Association between blood pressure variability and cerebral small-vessel disease: a systematic review and meta-analysis

Tully, P.J.; Yano, Y.; Launer, L.J.; Kario, K.; Nagai, M.; Mooijaart, S.P.; ... ; Variability Blood Pressure Brain

Association Between Blood Pressure Variability and Cerebral Small-Vessel Disease: A Systematic Review and Meta-Analysis

Phillip J. Tully, PhD; Yuichiro Yano, MD, PhD; Lenore J. Launer, PhD; Kazuomi Kario, MD, PhD; Michiaki Nagai, MD, PhD; Simon P. Mooijaart, MD, PhD; Jurgen A. H. R. Claassen, MD, PhD; Simona Lattanzi, MD, PhD; Andrew D. Vincent, PhD; Christophe Tzourio, MD, PhD; on behalf of the Variability in Blood Pressure and Brain Health Consortium*

***Background*—**Research links blood pressure variability (BPV) with stroke; however, the association with cerebral small-vessel disease (CSVD) remains unclear. As BPV and mean blood pressure are interrelated, it remains uncertain whether BPV adds additional information to understanding cerebrovascular morphological characteristics.

***Methods and Results*—**A systematic review was performed from inception until March 3, 2019. Eligibility criteria included population, adults without stroke (<4 weeks); exposure, BPV quantified by any metric over any duration; comparison, (1) low versus high or mean BPV and (2) people with versus without CSVD; and outcomes, (1) CSVD as subcortical infarct, lacunae, white matter hyperintensities, cerebral microbleeds, or enlarged perivascular spaces; and (2) standardized mean difference in BPV. A total of 27 articles were meta-analyzed, comprising 12 309 unique brain scans. A total of 31 odds ratios (ORs) were pooled, indicating that higher systolic BPV was associated with higher odds for CSVD (OR, 1.27; 95% CI, 1.14–1.42; I^2=85%) independent of mean systolic pressure. Likewise, higher diastolic BPV was associated with higher odds for CSVD (OR, 1.30; 95% CI, 1.14–1.48; I^2=53%) independent of mean diastolic pressure. There was no evidence of a pairwise interaction between systolic/diastolic and BPV/mean ORs (*P*=0.47), nor a difference between BPV versus mean pressure ORs (*P*=0.58). Fifty-four standardized mean differences were pooled and provided similar results for pairwise interaction (*P*=0.38) and difference between standardized mean differences (*P*=0.70).

***Conclusions*—**On the basis of the available studies, BPV was associated with CSVD independent of mean blood pressure. However, more high-quality longitudinal data are required to elucidate whether BPV contributes unique variance to CSVD morphological characteristics. **(*J Am Heart Assoc*. 2020;9:e013841. DOI: 10.1161/JAHA.119.013841.)**

Key Words: blood pressure measurement/monitoring • blood pressure variability • high blood pressure • meta-analysis • systematic review • white matter disease

Epidemiological studies show that cerebral small-vessel disease (CSVD) subtypes are a common incidental finding from brain imaging among older populations.[1–6] Regularly identified CSVD subtypes include white matter hyperintensities (WMHs), lacunae of presumed vascular origin (LPVO), cerebral microbleeds (CMBs), and enlarged perivascular spaces (EPVSs).[7] The heightened risk for stroke, dementia, depression, and mortality attributable to CSVD[8–10] underscores the importance of identifying modifiable vascular risk factors for the development and

From the Freemasons Foundation Centre for Men's Health, School of Medicine, The University of Adelaide, Australia (P.J.T., A.D.V.); Community and Family Medicine, Duke University, Durham, NC (Y.Y.); Intramural Research Program, National Institute on Aging, National Institutes of Health, Bethesda, MD (L.J.L.); Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan (K.K.); Department of Cardiology, Hiroshima City Asa Hospital, Hiroshima, Japan (M.N.); Department of Gerontology and Geriatrics, Leiden University Medical Center, Institute for Evidence-Based Medicine in Old Age, Leiden, the Netherlands (S.P.M.); Radboud Alzheimer Center and Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands (J.A.H.R.C.); Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy (S.L.); and Bordeaux Population Health, University of Bordeaux, Inserm, Team HEALTHY, UMR 1219, CHU Bordeaux, Bordeaux, France (C.T.).

Accompanying Data S1, Tables S1 through S12, and Figures S1 through S5 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013841

*A complete list of the Variability in Blood Pressure and Brain Consortium members can be found in the Appendix at the end of the article.

Correspondence to: Phillip J. Tully, PhD, Freemasons Foundation Centre for Men's Health, School of Medicine, Level 6 Allied Health and Medical Sciences (AHMS) Building, The University of Adelaide, Adelaide SA 5005, Australia. E-mail: phillip.tully@adelaide.edu.au

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Clinical Perspective

What Is New?

- Blood pressure (BP) variability was associated with cerebral small-vessel disease independent of mean BP in a pooled meta-analysis of 27 articles and 12 309 unique brain scans.
- There was no evidence of a pairwise interaction between systolic/diastolic and BP variability/mean BP effect sizes.
- The strength of evidence was rated as low for all primary outcomes.

What Are the Clinical Implications?

- The association between BP variability with cerebral small-vessel disease, independent of mean BP, may have implications for the monitoring of BP and selection of antihypertensive drugs that minimize BP variability in people with cerebral small-vessel disease.
- The strength of evidence was too low to make definitive clinical recommendations.

progression of CSVD to inform vascular risk management among at-risk populations.[11] Principle among vascular risk factors for CSVD, and its clinical sequelae stroke and dementia, is hypertension.[12–14] Randomized controlled trials (RCTs) and cohort studies provide mixed findings as to whether elevated blood pressure (BP) and its management with antihypertensive drugs mitigate CSVD risk and progression of CSVD.[15–19] The inconsistency in findings raise the possibility that factors beyond absolute BP level or treat-to-target BP could be important for CSVD development and progression.

A body of empirical work indicates that oscillation in BP between consecutive measures holds additional prognostic significance, alongside mean BP level, to predict subclinical target organ damage, including in the brain.[20,21] Once considered background "noise" or measurement error, intraindividual BP variation, known as BP variability (BPV), holds prognostic value to predict incident and recurrent stroke.[22–24] Higher BPV has indirect effects on the brain, including compromised cerebral autoregulation and transient hypoperfusion.[25,26] Recent interest in BPV's association with brain morphological characteristics[27,28] and dementia,[29,30] and debate surrounding the clinical relevance of BPV to stroke[31,32] and how to define and analyze BPV,[33,34] underscores the topical nature of BPV to brain health.

Previous meta-analyses on BPV reported associations with acute stroke and transient ischemic attack (TIA),[24,35] headache,[36] atrial fibrillation,[37] left ventricular mass index,[38] mortality,[39] cardiovascular outcomes,[40] and multiple end points, including, stroke, mortality, and cardiovascular outcomes.[41] Other systematic reviews and guidelines have focused on the statistical methods and technical aspects of quantifying BPV.[34,42,43] This systematic review adds to previous reviews by quantifying the association between BPV with CSVD using meta-analytic techniques. The objective of this review is to quantify the association between intraindividual BPV and CSVD in populations without recent stroke (subacute <4 weeks). A second objective is to compare the magnitude of association between BPV and CSVD with the effect sizes for mean BP, in studies reporting BPV.

Methods

Search Strategy

This review conforms to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Table S1).[44] A protocol was registered on PROSPERO (International Prospective Register of Systematic Reviews) (CRD42017081974). A systematic search of the MEDLINE, EMBASE, and SCOPUS electronic databases was performed from database inception without language restrictions; the last search was performed on March 3, 2019 (search string Table S2). Studies from database inception were eligible, as we had no a priori justification to limit studies to a certain era. The authors declare that all supporting data are available within the article and its online supplementary files (Data S1).

Eligibility Criteria

Population

The population of interest included participants aged ≥18 years who had BP quantified using a standardized measure, in which intraindividual BPV (systolic, diastolic, or both) was calculated and participants underwent brain imaging to determine CSVD (defined further below) by computed tomography (CT) or magnetic resonance imaging (MRI). Quantification of mean BP within samples, although desirable for our comparative analysis, was not a prespecified inclusion criterion, nor was the reporting of hypertension or systolic/diastolic load. Likewise, the use of BPV metrics accounting for interdependence with mean BP was not a prespecified inclusion criterion (eg, variance independent of the mean). Studies including people with a past stroke or TIA were eligible if: (1) the measurement of BPV and CSVD was not in the subacute stage (ie, <4 weeks) after a cerebral event requiring hospitalization and (2) the point prevalence of previous stroke or TIA did not exceed 50% of the sample. The rationale was that impaired BP

regulation in the acute and subacute stage would likely be a consequence of stroke[45] and that the association between BPV with stroke outcomes has already been extensively quantified by meta-analysis.[23,24]

Comparator/control

A bidirectional association was considered between BPV and CSVD. The analyses used comparator groups consisting of people with low BPV versus high BPV for outcome 1 and people without CSVD or with low severity of CSVD for the comparison of BPV means in outcome 2.

Outcomes

1. The association between BPV in any metric (independent variable) with the presence of CSVD determined by brain imaging with CT or MRI (dependent variable). CSVD subtypes were considered in the following categories:

Recent small subcortical infarct: ≤20 mm in the territory of one perforating arteriole.

LPVO: 3- to 15-mm round or ovoid, subcortical, fluid-filled cavity (similar signal as cerebrospinal fluid), consistent with a previous acute small deep brain infarct or hemorrhage in the territory of one perforating arteriole with hyperintense rim.[7]

Cerebral white matter changes or hyperintensity: hyperintense on T2-weighted sequences, isointense or hypointense on T1-weighted sequences,[7] or hypodense on CT,[46] determined by either visual grading with a recognized scale (eg, Fazekas, Scheltens, or Rezek)[46,47] or volumetry (fully or semiautomated).

CMBs: small hypointense lesions (round or ovoid blooming; ≤10 mm) that are visible on paramagnetic-sensitive MR sequences, such as T2*-weighted gradient-recalled echo or susceptibility-weighted sequences.[7]

EPVSs: also known as Virchow-Robin spaces, a fluid-filled space ≤2 mm that follows the typical course of a vessel as it goes through gray or white matter, with similar signal intensity to cerebrospinal fluid.[7]

2. Mean difference in BPV (dependent variable) between people with and without CSVD (independent variable). Mean differences were extracted by either the presence or the absence of CSVD or severity (eg, on Fazekas scale). All BPV metrics derived from ambulatory BP monitoring (ABPM), home BP monitoring, or visit-to-visit assessments were eligible on the basis of Rothwell's definition of intraindividual BPV,[22] including but not limited to SD, average real variability, and coefficient of variation.[34]

Study design

Quantitative studies of any design were eligible, including case-control, cohort, database registry, or RCT. No restriction was placed on sample size.

Exclusion Criteria

Studies were excluded if the study was performed on animal subjects; BPV was quantified during the acute or subacute stage (ie, <4 weeks) of stroke or TIA; BPV was reported in the context of BP instability, stress reactivity, or postural change, such as experimental designs with a stress challenge, orthostatic change, or head-up tilt-table testing; the cohort was designed to test the prognosis of coronary revascularization or renal denervation, or the cohort was designed to assess dementia, Parkinson disease, leukodystrophy, or other degenerative neurological disorder prognosis; the report described a case study; effect size data could not be extracted, calculated, or provided by the study authors; or the study reported only brain atrophy or brain volume. Inconsistencies in brain imaging terminology are well documented.[7,48] To optimally harmonize end points, cerebral infarctions >20 mm diameter were excluded from analyses irrespective of terminology (eg, lacunar infarction and lacunar stroke syndrome).

Literature Screening

Three reviewers (P.J.T., K.G., and M.O.) independently screened titles and abstracts of all the retrieved bibliographical records for eligibility using a data abstraction protocol.[49] A hand search was performed of the articles selected for full-text review and of narrative reviews,[50–53] supplementing the electronic search. In the case of title/abstract review disagreements, the study was subjected to full-text review. After determination of the study eligibility, data extraction was undertaken independently by 3 reviewers (P.D.P., K.G., and E.J.L.L.) and verified by a fourth reviewer (P.J.T.) to reduce reviewer errors, reduce bias, and achieve consensus. The data extracted pertained to study identification (first author, year of publication, country where recruitment took place, and name of study or trial), study design characteristics (sample size and study design) of the population under study (age, sex, use of antihypertensive medication, and prevalence of stroke), BP and BPV exposure (type of measure, BPV metrics, duration of BP measures, and observation period), CSVD adjudication (subtypes and definition and imaging methods), effect size (most adjusted effect size or raw numbers) adjustment for covariates (list of variables), and funding (grant numbers or acknowledgement).

A request for additional published, unpublished, and in progress articles was sent through the Variability in Blood Pressure and Brain Health consortium (members listed in acknowledgements).[54] The principal investigators of eligible studies were contacted to clarify published and unpublished data and duplicate articles. Study authors were contacted via e-mail to request the unreported data. If the initial e-mail was

not replied to within 2 weeks, a second e-mail was subsequently sent. Confirmation of ineligible data was provided by 1 author,[55] eligibility was confirmed for 2 studies,[56,57] and additional unpublished data were provided by 2 studies.[58,59]

Risk of Bias

The RTI item bank was used to identify methodological bias for primary outcomes 1 and 2 for all studies.[60] Risk of bias assessment was undertaken by 2 reviewers (E.J.L.L. and P.J.T.) with consensus achieved after discussion. Adjudication of the strength of evidence for the primary CSVD outcome and between-group differences was made according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria with GRADE Profiler 3.6.1.[61]

CSVD Grouping and Outcome Adjudication

1. *Primary outcome odds for CSVD attributable to BPV:* If BPV's association with CSVD was reported for >1 CSVD subtype, we prioritized the analysis with the largest number of CSVD end points, handling CSVD subtypes in stratified analyses. If models were adjusted, we extracted data from the most adjusted model. In instances where different levels of adjustment were made for mean and BPV data, we prioritized data from the same model to ensure equivalence in covariate adjustment. When >1 BPV metric was reported for CSVD subtypes, we prioritized the most adjusted model and models with the largest number of participants. If multiple metrics were available after applying this hierarchy, we extracted both outcomes and reported in sensitivity analyses.

2. *Difference between groups in CSVD:* If BPV mean±SD was reported in different CSVD pathological conditions or severities, the subgroup with the highest N was used, prioritizing statistical power over severity,[62] ensuring one effect size was analyzed per study rather than collapsing CSVD groups.[63] For the mean difference between CSVD groups, we prioritized the most common method of BPV in primary analyses (SD method) and reported other metrics in sensitivity analyses.

1 and 2. BPV data were extracted and prioritized in order, as follows: 24-hour ABPM, awake ABPM measures (versus sleep), office/clinic/casual (commonly referred to as visit to visit), and home BP monitoring.

Mean BP

Mean BP data were extracted for eligible studies. Odds ratios (ORs) and risk ratios for CSVD were standardized to 10/5–mm Hg increase, multiplying the log of the summary statistic by 10/5, depending on whether systolic BP or diastolic BP was being modeled. It was not possible to standardize the OR effect sizes per SD increase because of inconsistent reporting in the original studies. Between CSVD group differences in BP were modeled with standardized mean differences (SMDs); thus, no standardization was necessary.

Statistical Analysis

Primary outcome 1 was analyzed in R, version 3.5.2, using the *metafor* package. A multilevel meta-analysis was performed.[64] A key advantage of a multilevel meta-analysis, compared with a traditional meta-analysis, is that a single study contributes multiple effect sizes (eg, systolic BP, systolic BPV, diastolic BP, and diastolic BPV). Moreover, a multilevel meta-analysis accounts for the dependence in effect sizes within a study (ie, between BPV and mean BP, from which BPV is often calculated; and dependence of systolic and diastolic BP). A mixed effects model, with a random intercept per study, tested fixed effect moderators for BP type (diastolic versus systolic) and measure (mean versus variability) and their pairwise interaction. The heterogeneous CSVD subtypes were pooled together in the first instance as each is presumed to have a predominant ischemic origin[7] and CSVD is considered a whole-brain disease.[48] Likewise, ABPM, home, and visit-to-visit variability data were pooled together, consistent with a previous review,[41] as short- and longer-term BPVs are correlated[65] and share some postulated mechanisms, such as arterial reflex and compliance, and dosing/titration of antihypertensive drugs.[21] Original data pertaining to the likelihood of CSVD were reported as OR and risk ratio with 95% CIs. The estimates were pooled together in a meta-analysis because they are presumed to measure the same underlying effect,[66] and consensus exists that these are approximately equivalent for effect sizes <2.5 and follow-up <20 years.[67] Primary outcome 1 was analyzed stratified by CSVD subtype, BPV metric, day versus night ABPM measures, oscillometric versus auscultatory method of BP measurement, ABPM versus home or visit-to-visit BPV, visit-to-visit interval <6 and >6 months, use of MRI versus CT with or without MRI, and Asian versus non-Asian populations in ancillary analyses with RevMan, version 5.3.[68] The latter stratification is because of the purported higher morning surge component of BPV among Asian populations.[69]

The association between BPV and WMHs was modeled with RevMan, version 5.3,[68] for *d* family effect sizes and Comprehensive Meta-Analysis software[70] for *r* family effect sizes. To demonstrate the association between BPV and the CSVD subtype of WMH, the study effect sizes was reported as *r* (continuous outcome but no grouping by BPV) or *d* family (continuous or dichotomized, with grouping by BPV). Because no BPV subgroups were reported in the *r* family studies, the effect sizes were ineligible for combined pooling and were,

thus, pooled separately. The *r* family effect sizes were pooled with Comprehensive Meta-Analysis (CMA) software, which converts *r* values to Fisher Z distribution. In the studies where standardized β values were reported,[28,63,71,72] these values were converted to *r* using the formula outlined by Peterson and Brown[73]: $r=0.98\beta+0.05\lambda$, where λ is an indicator variable that equals 1 when β is nonnegative and 0 when β is negative. The formula applies to β values between −0.50 and 0.50.

The SMD in BPV between people with and without CSVD was pooled in R, version 3.5.2, using the *metafor* package, testing mixed effects models with a random intercept per study and fixed effect moderators for BP type (diastolic versus systolic) and measure (mean versus variability) and their pairwise interaction. The effect sizes (Hedges *g*) were interpreted according to Cohen's[74] criteria: 0.2 represents a small effect; 0.5, a moderate effect; and 0.8, a large effect. In studies that reported BPV mean and no SD or SE (eg, interquartile range), we calculated the *t*-statistic using the *P* value with RevMan and then calculated the SMD using the methods outlined by Hedges and Olkin.[75] SMD analyses were stratified by BPV metric, day versus night ABPM measures, oscillometric versus auscultatory method of BP measurement, ABPM versus home or visit-to-visit BPV, visit-to-visit interval <6 and >6 months, use of MRI versus CT, and Asian versus non-Asian populations in ancillary analyses using RevMan.

Random effects models (inverse-variance method) were used regardless of statistical heterogeneity under the assumption of high sampling variability between studies, different BPV metrics, and CSVD outcomes.[34] Statistical heterogeneity was evaluated with the I^2 statistic: I^2=0%–60% (not important to moderate), and I^2 >60% (substantial statistical heterogeneity).[76] Methodological heterogeneity was explored with meta-regression in relation to the primary outcomes, examining mean or median age, proportion of women, antihypertensive treatment or hypertension, prevalence of previous stroke or TIA, body mass index (kg/m^2), and tesla size of MRI (coded 0 for CT). It was not possible to perform a meta-regression with BP dipping because of inconsistent reporting within studies. The presence of publication bias was evaluated with the test of Egger et al,[77] the test of Begg and Mazumdar,[78] and Duval and Tweedie's trim-and-fill funnel plot.[79]

Results

Study Selection and Characteristics

The search yielded 8304 citations, from which 51 were reviewed in detail and 27 articles were retained (Table S3 and Figure S1). One study was close to meeting the inclusion threshold[80]; however, in this study, BPV was reported in relation to white matter integrity and brain health, quantified with fractional anisotropy. The 27 included articles reported on 26 unique samples, comprising a pooled sample of 12 309 unique brain scans, a mean sample size of 473 participants per study, a mean age of 73.0±5.2 years, 48.8±17.6% women, a mean 55.8±27.1% with hypertension or using antihypertensive treatment, a 5.1% stroke prevalence at baseline, and a mean body mass index of 26.2±1.9 kg/m^2 (study characteristics in Tables S4 and S5). The included studies originated primarily from Asia (10 studies), Europe (9 studies), and North America (7 studies), with 1 of these recruiting Americans with Japanese ancestry.[81] Studies were mostly cohort designs (13 studies), cross-sectional (6 studies), or case-control (5 studies). One sample was reported as both cross-sectional and cohort, and 1 study was RCT design. Most studies used MRI, 3 studies used CT, and only 1 study used MRI and CT. In 1 study, the imaging protocol was unclear. The studies using CT only reported data for analysis of primary outcome 2, SMDs in BPV. Most studies quantified WMH (n=20) or LPVO (n=7), with 6 studies including multiple CSVD outcomes, and few studies quantified CMBs or EPVSs (Table S6).

Assessment of Risk of Bias

The adjudication of risk of bias and precision is provided in Table S7. In 10 studies, inclusion criteria were insufficiently described. Seven studies were deemed underpowered to detect an effect size for the primary outcomes. Most studies (n=21) reported blinded outcome adjudication. Generally, BP was assessed with reliable methods, such as ABPM or clinic visit to visit with standardized protocols; 3 studies were rated as low for description of exposure.

Primary Outcome 1: Association Between BPV and CSVD

Systolic and diastolic BPV and risk for CSVD

A total of 31 estimated ORs were reported: 13 for systolic BPV, 9 for mean systolic BP, 6 for diastolic BPV, and 3 for diastolic BP. Higher systolic BPV was associated with higher odds for CSVD (OR, 1.27; 95% CI, 1.14–1.42; I^2=85%), independent of mean systolic BP per 10–mm Hg increase (OR, 1.17; 95% CI, 1. 09–1.25; I^2=52%) (Figure 1). Likewise, higher diastolic BPV was significantly associated with higher odds for CSVD (OR, 1.30; 95% CI, 1.14–1.48; I^2=53%), independent of mean diastolic BP per 5–mm Hg increase (OR, 1.14; 95% CI, 1.10–1.19; I^2=0%). There was no evidence of a pairwise interaction between BP type (diastolic versus systolic) and measure (mean versus variability; *P*=0.47; Akaike information criterion=−1.5), nor was there evidence of a difference between measures (mean versus variability; *P*=0.58; Akaike information criterion=−6.6).

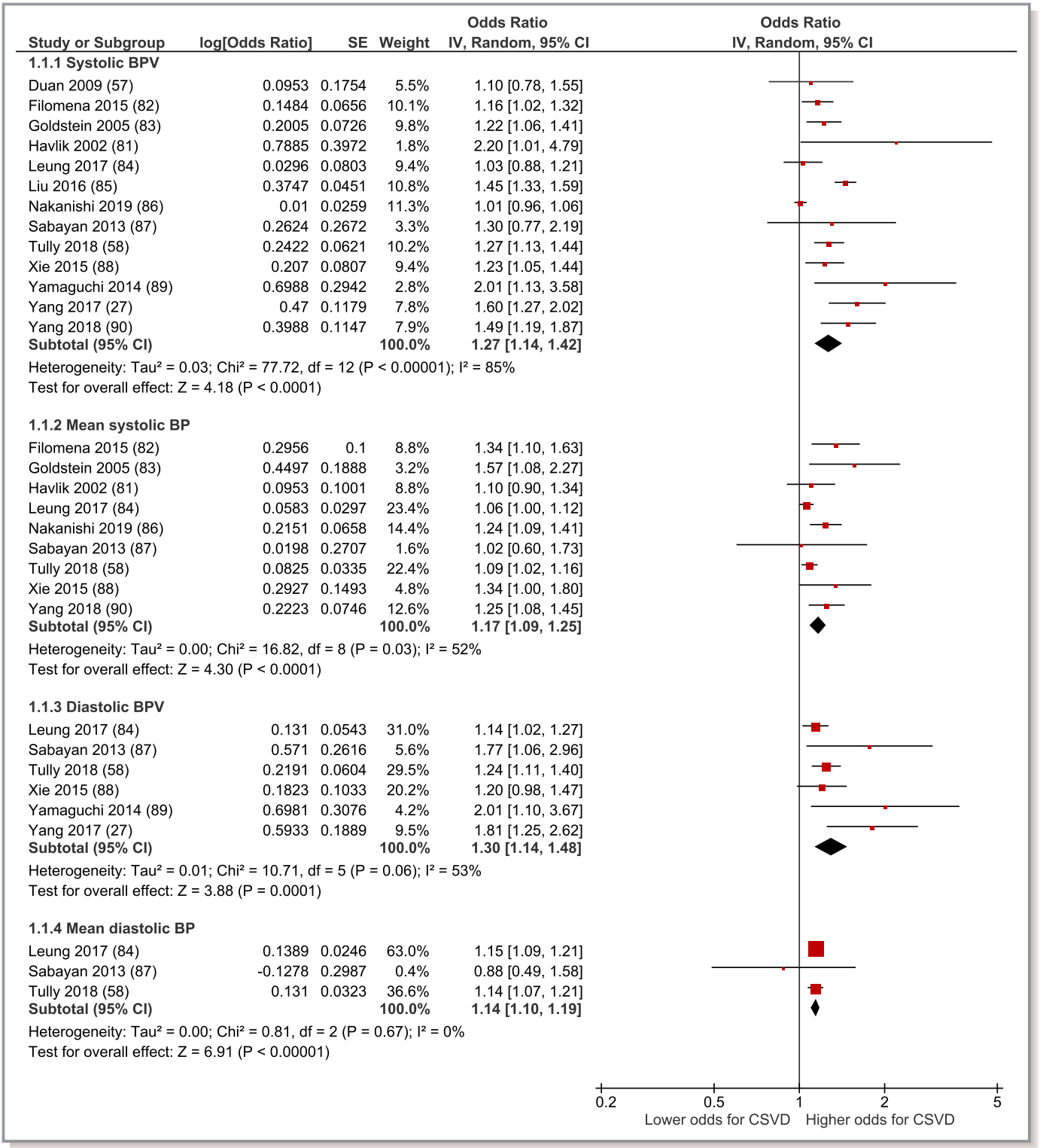

Figure 1. Forest plot showing the association between blood pressure variability (BPV) and mean blood pressure (BP) with odds for cerebral small-vessel disease (CSVD). Data are presented numerically (log odds ratio [OR] and SE) and graphically (forest plot), showing the CSVD risk in each of the included studies and the pooled effect size, stratified by systolic BPV and mean systolic BP per 10–mm Hg increase and diastolic BPV and mean diastolic BP per 5–mm Hg increase. Effect sizes are presented graphically (OR and 95% CI), and those to the right of the vertical line (OR=1) indicate higher odds for CSVD. Data were pooled together using the inverse variance method with random effects. IV indicates inverse variance.

Primary Outcome 2: Between CSVD Group Comparison on Mean BPV

Systolic and diastolic BPV and mean BPV

Fifty-four SMDs were reported between individuals with and without CSVD: 15 for systolic BPV, 13 for mean systolic BP, 14 for diastolic BPV, and 12 for diastolic mean BP. Systolic BPV was significantly higher in CSVD populations compared with their non-CSVD counterparts (g=0.21; 95% CI, 0.13–0.28; I^2=28%), as was mean systolic BP (g=0.28; 95% CI, 0.18–0.38; I^2=44%); however, the effect sizes were small (Figure 2). Likewise, diastolic BPV was higher in people with CSVD compared with their non-CSVD counterparts (g=0.13; 95% CI, 0.08–0.19; I^2=0%), as was mean diastolic BP (g=0.12; 95% CI, −0.00 to 0.24; I^2=66%), although effect sizes were small. There was no evidence of a pairwise interaction between BP type (diastolic versus systolic) and measure (mean versus variability; P=0.38; Akaike information criterion=−13.4), nor was there evidence of a difference between measures (mean versus variability; P=0.70; Akaike information criterion=−18.4).

Meta-Regression

The meta-regression results on the primary outcomes are presented in Table S8. Odds for CSVD attributable to systolic BPV were associated with increased age, nonuse of antihypertensives or hypertension, stroke prevalence, body mass index, and increased tesla of MRI. Odds for CSVD attributable to diastolic BPV were associated with younger age and stroke prevalence. Difference between people with and without CSVD in systolic BPV was associated with younger age, whereas difference between CSVD groups in diastolic BPV was associated with female sex; the effect for MRI tesla was marginal (P=0.061).

Publication Bias and GRADE Rating of Primary Outcomes

Evidence of publication bias was suspected for odds of CSVD attributable to systolic and diastolic BPV, evidenced by the test of Egger et al[77] and the funnel plot trim-and-fill method, although only 6 diastolic BPV studies were retrieved by our systematic review (Table S9 and Figures S2 through S5). GRADE rating of the quality of evidence was low for all outcomes across systolic and diastolic BPV metrics (Table S10).

Ancillary Analyses

The ancillary analyses stratified by CSVD subtype are presented online (Tables S11 and S12). Ancillary analyses by BPV metric, day versus night ABPM measures, ABPM versus home or visit-to-visit BPV, visit-to-visit interval <6 and >6 months, use of MRI versus CT with or without MRI, and Asian versus non-Asian populations are reported in Tables 1[82–90] and 2.[91–98] The ancillary analyses supported an association between systolic BPV with total and periventricular WMH, but not other subtypes. The association between systolic and diastolic BPV in primary outcomes 1 and 2 was generally replicated and consistent when stratified by different methodological factors. Specifically, primary outcome 1 demonstrated comparable magnitude of ORs when stratified by day versus night and 24-hour ABPM versus home BP monitoring and visit-to-visit BPV. There was, however, evidence of heterogeneity between Asian and non-Asian systolic BPV effect sizes for primary outcome 1. Likewise, for primary outcome 2, comparable magnitude of SMDs was evident when analyses were stratified by day versus night and 24-hour ABPM versus home BP monitoring and visit-to-visit BPV, as well as Asian versus non-Asian populations.

Discussion

This systematic review and meta-analysis indicated a higher odds for CSVD attributable to systolic BPV, independent of mean BP. Published data were significant but sparse for diastolic BPV and CSVD risk. When SMDs in BPV were compared between people with and without CSVD, higher systolic and diastolic BPV means were evident in CSVD populations, independent of mean BP. There was no evidence of a pairwise interaction between BP type (diastolic versus systolic) and measure (mean versus variability), nor was there evidence of a difference between measures (mean versus variability) for primary outcomes 1 and 2. Collectively, these findings suggest that BPV is associated with CSVD, independent of mean BP, in the retained articles. The findings were derived from mainly cross-sectional articles, with moderate to high heterogeneity and suspicion of publications bias; therefore, the GRADE rating of evidence was low for all primary outcomes.

The association between BPV with CSVD reported herein sits alongside previous BPV systematic reviews relating to neurological outcomes, including acute stroke or TIA[24] and headache.[36] Rothwell and colleagues[23] demonstrated the predictive utility of BPV in relation to incident and recurrent strokes by investigating ratio of variances and variance independent of the mean among antihypertensive drug versus placebo RCTs. By contrast, our review included only included 1 RCT, which might explain why the use of antihypertensive drug or hypertension prevalence at baseline was largely unrelated to CSVD effect sizes in the meta-regression. Differential effects of antihypertensive drug classes on BPV

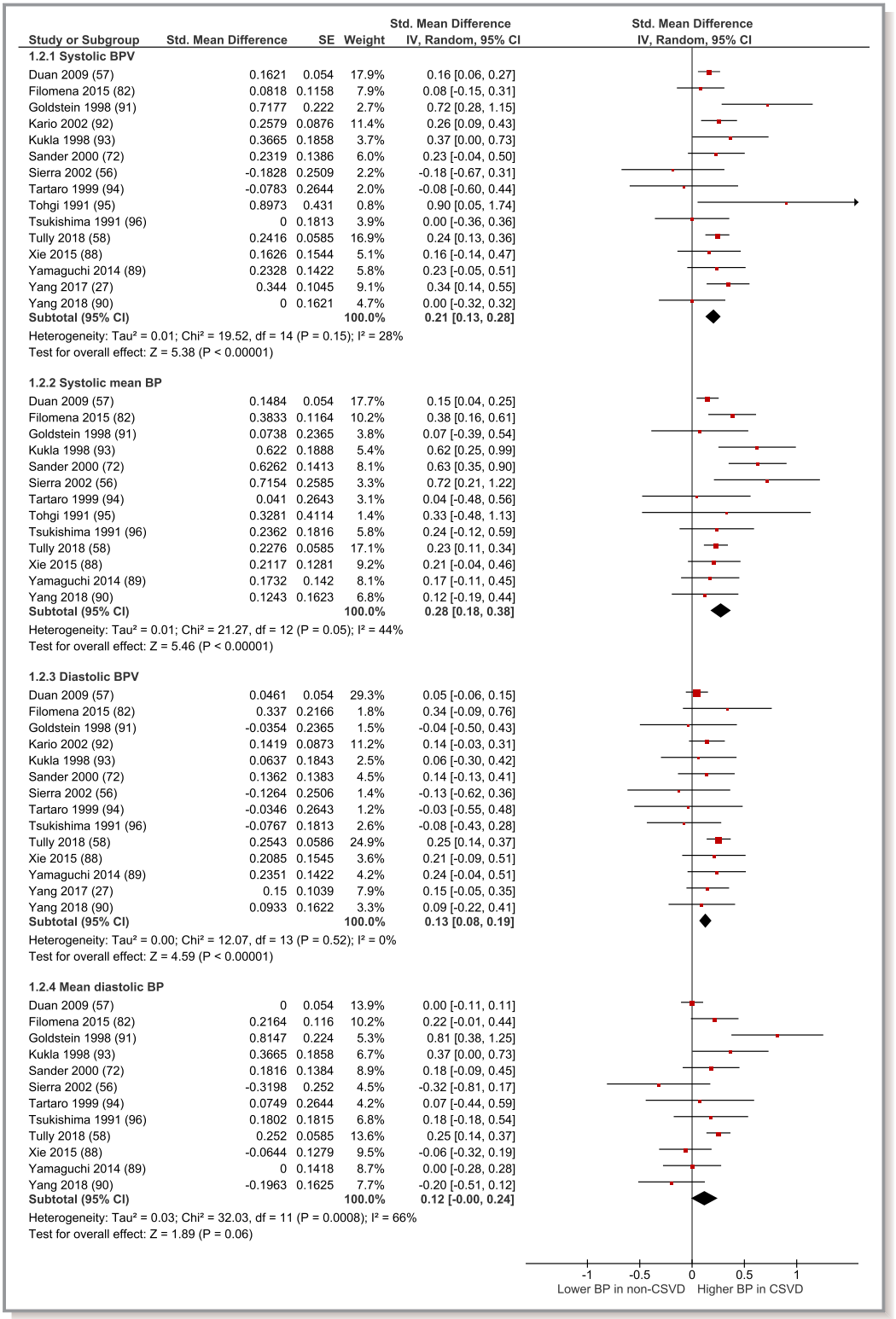

Figure 2. Forest plot showing the standardized mean difference (SMD) between cerebral small-vessel disease (CSVD) groups on blood pressure variability (BPV) and mean blood pressure (BP). Data are presented numerically (SMD as Hedges *g* and SE) and graphically (forest plot), showing the between CSVD group difference in each of the included studies and the pooled effect size, stratified by systolic BPV and mean systolic BP and diastolic BPV and mean diastolic BP. Effect sizes are presented graphically (Hedges *g* and 95% CI), and those to the right of the vertical line (SMD=0) indicate higher systolic BPV or BP in populations with CSVD. Data were pooled together using the inverse variance method with random effects. IV indicates inverse variance.

Table 1. Ancillary Analysis Results for Odds of CSVD, Stratified by BPV Metric, BP Measurement, and CSVD Assessment

BP Measure	Type of BPV Metric	No. of Studies[References]	OR	95% CI	I^2
Systolic	SD	6[27,57,83,88–90]	1.28*	1.19–1.39*	0
	Weighted SD	2[89,90]	1.75*	1.38–2.22*	0
	Coefficient of variation	6[27,58,86,88–90]	1.36*	1.12–1.67*	88
	Variance independent of the mean	1[88]	1.23	1.05–1.44	…
	Successive variation	1[88]	1.00	0.91–1.10	…
	Average real variability	2[82,89]	1.18 *	1.03–1.35*	2
	Variance in residuals	2[81,84]	1.36	0.66–2.79	71
	Oscillometric	10[27,57,58,82,83,85–87,89,90]	1.29*	1.13–1.48*	88
	Auscultatory	3[81,84,88]	1.18	0.95–1.46	62
	Day†	4[27,82,83,90]	1.25*	1.08–1.46*	72
	Night†	4[27,82,83,90]	1.19*	1.05–1.34*	63
	24-h ABPM	7[27,57,82,83,86,89,90]	1.26*	1.09–1.47*	82
	HBPM and visit to visit	6[58,81,84,85,87,88]	1.27*	1.11–1.45*	70
	Visit-to-visit BP interval <6 mo	2[87,88]	1.24*	1.06–1.44*	0
	Visit-to-visit BP interval >6 mo	3[58,81,84]	1.21	0.96–1.51	71
	MRI only	13[27,57,58,81–90]	1.27*	1.14–1.42*	85
	CT with or without MRI	…	…	…	…
	Primarily Asian	7[27,57,62,81,88–90]	1.42*	1.27–1.58*	36
	Non-Asian	6[58,82,84,86,87,97]	1.13 *	1.02–1.26*	73
Diastolic	SD	2[88,89]	1.24*	1.03–1.50*	0
	Weighted SD	1[89]	1.97	1.06–3.66	…
	Coefficient of variation	4[27,58,88,89]	1.33*	1.10–1.60*	63
	Variance independent of the mean	1[88]	1.20	0.98–1.47	…
	Successive variation	1[88]	1.08	0.95–1.23	…
	Average real variability	1[89]	1.56	0.89–2.73	
	Variance in residuals	…	…	…	…
	Day†	2[27,90]	1.46*	1.23–1.74*	0
	Night†	2[27,90]	1.27*	1.11–1.47*	23
	Oscillometric	4[27,58,87,89]	1.56*	1.19–2.04*	56
	Auscultatory	2[84,88]	1.15	1.05–1.27	0
	24-h ABPM	2[27,89]	1.86 *	1.36–2.55*	0
	HBPM and visit to visit	4[58,84,87,88]	1.22*	1.14–1.31*	13
	Visit-to-visit BP interval <6 mo	2[87,88]	1.35	0.95–1.92	48
	Visit-to-visit BP interval >6 mo	2[58,84]	1.19*	1.09–1.29*	15
	MRI only	6[27,58,84,87–89]	1.30*	1.14–1.48*	53
	CT with or without MRI	…	…	…	…
	Primarily Asian	3[27,88,89]	1.53 *	1.08–2.16*	63
	Non-Asian	3[58,84,87]	1.21*	1.08–1.37*	42

ABPM indicates ambulatory BP monitoring; BP, blood pressure; BPV, BP variability; CSVD, cerebral small-vessel disease; CT, computed tomography; HBPM, home BP monitoring; MRI, magnetic resonance imaging; OR, odds ratio.

*Significant values (when ≥2 studies).

†Any metric of BPV recorded from ABPM and subdivided by day and night measures.

Table 2. Ancillary Analysis Results for SMDs in BPV, Stratified by BPV Metric, BP Measurement, and CSVD Assessment

BP Measure	Type of BPV Metric	No. of Studies[References]	Hedges *g*	95% CI	I^2
Systolic	SD	12[27,56,57,72,82,88–91,93–95]	0.17*	0.09 to 0.26*	9
	Weighted SD	4[57,82,89,90]	0.17*	0.09 to 0.26*	0
	Coefficient of variation	9[27,58,82,88–90,94–96]	0.21*	0.12 to 0.30*	14
	Variance independent of the mean	1[88]	0.13	−0.17 to 0.43	…
	Successive variation	1[88]	0.15	−0.15 to 0.45	…
	Average real variability	2[82,89]	0.35*	0.18 to 0.53*	0
	Variance in residuals	…	…	…	…
	Day†	6[27,57,82,90,91,94]	0.13*	0.03 to 0.23*	17
	Night†	6[27,57,82,90,91,94]	0.21*	0.08 to 0.35*	35
	Oscillometric	13[27,56–58,72,82,89–95]	0.22*	0.14 to 0.30*	34
	Auscultatory	2[88,96]	0.09	−0.14 to 0.32	0
	24-h ABPM	12[27,56,57,72,82,90–95]	0.22*	0.12 to 0.31*	38
	HBPM and visit to visit	3[58,88,96]	0.21*	0.11 to 0.31*	0
	Visit-to-visit BP interval <6 mo	1[88]	0.16	−0.14 to 0.47	…
	Visit-to-visit BP interval >6 mo	2[58,96]	0.18	−0.02 to 0.39	38
	MRI only	11[27,56–58,72,82,88–92]	0.21*	0.13 to 0.29*	27
	CT with or without MRI	4[93–96]	0.21	−0.12 to 0.53	48
	Primarily Asian	8[27,57,88–90,95,96,98]	0.20*	0.11 to 0.29*	16
	Non-Asian	7[56,58,72,82,91,93,94]	0.21*	0.06 to 0.36 *	46
Diastolic	SD	11[27,56,57,72,82,88–91,93,94]	0.07*	0.00 to 0.14*	0
	Weighted SD	3[57,89,90]	0.14	−0.03 to 0.31	42
	Coefficient of variation	8[27,58,82,88–90,94,96]	0.20*	0.13 to 0.28*	0
	Variance independent of the mean	1[88]	0.21	−0.09 to 0.51	…
	Successive variation	1[88]	0.29	−0.01 to 0.59	…
	Average real variability	2[82,89]	0.19*	0.01 to 0.36*	0
	Variance in residuals	…	…	…	…
	Day†	6[27,57,82,90,91,94]	0.06	−0.02 to 0.14	0
	Night†	6[27,57,82,90,91,94]	0.09*	0.01 to 0.18*	0
	Oscillometric	12[27,56–58,72,82,89–94]	0.14*	0.08 to 0.20*	0
	Auscultatory	2[88,96]	0.08	−0.20 to 0.36	30
	24-h ABPM	11[27,56,57,72,82,89–94]	0.10 *	0.03 to 0.16*	0
	HBPM and visit to visit	3[58,88,96]	0.19 *	0.02 to 0.35*	34
	Visit-to-visit BP interval <6 mo	1[88]	0.21	−0.09 to 0.51	…
	Visit-to-visit BP interval >6 mo	2[58,96]	0.13	−0.18 to 0.45	67
	MRI only	11[27,56–58,72,82,88–92]	0.14*	0.08 to 0.20*	1
	CT with or without MRI	3[93,94,96]	−0.01	−0.24 to 0.21	0
	Primarily Asian	7[27,57,88–90,96,98]	0.10*	0.02 to 0.17*	0
	Non-Asian	7[56,58,72,82,91,93,94]	0.20*	0.10 to 0.29*	0

ABPM indicates ambulatory BP monitoring; BP, blood pressure; BPV, BP variability; CSVD, cerebral small-vessel disease; CT, computed tomography; HBPM, home BP monitoring; MRI, magnetic resonance imaging; SMD, standardized mean difference.

*Significant values (when ≥2 studies).

†Any metric of BPV recorded from ABPM and subdivided by day and night measures.

over the short- and long-term are documented, implicating calcium channel blockade and thiazide diuretics in optimal BPV control,[24,99] which might modulate the effects of BPV on CSVD.

In this review and previous systematic reviews,[24,36–41] the effect sizes for BPV were pooled together concurrently with mean BP effect sizes. However, our meta-analysis used multilevel modeling to account for within-study dependence between mean and BPV, as well as systolic and diastolic effect sizes.[64] There was generally no evidence for an interaction or heterogeneity between BPV and mean BP pooled effect sizes herein, suggesting that each is associated with CSVD and offers unique variance, and potentially that the magnitude of association with CSVD is comparable between mean and BPV effect sizes. One exception to this finding from ancillary analyses was that mean systolic BP but not systolic BPV increased risk for incident CSVD. Our pooled analyses are, however, limited by only modeling mean BP in the studies investigating BPV. It is likely that including all CSVD studies reporting mean BP, but not necessarily BPV, would quantify heterogeneity between effect sizes more robustly. This could be important given that mean and other indexes of BP (eg, pulse pressure, mean arterial pressure, and morning surge) are associated with CSVD.[98,100]

There were sparse published data for CSVD subtypes apart from WMH. WMH data were inconsistently reported and thus pooled separately for *r* and *d* family effect sizes. When total as well as deep and periventricular WMH volumes were pooled, the significant association with total WMH was largely attributable to periventricular and not deep WMH volumes. This finding contrasts to the conclusion by Kim and colleagues[101] that irregular periventricular WMHs are uniquely associated with chronic hemodynamic insufficiency or hypoperfusion caused by carotid atherosclerosis, whereas deep WMHs are more causatively related to hypertension and CSVD. Further investigation of BPV and regional WMH volumes could be an important avenue of future work, given that periventricular WMH burden is particularly implicated in cognitive decline in processing speed and executive function domains.[102,103] Recent studies indicate that BPV is associated with dementia and cognitive decline,[29,30,104–106] raising the possibility that BPV's impact on brain health might be through periventricular white matter pathways susceptible to chronic hemodynamic insufficiency or hypoperfusion.[101] As most published BPV data pooled herein relate to WMH, it is important to explore other pathways that lead to the development or progression of CSVD subtypes, such as LPVO,[57,58,86,87] CMBs,[87] and EPVSs.[27]

A lack of consensus on BPV methods contributes to substantial heterogeneity between studies with 36 different variability metrics (class, type, and timing) identified in a systematic review of ABPM studies by Taylor and colleagues.[34] Moreover, there is no consensus on the optimal metrics to study BPV independent of mean BP and the number of measurements required to quantify visit-to-visit BPV for risk stratification.[99] Because of this uncertainty in BPV measurement, we pooled different BPV metrics separately in ancillary analyses and found generally consistent results for the most common metrics (SD, coefficient of variation, and average real variability) for primary outcomes 1 and 2. Most studies reported either ABPM or visit-to-visit variability. The magnitude of association between systolic BPV and CSVD was comparable in studies adopting ABPM versus home or visit-to-visit variability for both primary outcomes. This finding suggests that both short- and long-term systolic BPVs are related to CSVD or that they share similar mechanisms insofar as the relationship with CSVD is concerned. Although the mechanisms underlying BPV are poorly understood, short- and longer-term BPVs are hypothesized to both reflect arterial reflex and compliance and dosing/titration of antihypertensive medications.[21] Previously meta-analytic findings indicate that long-term BPV is associated with cardiovascular outcomes and mortality, although ABPM evidence was sparse.[41] Further direct comparisons of ABPM and long-term BPV in CSVD are important given that casual cuff BPV measures are less predictive of stroke than those obtained from ABPM[107] and the mechanisms remain uncertain.[21]

This review found mixed evidence for discrete differences in BPV between Asian and non-Asian populations. The risk for CSVD attributable to systolic BPV was higher among Asian populations; however, there were no observed differences in SMDs of either systolic or diastolic BPV. Kario and Wang[69] posited that Asian populations exhibit higher morning surge in BP, a pressor component of BPV. The observed higher odds for CSVD in Asian populations was unlikely caused by method given that a comparable number of studies used 24-hour ABPM in the primarily Asian and non-Asian studies (4 versus 3). Potentially, the data derived from new investigations in Asian subpopulations could identify the extent to which BPV and its pressor components differ among people with and without CSVD.[108,109]

The strengths of this study include the large pooled sample, meta-regression, and ancillary analyses by CSVD subtypes, BPV metric, and BP measurement intervals. Several limitations temper the results of this review, including suspicion of publication bias. The included studies were predominantly case-control or cohort studies and thereby are prone to inherent biases, such as selection bias, attrition, and unmeasured confounding. Examples of unmeasured confounding include genetic risk factors; secondary causes, such as primary aldosteronism, renal artery stenosis, and sleep apnea; and lifestyle factors, such as physical fitness, sodium, potassium, and alcohol intake.[110] Moreover, adjustment for

antihypertensive medications controlling BP was inconsistent, as was inclusion and adjustment for clinical strokes. The absence of sufficient published data for incident CSVD and CSVD progression indicates that the direction of the association between BPV and CSVD cannot be determined. More specifically, it is possible that higher BPV is merely a consequence of CSVD, rather than a causative risk factor, as others have noted.[111] In support, mean systolic and diastolic BP, but not BPV, was associated with incident CSVD herein, although only ≤3 studies analyzed incident CSVD.

Another limitation of this systematic review is that the reporting in the retrieved studies precluded an adequately powered investigation of CSVD subtypes apart from WMH. Less information was available for other CSVD subtypes suspected to result from hypertensive vasculopathy, including deep and infratentorial CMBs[112] and EPVSs in the basal ganglia.[113] Moreover, we did not include atrophy or brain volume because of their diffuse and sometimes nonischemic causative pathways that are inconsistently reported in epidemiological studies.[7] The sparse evidence for CSVD subtypes is partly related to discrepant terminology and brain image interpretation, acquisition, and reporting in the literature.[7] Moreover, evidence suggests that WMH and LPVO increase the risk for CMBs pointing to overlap in CSVD burden and potential shared risk factors.[1,2] Close investigation of BPV in relation to CSVD subtypes could be an important area of investigation as a prior meta-analysis suggests a cumulative effect for increasing number of CSVD markers on stroke outcome.[8] Moreover, the meta-regression pointed to an association between tesla size and CSVD, and studies adopting CT are unable to detect CMBs and EPVSs. We opted to include these predominantly case-control studies (in primary outcome 2) as their exclusion would lead to upward bias in the pooled results for diastolic BPV. Moreover, access to and use of MRI technology is far from universal, affected by factors such as rural location, patient health insurance, MRI contraindications, and the preference for cheaper neuroimaging techniques.[114,115]

In conclusion, higher systolic BPV was associated with higher odds for CSVD, and the BPV means were generally higher among populations with CSVD compared with their counterparts without CSVD. Collectively, the extant BPV literature suggests that the magnitude of association between systolic BPV and CSVD is similar to that reported for mean BP, indicating BPV may contribute independent information and variance to the association with CSVD. Evidence was sparse in relation to diastolic BPV and CSVD subtypes apart from WMH, where it was found that BPV was associated with periventricular WMH especially. Given that these findings cannot rule out that high BPV is a consequence of CSVD, additional large RCTs as well as prospective cohort studies with ABPM, investigating CSVD subtypes with 3-T MRI, would strengthen the evidence base on whether BPV increases CSVD risk. Given the heterogeneity and suspicion of publication bias in primary outcome 1, an individual participant data meta-analysis of BP data sets might help answer important questions on hypertensive vasculopathy attributable to BPV in specific CSVD subtypes that are lesser reported, including infratentorial CMBs[112] and EPVSs in the basal ganglia.[113]

Appendix

Variability in Blood Pressure and Brain Consortium Members

Kaarin J. Anstey, PhD, Neuroscience Research Australia, University of New South Wales, Sydney, Australia. Nigel Beckett, MD, PhD, Guy's and St Thomas' National Health Service (NHS) Trust, London, United Kingdom; Imperial College London, London, United Kingdom. Alexa S. Beiser, PhD, Department of Neurology, Boston University School of Medicine, Boston, MA. Jonathan Birns, BSc, MBBS, PhD, Department of Ageing and Health, Guy's and St Thomas' Hospital, London, United Kingdom; School of Medicine, Health Education England, London, United Kingdom. Adam M. Brickman, PhD, Department of Neurology, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, NY. Nicholas R. Burns, PhD, School of Psychology, The University of Adelaide, Adelaide, Australia. Mahir Cengiz, MD, Department of Internal Medicine, Biruni University Faculty of Medicine, Istanbul, Turkey. Suzanne Cosh, PhD, School of Psychology and Behavioural Science, University of New England, Armidale, Australia. Rianne A. A. de Heus, MSc, Department of Geriatric Medicine, Radboud Alzheimer Center, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Nijmegen, the Netherlands. Peter W. de Leeuw, MD, Subdivision Vascular Medicine, Division of General Internal Medicine, Department of Internal Medicine, Maastricht University Medical Centre, Maastricht University, Maastricht, the Netherlands. Diana Dorstyn, M.Psych(Clin), PhD, School of Psychology, The University of Adelaide, Adelaide, Australia. Merrill F. Elias, PhD, Department of Psychology and Graduate School of Biomedical Science and Engineering, The University of Maine, Orono, ME. J. Wouter Jukema, MD, Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands. Masahiro Kikuya, MD, PhD, Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan. Abraham A. Kroon, MD, Subdivision Vascular Medicine, Division of General Internal Medicine, Department of Internal Medicine, Maastricht University Medical Centre, Maastricht University, Maastricht, the Netherlands. Rajiv Mahajan, MD, PhD, Centre for Heart Rhythm Disorders, South Australian Health and Medical

Research Institute, University of Adelaide and Lyell McEwin and Royal Adelaide Hospitals, Adelaide, Australia. Emer R. McGrath, MD, Department of Neurology, Massachusetts General Hospital; Harvard Medical School, Boston, MA. Eric P. Moll van Charante, MD, Department of General Practice, Department of Social Medicine, Amsterdam Public Health Research Institute, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands. Toshiharu Ninomiya, MD, PhD, Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan. Tomoyuki Ohara, MD, PhD, Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan. Takayoshi Ohkubo, MD, PhD, Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan. Emi Oishi, MD, Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan. Ruth Peters, PhD, Neuroscience Research Australia, University of New South Wales, Sydney, Australia. Edo Richard, MD, Department of Neurology, Academic Medical Center, Amsterdam, the Netherlands; Department of Neurology, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Nijmegen, the Netherlands. Michihiro Satoh, PhD, Division of Public Health, Hygiene and Epidemiology, Faculty of Medicine, Tohoku Medical and Pharmaceutical University, Sendai, Japan. Joseph Selvayanagam, MD, Cardiovascular Medicine, Flinders University, and Department of Cardiology, Flinders Medical Centre, Adelaide, Australia, where he is the Director of Non-Invasive Cardiac Imaging. Sudha Seshadri, MD, Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, University of Texas Health Sciences Center, San Antonio, TX; Neurology, Boston University School of Medicine, Boston, MA; Senior Investigator, the FHS (Framingham Heart Study), Boston, MA. David J. Stott, MD, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom. Stella Trompet, PhD, Section of Gerontology and Geriatrics, Department of Internal Medicine, Leiden University Medical Center, Leiden, the Netherlands. Willem A. van Gool, MD, Department of Neurology, Academic Medical Center, Amsterdam, the Netherlands. Tessa van Middelaar, MD, Department of Neurology, Academic Medical Center, Amsterdam, the Netherlands; Department of Neurology, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Nijmegen, the Netherlands. Deborah A. Turnbull, PhD, School of Psychology, The University of Adelaide, Adelaide, Australia.

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SUPPLEMENTAL MATERIAL

Data S1.

In the study by Aribisala et al.[1] BPV data were extracted for WMH from the online supplement, Table S2 (wave 1). Because the β value = 0.00 for systolic BPV's association with WMH could not be transformed under the method outlined by Peterson and Brown[2] and analyses imputed $\beta = 0.050$, which converts to $r = .099$. The same imputation method was applied to White et al.[3], and the results used to impute *r* values for Shimada et al.[4]. Data for SBP and DBP were extracted from Table 3 (wave 1).

In the study by Brickman et al.[5] mean and SD values for BPV were calculated from SBP and DBP [BP=(1/3 x systolic BP [SBP]) + (2/3 x diastolic BP [DBP]), thus the coefficient (β converted to *r*) reported for the association between BPV with WMH is equivalent for SBPV and DBPV. Brickman et al.[5] reported WMH analyses using a reference group of persons with low blood pressure and low variability (n=176; lower mean BP (<96.48 mmHg and lower fluctuation SD <7.21 mmHg. In our BPV analyses, the comparison group was group 3 (n=167; higher mean BP >96.48 mmHg and lower fluctuation SD <7.21 mmHg). The effect of BPV on WMH in our analyses used group 4 (n=177, higher mean BP >96.48 mmHg and higher fluctuation SD >7.21 mmHg). Hence, the sample sizes reported in our r analyses use different totals for BPV (353) and mean BP (343). This study also reported cerebral infarctions with no upper size limit and this data was ineligible for LPVO analyses. For diastolic BPV, the SD was assumed as 5.39 and not 53.90 as reported in Table 1 pg. 566.

The study by Duan et al.[6] was included as the study referred to incident lacunar infarctions as an outcome, and that participants "had no clinical evidence of a variety of acute attacks" pg. 1094. This was confirmed in correspondence with the study author, however, the CSVD outcome was not rated as incident as no baseline MRI was obtained. For the association between systolic BPV (SD method) and CSVD, we assumed a ratio of 1526 participants as 11:1 (pg. 1096) for the low versus high systolic BP variation yielding 803 vs. 73 persons in these groups, and rates of infarction at 31.2 and 34.7% respectively (panel b, Fig 2). For comparisons between persons with and without CSVD (table 3 & 5), we prioritized the SD data as this was the most common method reported by other studies.

In the study by Filomena[7] between group BPV variables were reported by any CSVD. For comparisons between persons with and without CSVD (table 2), only inter-quartile range was reported necessitating calculation of SMD from t and p values. We prioritized the SD data as this was the most common method reported by other studies and report other variability metrics in ancillary analyses. Though the authors reported % CSVD in ARV groups stratified by optimal BP control (Figure S3 A-C), the n for each group was not reported.

In the study by Goldstein et al.[8] BPV differences between WMH groups compared the mild/moderate WMH insuluar subcortex group (n=52) to those with no WMH in the insuluar subcortex (n=37) because of the larger n (compared to total WMH volumes). We prioritized wake measures for mean and BPV to ensure parity. In their follow-up study[9] the OR for WMH from wake systolic BPV was reported as; OR = 1.222 (95% CI 1.060 to 1.409, p = 0.01) in Table 5. Mean wake measures were extracted for SBP to provide comparison to wake-variability. In the original study the SBP OR was reported as 1.046 (95% CI 1.008 to 1.006, p = .02). When applying the lnOR we imputed the upper CI as 1.085 and standardized to a 10mmHg increase in SBP.

In the study by Gunstad[10] unadjusted r data were extracted from Table 2 for mean and variability in SBP and DBP (SD method) and we were unable to locate the CV data reported in the method section.

In the study by Havlik et al.[11] we used the total sample size (n=575) for mean BP and a sample size of 230 (high and low quintile) for BPV.

In the study by Kario et al.[12] the authors provided the M ± SD data upon request, comparing patients with and without CSVD on systolic and diastolic BPV.

In the study by Kukla et al.[13] we considered the absence of previous stroke (past 6 months) as justification for inclusion given that the CSVD marker was silent lacunae (<15 mm), and the control group were without lacunae. As only M (IQR) were reported for BP, we generated t-statistics from the p values reported in Table 1. Circadian variability (percent change between day vs. night) was not considered a BPV metric and thus OR in Figure 1 & 2 were not extracted.

In the study by Leung et al.[14] the authors reported incident covert brain infarction and also worsening white matter grade with sensitivity analyses including persons with baseline cardiovascular risk factors. We prioritized the white matter outcome in our primary analysis inclusive of persons with baseline cardiovascular risk factors (larger n) depicted in Table 4 with values reported in RR. The RR values for 10mmHg increase in diastolic BP and BPV were standardized to a 5 mmHg increase to remain consistent with other studies. Systolic values were presented in standardized 10mmHg increase format. Correlations with WMH were obtained from supplement table III and incident CSVD utilized worsening white matter grade from Table 2.

In the study by Liu et al.[15] WMH volumes % change were illustrated in figures and exact values were not reported. Descriptive data was estimated from the % change (panel a) as this data produced a t-value for conversion to r. Based on the total values depicted for a sample of 232 persons, the WMH volume % change was estimated from Fig 3a as; high tertile of CV (n = 77) M = 18 ± 11; lowest tertile of CV (n = 77), M = 11 ± 10, yielding t(153) = 4.13, p <.001. For periventricular WMH volumes % change reported in Fig 5 (panel a pg. 250) estimated values were; high tertile of CV (n = 77) M 20 ± 11; and lowest tertile of CV (n = 77), M = 12.5 ± 11, yielding t(153) = 4.23, p <.001. For deep WMH volumes % change reported in Fig 6 (panel a pg. 251) estimated values were; high tertile of CV (n = 77) M 12.0 ± 12, and lowest tertile of CV (n = 77), M = 8.0 ± 11, yielding t(153) = 2.164, p .033.

In the study by McNeil et al.[16] the association between BPV and WMH volumes were extracted from Model 2 in Table 2 for parity in adjustment of covariates with beta values reported for mean pressure.

In the study by Sabayan et al.[17] the authors reported relevant data for WMH, CMB, and cerebral infarctions (cortical and lacunar). As the size of lacunar infarctions was not specified[18] we prioritized CMB reported as OR (95% CI) in primary outcome analyses. The OR for mean BP and CMB was extracted from the "high BP" group, Table S6. Differences between BPV groups on WMH volumes were calculated from the M (SE) reported in Table 4 for high versus low BPV tertiles (n=137 and n=207 respectively). Data for mean BP were extracted from Table S6 for high versus low average BP (n=225 and n=151 respectively).

In the study by Sander et al.[19] we extracted WMH data from the multivariate regression model (Table 2) and converted β to r as data was available for systolic and diastolic mean and variability metrics. Circadian variability was not considered.

In the study of Shimada et al.[4] where a non-significant correlation was reported for BPV and periventricular WMH (with data not shown), a small correlation coefficient of $r = .10$ was imputed for systolic BPV in order to include this study in the pooled analyses (the effect size was based on the imputation results of Aribisala et al.[1]). Differences in diastolic BP between severity of periventricular WMH grade (I to III) was reported as p = .09 but insufficient data was available to impute an effect size, as only mean BP was presented in Figure 5.

In the study by Sierra et al.[20] day and night variability, quantified as Δ nocturnal fall, was ineligible for inclusion. Only the SD from ABPM was extracted.

In the study by Tartaro et al.[20] data extraction prioritized daytime measures for the SD method (most common method).

In the study by Tohgi et al.[21] data were extracted from the population who were treated with antihypertensives drugs. The rationale was that the proportion of control to recent small subcortical

infarction population was highest, and the non-treated sample was above the 50% threshold for previous stoke. The definition of recent small subcortical infarction or lacunae was not specified but described elsewhere.[22]

In the study by Tsukishima et al.[23] the largest CSVD group data was persons with silent infarction but free from WML (n=35). As the SD or SE values or t-statistics were not reported the SDs were imputed utilizing total group data reported in Table 2 pg. 191.

In the study by Tully et al.[24] additional analyses were performed for between group comparisons in BPV (CV method) according to extensive WMH. The definition of extensive WMH was derived from equal or above sex-specific upper quartiles within the cohort at baseline MRI; men (7.39 cm^3), women (5.73 cm^3)[25]. Logistic regression for extensive WMH adjusted for age and sex and were standardized to 10/5mmHg increase. Correlations with WMH were performed unadjusted utilizing the CV metric of BPV.

In the study by White et al.[3] a non-significant association was reported "various systolic BP variability measures (the SD of the 24-hour mean systolic BP, awake systolic BP, or sleep systolic BP) were not associated with WMH or functional parameters." We imputed a non-significant association between systolic BPV (SD method) and WMH as $\beta = .050$ as was applied to Aribisala et al.[1]. Two sample sizes were reported; 77 (31 males + 46 females, Table 1) and 72 in the eligible sample. We used the smaller conservative sample size.

In the dissertation by Xie [26] SMDs were extracted for persons with and without CMB as this was the CSVD sub-type with the highest N (Table 8.2) and SMDs were extracted from Table 6.5. The OR for CSVD were extracted for severe periventricular WMH for the main endpoint analysis (Table 8.6 – SD method; mean BP extracted from Table 6.9 SBP only). CV data are also shown here in our ancillary analysis. BPV data for CMBs was only reported using pulse pressure metrics and not systolic or diastolic BPV. The periventricular odds ratios were used to calculate d. The Spearman's rho correlations with WMH reported in Table 8.8 were deemed unsuitable for pooling.

In the study by Yamaguchi[27] the systolic CV [Table 3, total sample] was prioritized over the SD values for CSVD progression, as the systolic CV was presented in a multivariable adjusted model. The diastolic BPV analyses for CSVD progression also utilized CV to remain consistent (adjusted, model 2). Analysis of CSVD progression was restricted to the sample with CSVD (n=174) and adjusted CV-BPV analysis.

In the study by Yang et al.[28] the association between BPV with CSVD was available for EPVS in basal ganglia (Table 4, pg. 9) but not EPVS in the white matter. We extracted CV data (24-hours) as this data was available for systolic and diastolic BPV. For between group differences we compared EPVS in the basal ganglia (grade 3 versus 1), estimating the Mean from Fig 1 pg. 7 to calculate a t-statistic and SMD based on the reported p value (only median and IQR values were reported in Table 3).

In the study by Yang et al.[29] data total CSVD burden was extracted from Table 3 (Model 2) and the rationale was that both mean and BPV metrics were reported in this adjusted model. Data extracted for our primary analysis was for the SD method (CV and weighted SD also shown in our ancillary analysis). For comparative purposes with mean SBP, the ancillary analyses extracted data from Model 2 (including day vs. night effect sizes). For comparison of M ± SD, we selected the group with 1 marker of CSVD (highest N).

Table S1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	S1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	S1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	S1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	S1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	S1
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	S1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	S1
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	S1
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	S1
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	S1
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	S1

Section/topic	#	Checklist item	Reported on page #
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6-7, S1, S4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	S6, S7, S8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	S9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-8, Fig 1-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-8, Fig 1-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	S11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	S10, S13, S14, S15, S16,
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9,10 S12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

Table S2. Electronic Search String by Database

MEDLINE	EMBASE	SCOPUS
("blood pressure variability" OR "average real variability" OR "variance independent of the mean" OR "blood pressure oscillation*" OR "blood pressure fluctuation*" OR “blood pressure monitoring, ambulatory” [MeSH])	('blood pressure variability':ti,ab,kw OR 'average real variability':ti,ab,kw OR 'variance independent of the mean':ti,ab,kw OR 'blood pressure oscillation':ti,ab,kw OR 'blood pressure fluctuation':ti,ab,kw OR 'ambulatory blood pressure monitoring':ti,ab,kw)	(TITLE-ABS-KEY ("blood pressure variability" OR "average real variability" OR "variance independent of the mean" OR "blood pressure oscillation*" OR "blood pressure fluctuation*" OR "ambulatory blood pressure monitoring"))
AND ("cerebral small vessel disease*" OR lacun* "subcortical infarct*" OR “subcortical stroke” OR microinfarct* OR “subcortical lesion” OR cerebrovascular disorder [MeSH]) OR "perivascular space*" OR "Virchow-Robin space*" OR leukoaraiosis OR "white matter lesion*" OR "white matter hyperintens*" OR "cerebral microbleed*" OR “micro haemorrhag*”)	AND 'cerebrovascular disease':ti,ab,kw OR 'lacunes':ti,ab,kw OR 'subcortical infarction':ti,ab,kw OR 'subcortical stroke':ti,ab,kw OR 'microinfarct':ti,ab,kw OR 'subcortical lesion':ti,ab,kw OR 'cerebrovascular disorder':ti,ab,kw OR 'enlarged perivascular spaces':ti,ab,kw OR 'virchow-robin space':ti,ab,kw OR 'leukoaraiosis':ti,ab,kw OR 'white matter lesion':ti,ab,kw OR 'white matter hyperintensity':ti,ab,kw OR 'white matter hyperintensities':ti,ab,kw OR 'cerebral microbleed':ti,ab,kw OR 'micro haemorrhage':ti,ab,kw	AND (TITLE-ABS-KEY ("cerebral small vessel disease*" OR lacun* "subcortical infarct*" OR "subcortical stroke" OR microinfarct* OR "subcortical lesion" OR "cerebrovascular disorder" OR "perivascular space*" OR "Virchow-Robin space*" OR leukoaraiosis OR "white matter lesion*" OR "white matter hyperintens*" OR "cerebral microbleed*" OR "micro haemorrhag*"))

Table S3. Reason for Study Exclusion After Full Text Review

Study reference	Response from author	Classification	Reason for exclusion
[30, 31]	NC	Acute stroke	BP and BPV were quantified during the acute stage of hospital admission for stroke (i.e. <24 hours).
[32]	No	No BPV	BPV was not quantified, only 5mmHg increases or decreases in systolic and diastolic BP were evaluated in relation to WMH.
[33]	NC	Acute stroke	BPV was quantified during the in-patient stay and sub-acute period of lacunar infarction (i.e. 1-14 days).
[34]	Yes	No BPV	BPV was not quantified. Only dipping variability patterns were reported.
[35]	NC	Dementia	BPV and leukoaraiosis were analyzed in a mixed neurological sample, most (64%) with dementia.
[36]	No	CSVD ineligible	BPV was analyzed in relation to white matter integrity, quantified with fractional anisotropy. No marker of CSVD was reported according to this reviews definitions.
[37-39]	Yes	Duplicate	The collection of studies were reported as having overlapping samples in Kario et al.[12, 39]. No BPV data were reported in two studies[37, 38]. The authors supplied additional information for this meta-analysis.
[40]	Yes	No control group	There was no reference group without CSVD in the sample, stratified by nocturnal dipping status from ABPM.
[41]	NC	Acute stroke	24-hour ABPM was quantified during the sub-acute stage of lacunar infarction (i.e. 2-4 weeks). Only dipping status was reported in relation to CSVD.
[42]	NC	Acute stroke	24-hour ABPM was quantified during the acute stage of lacunar infarction (i.e. 1 day after admission).

Study reference	Response from author	Classification	Reason for exclusion
[43]	NC	No BPV	Though CSVD was quantified, there was an insufficient amount of BP measures to calculate BPV.
[44]	NC	Acute stroke	BPV measured during acute stage of intracerebral hemorrhage.
[45]	NC	Dementia	A visual rating of WMH was obtained in hospitalised lacunar stroke patients and the control group were patients with Binswager's disease.
[46, 47]	NC	Above 50% stroke prevalence threshold	The entire sample had a previous stroke in the Cilostazol versus Aspirin for Secondary Ischemic Stroke Prevention RCT.
[48]	Yes	Duplicate	Contact author confirmed this was an overlapping sample with [49] which has a larger sample.
[50]	NC	No BPV	This study underwent full-text review as it was cited as evidence for a lack of association between WMH and BPV in[1]. However, no BPV data was presented, only mean pressure (per SD increase).
[51]	No	Duplicate	Duplicate sample reporting BPV by male and female sex, overlapping the included cross-sectional [8]and longitudinal data [9].
[52]	NC	No BPV	No measures of BPV were reported in relation to white matter microstructure.
[53]	No	No CSVD	No CSVD outcome included in macrovascular endpoint.
[54]	No	No CSVD	No CSVD outcome in incident endpoint.

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; BPV, blood pressure variability; CSVD, cerebral small vessel disease; NC, not contacted; WMH, white matter hyperintensity;

Table S4. Descriptive Characteristics of Included Studies

Study reference	Country	Cohort name	Study design	N	Age M yrs ± SD or range width	Females %	Treated with HTN drug %[1]	History of stroke/TIA %[2]	BMI
Aribissala 2014[1]	UK	Lothian Birth Cohort	Cohort	694	72.6 ± 0.7	47	49[1]	7[2]	27.98
Brickman 2010[5]	USA	Washington Heights-Inwood Columbia Aging Project	Cohort	686	≥65, approximately 79	68	66	31[2]	NR
Duan 2009[6]	CHI	NR	Cross-sectional	1526	60-98	0	78	NR	NR
Filomena 2015[7]	ESP	Investigating Silent Strokes in Hypertensives	Cohort	487	49-67	47	95	0.0	29.8
Goldstein 1998[8] & 2005[9]	USA	NR	Cross-sectional & cohort	144	66.2 ± 6.0	57	10[1]	NR	24.6
Gunstad 2005[10]	USA	NR	Cohort	39	71.4 ± 7.4	33	77[1]	0.0	NR
Havlik 2002[11]	USA	Honolulu-Asia Aging Study	Cohort	575	81.6 ± 5.0	0	23	12	NR
Kario 2003[12]	JAP	NR	Cohort	532	72	64	55	0.0	24.2
Kukla 1998[13]	GER	NR	Case-control	118	70	41.5	45	0.0	NR
Leung 2017[14]	USA	Cardiovascular Health Study	Cohort	1844	74.0 ± 4.4	60	38.6	0.0	26.7

Study reference	Country	Cohort name	Study design	N	Age M yrs ± SD or range width	Females %	Treated with HTN drug %[1]	History of stroke/TIA %[2]	BMI
Liu 2016[47]	CHI	NR	Cohort	232	84.4 ± 2.5	75	51	0.0	23.5
McNeil 2018[16]	UK	Aberdeen Birth Cohort	Cohort	227	64.5 ± 0.81	52	45	NR	NR
Nakanishi 2019[55]	USA	Cardiovascular Abnormalities and Brain Lesions study	Cross-sectional	828	70.9 ± 9.0	60.1	78.5	0.0	28.3
Sabayan 2013[17]	NL, UK	PROspective Study of Pravastatin in the Elderly at Risk	RCT	553	74.9 ± 3.2	44	63[1]	16	26.7
Sander 2000[19]	GER	NR	Case-control	227	62-70	49	44[1]	NR	NR
Shimada 1990[4]	JAP	NR	Case-control	73	70 ± 6	67	21	0.0	NR
Sierra 2002[49]	ESP	NR	Case-control	66	50-60	38	100	0.0	29.1
Tartaro 1999[20]	ITA	NR	Cross-sectional	66	77	52	23[1]	0.0	NR
Tohgi 1991[21]	JAP	NR	Case-control	25	69 ± 10	52	100	40	NR
Tsukishima 2001[23]	JAP	NR	Cohort	300	72.9 ± 3.9	52	38[1]	0.0	NR
Tully 2018[24]	FRA	3 City	Cohort	1612	73.8 ± 5.3	64	49	2.1	25.3

Study reference	Country	Cohort name	Study design	N	Age M yrs ± SD or range width	Females %	Treated with HTN drug %[1]	History of stroke/TIA %[2]	BMI
White 2011[3]	USA	NR	Cohort	72	82.1 ± 3.9	60	64	0.0	26.3
Xie 2015[26]	CHI	NR	Cross-sectional	349	71.9 ± 5.2	45	100	0.0	24.9
Yamaguchi 2014[27]	JAP	NR	Cohort	210	70.9 ± 0.9	55	41	30	24.2
Yang 2017[28]	CHI	NR	Cross-sectional	573	69 (55-81)	38	60	0.0	25.6
Yang 2018[29]	CHI	NR	Cross-sectional	251	68	47	59	0.0	25.2

CHI, China; ESP, Spain; FRA, France; GER, Germany; ITA, Italy; JAP, Japan; MS, morning surge; NL, The Netherlands; NR, not reported; UK, United Kingdom; USA, United States of America;

1. *Prevalence of hypertension if antihypertensive drug treatment was not reported*
2. *Incidence of stroke when not reported at baseline.*

Table S5. Blood Pressure Monitoring Characteristics of Included Studies

Study reference	BP monitor, method	BP measures	Interval between consecutive BP measures	Total duration of consecutive measures	Night/sleep BP monitoring	Nocturnal Dipping (%)	BPV metrics	BPV mean comparison between CSVD groups
Aribissala 2014[1]	705IT (Omron Corp), oscillometric	Single clinic visit (6 readings; 3 sitting, 3 standing)	NR	NR (2 waves 3 yrs apart)	No	NA	SD, CV, ARV, SV, (only CV presented)	No
Brickman 2010[5]	Dinamap Pro 100 (Critikon Co), oscillometric	Clinic visit-to-visit (3 readings; over 9 minutes)	1-2 years	6-8 yrs	No	NA	SD	No
Duan 2009[6]	90217 (Spacelabs), oscillometric	ABPM	30 mins (day) 60 mins (night)	24 hrs	Yes (day 0600–2200 hr; night 2200–0600 hr)	NR	SD, wSD, SD'	Yes
Filomena 2015[7]	90217-5Q (Spacelabs), oscillometric	ABPM	20 mins (day) 30 mins (night) - 24 hours	24 hrs	Yes (day (0600–2259 hr; night 2300–0559 hr)	Partial; NR (57.1)	SD, ARV	Yes

Study reference	BP monitor, method	BP measures	Interval between consecutive BP measures	Total duration of consecutive measures	Night/sleep BP monitoring	Nocturnal Dipping (%)	BPV metrics	BPV mean comparison between CSVD groups
Goldstein 1998[8] & 2005[9]	Accutracker II (Suntech), oscillometric	ABPM	20 mins (day) 60 mins (night) - 24 hr ABPM repeated at 5 yrs	24 hrs	Yes –time of sleep and awakening (diary)	Yes; [awake/asleep]/awake, (13.3)	SD (CV NR)	Yes
Gunstad 2005[10]	Press-Mate 8800 (Colin Medical Instruments Corp), oscillometric	Single clinic visit (8 readings)	10 mins	2 hrs	No	NA	SD (CV NR)	No
Havlik 2002[11]	Mercury sphygmomanometer, auscultatory	Clinic visit-to-visit (2 to 3 readings)	2-3 yrs	6 yrs	No	NA	VIR	No
Kario 2003[12]	ABPM-630 (Nippon Colin Co) or TM-2421 or TM-2425 (A&D Co), oscillometric	ABPM	30 mins	24 hrs	Yes - time of sleep and awakening (NR)	Yes; [100 x (1-sleep SBP/awake SBP)] (66.0)	SD	Yes

Study reference	BP monitor, method	BP measures	Interval between consecutive BP measures	Total duration of consecutive measures	Night/sleep BP monitoring	Nocturnal Dipping (%)	BPV metrics	BPV mean comparison between CSVD groups
Kukla 1998[13]	ABD-90217 (Spacelabs), oscillometric	ABPM	15 mins	24 hours	Yes (day 0600–2200 hr; night 2200–0600 hr)	Yes; "average percentage change of nighttime compared with the daytime blood pressure values" (M 10% change)	SD	Yes
Leung 2017[14]	Mercury sphygmomanometer, auscultatory	Clinic visit-to-visit (3 readings, 2 used for BPV)	1 yr	4 yrs	No	NA	SD, VIR	No
Liu 2016[47]	BP3MX1-1 (Microlife), oscillometric	HBPM (2 morning and 2 evening readings)	2 mins (morning and night)	7 days	Yes (morning 0600–0900 hr; evening	NA	CV	No

Study reference	BP monitor, method	BP measures	Interval between consecutive BP measures	Total duration of consecutive measures	Night/sleep BP monitoring	Nocturnal Dipping (%)	BPV metrics	BPV mean comparison between CSVD groups
					1700–2100 hr)			
McNeil 2018[16]	Omicron (NR), oscillometric	Clinic visit-to-visit (3 readings)	2 yrs	4 yrs	No	NA	CV	No
Nakanishi 2019[55]	90217 (Spacelabs), oscillometric	ABPM	15 mins (day) 30 mins (night) - 24 hours	24 hrs	Yes - time of sleep and awakening (diary)	Yes; mean night-time BP/mean daytime BP, < 0.90 (35.9)	CV	No
Sabayan 2013[17]	M4 (Omron), oscillometric	Clinic visit-to-visit (NR)	3 mth	3.2 yrs	No	NA	SD	No
Sander 2000[19]	ABD-90217 (Spacelabs), oscillometric	ABPM	15 mins	24 hrs	Yes (day 0600–2200 hr; night 2200–0600 hr)	Yes; “average percentage change of nighttime BP compared with the daytime BP	SD	Yes

Study reference	BP monitor, method	BP measures	Interval between consecutive BP measures	Total duration of consecutive measures	Night/sleep BP monitoring	Nocturnal Dipping (%)	BPV metrics	BPV mean comparison between CSVD groups
						values" (-9.5 WML vs. -5.6 non-WML)		
Shimada 1990[4]	ABPM-630 (Nippon Kohrin Co), oscillometric	ABPM	30 mins	24 hrs	Yes - time of sleep and awakening (diary)	NR	SD	No
Sierra 2002[49]	90217 (Spacelabs), oscillometric	ABPM	15 mins	24 hrs	Yes (day 0800–2300 hr; night 2300–0800 hr)	Partial; "nocturnal BP fall more than 10%" (data NR)	SD	Yes
Tartaro 1999[20]	90217 (Spacelabs), oscillometric	ABPM	15 mins	24 hrs	Yes (day 0800–2200 hr; night 2200–0800 hr)	NR	SD, CV	Yes

Study reference	BP monitor, method	BP measures	Interval between consecutive BP measures	Total duration of consecutive measures	Night/sleep BP monitoring	Nocturnal Dipping (%)	BPV metrics	BPV mean comparison between CSVD groups
Tohgi 1991[21]	ABPM-630 (Colin Medical), oscillometric	ABPM	30 mins	24 hrs	Yes (day 0900–2000 hr; night 2300–0430 hr)	Partial; night-day difference (-8.2 control vs. -1.5 lacune)	SD, CV, MV	Yes
Tsukishima 2001[23]	Mercury sphygmomanometer, auscultatory	Clinic visit-to-visit (NR)	NR	10 yrs	No	NA	CV	Yes
Tully 2018[24]	M4 (Omron), oscillometric	Clinic visit-to-visit (3 readings)	2 mins	4 yrs	No	NA	CV	Yes
White 2011[3]	Oscar II (Suntech), oscillometric	ABPM	15 mins (day) 30 mins (night)	24 hrs	Yes (day 0600–2000 hr; night 2200–0600 hr)	Yes; " ≥10% decline in sleep vs. awake BP" (36.1)	SD	No
Xie 2015[26]	auscultatory and oscillometric (NR)	Clinic visit-to-visit (1-2 readings)	10-15 mins every 14 weeks	1 yrs	No	NA	SD, CV, VIM, SV	Yes

Study reference	BP monitor, method	BP measures	Interval between consecutive BP measures	Total duration of consecutive measures	Night/sleep BP monitoring	Nocturnal Dipping (%)	BPV metrics	BPV mean comparison between CSVD groups
Yamaguchi 2014[27]	FB-250 (Fukuda Denshi), oscillometric	ABPM	30 mins (day) 60 mins (night)	24 hrs	Yes (day 0800–2000 hr; night 1200–0600 hr)	NR	SD, wSD, CV, ARV	Yes
Yang 2017[28]	FB-250 (Fukuda Denshi), oscillometric	ABPM	30 mins (day) 60 mins (night)	24 hrs	Yes (day 0800–2300 hr; night 2300–0800 hr)	NR	SD, CV	Yes
Yang 2018[29]	TM-2430 (A&D), oscillometric	ABPM	30 mins (day) 60 mins (night)	24 hrs	Yes (day 0800–2300 hr; night 2300–0800 hr)	NR	SD, wSD, CV	Yes

ABPM, ambulatory blood pressure monitoring; ARV, average real variability; CMB, cerebral microbleed; CV, coefficient of variation; CSVD, cerebral small vessel disease; EPVS, enlarged perivascular space; LPVO, lacunae of presumed vascular origin; MV, maximal variation; NA, not applicable; NR, not reported; SD, standard deviation; SD', author's novel method of calculating standard deviation; SDIM, standard deviation independent of the mean; SV, successive

variation; VIM, variance independent of the mean; VIR, variance in residuals; WMH, white matter hyperintensity; WML, white matter lesion detected on Computed Tomography; wSD, weighted standard deviation;

Table S6. Imaging methods for CSVD in the Included Studies

Study reference	CSVD sub-types quantified and other imaging	Number with brain imaging	N with MRI	MRI/CT	Tesla of MRI	T1, T2	T2 GRE	T2*-, SWI	FLAIR/ PD	DWI/ DTI	κ
Aribissala 2014[1]	WMH (visual rating on Fazekas scale)	694	694	MRI	1.5	T1, T2	NR	T2*-	FLAIR	NR	NR[b]
Brickman 2010[5]	WMH (volumetry), BI (>3 mm)	686	686	MRI	1.5	T1, T2	NR	NR	FLAIR	NR	0.73-0.90
Duan 2009[6]	LPVO (2-15 mm)	1526	NR	MRI	NR	NR	NR	NR	NR	NR	NR
Filomena 2015[7]	Combined endpoint of WMH (visual rating on Fazekas) & LPVO (3-20 mm)	487	487	MRI	1.5	T1, T2	Yes	NR	FLAIR	NR	NR
Goldstein 1998[8] & 2005[9]	WMH (visual rating)	144	144	MRI	1.5	NR	NR	NR	NR	NR	NR
Gunstad 2005[10]	WMH (volumetry)	39	39	MRI	1.5	T1, T2	NR	NR	FLAIR	NR	>0.90
Havlik 2002[11]	WMH (visual rating)	575	575	MRI	1.5	T2	Yes	NR	PD	NR	NR
Kario 2003[12]	LPVO (3-15 mm)	519	519	MRI	1.5	T1, T2	NR	NR	NR	NR	0.70-0.00
Kukla 1998[13]	LPVO (<15 mm)	188	33	MRI & CT	1.5	T2	NR	NR	PD	NR	NR[b]
Leung 2017[14]	WMH (visual rating)	1844	1844	MRI	1.5	T1, T2	NR	NR	NR	NR	NR
Liu 2016[47]	WMH (volumetry)	232	232	MRI	3	T1, T2	NR	NR	FLAIR	NR	NR[c]

Study reference	CSVD sub-types quantified and other imaging	Number with brain imaging	N with MRI	MRI/CT	Tesla of MRI	T1, T2	T2 GRE	T2*-, SWI	FLAIR/ PD	DWI/ DTI	κ
McNeil 2018[16]	WMH (volumetry & visual rating on Schelten's scale)	227	227	MRI	1.5	T1, T2	NR	NR	FLAIR	NR	NR[c]
Nakanishi [55]	WMH (volumetry), LPVO (> 3mm)	828	828	MRI	1.5	T2	NR	NR	FLAIR	NR	NR
Sabayan 2013[17]	WMH (volumetry), LPVO, BI (size NR), CMB (size NR)	553	553	MRI	1.5	T2	Yes	NR	FLAIR	NR	NR
Sander 2000[19]	WMH (volumetry & visual rating)	227	227	MRI	1	T1, T2	NR	NR	PD	NR	NR
Shimada 1990[4]	WMH (visual rating), LPVO (<10 mm)	73	73	MRI	0.5	T1, T2	NR	NR	NR	NR	NR[b]
Sierra 2002[49]	WMH (visual rating)	66	66	MRI	1.5	T1, T2	NR	NR	PD	NR	NR
Tartaro 1999[20]	WMH (visual rating)	66	-	CT	NA	NA	NA	NA	NA	NA	NR
Tohgi 1991[21]	RSSCI (size NR), LPVO (size NR)	31	-	CT	NA	NA	NA	NA	NA	NA	NA
Tsukishima 2001[23]	WMH (visual rating), LPVO (size NR)	300	-	CT	NA	NA	NA	NA	NA	NA	0.92
Tully 2018[24]	WMH (volumetry)	1612	1612	MRI	1.5	T1, T2	NR	NR	NR	NR	NR[c]
White 2011[3]	WMH (volumetry)	72	72	MRI	3	T1, T2	NR	NR	FLAIR	NR	NR[c]
Xie 2015[26]	WMH (volumetry and visual rating on Fazekas scale), CMB (2-10 mm, BOMBS), BI (>3 mm)	236	236	MRI	3	T1, T2	NR	SWI	FLAIR, PD	DTI	NR[b]

Study reference	CSVD sub-types quantified and other imaging	Number with brain imaging	N with MRI	MRI/CT	Tesla of MRI	T1, T2	T2 GRE	T2*-, SWI	FLAIR/ PD	DWI/ DTI	κ
Yamaguchi 2014[27]	WMH (volumetry & visual rating on Fazekas scale), LPVO (3-15 mm)	210	210	MRI	0.5	T1, T2	NR	NR	FLAIR	NR	0.86 & 0.68
Yang 2017[28]	EPVS (<3 mm; visual grading basal ganglia and white matter)	573	573	MRI	3	T1, T2	NR	NR	FLAIR	NR	≥.80
Yang 2018[29]	Combined endpoint of WMH (Fazekas scale), CMB (size NR), LPVO (3-20 mm), EPVS (< 3 mm; basal ganglia), atrophy[a]	251	251	MRI	3	T1, T2	NR	SWI	FLAIR	NR	≥0.70

a. *Atrophy included in comparison between CSVD groups on M ± SD BPV*

b. *Single-rater*

c. *Volumetry only*

BI, brain infarcts; BOMBS, Brain Observer MicroBleed Scale; CMB, cerebral microbleed; CT, computed tomography; DTI, diffusion tensor imaging; DWI, diffusion weighted imaging; EPVS, enlarged perivascular space; FLAIR, fluid-attenuated inversion recovery; GRE, gradient recalled echo; LPVO, lacune of presumed vascular origin; MRI, magnetic resonance imaging; NA, not applicable; NR, not reported; PD, proton density; RSSCI, recent small sub-cortical infarction; SWI,susceptibility weighted imaging; WMH, white matter hyperintensity;

Table S7. RTI Scale Adjudication of Included Studies for Items 1-14

Study Reference	1. Retro/ prosp	2. Incl/ excl criteria stated	3. Incl/ excl criteria reliable	4. Incl/ excl criteria uniform	5. Recruitment across groups	6. Statistical power	7. Detail of exposure	8. Specification of outcomes	9. Appropriate comparison group	10. Attempt to balance	11. Adjustment for unintended exposure	12. Variation in execution of protocol	13. Blind outcomes assessment	14. Exposures assessed using valid and reliable measures
Aribissala 2014[1]	Prosp	No	CD	CD	NA	Yes	Medium	Yes	NA	NA	No	CD	CD	Yes
Brickman 2010[5]	Prosp	No	CD	CD	NA	Yes	High	Yes	Yes	Yes	Yes	CD	CD	Yes
Duan 2009[6]	Retro	No	CD	CD	NA	Yes	Low	Partial	CD	No	No	CD	CD	CD
Filomena 2015[7]	Prosp	Partial	CD	CD	CD	Yes	High	Yes	Yes	Yes	Yes	CD	Yes	Yes
Goldstein 1998[8] & 2005[9]	Prosp	Yes	Yes	Yes	NA	No	High	Yes	Yes	No	No	CD	Yes	Yes
Gunstad 2005[10]	Prosp	Yes	CD	CD	NA	No	Medium	Yes	NA	No	No	CD	CD	Yes
Havlik 2002[11]	Prosp	Yes	CD	CD	NA	Yes	Medium	Yes	NA	Yes	No	CD	Yes	Yes
Kario 2003[12]	Prosp	Yes	Yes	Yes	NA	Yes	High	Yes	CD	CD	CD	CD	Yes	Yes
Kukla 1998[13]	Prosp	Partial	CD	Partially	Yes	No	High	Yes	No	No	No	CD	Yes	Yes
Leung 2017[14]	Prosp	No	CD	CD	NA	Yes	Low	Yes	NA	Yes	Yes	CD	Yes	Yes
Liu 2016[47]	Prosp	Yes	CD	CD	NA	Yes	Medium	Yes	Yes	Yes	Yes	CD	Yes	Yes
McNeil 2018[16]	Prosp	No	CD	CD	NA	Yes	Low	Yes	NA	Yes	No	CD	CD	Yes
Nakanishi [55]	Prosp	No	CD	CD	NA	Yes	High	Yes	Yes	Yes	Yes	CD	Yes	Yes
Sabayan 2013[17]	Prosp	Yes	CD	Yes	Yes	Yes	Medium	Yes	Yes	Yes	No	No	Yes	Yes
Sander 2000[19]	Prosp	Yes	No	CD	No	Yes	High	Yes	Yes	No	No	CD	Yes	Yes
Shimada 1990[4]	Prosp	Yes	CD	Yes	No	No	Medium	Yes	NA	No	No	CD	Yes	Yes
Sierra 2002[49]	Prosp	Yes	CD	Yes	NA	Yes	High	Yes	Yes	Yes (partial)	No	CD	Yes	Yes
Tartaro 1999[20]	Prosp	Yes	CD	Yes	NA	No	High	Yes	Yes	No	No	CD	Yes	Yes

Study Reference	1. Retro/ prosp	2. Incl/ excl criteria stated	3. Incl/ excl criteria reliable	4. Incl/ excl criteria uniform	5. Recruitment across groups	6. Statistical power	7. Detail of exposure	8. Specification of outcomes	9. Appropriate comparison group	10. Attempt to balance	11. Adjustment for unintended exposure	12. Variation in execution of protocol	13. Blind outcomes assessment	14. Exposures assessed using valid and reliable measures
Tohgi 1991[21]	Prosp	No	CD	CD	CD	No	High	No	Yes	No	No	CD	Yes	Yes
Tsukishima 2001[23]	Prosp	Yes	CD	Yes	CD	Yes	High	Yes	Yes	No	Yes	CD	Yes	Yes
Tully 2018[24]	Prosp	Yes	Yes	Yes	NA	Yes	Medium	Partial	Yes	Yes	No	CD	Yes	Yes
White 2011[3]	Prosp	Yes	CD	CD	NA	No	High	Yes	NA	Yes (partial)	No	CD	Yes	Yes
Xie 2015[26]	Prosp	Yes	Yes	NA	NA	Yes	High	Yes	Yes	Yes (partial)	No	No	Yes	Yes
Yamaguchi 2014[27]	Prosp	No	CD	CD	CD	Yes	High	Yes	Yes	Yes	No	No	Yes	Yes
Yang 2017[28]	Prosp	Yes	CD	NA	NA	Yes	High	Yes	Yes	Yes	Yes	No	Yes	Yes
Yang 2018[29]	Prosp	Yes	CD	NA	NA	Yes	High	Yes	Yes	Yes	Yes	No	Yes	Yes

CD, cannot determine; Excl, exclusion; Incl, inclusion; ITT, intention to treat; NA, not applicable; Prosp, prospective; Retro, Retrospective

Table S7. Continued RTI Scale Adjudication of Included Studies for Items 15-29

Study Reference	15. Outcomes assessed using valid and reliable measures	16. Equality of length of f/u	17. Length of f/u adequate (> 5 years)	18. High attrition (30%)	19. Attrition difference	20. Baseline differences controlled	21. Measurement of confounding variables reliable	22. Confounding variables in design/analysis	23. ITT or sensitivity analysis for loss to f/u	24. Primary outcomes missing	25. Statistics appropriate	28. Appropriate interpretation	29. Funding
Aribissala 2014[1]	Yes	Yes	No	No	NA	NA	CD	Yes	CD	No	Yes	Yes	Yes
Brickman 2010[5]	Yes	Yes	Yes	Yes	CD	Yes	Yes	Partially	CD	No	Yes	Yes	Yes
Duan 2009[6]	Yes	NA	NA	NA	CD	No	Yes	NA	NA	No	Yes	Yes	Yes
Filomena 2015[7]	Yes	NA	NA	NA	CD	Yes	CD	Partially	NA	No	Yes	Yes	Yes
Goldstein 1998[8] & 2005[9]	Yes	Yes	Yes	No	CD	No	Yes	No	CD	No	Yes	Yes	Yes
Gunstad 2005[10]	Yes	NA	NA	NA	NA	No	CD	No	NA	No	Partially	Yes	Yes
Havlik 2002[11]	Yes	Yes	Yes	No	CD	Yes	CD	Yes	CD	No	Yes	Yes	Yes
Kario 2003[12]	Yes	Yes	No	No	CD	CD	Yes	CD	CD	No	Yes	Partially	Yes
Kukla 1998[13]	Yes	NA	NA	NA	NA	No	Yes	Partially	NA	No	Yes	Yes	Yes
Leung 2017[14]	Yes	NA	NA	NA	NA	Yes	CD	Yes	NA	No	Yes	Yes	Yes
Liu 2016[47]	Yes	NA	NA	NA	NA	Yes	CD	Yes	NA	No	Yes	Yes	Yes
McNeil 2018[16]	Yes	NA	NA	NA	NA	No	CD	No	NA	No	Yes	Yes	Yes
Nakanishi[55]	Yes	NA	NA	NA	NA	Yes	Yes	Yes	NA	No	Yes	Yes	Yes
Sabayan 2013[17]	Yes	Yes	No	CD	CD	Yes	CD	No	CD	No	Yes	Yes	Yes
Sander 2000[19]	Yes	NA	NA	NA	NA	No	No	No	NA	No	Partially	Yes	No
Shimada 1990[4]	Yes	NA	NA	NA	NA	NA	CD	No	NA	Yes	Partially	Yes	Yes
Sierra 2002[49]	Yes	NA	NA	NA	NA	No	CD	Partially	NA	No	Partially	Yes	No
Tartaro 1999[20]	Yes	NA	NA	NA	NA	No	CD	No	NA	No	Partially	Yes	No

Study Reference	15. Outcomes assessed using valid and reliable measures	16. Equality of length of f/u	17. Length of f/u adequate (> 5 years)	18. High attrition (30%)	19. Attrition difference	20. Baseline differences controlled	21. Measurement of confounding variables reliable	22. Confounding variables in design/analysis	23. ITT or sensitivity analysis for loss to f/u	24. Primary outcomes missing	25. Statistics appropriate	28. Appropriate interpretation	29. Funding
Tohgi 1991[21]	Yes	NA	NA	NA	NA	No	CD	No	NA	CD	Partially	CD	Yes
Tsukishima 2001[23]	Yes	CD	Yes	CD	CD	No	CD	Partially	CD	No	Partially	Yes	Yes
Tully 2018[24]	Yes	NA	NA	NA	NA	Yes	Yes	Yes	NA	CD	Partially	Yes	Yes
White 2011[3]	Yes	Yes	No	Yes	CD	NA	CD	Partially	CD	No	Yes	Yes	Yes
Xie 2015[26]	Yes	NA	NA	NA	NA	No	Yes	No	CD	No	Yes	Yes	No
Yamaguchi 2014[27]	Yes	Yes	No	No	CD	Yes	Yes	Yes	CD	No	Yes	Yes	No
Yang 2017[28]	Yes	NA	NA	NA	NA	Yes	Yes	Yes	NA	No	Yes	Yes	No
Yang 2018[29]	Yes	NA	NA	NA	NA	Yes	CD	Yes	NA	No	Yes	Yes	Yes

CD, cannot determine; NA, not applicable;

Item 26 and 27 dropped as they refer to harms from an intervention.

Complete List of RTI Items[56]

1. Is the study design prospective, retrospective, or mixed?
2. Are critical inclusion/exclusion criteria clearly stated (does not require the reader to infer)?
3. Are the inclusion/exclusion criteria measured using valid and reliable measures?
4. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups/arms of the study?
5. Was the strategy for recruiting participants into the study the same across study groups/arms of the study?
6. Was the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?
7. What is the level of detail in describing the intervention or exposure?

8. Are the important outcomes pre-specified by the researchers? Do not consider harms in answering this question unless they should have been pre-specified.
9. Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations
10. Any attempt to balance the allocation between the groups (e.g., through stratification, matching, propensity scores).
11. Did researchers isolate the impact from a concurrent intervention or an unintended exposure that might bias results, e.g., through multivariate analysis, stratification, or subgroup analysis?
12. Did execution of the study vary from the intervention protocol proposed by the investigators and therefore compromise the conclusions of the study?
13. Were the outcome assessors blinded to the intervention or exposure status of participants?
14. Are interventions/exposures assessed using valid and reliable measures, implemented consistently across all study participants?
15. Are outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
16. Is the length of follow-up the same for all groups?
17. Is the length of time following the intervention/exposure sufficient to support the evaluation of primary outcomes and harms?
18. Did attrition from any group exceed 20 percent for <1 year follow-up and 30 percent for > 1 year follow-up?
19. Did attrition from any group exceed [x] percent?
20. Does the analysis control for baseline differences between groups?
21. Are confounding and/or effect modifying variables assessed using valid and reliable measures across all study participants?
22. Were the important confounding and effect modifying variables taken into account in the design and/or analysis (e.g., through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment)?
23. In cases of high loss to follow-up (or differential loss to follow-up), is the impact assessed (e.g., through sensitivity analysis or other adjustment method)?
24. Are any important primary outcomes missing from the results?
25. Are the statistical methods used to assess the primary benefit outcomes appropriate to the data?
26. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?
27. Are the statistical methods used to assess the main harm or adverse event outcomes appropriate to the data?

28. Are results believable taking study limitations into consideration?
29. Is the source of funding identified?

Table S8. Meta-Regression Results for Primary Outcomes

Outcome	Variable	Point Estimate (95% CI)	SE	Q (df)	P
Odds for CSVD					
Systolic BPV	Age	**0.02 (0.01 to 0.02)**	**0.01**	**25.86 (1)**	**<0.001**
	Female sex	0.01 (-.01 to 0.01)	0.01	0.99 (1)	0.32
	Antihypertensive or hypertension	**-0.00 (-0.00 to 0.00)**	**0.00**	**16.23 (1)**	**<0.001**
	Dipping	NA	-	-	-
	Stroke	**0.02 (0.01 to 0.03)**	**0.01**	**6.73 (1)**	**0.009**
	Body mass index kg/m^2	**-0.06 (-0.08 to -0.05)**	**0.01**	**51.64 (1)**	**<0.001**
	Tesla of MRI	**0.17 (0.11 to 0.22)**	**0.03**	**41.27 (1)**	**<0.001**
Diastolic BPV	Age	**-0.06 (-0.12 to -0.01)**	**0.03**	**3.91 (1)**	**0.047**
	Female sex	-0.01 (-0.02 to 0.00)	0.00	2.29 (1)	0.13
	Antihypertensive or hypertension	0.00 (-0.01 to 0.01)	0.00	0.34 (1)	0.56
	Dipping	NA	-	-	-
	Stroke	**0.02 (0.00 to 0.04)**	**0.01**	**5.00 (1)**	**0.025**
	Body mass index kg/m^2	-0.06 (-0.15 to 0.03)	0.05	1.75 (1)	0.19
	Tesla of MRI	-0.01 (-0.14 to 0.13)	0.07	0.01 (1)	0.92
SMD in BPV					
Systolic BPV	Age	**-0.03 (-0.06 to -0.01)**	**0.02**	**4.03 (1)**	**0.045**
	Female sex	0.01 (-.01 to 0.00)	0.00	1.23 (1)	0.27
	Antihypertensive or hypertension	-0.00 (-0.01 to 0.01)	0.00	2.38 (1)	0.12
	Dipping	NA	-	-	-
	Stroke	0.00 (-0.00 to 0.01)	0.01	0.94 (1)	0.33

Outcome	Variable	Point Estimate (95% CI)	SE	Q (df)	P
	Body mass index kg/m^2	-0.04 (-0.09 to 0.01)	0.02	3.73 (1)	0.053
	Tesla of MRI	0.03 (-0.03 to 0.08)	0.03	0.96 (1)	0.33
Diastolic BPV	Age	0.01 (-0.02 to 0.04)	0.02	0.23 (1)	0.63
	Female sex	**0.00 (0.00 to 0.01)**	**0.00**	**4.99 (1)**	**0.025**
	Antihypertensive or hypertension	0.00 (-0.00 to 0.01)	0.00	0.15 (1)	0.69
	Dipping	NA	-	-	-
	Stroke	0.00 (-0.01 to 0.01)	0.01	0.03 (1)	0.87
	Body mass index kg/m^2	-0.03 (-0.09 to 0.04)	0.03	0.66 (1)	0.42
	Tesla of MRI	0.05 (-0.00 to 0.11)	0.03	3.49 (1)	0.061

For SMDs, Tesla of MRI was coded 0 for CT scans and in the study by Duan where T was not reported.

Significant values in bold

Dipping data reported in 3 or fewer studies

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; BPV, blood pressure variability; CI, confidence intervals; CSVD, cerebral small vessel disease; MRI, magnetic resonance imaging; NA, not available; SE, standard error; SMD, standardised mean difference;

Table S9. Table Showing Tests of Publication Bias for the Primary Outcomes

	Primary Outcome 1 – odds for CSVD		Primary Outcome 2 – SMD in BPV	
	Systolic BPV (13 studies)	Diastolic BPV (6 studies)	Systolic BPV (15 studies)	Diastolic BPV (14 studies)
Begg-Mazumdar[1]	τ = 0.09, p = 0.67	τ = 0.53, p = 0.14	τ = -0.04, p = 0.84	τ = -0.24, p = 0.23
Egger	**t(11) = 2.23, p = 0.047**	**t(4) = 4.06, p = 0.015**	t(13) = 0.17, p = 0.87	t(12) = 0.77, p = 0.45
Duval and Tweedie, estimate (95% CI) – n trimmed studies	0.14 (0.11 to 0.17) n = 2	0.20 (0.06 to 0.35) n = 2	0.21 (0.13 to 0.28) n = 0	0.13 (0.08 to 0.19) n = 0

1. *Kendall's tau with continuity correction*

BPV, blood pressure variability; CI, confidence interval; CSVD, cerebral small vessel disease;

Significant values in bold

Table S10. Assessment of Strength of Recommendations Using the GRADE Criteria

GRADE Item	Odds for CSVD – systolic BPV	Odds for CSVD diastolic BPV	SMD in BPV systolic BPV	SMD in BPV diastolic BPV
Number of studies	**13**	**6**	**15**	**14**
Effect size (95% CI)	**OR = 1.27 (1.14 to 1.42)**	**OR = 1.30 (1.14 to 1.48)**	***g* = 0.21 (0.13 to 0.28)**	***g* = 0.13 (0.08 to 0.19)**
Risk of bias	No	No	No	No
Inconsistency	No	No	No	No
Indirectness	No	No	No	No
Imprecision	No	No	No	No
Publication bias	Strongly suspected	Strongly suspected	Undetected	Undetected
Large effect	No	No	No	No
Plausible confounding would change the effect	No	No	No	No
Dose response gradient	No	No	No	No
Quality of evidence	**Low**	**Low**	**Low**	**Low**

GRADE assessment made using GRADE profiler 3.6.1 [57]

BPV, blood pressure variability; CSVD, cerebral small vessel disease; OR, odds ratio; RR, risk ratio; SMD, standardized mean difference

Table S11. Ancillary Analysis Results for Association Between BPV and WMH

WMH outcome	*r* or *d* family metric	BP measure	Studies n [references]	*Effect size*	95% CI	I^2	*p* for heterogeneity between effects
Total WMH	*r*	Systolic BPV	10 [1, 3-5, 10, 14, 16, 19, 24, 26]	**r = 0.13**	**0.07 to 0.19**	69	0.58
	r	Systolic BP (mean)	8 [1, 3, 5, 10, 14, 16, 19, 24]	**r = 0.11**	**0.04 to 0.18**	63	
	r	Diastolic BPV	8 [1, 5, 10, 14, 16, 19, 24, 26]	**r = 0.12**	**0.06 to 0.19**	78	0.28
	r	Diastolic BP (mean)	7 [1, 5, 10, 14, 16, 19, 24]	**r = 0.18**	**0.11 to 0.24**	67	
	d	Systolic BPV	8 [9, 11, 14, 15, 17, 24, 26, 55]	**OR = 1.21**	**1.05 to 1.39**	88	0.33
	d	Systolic BP (mean)	6 [9, 11, 14, 17, 24, 55]	**OR = 1.12**	**1.04 to 1.19**	41	
	d	Diastolic BPV	3 [14, 17, 24]	**OR = 1.18**	**1.09 to 1.28**	0	0.47
	d	Diastolic BP (mean)	3 [14, 24, 51]	**OR = 1.15**	**1.10 to 1.19**	0	
Deep WMH	*r*	Systolic BPV	3 [10, 24, 26]	*r* = 0.05	-0.06 to 0.16	58	0.86
	r	Systolic BP (mean)	2 [10, 24]	*r* = 0.03	-0.10 to 0.17	0	
	r	Diastolic BPV	3 [10, 24, 26]	*r* = 0.03	-0.09 to 0.15	0	0.64
	r	Diastolic BP (mean)	2 [10, 24]	*r* = 0.07	-0.07 to 0.22	80	
	d	Systolic BPV	3 [15, 24, 51]	OR = 1.12	0.99 to 1.27	0	0.29
	d	Systolic BP (mean)	2 [24, 51]	OR = 1.31	1.00 to 1.71	0	
	d	Diastolic BPV	1 [24]	OR = 1.16	0.73 to 1.86	-	-
	d	Diastolic BP (mean)	1[24]	OR = 2.11	1.31 to 3.38	-	
Periventricular WMH	*r*	Systolic BPV	4 [4, 10, 24, 26]	**r = 0.05**	**0.01 to 0.09**	**0**	0.21

WMH outcome	*r* or *d* family metric	BP measure	Studies n [references]	*Effect size*	95% CI	I^2	*p* for heterogeneity between effects
	r	Systolic BP (mean)	2 [10, 24]	**r = 0.09**	**0.04 to 0.14**	**0**	
	r	Diastolic BPV	3 [10, 24, 26]	**r = 0.10**	**0.03 to 0.16**	**11**	0.89
	r	Diastolic BP (mean)	2 [10, 24]	**r = 0.10**	**0.03 to 0.18**	**24**	
	d	Systolic BPV	3 [15, 24, 26]	**OR = 1.27**	**1.09 to 1.47**	0	-
	d	Systolic BP (mean)	1 [24]	OR = 1.11	1.07 to 2.59	-	
	d	Diastolic BPV	1 [24]	OR = 1.61	1.01 to 2.58	-	-
	d	Diastolic BP (mean)	1 [24]	OR = 1.78	1.11 to 2.86	-	

Significant values in bold (when 2 or more studies)

BP, blood pressure; BPV, blood pressure variability; CI, confidence interval; CSVD, cerebral small vessel disease; OR, odds ratio; WMH, white matter hyperintensity;

Table S12. Ancillary Analysis Results for Odds of CSVD Stratified by Sub-type

Ancillary analysis	BP measure	Studies n references	OR	95% CI	I^2	*p* for heterogeneity between effects
Incident CSVD	Systolic BPV	3 [14, 24, 27]	0.95	0.76 to 1.19	0	0.18
	Systolic BP (per 10 mmHg increase)	2 [14, 24]	**1.13**	**1.01 to 1.26**	37	
	Diastolic BPV	3 [14, 24, 27]	1.21	0.95 to 1.54	0	0.96
	Diastolic BP (per 5 mmHg increase)	2 [14, 24]	**1.20**	**1.06 to 1.36**	25	
CSVD progression	Systolic BPV	3 [14, 15, 27]	1.39	1.00 to 1.95	89	-
	Systolic BP (per 10 mmHg increase)	1 [14]	1.06	1.00 to 1.12	-	
	Diastolic BPV	2 [14, 27]	1.63	0.87 to 3.05	60	-
	Diastolic BP (per 5 mmHg increase)	1 [14]	1.15	1.09 to 1.21	-	
Lacune of presumed vascular origin	Systolic BPV	4 [6, 17, 24, 55]	1.00	0.94 to 1.06	0	0.26
	Systolic BP (per 10 mmHg increase)	3 [17, 24, 55]	1.06	0.97 to 1.16	0	
	Diastolic BPV	2 [17, 24]	1.06	0.87 to 1.29	0	0.67
	Diastolic BP (per 5 mmHg increase)	2 [17, 24]	1.18	0.75 to 1.85	59	
Cerebral microbleed	Systolic BPV	1 [17]	1.30	0.77 to 2.19	-	-
	Systolic BP (per 10 mmHg increase)	2 [17, 26]	1.19	1.00 to 1.42	0	
	Diastolic BPV	1 [17]	1.77	1.06 to 2.96	-	-
	Diastolic BP (per 5 mmHg increase)	1 [17]	0.88	0.49 to 1.58	-	
Enlarged perivascular space	Systolic BPV	1 [28]	1.60	1.27 to 2.02	-	-

Ancillary analysis	BP measure	Studies n references	OR	95% CI	I^2	*p* for heterogeneity between effects
	Systolic BP (per 10 mmHg increase)	-	-	-	-	
	Diastolic BPV	1 [28]	1.81	1.25 to 2.62	-	-
	Diastolic BP (per 5 mmHg increase)	-	-	-	-	

Significant values in bold (when 2 or more studies)

BP, blood pressure; BPV, blood pressure variability; CI, confidence interval; CSVD, cerebral small vessel disease; OR, odds ratio

Figure S1. Flow chart of literature search and article selection process

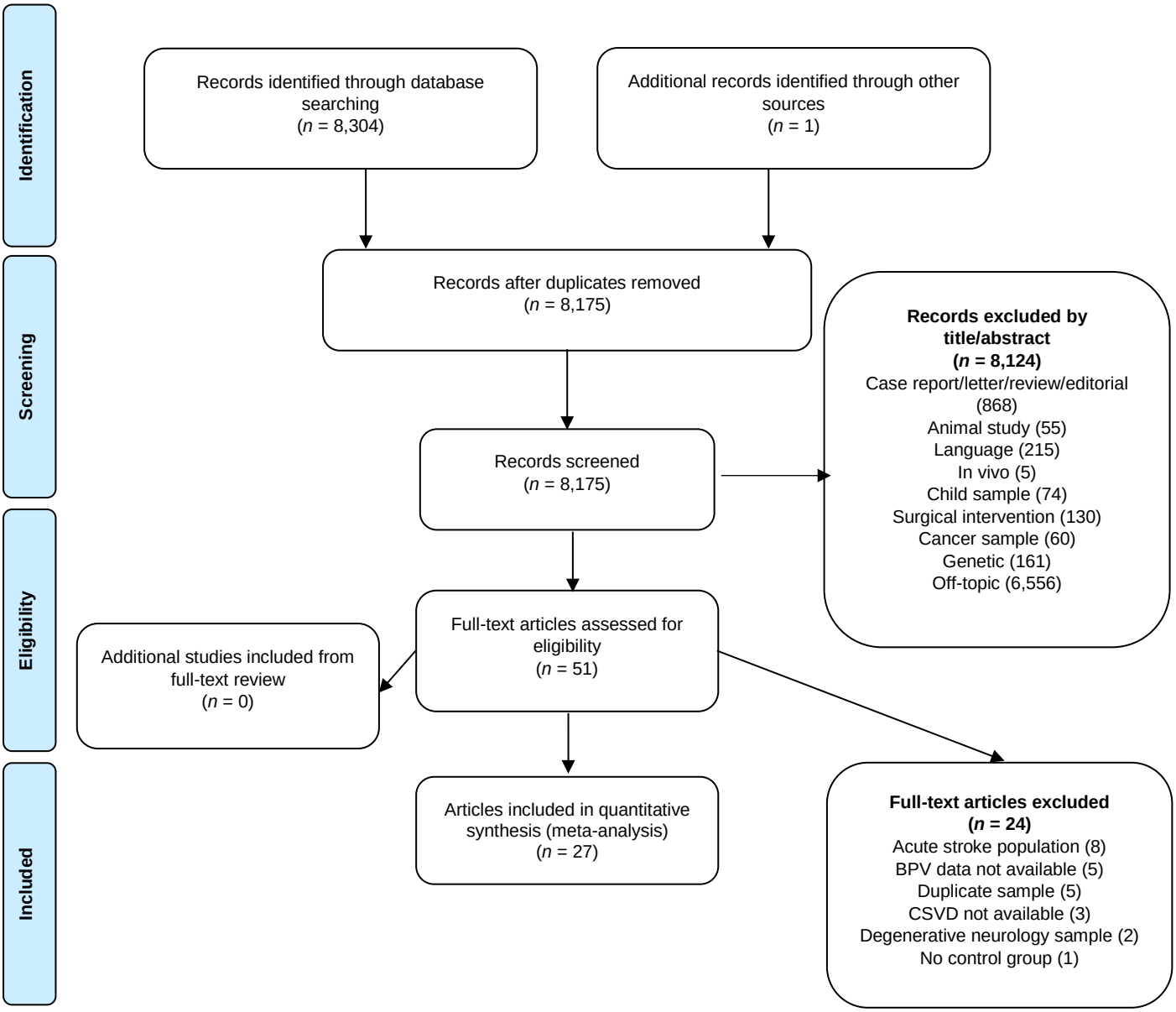
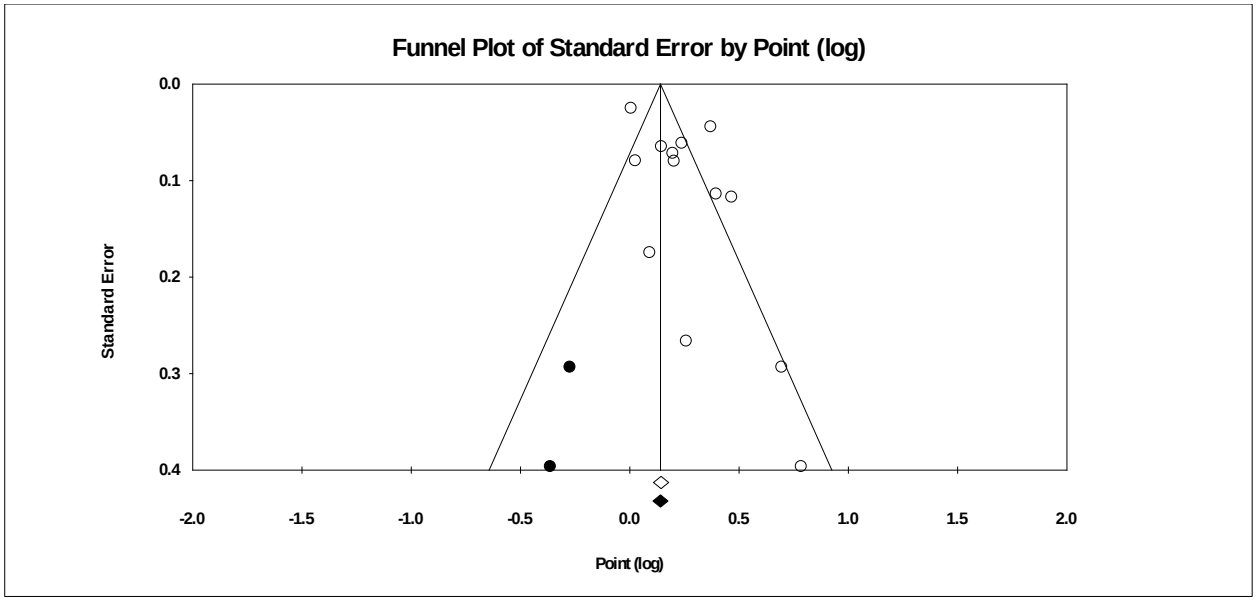


Figure describing the systematic search for articles, listing numbers excluded at each stage of the review according to PRISMA guidelines.

Figure S2. Funnel plot of odds for CSVD attributable to systolic BPV (trim and fill method)

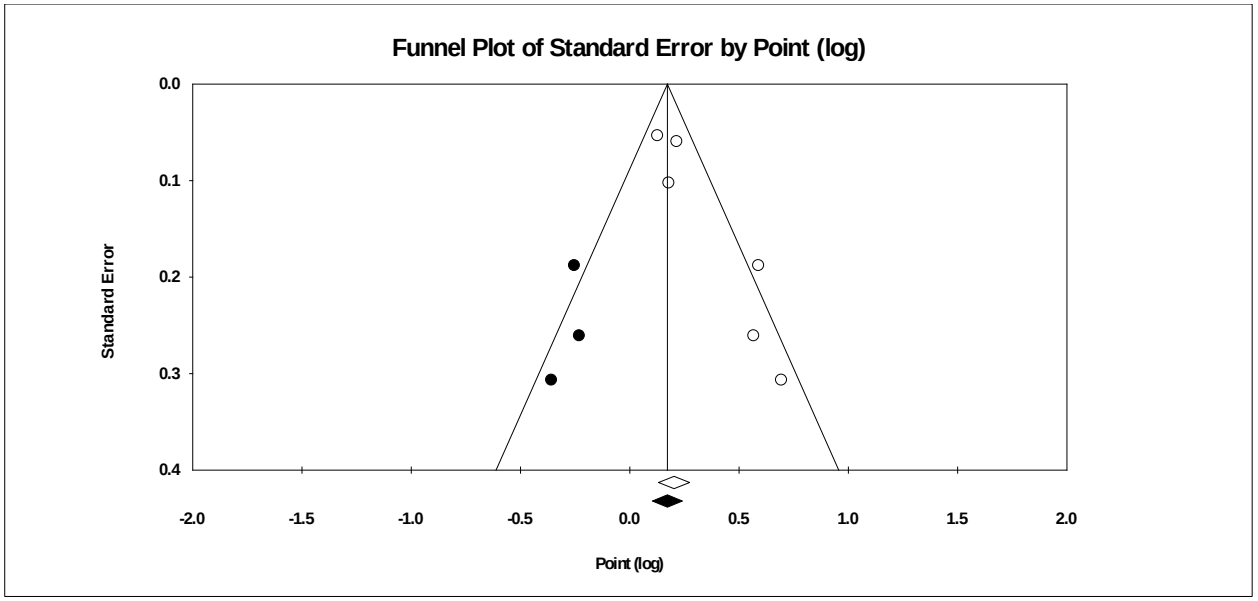


○ Non-shaded circles represent published effect sizes

● Shaded circles represent imputed effect sizes

BPV, blood pressure variability; CSVD, cerebral small vessel disease;

Figure S3. Funnel plot of odds for CSVD attributable to diastolic BPV (trim and fill method)

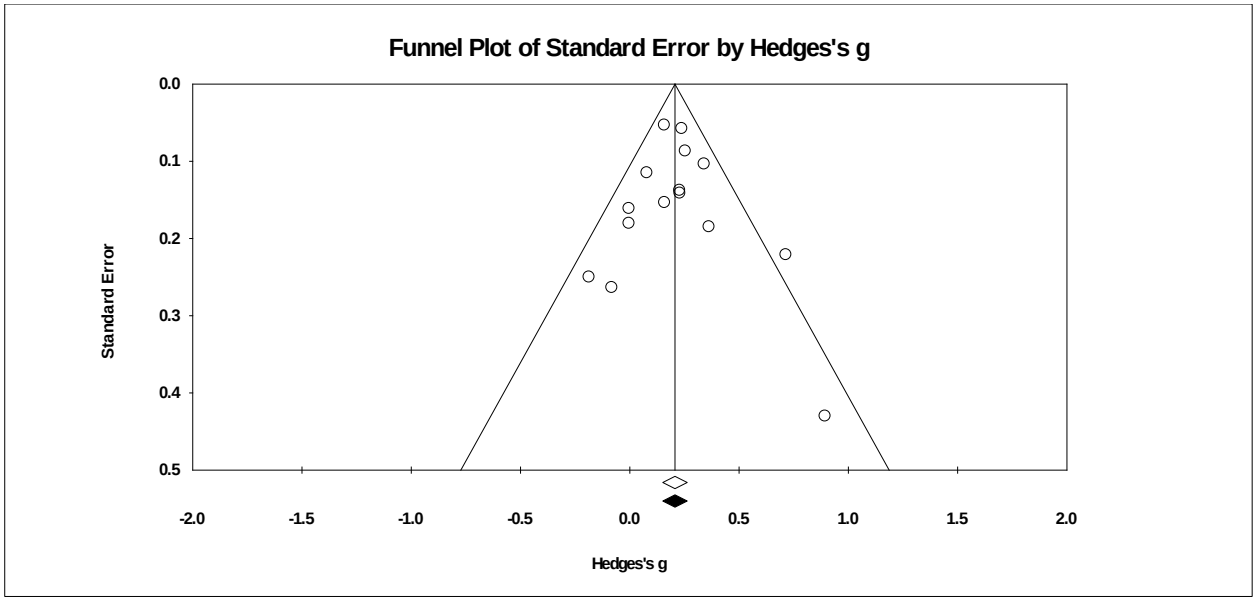


○ Non-shaded circles represent published effect sizes

● Shaded circles represent imputed effect sizes

BPV, blood pressure variability; CSVD, cerebral small vessel disease;

Figure S4. Funnel plot of standardized mean differences in systolic BPV between persons with and without CSVD (trim and fill method)

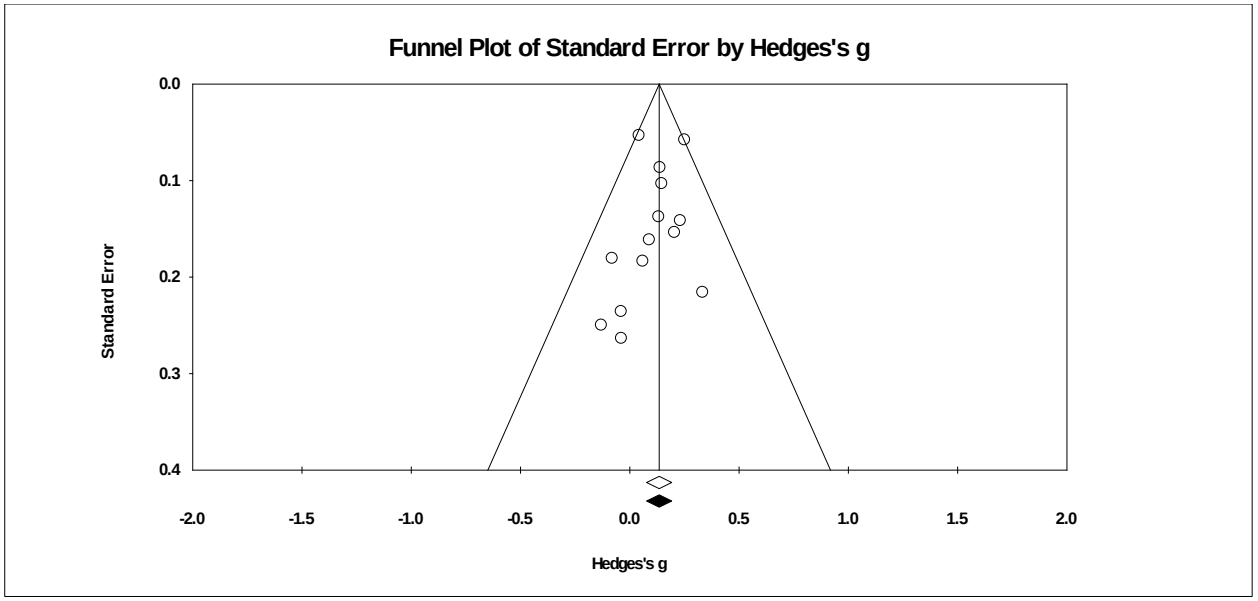


○ Non-shaded circles represent published effect sizes

● Shaded circles represent imputed effect sizes

BPV, blood pressure variability; CSVD, cerebral small vessel disease;

Figure S5. Funnel plot of standardized mean differences in diastolic BPV between persons with and without CSVD (trim and fill method)



○ Non-shaded circles represent published effect sizes

● Shaded circles represent imputed effect sizes

BPV, blood pressure variability; CSVD, cerebral small vessel diseases

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