JAMA Neurology | Original Investigation

Clinical Significance of Magnetic Resonance Imaging Markers of Vascular Brain Injury
A Systematic Review and Meta-analysis

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IMPORTANCE Covert vascular brain injury (VBI) is highly prevalent in community-dwelling older persons, but its clinical and therapeutic implications are debated.

OBJECTIVE To better understand the clinical significance of VBI to optimize prevention strategies for the most common age-related neurological diseases, stroke and dementia.

DATA SOURCE We searched for articles in PubMed between 1966 and December 22, 2017, studying the association of 4 magnetic resonance imaging (MRI) markers of covert VBI (white matter hyperintensities [WMHs] of presumed vascular origin, MRI-defined covert brain infarcts [BIs], cerebral microbleeds [CMBs], and perivascular spaces [PVSs]) with incident stroke, dementia, or death.

STUDY SELECTION Data were taken from prospective, longitudinal cohort studies including 50 or more adults.

DATA EXTRACTION AND SYNTHESIS We performed inverse variance–weighted meta-analyses with random effects and *z* score–based meta-analyses for WMH burden. The significance threshold was $P < .003$ (17 independent tests). We complied with the Meta-analyses of Observational Studies in Epidemiology guidelines.

MAIN OUTCOMES AND MEASURES Stroke (hemorrhagic and ischemic), dementia (all and Alzheimer disease), and death.

RESULTS Of 2846 articles identified, 94 studies were eligible, with up to 14 529 participants for WMH, 16 012 participants for BI, 15 693 participants for CMB, and 4587 participants for PVS. Extensive WMH burden was associated with higher risk of incident stroke (hazard ratio [HR], 2.45; 95% CI, 1.93-3.12; $P < .001$), ischemic stroke (HR, 2.39; 95% CI, 1.65-3.47; $P < .001$), intracerebral hemorrhage (HR, 3.17; 95% CI, 1.54-6.52; $P = .002$), dementia (HR, 1.84; 95% CI, 1.40-2.43; $P < .001$), Alzheimer disease (HR, 1.50; 95% CI, 1.22-1.84; $P < .001$), and death (HR, 2.00; 95% CI, 1.69-2.36; $P < .001$). Presence of MRI-defined BIs was associated with higher risk of incident stroke (HR, 2.38; 95% CI, 1.87-3.04; $P < .001$), ischemic stroke (HR, 2.18; 95% CI, 1.67-2.85; $P < .001$), intracerebral hemorrhage (HR, 3.81; 95% CI, 1.75-8.27; $P < .001$), and death (HR, 1.64; 95% CI, 1.40-1.91; $P < .001$). Presence of CMBs was associated with increased risk of stroke (HR, 1.98; 95% CI, 1.55-2.53; $P < .001$), ischemic stroke (HR, 1.92; 95% CI, 1.40-2.63; $P < .001$), intracerebral hemorrhage (HR, 3.82; 95% CI, 2.15-6.80; $P < .001$), and death (HR, 1.53; 95% CI, 1.31-1.80; $P < .001$). Data on PVS were limited and insufficient to conduct meta-analyses but suggested an association of high PVS burden with increased risk of stroke, dementia, and death; this requires confirmation.

CONCLUSIONS AND RELEVANCE We report evidence that MRI markers of VBI have major clinical significance. This research prompts careful evaluation of the benefit-risk ratio for available prevention strategies in individuals with covert VBI.

JAMA Neurol. 2019;76(1):81-94. doi:10.1001/jamaneurol.2018.3122
Published online October 22, 2018.

Supplemental content

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Large-scale brain imaging studies in the general population have shown that radiological evidence of covert vascular brain injury (VBI) is much more frequent than clinical stroke and is highly prevalent in community-dwelling older persons.[1-3] Such incidental findings are also often detected on magnetic resonance imaging (MRI) performed in routine clinical practice, and how they should be interpreted and acted on presents a common clinical challenge. Individual studies have suggested that MRI markers of covert VBI predict an increased risk of stroke, dementia, and death, but other studies did not show any association. Better understanding of the association of specific MRI markers of VBI with outcomes is crucial to optimize prevention strategies. Indeed, detection of covert VBI on MRI may provide a unique opportunity to prevent the occurrence of stroke and dementia, the 2 most common age-related neurological diseases, representing a major source of disability and mortality.[4]

Four radiological features of VBI are seen on routine MRI scans (**Figure 1**).[5] Magnetic resonance imaging–defined covert brain infarcts (BIs) represent areas of infarction, most commonly small and in subcortical regions, and are usually asymptomatic.[6] White matter hyperintensities (WMHs) of presumed vascular origin are seen as areas of high signal on T2-weighted MRI in the periventricular and deep white matter and represent areas of gliosis, axonal loss, and ischemic demyelination.[7] Cerebral microbleeds (CMBs) are seen as areas of low signal on gradient echo MRI sequences and represent susceptibility effects due to hemosiderin from previous microbleeds.[8] Perivascular spaces (PVSs) correspond to the dilation of spaces surrounding small perforating vessels filled with cerebrospinal fluid–like signal and lined by leptomeningeal cells.[9] These MRI markers of covert VBI are thought to primarily reflect consequences of underlying cerebral small vessel disease (SVD). The most common pathological substrates of SVD are arteriolosclerosis or lipohyalinosis and cerebral amyloid angiopathy.[10] We conducted a systematic review and meta-analyses of published studies to explore associations of the 4 main MRI markers of covert VBI with risk of incident stroke, dementia, and death.

Key Points

Question What is the clinical and therapeutic significance of magnetic resonance imaging markers of covert vascular brain injury (white matter hyperintensities of presumed vascular origin, magnetic resonance imaging–defined covert brain infarcts, cerebral microbleeds, and perivascular spaces) in community-dwelling older adults?

Findings In this systematic review and meta-analysis of more than 16 000 participants, there was evidence that white matter hyperintensities, brain infarcts, and cerebral microbleeds have a major clinical significance in community-dwelling older adults; they were associated with an increased risk of stroke (both hemorrhagic and ischemic for all markers), dementia, and death.

Meaning This research highlights the urgent need for randomized clinical trials to assess the benefit–risk ratio of prevention strategies for individuals carrying these markers, such as aspirin and intensive blood pressure–lowering treatment.

Methods

Search Strategy and Selection Criteria

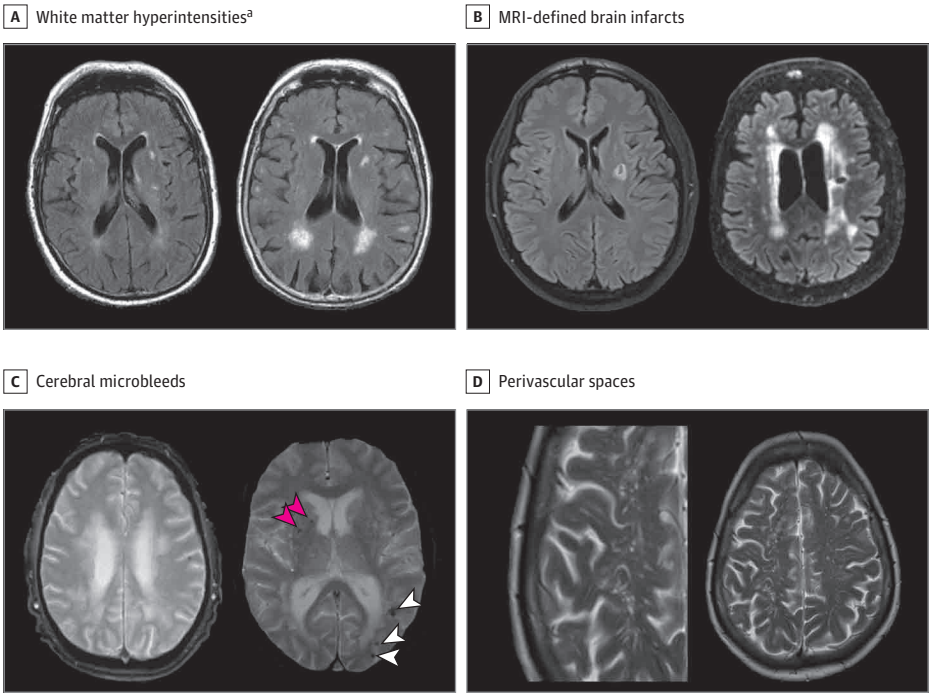
We did a systematic search of PubMed from 1966 to December 22, 2017, for English-only publications using predefined search terms (eMethods in the Supplement) and reviewed the reference list of relevant articles. Studies were searched and selected by 3 independent researchers (S.S., M.-G.D., and S.C.L.); differences were solved by discussion. We included published prospective studies with longitudinal data exploring the association of WMH, BI, CMB, and PVS with risk of incident stroke, dementia, or death, limited to studies in adults and in English language. We included studies carried out in the general population and in populations at high risk for vascular disease or dementia and present results separately for each. We excluded studies without effect estimates and confidence intervals or raw numbers enabling the calculation of these estimates. We also excluded studies with computed tomography evaluation only; with fewer than 50 individuals (considering these could not provide reliable effect estimates); and with WMH occurring in inflammatory conditions (eg, multiple sclerosis, lupus, or Sneddon syndrome), monogenic neurodegenerative or cerebrovascular diseases (eg, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), leukodystrophies, or studies on postthrombolysis outcome after ischemic stroke (IS). If several studies provided results on the same outcome and used overlapping groups of individuals, we included the study with the longest follow-up. If follow-up periods were equivalent, we included the study with the largest number of individuals. This review was not registered but complied with Meta-analyses of Observational Studies in Epidemiology guidelines.

Data Analysis

Data were extracted independently by S.S. and S.C.L. Extracted data consisted of population type (general or high-risk population), length of follow-up, MRI characteristics and sequence, definition of MRI marker, outcome definition (ie, stroke, IS, intracerebral hemorrhage [ICH], all-cause dementia, Alzheimer disease [AD], and death), number of incident events, and relative risk estimate for the association of the MRI marker with the outcome. Variable definitions are provided in the eMethods in the Supplement. The relative risk estimate was a hazard ratio (HR), a relative risk, or an odds ratio; odds ratios were used in the meta-analysis as an approximation of the HR.[11] We extracted quality criteria of included studies (eTable 1 in the Supplement) and used the Newcastle-Ottawa Scale to quantify study quality (eTable 2 in the Supplement).[12]

Meta-analyses were carried out when 3 or more studies were available for the same main outcome or 2 or more studies for the same outcome subtype (and only when possible for 3 or more MRI markers of covert VBI). We calculated pooled HRs using inverse variance–weighted meta-analysis with random effects to account for potential heterogeneity for associations with BI, CMB, or dichotomized WMH burden. Statistically significant heterogeneity was defined by a heterogeneity P value less than .05 or an I^2 greater than 50%. We also performed sample size–weighted

Figure 1. Magnetic Resonance Imaging (MRI) Markers of Covert Vascular Brain Injury



A, Minor (left) and extensive (right) white matter hyperintensities of presumed vascular origin on axial fluid-attenuated inversion recovery MRI sequences.[a] B, Magnetic resonance imaging–defined covert brain infarct without (left) and with (right) white matter hyperintensities on axial fluid-attenuated inversion recovery MRI sequences. C, Single cerebral microbleed (left) or multiple cerebral microbleeds (right), including lobar (white arrowheads) and deep (pink arrowheads) microbleeds, on gradient echo T2-weighted axial MRI sequences. D, Perivascular spaces following the shape of deep penetrating arteries on T2-weighted MRI.

[a] The definitions of extensive white matter hyperintensity burden differed across studies, ie, top half, tertile, quartile, or quintile; or moderate to severe white matter hyperintensity burden (or corresponding grades) on the following visual semiquantitative rating scales: Fazekas scale, Scheltens scale, or Age-Related White Matter Changes Scale (eTables 4-6 in the Supplement).

z score–based meta-analyses (providing significance values but no effect estimates) to combine studies using continuous WMH burden only with those using dichotomized WMH burden. Whenever available, we used the model adjusted for vascular risk factors. Primary meta-analyses combined all available studies, and secondary meta-analyses included studies in general or high-risk populations only (eMethods in the Supplement). *P* values less than .003 after applying a Bonferroni correction for 17 meta-analyses were considered statistically significant (this threshold is conservative, as MRI markers are correlated with each other), and all *P* values were 2-tailed.

Meta-regression analysis was conducted in Stata version 14.2 (StataCorp) to assess the effect of length of follow-up and potential confounding factors (ie, age, smoking, hypertension, diabetes, and education) on associations. Small-study bias, such as publication bias, was evaluated using Egger test.[13] *P* values less than .006 (accounting for 9 MRI marker × outcome associations) were considered statistically significant.

Results

The initial search in PubMed identified 2846 articles. Of these, 94 articles met our inclusion criteria (eFigure 1 in the Supplement). Some articles explored several MRI markers and associations with more than 1 outcome. Five articles, all on PVS burden, could not be included in the meta-analyses, as too few studies tested associations of the same MRI marker with the same outcome.

For WMH, 52 studies met our inclusion criteria: 25 for stroke,[6,14-37] 22 for dementia,[25,35,38-57] and 16 for death.[14,15,17,20,22,33,36,37,39,58-64] For BI, we included 24 studies: 14 for stroke,[16,17,21,25,33,36,39,65-71] 10 for dementia,[25,39,40,48,51,54,57,72-74] and 8 for death.[17,33,36,39,58,59,71,73] For CMB, 38 studies were retained: 28 for stroke,[16,18,19,24,28,30-32,75-92] 6 for dementia,[54,57,93-96] and 10 for death.[58,76,77,83,88,90,91,97-99] Of note, for 7 studies, association results of CMB with recurrent stroke or ICH risk were obtained from 3 previously published meta-analyses.[78,100,101] Regarding PVS, 5 studies were included: 3 for stroke,[18,102,103] 2 for dementia,[104,105] and 2 for death.[102,103]

White Matter Hyperintensity Burden

In 14 529 participants from 17 studies, we found a significant association of extensive WMH burden (n = 2859 participants) with risk of incident stroke (n = 1049 events) overall (heterogeneity test results, I^2 = 56%; *P* = .003), in the general population,[6,17,25,27,35,36] and in high risk populations[14,19,20,23,24,28,29,31-33,37] (**Table**; **Figure 2**) (eTables 3 and 4 in the Supplement). Adding 3 studies reporting

Table. Summary of Meta-analysis Results for the Association of Magnetic Resonance Imaging Markers of Vascular Brain Injury With Incident Stroke, Dementia, and Death

Vascular Brain Injury Type	Stroke	Ischemic Stroke	Intracerebral Hemorrhage	Dementia	Alzheimer Disease	Death
Extensive WMH burden						
Studies included, No.	17	9	7	12	6	13
No./total No.	2859/14 529	1159/7320	1572/7976	2402/9338	572/5206	1496/13 138
Events, No.	1049	696	148	1127	572	1700
HR (95% CI)	2.45 (1.93-3.12)	2.39 (1.65-3.47)	3.17 (1.54-6.52)	1.84 (1.40-2.43)	1.50 (1.22-1.84)	2.00 (1.69-2.36)
P value	<.001	<.001	.002	<.001	<.001	<.001
BI presence						
Studies, No.	12	6	5	9	3	8
No./total No.	3018/16 012	936/6873	878/8847	2759/10 772	1125/3429	1311/10 007
Events, No.	881	333	88	1029	414	1212
HR (95% CI)	2.38 (1.87-3.04)	2.18 (1.67-2.85)	3.81 (1.75-8.27)	1.29 (1.02-1.65)	1.06 (0.83-1.36)	1.64 (1.40-1.91)
P value	<.001	<.001	<.001	.04[a]	.64	<.001
CMB presence						
Studies, No.	22	20	23	5	6	10
No./total No.	3131/15 693	2557/13 125	3174/14 280	1498/8736	1514/8875	1433/9942
Events, No.	831	459	218	338	290	1134
HR (95% CI)	1.98 (1.55-2.53)	1.92 (1.40-2.63)	3.82 (2.15-6.80)	1.41 (0.90-2.21)	1.18 (0.73-1.89)	1.53 (1.31-1.80)
P value	<.001	<.001	<.001	.13	.49	<.001

Abbreviations: BI, brain infarct; CMB, cerebral microbleed; HR, hazard ratio; WMH, white matter hyperintensity.

[a] Of note, 1 population-based study[72] provided only effect estimates of dementia risk either comparing participants with at least 1 prevalent but no incident magnetic resonance imaging–defined BI with participants with neither prevalent nor incident magnetic resonance imaging–defined BI or comparing participants with at least 1 prevalent and 1 incident magnetic resonance imaging–defined BI with participants with neither prevalent nor incident magnetic resonance imaging–defined BI. By default, the effect estimates of the first comparison were included, but meta-analysis results were substantially unchanged overall when using effect estimates from the second comparison (HR, 1.52; 95% CI, 1.15-2.00; *P* = .003).

associations with continuous WMH burden in a sample size-weighted meta-analysis confirmed the association with incident stroke (n = 14 913 participants; n = 1114 events; *P* < .001).[15,22,30] Regarding stroke subtypes, extensive WMH burden was significantly associated with increased risk of incident IS overall (I^2 = 67%; *P* = .002), in the general population,[26,27,36] and in high-risk populations[14,20,23,29,31,33] and with increased risk of incident ICH overall (I^2 = 65%; *P* = .008)[16,18,21,24,26,31,34] and in the general population[16,21,26] (Table) (eTables 3 and 4 and eFigure 2 in the Supplement).

In 9338 participants from 12 studies, extensive WMH burden (n = 2402 participants) was significantly associated with incident dementia risk (n = 1127 events) overall (I^2 = 64%; *P* = .001) and in the general population,[25,39,48,52] while the association was only nominally significant in high-risk populations[38,41-46,53] (Table; Figure 2) (eTables 3 and 4 in the Supplement). Adding 6 studies reporting associations with continuous WMH burden in a sample size-weighted meta-analysis confirmed the association with incident dementia (n = 11 093 participants; n = 1163 events; *P* < .001).[40,47,49,51,55,57] Concerning dementia subtypes, we found a significant association of extensive WMH burden with risk of incident AD overall (I^2 = 0%; *P* = .79) and in the general population,[35,48] the association being only nominally significant in high-risk populations[38,41,46,54] (Table) (eTables 3 and 5 and eFigure 2 in the Supplement). Adding 4 studies reporting associations with continuous WMH burden in a sample size-weighted meta-analysis confirmed the association with incident AD (n = 7123 participants; n = 708 events; *P* < .001).[49,50,52,56]

We found a significant association in 13 138 participants from 13 studies of extensive WMH (n = 1496 participants) with mortality (n = 1700 deaths) overall (I^2 = 41%; *P* = .06), in the general population,[17,36,39,59,61] and in high-risk populations[14,20,33,37,58,60,62,63] (Table; Figure 2) (eTables 3 and 6 in the Supplement). Adding 3 studies reporting associations with continuous WMH burden in a sample size-weighted meta-analysis confirmed the association with increased mortality (n = 13 939 participants; n = 1818 events; *P* < .001).[15,22,64]

Magnetic Resonance Imaging–Defined Covert Brain Infarcts

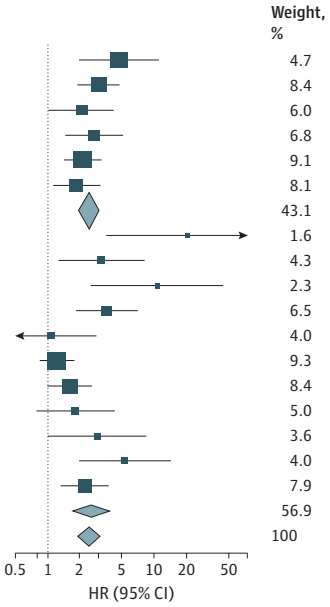
In 16 012 participants from 12 studies, presence of BI (n = 3018 participants) was associated significantly with incident stroke risk (n = 881 events) overall (I^2 = 54%; *P* = .01), in the general population,[17,25,36,39,65,66,69] and in high-risk populations[33,67,68,70,71] (Table; **Figure 3**) (eTables 3 and 7 in the Supplement). When considering stroke subtypes, presence of BI was significantly associated with increased risk of IS overall (I^2 = 0%; *P* = .70), in the general population,[16,26,36] and in high-risk populations[33,70,71] and with increased risk of incident ICH overall (I^2 = 40%; *P* = .15)[16,21,26,33,71] and in the general population[16,21,26] (Table) (eTables 3 and 7 and eFigure 3 in the Supplement).

In 10 772 participants from 9 studies,[25,39,40,48,51,57,72-74] presence of BI (n = 2759 participants) showed nominally significant association with incident dementia risk (n = 1029 events), which did not withstand correction for multiple testing (I^2 = 44%; *P* = .08) (Table; Figure 3) (eTables 3 and 8 in the Supplement). Presence of BI was not associated with inci-

Figure 2. Association of Extensive White Matter Hyperintensity (WMH) Burden With Incident Stroke, Dementia, and Death

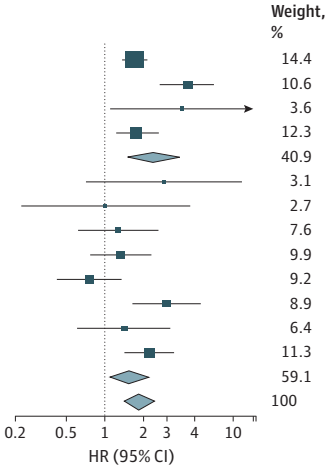
A Association of WMH with incident stroke

Source	No./Total No.	HR (95% CI)	Weight, %
Vermeer et al,[6] 2003	57/677	4.70 (2.00-11.20)	4.7
Kuller et al,[27] 2004	82/1395	3.00 (1.90-4.70)	8.4
Bokura et al,[17] 2006	102/2684	2.08 (1.04-4.17)	6.0
Weinstein et al,[35] 2013	45/1677	2.73 (1.48-5.02)	6.8
Windham et al,[36] 2015	157/1884	2.14 (1.45-3.16)	9.1
Kaffashian et al,[25] 2016	68/1677	1.88 (1.16-3.07)	8.1
GP	511/9731	2.43 (1.96-3.01)	43.1
Yamauchi et al,[37] 2002	7/89	20.50 (3.60-118.00)	1.6
Gerdes et al,[23] 2006	21/230	3.20 (1.30-8.40)	4.3
Naka et al,[31] 2006	26/266	10.70 (2.60-43.70)	2.3
Conijn et al,[20] 2011	22/492	3.60 (1.90-6.90)	6.5
Putaala et al,[33] 2011	69/634	1.07 (0.40-2.85)	4.0
Melkas et al,[29] 2012	127/320	1.23 (0.85-1.80)	9.3
Imaizumi et al,[24] 2014	111/807	1.61 (1.02-2.55)	8.4
Lim et al,[28] 2015	25/500	1.78 (0.78-4.09)	5.0
Charidimou et al,[19] 2016	17/119	2.99 (1.04-8.57)	3.6
Andersen et al,[14] 2017	21/385	5.28 (1.98-14.07)	4.0
Nam et al,[32] 2017	92/956	2.23 (1.35-3.70)	7.9
HRP	538/4798	2.55 (1.73-3.77)	56.9
Total	1049/14 529	2.45 (1.93-3.12)	100



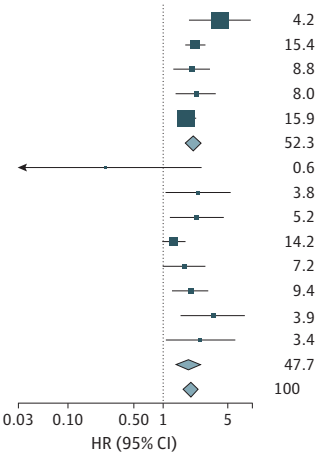
B Association of WMH with incident dementia

Source	No./Total No.	HR (95% CI)	Weight, %
Kuller et al,[48] 2003	480/2939	1.70 (1.36-2.10)	14.4
Prins et al,[52] 2004	27/815	4.40 (1.90-5.00)	10.6
Debette et al,[39] 2010	11/2013	3.97 (1.10-14.30)	3.6
Kaffashian et al,[25] 2016	124/1677	1.73 (1.24-2.59)	12.3
GP	642/7444	2.39 (1.49-3.84)	40.9
Geroldi et al,[43] 2006	11/52	2.90 (0.70-11.40)	3.1
Firbank et al,[42] 2007	14/79	1.00 (0.20-4.10)	2.7
Smith et al,[53] 2008	54/156	1.26 (0.61-2.59)	7.6
Bombois et al,[38] 2008	67/170	1.32 (0.77-2.24)	9.9
Kantarci et al,[45] 2009	75/103	0.75 (0.42-1.35)	9.2
Jokinen et al,[44] 2009	91/639	3.01 (1.64-5.55)	8.9
Eckerström et al,[41] 2015	34/73	1.40 (0.60-3.20)	6.4
Kim et al,[46] 2015	139/622	2.22 (1.43-3.43)	11.3
HRP	485/1894	1.55 (1.08-2.24)	59.1
Total	1127/9338	1.84 (1.40-2.43)	100



C Association of WMH with mortality

Source	No./Total No.	HR (95% CI)	Weight, %
Bokura et al,[17] 2006	93/2684	4.01 (1.91-8.45)	4.2
Kuller et al,[61] 2007	105/3245	2.22 (1.75-2.82)	15.4
Ikram et al,[59] 2009	191/245	2.05 (1.32-3.20)	8.8
Debette et al,[39] 2010	97/2208	2.27 (1.41-3.65)	8.0
Windham et al,[36] 2015	576/1884	1.78 (1.42-2.23)	15.9
GP	1062/10 266	2.10 (1.76-2.51)	52.3
Yamauchi et al,[37] 2002	4/89	0.26 (0.03-2.59)	0.6
Levy et al,[62] 2003	30/259	2.36 (1.07-5.21)	3.8
Kerber et al,[60] 2006	40/72	2.31 (1.21-4.40)	5.2
Oksala et al,[63] 2009	277/396	1.31 (1.00-1.71)	14.2
Henneman et al,[58] 2009	153/545	1.70 (1.00-2.80)	7.2
Conijn et al,[20] 2011	48/492	2.00 (1.30-3.00)	9.4
Putaala et al,[33] 2011	53/634	3.43 (1.58-7.42)	3.9
Andersen et al,[14] 2017	33/385	2.54 (1.10-5.83)	3.4
HRP	638/2872	1.89 (1.42-2.50)	47.7
Total	1700/13 138	2.00 (1.69-2.36)	100

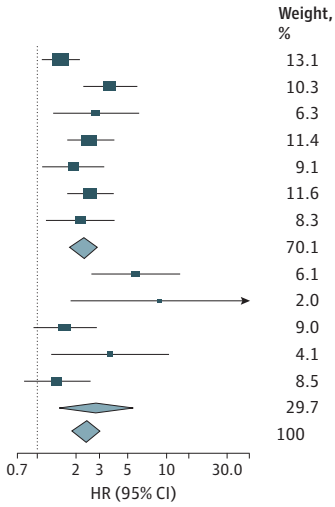


The association of extensive WMH of presumed vascular origin with incident stroke (A) (overall: I^2 = 56%; P = .003; in the general population [GP]: I^2 = 0%; P = .43; in high-risk populations [HRP]: I^2 = 67%; P < .001), incident dementia (B) (overall: I^2 = 64%; P = .001; GP: I^2 = 79%; P = .003; HRP: I^2 = 53%; P = .04), and mortality (C) (overall: I^2 = 41%; P = .06). Results correspond to hazard ratios (HRs) with 95% CIs for each study; the meta-analysis results (inverse variance–weighted meta-analysis with random effects) are shown in diamonds. The No./total No. corresponds to the number of individuals with the outcome of interest and the total sample size.

Figure 3. Association of Magnetic Resonance Imaging (MRI)–Defined Brain Infarct (BI) With Incident Stroke, Dementia, and Death

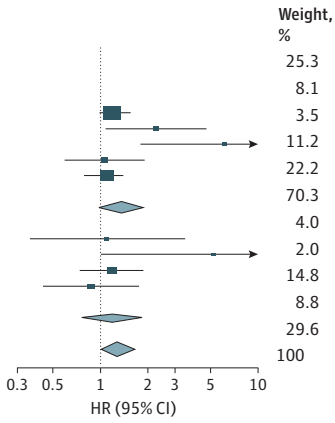
A Association of MRI-defined BI with incident stroke

Source	No./Total No.	HR (95% CI)	Weight, %
Bernick et al,[65] 2001	159/3275	1.52 (1.10-2.10)	13.1
Bokura et al,[17] 2006	102/2684	3.66 (2.28-5.89)	10.3
Debette et al,[39] 2010	32/2177	2.84 (1.32-6.10)	6.3
Poels et al,[69] 2012	99/1007	2.50 (1.70-3.90)	11.4
Di Tullio et al,[66] 2013	71/1235	1.90 (1.10-3.30)	9.1
Windham et al,[36] 2015	157/1831	2.54 (1.70-3.79)	11.6
Kaffashian et al,[25] 2016	68/1677	2.15 (1.18-3.93)	8.3
GP	688/13886	2.30 (1.80-2.93)	70.1
Kario et al,[67] 2001	45/585	5.83 (2.65-12.85)	6.1
Miwa et al,[68] 2010	8/282	9.01 (1.81-44.88)	2.0
Putaala et al,[33] 2011	81/655	1.62 (0.93-2.82)	9.0
Umemura et al,[70] 2011	13/190	3.65 (1.29-10.32)	4.1
Weber et al,[71] 2012	46/414	1.42 (0.79-2.56)	8.5
HRP	193/2126	2.86 (1.49-5.49)	29.7
Total	881/16012	2.38 (1.87-3.04)	100



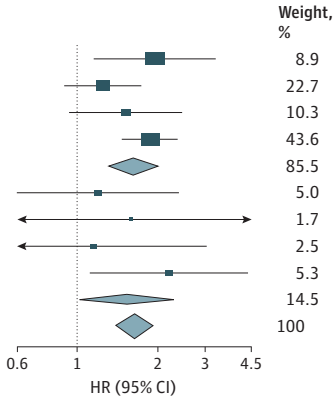
B Association of MRI-defined BI with incident dementia

Source	No./Total No.	HR (95% CI)	Weight, %
Kuller et al,[48] 2003	480/2939	1.20 (1.00-1.54)	25.3
Vermeer et al,[74] 2003	30/1015	2.26 (1.09-4.70)	8.1
Debette et al,[39] 2010	11/2013	6.12 (1.82-20.54)	3.5
Kaffashian et al,[25] 2016	124/1677	1.07 (0.60-1.92)	11.2
Sigurdsson et al,[72] 2017	234/2067	1.10 (0.80-1.40)	22.2
GP	879/9711	1.37 (0.99-1.89)	70.3
DeCarli et al,[40] 2004	17/52	1.11 (0.36-3.42)	4.0
Yamashita et al,[73] 2010	9/84	5.25 (1.02-27.01)	2.0
Prins et al,[51] 2013	81/426	1.19 (0.75-1.88)	14.8
van Uden et al,[57] 2016	43/499	0.88 (0.44-1.76)	8.8
HRP	150/1061	1.20 (0.76-1.87)	29.6
Total	1029/10772	1.29 (1.02-1.65)	100



C Association of MRI-defined BI with mortality

Source	No./Total No.	HR (95% CI)	Weight, %
Bokura et al,[17] 2006	93/2684	1.95 (1.16-3.29)	8.9
Ikram et al,[59] 2009	191/490	1.25 (0.90-1.73)	22.7
Debette et al,[39] 2010	97/2208	1.53 (0.94-2.48)	10.3
Windham et al,[36] 2015	579/1831	1.88 (1.48-2.37)	43.6
GP	957/7213	1.63 (1.31-2.03)	85.5
Henneman et al,[58] 2009	153/1110	1.20 (0.60-2.40)	5.0
Yamashita et al,[73] 2010	13/84	1.59 (0.49-5.23)	1.7
Putaala et al,[33] 2011	50/605	1.15 (0.43-3.04)	2.5
Weber et al,[71] 2012	39/995	2.22 (1.12-4.35)	5.3
HRP	255/2794	1.54 (1.02-2.31)	14.5
Total	1212/10007	1.64 (1.40-1.91)	100



The association of MRI-defined covert BI with incident stroke (A) (overall: I^2 = 54%; P = .01; in the general population [GP]: I^2 = 45%; P = .09; in high-risk populations [HRP]: I^2 = 69%; P = .01), incident dementia (B) (overall: I^2 = 44%; P = .08), and mortality (C) (overall: I^2 = 0%; P = .48). Results correspond to hazard ratios (HRs) with 95% CIs for each study; the meta-analysis results (inverse variance–weighted meta-analysis with random effects) are shown in diamonds. The No./total No. corresponds to the number of individuals with the outcome of interest and the total sample size.

dent AD, both in 1 general population study[48] and in 2 high-risk population studies[54,57] (eTable 8 and eFigure 3 in the Supplement).

In 10 007 participants from 8 studies, presence of BI (n = 1311 participants) was significantly associated with mortality (n = 1212 deaths) overall (I^2 = 0%; P = .48) and in the general population,[17,36,39,59] with the association in high-risk populations being only nominally significant[33,58,71,73] (Table; Figure 3) (eTables 3 and 9 in the Supplement).

Cerebral Microbleeds

In 15 693 participants from 22 studies, presence of CMB (n = 3131 participants) was significantly associated with incident stroke risk (n = 831 events) overall (I^2 = 49%; P = .005) and

in high-risk populations,[19,24,28,30-32,76-80,83,84,88-92] the association in the general population being only nominally significant[16,75] (Table; **Figure 4**) (eFigure 2 in the Supplement). With respect to stroke subtypes, presence of CMB was significantly associated with increased risk of incident IS overall (I^2 = 50%; P = .006)[16,19,24,28,30,31,75,77-80,83,84,89-92] and in high-risk populations[16,19,24,28,30,31,75-80,83,84,89-92] and with increased risk of incident ICH overall (I^2 = 60%; P < .001) and in high-risk populations,[18,19,24,30,31,76-78,80-92] with nominally significant associations in the general population[16,75] (eTables 3 and 10 and eFigure 4 in the Supplement).

In 8736 participants from 5 studies,[57,93-96] presence of CMB (n = 1498 participants) was not significantly associated with increased risk of incident dementia (Table; Figure 4) (eTables 3 and 11 in the Supplement). Presence of CMB was also not associated with risk of incident AD[54,57,93-96] (Table) (eTables 3 and 11 and eFigure 4 in the Supplement). In 9942 participants from 10 studies, presence of CMB (n = 1433 participants) was significantly associated with increased mortality (1134 deaths) overall (I^2 = 0%; P = .48) and in high-risk populations[58,76,77,83,88,90,91,97-99] (Table; Figure 4) (eTables 3 and 12 in the Supplement).

Information on lobar vs deep location of CMB was available only in a small minority of studies (eTables 10-12 in the Supplement). The results of these secondary meta-analyses are included in the eResults in the Supplement.

Perivascular Spaces

There were too few eligible studies on the clinical significance of PVSs to conduct meta-analyses. In one study in high-risk populations with IS or transient ischemic attack (n = 2002 participants),[103] high PVS burden (>20 vs <11 PVSs) in basal ganglia was associated with recurrent stroke and IS but not with ICH. In another study in 229 patients with cerebral amyloid angiopathy-related ICH,[18] high PVS burden in the centrum semiovale (≥20 PVSs) was associated with increased risk of ICH recurrence. In a single population-based study (n = 1228 participants),[102] participants in the highest tertile of PVS burden did not have a significantly higher risk of incident stroke after adjusting for vascular risk factors (eTable 13 in the Supplement).

In one population-based study (n = 1778 participants),[105] the highest grade of PVS burden in the basal ganglia and white matter was associated with increased risk of incident dementia. In another population-based study (n = 2612 participants),[104] the presence of large PVS (greater than 3 mm) overall and in the basal ganglia was significantly associated with increased risk of incident vascular dementia but not all dementia or AD (eTable 14 in the Supplement).

One study in high-risk patients with IS or transient ischemic attack (n = 2002 participants)[103] did not observe any significant association of high PVS burden (>20 vs <11 PVSs) with mortality. In a single population-based study (n = 1228 participants),[102] participants in the highest tertile of PVS burden had a higher rate of vascular death but not death overall after adjusting for vascular risk factors (eTable 15 in the Supplement).

Sensitivity Analyses

Study quality was mostly high (eTable 2 in the Supplement). After removing studies with medium to low quality (less than 7 stars on the Newcastle-Ottawa scale) or studies using ORs only, the main findings of meta-analyses were unchanged (eTable 16 in the Supplement). Meta-regression analyses indicated no association of length of follow-up or adjustment for potential confounders with associations (eTable 17 in the Supplement). Regarding assessment of possible publication bias, Egger test was only nominally significant for WMH and stroke (coefficient, 2.5; SE, 0.8; P = .006), with all HRs greater than 1 (eFigures 5-10 in the Supplement).

Discussion

In this systematic review and meta-analysis, we summarized data from 94 prospective studies with up to 14 529 participants for WMH, 16 012 participants for BI, 15 693 participants for CMB, and 4587 participants for PVS. We observed significant associations of extensive WMH burden, BI, and CMB with increased risk of incident stroke and both IS (risk more than doubled) and ICH (risk more than tripled). White matter hyperintensity burden was also associated with increased risk of incident dementia and AD, with hazard ratios between 1.5 and 1.8. White matter hyperintensity burden, BI, and CMB were all associated with increased risk of death, with hazard ratios between 1.5 and 2.0. These associations were mostly seen both in the general population and in high-risk individuals. Data on high PVS burden were limited and insufficient to conduct meta-analyses, with some but not all studies reporting a significant association with increased risk of stroke, dementia, and vascular death.

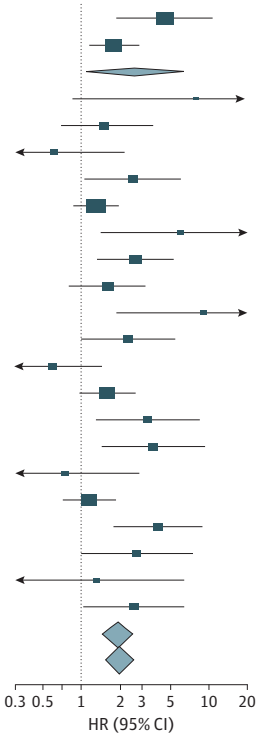
To our knowledge, this is the first systematic review and meta-analysis simultaneously gathering published data on the association of the 4 main MRI markers of VBI (ie, WMH, BI, CMB, and PVS) with risk of incident stroke, dementia, and death. Previous meta-analyses focused on 1 MRI marker at once (ie, WMH or CMB)[3,78,100,101,106,107] and mostly 1 outcome, sometimes in subpopulations. As well as integrating information on multiple MRI markers of VBI, our review adds numerous new studies.[14,16,18-21,24-26,28,29,32,33,35,36,41,46,49-51,57,58,64,72,75,84,88,95,96,99,102-105] We also present, to our knowledge, the first meta-analyses on the association of BI with stroke subtypes, dementia, and mortality and the first systematic review on the association of PVS with stroke, dementia, and mortality.

White matter hyperintensities, BI, CMB, and PVS are common incidental findings on MRI brain scans carried out for other reasons. They occur in about 10% to 28% of individuals 70 years or older for BI and CMB and in more than 80% for WMH and PVS, leading to study of them as extensive vs nonextensive burden (with frequencies of extensive WMH and PVS burden varying depending on definitions [Figure 1] but ranging approximately between 10% and 50%).[1-3,87,108-111] These MRI markers of VBI predominantly reflect underlying cerebral SVD, and in the vast majority of individuals, they are covert, ie, not associated with clinical stroke. The clinical and therapeutic significance of these findings is debated. Our analysis demonstrates that extensive WMH, BI, and CMB are predictors of a markedly increased risk of stroke and death and an increased risk of dementia for extensive WMH. Perivascular spaces have

Figure 4. Association of Cerebral Microbleeds (CMB) With Incident Stroke, Dementia, and Death

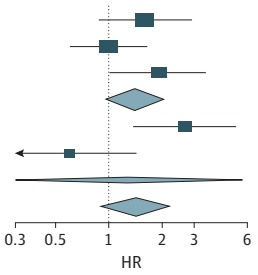
A Association of CMB with incident stroke

Source	No./Total No.	HR (95% CI)	Weight, %
Bokura et al,[16] 2011	44/2102	4.48 (2.20-12.20)	4.6
Akoudad et al,[75] 2015	93/4759	1.79 (1.16-2.78)	7.9
GP	137/6861	2.62 (1.08-6.36)	12.5
Fan et al,[90] 2003	16/121	7.90 (0.85-73.07)	1.1
Boulanger et al,[77] 2006	24/236	1.50 (0.70-3.60)	4.8
Naka et al,[31] 2006	26/266	0.61 (0.17-2.13)	2.8
Huang et al,[80] 2008	21/636	2.51 (1.06-5.97)	4.5
Soo et al,[91] 2008	96/908	1.30 (0.87-1.94)	8.2
Mok et al,[30] 2009	5/75	5.95 (1.42-24.95)	2.3
Nishikawa et al,[84] 2009	36/698	2.64 (1.34-5.19)	5.8
Thijs et al,[92] 2010	32/487	1.60 (0.80-3.10)	5.8
Fluri et al,[79] 2012	7/176	8.91 (1.87-42.51)	2.0
Kwa et al,[83] 2013	28/397	2.30 (1.00-5.30)	4.7
Song et al,[89] 2013	28/550	0.59 (0.25-1.44)	4.5
Imaizumi,[24] 2014	111/807	1.59 (0.97-2.63)	7.3
Benedictus et al,[76] 2015	23/301	3.30 (1.30-8.40)	4.1
Lim et al,[28] 2015	25/500	3.66 (1.47-9.09)	4.3
Charidimou et al,[19] 2016	17/119	0.74 (0.19-2.78)	2.5
Nam et al,[32] 2017	92/956	1.14 (0.71-1.84)	7.6
Shoamanesh et al,[88] 2017	62/943	4.00 (1.80-8.70)	5.0
Wilson et al,[78] 2016 (CROMIS-1)	12/68	2.68 (0.99-7.31)	3.8
Wilson et al,[78] 2016 (Heidelberg)	8/265	1.30 (0.27-6.27)	2.0
Wilson et al,[78] 2016 (OXVASC)	18/323	2.58 (1.04-6.38)	4.3
HRP	694/8832	1.92 (1.47-2.50)	87.4
Total	831/15693	1.98 (1.55-2.53)	100



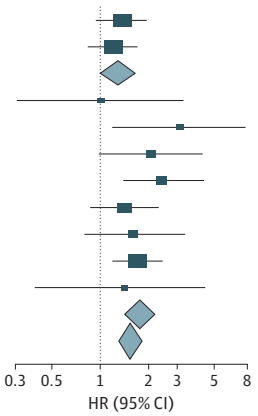
B Association of CMB with incident dementia

Source	No./Total No.	HR (95% CI)	Weight, %
Akoudad et al,[93] 2016	47/3816	1.59 (0.88-2.89)	21.0
Ding et al,[96] 2017	119/2601	1.00 (0.61-1.64)	23.8
Romero et al,[95] 2017	85/1296	1.89 (1.04-3.44)	20.9
GP	251/7713	1.40 (0.95-2.06)	65.7
Miwa et al,[94] 2014	44/524	2.67 (1.38-5.14)	19.4
van Uden et al,[57] 2016	43/499	0.60 (0.25-1.43)	14.8
HRP	87/1023	1.30 (0.30-5.62)	34.2
Total	338/8736	1.41 (0.90-2.21)	100



C Association of CMB with mortality

Source	No./Total No.	HR (95% CI)	Weight, %
Akoudad et al,[97] 2013	172/3979	1.37 (0.96-1.94)	20.9
Romero et al,[99] 2017	296/1818	1.20 (0.85-1.70)	21.5
GP	468/5797	1.28 (1.00-1.64)	42.4
Fan et al,[90] 2003	14/121	1.01 (0.31-3.21)	1.9
Boulanger et al,[77] 2006	20/236	3.10 (1.20-7.80)	3.0
Soo et al,[91] 2008	107/908	2.04 (0.98-4.27)	4.8
Henneman et al,[58] 2009	153/836	2.40 (1.40-4.30)	8.2
Altmann-Schneider et al,[98] 2011	131/371	1.41 (0.87-2.27)	11.2
Kwa et al,[83] 2013	40/397	1.60 (0.80-3.30)	5.2
Benedictus et al,[76] 2015	147/333	1.70 (1.20-2.50)	21.5
Shoamanesh et al,[88] 2017	54/943	1.40 (0.40-4.40)	1.8
HRP	666/4145	1.75 (1.42-2.17)	57.6
Total	1134/9942	1.53 (1.31-1.80)	100



Association of CMB with incident stroke (A) (overall: I^2 = 49%; P = .005; in the general population [GP]: I^2 = 71%; P = .06; in high-risk populations [HRP]: I^2 = 49%; P = .008), incident dementia (B) (overall: I^2 = 61%; P = .04; GP: I^2 = 32%; P = .23; HRP: I^2 = 86%; P = .007), and mortality (C) (overall: I^2 = 0%; P = .48). Results correspond to hazard ratios (HRs) with 95% CIs for each study; the meta-analysis results (inverse variance–weighted meta-analysis with random effects) are shown in diamonds. The No./total No. corresponds to the number of individuals with the outcome of interest and the total sample size.

recently been suggested as a further manifestation of cerebral SVD,[112-114] and some studies indicated that PVS burden correlates with cognitive outcomes.[105,115,116] We found only 5 longitudinal studies,[18,102-105] some of which reported a significant association of PVS burden with risk of stroke, dementia, and vascular death. Additional studies are warranted to explore the clinical significance of high PVS burden.

There are no guidelines for the management of covert, MRI-defined VBI, leading to wide variation in clinical practice. Often, these lesions are ignored, likely representing an important missed opportunity for prevention of stroke and dementia. When such findings are detected, it seems reasonable to give healthy cardiovascular lifestyle advice. However, it remains uncertain whether specific drug therapies should be given or more stringent lowering of risk factors be targeted to limit progression of VBI and prevent or slow down cognitive decline.[117] The major treatable risk factor for VBI is hypertension,[118] and some evidence from epidemiological studies and secondary outcomes of clinical trials suggests that treating hypertension in patients with extensive WMH reduces WMH progression[119,120] and stroke risk[120] and may reduce dementia risk.[121] However, it remains uncertain how intensively blood pressure should be lowered. Recently, trials have been launched to look at the effect of intensive blood pressure lowering on lesion progression in extensive WMH, either in stroke-free patients (NCT01650402; NCT02472028) or patients with lacunar stroke.[122] In patients with lacunar stroke included in the Secondary Prevention of Small Subcortical Strokes (SPS3) trial[123] (not selected to have extensive WMH burden), no significant association of intensive blood pressure lowering with reduction in stroke risk was observed.

Our finding that WMH and BI increase the risk of not only IS but also ICH is consistent with recent data suggesting that a similar small vessel arteriopathy underlies both ischemic and hemorrhagic SVD.[10,124] This has important potential implications for therapy. Antiplatelet agents such as aspirin are often empirically given to patients with WMH and BI detected on MRI. That they also predict ICH suggests that this strategy could lead to an increased hemorrhage rate. Antiplatelet agents also tend to be avoided in persons with CMB detected on MRI; however, our results highlight that persons with CMB are also at increased risk of IS. The SPS3 trial[117] reported no reduction in stroke recurrence when adding clopidogrel to aspirin in patients with symptomatic lacunar stroke but a significant increase in bleeding and death. Randomized clinical trials are required to determine whether any antiplatelet therapy is indicated in stroke-free persons with extensive WMH or BI and whether the benefit-risk ratio is modified by the presence of CMB.

Magnetic resonance imaging markers of VBI are correlated with each other, and using the data in our analysis, it is not possible to determine whether observed associations are independent of other MRI markers of VBI. Studies using multimodal MRI in patients with symptomatic SVD have demonstrated that BI and WMH as well as more subtle and diffuse changes in white matter microstructure detected using diffusion tensor imaging are the strongest predictors of cognitive impairment compared with other MRI features.[125,126] Results for CMB have been less conclusive, with some studies finding that they are independent predictors[93,127-129] while others found the associations with cognition to disappear when WMH and BI are controlled for.[130] Further studies, ideally combining individual-level data from large cohort studies, are needed to systematically explore the respective independent associations of MRI markers of VBI with vascular and cognitive outcomes. If valid genetic instruments become available in the near future, the causal relation of each MRI marker with clinical outcomes may also be explored by mendelian randomization. Exploring interactions of VBI markers with biomarkers of neurodegeneration in relation to dementia risk is another important future step, although specific biomarkers are still lacking for large cohort studies.

Although BI and CMB were associated with risk of stroke and death, they did not significantly predict dementia risk after correction for multiple testing. The lack of association in this data set may reflect that most individuals had a small number of BIs and CMBs, which therefore made a modest contribution to overall disease burden. This does not preclude an effect of BI or CMB on dementia risk in a subset of individuals with more extensive or rapidly progressing lesions.[125,131] In line with this hypothesis, recent population-based studies reported that dementia risk was significantly increased in individuals with both prevalent and incident BI[72] or with 3 or more CMBs.[96] Small vessel disease is thought to cause cognitive decline and dementia at least partly by disruption of white matter pathways underlying complex cortical-subcortical networks.[132,133] Recent studies have shown that the degree of network disruption, measured using advanced MRI techniques, is strongly correlated with cognitive decline[125,133] and subsequent dementia risk.[134] One or few BIs or CMBs are unlikely to have a significant effect on network disruption in contrast to extensive WMH, which may affect multiple white matter tracks. White matter hyperintensity volume may also be more linked with dementia-related neurodegenerative processes, including potential reverse causation with Wallerian degeneration secondary to cortical atrophy or with the frequent coexistence of AD and cerebral amyloid angiopathy.[135,136]

Limitations

Our study has limitations. Meta-analyses were conducted post hoc, based on available data with various sources of heterogeneity (eg, study population, measurement method of MRI markers and cutoffs used, MRI field strength, methods of incident event ascertainment, analytical model, and length of follow-up). We used random-effects meta-analyses and secondary sample size–weighted meta-analyses to account for this heterogeneity. Indeed, heterogeneity measures were statistically significant for several of the meta-analyses, although less so when looking at more homogeneous outcome subtypes, and mostly driven by differences in effect size rather than directionality of effect. Moreover, we conducted secondary analyses stratified by population type (general population vs high-risk populations, where heterogeneity was highest), excluding studies with lower methodological quality, and observed similar findings. Similarly, meta-regression analyses did not suggest any significant effect of differences between studies in length of follow-up or adjustment for confounders. Nevertheless, we acknowledge residual intrinsic sources of heterogeneity, such as differences in definition of

extensive WMH burden across studies. While most studies used HRs (or few relative risks), a few studies used ORs. The latter were pooled with HRs in meta-analyses, assuming that they numerically approximate one another, but we acknowledge this may not be perfectly verified for studies in high-risk populations with a higher incidence of events and higher risks.[11] Excluding studies that used ORs in sensitivity analyses led to similar results. All these sensitivity analyses suggest robustness of our findings. Because of a small number of studies, we did not include analyses of associations of longitudinal change in MRI markers of VBI with risk of clinical events. These may be important to better establish the potential role of these MRI markers as surrogate end points for prevention trials. We limited our review to articles published in English in peer-reviewed journals found in PubMed and through the reference list of relevant articles and did not systematically search other databases nor include articles published in languages other than English. This may have led to the omission of a small number of articles, most likely of lower methodological quality. We did not contact the authors of the 4 studies that did not provide an effect estimate or raw data to calculate one (4% of eligible studies); results of these studies are described in eTables 5 and 10 in the Supplement. Finally, although we did not identify any significant evidence for small-study bias, confirmation and in-depth exploration of our findings could be obtained by future prospective meta-analyses within large consortia using harmonized phenotypic criteria and analytical models, which would also enable estimation of age-specific population attributable risk.

Conclusions

In conclusion, this systematic review and meta-analysis provides evidence that WMH, BI, and CMB, all highly prevalent in the general population, have major clinical significance in that they indicate a significant increased risk of stroke, dementia, and death. From a practical perspective, the discovery of these MRI markers should prompt detailed assessment of a person's risk for stroke and dementia and careful evaluation of the benefit-risk ratio for available preventive strategies. Randomized clinical trials are required to determine whether specific therapies, particularly aspirin therapy and intensive blood pressure lowering, are beneficial when these MRI markers are noted as incidental findings.

ARTICLE INFORMATION

Accepted for Publication: July 30, 2018.

Published Online: October 22, 2018. doi:10.1001/jamaneurol.2018.3122

Author Contributions: Drs Debette and Markus had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Debette, Larsson, Markus.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Debette, Schilling, Markus.
Critical revision of the manuscript for important intellectual content: Duperron, Larsson.
Statistical analysis: Schilling.
Administrative, technical, or material support: Debette, Duperron.
Study supervision: Debette, Markus.

Conflict of Interest Disclosures: Dr Debette is supported by grant ANR-14-CE12-0016 from the French National Research Agency; grants from the Fondation Leducq (Transatlantic Network of Excellence on the Pathogenesis of SVD of the Brain); grants 640643, 643417, and 667375 from the European Union's Horizon 2020 Research and Innovation Programme, the European Research Council, the European Union Joint Programme–Neurodegenerative Disease Research, supported through several funding organizations under the aegis of the Joint Programme–Neurodegenerative Disease (Australia, National Health and Medical Research Council; Austria, Federal Ministry of Science, Research and Economy; Canada, Canadian Institutes of Health Research; France, French National Research Agency; Germany, Federal Ministry of Education and Research; the Netherlands, the Netherlands Organisation for Health Research and Development; and United Kingdom, Medical Research Council); and the Initiative of Excellence of Bordeaux University. Dr Markus is supported by a National Institute for Health Research Senior Investigator award, infrastructural support from the National Institute for Health Research Cambridge University Hospitals Biomedical Research Centre, and grant 667375 from the European Union's Horizon 2020 Research and Innovation Programme. No other disclosures were reported.

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