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Systematic Review

Left Ventricular Hypertrophy and Cerebral Small Vessel Disease: A Systematic Review and Meta-Analysis

Andreas Papadopoulos,[a,*] Konstantinos Palaiopanos,[a,*] Athanasios P. Protogerou,[b] George P. Paraskevas,[c] Georgios Tsivgoulis,[d,e] Marios K. Georgakis[f]

[a]Medical School, National and Kapodistrian University of Athens, Athens, Greece
[b]Cardiovascular Prevention and Research Unit, Department of Pathophysiology, National and Kapodistrian University of Athens, Athens, Greece
[c]Cognitive and Movement Disorders Unit and Unit of Neurochemistry and Biological Markers, First Department of Neurology, Eginition University Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[d]Second Department of Neurology, Attikon Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece
[e]Department of Neurology, University of Tennessee Health Science Center, Memphis, TN, USA
[f]Institute for Stroke and Dementia Research, LMU University Hospital, Ludwig-Maximilians-University (LMU), Munich, Germany

Background and Purpose Left ventricular hypertrophy (LVH) is associated with the risk of stroke and dementia independently of other vascular risk factors, but its association with cerebral small vessel disease (CSVD) remains unknown. Here, we employed a systematic review and meta-analysis to address this gap.

Methods Following the MOOSE guidelines (PROSPERO protocol: CRD42018110305), we systematically searched the literature for studies exploring the association between LVH or left ventricular (LV) mass, with neuroimaging markers of CSVD (lacunes, white matter hyperintensities [WMHs], cerebral microbleeds [CMBs]). We evaluated risk of bias and pooled association estimates with random-effects meta-analyses.

Results We identified 31 studies (n=25,562) meeting our eligibility criteria. In meta-analysis, LVH was associated with lacunes and extensive WMHs in studies of the general population (odds ratio [OR]$_{lacunes}$, 1.49; 95% confidence interval [CI], 1.12 to 2.00) (OR$_{WMH}$, 1.73; 95% CI, 1.38 to 2.17) and studies in high-risk populations (OR$_{lacunes}$: 2.39; 95% CI, 1.32 to 4.32) (OR$_{WMH}$, 2.01; 95% CI, 1.45 to 2.80). The results remained stable in general population studies adjusting for hypertension and other vascular risk factors, as well as in sub-analyses by LVH assessment method (echocardiography/electrocardiogram), study design (cross-sectional/cohort), and study quality. Across LV morphology patterns, we found gradually increasing ORs for concentric remodelling, eccentric hypertrophy, and concentric hypertrophy, as compared to normal LV geometry. LVH was further associated with CMBs in high-risk population studies.

Conclusions LVH is associated with neuroimaging markers of CSVD independently of hypertension and other vascular risk factors. Our findings suggest LVH as a novel risk factor for CSVD and highlight the link between subclinical heart and brain damage.

Keywords Hypertrophy, left ventricular; Cerebral small vessel diseases; Stroke, lacunar; Leukoaraiosis; Cerebral hemorrhage; Meta-analysis

Correspondence: Marios K. Georgakis
Institute for Stroke and Dementia Research, LMU University Hospital, Ludwig-Maximilians-University (LMU), Feodor-Lynen-Str. 17, 81377 Munich, Germany
Tel: +49-89-4400-46126
Fax: +49-89-4400-46040
E-mail: marios.georgakis@med.uni-muenchen.de

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*These authors contributed equally to the manuscript as first author.

Introduction

Cerebral small vessel disease (CSVD) describes any pathological processes affecting the perforating arterioles, capillaries, and venules of the brain.[1,2] CSVD is the leading cause of vascular cognitive impairment,[3] accounts for 25% of all ischemic strokes[4] and the majority of intracerebral hemorrhage cases,[5] and is an independent predictor of mortality.[6,7] Manifestations of CSVD are further associated with physical and psychological sequalae in the elderly including gait,[8] functional,[9] and mood[10] disturbances. CSVD can be defined by neuroimaging markers including lacunes, white matter hyperintensities (WMHs), cerebral microbleeds (CMBs) and enlarged perivascular spaces (EPVSs).[11] Despite the very high prevalence of CSVD in the ageing population (≥90% in individuals ≥65 years[12]), the underlying mechanisms are incompletely understood, thus impeding the development of effective prevention strategies.

Left ventricular hypertrophy (LVH), a pathological increase in left ventricular mass (LVM),[13] has been proposed as an independent risk factor for cardiovascular disease[14] and is included in the original 10-year Framingham stroke risk score for incident stroke prediction in the elderly.[15] LVH and increased LVM are clinical markers of hypertension-mediated organ damage and constitute surrogate indicators of the duration of exposure to hypertension and other vascular risk factors.[14] In large-scale population-based cohort studies, LVH and increased LVM have been associated with the risk of incident stroke in the elderly, independently of hypertension presence or duration and other traditional vascular risk factors.[16-18] Furthermore, in a recent meta-analysis, we showed similar associations of LVH with cognitive decline and risk of incident dementia in both the general and high-risk populations.[19]

These associations could be explained by effects of LVH on the microvasculature. Although several studies explore the associations between LVH or increased LVM and subclinical neuroimaging markers of CSVD,[20-22] the results vary widely, probably because of heterogeneity in the populations examined, small sample sizes, variable methodologies for LVH assessment or LVM indexing, and differences in CSVD neuroimaging definitions. Furthermore, the studies differ regarding their methods for adjustment for hypertension and other vascular risk factors. Hence, it remains unknown if LVH is independently associated with subclinical CSVD neuroimaging markers.

Here, we leveraged data from published literature and performed a systematic review of studies exploring associations between LVH with neuroimaging markers of CSVD, aiming to: (1) critically evaluate the methodology of the included studies and identify limitations of the existing literature; (2) quantify in meta-analyses the associations of LVH and LVM with lacunes, WMHs, CMBs, and EPVSs in general population and high-risk individuals; and (3) explore if these associations are independent of the presence and/or duration of hypertension and other vascular risk factors.

Methods

This systematic review was based on a predefined protocol registered to PROSPERO (30 October 2018, registration number: CRD42018110305, available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018110305), compliant with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[23]

Literature search

Two independent reviewers (A.P. and K.P.) systematically screened the Medline (through PubMed), Scopus and Cochrane databases from inception to December 28, 2019 to identify studies investigating the association between LVH and CSVD neuroimaging markers. The detailed search strategy is available in the Supplement (Supplementary methods). All reference lists of the derived eligible articles were hand-searched for potential eligible studies not identified through the database search ("snowball" procedure). No language or publication year restrictions were applied. Eligible studies were evaluated for possible population overlap according to geographical setting, chronological period, sample size, outcome under study, and type of statistical analysis. In case of overlap, we opted for the most recent study. We further contacted the corresponding authors of articles presenting evidence that relevant data were available but not quantifying the associations under study, in order to request supplementary analyses. Differences between the two reviewers were solved through team consensus.

Eligibility criteria

We considered as eligible cohort, cross-sectional, and case-control studies, as well as secondary analyses of randomized controlled trials exploring the association between LVH and neuroimaging markers of CSVD. Cases series, case reports, systematic or narrative reviews, animal and *in vitro* studies were excluded. We included studies of the general population or studies focused on specific high-risk populations, such as patients with stroke, hypertension, cardiovascular disease, diabetes mellitus, and chronic kidney disease. All analyses were performed separately for the general population and high-risk population studies. We excluded studies examining populations with genetic diseases predisposing to CSVD (e.g., Cerebral Au-

tosomal Dominant/Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy [CADASIL, CARASIL], Fabry disease), autoimmune diseases and vasculitis, primary cardiomyopathies (e.g., dilatative or hypertrophic) and those including solely dementia individuals. Studies without a non-LVH comparison group were also excluded.

The exposure variables of interest included: (1) dichotomously defined LVH, diagnosed by electrocardiography (ECG), transthoracic echocardiography (TTE), or cardiac magnetic resonance imaging (MRI), and (2) continuous LVM measures, indexed (LVMI) or not to body surface area, assessed by TTE or cardiac MRI. For TTE-assessed LVH, we preferably included studies defining LVH as LVM ≥115 g/m^2 in males and ≥95 g/m^2 in females,[13] but other cut-off points were also considered. ECG-assessed LVH should be defined by validated (e.g., Sokolow-Lyon indices or Cornell voltage criteria)[24,25] methods in standard 7 or 12-lead ECG. LVM should be calculated by TTE parameters according to the method of Devereux et al.[26]

The primary outcomes of our study included the following neuroimaging markers of CSVD, in accordance with the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE[11]): lacunes, WMHs, CMBs, and EPVSs. Eligible were considered MRI or computed tomography (CT) studies assessing lacunes and WMHs, as previous literature has described compliance validity between the two methods,[27,28] and MRI studies evaluating CMBs and EPVSs. We included studies defining lacunes as round or ovoid, subcortical, fluid-filled cavities, measuring between 3 and 15-mm in maximal diameter, consistent with a previous acute small deep brain infarct or hemorrhage in the territory of one perforating arteriole. Studies exploring lacunar strokes, defined as lacunes with acute clinical manifestations, were also included. We further *post hoc* decided to include studies examining "silent infarcts" provided that >80% of the included events were lacunes. WMHs should be identified as hyperintense areas on T2-weighted MRI sequences, isointense or hypointense on fluid-attenuated inversion recovery (FLAIR) imaging or as CT hypodensities. The studies should assess WMHs presence or severity through semi-quantitative visual rating scales (e.g., Fazekas) or WMH volume via automated or semi-automated methods. Due to the high prevalence of WMHs in the elderly,[12] the individual studies dichotomized WMH outcome based on specific burden levels (either based on a scale or a volumetric measurement) instead of mere presence. For simplicity, we use the term "extensive WMHs" to refer to this outcome although the individual studies used different methods for its assessment. CMBs had to be visualized as small (≤10 mm) areas of signal void with associated blooming on T2*-weighted MRI sequences. EPVSs should be defined as fluid-filled spaces following the course of a vessel with cerebrospinal fluid-like signal intensity.

Data extraction

A predefined spreadsheet was used to extract the following data: publication details (authors, year), study information (geographical region, recruitment period, design, population under study, sample size, follow-up parameters), study sample characteristics (age, gender, smoking, body mass index, hypertension history, diabetes mellitus, stroke, coronary artery disease), LVH/LVMI ascertainment (assessment method, definition, method/scale of quantification), CSVD assessment (marker under study, imaging modality, definition, method/scale of quantification, number of cases), and statistical analysis details (analysis type, effect estimates, 95% confidence intervals [CIs], adjusting variables). The corresponding author was contacted in case of missing data.

Quality assessment

We evaluated studies for risk of bias using the Newcastle-Ottawa scale.[29] As the vast majority of eligible studies were of cross-sectional or cohort design, we applied the nine-item cohort subscale to all studies. The following criteria were assessed: representativeness of the exposed population; selection of the non-exposed group; LVH ascertainment; outcome absence at study onset; comparability of the exposed and non-exposed group for age and hypertension; CSVD markers assessment; follow-up period length and completion. Cross-sectional studies, by definition, did not receive any points for longitudinal assessment items (outcome absence at study onset, follow-up period length and completion). The detailed pre-defined handling of each criterion for the purposes of this systematic review is outlined in the Supplementary Table 1.

Statistical analysis

For each eligible study, we extracted association estimates and 95% CIs between presence of LVH and presence or incidence of neuroimaging CSVD markers. In 21 out of the 27 studies in our meta-analysis, the association estimates were odds ratios (ORs) derived from logistic regression analyses. Two prospective studies presented relative risks (RRs), but as the prevalence of the examined outcome was <10% in their population we considered RRs to be comparable to ORs[30] and pooled them with the other studies. Where ORs were not presented, we hand-calculated unadjusted ORs using 2×2 tables, based on data from the published articles. In studies presenting only ORs stratified by LVMI increments, we obtained the OR for the presence or absence of LVH by applying the method described

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by Hamling et al.[31] For studies examining WMH volume or WMH severity measured as continuous outcomes, we transformed the presented beta coefficients to standardized mean differences and then used the latter to estimate the OR for a dichotomized WMH measure, based on validated formulae with the use of an online tool (https://campbellcollaboration.org/research-resources/effect-size-calculator.html).[32]

We then performed random-effects meta-analyses of the derived association estimates to obtain pooled ORs and 95% CIs for each outcome. The method described by DerSimonian and Laird[33] was our primary meta-analytical approach. For our main analyses we also performed alternative random-effects meta-analytical approaches (ORs calculated via the Paule-Mandel between-study variance estimator,[34] 95% CIs with the Hartung-Knapp[35] and modified Hartung-Knapp[36] methods), as detailed in the supplement (Supplementary methods).[34,36-46] All analyses were performed separately for the general population and high-risk population studies. The presence of heterogeneity was evaluated by the I^2 and the Cochran Q statistics. We defined low, moderate and high heterogeneity as an I^2 of <25%, 25% to 75%, and >75%, respectively (significance threshold: P<0.10).[47] To explore potential sources of heterogeneity, we performed sensitivity and subgroup analyses stratified by study design (cross-sectional, cohort), LVH assessment method (TTE, ECG), LVH definition criteria (ECG: only ↑ QRS voltage-based criteria; TTE: LVMI ≥115 g/m^2 in males and ≥95 g/m^2 in females, body surface indexed), CSVD assessment method (MRI, CT), level of adjustment (studies adjusted for age, sex, hypertension, and other vascular risk factors), and fulfilment of the quality criteria of the Newcastle-Ottawa scale. Where possible, we further performed analyses for different left ventricular (LV) morphology patterns: normal LV geometry, concentric remodeling, eccentric hypertrophy, and concentric hypertrophy.[13] In order to explore the effect of each individual study in the overall estimate we conducted "leave-one-out" sensitivity analyses.

The results of our main analyses were graphically presented with funnel plots. The effect of potential publication bias (small-study effects) was explored in cases of ≥10 pooled studies using the Egger's test (significance threshold: P<0.10).[48] In case of statistically significant small-study effects, we adjusted the pooled effect estimates for publication bias using a "trim and fill" analysis.[49]

Statistical significance for the main analyses was set at a two-sided P<0.05. All analyses were conducted with the STATA Software version 13.0 (Stata Corporation, College Station, TX, USA).

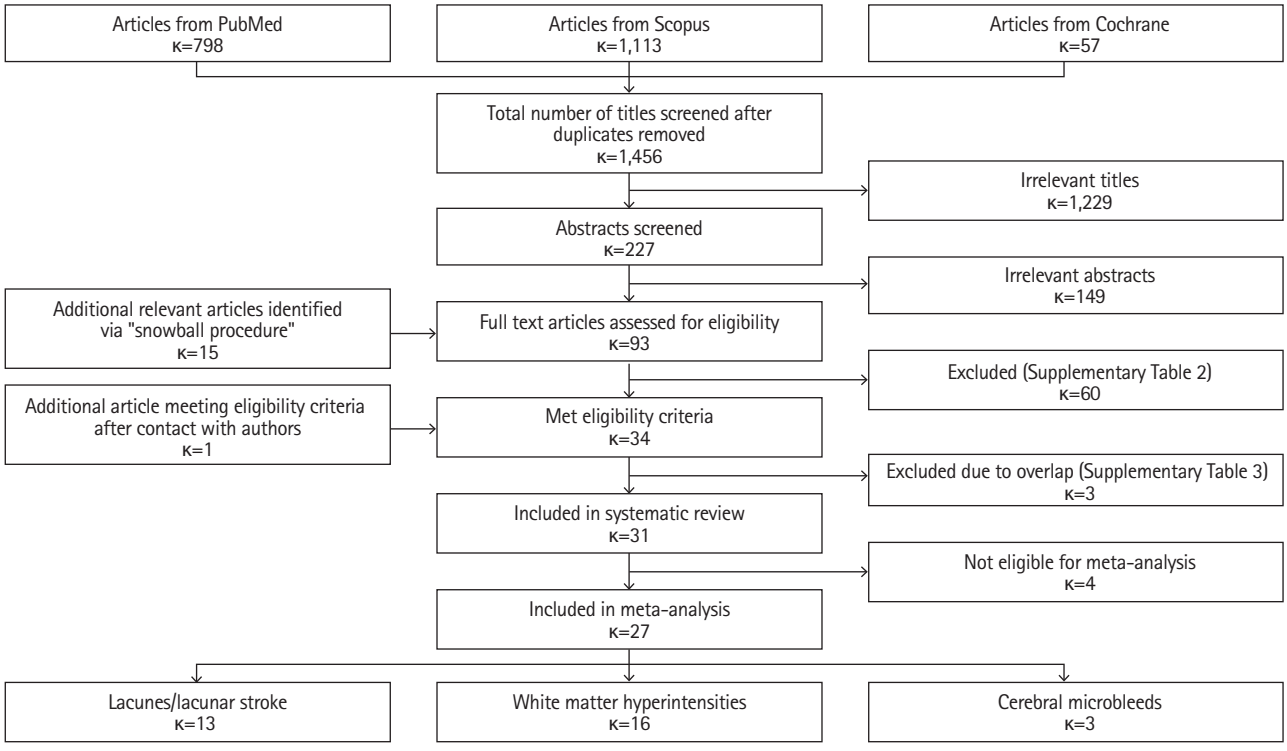

Figure 1. Flowchart of the study selection process. The included articles for each of the outcomes do not sum up to the total number of included articles because several studies provided data for more than one outcome.

Results

Review of literature

Figure 1 summarizes the study selection process. Following screening of 1,456 articles yielded by the literature search, we identified 34 articles meeting our eligibility criteria (60 studies were excluded after full-text screening as described in Supplementary Table 2). Three of them were excluded due to population overlap (Supplementary Table 3).[50-52] Of the 31 studies[20-22,53-80] (n=25,562) included in our systematic review, only 27[21,22,53-60,62-69,72-80] (n=21,010) provided appropriate data to also be used in the meta-analysis. Quantitative synthesis of articles examining associations between LVMI and WMH severity or volume as continuous variables was not possible because of the highly heterogeneous statistical methodologies. Of the studies included in meta-analysis, 13 examined presence of lacunes, 16 assessed extensive WMHs and three examined presence of CMBs. No eligible articles investigating EPVSs were identified.

Study characteristics

The descriptive characteristics of the included studies are presented in Table 1.

Assessment of left ventricular hypertrophy

The most commonly used definition for ECG-based diagnosis of LVH was the Sokolo-Lyon and/or Cornell definition, but some older studies[56,57,65-67,77] considered isolated QRS changes "normal" and defined LVH only if additional ST-segment and/or T-wave changes were present. Regarding TTE-defined LVH, the diagnosis was usually made according to internationally accepted standards, i.e., LVMI ≥115 g/m^2 for men and ≥95 g/m^2 for women (indexed to body surface area). Some studies, however, used different cut-off points,[55,68,69,78] no indexing (g),[71] or height-based indexes (e.g., g/m$^{2.7}$).[59,72,76] Six studies (n=1,279)[22,53,68,72,76,78] also evaluated LV morphology, classifying it as normal LV geometry, concentric remodeling, eccentric hypertrophy, or concentric hypertrophy.

Lacunes

Of the 13 studies[21,22,56,57,64,65,67,68,73,74,76,79,80] examining lacunes (n=13,529), nine were of cross-sectional (n=6,272), three of cohort (n=7,020), and one of case-control (n=237) design. Overall, lacunes were identified in 1,588 individuals. Five of the studies (n=6,650) were based on the general population and the remaining eight (n=6,879) on high-risk population subsets. Mean age of all the individuals was 67 years (range, 57 to 76). Lacunes were assessed by MRI in eight studies (n=6,091), by CT in two (n=844), whereas the three studies examining clinically manifest lacunar stroke utilized either MRI or CT (n=6,594).

White matter hyperintensities

Twenty-two studies[20-22,53-55,58,59,61-64,66,68-72,75,77,78,80] investigated WMHs (n=15,636). In 14 of these studies (n=8,540) the outcome was presence of extensive WMHs, whereas six studies (n=6,319) examined WMHs severity or volume as continuous outcomes. Two studies (n=777) presented both types of data. Eighteen studies were of cross-sectional (n=13,494) and three of cohort design (n=2,011), whereas one study presented both a cross-sectional (n=131) and a cohort analysis (n=113). Overall, nine of the studies (n=10,432) were based on the general population and the remaining 13 (n=5,204) on high-risk population subsets. Mean age of all individuals was 65 years (range, 30 to 76). WMHs were assessed by MRI in 21 studies (n=15,026) and CT in one (n=610). Presence of extensive WMHs was defined by the Fazekas-scale in seven studies (n=816). There was, however, heterogeneity regarding the cut-off point used to define extensive WMHs as well as the location of WMHs assessment (periventricular, deep, or both). Regarding continuous WMH data, either semi-quantitative scales were used to assess WMH severity, or semi-automated and automated computer-based algorithms calculated WMH volume. Two recent studies[20,54] examined the association between LVMI and diffusion tensor imaging parameters of WM integrity.

Cerebral microbleeds

All three studies[60,63,69] (n=493) examining presence of CMBs were of cross-sectional design and based on high-risk population subsets. CMBs were identified in 151 individuals. Mean age of all the individuals was 63 years (range, 52 to 72). All studies utilized the same MRI-based definition.

Quality assessment of included studies

The overall study quality was moderate. Only one study[79] (3%) fulfilled all nine criteria of the Newcastle-Ottawa scale (Supplementary Table 4). The median quality score was 5/9 for studies examining lacunes and WMHs and 4/9 for those examining CMBs. This could be explained by the cross-sectional design employed by 25 studies (81%), thus inherently limiting their maximum score to 6/9. Furthermore, only 10 studies (32%) were based on the general population, thus fulfilling the representativeness of the exposed cohort criterion. Most studies fulfilled the criteria for exposure and outcome assessment methods (87% and 94%, respectively), despite the between-study heterogeneity. Regarding the comparability criteria for age and hypertension, 15 (49%) studies controlled for both, 10 (32%)

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Table 1. Characteristics of studies investigating the associations between left ventricular hypertrophy or left ventricular mass (index) and lacunes, white matter hyperintensities, or cerebral microbleeds

Study	Region (recruitment period)	Study type (follow-up)	Population type	No.	Mean age (yr)	Men (%)	Ht (%)	DM (%)	CVD (%)	No. of cases	Exposure examined and ascertainment	Outcome examined and ascertainment
Lacunes												
Das et al. (2008)[56]	US (1996–1998)	Cross-sectional	General population	2,040	62	47	37	9	Stroke: 0 CAD: 7.7	220	LVH: (ECG) ↑QRS voltage (R in V5+S in V1 ≥3.5 mV)+ST segment depression or flat/diphasic T waves	Lacunes*: (MRI) PD-W, T2-W, lesions ≥3 mm
Hirose et al. (2011)[64]	Japan (1998)	Cross-sectional	General population	659	66	32	40†	14	Stroke: 0 CAD: NR	190	LVH: (ECG) Sokolow-Lyon/Cornell	Lacunes: (MRI) T1-W, T2-W, lesions 3–15 mm
Ikeda et al. (1994)[65]	Japan (1991–1992)	Cross-sectional	Hypertensive patients	249	69	42	100	0	Stroke: 0 CAD: 0	51	LVH: (ECG) ↑QRS voltage (R in V5+S in V1 ≥3.5 mV)+ST segment depression (0–5 to 1.0 mV) and flat or diphasic T waves	Lacunes: (CT) lesions ≤15 mm
Johansen et al. (2018)[21]	US (2011–2013)	Cross-sectional	General population	1,665	76	40	68	29	Stroke: 10 CAD: 5‡	366	LVMI§: (TTE) measured as a continuous variable (mean=78.7 g/m^2, SD=19.5 g/m^2, body surface)	Lacunes: (MRI) MP-RAGE, axial GRE T2*, axial FLAIR, axial DTI, lesions 3–20 mm
Kawamoto et al. (1991)[67]	Japan (NR)	Cross-sectional	Hypertensive patients	54	69	44	100	0	Stroke: 0 CAD: 0	11	LVH: (ECG) ↑QRS voltage (R in V5+S in V1 ≥3.5 mV)+flat T waves (<10% R) or ST-segment depression and diphasic T waves	Lacunes: (MRI) T1-W, T2-W, lesions ≤10 mm
Kohara et al. (1999)[68]	Japan (1992–1998)	Cross-sectional	Hypertensive patients	150	58	48	100	NR	Stroke: 0 CAD: 0	101	LVH: (TTE) LVMI ≥108 g/m^2 for women and ≥118 g/m^2 for men (body surface)	Lacunes: (MRI) T1-W, T2-W, lesions 3–15 mm
Mounier-Vehier et al. (1993)[73]	France (1989–1992)	Cross-sectional	Stroke patients	595	66	50	56	19	Stroke: 100 CAD: 6.6‖	116	LVH: (ECG and TTE), no criteria reported	Lacunes*: (CT) lesions ≤15 mm
Nakanishi et al. (2017)[22]	US (2005–2010)	Cross-sectional	General population	665	71	41	78	28	Stroke: 0 CAD: 6.5	94	LVH: (TTE) LVMI ≥95 g/m^2 for women and ≥115 g/m^2 for men (body surface)	Lacunes*: (MRI) FLAIR, lesions ≥3 mm
Selvetella et al. (2003)[76]	Italy (2000–2002)	Cross-sectional	Hypertensive patients	195	61	44	100	21	Stroke: 0 CAD: 0	62	LVH: (TTE) LVMI ≥ 50 g/m$^{2.7}$ (height corrected)	Lacunes: (MRI) T1-W, T2-W, lesions ≤10 mm
Davis et al. (1998)[57]	US (1985–1988)	Cohort (4.5 yr)	Hypertensive patients	4,736	72	43	100	10	Stroke: 1.4 CAD: 5.4	66	LVH: (ECG) Minnesota codes (3.1 plus 4.1–4.3 or 5.1–5.3) or (3.3 plus 4.1–4.3 or 5.1–5.3)	Lacunar strokes: (MRI or CT) clinical lacunar syndrome+lesion ≤20 mm or autopsy proven
Tanizaki et al. (2000)[79]	Japan (1961)	Cohort (max 32 yr)	General population	1,621	57	44	2†	8	Stroke: 0 CAD: 3.1‖	167	LVH: (ECG) Minnesota code 3-1	Lacunar strokes: (MRI or CT) focal neurological deficit+lesion ≤15 mm
van der Veen et al. (2015)[80]	Holland (2001–2005)	Cohort (3.9 yr)	CVD patients	663	57	81	61†	13	Stroke: 23 CAD: 62	60	LVH: (ECG) Sokolow-Lyon/Cornell	Lacunes: (MRI) T1-W, T2-W, FLAIR, lesions 3–15 mm
Pirinen et al. (2017)[74]	Finland (1994–2007)	Case-control	NA	237¶	43**	64	85††	5	Stroke: 100 CAD: 2.4	84	LVH: (ECG) Sokolow-Lyon/Cornell	Lacunar strokes: (MRI or CT) lesion ≤15 mm (verified stroke cases from the Helsinki Young Stroke Registry)

Table 1. Continued

Study	Region (recruitment period)	Study type (follow-up)	Population type	No.	Mean age (yr)	Men (%)	Ht (%)	DM (%)	CVD (%)	No. of cases	Exposure examined and ascertainment	Outcome examined and ascertainment
White matter hyperintensities												
Butenaerts et al. (2016)[53]	Poland (2014)	Cross-sectional	Stroke patients	155	62**	49	71	26	Stroke: 100 CAD: 25.2	61	LVH: (TTE) LVMI ≥95 g/m^2 for women and ≥115 g/m^2 for men (body surface)	Occurrence of severe WMH: (MRI) FLAIR, Fazekas total score ≥3 (dWMHs+pWMHs; scale range 0–6)
Fox et al. (2005)[59]	US (1993–1994)	Cross-sectional	General population	667	62	37	68	21	Stroke: 2.7 CAD: 4.2†	92	LVH: (TTE) LVMI ≥121 g/m for women and ≥163 g/m for men (height corrected)	Occurrence of severe WMH: (MRI) PD-W, T2-W, grade ≥4 on self-designed scale (scale range, 1–10)
Hénon et al. (1996)[62]	France (1991–1993)	Cross-sectional	Stroke patients	610	64	57	49	14	Stroke: 100 CAD: 16.4	88	LVH: (ECG), no criteria reported	WMH severity§§: (CT) Inzitari's criteria (definition), Blennow's scale (extension range, 0–3; severity range, 0–3). Total score=(extension+severity)/2
Henskens et al. (2009)[63]	Netherlands (2004–2006)	Cross-sectional	Hypertensive patients	192	52	51	100	0	Stroke: 0 CAD: 0	39	LVH: (TTE) LVMI ≥95 g/m^2 for women and ≥115 g/m^2 for men (body surface)	Occurrence of severe WMH: (MRI) T2-W, FLAIR, Fazekas scale; dWMHs grade ≥2 or pWMHs grade 3 (scale range, 0–3)
Hirose et al. (2011)[64]	Japan (1998)	Cross-sectional	General population	659	66	32	40†	14	Stroke: 0 CAD: NR	274	LVH: (ECG) Sokolow-Lyon/Cornell	Occurrence of severe WMH: (MRI) T1-W, T2-W, large caps (≥5×10 mm)
Jeerakathil et al. (2004)[66]	US (1991–1995)	Cross-sectional	General population	1,814	53	47	18	5	Stroke: 0 CAD: 5.8	240	LVH: (ECG) ↑QRS voltage (R in V5+S in V1 ≥3.5 mV)+ST segment depression or flat/diphasic T waves	Occurrence of severe WMH: (MRI) T2-W, >1 age-specific SD of WMHV
Johansen et al. (2018)[21]	US (2011–2013)	Cross-sectional	General population	1,665	76	40	68	29	Stroke: 10 CAD: 5†	NA††	LVMI: (TTE) continuous variable (mean=78.7 g/m^2, SD=19.5 g/m^2, body surface)	WMH volume: (MRI) axial FLAIR, quantification by semi-automated algorithm
Kohara et al. (1999)[68]	Japan (1992–1998)	Cross-sectional	Hypertensive patients	150	58	48	100	NR	Stroke: 0 CAD: 0	25, NA††	LVH: (TTE) LVMI ≥108 g/m^2 for women and ≥118 g/m^2 for men, also used as continuous variable (mean=122.8 g/m^2, SD=24.8 m^2, body surface)	Occurrence of severe WMH: (MRI) T2-W, Fazekas scale for pWMHs ≥2 (scale range, 0–3) WMH severity: (MRI) T2-W, Fazekas scale for pWMHs (scale range, 0–3)
Lee et al. (2004)[69]	South Korea (1998–2000)	Cross-sectional	Hypertensive patients with stroke	102	64	59	100	17	Stroke: 100 CAD: 0	NA††	LVMI: (TTE) continuous variable (mean=156.7 g/m^2, SD=50.6 g/m^2, body surface)	WMH severity: (MRI) T2-W, Fazekas scale for pWMHs (scale range, 0–3)
Lee et al. (2018)[70]	South Korea (2008–2016)	Cross-sectional	VHD patients	217	66	44	46	20	Stroke: 11.6 CAD: 0	NA††	LVMI: (TTE) continuous variable (mean=109.9 g/m^2, SD=32.5 g/m^2, body surface)	WMH volume: (MRI) FLAIR, manually identified hyperintense lesions semi-automatically drawn
Longstreth et al. (1996)[71]	US (1989–1990)	Cross-sectional	General population	3,301	75	42	45	10	Stroke: 0 CAD: 23	NA††	LVM: (TTE) continuous variable (mean, SD not reported)	WMH severity: (MRI) PD-W, self-designed scale (scale range, 1–8)
Martinez-Vea et al. (2006)[72]	Spain (NR)	Cross-sectional	CKD patients	52	49	73	100	0	Stroke: 0 CAD: 9.7	17	LVH: (TTE) LVMI ≥47 g/m$^{2.7}$ for women and ≥49 g/m$^{2.7}$ for men (height corrected)	Occurrence of severe WMH: (MRI) T1-W, T2-W, FLAIR, Fazekas scale; dWMHs grade ≥2 or pWMHs grade ≥2 (scale range, 0–3)

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Table 1. Continued

Study	Region (recruitment period)	Study type (follow-up)	Population type	No.	Mean age (yr)	Men (%)	Ht (%)	DM (%)	CVD (%)	No. of cases	Exposure examined and ascertainment	Outcome examined and ascertainment
Moore et al. (2018)[20]	US (2012–2014)	Cross-sectional	General population‖	313	73	58	53†	17	Stroke: 0 CAD: 4	NA††	LVMI: (CMR) continuous variable (mean=51 g/m^2, SD=10 g/m^2, body surface)	Alterations in white matter microstructure: (MRI) DTI, parameters measured; fractional anisotropy, mean, radial, and axial diffusivity
Nakanishi et al. (2017)[22]	US (2005–2010)	Cross-sectional	General population	665	71	41	78	28	Stroke: 0 CAD: 6.5	166	LVH: (TTE) LVMI ≥95 g/m^2 for women and ≥115 g/m^2 for men (body surface)	Occurrence of severe WMH: (MRI) FLAIR, upper quartile of WMHV
Ryu et al. (2014)[75]	South Korea (2011–2012)	Cross-sectional	Stroke patients	2,669	67	60	66	32	Stroke: 100 CAD: 11.7	NA††	LVH: (ECG or TTE), no criteria reported	WMH volume§§: (MRI) FLAIR, lesions were segmented and registered semi-automatically
Shimada et al. (1990)[77]	Japan (NR)	Cross-sectional	Hypertensive patients	34	69	33	100	0	Stroke: 0 CAD: 0	11	LVH: (ECG) ↑QRS voltage (R in V5+S in V1 ≥3.5 mV)+flat T waves (<10% R) or ST-segment depression and diphasic T waves	Occurrence of severe WMH: (MRI) T2-W, Fazekas scale for pWMHs ≥2 (scale range, 0–3)
Sierra et al. (2002)[78]	Spain (NR)	Cross-sectional	Hypertensive patients	62	54	63	100	0	Stroke: 0 CAD: 0	26	LVH: (TTE) LVMI 110 g/m^2 for women and 130 g/m^2 for men (body surface)	Occurrence of severe WMH: (MRI) no sequence reported, van Swieten scale grade ≥1 (scale range, 0–2)
Vedala et al. (2019)[55]	US (2010-2014)	Cross-sectional	Stroke patients	167	62	46	73	37	Stroke: 100 CAD: NR	NA††	LVH: (TTE) LVMI 122 g/m^2 for women and 149 g/m^2 for men (body surface)	WMH severity§§: (MRI) FLAIR, Wahlund scale for WMHs (scale range, 0–15; only hemisphere contralateral to stroke was assessed)
Cermakova et al. (2017)[54]	US (1990)	Cohort (20 yr)	General population	627	30	48	-¶¶	-¶¶	Stroke: NR CAD: NR	269	LVMI§: (TTE) continuous variable (mean=79.9 g/m^2, SD=18.4 g/m^2, body surface)	Occurrence of severe WMH: (MRI) T1 & T2-FLAIR, WMHV >0.3 cm^3 Alterations in white matter microstructure: (MRI) DTI, parameter measured; fractional anisotropy
Ferreira et al. (2017)[58]	France (2003–2005)	Cross-sectional, cohort (7.7 yr)	Hypertensive patients	131/ 113***	68	48	100	12	Stroke: 2.3 CAD: 6.9	83	LVH: (ECG) Sokolow-Lyon/Cornell	(1) Cross-sectional: Occurrence of severe WMH: (MRI) T2-W, Fazekas total score ≥2 (dWMHs+pWMHs; scale range, 0–6) (2) Cohort: WMH severity§§: (MRI) T2-W, change in Fazekas score from baseline
Haring et al. (2017)[61]	US (1993–1995)	Cohort (17.3 yr)	General population	721	56	31	31	29	Stroke: 0 CAD: 11.9	NA††	LVM: (TTE) continuous variable (mean=150.1 g, SD=32.1 g)	WMH volume/severity: (MRI) FLAIR; (1) quantitative volumetric brain data using automated software, (2) self-designed semi-quantitative 10-point scale
van der Veen et al. (2015)[80]	Holland (2001–2005)	Cohort (3.9 yr)	CVD patients	663	57	81	61†	13	Stroke: 23 CAD: 62	NA††	LVH: (ECG) Sokolow-Lyon/Cornell	WMH volume§§: (MRI) T1-W, T2-W, FLAIR, automatically measured and visually checked
Cerebral microbleeds												
Görner et al. (2007)[60]	Belgium (2003–2004)	Cross-sectional	Stroke patients	199	72	59	48	18	Stroke: 100 CAD: NR	56	LVH: (ECG) Sokolow-Lyon/ Cornell	Microbleeds: (MRI) GRE T2*, ≤5 mm

Table 1. Continued

Study	Region (recruitment period)	Study type (follow-up)	Population type	No.	Mean age (yr)	Men (%)	Ht (%)	DM (%)	CVD (%)	No. of cases	Exposure examined and ascertainment	Outcome examined and ascertainment
Henskens et al. (2009)[63]	Netherlands (2004–2006)	Cross-sectional	Hypertensive patients	192	52	51	100	0	Stroke: 0 CAD: 0	29	LVH: (TTE) LVMI ≥95 g/m^2 for women and ≥115 g/m^2 for men (body surface)	Microbleeds: (MRI) GRE T2*, ≤5 mm
Lee et al. (2004)[69]	South Korea (1998–2000)	Cross-sectional	Hypertensive patients with stroke	102	64	59	100	17	Stroke: 100 CAD: 0	66	LVH: (TTE) LVMI ≥110 g/m^2 for women and ≥135 g/m^2 for men (body surface)	Microbleeds: (MRI) GRE T2*, ≤5 mm

Ht, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease; CAD, coronary artery disease; LVH, left ventricular hypertrophy; ECG, electrocardiogram; MRI, magnetic resonance imaging; PD-W, proton density weighted; NR, not reported; CT, computed tomography; LVMI, left ventricular mass index; TTE, transthoracic echocardiogram; SD, standard deviation; MP-RAGE, magnetization prepared-rapid gradient echo; GRE, gradient echo; FLAIR, fluid attenuated inversion recovery; DTI, diffusion tensor imaging; NA, not applicable; WMH, white matter hyperintensity; dWMH, deep white matter hyperintensity; pWMH, periventricular white matter hyperintensity; WMHV, white matter hyperintensity volume; VHD, valvular heart disease; LVM, left ventricular mass; CKD, chronic kidney disease; CMR, cardiac magnetic resonance.
*Due to definition inadequacy, a proportion of lesions categorized as "lacunes" were in fact silent cortical infarcts, but there were no available data selectively for lacunes. The % of cortical infarcts was <20% in each of these studies; †Percentage of individuals under antihypertensive medication(s); ‡Myocardial infarction specifically; §Effect size provided by these studies (odds ratio for LVMI increments) was appropriately converted to an overall odds ratio using cut off values of 95 g/m^2 for women and 115 g/m^2 for men; ‖ST-depression (Minnesota code 4-1,2,3 except for 3-1); ¶Small vessel disease cases (n=84)+their controls (n=153); **Median; ††Refers only to cases; ‡‡White matter hyperintensities examined as a quantitative or scaled outcome; §§Continuous effect sizes provided by these studies were appropriately converted to odds ratios in the meta-analysis; ‖‖A 48% of the individuals were categorized as having either early mild cognitive impairment (n=27) or mild cognitive impairment (n=122); ¶¶Only data for the follow-up visit are reported (2010) (systolic blood pressure, 117 mm Hg [SD=17 mm Hg]; diastolic blood pressure, 73 mm Hg [SD=11 mm Hg]; fasting plasma glucose, 96 mg/dL [SD=29 mg/dL]); ***Study number is 131 for cross-sectional and 113 for cohort analyses.

controlled for age but not hypertension, while only six studies (19%) presented unadjusted results. Lastly, concerning the cohort-specific criteria, three of the six cohort studies assessed CSVD markers at study onset, all six had follow-ups longer than 3 years, and attrition rates were <20% for three studies.

Meta-analysis: associations between LVH and CSVD

In studies of the general population we found presence of LVH to be associated with the odds of lacunes (OR, 1.49; 95% CI, 1.12 to 2.00; five studies; 6,650 individuals; 1,037 cases) and extensive WMHs (OR, 1.73; 95% CI, 1.38 to 2.17; five studies; 4,432 individuals) (Figure 2). Similar results were also obtained from studies in high-risk populations (lacunes: OR, 2.39; 95% CI, 1.32 to 4.32; eight studies; 6,879 individuals; 551 cases) (extensive WMHs: OR, 2.01; 95% CI, 1.45 to 2.80; 11 studies; 4,885 individuals) (Figure 2). A meta-analysis of the three high-risk population studies with data on CMBs also showed a significant association between LVH and presence of CMBs (OR, 2.54; 95% CI, 1.04 to 6.22; three studies; 493 individuals; 151 cases) (Supplementary Figure 1). When using various alternative meta-analytical approaches the associations for lacunes and extensive WMHs remained statistically significant, indicating the robustness of our findings (Supplementary Table 5).

Of note, the results for lacunes and extensive WMHs in the general population were also stable across studies adjusting their analyses for hypertension and other vascular risk factors on top of age and sex (lacunes: adjusted OR, 1.50; 95% CI, 1.09 to 2.06) (extensive WMHs: adjusted OR, 1.74; 95% CI, 1.34 to 2.25) (Figure 3).

When exploring LV geometry patterns and LVH subtypes, we documented different magnitudes of associations with lacunes and extensive WMHs (Figure 4). Specifically, in both studies of the general and high-risk-populations, we found gradually increasing associations estimates for concentric remodeling, eccentric hypertrophy, and concentric hypertrophy with the odds of lacunes and extensive WMHs.

Table 2 summarizes the results derived from eight studies (five in the general, three in high-risk populations) exploring associations between LVM or LVMI and heterogeneous methods for a continuous or ordinal assessment of WMHs severity or volume, which could not be included in the meta-analysis. In accordance with our main results, five of the eight studies showed statistically significant associations between higher LVM or LVMI and higher WMH severity or volume, while the association estimates were directionally consistent across all studies.

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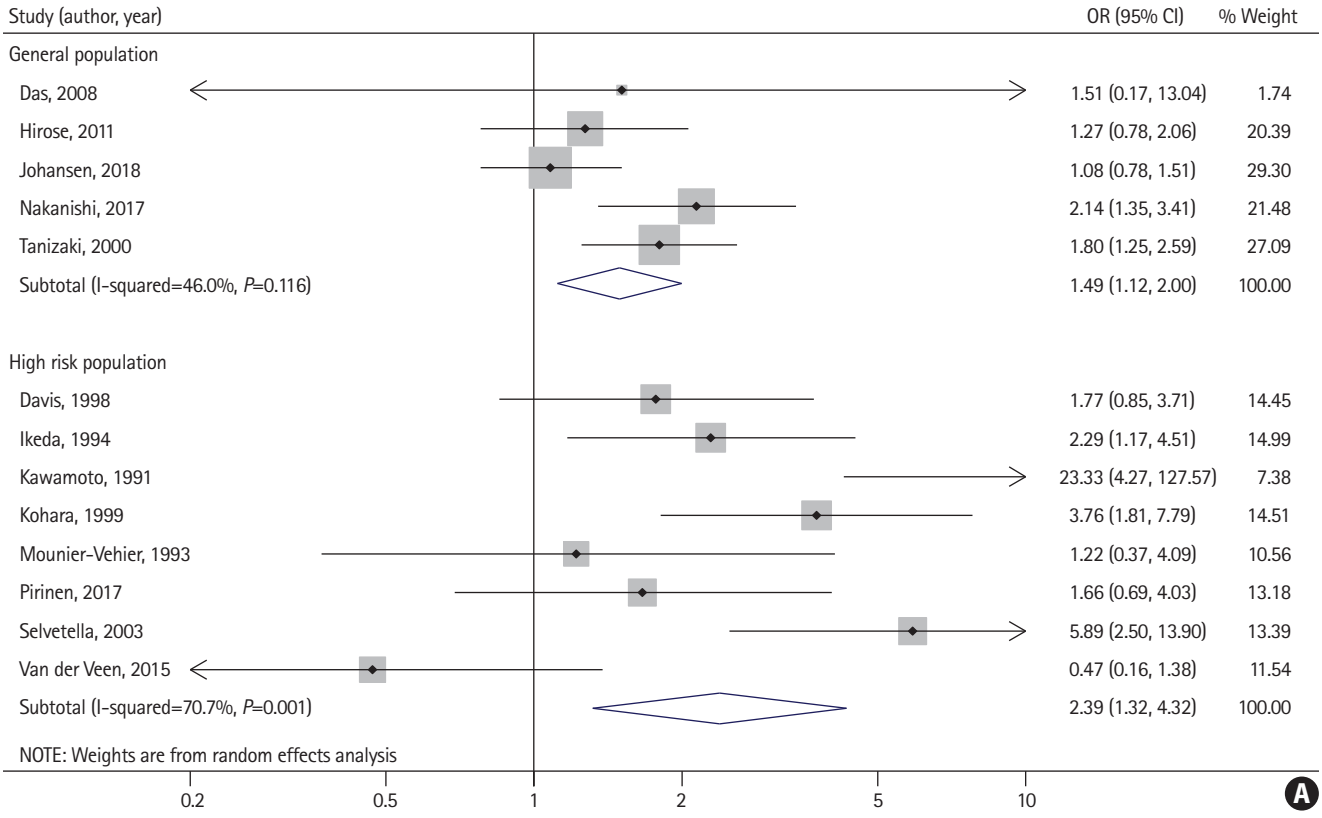

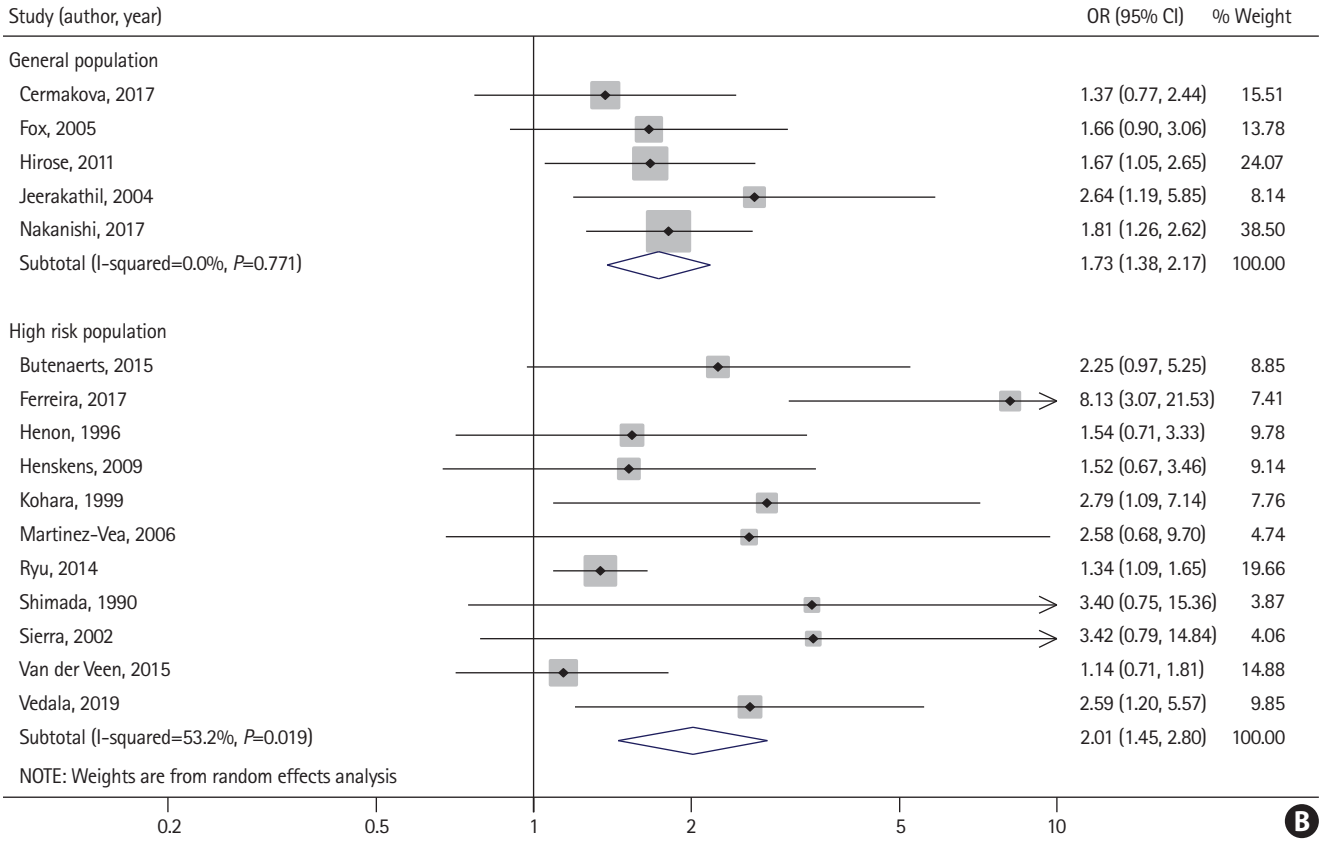

Figure 2. Associations of left ventricular hypertrophy with (A) lacunes, and (B) extensive white matter hyperintensities in general and high-risk population studies. Odds ratios (ORs) of each study are depicted as data markers; shaded boxes around the data markers indicate the statistical weight of the respective study; 95% confidence intervals (CIs) are indicated by the error bars; pooled-effect estimates for general and high-risk populations along with their 95% CI are reflected as a diamond.

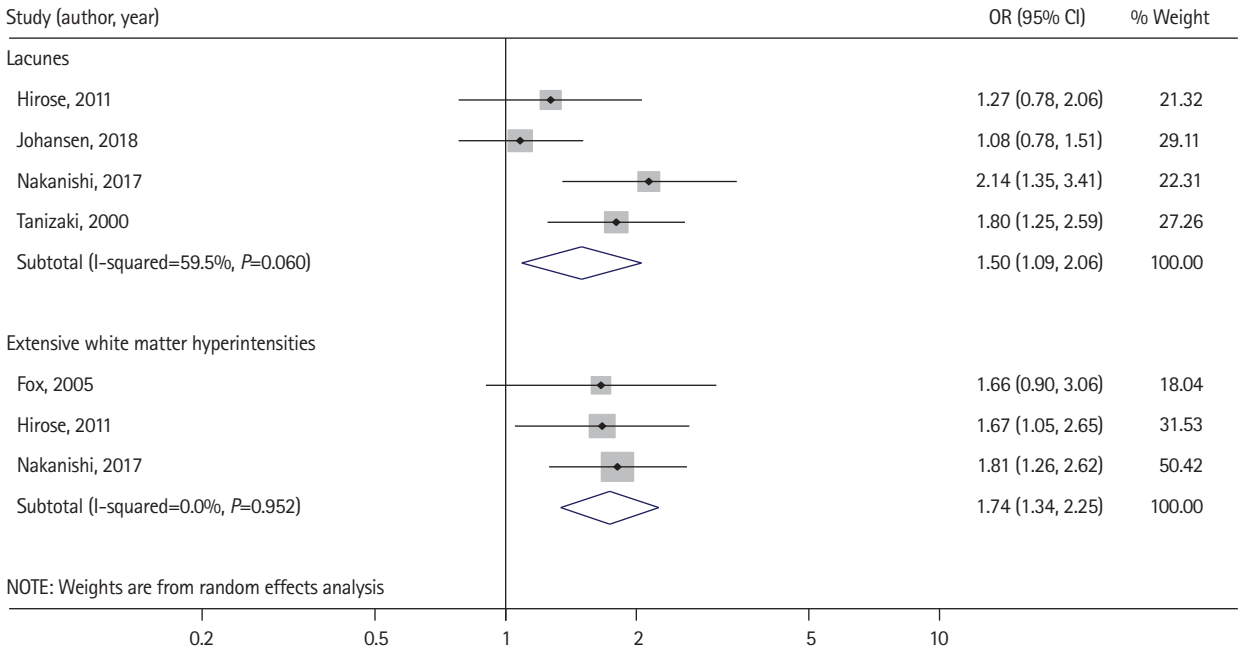

Figure 3. Associations of left ventricular hypertrophy with lacunes and extensive white matter hyperintensities in general population studies adjusting for age, sex, hypertension, and other vascular risk factors. Odds ratios (ORs) of each study are depicted as data markers; shaded boxes around the data markers indicate the statistical weight of the respective study; 95% confidence intervals (CIs) are indicated by the error bars; pooled-effect estimates for general populations along with their 95% CI are reflected as a diamond.

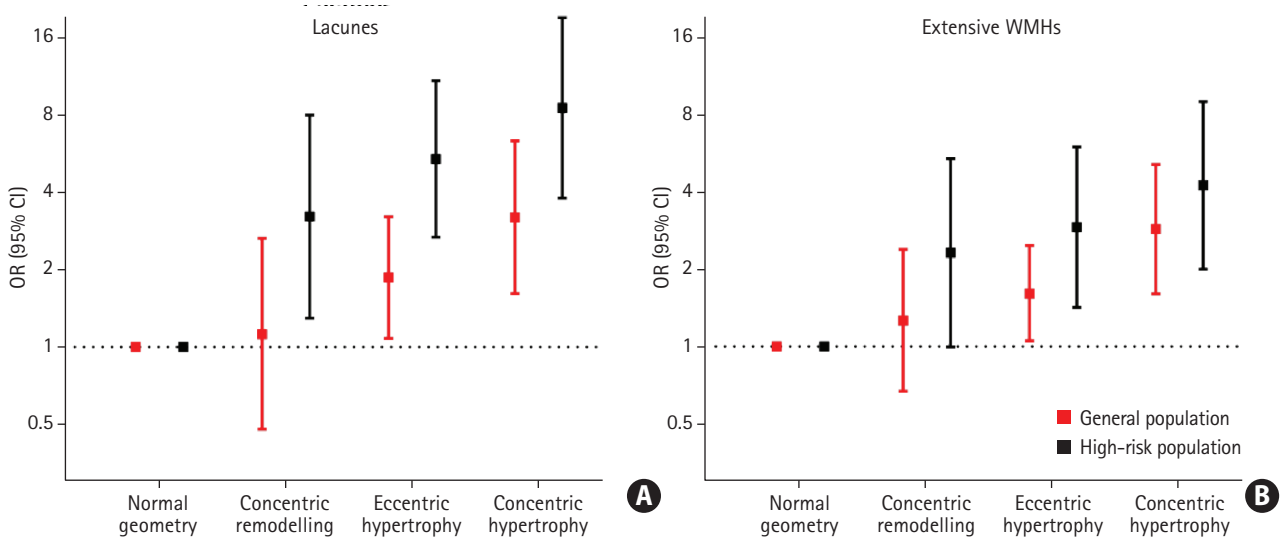

Figure 4. Associations of left ventricular morphology patterns (normal geometry, concentric remodeling, eccentric and concentric hypertrophy) with (A) lacunes and (B) extensive white matter hyperintensities (WMHs) in general (red lines) and high-risk (black lines) population studies. Odds ratios (ORs) are depicted as data markers and 95% confidence intervals (CIs) are indicated by the error bars. All comparisons use "normal geometry" as the reference group (total number: lacunes general population, 665; lacunes high-risk population, 345; extensive WMHs general population, 665; extensive WMHs high-risk population, 419).

Heterogeneity, subgroup and sensitivity analyses

In studies of the general population, meta-analyses of WMHs studies showed no heterogeneity (I^2=0%, *P*=0.77), while those of lacunes only moderate heterogeneity (I^2=46%, *P*=0.12) (Figure 2). In subgroup analyses the results were stable for both cross-sectional and cohort studies, as well as for studies assessing LVH by either ECG or TTE (Table 3). Additionally, when restricting our analyses to studies defining LVH with the currently considered most optimal approaches (ECG: only ↑ QRS voltage-based criteria; TTE: LVMI ≥95 g/m^2 for women and

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Table 2. Review of the results of studies examining the association between left ventricular mass or left ventricular mass index and white matter hyperintensity severity or volume that were not included in the meta-analysis

Study	Population (total no.)	Association examined	Adjustments	Results
Cermakova et al. (2017)[54]	General population (n=627)	LVMI (per 1 SD, g/m^2) with the DTI metric of white matter fractional anisotropy*	Age, sex, hypertension, diabetes, smoking, alcohol, BMI, TC, education, race, study site, sedentary time, intracranial volume, ApoE-ε4 genotype	Exposure standardized beta coefficient β=−0.001 (−0.003 to 0.0003), *P*=0.11
Haring et al. (2017)[61]	General population (n=721)	LVM (per 25 g) with (1) WMH volume (%), normalized to total intracranial volume; (2) graded using a 10-point scale	Age, sex, hypertension, diabetes, smoking, alcohol, BMI, aFib, study site, education, income, anxiety, ApoE-ε4 genotype, follow-up duration	(1) Unstandardized beta coefficient β=0.019 (−0.017 to 0.054), *P*=0.30, (2) Unstandardized beta coefficient β=0.077 (−0.001 to 0.155), *P*=0.05
Johansen et al. (2018)[21]	General population (n=1,665)	LVMI (per 10 g/m^2) with WMH volume (cm^3), modelled by generalized linear models with γ families and identity links	Age, sex, hypertension, diabetes, smoking, alcohol, BMI, LDL-C, MI, education, total intracranial volume	Unstandardized beta coefficient β=0.64 (0.19 to 1.08)†, *P*<0.01
Kohara et al. (1999)[68]	Hypertensive patients (n=150)	LVMI (g/m^2) with WMH grade (scale 1–4)	Age, hypertension, BMI, relative wall thickness	Partial correlation coefficient r=0.33 (0.195 to 0.465)†, *P*<0.01
Lee et al. (2018)[70]	Valvular heart disease patients (n=217)	LVMI (g/m^2) with WMH volume (mL)	Unadjusted	Correlation coefficient r=0.072 (−0.061 to 0.205), *P*=0.29
Lee et al. (2004)[69]	Hypertensive patients with stroke (n=102)	LVMI grade (scale 0–3) with WMH grade (scale 0–3)	Age, sex, hypertension, duration of hypertension, diabetes, glucose, smoking, BMI, total cholesterol, haematocrit, creatinine, antiplatelet use, prior stroke	Ordinal logistic regression OR, 1.51 (1.07 to 2.12)†, *P*<0.05
Longstreth et al. (1996)[71]	General population (n=3,301)	LVM (g) with WMH grade (scale 1–8)	Age, sex	Partial correlation coefficient r=0.067 (0.021 to 0.113)†, *P*<0.01
Moore et al. (2018)[20]	General population (n=313)	LVMI (per 1 SD, g/m^2) with DTI metrics (per 1 SD) of white matter microstructure (fractional anisotropy*, mean, radial, axial diffusivity)	Age, sex, hypertension, anti-hypertensive drug usage, diabetes, smoking, CVD, aFib, education, race/ethnicity, cognitive status, ApoE-ε4 genotype	Standardized beta coefficients provided, all *P*-values corrected for multiple comparisons <0.05†

LVMI, left ventricular mass index; SD, standard deviation; DTI, diffusion tensor imaging; BMI, body mass index; TC, total cholesterol; LVM, left ventricular hypertrophy; WMH, white matter hyperintensities; aFib, atrial fibrillation; ApoE, apolipoprotein E; LDL-C, low density lipoprotein cholesterol; MI, myocardial infarction; CVD, cardiovascular disease.
*Lower values of fractional anisotropy indicate loss of white matter integrity; †Results indicate statistical significance.

≥115 g/m^2 for men, body surface indexed) the results remained stable (Table 3). Yet, we found moderate heterogeneity in studies of high-risk populations for both lacunes and WMHs (I^2=71%, *P*=0.001 and I^2=53%, *P*=0.02, respectively) (Figure 2). Although none of the sub-analyses entirely resolved the heterogeneity, the results were stable across the examined subgroups (Table 3). Overall, sensitivity analyses restricted to studies fulfilling each one of the Newcastle-Ottawa criteria showed consistent associations of LVH with both lacunes and WMHs (Supplementary Table 6). In "leave-one-out" sensitivity meta-analyses, we found no evidence that any single study significantly influenced the results of the main analyses (Supplementary Figure 2).

Assessment of publication bias

Funnel plots for the main analyses are presented in the supplement (Supplementary Figure 3). We did not perform the Egger's test for meta-analyses of studies of the general population, or for high risk populations for the outcome lacunes due to <10 pooled studies. The Egger's test showed statistically significant small-study effects for the 11 high risk WMHs studies (*P*=0.01). After adjusting this analysis for publication bias with the "trim and fill" method[49] the association remained statistically significant (OR, 1.45; 95% CI, 1.03 to 2.04) (Supplementary Figure 4).

Discussion

Polling data from 31 studies and >20,000 individuals, we found LVH to be associated with neuroimaging markers of CSVD in both the general population and specific high-risk populations. Specifically, LVH, defined by TTE or ECG, and increased LVM, assessed by TTE, were associated with lacunes, WMHs, and

Table 3. Sensitivity and subgroup analyses for the associations between left ventricular hypertrophy and lacunes or extensive white matter hyperintensities in general and high-risk population studies stratified by study type, exposure and outcome assessment methods, and specific population subsets

Sensitivity and subgroup analyses LVH vs. no LVH	Lacunes					WMHs				
	k*	Total no.	OR (95% CI)	Heterogeneity, I^2, *P*	*P* for subgroup difference	k*	Total no.	OR (95% CI)	Heterogeneity, I^2, *P*	*P* for subgroup difference
General population										
Overall analysis	5	6,650	1.49 (1.12–2.00)†	46%, 0.12		5	4,432	1.73 (1.38–2.17)†	0%, 0.77	
Study type					0.12					0.77
Cross-sectional	4	5,029	1.40 (0.97–2.01)	47%, 0.13		4	3,805	1.81 (1.41–2.32)†	0%, 0.79	
Cohort	1	1,621	1.80 (1.25–2.59)†	NA		1	627	1.37 (0.77–2.44)	-	
Exposure assessment					0.12‡					0.77‡
ECG	3	4,320	1.59 (1.19–2.12)†	0%, 0.53		2	2,473	1.87 (1.26–2.80)†	0%, 0.33	
Only ↑QRS voltage-based criteria	2	2,280	1.57 (1.13–2.19)†	21%, 0.26	0.06§	1	659	1.67 (1.05–2.65)†	-	0.73§
TTE	2	2,330	1.49 (0.76–2.91)	82%, 0.02		3	1,959	1.67 (1.27–2.20)†	0%, 0.73	
LVMI ≥95 g/m^2 (F), ≥115 g/m^2 (M)	2	2,330	1.49 (0.76–2.91)	82%, 0.02		2	1,292	1.67 (1.23–2.28)†	0%, 0.42	
Outcome assessment					-					-
CT	0	-	-	-		0	-	-	-	
MRI	4	5,029	1.40 (0.97–2.01)	47%, 0.13		5	4,432	1.73 (1.38–2.17)†	0%, 0.77	
High-risk populations										
Overall analysis	8	6,879	2.39 (1.32–4.32)†	71%, 0.00		11	4,867	2.01 (1.45–2.80)†	53%, 0.02	
Study type					0.00					0.02
Cross-sectional	6	1,480	3.20 (1.75–5.87)†	61%, 0.02		10	4,222	1.74 (1.36–2.22)†	12%, 0.34	
Cohort	2	5,399	0.97 (0.27–3.53)	75%, 0.05		2	776	2.90 (0.42–19.84)	92%, 0.00	
Exposure assessment					0.00‡					0.06‡
ECG	6	6,534	1.73 (0.85–3.55)	71%, 0.00		4	1,420	2.41 (0.98–5.90)	78%, 0.00	
Only ↑QRS voltage-based criteria	2	900	0.92 (0.27–3.16)	68%, 0.08	-	2	776	2.90 (0.42–19.84)	92%, 0.00	0.00§
TTE	3	940	3.33 (1.53–7.24)†	54%, 0.11		6	778	2.31 (1.57–3.39)†	0%, 0.91	
LVMI ≥95 g/m^2 (F), ≥115 g/m^2 (M)	0	-	-	-		2	347	1.84 (1.02–3.31)†	0%, 0.51	
Outcome assessment					0.00					0.02
CT	2	844	1.97 (1.09–3.55)†	0%, 0.37		1	610	1.54 (0.71–3.33)	NA	
MRI	4	1,062	3.62 (1.00–13.14)†	85%, 0.00		10	4,257	2.11 (1.47–3.04)†	58%, 0.01	
Specific high-risk population subsets					0.02					0.02
Hypertensive patients	5	5,384	3.67 (1.97–6.86)†	63%, 0.03		5	551	3.18 (1.70–5.97)†	41%, 0.15	
Stroke patients	1	595	1.22 (0.37–4.09)	NA		4	3,601	1.57 (1.17–2.11)†	21%, 0.28	

LVH, left ventricular hypertrophy; WMH, white matter hyperintensity; OR, odds ratio; CI, confidence interval; ECG, electrocardiogram; TTE, transthoracic echocardiogram; LVMI, left ventricular mass index; F, female; M, male; CT, computed tomography; MRI, magnetic resonance imaging; NA, not applicable.

*Numbers of studies in each category do not always add up to the total for a number of different reasons, e.g., article presents additional analyses, article does not fit in any group, etc.; †Results indicate statistical significance; ‡Subgroup comparison: "ECG" with "TTE"; §Subgroup comparison: "Only ↑ QRS voltage-based criteria" (i.e., Sokolow-Lyon/ Cornell/ Minessota code 3–1) with "LVMI ≥95 g/m^2 (female), ≥115 g/m^2 (male)".

CMBs. Both eccentric and concentric LVH were associated with CSVD manifestations, but the latter presented larger association estimates. The results remained stable after adjustments for age, hypertension, and other vascular risk factors, in both cross-sectional and cohort studies, as well as in sensitivity analyses controlling for study quality. Among studies of the general population, there was no evidence of heterogeneity for studies assessing WMHs and only moderate heterogeneity for

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studies assessing lacunes.

Our results demonstrate an association of LVH with lacunes, WMHs, and CMBs, independently of age, hypertension, and other vascular risk factors. This is in accordance with studies exploring other vascular beds and endpoints. Particularly, both electrocardiographic and echocardiographic LVH has been previously associated with the risk of incident adverse coronary events,[14] ischemic stroke,[16-18] and all-cause mortality[14,81] in studies of the general population. Similar to our results, these associations appear to be independent of hypertension, and taken all together, suggest that LVH is an independent risk factor for global vascular disease.

However, the underlying hemodynamic mechanisms remain largely elusive. During the course of LVH there is initially preserved systolic function and only mild diastolic dysfunction,[13] but over time both systolic and diastolic dysfunction ensue.[82] The decrease in stroke volume with its accompanying systemic hypoperfusion could predispose to cerebral ischemia and CSVD.[83,84] Additionally, the concomitant increased fibroblastic activity in the cardiac extracellular matrix can induce arrhythmias,[13] which may cause hypotensive episodes, cerebral hypoperfusion, and CSVD.[85] Yet, it remains unknown if LVH could also influence the risk of CSVD during its earlier stages, when no systolic or diastolic dysfunction has developed.

Apart from LVM itself, when further exploring different LV geometry patterns, we documented that concentric hypertrophy showed the strongest association with lacunes and WMHs. In patients with hypertension and abnormal LV geometry, concentric patterns appear to be more common than eccentric, due to pressure but not volume overload.[13] Concentric hypertrophy has been associated with the highest risk of both ischemic stroke,[86] as well as cardiovascular and all-cause mortality,[81] when compared to other abnormal LV geometry patterns. A possible explanation for this could be related to the fact that concentric hypertrophy, in comparison to eccentric, is generally associated with higher LVM, as was also observed in some of the included studies in the current review.[22,68] Furthermore, specific LV geometry patterns reflect not only differences in hemodynamic load but also genetic predisposition.[87,88] It is therefore plausible that our observations could result from a common genetic predisposition to both cerebral microvascular disease and cardiac maladaptive remodelling in response to hemodynamic load. Regardless of the potential mechanism(s), our results highlight the need for further exploration of LV geometry patterns in future CSVD studies.

Our study finding for an association between LVH and CSVD could explain previous observations regarding the effects of LVH on other endpoints.[18,19] Specifically, in a previous meta-analysis, we found LVH to be strongly associated with cognitive impairment and decline,[19] whereas more recent longitudinal studies have shown LVH to be associated with the risk of incident dementia independently of known vascular risk factors.[89,90] Furthermore, multiple studies have shown that LVH is an independent risk factor for stroke.[16-18] With CSVD being a well-established cause of vascular cognitive impairment, ischemic and hemorrhagic stroke, our findings implicate LVH as a potential mediator in these associations. Future longitudinal studies utilizing serial assessments of LVH, CSVD, cognitive, and vascular endpoints should formally explore this hypothesis.

According to current guidelines, patients with hypertension may undergo brain imaging for assessment of hypertension-mediated organ damage only if neurological symptoms or cognitive decline are present.[91] Future large studies should explore the potential benefit of performing brain imaging for all hypertensive patients diagnosed with LVH. Notably, it has been demonstrated that LVH regression via antihypertensive medications leads to risk reduction for future major cardiovascular events.[92,93] On the basis of our findings, future randomized-controlled clinical trials exploring pharmacological LVH regression should include CSVD neuroimaging assessment as a secondary outcome.

Despite the consistency of our findings when controlling for hypertension, our results could still be explained by residual confounding due to insufficient adjustments for high blood pressure duration in the individual studies. Hypertension is the primary risk factor for both LVH[13] and CSVD,[1,2,94] increasing the risk in a time-dependent manner. In our study set, the cross-sectional design of the majority of the included studies precluded serial blood pressure measurements. Although some studies variably adjusted for hypertension duration,[58,69] this also does not entirely capture its actual duration, as a highly variable subclinical period of high blood pressure often precedes the clinical diagnosis. Future studies should address this critical issue.

Our study also has limitations. First, the studies used highly heterogeneous ECG and TTE-based LVH definitions, and assessed CSVD markers, especially WMHs, with variable approaches. Yet, only moderate heterogeneity was identified in studies of the general population and the results remained stable across sub-analyses grouped by different methods of LVH or CSVD assessment. Second, the risk of bias assessment identified key methodological limitations among the included studies. These limitations were mainly related to the cross-sectional design the majority of the included studies employed and to inadequate adjustments for major confounding factors. For several of the included studies it was only possible to use unadjusted or minorly adjusted effect estimates in the meta-analysis, which are biased by confounding. Yet, sensitivity

analyses, where possible, demonstrated consistency of our results among cohort studies and studies controlling for age, hypertension and other vascular risk factors. Third, the heterogeneous statistical methods applied across studies did not allow us to include all studies in the meta-analysis. However, the individual findings from these studies consistently support our pooled results. Fourth, no study utilized a composite CSVD score, which could add information regarding the entire spectrum of CSVD manifestations. Fifth, the lack of prospective studies did not allow us to dynamically explore the association between LVH progression and neuroimaging markers of CSVD.

Conclusions

Our results support an association of echocardiographically or electrocardiographically-defined LVH and echocardiographically-assessed LVM increase with a broad range of CSVD neuroimaging markers, including lacunes, WMHs and CMBs, independently of hypertension and other vascular risk factors. As such, our findings highlight a link between subclinical heart disease and CSVD and indicate LVH as a potential novel risk factor for CSVD and its clinical sequelae.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2019.03335.

Disclosure

The authors have no financial conflicts of interest.

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Supplementary methods

Search algorithm

Our literature search was performed for titles, abstracts and keywords on three databases (Medline, Scopus, Cochrane) using the following combination of search terms (algorithm):

(((cerebral OR brain) AND (microangiopathy OR micro-angiopathy OR microvessel OR "small vessel" OR small-vessel OR microvascular OR microbleed* OR microhemorrhage* OR dot-like hemosiderin OR leukoaraiosis OR "Virchow-Robin" OR (perivascular AND space*) OR ((lacunar OR lacunae OR lacunes) AND (infarct* OR stroke*)))) OR ("white matter" AND (disease OR diseases OR hyperintensit* OR lesion OR lesions)))

AND

(((cardiac OR cardio OR heart OR ventricular OR ventricle OR myocardium OR myocardial) AND (mass OR hypertrophy OR hypertrophic OR thickened OR thickening OR enlargement OR enlarged)) OR LVMI OR LVM)

The search was originally performed in the Medline (through PubMed) database on 23 May 2018 and was then updated on 28 December 2019 with the additional inclusion of the Scopus and Cochrane databases. The search yielded a total of 1,959 articles (PubMed, 798; Scopus, 1,113; Cochrane, 57), which were reduced to 1,456 after removing the duplicates. Thus, 1,456 unique titles derived through our search were cumulatively screened for eligibility. Articles derived through the search were sorted by publication date.

Statistical analysis

We performed random-effect meta-analysis to pool our data. Our main approach utilized the DerSirmonian and Laird (DL) method for calculation of the between-study variance, the estimate of the combined effect for heterogeneity via the Mantel–Haenszel method and the calculation of confidence intervals (CI) with the Wald-type normal distribution.[37] This standard approach is currently the most widely used.[38] However, for our main analyses, we also sought to perform four additional approaches, in order to confirm the robustness of our findings:

(1) We used the Paule-Mandel (PM) estimator (equivalent to the Empirical Bayes [EB] estimator[39]) to calculate the between-study variance. It has been shown that the PM estimator performs better than the DL, mainly when heterogeneity increases; in those cases it approximates τ^2 better than the DL.[40] Additionally, despite it being an iterative method, it has been mathematically proven that convergence of the iteration process always occurs.[34]

(2) We used the (original) Hartung-Knapp (HK) method (also known as Hartung-Knapp-Sidik-Jonkman [HKSJ] method[41]) to calculate the overall effect CI. This method utilizes a modification factor (q) that is used to multiply the overall effect variance and then provides the CI via a *t*-distribution. It has been shown to perform better than the standard approach in many instances.[38,42] However, there are several concerns regarding the use of this method. For instance, when few (≤5) studies are pooled the method may be too conservative.[37,38] Additionally, in those cases the implications of using the modification factor for any given meta-analysis are hard to predict.[43] On the contrary, in instances where heterogeneity is very low, the method may produce a CI that is counterintuitively narrower than the standard approach.[41,43,44]

(3) In order to specifically address this last issue, a modification to the HK method has been proposed by Knapp and Hartung,[36] termed here mHK. We used the mHK approach to calculate the overall effect CI as our 3rd approach. In this method the multiplicative term of HK is constrained at $q \geq 1$. This forces the CI to be at least as wide as in the standard approach. Use of the mHK method has been supported, mainly when few studies are pooled and the involved standard errors vary.[41] However, when very few studies are pooled, the method is overly conservative and leads to significant loss in power.[43] As such, many have suggested various other modification methods in order to better refine the HK method, which will not be discussed here.[43,45]

(4) Finally, we simultaneously used the PM estimator along with the HK method. The PM iteration process attempts to find a positive τ^2 such that $q=1$.[36] It is therefore apparent that if the PM estimator of τ^2 is in fact positive, then $q=1$ and the HK modification will produce no effect on the overall effect variance.[36,37] Therefore this approach is comparable to *approach (1)* with the exception that it utilizes a *t*-distribution, instead of the normal. This is often beneficial, as it has been shown that for a small (<16) number of pooled studies the *t*-distribution performs better in terms of coverage than the normal.[46] However, this method becomes overly conservative as the number of studies decreases. If, on the other hand, τ^2 is negative in the first cycle of the PM iteration, then the process stops, τ^2 is set at 0 and q is calculated at a value <1.[36,41] In that special case, applying the HK modification will result in a quantitatively smaller overall effect variance (than that of *approach 1*), potentially producing a narrower CI (than that of *approach 1*).

Supplementary Table 1. Management of the quality scoring criteria of the cohort subscale of the Newcastle-Ottawa assessment scale for the purposes of the current study*

	Selection				Comparability		Outcome		
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Exclusion of outcome presence at start of study	Comparability for age	Comparability for hypertension	Assessment of outcome	Length of follow-up	Adequacy of follow-up
Point awarded if…	General population-based study	Drawn from the same community as the exposed cohort	1. For LVH: method and criteria used are reported 2. For LVM(I): method and equations used are reported	1. Cohort studies in which the outcome addressed is assessed at baseline and either subjects with the outcome are excluded from the study or the increment of the outcome is assessed 2. Cohort studies in which the outcome is "lacunar stroke" and subjects with stroke (self-reported, medical file or imaging ascertained) are excluded at baseline	Any age adjustment	1. In hypertensive patient-based studies: adjustment for hypertension duration 2. In all other studies: any of the adjustments; SBP, DBP, anti-hypertensive drug usage, duration of hypertension	1. For dichotomous, scaled and continuous outcomes: criteria/method of quantification used are reported 2. For the outcome "lacunar stroke": relevant clinical presentation and criteria used for lacunar stroke identification are reported	Cohort studies with ≥36 mo mean follow-up length	Cohort studies with ≥80% of participants examined at baseline not lost to follow-up at end-point
Point not awarded if…	High-risk population-based study (hypertensive, stroke patients etc.)	1. Drawn from a different source 2. No description of the derivation of the non-exposed cohort	1. Self-reported 2. Method and/or criteria used not reported	1. Cross-sectional studies 2. Cohort studies which do not fulfil the above criteria	No age adjustment	No hypertension adjustment or does not fulfil above criteria	1. Self-reported 2. Method of assessment not reported 3. Defining lacunes in the context of silent brain infarcts including not only lacunes but also some (<20%) larger cortical infarcts	1. Cross-sectional studies 2. Cohort studies with <36 mo mean follow-up length	1. Cross-sectional studies 2. Cohort studies with <80% of baseline participants following-up at end-point or follow-up % not reported

LVH, left ventricular hypertrophy; LVM(I): left ventricular mass (index); SBP, systolic blood pressure; DBP, diastolic blood pressure.
*The only case-control study included in out review (Pirinen et al.,[74] 2017) was also graded according to this scale.

Supplementary Table 2. Number of articles excluded after screening the full-text by reason

Reasons for exclusion	No. of articles
Cardiac parameters were measured (ECG, TTE) but LVH or LVM(I) were not assessed	22
Article not presenting relevant quantitative data- author contacted but did not reply	9
Stroke studies where the comparison group consisted of patients with non-lacunar stroke	6
Article not presenting relevant quantitative data- author was contacted but data was unavailable	6
Study population not eligible (miscellaneous neurologic diagnoses, dementia, primary cardiomyopathies, etc.)	5
Articles exploring silent infarcts not including predominantly lacunes (silent cortical infarcts >20%)	4
All participants in the study fulfilling diagnostic criteria for LVH	4
Outcome assessed was not relevant (i.e., brain atrophy)	2
Studies with inappropriate comparison group (i.e., comparisons between subjects with different CMBs subtypes)	1
Study protocol: study not yet published	1
Total articles excluded	60

ECG, electrocardiogram; TTE, transthoracic echocardiogram; LVH, left ventricular hypertrophy; LVM(I), left ventricular mass (index); CMB, cerebral microbleed.

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Supplementary Table 3. Results of the assessment of potential population overlap between the studies meeting eligibility criteria

Study	Study name (if reported)	Recruitment period	Geographical region of participants recruitment	Total no. relevant to our meta-analysis	Outcome examined	Overlapping status
Bezerra et al. (2012)[50]	Atherosclerotic Risk in Communities Study (ARIC)	1993–1995 Sample of 3rd ARIC visit	Forsyth County (NC) and Jackson (MS), US	1,827	Lacunes	Excluded. Overlap with Johansen et al. (2018)[21]
Butenaerts et al. (2016)[53]	NR	2014	Jagiellonian University, Krakow, Poland	155	WMHs	No
Cermakova et al. (2017)[54]	Coronary Artery Risk Development in Young Adults (CARDIA)	1990 5th follow-up visit	Birmingham (AL), Minneapolis (MN), Oakland (CA), US	627	WMHs	No
Das et al. (2008)[56]	Framingham Offspring Study (FOS)	1996–1998 6th FOS examination	>80% from New England, US	2,040	Lacunes	Eligible. Overlap with Jeerakathil et al. (2004),[66] different outcome
Davis et al. (1998)[57]	Systolic Hypertension in the Elderly Program (SHEP)	1985–1988	Mass mailing and community screening (random), US	4,736	Lacunar stroke	No
Ferreira et al. (2017)[58]	Vascular Alteration and Evolution of Cognitive Impairment Study-2 (ADELAHYDE-2)	2003–2005	Nancy, France	131	WMHs	No
Fox et al. (2005)[59]	Atherosclerotic Risk in Communities Study (ARIC)	1993–1994 Sample of 3rd ARIC visit	Jackson (MS), US	667	WMHs	Eligible. Overlap with Johansen et al. (2018)[21] data not meta-analysed together
Görner et al. (2007)[60]	NR	2003–2004	Leuven, Belgium	199	CMBs	No
Haring et al. (2017)[61]	Cerebrovascular Disease and Its Consequences in American Indians Study (CDCAI), based on the Strong Heart Study (SHS)	1993–1995 2nd SHS visit was used for TTE measurements	Arizona (AZ), Oklahoma (OK), North Dakota (ND) and South Dakota (SD), US	721	WMHs	No
Hénon et al. (1996)[62]	NR	1991–1993	Lille, France	610	WMHs	Eligible. Overlap with Mounier-Vehier et al. (1993),[73] different outcome
Henskens et al. (2009)[63]	NR	2004–2006	Maastricht, Netherlands	192	WMHs, CMBs	No
Hirose et al. (2011)[64]	Ohasama study	1998	Ohasama, Japan	659	Lacunes, WMHs	No
Ikeda et al. (1994)[65]	NR	1991–1992	Shizuoka, Japan	249	Lacunes	No
Jeerakathil et al. (2004)[66]	Framingham offspring Study (FOS)	1991–1995 5th FOS examination	>80% from New England, US	1,814	WMHs	Eligible. Overlap with Das et al. (2008),[56] different outcome
Johansen et al. (2018)[21]	Atherosclerotic Risk in Communities Study (ARIC)	2011–2013 5th ARIC visit	Washington County (MD), Forsyth County (NC), Minneapolis (MN) and Jackson (MS), US	1,665	Lacunes, WMHs	Eligible. See other ARIC studies
Kawamoto et al. (1991)[67]	NR	NR	Kochi, Japan	54	Lacunes	Eligible. Probable overlap with Shimada et al. (1990),[77] different outcome
Kohara et al. (1999)[68]	NR	1992–1998	Ehime, Japan	150	Lacunes, WMHs	Eligible. See Kohara et al. (1997)[51]
Kohara et al. (1997)[51]	NR	NR	Ehime, Japan	100	Lacunes	Excluded. Overlap with Kohara et al. (1999)[68]

Supplementary Table 3. Continued

Study	Study name (if reported)	Recruitment period	Geographical region of participants recruitment	Total no. relevant to our meta-analysis	Outcome examined	Overlapping status
Lee et al. (2004)[69]	NR	1998–2000	Seoul, South Korea	102	WMHs, CMBs	No
Lee et al. (2018)[70]	NR	2008–2016	Seoul, South Korea	217	WMHs	No
Longstreth et al. (1996)[71]	Cardiovascular Health Study (CHS)	1989–1990	Forsyth County (NC), Sacramento County (CA), Washington County (MD) and Pittsburgh (PA), US	3,301	WMHs	No
Martinez-Vea et al. (2006)[72]	NR	NR	Tarragona, Spain	55	WMHs	No
Moore et al. (2018)[20]	Vanderbilt Memory & Aging Project	2012–2014	Nashville (TN), US	313	WMHs	No
Mounier-Vehier et al. (1993)[73]	NR	1989–1992	Lille, France	595	Lacunes	Eligible. Overlap with Hénon et al. (1996),[62] different outcome
Nakanishi et al. (2017)[22]	Subset of the Cardiovascular Abnormalities and Brain Lesions (CABL) Study, based on the Northern Manhattan Study (NOMAS)	2005–2010	Manhattan (NY), US	665	Lacunes, WMHs	No
Ohira et al. (2006)[52]	Atherosclerosis Risk in Communities Study (ARIC)	1987–1989 1st ARIC visit	Washington County (MD), Forsyth County (NC), Minneapolis (MN) and Jackson (MS), US	14,488	Lacunar stroke	Excluded. Overlap with Johansen et al. (2018)[21]
Pirinen et al. (2017)[74]	NR	1994–2007	Helsinki, Finland	237	Lacunar stroke	No
Ryu et al. (2014)[75]	NR	2011–2012	Multicenter, South Korea	2,669	WMHs	No
Selvetella et al. (2003)[76]	NR	2000–2002	Pozzilli, Italy	195	Lacunes	No
Shimada et al. (1990)[77]	NR	NR	Kochi, Japan	34	WMHs	Eligible. Probable overlap with Kawamoto et al. (1991),[67] different outcome
Sierra et al. (2002)[78]	NR	NR	Barcelona, Spain	62	WMHs	No
Tanizaki et al. (2000)[79]	Hisayama Study	1961	Hisayama, Japan	1,621	Lacunar stroke	No
van der Veen et al. (2015)[80]	Second Manifestations of Arterial Disease–Magnetic Resonance Study (SMART-MR)	2001–2005	Utrecht, Netherlands	663	Lacunes, WMHs	No
Vedala et al. (2019)[55]	NR	2010–2014	Augusta (GA), US	167	WMHs	No

US, United States; NR, not reported; WMH, white matter hyperintensity; CMB, cerebral microbleed.

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Supplementary Table 4. Results of the quality assessment of eligible studies according to the cohort subscale of the Newcastle-Ottawa scale

Study	Selection	Comparability	Outcome	Total score
Tanizaki et al. (2000)[79]	★★★★	★★	★★★	9
van der Veen et al. (2015)[80]	☆★★★	★★	★★☆	7
Haring et al. (2017)[61]	★★★☆	★★	★★☆	7
Cermakova et al. (2017)[54]	★★★☆	★☆	★★★	7
Davis et al. (1998)[57]	☆★★★	☆☆	★★★	6
Fox et al. (2005)[59]	★★★☆	★★	★☆☆	6
Ferreira et al. (2017)[58]	☆★★☆	★★	★★☆	6
Johansen et al. (2018)[21]	★★★☆	★★	★☆☆	6
Hirose et al. (2011)[64]	★★★☆	★★	★☆☆	6
Moore et al. (2018)[20]	★★★☆	★★	★☆☆	6
Nakanishi et al. (2017)[22]	★★★☆	★★	★☆☆	6*
Pirinen et al. (2017)[74†]	☆★★☆	★★	★☆☆	5
Lee et al. (2004)[69]	☆★★☆	★★	★☆☆	5
Butenaerts et al. (2016)[53]	☆★★☆	★★	★☆☆	5
Martinez-Vea et al. (2006)[72]	☆★★☆	★★	★☆☆	5
Jeerakathil et al. (2004)[66]	★★★☆	★☆	★☆☆	5
Vedala et al. (2019)[55]	☆★★☆	★★	★☆☆	5
Kohara et al. (1999)[68]	☆★★☆	★☆	★☆☆	4
Das et al. (2008)[56]	★★★☆	★☆	☆☆☆	4
Henskens et al. (2009)[63]	☆★★☆	★☆	★☆☆	4
Ryu et al. (2014)[75]	☆★☆☆	★★	★☆☆	4
Selvetella et al. (2003)[76]	☆★★☆	☆☆	★☆☆	3
Kawamoto et al. (1991)[67]	☆★★☆	☆☆	★☆☆	3
Ikeda et al. (1994)[65]	☆★★☆	☆☆	★☆☆	3
Görner et al. (2007)[60]	☆★★☆	☆☆	★☆☆	3
Sierra et al. (2002)[78]	☆★★☆	☆☆	★☆☆	3
Shimada et al. (1990)[77]	☆★★☆	☆☆	★☆☆	3
Hénon et al. (1996)[62]	☆★☆☆	★☆	★☆☆	3
Longstreth et al. (1996)[71]	☆★☆☆	★☆	★☆☆	3
Lee et al. (2018)[70]	☆★★☆	☆☆	★☆☆	3
Mounier-Vehier et al. (1993)[73]	☆★☆☆	☆☆	☆☆☆	1

Selection items include: representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and exclusion of outcome presence at start of study. Comparability items include: comparability for age and for hypertension. Outcome items include: assessment of outcome, length of follow-up, and adequacy of follow-up cohorts. Articles are sorted in order of decreasing total quality score.

*Only 5 points are scored regarding the outcome "lacunes" due to inadequate assessment of outcome; †Case-control study. No point is awarded for the representativeness of the exposed cohort criterion.

Supplementary Table 5. Alternative random-effect meta-analytical approaches for obtaining pooled OR and 95% CI for the main analyses exploring the associations between left ventricular hypertrophy and lacunes, extensive WMHs and CMBs in general and high risk population studies

Random-effect approach	Lacunes			WMHs			CMBs		
	OR (95% CI)	τ^2	I^2, *P*	OR (95% CI)	τ^2	I^2, *P*	OR (95% CI)	τ^2	I^2, *P*
General population									
Main approach	1.49 (1.12–2.00)*	0.0471	46%, 0.116	1.73 (1.38–2.17)*	0	0%, 0.771	-	-	-
Alternative approach 1	1.49 (1.14–1.94)*	0.0323	46%, 0.116	1.73 (1.38–2.17)*	0	0%, 0.771	-	-	-
Alternative approach 2	1.49 (1.03–2.18)*	0.0471	46%, 0.116	1.73 (1.40–2.15)*	0	0%, 0.771	-	-	-
Alternative approach 3	1.49 (0.99–2.26)	0.0471	46%, 0.116	1.73 (1.26–2.39)*	0	0%, 0.771	-	-	-
Alternative approach 4	1.49 (1.02–2.17)*	0.0323	46%, 0.116	1.73 (1.40–2.15)*	0	0%, 0.771	-	-	-
High risk population									
Main approach	2.39 (1.32–4.32)*	0.4957	70.7%, 0.001	2.01 (1.45–2.80)*	0.1315	53.2%, 0.019	2.54 (1.04–6.22)*	0.4214	67.7%, 0.045
Alternative approach 1	2.42 (1.16–5.05)*	0.8710	70.7%, 0.001	2.01 (1.45–2.79)*	0.1309	53.2%, 0.019	2.53 (1.02–6.30)*	0.4442	
Alternative approach 2	2.39 (1.02–5.59)*	0.4957	70.7%, 0.001	2.01 (1.39–2.92)*	0.1315	53.2%, 0.019	2.54 (0.34–18.78)	0.4214	67.7%, 0.045
Alternative approach 3	2.39 (1.02–5.59)*	0.4957	70.7%, 0.001	2.01 (1.39–2.92)*	0.1315	53.2%, 0.019	2.54 (0.34–18.78)	0.4214	67.7%, 0.045
Alternative approach 4	2.42 (1.00–5.87)*	0.8710	70.7%, 0.001	2.01 (1.39–2.92)*	0.1309	53.2%, 0.019	2.53 (0.34–18.76)	0.4442	67.7%, 0.045

Number of studies pooled: lacunes, general population, 5; lacunes, high risk population, 8; WMHs, general population, 5; WMHs, high risk population, 11; CMBs, high risk population, 3. τ^2, measuring the extent of variation among the effects observed in different studies (between-study variance), is also provided. I^2 is calculated via the Cochran's Q test and the *P*-value is obtained by comparing the statistic with a chi-square distribution with *k*-1 degrees of freedom (*k*, number of studies).

Main approach: DerSirmonian and Laird (DL) method for calculation of the between-study variance, estimate of the combined effect for heterogeneity with the Mantel-Haenszel method, CI calculated with Wald-type normal distribution.

Alternative approach 1: use of the Paule-Mandel (PM) estimator (identical to the empirical Bayes [EB] method) for calculation of the between-study variance.

Alternative approach 2: use of the (original) Hartung-Knapp (also known as the Hartung-Knapp-Sidik-Jonkman) method (HK or HKSJ) for calculation of the CI. An overall effect modification factor, q, is used to multiply the overall effect variance and the final CI is given by a t-distribution.

Alternative approach 3: use of the modified Hartung-Knapp (mHK) method for calculation of the CI. Here, the modification factor q is constrained at ≥1.

Alternative approach 4: simultaneous use of the PM estimator and the HK method. In cases where $\tau^2 > 0$, q=1; therefore, this approach yields the same overall effect variance as *alternative approach 1*, but utilizes a t-distribution (instead of the normal) to calculate the CI. In the special case of $\tau^2 < 0$ (set at 0) the overall effect variance is affected (becomes smaller) by the HK method, due to the q being <1.

OR, odds ratio; CI, confidence interval; WMH, white matter hyperintensite; CMB, cerebral microbleed.

*Results indicate statistical significance at a two-sided *P*<0.05.

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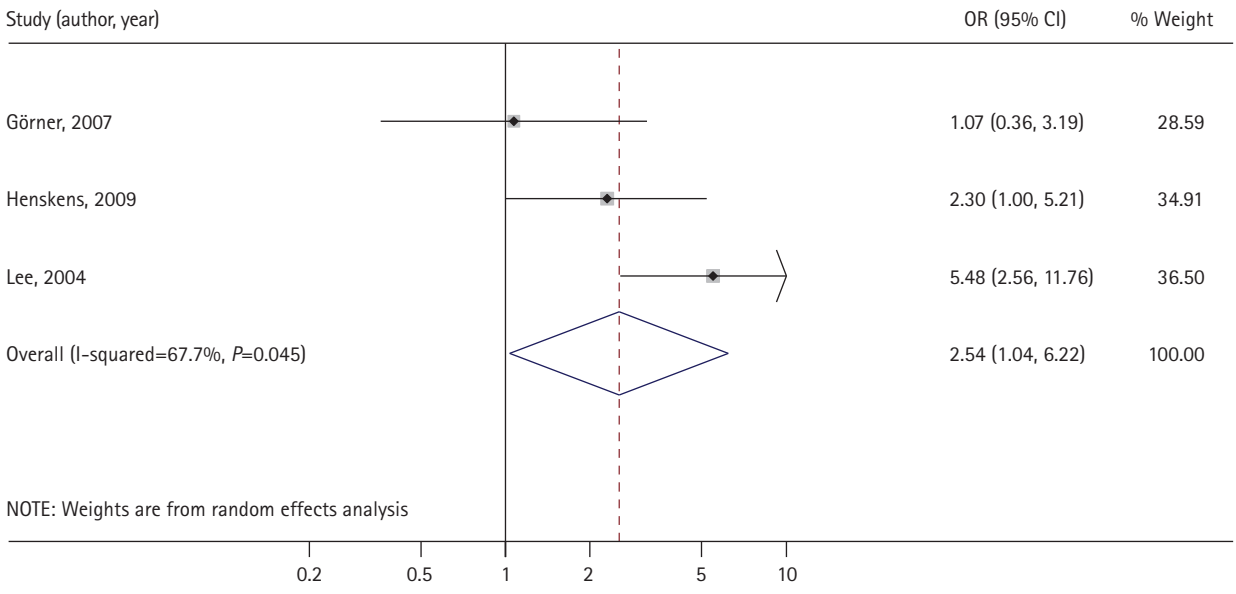
Supplementary Table 6. Sensitivity analyses by fulfilment of each specific criterion of the cohort subscale of the Newcastle-Ottawa assessment scale for the associations between left ventricular hypertrophy and lacunes, extensive WMHs, CMBs in general and high-risk population studies

Variable	Lacunes		WMH		CMB	
	k	OR (95% CI)	k	OR (95% CI)	k	OR (95% CI)
General population						
Overall analysis	5	1.49 (1.12–2.00)*	5	1.73 (1.38–2.17)*	0	-
Newcastle-Ottawa scale items						
Selection						
Representativeness of the exposed cohort	5	1.49 (1.12–2.00)*	5	1.73 (1.38–2.17)*	0	-
Selection of the non-exposed cohort	5	1.49 (1.12–2.00)*	5	1.73 (1.38–2.17)*	0	-
Ascertainment of exposure	5	1.49 (1.12–2.00)*	5	1.73 (1.38–2.17)*	0	-
Exclusion of outcome presence at start of study	1	1.80 (1.25–2.59)*	0	-	0	-
Comparability						
Comparability for age	5	1.49 (1.12–2.00)*	5	1.73 (1.38–2.17)*	0	-
Comparability for hypertension	4	1.50 (1.09–2.06)*	3	1.74 (1.34–2.25)*	0	-
Outcome						
Assessment of outcome	3	1.35 (0.98–1.87)	5	1.73 (1.38–2.17)*	0	-
Length of follow-up	1	1.80 (1.25–2.59)*	1	1.37 (0.77–2.44)	0	-
Adequacy of follow-up cohorts	1	1.80 (1.25–2.59)*	1	1.37 (0.77–2.44)	0	-
High-risk population						
Overall analysis	8	2.39 (1.32–4.32)*	11	2.01 (1.45–2.80)*	3	2.54 (1.04–6.22)*
Newcastle-Ottawa scale items						
Selection						
Representativeness of the exposed cohort	0	–	0	-	0	-
Selection of the non-exposed cohort	8	2.39 (1.32–4.32)*	11	2.01 (1.45–2.80)*	3	2.54 (1.04–6.22)*
Ascertainment of exposure	7	2.59 (1.36–4.94)*	9	2.40 (1.56–3.71)*	3	2.54 (1.04–6.22)*
Exclusion of outcome presence at start of study	2	0.97 (0.27–3.54)	1	1.14 (0.71–1.82)	0	-
Comparability						
Comparability for age	3	1.51 (0.48–4.73)	9	1.93 (1.37–2.73)*	2	3.60 (1.54–8.43)*
Comparability for hypertension	2	0.92 (0.27–3.16)	6	2.07 (1.29–3.33)*	1	5.48 (2.56–11.75)*
Outcome						
Assessment of outcome	7	2.59 (1.36–4.94)*	11	2.01 (1.45–2.80)*	3	2.54 (1.04–6.22)*
Length of follow-up	2	0.97 (0.27–3.54)	2	2.90 (0.42–19.84)	0	-
Adequacy of follow-up cohorts	1	1.77 (0.85–3.70)	0	-	0	-

WMH, white matter hyperintensity; CMB, cerebral microbleed; k, number of pooled studies; OR, odds ratio; CI, confidence interval.
*Results indicate statistical significance.



Supplementary Figure 1. Forest plot of the meta-analysis association estimates between left ventricular hypertrophy and cerebral microbleeds in high-risk population studies. Odds ratios (ORs) of each study are depicted as data markers; shaded boxes around the data markers indicate the statistical weight of the respective study; 95% confidence intervals (CIs) are indicated by the error bars; pooled-effect estimate along with its 95% CI is as a diamond.

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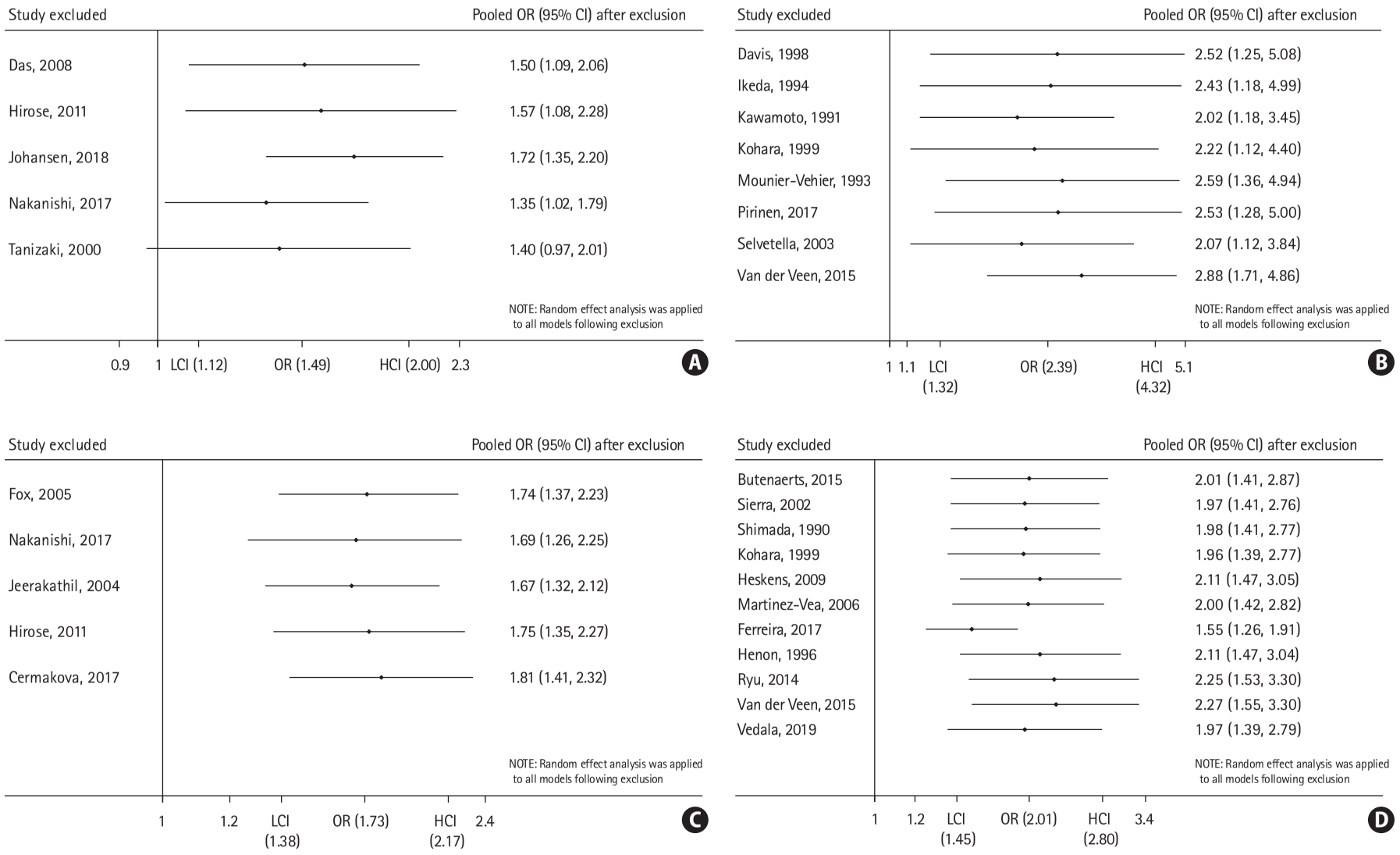
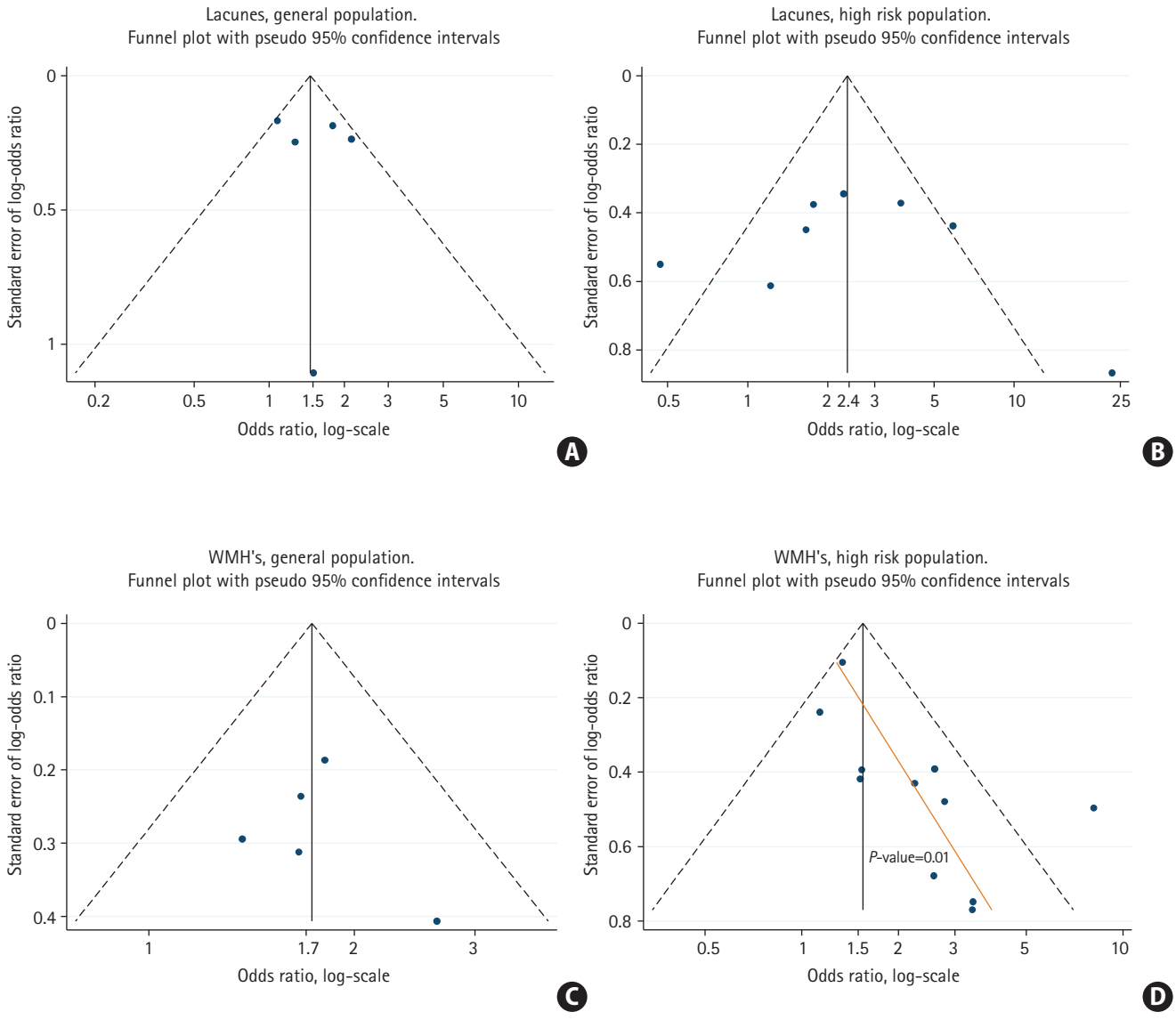


Supplementary Figure 2. Leave-one out sensitivity analyses for the primary meta-analysis association estimates between left ventricular hypertrophy and lacunes (A, B) or extensive white matter hyperintensities (C, D) in general (A, C) and high-risk population studies (B, D). Odds ratios (ORs) for the meta-analysis estimate after exclusion of each study are depicted as data markers. 95% Confidence intervals (CIs) are indicated as error bars. Low confidence interval (LCI), OR, and high confidence interval (HCI) mark the overall meta-analysis results presented in Figure 2.



Supplementary Figure 3. Funnel plots of the meta-analyses for the associations between left ventricular hypertrophy and lacunes (A, B) or extensive white matter hyperintensities (C, D) in general (A, C) and high-risk population studies (B, D). Each study is depicted as a dot; the black vertical line indicates the overall fixed-effect estimate; pseudo 95% confidence intervals (CIs) are represented by the dashed lines; in cases where ≥10 studies were pooled, the Egger line is drawn in orange along with its accompanying *P*-value.

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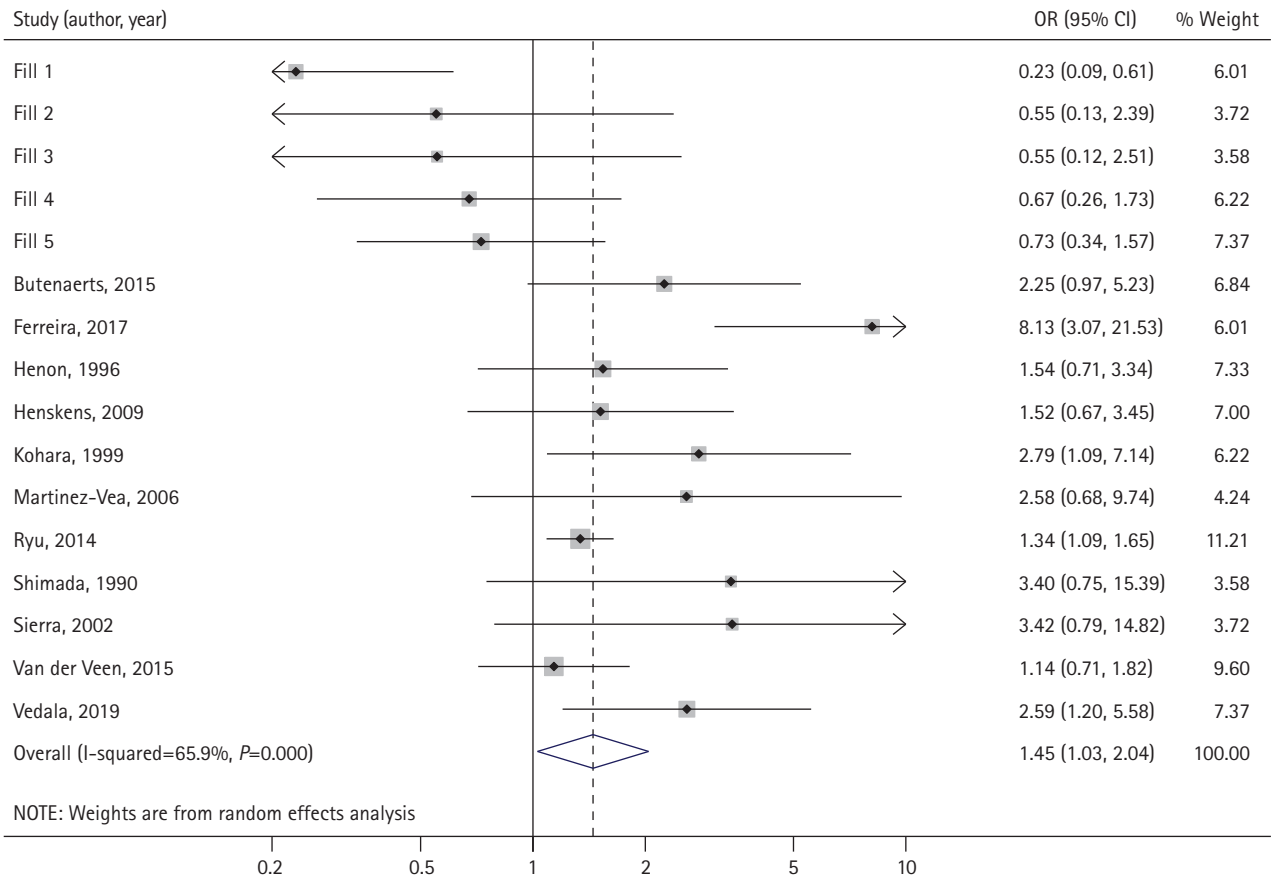

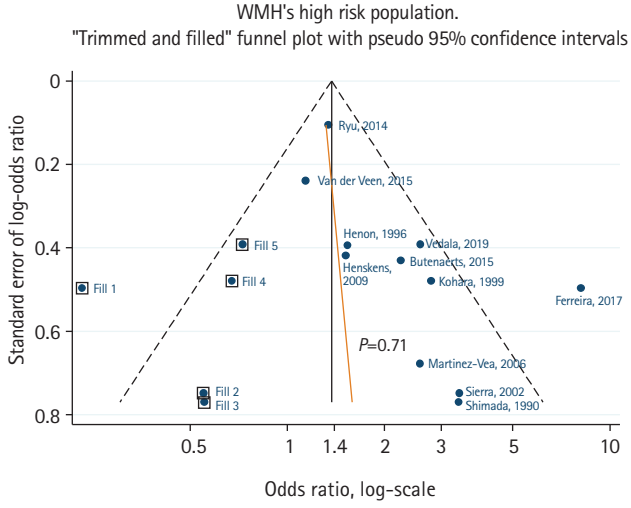

Supplementary Figure 4. "Trim and fill method" (forest and funnel plot) for the association between left ventricular hypertrophy and extensive white matter hyperintensities in high-risk population studies, where significant small study effects were identified with the Egger's method. (A) "Filled" forest plot, (B) "filled" funnel plot; a total of 5 "missing studies" were added, labelled as "Fill 1–5." OR, odds ratio; CI, confidence interval.