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Research article

Impact of blood pressure variability and cerebral small vessel disease: A systematic review and meta-analysis

Bingqing Zhao [a], Weihua Jia [a,*], Ye Yuan [a], Ying Chen [a], Yali Gao [a], Baoling Yang [a], Wei Zhao [a], Jingyi Wu [b]

[a] Department of Neurology, Beijing Shijingshan Hospital Capital Medical University Shjingshan Teaching Hospital, China
[b] University of Glasgow, United kingdom

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ABSTRACT

Importance: Abnormal blood pressure pattern is an independent risk factor for vascular events. Blood pressure variability can predict cardiovascular and cerebrovascular disease outcomes and is closely associated with the risk of cognitive impairment. However, the relationship between blood pressure variability and cerebral small vessel disease neuroimaging markers remains unclear. This study aimed to evaluate the relationship between blood pressure variability and cerebral small vessel disease neuroimaging markers.

Data sources: We searched multiple databases, including Embase, Web of Science, PubMed, Cochrane Library, UpToDate, and World of Science, from their inception until November 27, 2023.

Main Outcomes and Measures: A meta-analysis of 19 observational studies involving 14519 participants was performed. Findings: ①Systolic blood pressure variability was correlated with the cerebral small vessel disease total burden, white matter hyperintensities and lacunar infarction; ② Diastolic blood pressure variability was correlated with the cerebral small vessel disease total burden, white matter hyperintensities and cerebral microbleeds; ③ Non-dipping patterns were correlated with white matter hyperintensities and lacunar infarction. ④ Reverse-dipping patterns were significantly correlated with white matter hyperintensities and cerebral microbleeds.

Conclusions: and Relevance: Blood pressure variability correlates with neuroimaging markers of cerebral small vessel disease and its burden. Hence, early monitoring and intervention of blood pressure variability may be essential for the early diagnosis, prevention and treatment of cerebral small vessel disease.

1. Introduction

Cerebral small vessel disease (CSVD) is a syndrome in which cerebral arterioles, capillaries, venules, and other lesions are affected by various factors, leading to clinical, imaging, and pathological changes [1]. The main magnetic resonance imaging (MRI) findings include cerebral microbleeds (CMB), lacunar infarction (LI), white matter hyperintensities (WMHs), and enlarged perivascular spaces (EPVS) [2]. These neuroimaging markers may manifest alone, sequentially, or simultaneously [3]. CSVD total burden score integrates

* Corresponding author.
E-mail address: weihuajia5036@163.com (W. Jia).

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CSVD imaging markers into a whole, scoring CMB, LI, WMHs and EPVSs respectively, with a total score ranging from 0 to 4 [4], which can more comprehensively evaluate the severity of CSVD injury [5]. CSVD is common in the elderly population, and its incidence may increase with age. Most individuals with CSVD display a slow onset of development and may not present clinical symptoms during the early stages [6]. According to research statistics, 25 % of stroke patients and 45 % of dementia patients worldwide have CSVD [7]. An increase in CSVD burden can manifest as cognitive impairment, dementia, mental disorders, gait abnormalities, and urinary and stool disorders [8]. Therefore, attention should be given to this condition by clinicians.

To date, hypertension has been confirmed as the most obvious and important intervention risk factor for CSVD; its main pathogenesis involves its crucial role in vascular endothelial injury [9]. Rothwell et al. [10] suggested that the risk of stroke was related to systolic blood pressure variability (SBPV) and maximum systolic blood pressure during follow-up, but not to average systolic blood pressure. Tully et al. 's meta-analysis showed that both SBPV and Diastolic blood pressure variability (DBPV) were closely related to CSVD [11]. The study further noted that the correlation between blood pressure variability (BPV) and CSVD was independent of mean blood pressure. There is study have confirmed that the damage to CSVD caused by BPV and abnormal blood pressure rhythm is more than the average blood pressure level [12]. Blood pressure circadian rhythm refers to the blood pressure fluctuations in the change of day and night. When the mean nighttime blood pressure drops less than 10 % from the mean daytime blood pressure, it is called non-dipping, while the mean nighttime blood pressure increases from the mean daytime blood pressure, it is called reverse-dipping [13]. BPV and blood pressure rhythm are closely related to the occurrence and development of CSVD [14–16], but most of them are limited to a certain CSVD image marker. However, the correlation between different types of BPV and total CSVD burden remains unclear.

This study investigated the relationship between BPV, including systolic blood pressure variability (SBPV), diastolic blood pressure variability (DBPV), and non-dipping and reverse-dipping patterns, and CSVD neuroimaging markers through a systematic review and meta-analysis of relevant published literature.

2. Methods

We performed a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol for this systematic review was registered in PROSPERO (CRD42023443341).

2.1. Data sources and searches

We conducted comprehensive searches in Embase, Web of Science, PubMed, Cochrane Library, UpToDate, and WOS. The search strategy covered the period from database inception to November 27, 2023. The search keywords and medical subject terms included: “cerebral small vessel disease,” “white matter hyperintensity,” “lacunar infarction,” “cerebral microbleed,” “blood pressure variability,” “non-dipping,” “reverse-dipping,” etc. (Full searches are provided in the supplementary material.)

2.2. Inclusion and exclusion criteria

Studies meeting the following criteria were included: (1) investigated the correlation between BPV and neuroimaging markers of CSVD; (2) were observational studies, including cohort studies, case-control studies, and cross-sectional studies, with the articles published in full; (3) reported multivariate adjustment effect estimates (risk ratios, hazard ratios, or odds ratios [ORs]) with 95 % confidence intervals (CIs) or other estimates that could be converted to ORs; and (4) were published in English. The exclusion criteria were as follows: (1) publication as a review, letter, editorial, or population-based study; (2) unavailable outcome measures; (3) duplicated populations; and (4) small study series (i.e., studies with sample sizes of <50).

2.3. Outcomes

(1) The included studies examined blood pressure variability over time, including hourly variability from 24-h ambulatory blood pressure measurements, and blood pressure follow-up variability measured across months or years in a cohort setting. (2) BPV includes: coefficient of variation (CV), standard deviation (SD), variability independent of mean (VIM), average real variability (ARV) and residual variability. In this study, SD was used to assess BPV. (3) All included studies completed MRI (Tesla, including 0.5T, l.5T, and 3.0T; Sequence: T1WI, T2WI, FLAIR, DWI and SWI). CSVD image burden was evaluated according to the following criteria:WMH: According to the Fazekas scale score, 1 point was recorded when the high signal of the lateral ventricle was 3 or the high signal of the deep white matter was 2 or 3. LI: LI $\geq$ 1, counted as 1 point; CMB: $\geq$1 deep or subtentorial CMB, counted as 1 point; EPVS: The level with the largest number of EPVS on one side of the brain in the basal ganglia region was counted semi-quantitatively. When there were $\geq$11 EPVS, 1 point was counted. Total CSVD image burden: The score of total CSVD image burden was obtained by adding the above 4 CSVD image marker scores, ranging from 0 to 4 points. According to the degree of CSVD burden, they were divided into mild and moderate groups (0–2 points) and severe groups (3–4 points) [17].

2.4. Data extraction

After our initial eligibility assessment, two authors (Wu and Jia) independently completed a data extraction form. Any disagreements were resolved by a third reviewer (Yuan). Characteristics of the studies, including first authors, publication years, study

locations, patient demographic data, MRI sequences, imaging parameters, study designs, CSVD outcome definitions, and reported ORs were extracted.

2.5. Risk of bias assessment

Zhao and Yang evaluated the quality of the included studies. The Newcastle–Ottawa scale (NOS) [18] was used to assess quality in cohort studies. The scale comprised three parts, selection, comparability, and outcome, and the quality of the included literature was assessed across eight sections from these parts. The highest possible NOS score was 9, and a total score of $\geq$7 was classified as high-quality research. The Agency for Healthcare Research and Quality (AHRQ) [19] quality rating scale was used to assess risk of bias for cross-sectional studies. It consisted of 11 items that could be answered with "yes," "no," or "unclear." "Yes" was denoted by 1 point and "no" or "unclear" by 0 points, with the total possible score being 11 points. Subsequently, the literature was classified as low-quality (0–3 points), medium-quality (4–7 points), or high-quality (8–11 points).

2.6. Statistical analysis

Review Manager 5 and Stata 16.0 were used for statistical analysis. A meta-analysis of high-quality literature was performed. Using multiple meta-analyses and providing multiple effect sizes (e.g., SBPV, DBPV, the non-dipping and reverse-dipping patterns) is the highlight of this study. Using a random effects model, the binary classification results were analyzed using odds ratios (OR) and 95 % confidence intervals (CI). This study was performed based on the original data from the included studies OR and risk ratios with 95 % confidence intervals. Hazard ratios was directly considered as RR. In the data transformation, adjusted risk ratios (aRRs) were transformed to ORs [20]. Cochrane Q statistics were used to assess inter-study heterogeneity, with $P \leq 0.1$, or $I2 \geq 50$ % indicating heterogeneity, and $P > 0.1$, or $I2 < 50$ % indicating non-heterogeneity. All effect estimates were reported using 95 % confidence intervals. $P < 0.05$ was considered to be statistically significant. Sensitivity analysis was carried out by conversion effect models and a one-by-one exclusion method, and the source of heterogeneity was investigated by subgroup analysis. The results of meta-analysis

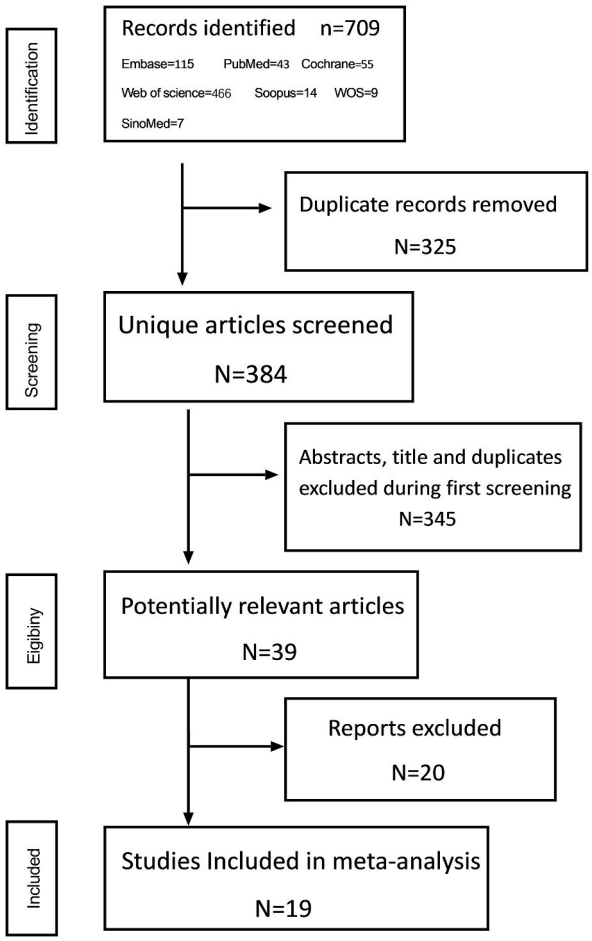
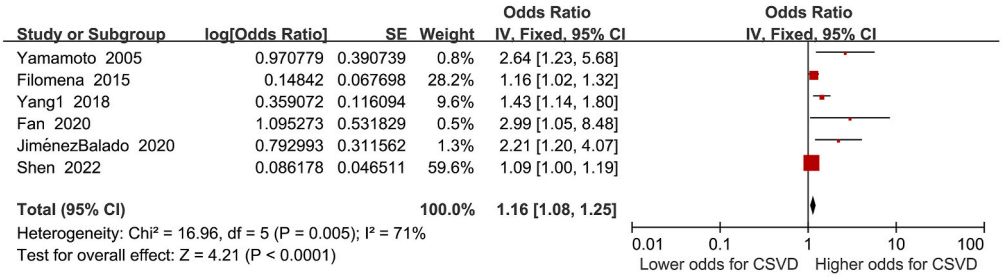


Fig. 1. Flow chart of literature search and article selection process.

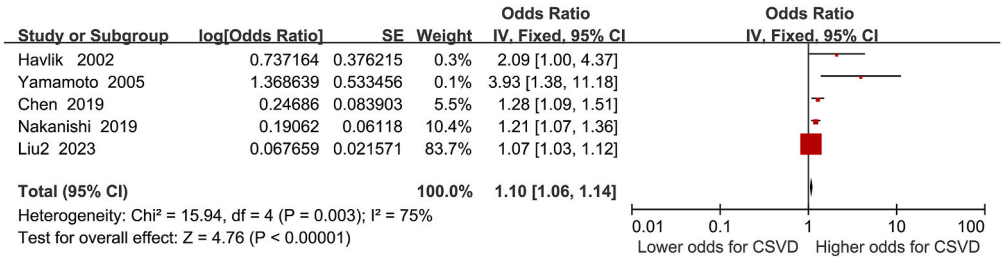
Table 1
Basic features of included studies BP,systolic blood pressure.

First author	Year	Country	Sample size	Sex (male)	Mean age years	Hypertension	BP variability	BP Monitoring	MRI Tesla	Study type	Quality evaluation
Havlik[22]	2002	America	575	575	81.6 ± 5.0	575(100 %)	SD	Visit-to-visit	1.5T	Cohort study	6
Yamamot[23]	2005	Japan	200	101	68.8 ± 9.3	200(100 %)	SD	24-h ABPM	1.5T	Cross-sectional study	9
Lee[24]	2005	Korea	703	334	58.3 ± 6.0	/	SD	24-h ABPM	1.5T	Cross-sectional study	9
Ma[25]	2010	China	188	80	64 ± 7	188(100 %)	SD	24-h ABPM	MRI	Cross-sectional study	6
Shimizu[26]	2011	Japan	514	191	72.3 ± 8.7	514(100 %)	SD	24-h ABPM	1.5T	Cohort study	9
Liu[27]	2012	China	597	415	59.7 ± 9.8	111(18.6 %)	SD	Visit-to-visit	1.5T	Cohort study	7
Sabayan[28]	2013	Netherland	5461	2637	75.3 ± 3.3	3399(62.2 %)	SD	Visit-to-visit	1.5T	Cohort study	7
Kwon[29]	2014	Korea	162	100	65.33 ± 10.32	162(100 %)	SD	24-h ABPM	1.5T	Cross-sectional study	7
Filomena[30]	2015	Spain	487	59	64	487(100 %)	SD	24-h ABPM	1.5T	Cross-sectional study	6
Yang1[31]	2018	China	251	132	58.2 ± 13.4	168(66.9 %)	SD	24-h ABPM	3.0 T	Cross-sectional study	8
Chen[32]	2019	China	140	75	69.24 ± 10.54	140(100 %)	SD	24-h ABPM	1.5T	Cross-sectional study	7
Nakanishi[33]	2019	America	828	330	70.9 ± 9.0	650(78.5 %)	SD	24-h ABPM	1.5T	Cross-sectional study	6
Zhang[34]	2019	China	2091	330	67.81 ± 5.69	1409(67.4 %)	SD	24-h ABPM	3.0 T	Cohort study	8
Fan[35]	2020	China	140	94	65.6 ± 12.4	140(100 %)	SD	24-h ABPM	1.5T,3.0T	Cross-sectional study	8
Yang2[36]	2020	China	1267	702	65 ± 13	1267(100 %)	SD	24-h ABPM	MRI	Cross-sectional study	7
JiménezBalado[37]	2020	Spain	212	119	65	212(100 %)	SD	24-h ABPM	1.5T	Cohort study	8
Shen[38]	2022	China	115	76	67:8 ± 10:2	89(77.4 %)	SD	24-h ABPM	3.0 T	Cross-sectional study	9
Liu2[39]	2023	China	457	234	61.79 ± 8.11	130(28.4 %)	SD	Day-to-day	3.0 T	Cross-sectional study	7
Bao[15]	2023	China	131	84	70	53(40.5 %)	SD	24-h ABPM	1.5T	Cross-sectional study	6

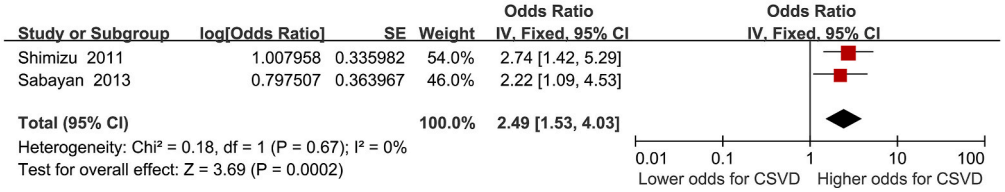
A The relationship between SBPV and CSVD total burden



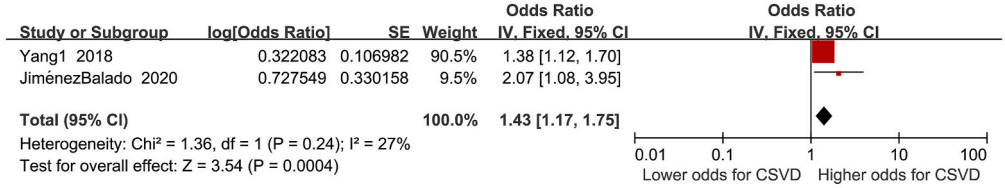
B The relationship between SBPV and WMH



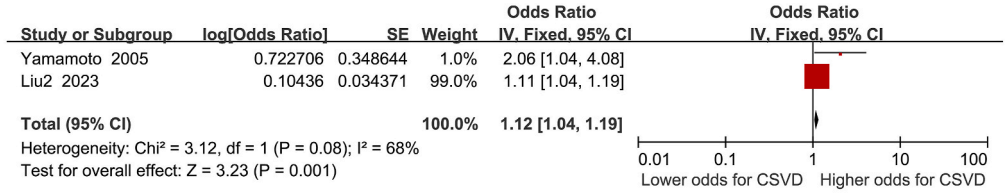
C The relationship between SBPV and LI



D The relationship between DBPV and CSVD total burden



E The relationship between DBPV and WMH



F The relationship between DBPV and CMB

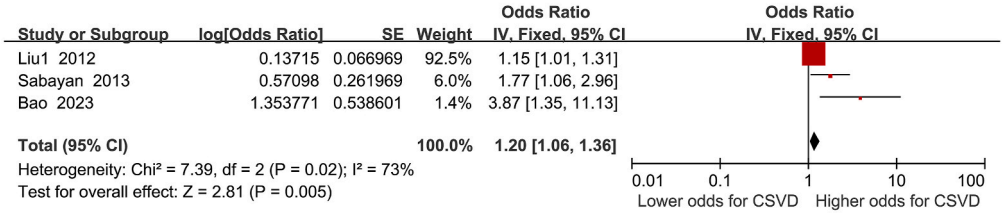


Fig. 2. (A–F) The relationship between CSVD and SBPV and DBPV respectively.

were presented using forest plots. Egger's test and funnel plot were used to detect publication bias of the primary endpoint 5 or more works were included in the plot. All effect estimates were reported using 95 % confidence intervals. $P < 0.05$ was considered to be statistically significant. If publication bias existed, the clip-complement method was used to adjust the effect size.

2.7. Certainty assessment

The overall certainty of observational research evidence was assessed according to the guidelines of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE). For most risk factors of imprecision, risk of bias, publication bias, or heterogeneity, further downgrades were made. According to the corresponding evaluation criteria, the quality of evidence was divided into four categories: high, moderate, low and very low [21].

3. Results

3.1. Study selection

Based on the search method, 709 studies were found, 325 duplicates were removed, and 364 articles, including titles and abstracts, were excluded. After careful evaluation, 19 observational studies (6 cohort studies and 13 cross-sectional studies) were finally included, as per the inclusion criteria (Fig. 1).

3.2. Study characteristics

Our analysis included 19 studies [15,22–39] involving 14519 participants. Among them, 10 studies were from China, 2 each from Japan, South Korea,the United States and the Netherlands, and one from Spain; A total of 6668 male patients, 7851 female patients. Among all patients, 9894 patients had a history of hypertension, and all patients underwent MRI. Standard deviation (SD) was used to measure blood pressure variability. MRI imaging parameters were not provided in 2 studies [25,36] (Table 1).

3.3. Quality assessment

The NOS was used to score the six cohort studies, and the results showed that one had a total score of 9 [26], two had a total score of 8 [34,37], two had total scores of 7 [27,28], and one had a total score of 6 [22]. The AHRQ was used to score the 13 cross-sectional research papers. The results showed that scores of 9, 8, 7, and 6 were obtained by three [23,24,38], two [31,35], four [29,32,36,39], and four papers [15,25,30,33], respectively.

3.4. Results of meta-analysis

The relationship between BPV and CSVD neuroimaging markers was investigated in 19 of the included studies. These markers included SBPV (n = 12), DBPV (n = 7), non-dipping patterns (n = 3), and reverse-dipping patterns (n = 4).

3.4.1. The relationship between SBPV and CSVD neuroimaging markers and CSVD total burden respectively

Twelve studies (four cohort studies and eight cross-sectional studies) analyzed the relationship between SBPV and neuroimaging markers of CSVD and CSVD total burden. Six studies (five cross-sectional studies and one cohort study) suggested a correlation between higher SBPV and CSVD total burden (OR, 1.16; 95 % CI, 1.08–1.25; $I^2 = 71$ %). Five studies (four cross-sectional studies and one cohort study) identified a correlation between SBPV and WMH, and a correlation was identified between the two (OR, 1.10; 95 % CI, 1.06–1.14; $I^2 = 75$ %). Two cohort studies reported a significant association between SBPV and LI (OR, 2.49; 95 % CI, 1.53–4.03; $I^2 = 0$ %) (Fig. 2 A-F).

3.4.2. The relationship between DBPV and CSVD neuroimaging markers and CSVD total burden respectively

Seven studies (3 cohort studies and 4 cross-sectional studies) analyzed the relationship between DBPV and CSVD neuroimaging markers and CSVD total burden. Two studies (1 cross-sectional study and 1 cohort study) suggested a correlation between higher DBPV and CSVD total burden (OR,1.43; 95 % CI,1.17–1.75 $I^2 = 27$ %); Two cross-sectional studies reported a correlation between DBPV and WMH (OR, 1.12; 95 % CI, 1.04–1.19; $I^2 = 68$ %), and three studies(one cross-sectional study and two cohort studies) reported a correlation between DBPV and CMB (OR, 1.20; 95 % CI, 1.06–1.36; $I^2 = 73$ %) (Fig. 2A–F).

3.4.3. Relationship between reverse dipping patterns and neuroimaging markers of CSVD

Five studies (three cross-sectional studies and two cohort studies) analyzed the relationship between reverse-dipping patterns and neuroimaging markers of CSVD. Three studies (two cross-sectional studies and one cohort study) reported correlations between reverse-dipping patterns and WMH (OR, 1.72; 95 % CI, 1.33–2.22; $I^2 = 0$ %). Two studies (one cross-sectional study and one cohort study) reported a clear association between reverse-dipping patterns and CMB (OR, 2.43; 95 % CI, 1.57–3.76; $I^2 = 0$ %) (Fig. 3A–F).

3.4.4. Relationship between non-dipping patterns and neuroimaging markers of CSVD

Among the literature searched, three articles (two cross-sectional studies and one cohort study) discussed the relationship between

non-dipping patterns and neuroimaging markers of CSVD. Two studies (ono cross-sectional study and one cohort study) reported that non-dipping patterns were correlated with WMH (OR, 2.07; 95 % CI, 1.43–2.99; $I^2 = 0$ %). Two studies (one cross-sectional study and one cohort study) reported the relationship between non-dipping patterns and LI. The results showed a clear correlation between the two. (OR, 2.94; 95 % CI, 2.05–4.22; $I^2 = 86$ %) (Fig. 3A–D) (Table 2)

4. Discussion

The pathogenesis of CSVD induced by increased BPV remains unclear. Excessive fluctuations in blood pressure may cause hemodynamic instability, leading to vascular wall destruction, vascular endothelial function impairment, brain tissue ischemia and

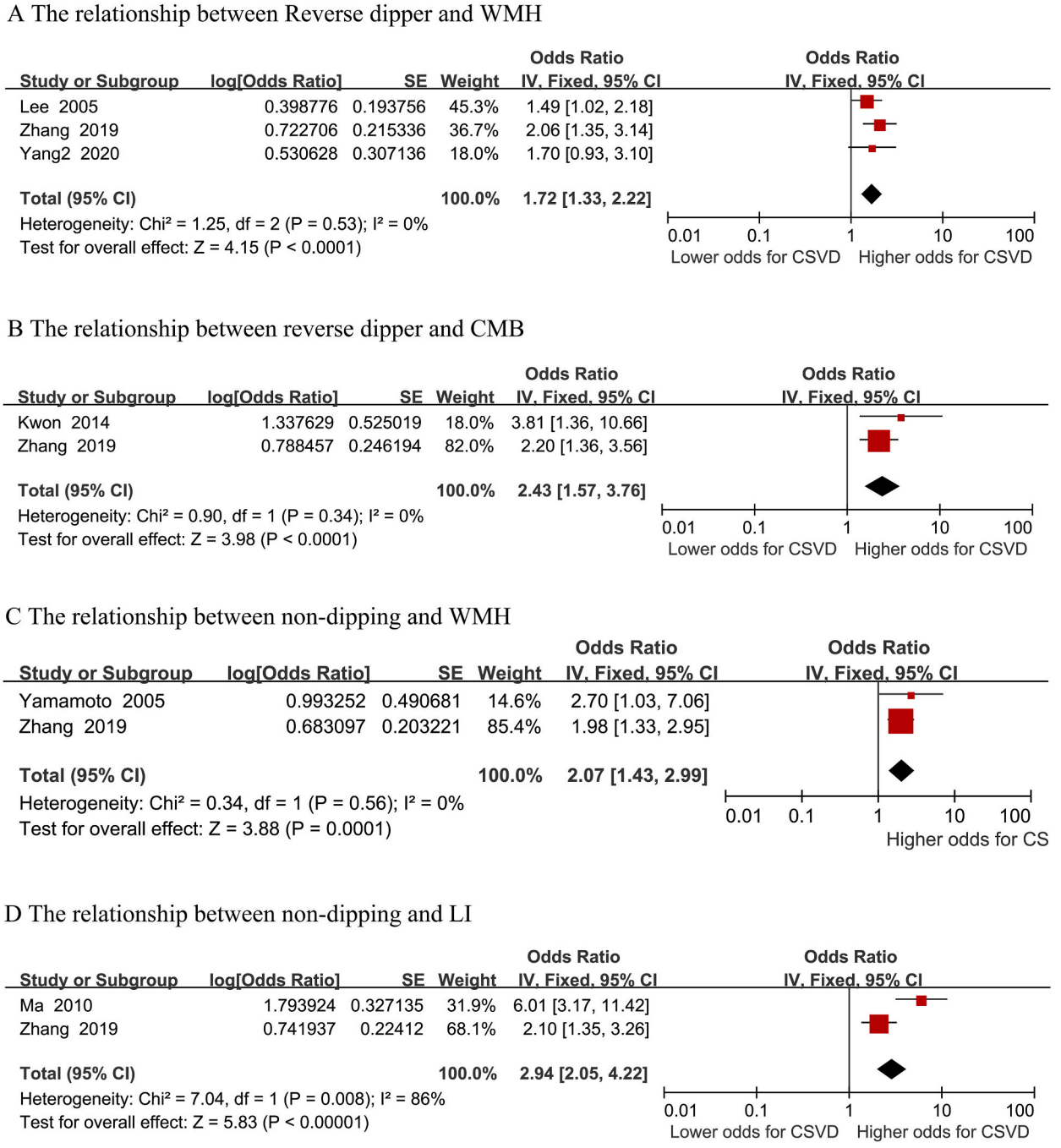


Fig. 3. (A–D) The relationship between CSVD and Reverse dipper and Non-dipping respectively.

Table 2
Certainty of evidence and summary effect estimates assessed by GRADE (grading of recommendations, assessment, development, and evaluation) of the study outcomes.

Outcomes	Summary of findings		Quality assessment					Certainty of evidence
	No. studies	OR (95%CI)	Study design[a]	Inconsistency[b]	Indirectness	Imprecision[c]	Other consideration	
SBPV and CSVD total burden	6	1.16 (1.08–1.25)	serious	serious	not serious	serious	Funnel plot bias	⊕OOO VERY LOW
SBPV and WMH	5	1.10 (1.06–1.14)	serious	serious	not serious	serious	Funnel plot bias	⊕OOO VERY LOW
SBPV and LI	2	2.49 (1.53–4.03)	not serious	not serious	not serious	not serious	none	⊕⊕OO LOW
DBPV and CSVD total burden	2	1.43 (1.17–1.75)	not serious	not serious	not serious	not serious	none	⊕⊕OO LOW
DBPV and WMH	2	1.12 (1.04–1.19)	serious	serious	not serious	serious	none	⊕OOO VERY LOW
DBPV and CMB	3	1.20 (1.06–1.36)	serious	serious	not serious	serious	none	⊕OOO VERY LOW
Reverse dipper and WMH	3	1.72 (1.33–2.22)	serious	not serious	not serious	not serious	none	⊕OOO VERY LOW
Reverse dipper and CMB	2	2.43 (1.57–3.76)	serious	not serious	not serious	not serious	none	⊕OOO VERY LOW
Non-dipper and WMH	2	2.07 (1.43–2.99)	not serious	not serious	not serious	not serious	none	⊕⊕OO LOW
Non-dipper and LI	2	2.94 (2.05–4.22)	serious	very serious	not serious	not serious	none	⊕OOO VERY LOW

Downgraded by one level if Funnel plot bias.
[a] Downgraded by one level if moderate risk of bias studies.
[b] Downgraded by one level if heterogeneity (I2) >50 %, Downgraded by two level if heterogeneity (I2) >75 %.
[c] Downgraded by one level if the limits of the 95 % CI for risk estimates are wide or cross a minimally important difference of 10 % for outcomes.

hypoperfusion, and other factors [40–42].In our systematic review and meta-analysis, we found that SBPV and DBPV were closely related to the CSVD total burden score. This is consistent with the results of Tully et al. 's meta-analysis, which showed that increased SBPV and DBPV can promote the occurrence of CSVD. The study further suggests that SBPV may have a higher impact on CSVD than DBPV [11]. Fan et al. [35] found that SBPV is not only an independent risk factor for the total burden of CSVD, it can be used as an independent predictor of CSVD progression. The above studies suggest that SBPV has a greater impact on CSVD, which may be related to the greater impact of SBPV on vascular risk factors than DBPV [31]. There are few studies on BPV and CSVD total burden, and more studies are needed to explore the impact of BPV on CSVD total burden in the future. As the most common clinical feature of CSVD, WMHs has garnered much attention from scholars. Its association with high blood pressure has been frequently reported. However, the relationship between BPV and WMH has been controversial. In this study, we used the standard deviation of blood pressure (SDBP) to represent BPV. We found that both SBPV and DBPV can promote WMH development. In addition, by studying the relationship between Blood pressure CV and WMH, Zhang et al. found that systolic blood pressure CV (OR = 1.589,95 % CI 1.273–1.983) and diastolic blood pressure CV (OR = 1.363,95 % CI 1.150–1.616) were significantly correlated with Fazekas score ($P < 0.05$) [43]. Moreover, some studies have further pointed out that both short-term SBPV and long-term SBPV cause varying degrees of damage to WMH [32,44]. After a 2-year follow-up, Starmans et al. found that 24-h DBPV can promote WMH volume progression [44]. Therefore, controlling BPV may be beneficial for delaying the progression of WMH. Our study indicates a clear association between SBPV and LI (OR,2.49; 95 % CI,1.53–4.03 I2 = 0 %). Short-term SBPV has also been found to predict the risk of LI occurrence. Long-term SBPV is an important predictor of risk of all-cause death and cardiovascular mortality in patients with lacunar stroke [30,45]. Some studies have explored the correlation between BPV and CMB. In a study of 720 patients with ischemic stroke followed for 12–18 months, SBPV was found to be an independent risk factor for deep and subtentorial CMB progression [27]. Due to the lack of relevant literature, our study could not analyze the correlation between SBPV and CMB. However, there is a correlation between DBPV and CMB (OR,1.20; 95 % CI, 1.06–1.36). Brauner et al. further suggested that DBPV increased the future occurrence of ICH in CMB patients (OR, 2.06, 95%CI, 1.13–3.77) [46].

Circadian rhythms are crucial for regulating and maintaining normal physiological functions in the body. Non-dipping and reverse-dipping patterns are considered the strong predictors of cardiovascular and cerebrovascular disease mortality and damage from chronic kidney disease [47,48]. Xu et al. [49] studied 1996 patients with ischemic stroke (IS)/transient ischemic attack to evaluate the impact of different blood pressure patterns on stroke recurrence and found that the risk of stroke recurrence for reverse-dipping patterns over three months increased by 31 %. Few studies have examined the effect of blood pressure rhythm on CSVD. Our findings suggest that non-dipping and reverse-dippers patterns were strongly associated with CSVD imaging markers (WMH, LI, CMB) and were risk factors contributing to a high prevalence of CSVD. This may be related to abnormal blood pressure rhythms, vascular endothelial dysfunction, decreased sensitivity of the baroreceptor reflex, autonomic nervous system dysfunction, and other factors [50,51]. Factors and diseases that can cause such physiological changes in these patients include age, diabetes, neurodegenerative diseases, chronic kidney disease, and obstructive sleep apnea [52,53].

BPV is closely related to CSVD neuroimaging markers and CSVD total burden. In our study, SBPV, DBPV, non-dipping and reverse-dipping patterns were more closely related to CSVD. Rational blood pressure reduction is essential for patients with CSVD. Therefore, BPV intervention is important in controlling the development of CSVD [32,34]. Further, studies are needed to evaluate the significance of BPV in the early diagnosis and prevention of CSVD.

5. Limitations of the study

First, in our systematic review and meta-analysis, heterogeneity and bias was obvious, likely due to significant differences across all studies, in terms of design methods, inclusion criteria, data collection, and analysis, thus affecting the results of the meta-analysis; Additionally, in the included studies, the Asian population accounted for a large proportion, compared with the non-Asian population, resulting in a demographic bias. CSVD is more common in Asians than in Caucasians [54,55]. Thus, regional differences in CSVD are worth consideration. Second, due to an insufficient number of existing studies, we did not explore the relationship between BPV and EPVS expansion. Finally, many cross-sectional studies were included in our meta-analysis, and large-scale prospective cohort studies or randomized controlled trials are required for a more comprehensive analysis.

6. Conclusion

In this systematic review and meta-analysis of observational studies, blood pressure variability correlates with neuroimaging markers of cerebral small vessel disease and its burden. Hence, early monitoring and intervention of blood pressure variability may be essential for the early diagnosis, prevention and treatment of cerebral small vessel disease.

Funding support

None funding available.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethical approval

The protocol for this systematic review was registered in PROSPERO (CRD42023443341).

CRediT authorship contribution statement

Bingqing Zhao: Writing – review & editing, Writing – original draft, Software, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Weihua Jia:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis, Data curation. **Ye Yuan:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Ying Chen:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Yali Gao:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Baoling Yang:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Wei Zhao:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Jingyi Wu:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33264.

References

[1] B. Zhao, W. Jia, Y. Yuan, Z. Li, X. Fu, Effects of intensive blood pressure control on cognitive function in patients with cerebral small vessel disease, J. Stroke Cerebrovasc. Dis. 32 (2023) 107289, https://doi.org/10.1016/j.jstrokecerebrovasdis.2023.107289.

[2] H. van den Brink, F.N. Doubal, M. Duering, Advanced MRI in cerebral small vessel disease, Int. J. Stroke 18 (2023) 28–35, https://doi.org/10.1177/17474930221091879.

[3] R. Brown, H. Benveniste, S.E. Black, S. Charpak, M. Dichgans, A. Joutel, M. Nedergaard, K.J. Smith, B.V. Zlokovic, J.M. Wardlaw, Understanding the role of the perivascular space in cerebral small vessel disease, Cardiovasc. Res. 114 (2018) 1462–1473, https://doi.org/10.1093/cvr/cvy113.

[4] M. Huijts, A. Duits, R.J. van Oostenbrugge, A.A. Kroon, P.W. de Leeuw, J. Staals, Accumulation of MRI markers of cerebral small vessel disease is associated with decreased cognitive function. A study in first-ever lacunar stroke and hypertensive patients, Front. Aging Neurosci. 5 (2013) 72, https://doi.org/10.3389/fnagi.2013.00072.

[5] S.P. Rensma, T.T. van Sloten, L.J. Launer, C.D.A. Stehouwer, Cerebral small vessel disease and risk of incident stroke, dementia and depression, and all-cause mortality: a systematic review and meta-analysis, Neurosci. Biobehav. Rev. 90 (2018) 164–173, https://doi.org/10.1016/j.neubiorev.2018.04.003.

[6] J.M. Wardlaw, C. Smith, M. Dichgans, Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging, Lancet Neurol. 12 (2013) 483–497, https://doi.org/10.1016/S1474-4422(13)70060-7.

[7] R. Uiterwijk, R.J. van Oostenbrugge, M. Huijts, P.W. De Leeuw, A.A. Kroon, J. Staals, Total cerebral small vessel disease MRI score is associated with cognitive decline in executive function in patients with hypertension, Front. Aging Neurosci. 8 (2016) 301, https://doi.org/10.3389/fnagi.2016.00301.

[8] Chinese Neuroscience Society, Cerebrovascular Group of Chinese Neuroscience Society, Guidelines for Diagnosis and Treatment of small cerebral vascular diseases in China 2020, Chin. J. Neurol. 55 (2022) 807–818.

[9] J.M. Wardlaw, C. Smith, M. Dichgans, Small vessel disease: mechanisms and clinical implications, Lancet Neurol. 18 (2019) 684–696, https://doi.org/10.1016/S1474-4422(19)30079-1.

[10] P.M. Rothwell, S.C. Howard, E. Dolan, E. O'Brien, J.E. Dobson, B. Dahlöf, P.S. Sever, N.R. Poulter, Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension, Lancet 375 (2010) 895–905, https://doi.org/10.1016/S0140-6736(10)60308-X.

[11] P.J. Tully, Y. Yano, L.J. Launer, K. Kario, M. Nagai, S.P. Mooijaart, J.A.H.R. Claassen, S. Lattanzi, A.D. Vincent, C. Tzourio, Association between blood pressure variability and cerebral small-vessel disease: a systematic review and meta-analysis, J. Am. Heart Assoc. 9 (2020) e013841, https://doi.org/10.1161/JAHA.119.013841.

[12] S. Tan, L. Li, X. Liu, M. He, Impact of circadian rhythm of blood pressure and blood pressure variability on cerebral small vessel disease, J. Clin. Neurol. 37 (2024) 145–148.

[13] H.M. Costello, M.L. Gumz, Circadian rhythm, clock genes, and hypertension: recent advances in hypertension, Hypertension 78 (2021) 1185–1196, https://doi.org/10.1161/HYPERTENSIONAHA.121.14519.

[14] A. Chokesuwattanaskul, W. Cheungpasitporn, C. Thongprayoon, S. Vallabhajosyula, T. Bathini, M.A. Mao, L.D. Cato, R. Chokesuwattanaskul, Impact of circadian blood pressure pattern on silent cerebral small vessel disease: a systematic review and meta-analysis, J. Am. Heart Assoc. 9 (2020) e016299, https://doi.org/10.1161/JAHA.119.016299.

[15] Y. Bao, J. Gu, T. Lv, M. Chen, K. Zhao, Y. Yang, D. Gu, Correlation between blood pressure variability and deep cerebral microbleeds in patients with acute ischemic stroke, Folia Neuropathol. 61 (2023) 309–316, https://doi.org/10.5114/fn.2023.130006.

[16] B. Yan, L. Peng, Q. Dong, F. Zheng, P. Yang, L. Sun, S. Gong, L. Zeng, G. Wang, Reverse-dipper pattern of blood pressure may predict lacunar infarction in patients with essential hypertension, Eur. J. Neurol. 22 (2015) 1022–1025, https://doi.org/10.1111/ene.12659.

[17] J. Staals, S.D.J. Makin, F.N. Doubal, M.S. Dennis, J.M. Wardlaw, Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden, Neurology 83 (2014) 1228–1234, https://doi.org/10.1212/WNL.0000000000000837.

[18] A. Stang, Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses, Eur. J. Epidemiol. 25 (2010) 603–605, https://doi.org/10.1007/s10654-010-9491-z.

[19] C. Venter, C. Agostoni, S.H. Arshad, M. Ben-Abdallah, G. Du Toit, D.M. Fleischer, M. Greenhawt, D.H. Glueck, M. Groetch, N. Lunjani, K. Maslin, A. Maiorella, R. Meyer, M. Antonella, M.J. Netting, B. Ibeabughichi Nwaru, D.J. Palmer, M.P. Palumbo, G. Roberts, C. Roduit, P. Smith, E. Untersmayr, L.A. Vanderlinden, L. O'Mahony, Dietary factors during pregnancy and atopic outcomes in childhood: a systematic review from the European Academy of Allergy and Clinical Immunology, Pediatr. Allergy Immunol. 31 (2020) 889–912, https://doi.org/10.1111/pai.13303.

[20] R.L. Grant, Converting an odds ratio to a range of plausible relative risks for better communication of research findings. https://doi.org/10.1136/bmj.f7450, 2014.

[21] N.D. Berkman, K.N. Lohr, M.T. Ansari, E.M. Balk, R. Kane, M. McDonagh, S.C. Morton, M. Viswanathan, E.B. Bass, M. Butler, G. Gartlehner, L. Hartling, M. McPheeters, L.C. Morgan, J. Reston, P. Sista, E. Whitlock, S. Chang, Grading the strength of a body of evidence when assessing health care interventions: an EPC update, J. Clin. Epidemiol. 68 (2015) 1312–1324, https://doi.org/10.1016/j.jclinepi.2014.11.023.

[22] R.J. Havlik, D.J. Foley, B. Sayer, K. Masaki, L. White, L.J. Launer, Variability in midlife systolic blood pressure is related to late-life brain white matter lesions: the Honolulu-Asia Aging study, Stroke 33 (2002) 26–30, https://doi.org/10.1161/hs0102.101890.

[23] Y. Yamamoto, I. Akiguchi, K. Oiwa, M. Hayashi, T. Ohara, K. Ozasa, The relationship between 24-hour blood pressure readings, subcortical ischemic lesions and vascular dementia, Cerebrovasc. Dis. 19 (2005) 302–308, https://doi.org/10.1159/000084498.

[24] S. Lee, R.J. Thomas, H. Kim, H.S. Seo, I. Baik, D.W. Yoon, S.J. Kim, S.K. Lee, C. Shin, Association between high nocturnal blood pressure and white matter change and its interaction by obstructive sleep apnoea among normotensive adults, J. Hypertens. 32 (2014) 2005–2012, https://doi.org/10.1097/HJH.0000000000000290. ; discussion 2012.

[25] J.F. Ma, J.L. Sun, J. Zhao, X. Wei, B.S. Wang, Y. Fu, Relationship between nocturnal blood pressure variation and silent cerebral infarction in Chinese hypertensive patients, J. Neurol. Sci. 294 (2010) 67–69, https://doi.org/10.1016/j.jns.2010.04.002.

[26] M. Shimizu, J. Ishikawa, Y. Yano, S. Hoshide, K. Shimada, K. Kario, The relationship between the morning blood pressure surge and low-grade inflammation on silent cerebral infarct and clinical stroke events, Atherosclerosis 219 (2011) 316–321, https://doi.org/10.1016/j.atherosclerosis.2011.06.030.

[27] W. Liu, R. Liu, W. Sun, Q. Peng, W. Zhang, E. Xu, Y. Cheng, M. Ding, Y. Li, Z. Hong, J. Wu, J. Zeng, C. Yao, Y. Huang, Different impacts of blood pressure variability on the progression of cerebral microbleeds and white matter lesions, Stroke 43 (2012) 2916–2922, https://doi.org/10.1161/STROKEAHA.112.658369.

[28] B. Sabayan, L.W. Wijsman, J.C. Foster-Dingley, D.J. Stott, I. Ford, B.M. Buckley, N. Sattar, J.W. Jukema, M.J.P. van Osch, J. van der Grond, M.A. van Buchem, R. G.J. Westendorp, A.J.M. de Craen, S.P. Mooijaart, Association of visit-to-visit variability in blood pressure with cognitive function in old age: prospective cohort study, BMJ 347 (2013) f4600, https://doi.org/10.1136/bmj.f4600.

[29] H.-M. Kwon, J.-S. Lim, Y.S. Kim, J. Moon, H. Park, H.Y. Kim, Y.-H. Lim, H. Nam, Cerebral microbleeds are associated with nocturnal reverse dipping in hypertensive patients with ischemic stroke, BMC Neurol. 14 (2014) 8, https://doi.org/10.1186/1471-2377-14-8.

[30] J. Filomena, I. Riba-Llena, E. Vinyoles, J.L. Tovar, X. Mundet, X. Castañé, A. Vilar, A. López-Rueda, J. Jiménez-Baladó, A. Cartanyà, J. Montaner, P. Delgado, Short-term blood pressure variability relates to the presence of subclinical brain small vessel disease in primary hypertension, Hypertension 66 (2015) 634–640, https://doi.org/10.1161/HYPERTENSIONAHA.115.05440. ; discussion 445.

[31] S. Yang, J. Yuan, W. Qin, L. Yang, H. Fan, Y. Li, W. Hu, Twenty-four-hour ambulatory blood pressure variability is associated with total magnetic resonance imaging burden of cerebral small-vessel disease, Clin. Interv. Aging 13 (2018) 1419–1427, https://doi.org/10.2147/CIA.S171261.

[32] X. Chen, Y. Zhu, S. Geng, Q. Li, H. Jiang, Association of blood pressure variability and intima-media thickness with white matter hyperintensities in hypertensive patients, Front. Aging Neurosci. 11 (2019) 192, https://doi.org/10.3389/fnagi.2019.00192.

[33] K. Nakanishi, Z. Jin, S. Homma, M.S.V. Elkind, T. Rundek, J.E. Schwartz, T.C. Lee, A. Tugcu, M. Yoshita, C. DeCarli, C.B. Wright, R.L. Sacco, M.R. Di Tullio, Night-time systolic blood pressure and subclinical cerebrovascular disease: the Cardiovascular Abnormalities and Brain Lesions (CABL) study, Eur Heart J Cardiovasc Imaging 20 (2019) 765–771, https://doi.org/10.1093/ehjci/jey221.

[34] H. Zhang, Y. Cui, Y. Zhao, Y. Dong, J. Wang, D. Duan, T. Ji, T. Zhou, W. Hu, Y. Chen, S. Sun, G. Gong, Q. Chai, Z. Liu, Association of circadian rhythm of blood pressure and cerebral small vessel disease in community-based elderly population, J Gerontol A Biol Sci Med Sci 74 (2019) 1322–1330, https://doi.org/10.1093/gerona/gly212.

[35] Y. Fan, C. Hou, L. Peng, X. Gao, Y. Xu, Twenty-four-hour ambulatory blood pressure variability associated with cerebral small vessel disease MRI burden and its progression in inpatients with cerebrovascular disease, Front. Neurol. 11 (2020) 513067, https://doi.org/10.3389/fneur.2020.513067.

[36] K. Yang, X. Zhu, Y. Feng, F. Shen, J. Chen, N. Fu, J. Sun, Y. Fu, Abnormal blood pressure circadian rhythms are relevant to cerebral infarction and Leukoaraiosis in hypertensive patients, BMC Neurol. 20 (2020) 36, https://doi.org/10.1186/s12883-020-1626-6.

[37] J. Jiménez-Balado, I. Riba-Llena, O. Maisterra, J. Pizarro, A. Palasí, F. Pujadas, X. Mundet, E. Vinyoles, P. Delgado, Ambulatory blood pressure levels in the prediction of progression of cerebral small vessel disease, J. Am. Geriatr. Soc. 68 (2020) 2232–2239, https://doi.org/10.1111/jgs.16568.
[38] J. Shen, L. Yang, Z. Xu, W. Wei, Association between twenty-four-hour ambulatory blood pressure variability and cerebral small vessel disease burden in acute ischemic stroke, Behav. Neurol. 2022 (2022) 3769577, https://doi.org/10.1155/2022/3769577.
[39] S. Liu, M. Wang, D. Gu, Y. Li, X. Zhang, H. Li, C. Ji, X. Nie, J. Liu, Optimal systolic and diastolic blood pressure threshold that associated with lower risk of white matter hyperintensity progression, Front. Aging Neurosci. 15 (2023) 1254463, https://doi.org/10.3389/fnagi.2023.1254463.
[40] J. Kroon, N. Heemskerk, M.J.T. Kalsbeek, V. de Waard, J. van Rijssel, J.D. van Buul, Flow-induced endothelial cell alignment requires the RhoGEF Trio as a scaffold protein to polarize active Rac1 distribution, Mol. Biol. Cell 28 (2017) 1745–1753, https://doi.org/10.1091/mbc.E16-06-0389.
[41] K.M. Diaz, P. Veerabhadrappa, M.A. Kashem, D.L. Feairheller, K.M. Sturgeon, S.T. Williamson, D.L. Crabbe, M.D. Brown, Relationship of visit-to-visit and ambulatory blood pressure variability to vascular function in African Americans, Hypertens. Res. 35 (2012) 55–61, https://doi.org/10.1038/hr.2011.135.
[42] P.J. Tully, S. Qchiqach, E. Pereira, S. Debette, B. Mazoyer, C. Tzourio, Development and validation of a priori risk model for extensive white matter lesions in people age 65 years or older: the Dijon MRI study, BMJ Open 7 (2017) e018328, https://doi.org/10.1136/bmjopen-2017-018328.
[43] D. Zhang, M. He, Q. He, Z. Li, Blood pressure rhythm and blood pressure variability as risk factors for white matter lesions: a cross-sectional study, Med Sci Monit 28 (2022) e933880, https://doi.org/10.12659/MSM.933880.
[44] N.L. Starmans, F.J. Wolters, A.E. Leeuwis, E.E. Bron, H.-P. Brunner La Rocca, J. Staals, G.J. Biessels, L.J. Kappelle, Twenty-four hour blood pressure variability and the prevalence and the progression of cerebral white matter hyperintensities, J Cereb Blood Flow Metab 43 (2023) 801–811, https://doi.org/10.1177/0271678X221149937.
[45] E. Ku, R. Scherzer, M.C. Odden, M. Shlipak, C.L. White, T.S. Field, O. Benavente, P.E. Pergola, C.A. Peralta, Patterns of Blood Pressure Response during Intensive BP Lowering and Clinical Events: Results from the Secondary Prevention of Small Subcortical Strokes Trial, vol.27, Blood Press, 2018, pp. 73–81, https://doi.org/10.1080/08037051.2017.1382310.
[46] R. Brauner, B. Gory, B. Lapergue, I. Sibon, S. Richard, M. Kyheng, J. Labreuche, J.-P. Desilles, R. Blanc, M. Piotin, J.-M. Halimi, M. Mazighi, B. Maïer, Effect of small vessel disease severity on blood pressure management after endovascular therapy in the BP TARGET trial, Eur. J. Neurol. 30 (2023) 1676–1685, https://doi.org/10.1111/ene.15759.
[47] W.-Y. Yang, J.D. Melgarejo, L. Thijs, Z.-Y. Zhang, J. Boggia, F.-F. Wei, T.W. Hansen, K. Asayama, T. Ohkubo, J. Jeppesen, E. Dolan, K. Stolarz-Skrzypek, S. Malyutina, E. Casiglia, L. Lind, J. Filipovský, G.E. Maestre, Y. Li, J.-G. Wang, Y. Imai, K. Kawecka-Jaszcz, E. Sandoya, K. Narkiewicz, E. O'Brien, P. Verhamme, J.A. Staessen, Association of office and ambulatory blood pressure with mortality and cardiovascular outcomes, JAMA 322 (2019) 409–420, https://doi.org/10.1001/jama.2019.9811.
[48] C. Wang, J. Zhang, X. Liu, C. Li, Z. Ye, H. Peng, Z. Chen, T. Lou, Reversed dipper blood-pressure pattern is closely related to severe renal and cardiovascular damage in patients with chronic kidney disease, PLoS One 8 (2013) e55419, https://doi.org/10.1371/journal.pone.0055419.
[49] J. Xu, F. Jiang, A. Wang, H. Zhi, Y. Gao, J. Tian, J. Mo, Z. Chen, A.-D. Xu, B. Luo, B. Hu, Y. Zhang, X. Zhao, Y. Wang, H. Li, H. Shen, Y. Wang, Ambulatory blood pressure profile and stroke recurrence, Stroke Vasc Neurol 6 (2021) 352–358, https://doi.org/10.1136/svn-2020-000526.
[50] R. Maio, M. Perticone, A. Sciacqua, E.J. Tassone, P. Naccarato, C. Bagnato, G. Iannopollo, G. Sesti, F. Perticone, Oxidative stress impairs endothelial function in nondipper hypertensive patients, Cardiovasc Ther 30 (2012) 85–92, https://doi.org/10.1111/j.1755-5922.2010.00183.x.
[51] C.H. Gibbons, P. Schmidt, I. Biaggioni, C. Frazier-Mills, R. Freeman, S. Isaacson, B. Karabin, L. Kuritzky, M. Lew, P. Low, A. Mehdirad, S.R. Raj, S. Vernino, H. Kaufmann, The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension, J. Neurol. 264 (2017) 1567–1582, https://doi.org/10.1007/s00415-016-8375-x.
[52] A.M. Birkenhäger, A.H. van den Meiracker, Causes and consequences of a non-dipping blood pressure profile, Neth. J. Med. 65 (2007) 127–131.
[53] K. Kario, Nocturnal hypertension: new technology and evidence, Hypertension 71 (2018) 997–1009, https://doi.org/10.1161/HYPERTENSIONAHA.118.10971.
[54] S. Hilal, V. Mok, Y.C. Youn, A. Wong, M.K. Ikram, C.L.-H. Chen, Prevalence, risk factors and consequences of cerebral small vessel diseases: data from three Asian countries, J. Neurol. Neurosurg. Psychiatry 88 (2017) 669–674, https://doi.org/10.1136/jnnp-2016-315324.
[55] Y. Shi, J.M. Wardlaw, Update on cerebral small vessel disease: a dynamic whole-brain disease, Stroke Vasc Neurol 1 (2016) 83–92, https://doi.org/10.1136/svn-2016-000035.