meta-Analysis

Appendix

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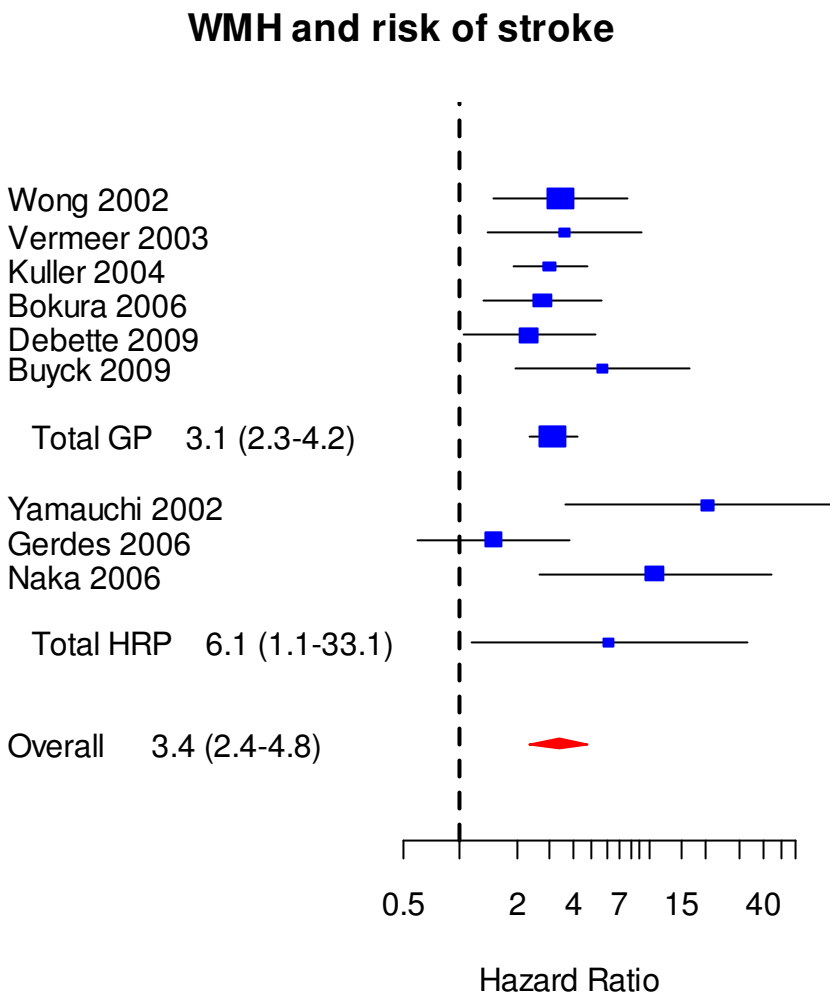
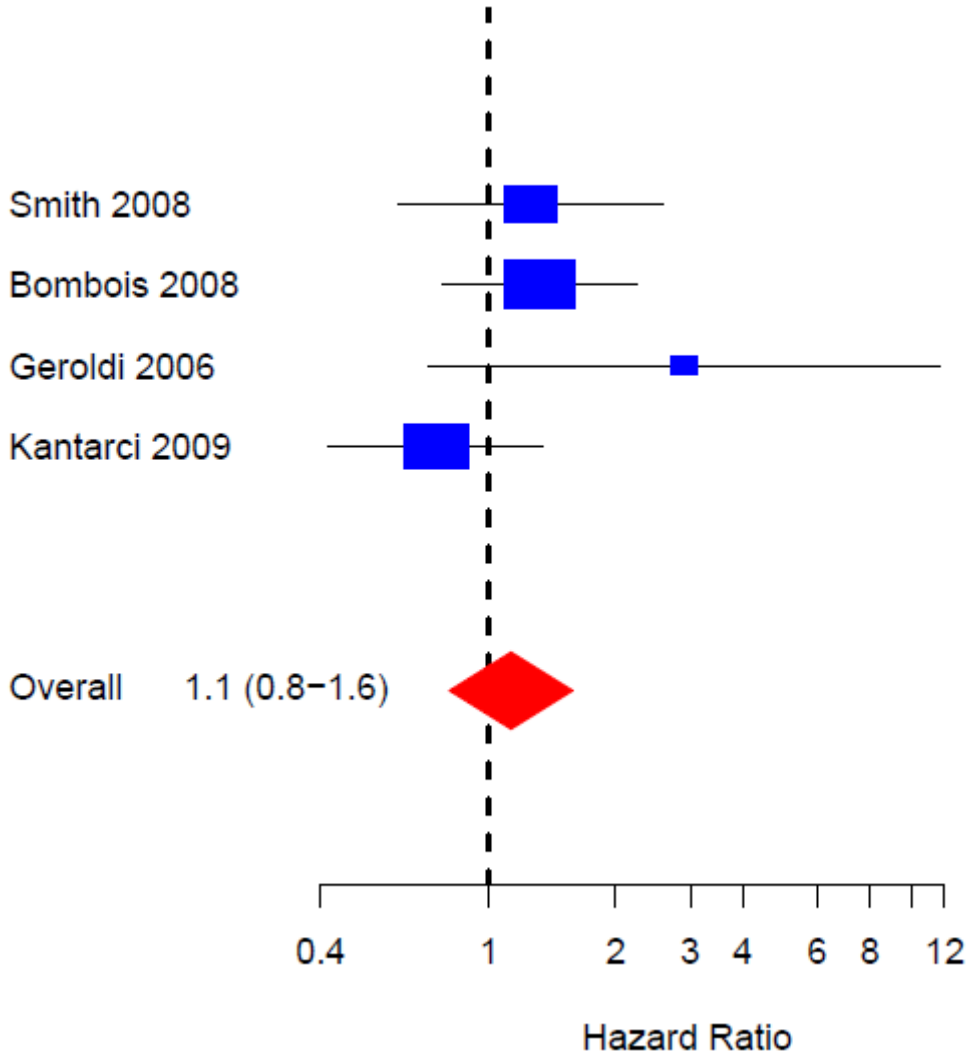
1.1. Supplemental Figure 1: Meta-analysis of studies testing the association of WMH with incident stroke (PVH replaced by DWMH for studies that do not have results for total WMH burden[1-3])



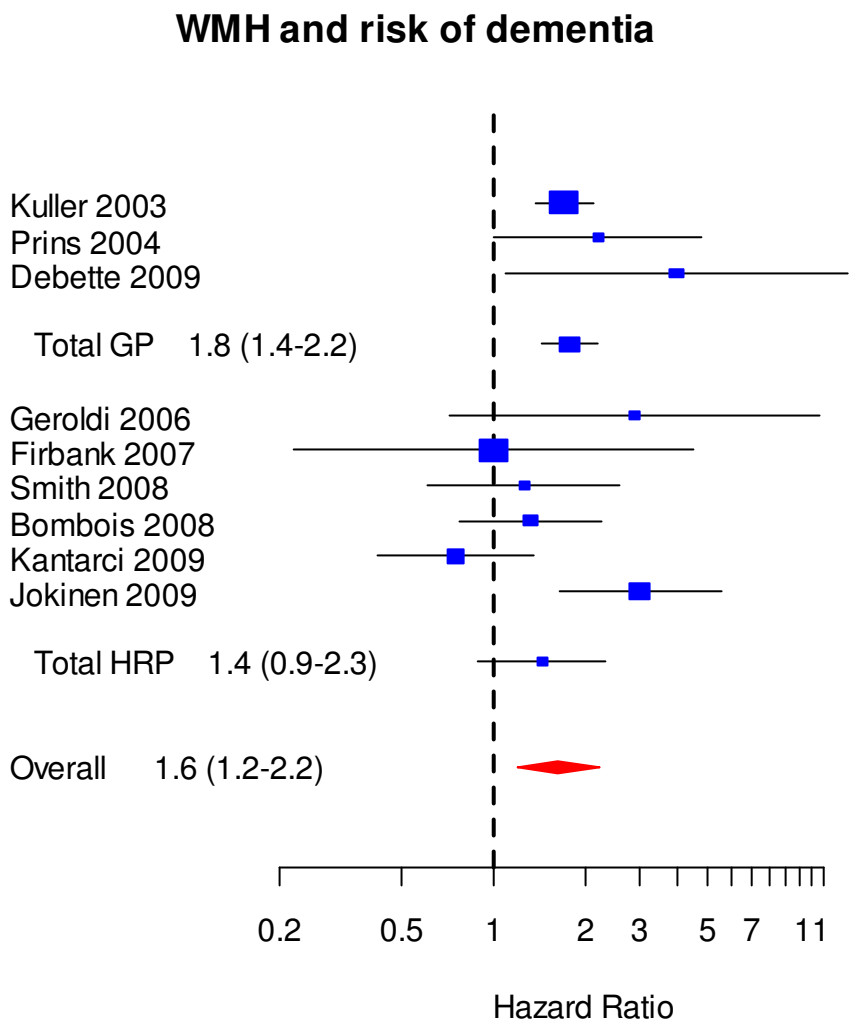
DWMH: deep white matter hyperintensities; PVH: periventricular hyperintensities; WMH: white matter hyperintensities; Inverse variance meta-analysis; GP: general population; HRP: high risk population; all: overall meta-analysis; p for heterogeneity = 0.84, 0.008, and 0.16 for GP, HRP and all respectively; I^2 = 0%, 79.1%, and 32.5%, for GP, HRP and all respectively

1.2. Supplemental Figure 2: Meta-analysis of studies testing the association of WMH with incident dementia in patients with MCI



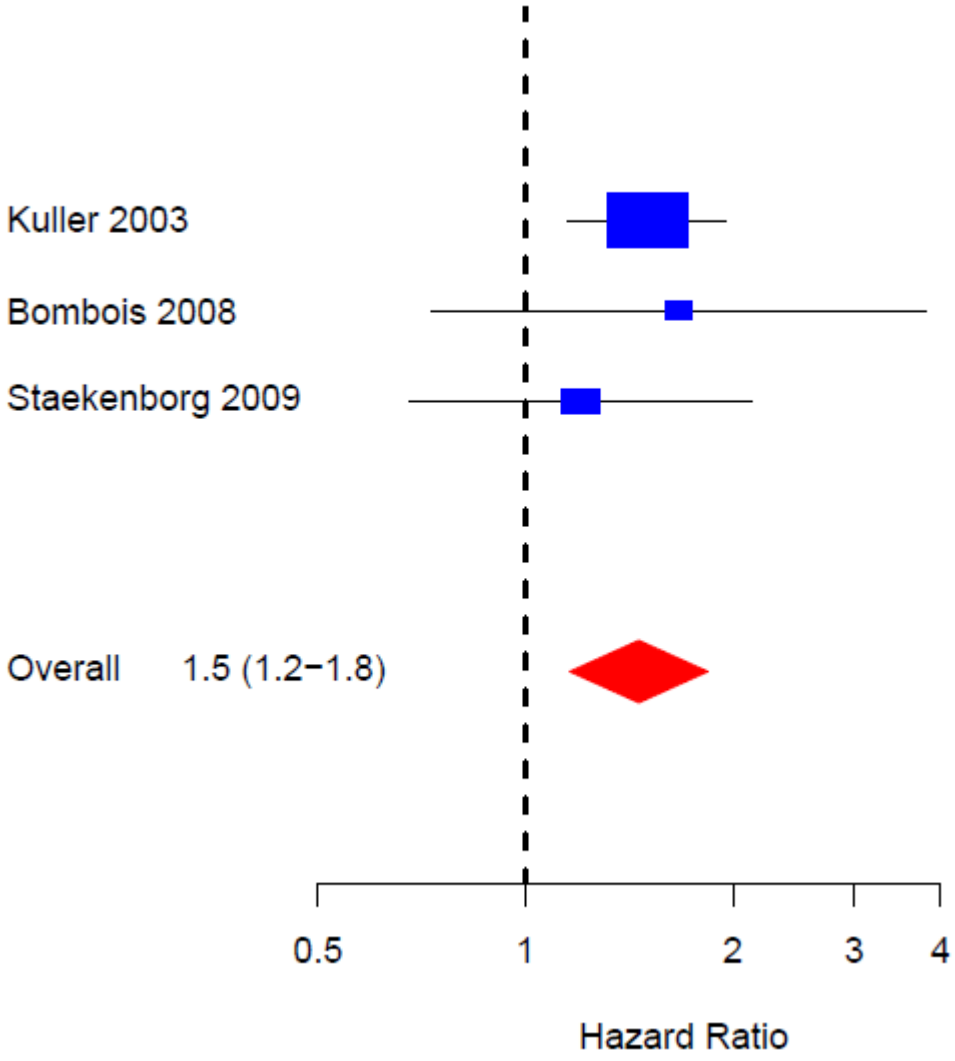
MCI: Mild Cognitive Impairment; Inverse variance meta-analysis; p for heterogeneity = 0.26, I^2 = 26.1%

1.3. Supplemental Figure 3: Meta-analysis of studies testing the association of WMH with incident dementia (PVH replaced by DWMH for studies that do not have results for total WMH burden [4])



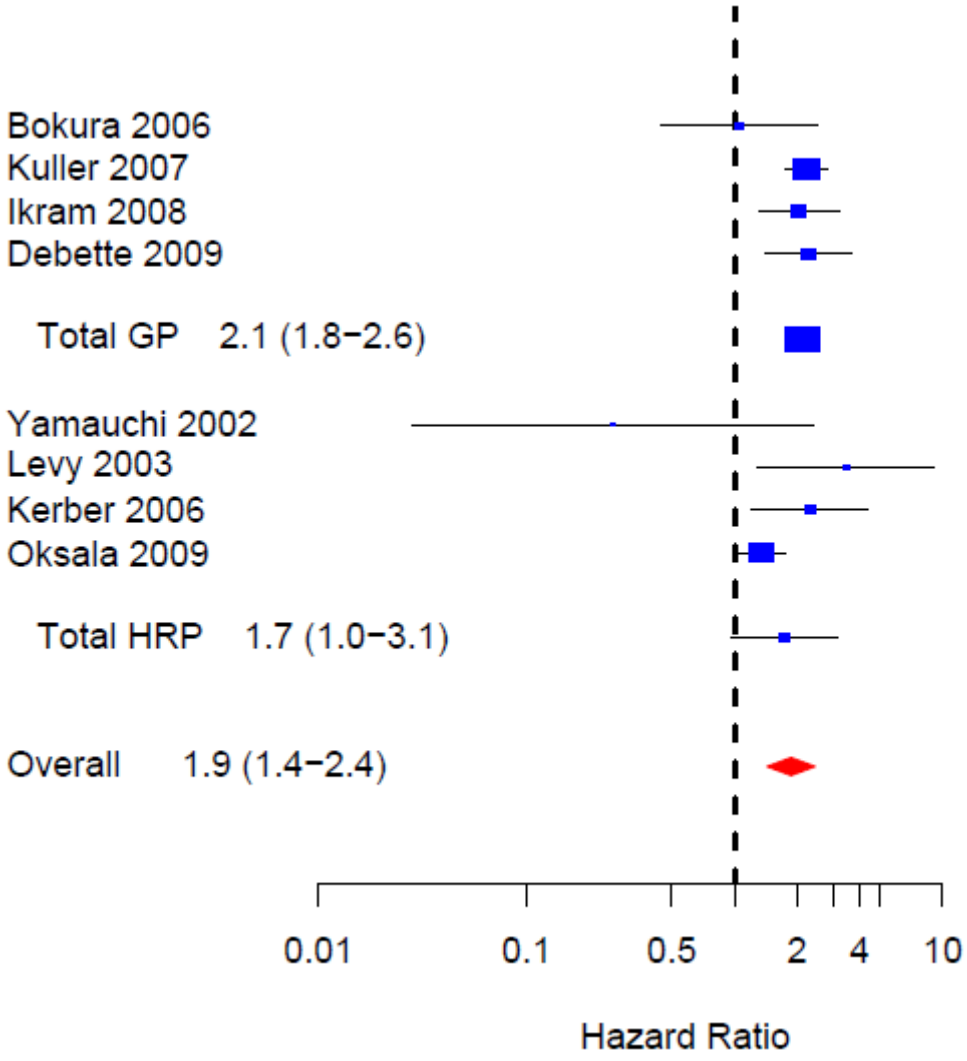
DWMH: deep white matter hyperintensities; PVH: periventricular hyperintensities; WMH: white matter hyperintensities; Inverse variance meta-analysis; GP: general population; HRP: high risk population; all: overall meta-analysis; p for heterogeneity = 0.38, 0.04, and 0.05 for GP, HRP and all respectively; I^2 = 0%, 57.7%, and 48.0%, for GP, HRP and all respectively

1.4. Supplemental Figure 4: Meta-analysis of studies testing the association of WMH with incident AD



AD: Alzheimer Disease; Inverse variance meta-analysis; p for heterogeneity = 0.74, I^2 = 0%

1.5. Supplemental Figure 5: Meta-analysis of studies testing the association of WMH with mortality (PVH replaced by DWMH for studies that do not have results for total WMH burden [25])



DWMH: deep white matter hyperintensities; PVH: periventricular hyperintensities; WMH: white matter hyperintensities; Inverse variance meta-analysis; GP: general population; HRP: high risk population; all: overall meta-analysis; p for heterogeneity = 0.44, 0.06, and 0.03 for GP, HRP and all respectively; I^2 = 0%, 60.4%, and 55.3%, for GP, HRP and all respectively

2. Supplemental Tables

2.1. Supplemental Table 1: Association of WMH with incident stroke

Author	Mean	Population	N	Fu (yrs)	MRI characteristics	WMH measure	Incident	Results
General population								
Wong, 2002 [6]	62.3	ARIC study	1684	4.7	1.5T; T1, T2, PD	SQ (0-9), dichotomized (≥3 vs. <3)	32 (25 IS, 5 ICH, 2 mixed)	HR=3.7(95%CI:1.7-7.8) † for WMH ≥3 vs. <3 HR=3.4(1.5-7.7) ‡ for WMH ≥3 vs. <3
Vermeer, 2003 [1]	72	Rotterdam study	1077	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 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 Risk of stroke did not increase linearly with DWMH
Kuller, 2004 [7]	75.0	CHS study	3293	7	1.5T (+0.35 in one of the 4 centres); T1, T2, PD	SQ (0-9), 6 classes: 0, 1, 2, 3, 4, ≥5 (reference = 0)	278 (225 IS)	HR=3.0(1.9-4.7) § for grade ≥5, for all stroke HR=2.9(1.7-4.8) for grade ≥5, for IS
Bokura, 2006 [2]	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
Buyck, 2009 [8]	72.3	3C-study	1648	4.9	1.5T; T1, T2, PD	quantitative (automated), studied in quartiles	28 (22 IS, 5 ICH, 1 unspecified)	HR=5.7(2.0–16.4) for quartile 4 vs. quartile 1+2 of WMH ‡ HR=6.2(2.0-19.5) for quartile 4 vs. quartile 1+2 of PVH ‡ HR=4.1(1.5-11.3) for quartile 4 vs. quartile 1+2 of DWMH ‡
Debette, 2009 [9]	62	Framingham Offspring study	2177	5.6	1.0T, 1.5T; T2	quantitative (automated), studied continuously, also dichotomized [a]	32 (26 IS, 5 ICH,1 unspecified)	HR=1.33(0.93-1.90) for increasing WMH volume ‡ HR=2.28(1.02-5.13) for extensive WMH ‡

Author	Mean	Population	N	Fu (yrs)	MRI characteristics	WMH measure	Incident strokes (n)	Results
High risk population								
Yamauchi, 2002 [10]	66.0	patients with lacunar stroke, headache or dizziness	89	4.3	0.5T; T1, T2, PD	SQ [c] studied continuously and dichotomous (severe vs. mild or absent)	7 (5 IS, 2 ICH)	HR=1.60(1.02-2.54) [e] OR=20.5(3.6-118.0) [f]
Smith, 2004 [11]	76.3 [b]	lobar ICH patients	82 [b]	2.7 [b]	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 [12]	66.4	lacunar stroke patients	81	5.0	1.0T; T2	SQ [d], studied continuously	24 (21 IS, 2 ICH, 1 unspecified)	HR=1.7(1.2-2.7) [g]
Fu, 2005 [13]	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 [3]	62	patients with recent IS, myocardial infarction or peripheral artery disease	230	3.5	1.5T; T1, T2, PD	SQ (PVH+/-, DWMH+/- and for total WMH: none, <50%, ≥50% of total white matter)	21 (IS)	HR=4.4(1.8-11.0) for PVH+/- HR=3.2(1.3-8.4) [h] for PVH+/- HR=1.5 (0.6–3.8) for DWMH+/-
Naka, 2006 [14]	67.2	stroke patients	266	1.5	1T; T2, T2*	SQ (0-3); dichotomized (≥2 vs. <2)	26 (16 IS, 10 ICH)	HR=10.7(2.6-43.7) for IS [i] HR=0.016(0.001-0.258) for ICH [i]

CVD: cerebrovascular disease; DWMH: deep white matter hyperintensities; Fu: follow-up; HR: hazard ratio; ICH: intracerebral hemorrhage; IS: ischemic stroke; 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; * approximation (based on number and size of lesions); † adjusted for age, sex; ‡ 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] with MRI (182 patients overall, 100 had computed tomography only), mean follow-up and age are for overall group; [c] van Swieten[15]; [d] Wahlund scale[16]; [e] adjusted for age, sex, vascular risk factors, multiple lacunar infarcts; [f] computed by authors of meta-analysis from published raw numbers, for severe vs. mild or no WMH; [g] adjusted for age, ischemic heart disease, impairment score, MMSE, basal ganglia score; [h] adjusted for age, hypertension, type of atherosclerotic disease at entry; [i] adjusted for age, sex, vascular risk factors, stroke type, days from stroke onset, microbleeds

2.2. Supplemental Table 2: Association of WMH with incident dementia

Author	Mean age	Population	N	Fu (yrs)	MRI characteristics	WMH measure	Incident dementia, n	Dementia type	Results
General population									
Kuller, 2003 [17]	≥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 AD VaD/MD	HR=1.7(95%CI:1.36-2.10) for WMH>3 [†] HR=1.5(1.17-1.99) for WMH>3 [†] HR=2.1(1.36-3.11) for WMH>3 [†]
Prins, 2004 [4]	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 AD	HR=1.67(1.25-2.24) [‡] for PVH (NS for DWMH) HR=2.2(1.0-4.8) for DWMH >6 [a] HR=4.4(1.9-5.0) for PVH >6 [a] HR=1.41(1.01-1.98) [‡] for PVH (NS for DWMH)
Meguro, 2007 [18]	≥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 (NINDS-AIREN)	AD VaD	OR=0.78(NS) for increasing PVH OR=1.07, 1.02(NS) for DWMH right and left OR=4.14(p<0.005) for PVH OR=4.04, 3.27(p<0.05) for DWVH right and left
Debette, 2009 [9]	62	Framingham Offspring study	2013	5.9	1.0T, 1.5T; T2	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

Author	Mean age	Population	N	Fu (yrs)	MRI characteristics	WMH measure	Incident dementia, n	Dementia type	Results
High risk population									
Steffens, 2000 [19]	>60	depression	182	1 to 5	1.5T; T2	quantitative (automated)	26 (criteria not specified), type unspecified	All dem	No association
Korf, 2004 [20]	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)
De Carli, 2004 [21]	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 [22]	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)
Steffens, 2007 [23]	69.2	depression	161	5.4	1.5T; T2	quantitative (automated)	20 (DSM-IV): 10 AD, 3 VaD, 7 undetermined	All dem	No association [i]
Firbank, 2007 [24]	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]
Smith, 2008 [25]	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 [26]	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 [27]	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 VaD/MD AD	HR=1.01(0.97-1.05) per unit WMH [k] HR=1.32(0.77-2.24) for WMH >6 [k,l] HR=1.14(1.06-1.24) per unit WMH [k] HR=10.00(1.55-64.39) for WMH >6 [k] HR=2.71(1.60-4.58) per unit PVH [k] HR=1.02(0.96-1.09) per unit WMH [k,l] HR=1.67(0.73-3.81) for WMH >6 [k,l]
Van Straaten, 2008 [28]	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

Author	Mean age	Population	N	Fu (yrs)	MRI characteristics	WMH measure	Incident dementia, n	Dementia type	Results
High risk population									
Kantarci, 2009 [29]	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]
Jokinen, 2009 [30]	73.5	with WMH and minor neurological problems	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 [31]	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 (NINCDS-ADRDA), 16 non-AD (7 VaD, 5 FTLD, 2 DLB, 1 PD, 1 alcohol dementia)	AD Non-AD	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 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

AD: Alzheimer's disease; All dem: all types of dementia; CDR: Clinical Dementia Rating scale [32]; DLB: dementia with Lewy bodies; DSM-III: Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition [33]; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [34]; DWMH: deep white matter hyperintensities; FTLD; frontotemporal lobe dementia; Fu: follow-up; HR: hazard ratio; MCI: mild cognitive impairment; MD: mixed dementia; NA: not available; 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 [35]; NINDS-AIREN: National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences [36]; NS: non significant; OR: odds ratio; PD: proton density; PVH: periventricular hyperintensities; SIVD: subcortical ischemic vascular disease, defined by either severe WMH (Fazekas scale[37]) plus ≥1 lacune or moderate WMH[37] plus >5 lacunes; SQ: semi-quantitative; VaD: vascular dementia; WMH: white matter hyperintensities; [*] approximation (based on number and size of lesions); [†] adjusted for age, sex, race, education, baseline cognition, ApoEε4, 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[16]; [d] grade 1 to 3 from Fazekas scale[37]; [e] extensive WMH if total score>6 or any regional score>2; [f] extensive WMH if log-transformed >mean+1SD; [g] Scheltens scale[38]; [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

2.3. Supplemental Table 3: Association of WMH with cognitive decline

Author	Mean age	Population	N	Fu (yrs)	MRI characteristics	WMH measure	Cognitive decline measure	Results
General population								
Kuller, 1998 [39]	≥65	CHS	3469	3	1.5T; T1, T2, PD	SQ (0-9), dichotomized (≥3 vs. <3)	*global* (3MSE)	no association with loss of ≥5 points on 3MSE; OR=1.4(95%CI:1.0-1.9) for 3MSE<80 at the end of fu
Schmidt, 2005 [40]	60.2	ASPS	329	6	1.5T; T1, T2, PD	quantitative (automated), continuous	*domain-specific* (composite z-score for each cognitive domain [memory, conceptualization, visuopractical skills, attention/speed])	no association of baseline WMH volume with decline in composite z-score †
Prins, 2005 [41]	71	Rotterdam study	832	5.2	1.5T; T1, T2, PD	SQ (0-9) for PVH, quantitative for DWMH, studied in quintiles	*global* (MMSE and cognitive index) and *domain-specific* (Stroop, Letter Digit Substitution Task, Verbal Fluency test, 15-word verbal learning test)	per SD increase in PVH, the annual MMSE decline increased by 0.035 points (0.003-0.066); decline in Stroop naming and Letter Digit Substitution Test associated with PVH (p=0.04, <0.01); no association with DWMH
Smith, 2008 [25]	71.2	cognitively intact	67	5.1	1.5T; T2, PD	quantitative (automated), dichotomized *	*global* (conversion to MCI [n=26])	HR=2.59(1.07-6.25) HR=3.30(1.33-8.17) ‡ for progression to MCI in subjects with extensive WMH
Debette, 2009 [9]	62	Framingham Offspring study	1344	6.2	1.0T, 1.5T; T2	quantitative (automated), continuous, also dichotomized [c]	*global* (conversion to MCI [n=93/1344], and to amnestic MCI [n=93/1134])	incident all MCI: HR=1.06(0.83-1.36) § for increasing WMH volume HR=1.26(0.67-2.39) § for extensive WMH incident amnestic MCI: HR=1.24(0.98-1.57) § for increasing WMH volume [a] HR=1.67(0.96-2.93) § for extensive WMH [a]
Silbert, 2009 [42]	62	cognitively intact	98	9.5	1.5T; T1, T2, PD	quantitative (automated), continuous	*global* (conversion to permanent cognitive impairment [n=53/98])	HR=1.04(1.00-1.07) [b] for increasing total WMH HR=1.06(1.01-1.10) [b] for increasing PVH

Author	Mean age	Population	N	Fu (yrs)	MRI characteristics	WMH measure	Cognitive decline measure	Results
High risk population								
Mungas, 2002 [43]	73.0	memory clinic: 68 CDR=0; 38 CDR=0.5; 14 CDR≥1	120	3.0	1.5T; T1, T2, PD	quantitative (automated), continuous	*global* (global cognitive change derived from word list learning test, digit span, letter fluency, animal category fluency)	WMH was not related to global cognitive change (p=0.36) [g]
Smith, 2004 [11]	76.3	lobar ICH	82 [c]	2.7 [*]	NA; Flair	SQ (0-9) for PVH, quantitative for DWMH, dichotomized (middle or high vs. low tertile)	*global* (incident cognitive impairment [deficits in memory or other cognitive areas interfering with tasks of daily living])	no association of PVH (p=0.85) or DMWH (p=0.44) with incident cognitive impairment
Appelros, 2005 [12]	66.4	lacunar stroke	81	5.0	1.0T; T2	SQ [d], studied continuously	*global* (MMSE)	correlation coefficient =0.21 (NS) for decline in MMSE, =0.41 (p<0.01) for MMSE at 5 yrs
Van der Flier, 2005 [44]	73	memory complaints, MCI or normal	59	1.8	1.5T; T1, T2, PD, Flair	quantitative (automated), continuous	*global* (CAMCOG)	WMH volume was significantly associated with annual change in CAMCOG (β=−0.1; p<0.05) [h]
Mungas, 2005 [45]	73.8	memory clinic: 58 CDR=0; 34 CDR=0.5; 11 CDR≥1	103	4.8	1.5T; T1, T2, PD	quantitative (automated), continuous	*domain-specific* (composite memory measure derived from delayed, cued recall and word list learning task; composite executive function scale using letter fluency, digit span backward, visual span backward, initiation-perseveration scale)	baseline WMHV was related to change in executive functions (p=0.02), [f] NS after additional adjustments [i]
Van den Heuvel, 2006 [46]	75	vascular risk + MMSE≥24	554	3	1.5T; T2, PD, Flair	quantitative (automated), studied in 3 strata (low, intermediate, high)	*domain-specific* (picture word learning test; letter digit coding test; abbreviated Stroop test)	higher PVH at baseline associated with more time to complete the Stroop test (p=0.008) [j], no association with DWMH
Debette, 2007 [47]	68.1	MCI	170	3.8	1.5T; T1, T2, PD	SQ [e], dichotomous (>vs<median) and in tertiles	*global* (MMSE and DRS) and *domain-specific* (DRS subitems)	decliners more often had PVH or DWMH > median; mean annual decline in MMSE and DRS-initiation higher with increasing PVH tertiles; decline in MMSE associated with PVH > median [k]

Author	Mean age	Population	N	Fu (yrs)	MRI characteristics	WMH measure	Cognitive decline measure	Results
High risk population								
Firbank, 2007 [24]	80.1	Stroke	79	2	1.5T; T1, Flair	quantitative (automated), continuous	*global* (CAMCOG)	no association of CAMCOG score at 2 years with WMH at baseline (β=−0.08; p=0.5)
Jokinen, 2009 [30]	73.5	with WMH and minor neurological problems	639	3	0.5T, 1.5T; T1, T2, Flair	SQ [f], dichotomized into presence (or absence of SIVD)	*global* (MMSE); *domain-specific* (immediate and delayed word recall, Stroop, trail making test A and B-A, verbal fluency, symbol digit modalities and digit cancellation test, digit span backward)	participants with SIVD had a steeper decline for MMSE (p=0.03), verbal fluency (p=0.007), Stroop I (p=0.007), Stroop II (p=0.005), TMT A (p<0.001)
Dufouil, 2009 [48]	60.5	stroke or TIA, in PROGRESS trial	226	4	1.0T, 1.5T; T2/PD	SQ [e], categorized in 4 grades (none, mild, moderate, severe)	*global* (dementia [DSM-IV] or severe cognitive decline (decline in MMSE of >= 3 points)	RR=7.6 (1.9–31.2) for severe vs. none [l]

3MSE: Modified Mini-Mental State Examination [49]; CAMCOG: Cambridge Assessment Mental Disorders in the Elderly, section B [50]; CDR: Clinical Dementia Rating scale [32] ; DRS: Dementia Rating Scale [51]; DWMH: deep white matter hyperintensities; HR: Hazard ratio; MCI: mild cognitive impairment; MMSE: mini-mental state examination [52]; OR: odds ratio; PVH: periventricular hyperintensities; RR: relative risk; SIVD: subcortical ischemic vascular disease, defined by either severe WMH (Fazekas scale[37]) plus ≥1 lacune or moderate WMH[37] plus >5 lacunes; SQ: semi-quantitative; * extensive if log-transformed >1SD from study mean; † no numbers; ‡ adjusted for ApoEε4, age, sex, education, smoking, CDR sum of boxes; § adjusted for age, sex, education, vascular risk factors, duration of follow-up ; [a] significant in participants aged ≥60 years; [b] adjusted for age, hypertension, MMSE, ApoEε4, intracranial and hippocampal volume; [c] with MRI (182 patients overall, 100 had computed tomography only), mean follow-up and mean age is for overall group; [d] Wahlund scale[16]; [e] Scheltens scale[38]; [f] grade 1 to 3 from Fazekas scale[37]; [g] adjusted for age, education, sex; [h] adjusted for age, sex and duration of follow up; [i] additionally adjusted for hippocampal volume, cortical gray matter volume, presence of lacunes; [j] adjusted for sex, age, education, treatment group, and test version when applicable; [k] adjusted for age, sex, education, vascular risk factors, medial temporal lobe atrophy, MCI subtype, +/- baseline cognitive performances; [l] adjusted for age, sex, education, hypertension, physical impairment, baseline MMSE and treatment allocation

2.4. Supplemental Table 4: Association of WMH progression with cognitive decline

Author	Mean	Population	N	Fu	MRI	WMH progression	Cognitive decline measure	Results
General population								
Longstreth, 2005 [53]	74.1	CHS	1919	5	1.5T; T1, T2, PD	SQ, worsening WMH grade (0-9), defined by 3 levels (increase of 0, 1, ≥2 points)	*global* (3MSE) and *domain-specific* (digit symbol substitution test)	3MSE and digit symbol substitution test scores deteriorated significantly more with increasing WMH progression ‡
Schmidt, 2005 [40]	60.2	ASPS	329	6	1.5T; T1, T2, PD	quantitative (automated), continuous	*domain-specific* (composite z-score each domain: memory, conceptualization, visuopractical skills, attention/speed)	progression of WMH significantly associated with declining performance in memory, conceptualization and visuopractical skills [a]
Kramer, 2007 [54]	73.9	healthy elderly subjects	50	3.8	1.5T; T1, T2, PD	quantitative (automated), continuous	*domain-specific* (composite memory measure derived from delayed and cued recall and word list learning task; composite executive function score using letter fluency, digit span backward, visual span backward, and an initiation-perseveration scale)	delta-WMH volume significantly associated with composite executive function score at the end of follow-up (ß=0.261, p=0.022) [c], no significant association of delta-WMH volume with composite memory measure at the end of follow-up
Van Dijk, 2008 [55]	71	Rotterdam	668	3.4	1.5T; T1, T2, PD	SQ, studied in 3 classes (no progression, minor progression, marked progression)	*global* (MMSE, composite score for global cognitive function) and *domain-specific* (z-scores for memory performance and psychomotor speed)	increased mean change in MMSE (p=0.02) for marked PVH progression, in psychomotor speed for any or marked PVH progression (p<0.01), in global cognitive function for any (p<0.01) and marked (p=0.02) PVH progression; no association with DWMH change

Author	Mean	Population	N	Fu	MRI	WMH progression	Cognitive decline measure	Results
High risk population								
Van den Heuvel, 2006 [46]	75	vascular risk + MMSE≥24	554	3	1.5T; T2, PD, Flair	quantitative (automated), studied in 3 strata (low, intermediate, high)	*domain-specific* (memory: picture word learning test; executive functioning and attention: letter digit coding test and abbreviated Stroop color word test)	larger progression in PVH volume associated with more time to complete the Stroop test (p=0.02) [b]
Mungas, 2005 [45]	73.8	memory clinic: 58 CDR=0, 34 CDR=0.5, 11 CDR≥1	103	4.8	1.5T; T1, T2, PD	quantitative (automated), continuous	*domain-specific* (composite memory measure derived from delayed and cued recall and word list learning task; composite executive function scale using letter fluency, digit span backward, visual span backward, and an initiation-perseveration scale)	no association with WMH change [§]

3MSE: Modified Mini-Mental State Examination [49]; CDR: Clinical Dementia Rating scale [32]; DWMH: deep white matter hyperintensities; MMSE: mini-mental state examination [52]; PVH: periventricular hyperintensities; SQ: semi-quantitative; TIA: transient ischemic attack; WMH: white matter hyperintensities; [*] no neuropsychiatric disease at baseline; [‡] adjusted for age, sex, education, performance and WMH grade at baseline, occurrence of TIA or stroke (unchanged when adding worsening atrophy and presence of infarcts to model); [§] adjusted for age, education, sex; [a] adjusted for sex, age, education, major vascular risk factors (non significant after adjusting for brain volume change); [b] adjusted for sex, age, education, treatment group, and test version when applicable (non significant after adjusting for incident brain infarction; [c] adjusted for baseline executive function, change in hippocampal volume, cortical grey matter, and lacunes

2.5. Supplemental Table 5: Association of WMH with mortality

Author	Mean age	Population	N	Fu (yrs)	MRI characteristics	WMH measure	Incident deaths (n)	Results
General population								
Bokura, 2006 [2]	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 [56]	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) ‡
Ikram, 2007 [57]	73.4	Rotterdam study	490	8.4	1.5T; T1, T2, PD, HASTE	quantitative (automated), continuous and in quartiles	191	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 §,a
Debette, 2009 [9]	62	Framingham Offspring study	2208	5.2	1.0T, 1.5T; T2	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
High risk population								
Yamauchi, 2002 [10]	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) e
Levy, 2003 [5]	70	depression	259	5.5	1.5T; T1,T2	SQ: 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) for DWMH f OR=2.36(1.07-5.21) for PVH j association with PVH non significant in Cox regression including DWMH
Appelros, 2005 [12]	66.4	lacunar stroke	81	5.0	1.0T; T2	SQ d, studied continuously	15	HR=1.6(1.2-2.2) g
Fu, 2005 [13]	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) †
Kerber, 2006 [58]	>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) h for grade 2 vs. 0
Oksala, 2009 [59]	70.8	stroke	396	7.5	1.0T; T1, T2, PD	SQ d, dichotomized: severe vs. mild to moderate	277	HR=1.31(1.00-1.71) i,a

DWMH: deep white matter hyperintensities; DWI: diffusion-weighted imaging; Fu: follow-up; HASTE: 3D half-Fourier acquisition single-shot turbo spin echo sequence; HR: hazard ratio; OR: odds ratio; PD: proton density; PVH: periventricular hyperintensities; SGMH: subcortical grey matter hyperintensities; SQ: semi-quantitative; WMH: white matter hyperintensities; * 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] the association was stronger with vascular death; [b] Wahlund scale[16]; [c] none to mild, moderate, severe (modified Fazekas scale[37]); [d] van Swieten[15]; [e] OR computed by authors of meta-analysis from published raw numbers; [f] adjusted for age, sex, race, measure of comorbidity, MMSE; [g] non significant in multivariable model; [h] age- and sex-matched and adjusted for vascular risk factors and coronary heart disease; [i] stepwise model including age, sex, vascular risk factors, vascular disease and poor modified Rankin score; [j] OR computed by authors of meta-analysis using raw numbers

3. Supplemental Methods

3.1. Supplemental Methods 1: Data sources

References for this review were identified through searches of PubMed from 1966, to November 23rd 2009, using pre-defined search terms ("white matter" or "periventricular" or "subcortical" or ("Leukoaraiosis"[Mesh] or "Leukoaraiosis/pathology"[Mesh])) and ("Dementia" or "Alzheimer disease" or "Vascular dementia" or "Stroke" or "Brain Infarction" or "Cerebral Hemorrhage" or "Death" or "Mortality" or "cognitive" or ("Stroke"[Mesh] or "Stroke/epidemiology"[Mesh]) or ("Dementia"[Mesh] or "Dementia/epidemiology"[Mesh]) or "Death"[Mesh] or "Mortality"[Mesh]) and ("Magnetic Resonance Imaging"[Mesh]) and ("Risk Factors"[Mesh] or "Longitudinal Studies"[Mesh] or "Cohort Studies"[Mesh]), restricted to research in humans.
Only papers published in peer-reviewed journals were selected.

3.2. Supplemental Methods 2: Study selection

We excluded studies on white matter lesions occurring in inflammatory or neurodegenerative conditions such as multiple sclerosis, auto-immune disorders such as lupus or Sneddon syndrome, or in monogenic neurodegenerative diseases such as Huntington's disease, neurofibromatosis, and leukodystrophies, as well as studies on WMH in monogenic cerebrovascular disease such as CADASIL, Fabry disease, and sickle cell disease. We also did not include studies where the outcome was MRI-defined (including silent) brain infarcts instead of clinical stroke, or subjective cognitive decline instead of objective cognitive decline evaluated by standardized neuropsychological tests, as well as studies on the association of WMH with cognitive decline in already demented individuals.
We reviewed abstracts of identified articles in all languages. For those potentially meeting the inclusion criteria the full paper was reviewed.

3.3. Supplemental Methods 3: Statistical analyses

For studies that measured deep WMH (DWMH) and periventricular hyperintensities (PVH) separately, and did not provide a global risk estimate for WMH, the results for PVH were used for the meta-analysis. Indeed, it has been shown that although PVH and DWMH volumes are both very strongly associated with global WMH burden, there is a steeper slope of change in PVH volume with increasing total WMH volume.[60]

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