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ORIGINAL RESEARCH

Associations of Cerebrovascular Regulation and Arterial Stiffness With Cerebral Small Vessel Disease: A Systematic Review and Meta-Analysis

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BACKGROUND: Cerebral small vessel disease (cSVD) is a major contributing factor to ischemic stroke and dementia. However, the vascular pathologies of cSVD remain inconclusive. The aim of this systematic review and meta-analysis was to characterize the associations between cSVD and cerebrovascular reactivity (CVR), cerebral autoregulation, and arterial stiffness (AS).

METHODS AND RESULTS: MEDLINE, Web of Science, and Embase were searched from inception to September 2023 for studies reporting CVR, cerebral autoregulation, or AS in relation to radiological markers of cSVD. Data were extracted in predefined tables, reviewed, and meta-analyses performed using inverse-variance random effects models to determine pooled odds ratios (ORs). A total of 1611 studies were identified; 142 were included in the systematic review, of which 60 had data available for meta-analyses. Systematic review revealed that CVR, cerebral autoregulation, and AS were consistently associated with cSVD (80.4%, 78.6%, and 85.4% of studies, respectively). Meta-analysis in 7 studies (536 participants, 32.9% women) revealed a borderline association between impaired CVR and cSVD (OR, 2.26 [95% CI, 0.99–5.14]; P=0.05). In 37 studies (27 952 participants, 53.0% women) increased AS, per SD, was associated with cSVD (OR, 1.24 [95% CI, 1.15–1.33]; P<0.01). Meta-regression adjusted for comorbidities accounted for one-third of the AS model variance (R^2=29.4%, $P_{moderators}$=0.02). Subgroup analysis of AS studies demonstrated an association with white matter hyperintensities (OR, 1.42 [95% CI, 1.18–1.70]; P<0.01).

CONCLUSIONS: The collective findings of the present systematic review and meta-analyses suggest an association between cSVD and impaired CVR and elevated AS. However, longitudinal investigations into vascular stiffness and regulatory function as possible risk factors for cSVD remain warranted.

Key Words: arterial stiffness ■ cerebral autoregulation ■ cerebral small vessel disease ■ cerebrovascular reactivity

Cerebral small vessel disease (cSVD) is responsible for roughly one-fifth of ischemic strokes, contributes to 45% of dementias, and is associated with poor outcomes in Alzheimer's disease and cancer, 2 of the leading causes of death in the United States.[1–3] cSVD in itself is a complex pathology affecting the small (40–200 μm) perforating arterioles that supply blood to the subcortical white matter of the brain, manifesting as lesions observed with advanced neuroimaging as described by the Standards for Reporting Vascular Changes on Neuroimaging criteria.[4,5] In addition to the elevated risk for cerebrovascular events, cSVD increases the risk for reduced quality of life and mortality, highlighting the

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CLINICAL PERSPECTIVE

What Is New?

- Decreases in cerebrovascular reactivity and increases in arterial stiffness are associated with greater cerebral small vessel disease burden between healthy individuals and those with cerebral small vessel disease.
- Approximately 30% of the heterogeneity in the relationship between arterial stiffness and cerebral small vessel disease was explained by multivariate adjustment for hypertension, diabetes, hyperlipidemia, or the use of medications targeting these conditions.

What Are the Clinical Implications?

- Currently, the understanding of the pathophysiology of cerebral small vessel disease is limited.
- The present findings support the use of noninvasive vascular monitoring strategies, alongside the assessment of traditional cardiovascular risk factors, to further our understanding of the underlying mechanisms of cerebral small vessel disease.
- Furthermore, the present systematic review and meta-analyses suggest that dysfunction in both local cerebral vasculature and systemic central and conduit arteries are associated with cerebral small vessel disease.

Nonstandard Abbreviations and Acronyms

cfPWV	carotid-femoral pulse wave velocity
cSVD	cerebral small vessel disease
PWV	pulse wave velocity

critical importance of identifying risk factors for cSVD to better understand its pathophysiology and inform risk management practices.[6,7] Common risk factors, particularly hypertension, have been the most prominently investigated underlying mechanisms preceding the onset or progression of cSVD.[8–10] However, combining the most common cardiovascular risk factors (eg, hypertension, smoking, diabetes, hyperlipidemia, and elevated homocysteine) still explains only ≈2% of the variance in cSVD.[11]

Although the underlying pathophysiology of cSVD is not fully delineated, several studies have suggested that patients with cSVD exhibit vascular vulnerabilities independent of hypertension.[11–13] Interestingly, patients with normal blood pressure in these studies often had underlying conditions associated with increased arterial stiffness,[14–16] a vascular property of critical importance in health and disease.[17] Stiffening of central (aorta) and conduit (extracranial and intracranial) arteries potentiate small vessel injury in the brain as a result of increased transmission of pulsatile energy,[18–20] which may cause or develop in parallel with disruption of local regulatory mechanisms such as cerebrovascular reactivity or cerebral autoregulation.[18,21] Importantly, in a comprehensive review, Wardlaw et al[12] recently proposed that the development of cSVD may incorporate the loss of these regulatory functions, suggesting that exploring topics like arterial stiffness and local regulatory mechanisms, such as cerebrovascular reactivity or cerebral autoregulation, could significantly advance our comprehension of cSVD pathogenesis. However, interpretation of the current evidence base is complicated by small sample sizes, varied study methodologies, limited longitudinal studies, and different populations of interest. Therefore, we conducted the present systematic review and meta-analyses to provide an overview of the current evidence for cerebrovascular reactivity, cerebral autoregulation, and arterial stiffness as potential local and global vascular mechanisms associated with cSVD.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files. The analysis was carried out and reported following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Cochrane Collaboration. Additionally, it was registered with the International Prospective Register of Systematic Reviews under the ID number 42023448225.

Search Strategy

Three separate systematic searches of the English literature were performed in the MEDLINE, Web of Science, and Embase electronic databases using the search strategies outlined in Tables S1 to S3 in order to evaluate the relationship between cerebral small vessel disease and cerebrovascular reactivity, cerebrovascular autoregulation, or arterial stiffness. Additional studies were identified through manual searches of reference lists in the publications retrieved. The last database search was performed on September 30, 2023. There were no a priori limitations for constraining searches to specific time frames; thus, searches included studies published from database inception to the date of the final search. Literature searches and selection of studies were performed by 3 independent reviewers (B.S., V.T., O.K.), and disagreements were resolved by consensus.

Eligibility Criteria

Studies were considered eligible for the systematic review and meta-analysis if they met the following criteria: (1) full-length publication in a peer-reviewed journal, (2) included participants aged ≥18 years who had brain imaging for detection of cSVD by magnetic resonance imaging (MRI), and (3) reported markers of cSVD compared against a valid, quantified measure of cerebrovascular reactivity, cerebrovascular autoregulation, or arterial stiffness. Although previous reports have assessed cSVD burden using computed tomography (CT)[22–24] and have noted good agreement between CT- and MRI-derived cSVD features, the features detected on CT are limited to only a couple of the full range of markers recommended for quantification by guidelines.[4,25] Research standards currently recommend MRI due to the higher sensitivity and specificity for determining cSVD load,[4] and therefore, the present review and meta-analyses exclude studies using only CT. Studies including populations with a previous stroke or other cerebrovascular event (eg, prior transient ischemic attack, intracranial arterial stenosis) were eligible. The nature of the present research question did not preclude the inclusion of specific study designs. Therefore, cross-sectional or longitudinal studies of any quantitative design were eligible for selection. Studies were excluded if the report was not an original research article; the study was performed using cell, animal, or postmortem subjects; the study used CT to assess cerebral injury; or cerebral atrophy was the only marker reported. The studies remaining at this step were eligible for qualitative synthesis in the systematic review and were further examined for eligibility for inclusion in quantitative meta-analyses. Studies were not eligible for the subsequent meta-analysis if they did not report an odds ratio (OR) or provide values for the presence of cSVD in the study sample that allowed for the calculation of OR from crude event rates[26]; however, these studies remained eligible for qualitative synthesis in the systematic review.

Exposure Modalities

The primary exposures extracted were local and systemic measures of cerebrovascular reactivity, cerebral autoregulation, and arterial stiffness:

1. Cerebrovascular reactivity is defined as an index of the change in cerebrovascular tone for a given change in the arterial partial pressure of carbon dioxide.[27,28] The 2 primary means of assessing cerebrovascular reactivity included in the present analysis evaluated cerebral blood flow/velocity during changes in arterial partial pressure of carbon dioxide. The first approach included the breath-hold index, which calculates cerebrovascular reactivity as the percent change in cerebral perfusion divided by the length of the breath-hold phase. The second approach uses controlled mixtures of inhaled gases and calculates cerebrovascular reactivity as the change in cerebral perfusion divided by the change in arterial carbon dioxide.[29]
2. Cerebral autoregulation is the ability of the brain to adapt vascular tone to maintain a constant cerebral perfusion across a range of perfusion pressures.[30,31] As a noninvasive measurement, cerebral autoregulation is assessed as the change in cerebral perfusion relative to a change in arterial blood pressure. Evaluation of cerebral autoregulation typically examines either spontaneous or induced oscillations in blood pressure and quantification of cerebral autoregulation may include time domain or frequency domain calculations. Frequency domain cerebral autoregulation reports gain and phase values, which estimate the association and time-lag between cerebral perfusion and blood pressure.[32,33] Time domain cerebral autoregulation instead assesses the correlation between blood pressure and cerebral perfusion, providing a correlation coefficient over time windows lasting at least 2 minutes.[34]
3. Arterial stiffness is defined as the resistance of the arterial walls to deformation. Arterial stiffness can be a local or regional measure, depending on the method of determination.[17] In the present analysis, the most frequent assessment of arterial stiffness was carotid-femoral pulse wave velocity (cfPWV). Calculated as the ratio of the distance between 2 sites over the transit time for a pulse wave to reach the sites, cfPWV characterizes global arterial health and structure.[17,20] Two clinically relevant alternative indices of global arterial function (brachial-ankle PWV and Cardio-Ankle Vascular Index) were also reported in the included studies. We also included local (local PWV, β-stiffness index, distensibility coefficient) measures of arterial stiffness in the carotid artery as a conduit vessel along the vascular path in the heart–brain axis. Recent reports of elevated carotid artery stiffness demonstrating an association with cerebral injury justified, including local stiffness measures.[35–37]

Outcomes

The primary outcome of this study is the presence of cSVD, determined in accordance with the standardized Standards for Reporting Vascular Changes on Neuroimaging guidelines as follows[4]:

1. Recent small subcortical infarcts: recent infarction (≤20 mm in diameter) in the territory of a perforating arteriole, occurring within the previous few weeks.
2. Lacune: approximately circular, fluid-filled cavity between 3 and 15 mm in diameter.
3. White matter hyperintensity: hyperintense regions identified on T2-weighted sequences, not located within subcortical gray matter or the brainstem.
4. Perivascular spaces: fluid-filled spaces that follow a typical course of a blood vessel, with a diameter typically <3 mm. In the basal ganglia, perivascular spaces may be enlarged (up to 10–20 mm).
5. Cerebral microbleeds: small (often 2–5 mm in diameter but may range up to 10 mm) areas of signal void seen on T2*-weighted MRI but not seen on fluid attenuated inversion recovery, T1-weighted, or T2-weighted sequences.

Significant inconsistency has been noted with the reporting of cerebral lesions.[38] To ensure thorough systematic literature searches, the alternate terminology for each cSVD marker reported by Wardlaw et al was also incorporated into the search strategies.[4] We included studies that described "silent cerebral infarcts" due to the common use of this term to describe neuroimaging markers of cSVD[38]; the cSVD subtype that these studies analyzed was determined by consensus review of the study methods and comparison against the criteria laid out in the Standards for Reporting Vascular Changes on Neuroimaging guidelines.[4] Brain atrophy alone did not qualify a study for inclusion because cerebral atrophy itself is not a specific marker of cSVD[4,25] and because of inconsistent reporting.[39] Additionally, we omitted *cortical superficial siderosis* as this was more recently incorporated as a marker for cSVD and cerebral amyloid angiopathy and thus has not been extensively investigated or incorporated into summary scoring of cSVD burden.[25]

Literature Screening and Data Extraction

All search results retrieved from the online databases were downloaded to a commercially available research publication and citation management system (Endnote, Clarivate Analytics). Literature processing began with the removal of duplicates, review articles, conference abstracts, letters to the editor, and case studies. Reviewers (B.S., V.T., O.K.) independently screened remaining full-text records for eligibility before extracting data from eligible publications. The data extracted from records included factors for study identification (authors, year of publication, journal), study design characteristics (recruitment procedures, study protocols), descriptions of the study samples (sample size, age, sex, past or present cardiovascular or cerebral/cerebrovascular disease, use of medications), details of the exposure or predictor (type of measure, methods of assessment), cerebral small vessel disease markers (along with modality or modalities used for assessment), effect size (OR reported by the study or calculated from reported crude event rates), and adjustments for covariates. Some studies reported multiple measures of the specific exposure; authors agreed on consensus for extraction in these cases.

Risk of Bias Assessment

The risk of bias was evaluated with the Newcastle-Ottawa Scale,[40] in which the quality of each report is assessed on categories of bias, including selection, comparability, and exposure. Studies were predominantly of cross-sectional or case–control design; therefore, we applied the 9-item scale to assess the risk of bias. No study was excluded on the basis of quality alone.

Statistical Analysis

Primary Analyses

All statistical analyses were performed using GraphPad Prism (version 9.0) and the software R (version 4.1.2) with packages *meta* and *metafor*. Consistent with previous meta-analysis approaches, the cSVD subtypes were first pooled for analysis due to the limited number of studies available with each individual subtype.[39,41] When possible we performed subgroup analyses examining individual subtypes of cSVD to account for differences in the pathogenesis processes when feasible, specifically white matter hyperintensities and lacunes.[5,11,12] Subgroup analyses were also performed by stratifying studies by cerebral region within cSVD subtypes, where feasible, due to variable risk factor contributions depending on location.[5,42] To further explore a potential source of heterogeneity in the studies reporting arterial stiffness measures, we performed a subgroup analysis including only the studies that assessed arterial stiffness as cfPWV, the gold-standard approach.[17,20] Finally, subgroup analyses were also performed with the arterial stiffness data to examine the possibility of artery-specific relationships by conducting separate analyses on the studies that measured central artery stiffness (cfPWV or MRI-derived aortic PWV) or carotid stiffness (local carotid PWV, carotid distensibility coefficient, or carotid β-stiffness).

Extracted data for each predictor variable were divided into continuous or dichotomous before separate analyses were performed. In order to standardize effect sizes for meta-analyses in which the exposure variable was a continuous measure, OR from each

study were adjusted by multiplying the natural-log of the OR by the study-specific SD (ie, adjusted OR=exp[SD×ln(OR)]). If interquartile ranges were provided, SDs were calculated as (Quartile 3 – Quartile 1)/1.35, consistent with guidelines.[43,44] If SDs were reported by subgroup, pooled SDs were calculated as described in the Cochrane Handbook.[43] For arterial stiffness, differences in directionality for the carotid distensibility coefficient (ie, decreases in carotid distensibility coefficient indicate increases in arterial stiffness, whereas increases in PWV, Cardio-Ankle Vascular Index, and β-stiffness indicate increases in arterial stiffness) were corrected by taking the inverse of the reported effect sizes as directed by the Cochrane Handbook.[43] Studies that reported risk ratios were included in accordance with the previous consensus that these are roughly equivalent in smaller effect sizes.[45] For meta-analyses in which the exposure variable was dichotomous, studies that did not directly report an OR but provided sufficient information to generate a 2×2 contingency table were included after calculating the OR as described in the Cochrane Handbook.[43] GraphPad Prism version 9.0 was used to calculate the OR and associated CIs. Given the wide variance in methods of assessing each predictor variable, we proceeded with a random-effects model to minimize potential bias.[46] Heterogeneity was assessed with the Cochran Q test, the Higgins I^2 statistic, and the τ^2 statistic. Forest plots were generated describing the OR, 95% CIs, and pooled summary estimates. Effect sizes were considered significant at $P<0.05$. Certainty of evidence for each meta-analysis performed was assessed using the Grading of Recommendations Assessment, Development, and Evaluation system.[47,48]

Secondary Analyses

For the investigation of a temporal relationship between the exposure measures and cSVD, we performed secondary analyses incorporating only the reports with longitudinal study designs where possible. Meta-regression analyses were performed to explore the influence of the 3 most reported vascular risk factors/diseases (hypertension, diabetes, and hyperlipidemia) on the outcomes derived from primary analyses. For all secondary analyses performed, the effect size was considered significant if $P<0.05$.

Sensitivity Analyses

The presence of *small study effects* was examined using funnel plots, as described by the test of Egger et al.[49,50] Sensitivity analyses were conducted using a leave-one-out approach, in which the pooled treatment effects were iteratively calculated after excluding each study one at a time and recording the pooled OR, CI, and *P* value. We performed further sensitivity analysis by recalculating the pooled effect size using fixed-effects analyses in order to investigate the impact of the number of studies quantitatively synthesized on the precision of τ^2 estimates.[50]

RESULTS

Systematic Review and Qualitative Synthesis

Cerebrovascular Reactivity and Cerebral Small Vessel Disease

Our initial database and manual search of references identified 479 records assessing the relationship between cerebrovascular reactivity and cSVD, which was reduced to 429 preliminary records after excluding duplicates (Figure S1). Abstract screening and exclusion of nonoriginal research, records lacking full text, or records that did not quantitatively assess a relationship between cerebrovascular reactivity and cSVD resulted in 46 publications for qualitative synthesis in the systematic review. Of the 46 articles, 3 assessed recent small subcortical infarcts,[51–53] 8 assessed the presence of lacunes,[54–61] 7 assessed enlarged perivascular spaces,[52,57–59,62–64] 9 assessed cerebral microbleeds,[52,54,56–61,65] 41 assessed white matter hyperintensities,[51,52,54,56–61,64–95] and 5 assessed a total cSVD score.[58,59,65,82,96] The total population across the included reports consisted of healthy/aging individuals with or without vascular risk factors (70% of studies), neurocognitive or neurodegenerative disorders (22%), non-cSVD cerebrovascular disease (20%), and those with prior diagnoses of cSVD (39%). All included studies used only MRI for determining the presence of radiological markers of cSVD. MRI was also the primary modality in the studies included (61% of included studies) for assessing cerebrovascular reactivity, with the remaining studies using transcranial Doppler (39% of included studies). Moreover, diverse techniques were used, including different MRI assessment methods like blood-oxygen level dependent (39% of included studies) and arterial spin labeling (13% of included studies), examined various transcranial Doppler target vessels such as the middle cerebral artery and posterior communicating artery, and employed different approaches to induce cerebrovascular hyperemia, such as the CO_2 challenge (56.5% of included studies), acetazolamide or dipyridamole (13% of included studies), and breathholds (28% of included studies).[29,97–99]

Of the included studies, 39 were cross-sectional in design, with 32 reporting a significant association between cerebrovascular reactivity and cSVD.[51–54,56–59,62,63,65–70,72–77,80–86,91,92,94] Twenty-one of the cross-sectional studies were case–control

studies.[51–53,58,63,65–71,75,77,78,80,81,83,86,87,91] The remaining 18 studies were prospective or retrospective cohort studies.[54–57,59,62,72–74,76,79,82,84,85,92–95] In 203 patients with leukoaraiosis, Bian et al[91] demonstrated that patients exhibiting more severe white matter hyperintensities (Fazekas grades II and III) had a significantly reduced cerebrovascular reactivity compared with those with lower severity. In another larger cohort study, Staszewski et al[58] reported that in 120 subjects, the lowest tertile of cerebrovascular reactivity had a 19-fold greater likelihood of having cSVD compared with the highest tertile. This is supported by Silvestrini et al,[53] who found that each 0.1 decrease in breath-hold index was associated with a 2-fold greater risk of cSVD. Contrary to these findings, Bisschops et al[55] found that cerebrovascular reactivity had no relationship with radiological markers of cSVD. This was the only study in the systematic review to focus solely on participants with internal carotid artery occlusion, which has been previously shown to alter transcranial Doppler assessments of cerebral hemodynamics.[100,101]

Of the 7 longitudinal studies,[60,61,64,88–90,96] only 2[60,90] did not find an association between cerebrovascular reactivity and progression of cSVD, with follow-up times ranging from 1 to 7 years after the initial assessment of cerebrovascular reactivity. These longitudinal studies primarily focused on white matter hyperintensities; for example, Liem et al[61] divided 38 participants into 2 groups by the median cerebrovascular reactivity and reported that in participants with a high cerebrovascular reactivity at baseline, the increase in white matter hyperintensity volume over 7.1 years was 0.37% compared with 2.9% in those with a low cerebrovascular reactivity. This relationship was supported by Staszewski et al,[96] who determined in 60 patients with cSVD and 20 healthy controls that the participants with a progression of cSVD had a significantly lower cerebrovascular reactivity at baseline. Conversely, Moreton et al[60] found no association between baseline cerebrovascular reactivity and development of incident cSVD in 14 subjects over a 2-year follow-up. In the work by Smolinski et al,[90] similar results to Moreton et al[60] were found when the measures of cerebrovascular reactivity were compared with cSVD progression in a group of 43 patients with multiple sclerosis in remission.

Cerebral Autoregulation and Cerebral Small Vessel Disease

Our initial database and manual search of references identified 254 records assessing the relationship between cerebral autoregulation and cSVD, which was reduced to 202 preliminary records after excluding duplicates (Figure S2). Abstract screening and exclusion of nonoriginal research, records lacking full text, or records that did not quantitatively assess a relationship between cerebral autoregulation and cSVD resulted in 14 publications for systematic review. Of the 14 articles, 4 assessed recent small subcortical infarcts,[102–105] 1 assessed the presence of lacunes,[106] 2 assessed enlarged perivascular spaces,[106,107] 3 assessed cerebral microbleeds,[106–108] 8 assessed white matter hyperintensities,[106,107,109–114] and 4 assessed the total cSVD score.[106,107,110,115] All included studies were cross-sectional in design. The total population consisted of healthy/aging individuals with or without vascular risk factors (57% of included studies), previously diagnosed cSVD (36%), cerebrovascular events (36%), and patients undergoing cardiac surgery (7%). All included studies used only MRI for determining the presence of radiological markers of cSVD. Only 1 included study did not use transcranial Doppler ultrasound to assess cerebral autoregulation; Meyer et al[104] calculated blood flow from clearance curves after bolus infusion.

All[102–104,107–112,114,115] but 3[105,106,113] studies demonstrated a significant association between cerebral autoregulation impairments and greater cSVD burden. Six studies were case–control studies[102,103,105,107,108,113] and 8 studies were prospective or retrospective cohort studies.[104,106,109–112,114,115] In a study of 346 patients undergoing cardiopulmonary bypass, Nomura et al[110] reported that cSVD was associated with a 3-fold greater odds of impaired cerebral autoregulation. Liu et al[107] analyzed 113 patients with cSVD and 83 cSVD-free controls and similarly found a significantly reduced cerebral autoregulation in the patients with cSVD. Multivariate regression models adjusted for age, sex, and heart rate revealed that cerebral autoregulation in the total population was independently associated with individual cSVD markers (except lacunes) and a total cSVD score. Guo et al[102] extended the findings from these studies by following up the patients after initial cross-sectional analysis and demonstrated that the observation of impaired cerebral autoregulation in the groups with cSVD was diffuse and persisted for 6 months after the initial lacunar infarction. Contrary to most studies included, both Wu et al[106] and Xiong et al[105] reported no association between cerebral autoregulation and any radiological markers of cSVD. However, both studies used approaches to determining cerebral autoregulation that differed from those previously discussed.[116,117]

Less than half of the studies[103,106,110–112,114] accounted for vascular risk factors either in baseline comparisons or with statistical methods. Five[103,110–112,114] of the 6 studies that adjusted for risk factors found that the relationship between cerebral autoregulation and cSVD persisted, and one[106] instead found only a relationship between the vascular risk factors (hypertension and diabetes) and cSVD.

Arterial Stiffness and Cerebral Small Vessel Disease

Our initial database and manual search of references identified 878 records assessing the relationship between arterial stiffness and cSVD, which was reduced to 694 preliminary records after excluding duplicates (Figure S3). Abstract screening and exclusion of nonoriginal research, records lacking full text, or records that did not quantitatively assess a relationship between arterial stiffness and cSVD resulted in 82 publications for systematic review. Of the 82 articles, 12 assessed recent small subcortical infarcts,[118–129] 24 assessed the presence of lacunes,[21,130–152] 9 assessed enlarged perivascular spaces,[118,138,144,145,150,152–155] 23 assessed cerebral microbleeds,[37,118,120,123–127,131–134,138,139,144,145,149,150,152,153,156–158] 59 assessed white matter hyperintensities,[21,36,118,119,122,123,125–127,130–134,138–142,145,150–152,155,156,159–192] and 8 assessed the total cSVD score.[133,138,139,152,193–196] The total population consisted of healthy/aging individuals with or without vascular risk factors (77% of included studies), previously diagnosed cSVD (6%), cerebrovascular events (8%), cognitive decline or complaints (5%), cardiovascular disease including myocardial infarction and heart failure (13%), and metabolic syndromes or renal disease (11%). All included studies used only MRI for determining the presence of radiological markers of cSVD. Central or large artery stiffness was the primary assessment (69 studies, or 84%); only 13 studies measured conduit artery stiffness. The most frequently used approach was cfPWV (26 studies, 32%), followed by brachial-ankle PWV (20 studies, 24%).

The majority of studies included in the systematic review were cross-sectional in nature; with 86% of the cross-sectional studies reporting a significant association between arterial stiffness and cSVD.[21,118–121,123–128,130–134,136–145,147,148,150–154,156–158,160,161,163,165–167,169,171–173,176–179,182,183,185–187,190,193–195] Of the 69 cross-sectional studies, 13 were case–control studies[118,127,128,155,166,168,171,173,177,179,182,192,195] and 56 were prospective or retrospective cohort studies.[21,119–121,123–126,130–154,156–158,160–163,165,167,169,172,176,178,181,183,185–188,190,193,194,196] Using the Framingham Heart Study third generation cohort, Pase et al[137] demonstrated a significant association between arterial stiffness and white matter hyperintensity volume that was unaffected by adjustment for age, sex, and common vascular risk factors. Van Sloten et al[143] extended these findings to other cSVD markers in 2058 older participants (mean age of 79.6 years, 59% women) and reported that a 1-SD increase in cfPWV increased the risk of subcortical infarcts, enlarged perivascular spaces, and cerebral microbleeds by 27%, 15%, and 9%, respectively. This concept is supported by the data from 1820 subjects analyzed by Cooper et al,[120] who showed that not only was cfPWV related to white matter hyperintensities but also that in mediation analyses, ≈41% of the effect of cfPWV on cognitive function was explained by the relationship between cfPWV and cSVD. In contrast, Rundek et al[146] did not find any association between arterial stiffness and cSVD in a cohort of 1166 participants of NOMAS (Northern Manhattan Study). The sample from the study by Rundek et al was older (71±9 years), 40% were on antihypertensive medication, and 53% were current or former smokers.[146]

Of the 13 longitudinal studies[36,37,122,129,159,164,170,174,175,180,184,189,191] included in the systematic review, 11 of the 13 reported significant associations between arterial stiffness and cSVD. The average follow-up time was 7.0 years from baseline (range 2–21.5 years). King et al[184] demonstrated that arterial stiffness was a significant predictor of white matter hyperintensity progression over 7 years in 1270 subjects, such that a 1% increase in aortic arch stiffness was associated with a 0.3% increase in subsequent white matter hyperintensity volume. Using the gold-standard cfPWV, Rosano et al[170] found that a higher arterial stiffness predicted the presence of cSVD over a 10-year follow-up, even after multivariate adjustment including vascular risk factors, incident stroke, incident myocardial infarction, and changes in arterial blood pressure. Ding et al[37] analyzed the association between baseline carotid artery stiffness and incident cSVD in a sample of 2512 participants from the AGES-Reykjavik (Age, Gene/Environment Susceptibility) study and demonstrated that the risk of incident cerebral microbleeds was 11% higher per SD decrease in baseline carotid arterial strain. This relationship was not attenuated by adjustment for age, sex, arterial blood pressure, and other vascular risk factors. Conversely, the study from Suri et al[189] was 1 of 2 reports to find no association between arterial stiffness and cSVD. Specifically, the authors demonstrated no relationship between cfPWV and the progression of white matter hyperintensity volume. Tsao et al[191] similarly found no association between arterial stiffness and cSVD. Of their 1223 older participants (mean age of 61 years) from the Framingham Heart Study only 28% reported antihypertensive medication use and 9% reported prior diagnoses of diabetes, both lower than expected age-specific prevalence.[197,198]

Meta-Analyses

Six separate meta-analyses were planned before beginning the literature search to determine if cerebrovascular regulatory functions or properties of arterial stiffness were associated with cSVD. Measures were separated by whether the predictor variable was analyzed as a continuous or dichotomous variable. For dichotomous predictors, the cutoff values varied significantly across studies due to differences in study

methodology. For cerebral autoregulation specifically, we found articles reporting only OR or crude event rates with cerebral autoregulation as a dichotomized measure.

Cerebrovascular Reactivity and Cerebral Small Vessel Disease

Of the studies included in the qualitative synthesis and systematic review of the association between cerebrovascular reactivity and cSVD, 10 studies were eligible for inclusion in the quantitative meta-analysis. The analyses of these 10 included 4 studies (pooled sample n=387, 37.7% women) that used a continuous predictor and 7 studies (pooled sample n=536, 32.9% women) that used a dichotomous predictor; 1 study presented cerebrovascular reactivity as both a continuous and dichotomous predictor variable (Table 1). A sample size of 4 studies was deemed too low for quantitative synthesis, therefore, the individual results of these studies are presented qualitatively in Figure 1. Of note, all 4 studies reported a significant association between impaired cerebrovascular reactivity and cSVD. For the dichotomous exposure measure of cerebrovascular reactivity, Cochran Q statistics indicated that there was significant heterogeneity in the dichotomous predictor data (Q=18.62, P=0.005).The Higgins' I^2 value was 67.8% (95% CI, 28.5–85.5%) and τ^2 was 0.82 (95% CI, 0.11–6.44). Shown in Figure 2, meta-analysis of dichotomous cerebrovascular reactivity revealed a borderline significant association between an impaired cerebrovascular reactivity and an increased prevalence of cSVD (dichotomous predictor pooled OR, 2.26 [95% CI, 0.99–5.14], P=0.05).

Funnel plots were inappropriate for the cerebral predictors, given that each category had less than 10 studies.[199] The leave-one-out analysis conducted with dichotomous cerebrovascular reactivity measures demonstrated fluctuations in both the effect sizes (OR range, 1.58–2.79; number of studies per run=6) and the P values (range 0.02–0.14), including reporting significance (P<0.05) with the removal of either Bisschops et al[55] or Tawfik et al.[59] In further sensitivity analyses, the fixed-effect model for dichotomous cerebrovascular reactivity demonstrated significance (OR, 1.73 [95% CI,

Table 1. Cerebrovascular Reactivity Studies Presenting Odds Ratios or Crude Event Rates

Study	Assessment modalities	cSVD subtype(s)	Sample, n, % women	Age, y	Subject characteristics	Risk of bias score (max of 9)
Continuous predictors						
Bakker et al[84]	TCD	WMH	73, 26.0%	70.2±8.0	Healthy elderly	7
Lee et al[81]	MRI	WMH	62, 67.7%	Controls: 33.8±8.0, Cases: 34.0±8.1	Patients with migraine vs nonmigraine controls	7
Molina et al[51]	TCD	RSCCI	92, 30.4%	Controls: 58.3±12.0, Cases: 56.6±13.4	Controls vs first-ever patients with lacunar infarction	8
Silvestrini et al[53]	TCD	RSCCI	160, 35.6%	Controls: 59.8±9.2, Cases: 67.6±8.7	Controls vs patients with lacunar stroke	8
Dichotomous predictors						
Bakker et al[84]	TCD	WMH	73, 26.0%	70.2±8.0	Healthy elderly	7
Bisschops et al[55]	TCD	Lacunes	70, 27.1%	59, range: (35–71)	Unilateral occlusion of internal carotid artery	7
Deplanque et al[52]	TCD	RSSCI, WMH, PVS, CMB	162, 27.2%	Controls: 63.2±10.4, Cases: 62.1±11.4	Patients with cSVD vs non-cSVD controls	6
Liem et al[61]	MRI	RSSCI, WMH, CMB	38, 52.6%	Controls: 36.7±8.0, Cases: 42.2±10.0	Controls vs NOTCH3 mutation carriers	7
Palaiodimou et al[93]	TCD	WMH	23, 43.0%	51±13	Patients with Fabry disease	8
Staszewski et al[58]	TCD	Lacunes, WMH, PVS, CMB, cSVD score	120, 40.0%	Controls: 71.7±3.4, Cases: 71.8±3.4	Patients with cSVD vs non-cSVD controls	5
Tawfik et al[59]	TCD	Lacunes, WMH, PVS, CMB, cSVD score	50, *	*	Patients with lacunar stroke	6

*Data missing from the original publication.

CMB indicates cerebral microbleed; cSVD, cerebral small vessel disease; MRI, magnetic resonance imaging; PVS, perivascular space(s); RSCCI, recent small subcortical infarct; TCD, transcranial Doppler; and WMH, white matter hyperintensities.

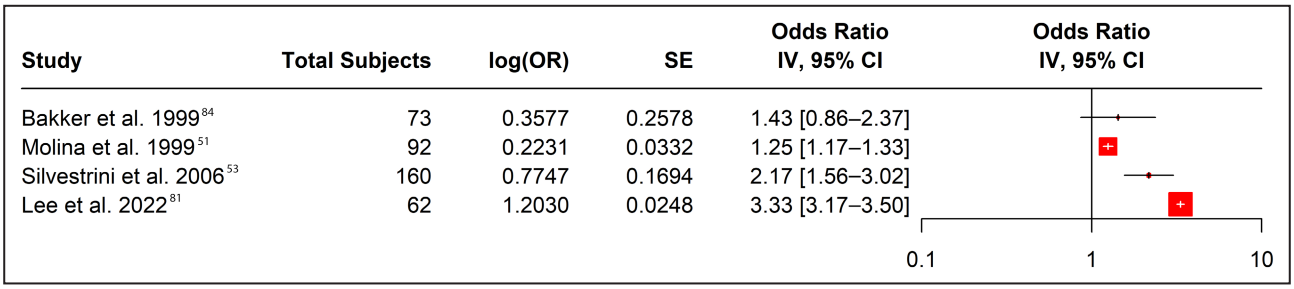

Figure 1. Individual results from studies reporting cerebrovascular reactivity as a continuous exposure measure.
Forest plot illustrating the individual effect sizes for each study reporting continuous cerebrovascular reactivity in relation to cerebral small vessel disease burden. IV indicates inverse-variance; and OR, odds ratio.

1.25–2.40], *P*=0.001) in contrast to the borderline significant results of the random-effects analysis.

Cerebral Autoregulation and Cerebral Small Vessel Disease

Of the studies included in the qualitative synthesis and systematic review of the association between cerebral autoregulation and cSVD, 3 studies (pooled sample n=455, 30.1% women) were eligible for inclusion in the quantitative meta-analysis, with all reporting cerebral autoregulation as a dichotomous variable (Table 2). A sample size of 3 studies was deemed insufficient for quantitative analysis; therefore, the individual results of the studies are presented qualitatively in Figure 3.

Arterial Stiffness and Cerebral Small Vessel Disease

Of the studies included in the systematic review of the association between arterial stiffness and cSVD, 47 were eligible for inclusion in the meta-analysis. The analyses for studies assessing arterial stiffness included 37 studies (pooled sample n=27 952, 53.0% women) that used arterial stiffness as a continuous predictor and 13 studies (pooled sample n=10 140, 53.1% women) that used arterial stiffness as a dichotomous predictor; 4 of these studies presented data for arterial stiffness as both a continuous and a dichotomous predictor variable (Table 3). Both the continuous and dichotomous models demonstrated significant (*P*<0.0001) heterogeneity assessed as the Q statistic (continuous: 126.97, dichotomous: 72.96). In the continuous model, Higgins' I^2 value was 71.6% (95% CI, 60.6–79.6%), and the τ^2 value was 0.024 (95% CI, 0.020–0.22). In the dichotomous model, Higgins' I^2 was 83.6% (95% CI, 73.3–89.9%), and the τ^2 was 0.15 (95% CI, 0.038–0.62). Regardless of whether the arterial stiffness predictor was continuous (Figure 4) or dichotomized (Figure 5), an increased arterial stiffness was associated with an increased burden of cSVD. Random effects meta-analyses indicated this for both measures (continuous predictor pooled OR, 1.24 [95% CI, 1.15–1.33], *P*<0.0001) (dichotomous predictor pooled OR, 1.86 [95% CI, 1.41–2.45], *P*<0.0001).

For specific subtypes of cSVD, only subgroup analyses between continuous arterial stiffness and white matter hyperintensities or lacunes had enough studies to be appropriately powered. Eleven studies[119,125,132,156,163–166,169,171,172] investigated white matter hyperintensities. The pooled random effects

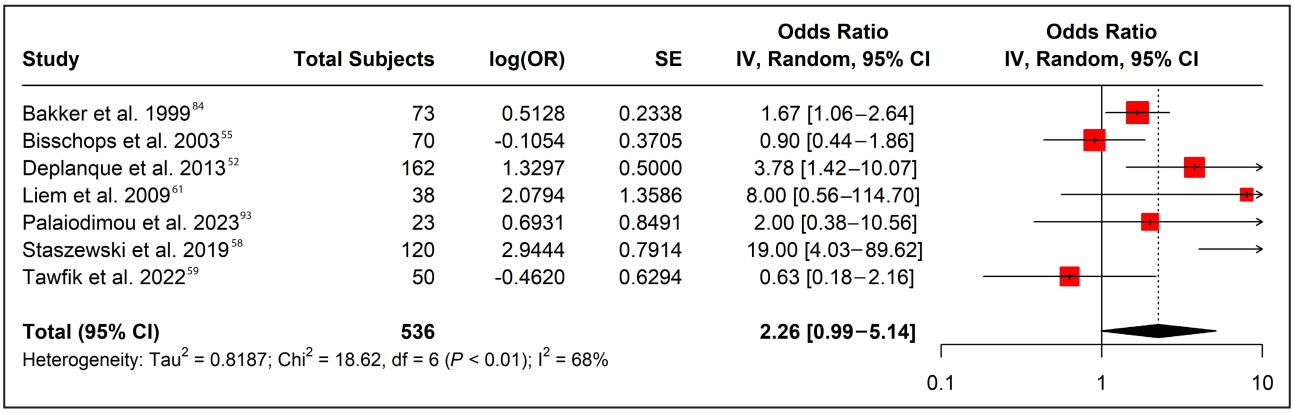

Figure 2. Odds ratio results from pooled studies reporting cerebrovascular reactivity as a dichotomous exposure variable.
Forest plot illustrating the effect sizes reported for dichotomous cerebrovascular reactivity in relation to cSVD burden. There was a borderline significant association between impaired cerebrovascular reactivity and a greater cSVD burden (OR, 2.26 [95% CI, 0.99–5.14]). cSVD indicates cerebral small vessel disease; IV, inverse-variance; OR, odds ratio.

Table 2. Cerebral Autoregulation Studies Presenting Odds Ratios or Crude Event Rates

Study	Assessment modalities	cSVD subtype(s)	Sample, n, % women	Age, y	Subject characteristics	Risk of bias score (max of 9)
Dichotomous predictors						
Castro et al[109]	TCD	WMH	46, 58.7%	73.0±12.0	Patients with ischemic stroke patients	6
Nomura et al[110]	TCD	WMH, cSVD Score	346, 29.5%	Controls: 71.2±7.8, Cases: 69.9±8.3	Controls vs patients with impaired cerebral autoregulation	7
Wu et al[106]	TCD	Lacunes, WMH, PVS, CMB, cSVD score	63, 12.7%	56.3±9.9	Patients with small artery occlusion	7

CMB indicates cerebral microbleed; cSVD, cerebral small vessel disease; PVS, perivascular space(s); TCD, transcranial Doppler; and WMH, white matter hyperintensities.

OR was 1.42 (95% CI, 1.18–1.70; number of studies=11), and the heterogeneity was not significant (I^2=31%, τ^2=0.023, P=0.15; Figure S4). Thirteen studies[21,130,135–137,139–144,146,147] investigated lacunes specifically. For this analysis, the pooled random effects OR was 1.28 (95% CI, 1.10–1.49; number of studies=13) with significant heterogeneity (I^2=70%, τ^2=0.038, P<0.01) (Figure S4).

Within the subtype of white matter hyperintensities, only 4 studies[125,130,138,169] reported measures separately for deep white matter hyperintensities and periventricular white matter hyperintensities. Within the subtype of cerebral microbleeds, only 5 studies[37,123,133,144,158] reported separate effect sizes for strictly lobar cerebral microbleeds and deep cerebral microbleeds. The limited number of studies precluded formal meta-analyses, so the individual results of these studies are presented qualitatively in Figure S5.

Fourteen studies[21,120,123,132,137,138,143,147,156,163–166,172] specifically assessed arterial stiffness with the gold standard, cfPWV, as a continuous measure. In this secondary analysis, the pooled random effects OR was 1.23 (95% CI, 1.09–1.39, P=0.001; number of studies=14). The model demonstrated significant heterogeneity (I^2=47.5%, τ^2=0.021, P=0.03). This model suggests that for each SD increase in the clinically relevant cfPWV, the odds of cSVD increase by 23% (Figure S6).

The continuous arterial stiffness measures were analyzed to investigate the differences between central arterial stiffness and conduit (carotid) arterial stiffness. Six studies[37,119,122,139,146,171] reported measures of carotid arterial stiffness, and 18 studies[21,118,120,123,125,130,132,137,138,142,143,147,156,163–166,172] reported measures of central arterial stiffness. Both carotid artery assessments (OR, 1.15 [95% CI, 1.00–1.31]; number of studies=6) and central artery assessments (OR, 1.26 [95% CI, 1.10–1.44]; number of studies=18) were associated with pooled markers of cSVD. Random-effects analysis of subgroup differences did not reveal significant differences (P=0.34), suggesting that central and conduit arterial stiffness may be associated with cSVD burden (Figure S7).

Analysis of the funnel plots for continuous and dichotomous arterial stiffness measures (Figures S8 and S9) suggested suspicion of evidence of publication bias. Conducting sensitivity analyses using the leave-one-out approach revealed that the significance in the random effects models for continuous and dichotomous arterial stiffness was maintained throughout the analysis. In further sensitivity analysis, numerical differences but not statistical differences were detected

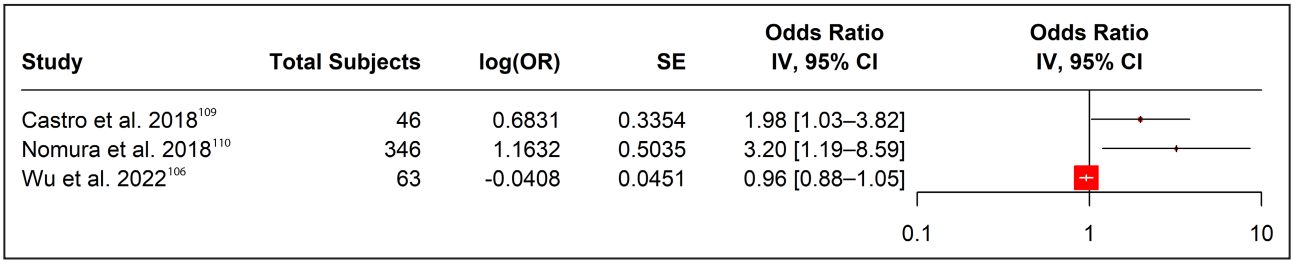

Figure 3. Individual results from studies reporting cerebral autoregulation as a dichotomous exposure measure.
Forest plot illustrating the individual effect sizes for each study reporting dichotomous cerebral autoregulation in relation to cerebral small vessel disease burden. IV indicates inverse-variance; and OR, odds ratio.

Table 3. Arterial Stiffness Studies Presenting Odds Ratios or Crude Event Rates

Study	Assessment modality for AS	cSVD subtype(s)	Sample, n, % women	Age, y	Subject characteristics	Risk of bias score (max of 9)
Continuous predictors						
Amier et al[118]	MRI, aortic PWV	RSSCI, WMH, PVS, CMB	559, 35.8%	67.9±8.8	Healthy, cognitive impairment, CVD	9
Brandts et al[130]	MRI, aortic PWV	RSSCI, WMH	50, 62.0%	49.2±12.7	Hypertensive	9
Brisset et al[119]	Carotid DC	RSSCI, WMH	1800, 59.9%	72.5±4.1	Healthy	8
Choi et al[131]	CAVI	WMH, lacunes, CMB	484, 35.5%	50±7	Healthy	7
Cooper et al[120]	cfPWV	RSSCI, CMB	1820, 60.0%	80±5	Healthy	9
Coutinho et al[172]	cfPWV	WMH	812, 57.6%	58.4±9.7	Healthy with hypertensive family members	9
Ding et al[37]	Carotid DC	CMB	2512, 58.5%	74.6	Healthy	9
Gustavsson et al[156]	cfPWV	WMH, CMB	208, 59.1%	71.0±4.8	Healthy	8
Hashimoto et al[121]	btPWV	RSSCI	351, 71.8%	65±6	Healthy	8
Hashimoto et al[163]	cfPWV	WMH	286, 60.1%	54±13	Patients referred for hypertension, CVD risk	8
Henskens et al[132]	cfPWV	WMH, lacunes, CMB	167, 49.1%	51.8±13.1	Patients referred for hypertension	8
Hughes et al[164]	cfPWV	WMH	91, 34.1%	86.9±2.8	Healthy elderly	9
Hughes et al[165]	cfPWV	WMH	19, *	*	Healthy	9
Jochemsen et al[122]	Carotid DC	WMH, RSSCI	526, 17.0%	59±10	Healthy	8
Kim et al[133]	baPWV	WMH, lacunes, CMB, cSVD score	1282, 42.3%	67.6±12.2	Patients with ischemic or transient stroke	6
Laugesen et al[166]	cfPWV	WMH	178, 48.3%	59±10	Type 2 diabetes	9
Liu et al[194]	baPWV	cSVD score	684, 34.5%	54.0, IQR: 48.0–60.0	Healthy	8
Matsumoto et al[135]	baPWV	Lacunes	476, 42.6%	51.5±7.8	Healthy	6
Mitchell et al[21]	cfPWV	RSSCI, WMH	668, 56.6%	75.4±4.0	Healthy	9
Ochi et al[136]	baPWV	Lacunes	500, 61.8%	66.9±8.4	Healthy elderly	8
Ohmine et al[169]	baPWV	WMH	144, 62.9%	70.3±9.0	Healthy elderly	9
Pase et al[137]	cfPWV	Lacunes	3207, 53.1%	46±9	Healthy	9
Poels et al[123]	cfPWV	RSSCI, WMH, CMB	1460, 55.4%	58.2±7.2	Healthy	9
Riba-Llena et al[138]	cfPWV	WMH, lacunes, PVS, CMB, cSVD score	782, 49.6%	62.7±5.4	Healthy	9
Robert et al[139]	Carotid PWV	WMH, lacunes, CMB, cSVD score	272, 57.7%	75.4±6.8	Healthy	8
Rundek et al[146]	Carotid β-stiffness	Lacunes	1166, 60.0%	71±9	Healthy	9
Saji et al[140]	baPWV	WMH, lacunes	240, 49.6%	69±9	Healthy	8
Saji et al[141]	CAVI	WMH, lacunes	220, 40.4%	69±10	Healthy	8
Shan et al[142]	MRI, aortic arch PWV	RSSCI, WMH	62, 40.3%	56.8±7.5	Patients with type 2 diabetes	8
Shimoyama et al[157]	CAVI	CMB	105, 32.4%	70.0, IQR: 68.0–76.5	Patients with cerebral infarct or transient ischemic stroke	8
Song et al[158]	baPWV	CMB	1137, 37.7%	65±12	Patients with cerebral infarct or transient ischemic stroke	8
Tsao et al[147]	cfPWV	Lacunes	1587, 55.0%	61±9	Healthy	9
Turk et al[171]	Carotid PWV	WMH	96, 43.8%	53.8±7.9	Controls vs patients who were WMH-positive	5
van Elderen et al[125]	MRI, aortic PWV	RSSCI, WMH, CMB	86, 43.0%	46.9±11.7	Patients with type 1 diabetes	8

(*Continued*)

Table 3. Continued

Study	Assessment modality for AS	cSVD subtype(s)	Sample, n, % women	Age, y	Subject characteristics	Risk of bias score (max of 9)
van Sloten et al[143]	cfPWV	RSSCI	2058, 59.0%	79.6±4.6	Healthy	9
Zhai et al[144]	baPWV	Lacunes, PVS, CMB	953, 62.5%	55.7±9.4	Healthy	9
Zhang et al[145]	baPWV	WMH, lacunes, PVS, CMB	904, 55.3%	59.7±3.0	Healthy	7
Dichotomous predictors						
Bae et al[153]	baPWV	PVS, CMB	854, 48.2%	68.2±12.5	Patients with ischemic or transient stroke	9
Chang et al[196]	baPWV	cSVD score	820, 39.9%	68.0, IQR: 59.0–78.0	Patients with ischemic stroke	5
Choi et al[131]	CAVI	WMH, lacunes, CMB	484, 35.5%	50±7	Healthy	7
Kinjo et al[134]	baPWV	WMH, lacunes, CMB	990, 53.6%	53, range: 24–86	Recruited from brain checkups	8
Liu et al[152]	CAVI	WMH	1176, 51.3%	67.5±13.2	Healthy	7
Palta et al[126]	cfPWV	RSSCI, WMH, CMB	3703, 59.3%	75.2±5.0	Healthy	9
Rosano et al[170]	cfPWV	WMH	303, 56.0%	82.9	Healthy	9
Saji et al[140]	baPWV	WMH, lacunes	240, 49.6%	69±9	Healthy	8
Saji et al[141]	CAVI	WMH, lacunes	220, 40.4%	69±10	Healthy	8
Shimoyama et al[157]	CAVI	CMB	105, 32.4%	70.0, IQR: 68.0–76.5	Patients with cerebral infarct or transient ischemic stroke	8
Tabata et al[124]	baPWV	RSSCI, CMB	149, 32.9%	70.8±10.0	Patients with coronary artery disease	6
Zijlstra et al[149]	MRI; aortic PWV	Lacunes, CMB	85, 34.1%	75.6±6.9	Healthy	4
Zhou et al[148]	Estimated PWV	Lacunes	1011, 64.5%	64.2±9.1	Healthy	7

*Data missing from the original publication.

baPWV indicates brachial–ankle pulse wave velocity; btPWV, brachial-tibial pulse wave velocity; CAVI, Cardio-Ankle Vascular Index; cfPWV, carotid-femoral pulse wave velocity; CMB, cerebral microbleed; cSVD, cerebral small vessel disease; CVD, cardiovascular disease; DC, distensibility coefficient; IQR, interquartile range; MRI, magnetic resonance imaging; PVS, perivascular space(s); PWV, pulse wave velocity; RSCCI, recent small subcortical infarct; and WMH, white matter hyperintensities.

when applying fixed-effects analysis to continuous arterial stiffness (OR, 1.04 [95% CI, 1.04–1.05]) or to dichotomous arterial stiffness (OR, 1.001 [95% CI, 1.000–1.002]).

Secondary Analyses

Meta-analysis of longitudinal studies from the studies included in quantitative primary statistical analysis was not feasible due to a limited number of studies. One study[61] investigated the longitudinal relationship between dichotomous cerebrovascular reactivity and cSVD, 3 studies[37,122,147] investigated longitudinal relationships between continuous measures of arterial stiffness and cSVD, and 1 study[170] investigated the longitudinal relationship between arterial stiffness as a dichotomous exposure and cSVD. The individual results of these studies are presented qualitatively in Figure S10.

The multivariate meta-regression results are presented in Table S4. Only the continuous arterial stiffness category of studies was applicable for appropriately powered analysis.[200,201] Therefore, we conducted multivariate meta-regression with the continuous arterial stiffness model, incorporating the study-level covariates of hypertension, diabetes, and hyperlipidemia (or medication use targeting these conditions). Twelve studies[125,130,132,137,142–144,146,147,164,165,171] were removed from the original 37 studies on the basis of incomplete demographic information, leaving 25 studies for meta-regression. The random-effects meta-analysis of the remaining studies remained statistically significant (OR, 1.21 [95% CI, 1.12–1.32], $P<0.0001$; number of studies=25). In the risk factor-adjusted model, the 3 risk factors (hypertension, diabetes, and hyperlipidemia) extracted from study-level data, not individual patient data, accounted for 29.4% of the model heterogeneity. Among the 25 studies analyzed, the majority (20 out of 25, 80%) centered around generally healthy participants with different risk factors, whereas 7 out of the 12 (58%) not included in the meta-regression focused on healthy populations. Meta-regression results for the model adjusted for each factor individually and for all 3 risk factors are presented in Table S4. Bubble plots for the individual covariates are presented in Figures S11–S13.

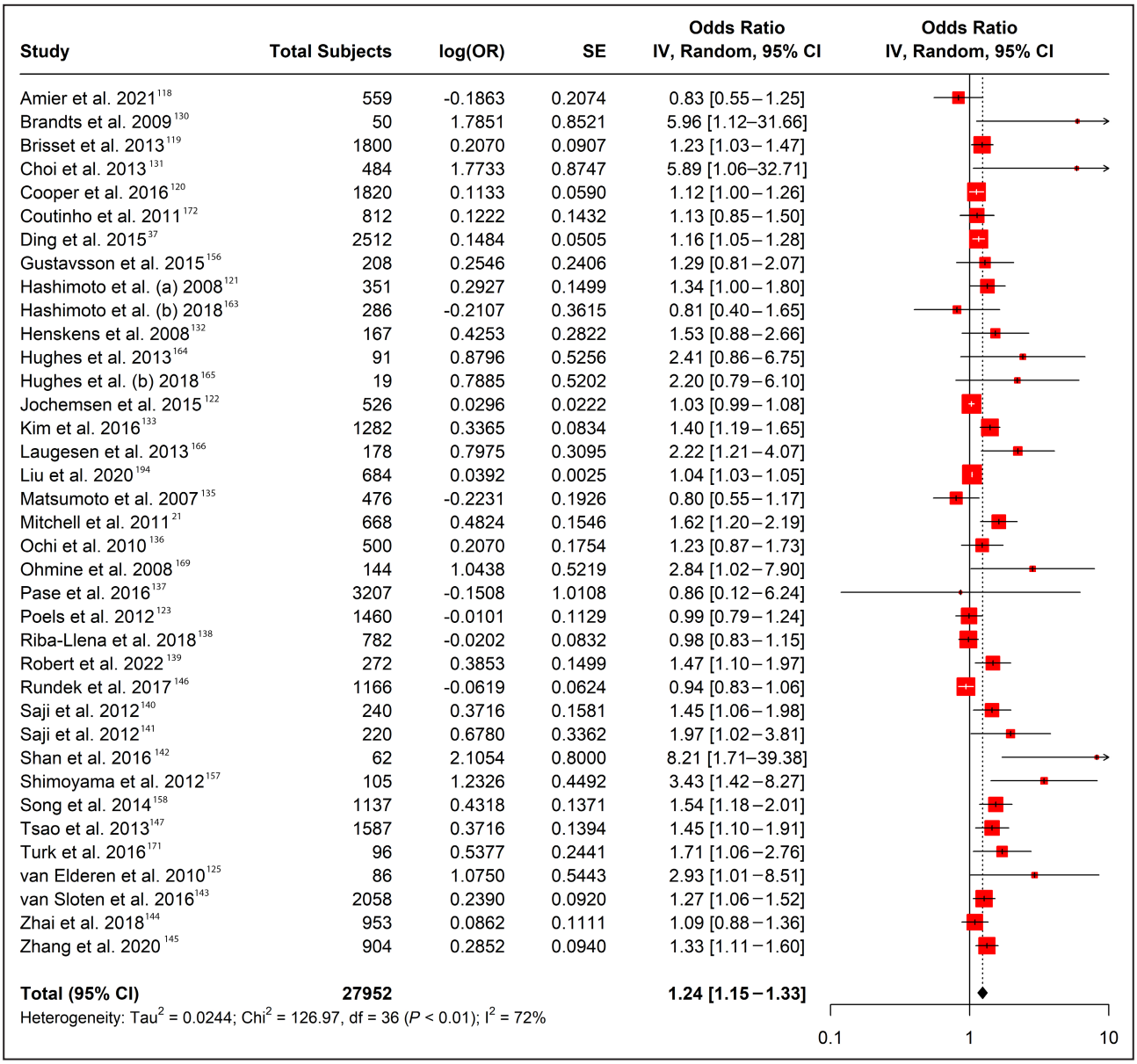

Figure 4. Odds ratio results from pooled studies reporting arterial stiffness as a continuous exposure variable.
Forest plot illustrating the effect sizes for studies reporting continuous arterial stiffness in relation to cSVD burden. Effect sizes are reported per 1-SD increase. The overall effect favored a greater presence of cSVD as arterial stiffness increases (OR, 1.24 [95% CI, 1.15–1.33]). cSVD indicates cerebral small vessel disease; IV, inverse-variance; and OR, odds ratio.

Risk of Bias Assessment and Grading of Recommendations Assessment, Development, and Evaluation Rating of Primary Outcomes

Studies included in quantitative meta-analyses for primary outcomes were assessed for risk of bias using the Newcastle-Ottawa scale. The average risk of bias for studies reporting dichotomous cerebrovascular reactivity was 6.6±1.0, for studies reporting continuous arterial stiffness measures was 8.2±1.0, and for studies reporting dichotomous arterial stiffness was 7.3±1.5. Individual study assessment outcomes are reported in Tables 1 and 3. The Grading of Recommendations Assessment, Development, and Evaluation assessment of the certainty of evidence for the primary outcomes is presented in Table S5.

DISCUSSION

The present systematic review and meta-analyses represent the most recent and updated work summarizing the relationship between cerebral autoregulation,

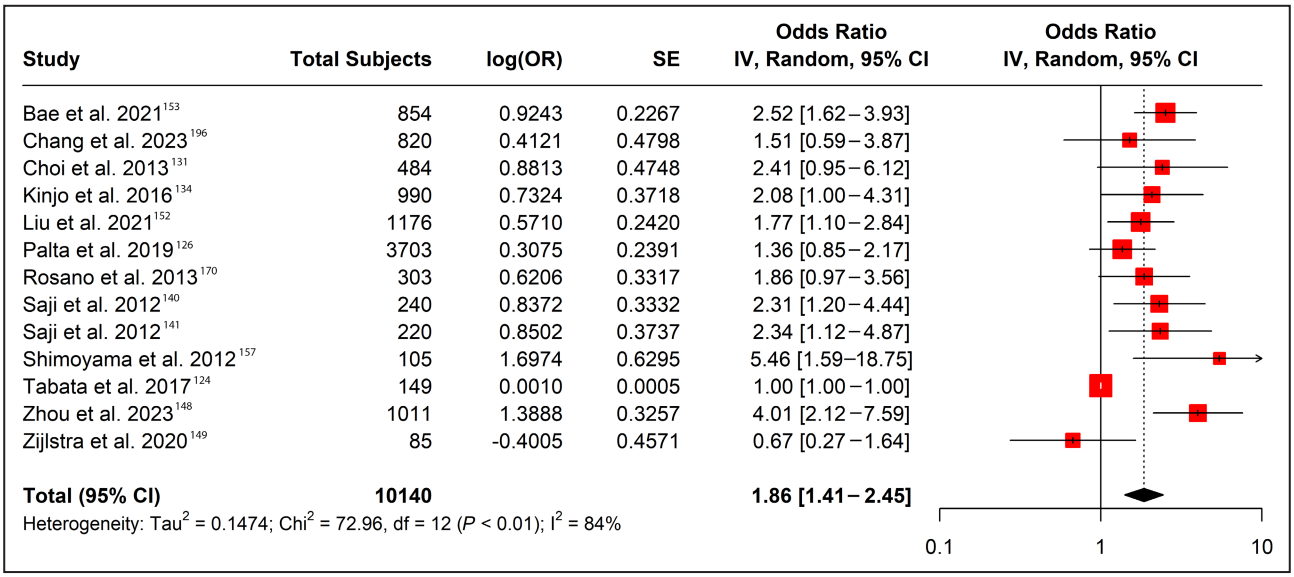

Figure 5. Odds ratio results from pooled studies reporting arterial stiffness as a dichotomous exposure variable.
Forest plot illustrating the effect sizes for studies reporting dichotomous arterial stiffness in relation to cSVD burden. Effect sizes are reported per 1-SD increase. The overall effect suggested a greater arterial stiffness was associated with a greater presence of cSVD (OR, 1.86 [95% CI, 1.41–2.45]). cSVD indicates cerebral small vessel disease; IV, inverse-variance; and OR, odds ratio.

cerebrovascular reactivity, and arterial stiffness in relation to cSVD burden. The main findings of the present systematic review are as follows: (1) the majority of studies included in the qualitative systematic review found associations between cSVD and cerebrovascular reactivity (80.4% of studies), cerebral autoregulation (78.6% of studies), and arterial stiffness (85.4% of studies); and (2) in quantitative meta-analyses, cSVD was associated with increases in arterial stiffness and borderline associated with impaired cerebrovascular reactivity. Although the vast majority of literature, to date, surrounding the risk of cSVD has focused on traditional vascular risk factors, specifically hypertension, their role as dominant factors in the pathogenesis of cSVD has been challenged.[12,202,203] Emerging theories propose complex vascular pathologies, including an impaired cerebrovascular function, as important factors mediating cSVD, alongside or independent of hypertension.[12,18] These relate to the varied complexities of the vascular pathologies proposed for cSVD subtypes, given cerebrovascular regulatory functions are mediated, in part, by local endothelial function[27,28] and arterial stiffness is, in part, dictated by vascular matrix composition and endothelial dysregulation of vascular smooth muscle tone.[17,204,205] Importantly, the collective findings of the present systematic review expand our current understanding of the pathogenesis of cSVD by demonstrating associations of increasing cSVD burden with reductions in cerebrovascular reactivity (37 of 46 studies, or 80.4%), impairments in cerebral autoregulation (11 of 14 studies, or 78.6%), and increases in arterial stiffness (70 of 82 studies, or 85.4%) (Figure 6).

In addition, our subsequent meta-analysis of eligible studies comprising 27 952 participants (53.0% women) revealed a significant association between increases in arterial stiffness and cSVD. In a limited number of studies however, meta-analysis revealed only a borderline association between cerebrovascular reactivity and cSVD. However, the heterogeneity and limited data result in uncertainty as to the strength of these relationships and highlight the need for longitudinal investigations into vascular stiffness and regulatory function as possible risk factors for cSVD.

Cerebrovascular Reactivity

The present study suggests that reduced cerebrovascular reactivity is associated with an increased cSVD burden. As one of the standard measures of cerebrovascular reactivity first used in 1990 by Ratnatunga and Adiseshiah,[207] the breath-hold index has demonstrated predictive capabilities in patients with asymptomatic carotid artery stenosis for the risk of ischemic stroke events.[208] Although typically measured in the context of cerebrovascular disease,[29,209] cerebrovascular reactivity has been previously shown to relate to cardiac arrythmias,[210] cardiorespiratory fitness,[211] and all-cause mortality,[212] which suggests systemic influences. This may be due to the assessment of cerebrovascular reactivity as an indicator of endothelial function, a known predictor of regional and global cardiovascular dysfunction.[27,28]

Although hypertension and other vascular risk factors are often referred to as critical factors in the

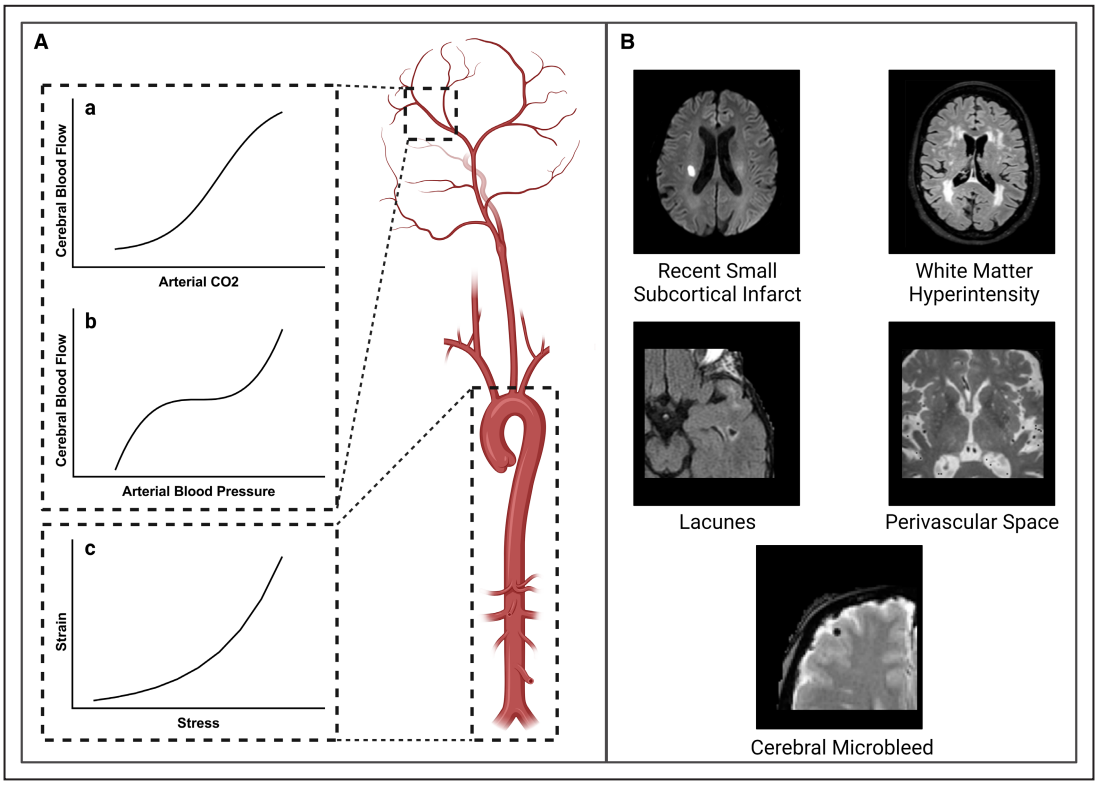

Figure 6. Characterization of arterial stiffness and cerebrovascular regulation in relation to cSVD.
A, Cerebrovascular reactivity is an aspect of the chemo-regulation of cerebral blood flow, where a healthy cerebrovascular system should demonstrate a positive relationship between cerebral blood flow and arterial carbon dioxide content (arterial CO_2). **B**, Cerebral autoregulation is the regulatory process by which the cerebral circulation maintains relatively stable perfusion through a range of arterial blood pressures. **C**, In vivo measurements of arterial stiffness capture incremental stress–strain relationships, describing the overall impact that arterial structural and functional components have on arterial elasticity, buffering of pulsatile pressures, etc. Examples of MRI images depicting the 5 primary radiological markers of cSVD are shown. Created with BioRender.com. MRI images adapted from Bennett et al[206] used under CC BY 4.0. cSVD indicates cerebral small vessel disease; and MRI, magnetic resonance imaging.

development and progression of cSVD, more recent evidence suggests that the cause of cSVD is complex and likely extends beyond arterial blood pressure.[11,12] The hypothesis that the characterization of cSVD may include reductions in cerebrovascular reactivity alongside other risk factors is supported by Molina et al,[51] who reported that in 92 participants, cerebrovascular reactivity and hypertension were both significantly associated with lacunar infarction.

It is worth noting that the limited number of studies available for meta-analysis coupled with different methods of assessing cerebrovascular reactivity could affect the strength of the relationship between cerebrovascular reactivity and cSVD. The wide variability in approaches may have contributed to the considerable heterogeneity (I^2=68%) observed in the meta-analysis of dichotomous cerebrovascular reactivity. Due to the limited number of studies and inconsistencies in determining cutoff values, it was not possible to explore this possible source of heterogeneity further in the present analyses. Adapting a standard approach in future investigations may help establish cerebrovascular reactivity as a functional assessment of the cerebrovasculature for further investigations. Moreover, of the eligible studies for inclusion in the quantitative meta-analysis, we were able to pool the results from only 7 studies out of the 46 included in the systematic review, highlighting a critical need for expansion of the body of evidence.

Cerebral Autoregulation

Cerebral autoregulation is a regulatory mechanism serving to maintain cerebral perfusion throughout a range of physiological variations in perfusion pressure.[32] Of the 14 articles extracted for cerebral autoregulation in the systematic analysis, 11 studies suggested a significant association between impaired cerebral autoregulation and greater cSVD. However, numerous methods exist for determining cerebral autoregulation, limiting formal interpretation across studies. One prominent approach uses frequency domain

transformations of arterial blood pressure and cerebral artery blood velocity, calculating gain and phase from frequency data.[32,33] Other approaches incorporate time domain indices, including moving correlation coefficients between blood pressure and cerebral artery blood velocity.[34] Work beginning less than a decade ago has attempted to establish a standardized approach,[213] but methodological convergence is still progressing.[34,214] Present qualitative findings suggest the possibility of cerebral autoregulatory impairments as a target for understanding the pathophysiology of cSVD. However, the limited number of studies eligible for meta-analysis demonstrates an avenue for future work to expand on the contributions of impaired cerebral autoregulation to cSVD.

Arterial Stiffness

Central arterial stiffening, which occurs with healthy aging and in many pathological states, leads to a diminished impedance gradient between the proximal aorta, carotid arteries, and cerebral vasculature.[17–19] This reduces wave reflection and enhances the transmission of pulsatile waves deeper into the cerebral vascular bed.[18,20] Preclinical models using transverse aortic constriction surgery[215] or a genetic model of arterial stiffness[216] to increase carotid artery pulse pressure have suggested that enhanced cerebrovascular pulsatility impaired endothelium-dependent vasodilation,[216] disrupted blood–brain barrier function, and resulted in cerebral microbleeds.[215] Although our qualitative and quantitative syntheses of studies do not have enough longitudinal information to address the specific underlying pathophysiological mechanisms that precede cSVD development, the significant associations between arterial stiffness, cerebrovascular reactivity, and cSVD demonstrated herein suggest possible mechanisms associated with the presence of cSVD.

Both the continuous arterial stiffness meta-analysis and the dichotomous arterial stiffness meta-analysis displayed significant heterogeneity (I^2=72% and 84%, respectively). To address this, we performed a subanalysis analysis using only the studies that measured cfPWV to support this point, which revealed a heterogeneity numerically less than observed in the primary analysis. Another possible explanation is the challenge of disentangling arterial stiffness from lifestyle factors and comorbidities associated with arterial stiffness and cSVD. Positive lifestyle activities, such as physical activity, have previously been shown to reduce arterial stiffness.[217,218] It is possible that this may have been a factor in studies such as Amier et al[118] or Hashimoto et al,[163] where the average cfPWV values of participants were lower than expected for the sample age and blood pressure.[219] However, physical activity assessments were not commonly reported in presently-included studies, and none incorporated laboratory measurements of gold-standard indices of cardiorespiratory fitness (ie, VO_2 peak or maximal values) that have been shown to be associated with arterial stiffness.[217] We performed meta-regression to investigate further sources of heterogeneity associated with 3 comorbidities (hypertension, diabetes, and hypercholesterolemia), demonstrating that including these 3 study-level covariates explained ≈30% of the overall model heterogeneity. However, caution with interpretation is warranted; these covariates were extracted from study-level data, not individual patient data. Therefore, extrapolation of this information is dependent on the study samples included. Of relevance, the majority of the studies included (20 of the 25, 80%) focused on generally healthy participants with varying proportions of risk factors. In contrast, only 7 of the remaining 12 studies (58%) not included in the meta-regression focused on healthy populations.

An additional cause of heterogeneity in the present study is the different pathogenic processes of the individual cSVD subtypes. In subgroup analyses between arterial stiffness, white matter hyperintensities, and lacunes, the heterogeneity was not significant in the white matter hyperintensity analysis (I^2=31%, P=0.15), whereas the lacune analysis remained considerably heterogeneous (I^2=70%). These findings may be related to a strong dependence of lacunes on age,[144] whereas white matter hyperintensities have been suggested to be associated with arterial stiffness, vascular injury, and blood–brain barrier dysfunction.[4,12,220,221]

Implications

The implications of the present work are that impairments in cerebrovascular regulatory functions and increased arterial stiffness are associated with cSVD burden. Assessing these vascular traits may aid in further understanding the vascular pathologies or pathophysiological progression of cSVD. Despite a prevalence of cSVD that has been suggested to be ≥90% in aging populations,[222] the underlying mechanisms of cSVD are still incompletely understood. Previous literature has established the contributions of high blood pressure and hypertension[223,224] to cSVD. However, studies using antihypertensive medications targeting reductions in cSVD have been sparse[8] and demonstrate overall mixed responses,[225–228] suggesting that additional contributing factors may interact with or independent of hypertension and other traditional comorbidities. In line with the present study's findings, a recent series of randomized controlled trials, LACI-1 and LACI-2 (Lacunar Intervention Trial-1 and Trial-2), demonstrated that treatments targeting vascular endothelial function improved cerebrovascular reactivity in patients with cSVD [229] and improved

their outcomes.[230] Importantly, the results of the present study do not suggest replacing monitoring or treatment of hypertension but suggest that additional assessments of cerebrovascular autoregulation, cerebrovascular reactivity, and/or arterial stiffness may be useful. When assessed alongside traditional cardiovascular measurements (ie, blood pressure testing, echocardiography), incorporating these 3 measures of vascular structure and function in longitudinal studies or studies focusing on clinically relevant populations may provide further critical insight into the underlying pathophysiology that contributes to the development or progression of cSVD.

Study Limitations

There were 3 main limitations in the present study. First, age and hypertension are important cardiovascular risk factors that may contribute to the development or progression of cSVD. These factors also affect the 3 primary measures incorporated into the present review and meta-analyses.[137,163,231–233] Although blood pressure or hypertension may be a confounding factor, many studies adjusted for this. However, it is worth noting that we did not have any randomized-controlled trials in our meta-analyses, which may partly explain discrepancies regarding the impact of hypertension on cSVD.[41,234] Second, there was significant heterogeneity between studies in terms of study population demographics, methods of assessing the primary predictor variable, and the subtype(s) of cSVD used as the outcome. A key possibility that may have affected all 3 primary exposures is the presence of large or small artery disease, such as arterial stenosis. Stenotic intracranial and extracranial arteries have been associated with an increased burden of cSVD[235] alongside separate associations of arterial stenosis with increased arterial stiffness,[236] impaired cerebrovascular reactivity,[237] and impaired cerebral autoregulation.[238] As pointed out in a recent consensus statement,[239] current measures of arterial stenosis do not provide deeper information into the mechanisms linking stenosis and cSVD. Although outside the scope of the present analyses, the findings presented herein suggest that incorporating measures of cerebrovascular regulation and arterial stiffness as mediators of the link between stenosis and cSVD could further our understanding of the pathophysiology. Finally, we acknowledge that there are statistical limitations in using pooled OR as the primary outcome in that these pooled measures may come from different methodological designs and result in high levels of heterogeneity.

CONCLUSIONS

The present systematic review and meta-analyses demonstrate significant associations between impaired cerebrovascular reactivity, increased arterial stiffness, and cSVD. Collectively, the current literature suggests that measurements of cerebrovascular regulation and arterial stiffness may provide feasible means of further investigating the mechanisms involved in the development or progression of cSVD. These findings highlight the utility of vascular assessment in furthering our understanding of the underlying pathophysiology of cSVD.

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Supplemental Material

Tables S1–S5
Figures S1–S13

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