Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Impact of Circadian Blood Pressure Pattern on Silent Cerebral Small Vessel Disease: A Systematic Review and Meta-Analysis

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BACKGROUND: Abnormal circadian blood pressure (BP) variations during sleep, specifically the non-dipping (<10% fall in nocturnal BP) and reverse-dipping patterns (rise in nocturnal BP), have been associated with an increased risk of cardiovascular events and target organ damage. However, the relationship between abnormal sleep BP variations and cerebral small vessel disease markers is poorly established. This study aims to assess the association between non-dipping and reverse-dipping BP patterns with markers of silent cerebral small vessel disease.

METHODS AND RESULTS: MEDLINE, Embase, and Cochrane Databases were searched from inception through November 2019. Studies that reported the odds ratios (ORs) for cerebral small vessel disease markers in patients with non-dipping or reverse-dipping BP patterns were included. Effect estimates from the individual studies were extracted and combined using the random-effect, generic inverse variance method of DerSimonian and Laird. Twelve observational studies composed of 3497 patients were included in this analysis. The reverse-dipping compared with normal dipping BP pattern was associated with a higher prevalence of white matter hyperintensity with a pooled adjusted OR of 2.00 (95% CI, 1.13–2.37; I^2=36%). Non-dipping BP pattern compared with normal dipping BP pattern was associated with higher prevalence of white matter hyperintensity and asymptomatic lacunar infarction, with pooled ORs of 1.38 (95% CI, 0.95–2.02; I^2=52%) and 2.33 (95% CI, 1.30–4.18; I^2=73%), respectively. Limiting to only studies with confounder-adjusted analysis resulted in a pooled OR of 1.38 (95% CI, 0.95–2.02; I^2=52%) for white matter hyperintensity and 1.44 (95% CI, 0.97–2.13; I^2=0%) for asymptomatic lacunar infarction.

CONCLUSIONS: The non-dipping and reverse-dipping BP patterns are associated with neuroimaging cerebral small vessel disease markers.

Key Words: blood pressure variability ■ circadian ■ meta-analysis ■ microbleed ■ white matter

Circadian rhythm plays an important role in the governance and maintenance of homeostasis in the human body.[1] The normal circadian blood pressure pattern is characterized by a mild decrease in blood pressure during sleep that reaches its trough around midnight when the deep sleep stages are most abundant (nocturnal dip), with a subsequent gradual rise towards the end of sleep (morning surge). However, in some individuals during sleep, the nocturnal dip is blunted or reversed. This results in the absence of a nocturnal dip or even a slight increase in blood pressure, termed "non-dipper" and "reverse-dipper", respectively.[2,3]

Studies have found that these abnormal blood pressure patterns are linked to an increased risk for cardiovascular events and target organ damage in both normotensive and hypertensive individuals.[4–11] Moreover, better control of sleep blood pressures has been shown to exert greater protection against stroke and cardiovascular events in many studies.[12,13] The

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CLINICAL PERSPECTIVE

What Is New?

- This systematic review and meta-analysis of 3497 patients from 12 studies demonstrated an association between abnormal circadian blood pressure pattern, reverse-dipping and non-dipping nighttime blood pressure patterns, and prevalent cerebral small vessel disease.

What Are the Clinical Implications?

- These results further support the concerns about the abnormal circadian blood pressure pattern and 24-hour blood pressure control on target organ damages.
- This study demonstrates the usefulness of neuroimaging markers of silent cerebral small vessel disease as a presymptomatic marker of cerebrovascular disease.

Nonstandard Abbreviation and Acronyms

ALI	asymptomatic lacunar infarction
CMB	cerebral microbleed
CSVD	cerebral small vessel disease
PVS	perivascular space
WMH	white matter hyperintensity

insurmountable evidence linking these 2 abnormal blood pressure patterns to target organ damages and cardiovascular events lead us to explore its association to presymptomatic markers of cerebrovascular disease, the neuroimaging markers of cerebral small vessel disease (CSVD).

Silent findings of CSVD on neuroimaging studies, such as white matter hyperintensities (WMH), asymptomatic lacunar infarction (ALI), cerebral microbleeds (CMBs), and enlarged perivascular spaces (PVS), have recently emerged as important surrogate markers for cerebrovascular disease.[14] Elevated blood pressures are one of the main risk factors for CSVD, and better control of blood pressure has been shown to decrease WMH progression.[15–17] However, the relationship between abnormal circadian blood pressure variations and CSVD neuroimaging markers has not been well established.

This study investigates the association between abnormal circadian blood pressure variations, specifically the non-dipping and reverse-dipping patterns, and silent CSVD neuroimaging markers by performing a systematic review and meta-analysis of the relevant published literature.
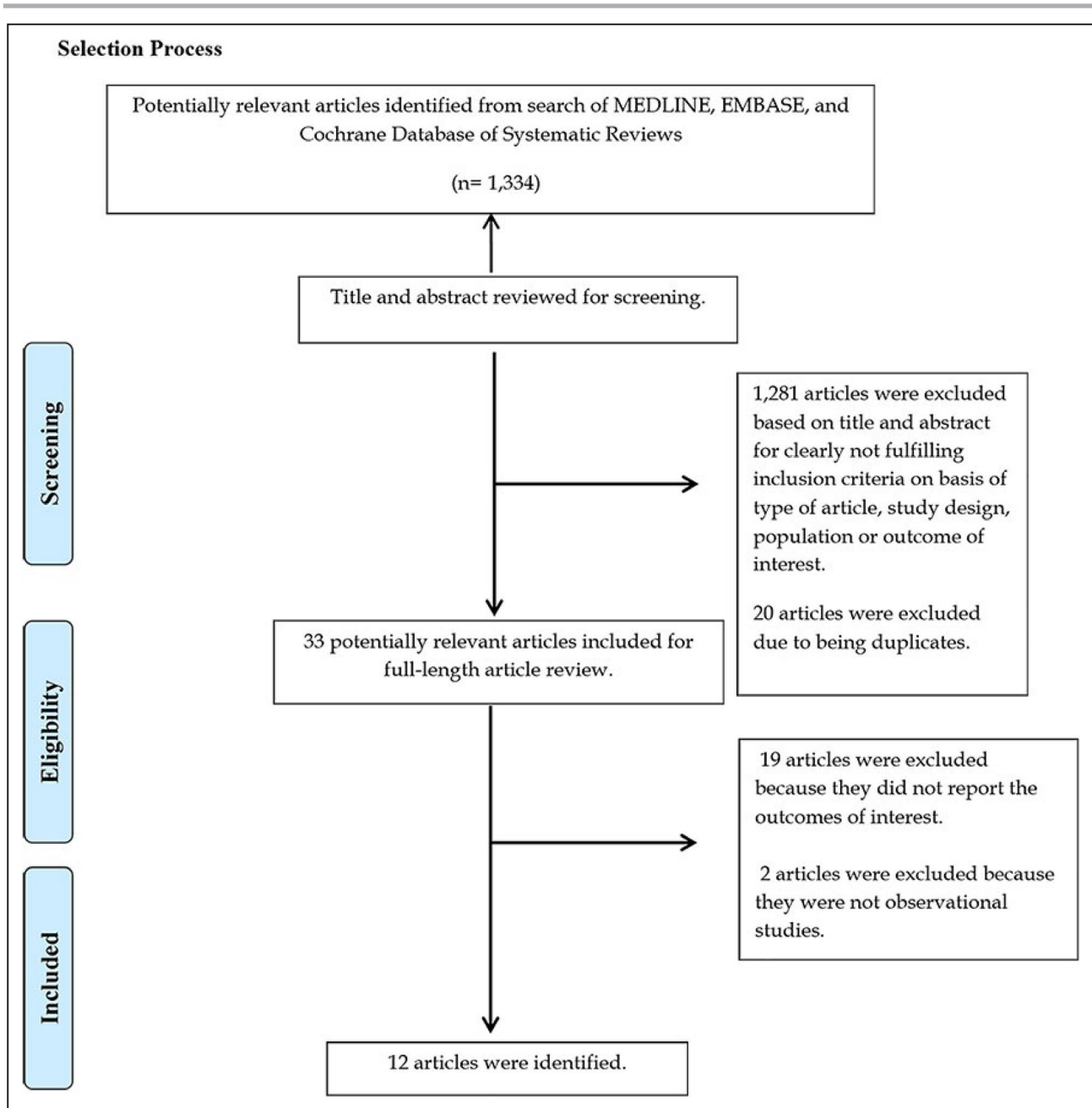
METHODS

The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42020147729). The data for this systematic review and all potentially eligible studies are publicly available through the Open Science Framework (URL: https://osf.io/gf8pr/).

Search Strategy and Literature Review

A systematic literature search of EMBASE (1988 to November 2019), Ovid MEDLINE (1946 to November 2019), and the Cochrane Database of Systematic Reviews (database inception to November 2019) was performed to assess the association of abnormal circadian sleep blood pressure variations, specifically the non-dipping and reverse-dipping blood pressure patterns, on CSVD neuroimaging markers consisting of WMH, ALI, CMBs, and enlarged PVS. The non-dipping blood pressure pattern refers to a nocturnal blood pressure fall of <10% from the awake blood pressures, and the reverse-dipping blood pressure pattern refers to a rise in nocturnal blood pressures.[18] The systematic literature review was undertaken independently by 2 investigators (A.C. and R.C.) using a search approach that incorporated the terms "dipping" OR "non-dipping" OR "dipper" OR "non-dipper" OR "reverse-dipping" OR "reverse-dipper" OR "circadian blood pressure" OR "nocturnal blood pressure", "night-time blood pressure", "ambulatory blood pressure", "ambulatory blood pressure monitoring" AND "silent cerebrovascular disease" OR "silent stroke" OR "silent ischemic stroke" OR "white matter hyperintensity" OR "lacunar infarct" OR "cerebral microbleed" OR "brain microbleed" OR "small vessel disease" OR "cerebrovascular disease" OR "silent cerebral infarct" OR "white matter change" OR "perivascular space". The search strategy used for each database is provided in Data S1. No language limitation was applied. A manual search for conceivably relevant studies using the references of included articles was also performed. This study was conducted by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement,[19] as provided in Data S1.

Selection Criteria

To be included in the meta-analysis, studies were required to meet the following criteria: (1) observational studies including cohort, case-control, or cross-sectional studies (2) reported the association of non-dipping or reverse-dipping blood pressure patterns on WMH, ALI, CMBs, or enlarged PVS, (3) an outcome definition was provided, (4) and reported odds ratios (OR) of any CSVD neuroimaging markers. Review articles and case reports were excluded from this meta-analysis. Retrieved articles were individually reviewed

Selection Process

Potentially relevant articles identified from search of MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews

(n= 1,334)

Title and abstract reviewed for screening.

Screening

1,281 articles were excluded based on title and abstract for clearly not fulfilling inclusion criteria on basis of type of article, study design, population or outcome of interest.

20 articles were excluded due to being duplicates.

33 potentially relevant articles included for full-length article review.

Eligibility

19 articles were excluded because they did not report the outcomes of interest.

2 articles were excluded because they were not observational studies.

Included

12 articles were identified.

Figure 1.   Outline of our selection process.

for eligibility by the 2 investigators (A.B. and R.C.). Discrepancies were addressed and solved by mutual agreement. Inclusion was not limited by the size of the study. Newcastle-Ottawa quality assessment scale was used to appraise the quality of the included observational studies.[20]

Data Abstraction

Characteristics of the study including first author, study location, publication year, study design, patient demographic data, CSVD outcome definition, exposure and measurement of exposure, follow up time, and confounder adjustments were retrieved. ORs reported in each study were extracted.

Statistical Analysis

All statistical analyses were performed using the Comprehensive Meta-Analysis version 3 software (Eaglewood, NJ, USA). The pooled ORs of silent CSVD neuroimaging markers in patients with non-dipping or reverse-dipping blood pressure patterns were calculated using a generic inverse method of DerSimonian

Table. Study Characteristics

Study, Y/Study Design	Country/ Population	Number (%Male)	Mean Age±SD	BP Monitoring	BP Pattern	Imaging	CSVD Feature(s)	Confounder Adjusted	Quality Assessment (NOS)
Hamada et al,[23] 2003/ cross-sectional	Japan/adults aged 50–76 y with depression	36 (50%)	64.46±5.9	Automated 24-h ambulatory BP	Non-dipping	1.5 T MRI	ALI	N/A	S3 C0 O3
Yamamoto et al,[24] 2005/ cross-sectional	Japan/acute lacunar infarction	200 (61%)	68.8±9.3	Automated 24-h ambulatory BP (2–4 wk after stroke)	Non-dipping, reverse-dipping	1.5 T MRI	ALI, WMH by Fazekas scale	Age, sex	S4 C2 O3
Henskens et al,[25] 2008/ cross-sectional	Netherlands/ untreated hypertensive patients	218 (50.5%)	52.5±12.6	Automated 24-h ambulatory BP	Non-dipping	1.5 T MRI	CMBs on T2*- weighted GE image	Age (y), sex, duration of hypertension, prior BP-lowering agent, smoking, ratio of total/HDL, advanced WMH	S5 C2 O3
Staals et al,[26] 2009/ cross-sectional	Netherlands/first lacunar stroke	97 (61%)	64.6±11.7	Automated 24-h ambulatory BP (1–6 mo after stroke)	Nocturnal SBP dip	1.5 T MRI	CMBs on T2*- weighted GE image	Age, sex, number of BP-lowering agents, asymptomatic lacunar infarction, extensive white matter lesions	S5 C2 O3
Ma et al,[27] 2010/ cross-sectional	China/ hypertensive patients	188 (42.5%)	64±6.6	Automated 24-h ambulatory BP	Non-dipping	MRI	ALI	N/A	S4 C0 O3
Yamamoto et al,[28] 2011/ cross-sectional	Japan/acute lacunar infarction	224 (60%)	69.8±9.34	Automated 24-h ambulatory BP (>2 wk after stroke)	Non-dipper, reverse-dipping	1.5 T MRI	Multiple ALI gr 3 vs gr 1, WMH Fazekas scale gr 3 vs gr 1	eGFR level	S4 C1 O3
Shimizu et al,[29] 2011/ cross-sectional	Japan/ hypertensive patients	514 (37%)	72.3±8.7	Automated 24-h ambulatory BP	Non-dipping	1.5 T MRI	ALI	N/A	S4 C2 O3
Lee et al,[30] 2014/ cross-sectional	Korea/adults aged 40–69 y (exclude hypertension)	703 (47.5%)	59.43±6.79	Automated 24-h ambulatory BP	Non-dipping, reverse-dipping	1.5 T MRI	WMH by ARWMC scale	Age (y), sex, BMI, total cholesterol, hs-CRP, DM, smoking, alcohol	S4 C2 O3
Kwon et al,[31] 2014/ cross-sectional	Korea/acute ischemic stroke with hypertension	162 (61.7%)	65.33±10.32	Automated 24-h ambulatory BP	Non-dipping, reverse-dipping	1.5 T MRI	CMBs on T2*- weighted GE image	Age (y), sex, LDL, 24 h mean SBP/ DBP	S4 C2 O3
Yamashiro et al,[32] 2018/ cross-sectional	Japan/Parkinson disease	128 (43%)	82.1±3.9	Automated 24-h ambulatory BP	Non-dipping	3 T MRI	CMBs on T2* by Microbleed Anatomical Rating Scale	N/A	S4 C0 O3

(Continued)

Table. Continued

Study, Y/Study Design	Country/Population	Number (%Male)	Mean Age±SD	BP Monitoring	BP Pattern	Imaging	CSVD Feature(s)	Confounder Adjusted	Quality Assessment (NOS)
White et al,[33] 2018/cross-sectional	USA/elderly aged ≥75 y	199 (45.7%)	81.2±4.1	Automated 24-h ambulatory BP	Non-dipping	1.5 T MRI	WMH volume	N/A	S4 C0 O3
Nakanishi et al,[34] 2019/cross-sectional	/adults aged ≥55 y (exclude history of stroke)	828 (39.9%)	70.9±9	Automated 24-h ambulatory BP	Non-dipping	1.5 T MRI	ALI, High WMH volume (upper quartile)	ALI: age (y), sex, hypertension, AF, LV mass index, interval between ABPM and MRI WMH: age, race, hypertension, AF, LV mass index, LA diameter, interval between ABPM and MRI	S4 C2 O3

ABPM indicates ambulatory blood pressure monitoring; AF, atrial fibrillation; ALI, asymptomatic lacunar infarct; ARWMC, age-related white mater changes; BMI, body mass index; CMBs, cerebral microbleeds; CSVD, cerebral small vessel disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GE, gradient echo; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LA, left atrium; LDL, low-density lipoprotein; LV, left ventricle; MRI, magnetic resonance imaging; N/A, not available; NOS, Newcastle Ottawa Scale; OR, odds ratio; S, C, O, selection, comparability, and outcome; SBP, systolic blood pressure; and WMH, white matter hyperintensity.

and Laird.[21] A random-effects model was used, given the high likelihood of between study variance. Cochran Q-test, which is supplemented by I^2 statistic, was used to evaluate statistical heterogeneity. The I^2 statistic quantifies the proportion of total variation across studies that is because of true heterogeneity rather than chance. A value of I^2 of 0% to 25% denotes trivial heterogeneity, 25% to ≤50% denotes low heterogeneity, 50% to ≤75% denotes moderate heterogeneity, and >75% represents high heterogeneity.[22]

RESULTS

We identified a total of 1334 potentially eligible studies from our search strategy. After title and abstract review, 20 studies were excluded because they were duplicates and 1281 studies were excluded because they did not fulfill the inclusion criteria based on the type of article, study design, study population, or outcome of interest. Thirty-three articles were left for full-length review. Nineteen articles were subsequently excluded because they did not report the odds ratios for neuro-imaging CSVD findings in relationship to non-dipping or reverse-dipping blood pressure pattern. Another 2 studies were excluded because they were not observational studies. Ultimately, 12 cross-sectional studies comprising 3497 individuals were enrolled.[23–34] The literature retrieval, review, and selection process are demonstrated in Figure 1. The characteristics of the included studies are presented in Table.

Association of a Blood Pressure Reverse-Dipping Pattern With CSVD Neuroimaging Features

There was a significant association between the nocturnal blood pressure reverse-dipping pattern and WMH with a pooled adjusted OR of 2.00 (95% CI, 1.13–2.37; I^2=36%), when compared with patients with normal nocturnal dip (Figure 2A).[24,28,30] Sensitivity analysis was performed including only clinic-based cross-sectional studies and demonstrated a significant association between the nocturnal blood pressure reverse-dipping pattern and WMH with a pooled adjusted OR of 3.16 (95% CI, 1.44–6.93; I^2=0%).[24,28]

Two studies assessed the association of the reverse-dipping pattern and ALI compared with normal dipping pattern. The pooled adjusted OR was 2.77 (95% CI, 0.68–11.34; I^2=43%) for reverse-dipping pattern (Figure 2B).[24,28]

Association of Blood Pressure Non-Dipping Pattern With CSVD Neuroimaging Features

There was a significant association between the non-dipping blood pressure pattern and WMH with
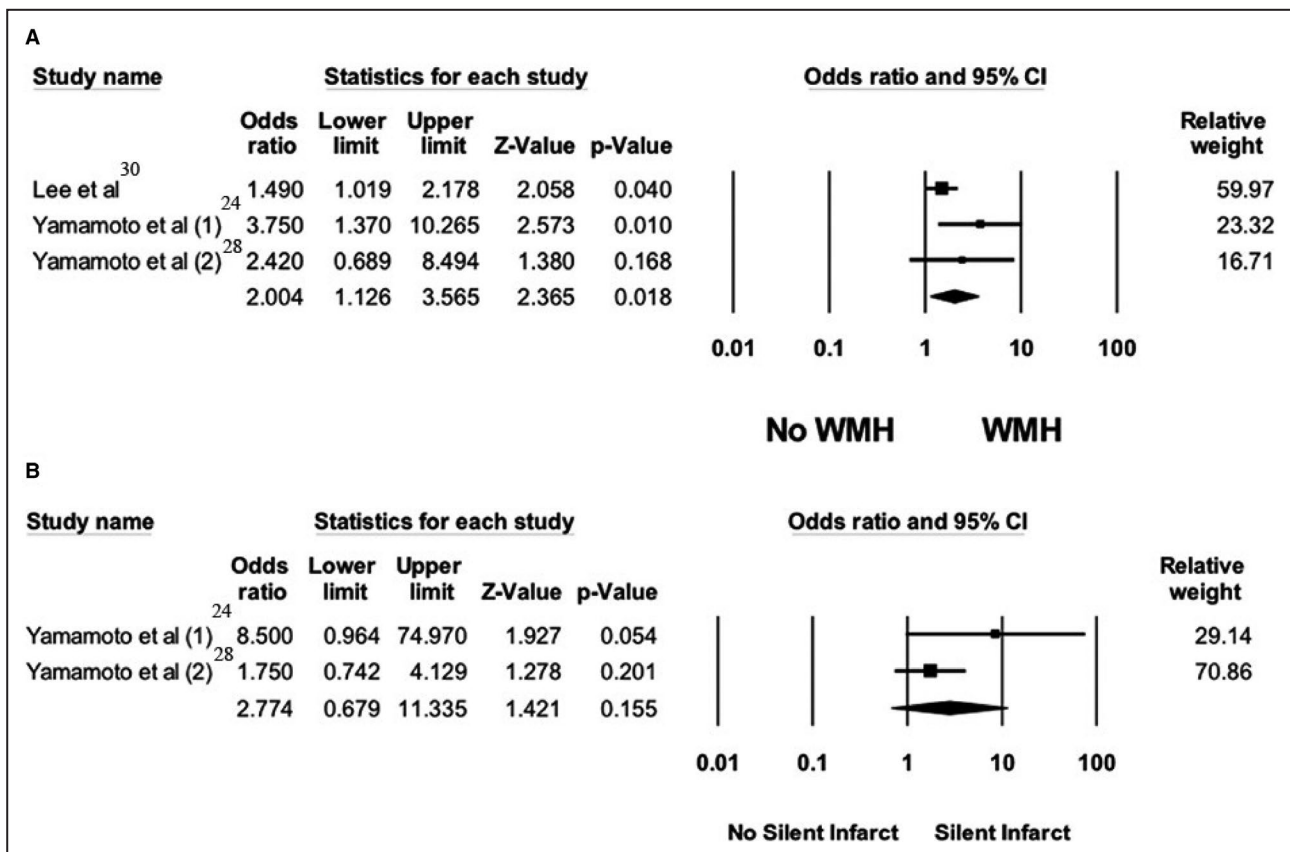
Figure 2. Forest plot of the association between reverse-dipping pattern and silent cerebral small vessel disease neuroimaging features.
A, Forest plots of included studies assessing the association between reverse-dipping pattern and white matter hyperintensity. **B**, Forest plots of the included studies assessing the association between reverse-dipping pattern and asymptomatic lacunar infarct. A diamond data marker depicts the overall rate from included studies (square data markers) and 95% CI. WMH indicates white matter hypersensitivity.

a pooled OR of 1.51 (95% CI, 1.06–2.14, I^2=55%), when compared with patients with a normal nocturnal dip (Figure 3A).[24,28,30,33,34] Sensitivity analysis was performed including only clinic-based cross-sectional studies and demonstrated a significant association between the non-dipping blood pressure pattern and WMH with a pooled adjusted OR of 1.99 (95% CI, 1.29–3.05; I^2=0%).[24,28,33] Meta-analysis limited to studies with confounder-adjusted analysis was performed. The adjusted pooled OR for WMH was 1.38 (95% CI, 0.95–2.02; I^2=52%) among patients with non-dipping nocturnal blood pressure pattern (Figure S1).[24,28,30,34]

An analysis of all studies assessing the association between ALI and non-dipping blood pressure pattern compared with normal dipping blood pressure pattern revealed a significant association with a pooled OR of 2.33 (95% CI, 1.30–4.18; I^2=73%) (Figure 3B).[23,24,27–29,34] Sensitivity analysis was performed including only clinic-based cross-sectional studies and demonstrated a significant association between the non-dipping blood pressure pattern and ALI with a pooled adjusted OR of 2.82 (95% CI,

1.34–5.95; I^2=74%).[23,24,27–29] However, when the analysis was limited to only confounder-adjusted studies, the association was not statistically significant, with a pooled adjusted OR of 1.44 (95% CI, 0.97–2.13; I^2=0%) (Figure S2).[24,28,34]

There was no significant association between nocturnal blood pressure non-dipping pattern and CMBs when compared with normal nocturnal dipping pattern in all included studies. The pooled OR was 1.17 (95% CI, 0.82–1.67; I^2=0%) (Figure 3C)[25,26,31,32] and the pooled adjusted OR was 1.14 (95% CI, 0.79–1.64; I^2=0%) (Figure S3).[25,26,31]

Data on the association between abnormal circadian blood pressure variations and enlarged PVS were limited and thus a meta-analysis could not be performed.

Evaluation for Publication Bias

Since tests for funnel plot asymmetry should be used only when there are at least 10 study groups, a funnel plot was not drawn because of the limited number of studies.[35] Egger regression asymmetry test
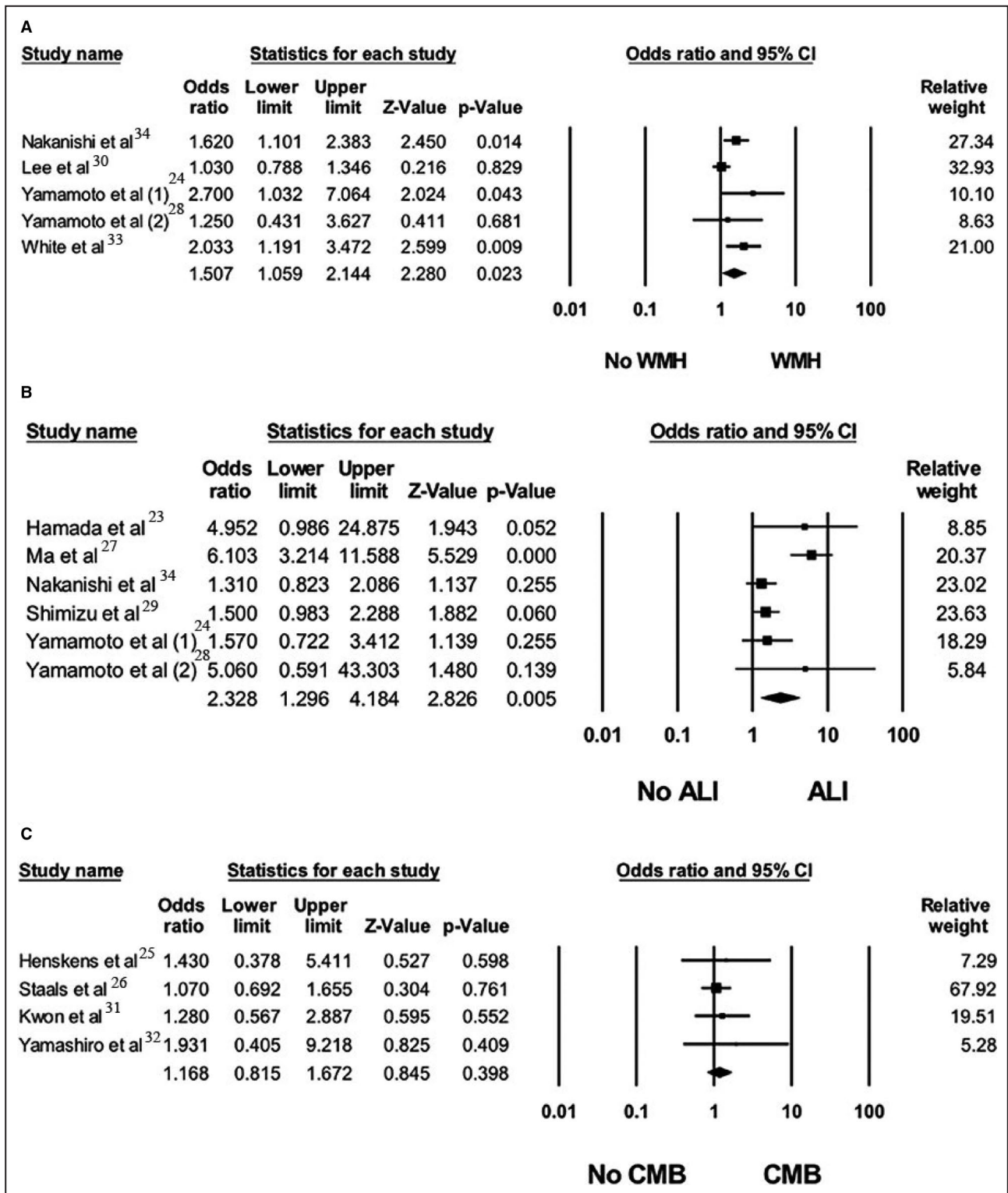
Figure 3. **Forest plot of the association between non-dipping pattern and silent cerebral small vessel disease neuroimaging features.**
A, Forest plots of the included studies assessing the association between non-dipping pattern and white matter hyperintensity. **B**, Forest plots of the included studies assessing association between non-dipping pattern and asymptomatic lacunar infarction . **C**, Forest plots of the included studies assessing association between non-dipping pattern and cerebral microbleeds. A diamond data marker depicts the overall rate from included studies (square data markers) and 95% CI. CMB indicates cerebral microbleeds; and WMH, white matter hypersensitivity.

was performed and showed no publication bias with *P*<0.05 for all analyses.

DISCUSSION

Our study demonstrated a significant association between a reverse-dipping blood pressure pattern and a higher prevalence of WMH, but not ALI. A significant unadjusted association was also found between a non-dipping blood pressure pattern and an increased prevalence of both WMH and ALI. However, when limiting the analysis to only confounder-adjusted studies (4 studies for WMH and 3 studies for ALI), the results were no longer statistically significant. We did not find an association between a non-dipping blood pressure pattern and CMBs.

Hypertension is known to cause damage to both large and small vessels leading to target organ damages, most importantly the heart, brain, and kidneys.[36,37] In hypertensive cerebral small vessel disease, researchers found that hypertension primarily causes endothelial dysfunction leading to subsequent blood-brain barrier dysfunction, formation of microaneurysms, decreased cerebrovascular reactivity, cerebral hypoperfusion, and neuroinflammation.[16,38–41] These pathological processes in the brain parenchyma can produce either "silent" findings on neuroimaging studies or symptoms such as strokes.

The circadian rhythm is essential for the regulation and maintenance of normal physiologic functions in the body. The circadian control of the cardiovascular system is most evident with the diurnal blood pressure pattern, characterized by a rise in blood pressure in the morning before awakening and a decrease while sleeping in the night.[42,43] This control is achieved through a synergy of several processes, including neurohormonal factors, vascular tone, the autonomic nervous system, and renal system.[1,5,42,44] Abnormal function of these processes or certain environmental changes could lead to disruption of this normal circadian blood pressure pattern through either increased cardiac output or systemic vascular resistance during sleep. Common diseases associated with this disruption include diabetes mellitus, neurodegenerative diseases with autonomic dysfunction, chronic kidney disease, obstructive sleep apnea, and most secondary causes of hypertension.[2,5,45]

An abnormal circadian blood pressure pattern, consisting of non-dipping or reverse-dipping, has been shown in several studies to increase the risk of cardiovascular disease. Studies have found an increased risk of myocardial infarction, peripheral artery disease, increased prevalence of vascular disease markers (eg, carotid plaque), and other cardiovascular events in individuals with non-dipping or reverse-dipping patterns.[4–7,9,10,46,47] Karadag et al showed that

a non-dipping blood pressure pattern was associated with a higher risk of microalbuminuria and hypertensive retinopathy in hypertensive patients.[8] Another study by Yan et al found a significantly increased risk of lacunar infarction in reverse-dipping compared with non- and normal-dipping hypertensive patients.[11]

The pathophysiologic mechanism of non-dipping and reverse-dipping blood pressure pattern on vessels remains unclear. Some have proposed that the non-dipping and the reverse-dipping blood pressure patterns result in a higher 24-hour mean blood pressure level, thereby imposing a greater overall pressure load and shear stress to vessels, resulting in accelerated atherosclerotic disease.[26,30,34] This hypothesis is supported by studies that have demonstrated that reverse-dippers are more affected than non-dippers.[11,24,28,30] Our findings provide further evidence revealing an association between abnormal circadian blood pressure pattern and silent CSVD markers, and with reverse-dippers having a more significant risk compared with non-dippers. However, it remains to be elucidated if other mechanisms are involved in the process.

The neuroimaging features of silent CSVD, such as WMH, ALI, CMBs, and enlarged PVS, have recently been widely adopted as markers of small vessel cerebrovascular disease. Its main advantage is the ability to detect disease in its presymptomatic stage.[14,48] Discrepancies between each neuroimaging markers and their clinical importance have been reported. This may be largely because of the sensitivity of each marker on magnetic resonance imaging, the different techniques used to identify each marker, and the slightly different pathogenic processes for each marker.[49] This discrepancy was also evident in our study. In addition, it is also worth noting that the magnetic resonance imaging used in most of the included studies in this meta-analysis was performed using 1.5 T magnetic resonance imaging, which is less sensitive for pathological changes than the 3 T magnetic resonance imaging used in most current research studies. Moreover, detection of CMBs in the included studies was done on gradient echo (GRE) sequence rather than the currently recommended susceptibility-weighted imaging, which offers more diagnostic sensitivity.[50] Hence, because of the known technical limitations with the neuroimaging techniques used in these prior studies, the actual prevalence of WMH, ALI, and CMBs may be higher and the association more prominent if current and more sensitive neuroimaging techniques were used.

Interestingly, restoration of the normal physiologic blood pressure pattern by decreasing nighttime blood pressure has been explored in several studies.[51,52] The MAPEC (Spanish hypertensive cohort study [PMID: 20854139]) study, which aimed to compare bedtime long-acting anti-hypertensive medication

administration (chronotherapy) to conventional morning time therapy, reported better control of 24-hour blood pressure, lower prevalence of non-dipper, and decreased total and major cardiovascular events in the bedtime treatment group.[13] Another cohort study in both normotensive and hypertensive patients found that the decrease in nighttime systolic blood pressure was the most significant predictor for cardiovascular event-free survival after 5 years of follow-up, regardless of awake or office systolic blood pressure.[4] Finally, a meta-analysis of 9 cohort studies in hypertensive patients found that an increased nighttime systolic blood pressure was the best predictor of adverse cardiovascular events.[53] These studies highlight the importance of nighttime blood pressure in the pathogenesis of vascular diseases.

This study has several limitations. First, a causal relationship between abnormal circadian blood pressure patterns and CSVD cannot be established because of the cross-sectional design of the studies. Second, the number of studies is relatively limited. There are even fewer studies that explored the prevalence of CMBs in reverse-dippers,[31] and there are no available studies that explored the association of enlarged PVS with abnormal circadian blood pressure patterns. Consequently, the number of available studies exploring the association with certain CSVD neuroimaging findings may be too few to achieve a statistically significant result. Third, most studies used a single 24-hour ambulatory blood pressure measurement, which could not demonstrate the reproducibility or persistence of the abnormal circadian blood pressure pattern in each individual. Finally, the classification of nocturnal blood pressure decrease into dipping, non-dipping, and reverse-dipping groups rather than analyzing the quantitative measurement of the changes in nocturnal blood pressure further limits the extent of the analysis.

CONCLUSIONS

The non-dipping and reverse-dipping blood pressure patterns are associated with neuroimaging markers of CSVD. However, whether restoration of a normal physiologic nocturnal blood pressure pattern would prevent further progression of CSVD is unknown. Future studies with a longitudinal design assessing the treatment effect of chronotherapy on CSVD neuroimaging features are needed.

ARTICLE INFORMATION

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Acknowledgments

Sources of Funding

Disclosures

Supplementary Materials

Data S1
Figures S1–S3
References 24–26, 28, 30–31, and 34

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Search terms for systematic review (Databases: Ovid MEDLINE, Database: EMBASE, and Cochrane Database, N = 1334).
Database: EMBASE (1,288 articles)
('non dipping' OR 'dipping' OR 'dipper' OR 'non dipper' OR 'non dipper hypertension' OR 'reverse dipping' OR (circadian AND blood AND pressure) OR 'nocturnal blood pressure' OR 'nocturnal blood pressure dipping' OR 'night-time blood pressure' OR 'blood pressure monitoring' OR 'ambulatory blood pressure' OR 'ambulatory blood pressure measurement') AND ('silent cerebrovascular disease' OR 'ischemic stroke' OR 'white matter hyperintensity' OR 'lacunar infarct' OR 'cerebral microbleed' OR 'brain microbleed' OR 'small vessel disease' OR 'cerebrovascular disease' OR 'occlusive cerebrovascular disease' OR 'silent cerebral infarction' OR 'silent cerebral infarct' OR 'white matter change' OR 'perivascular space')

Database: Ovid MEDLINE (46 articles)
1   dipper.mp.
2   dipping.mp.
3   non dipper.mp.
4   non dipping.mp.
5   reverse-dipping.mp.
6   reverse dipper.mp.
7   circadian blood pressure.mp.
8   nocturnal blood pressure.mp.
9   night-time blood pressure.mp.
10   ambulatory blood pressure.mp.
11   ambulatory blood pressure monitoring.mp.
12   1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13   silent cerebrovascular disease.mp.
14   silent stroke.mp.
15   silent ischemic stroke.mp.
16   white matter hyperintensity.mp.
17   lacunar infarct.mp.
18   cerebral microbleed$.mp.
19   brain microbleed$.mp.
20   small vessel disease.mp.
21   cerebrovascular disease.mp.
22   silent cerebral infarct.mp.
23   white matter change.mp.
24   perivascular space$.mp.
25   13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26   13 and 25

Cochrane Database (0 articles)

('non dipping' OR 'dipping' OR 'dipper' OR 'non dipper' OR 'non dipper hypertension' OR 'reverse dipping' OR (circadian AND blood AND pressure) OR 'nocturnal blood pressure' OR 'nocturnal blood pressure dipping' OR 'night-time blood pressure' OR 'blood pressure monitoring' OR 'ambulatory blood pressure' OR 'ambulatory blood pressure measurement') AND ('silent cerebrovascular disease' OR 'ischemic stroke' OR 'white matter hyperintensity' OR 'lacunar infarct' OR 'cerebral microbleed' OR 'brain microbleed' OR 'small vessel disease' OR 'cerebrovascular disease' OR 'occlusive cerebrovascular disease' OR 'silent cerebral infarction' OR 'silent cerebral infarct' OR 'white matter change' OR 'perivascular space')
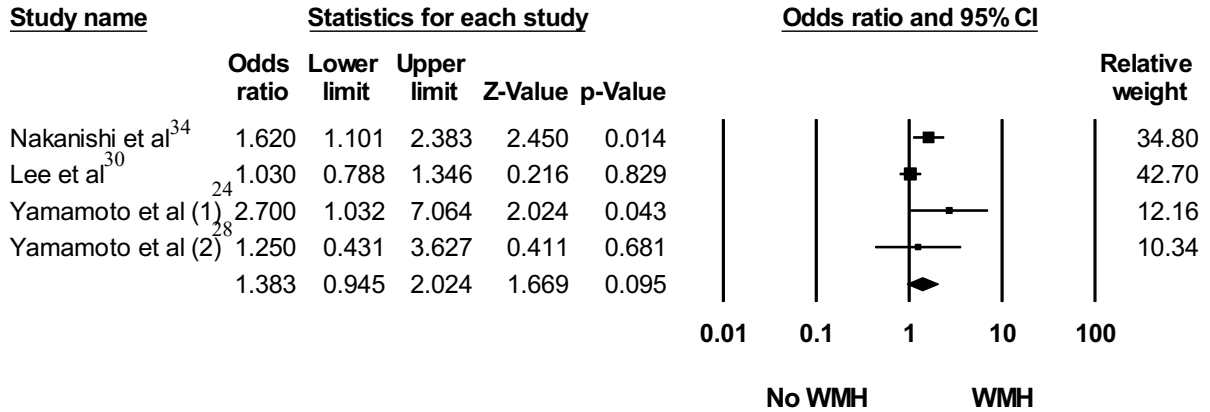
PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
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.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
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.	4
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.	4-5
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.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4-5
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).	5
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.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
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.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
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.	6

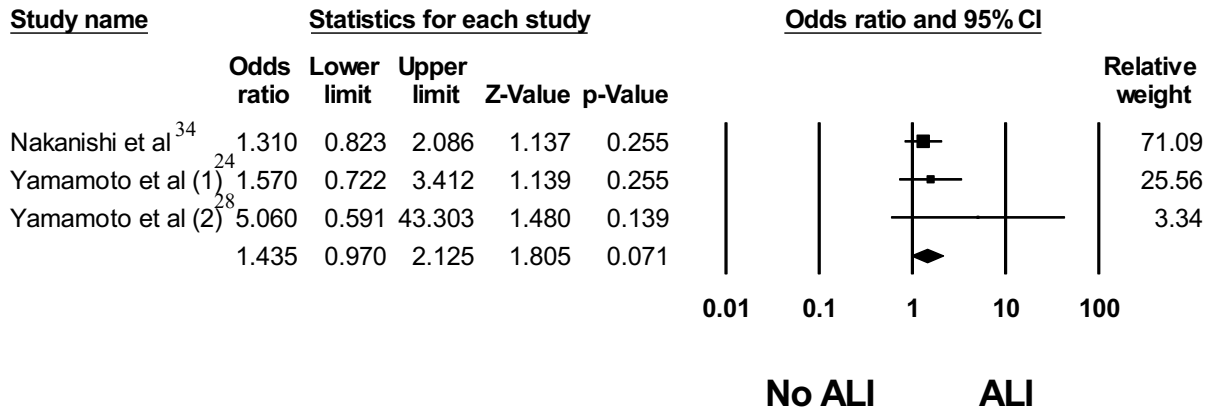| Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
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
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.	Table 1
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).	Table 1
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.	Figure 2-3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-8
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).	9-12
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).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
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.	13

For more information, visit: **www.prisma-statement.org**.

Figure S1. Forest plots of studies with confounder-adjusted analysis assessing association between a non-dipping pattern and WMH. A diamond data marker depicts the overall rate from included studies (square data markers) and 95%CI

Study name	Statistics for each study					Odds ratio and 95% CI	Relative weight
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value		
Nakanishi et al[34]	1.620	1.101	2.383	2.450	0.014		34.80
Lee et al[30]	1.030	0.788	1.346	0.216	0.829		42.70
Yamamoto et al (1)[24]	2.700	1.032	7.064	2.024	0.043		12.16
Yamamoto et al (2)[28]	1.250	0.431	3.627	0.411	0.681		10.34
	1.383	0.945	2.024	1.669	0.095		

0.01   0.1   1   10   100

No WMH   WMH

Figure S2. Forest plots of studies with confounder-adjusted analysis assessing association between a non-dipping pattern and ALI. A diamond data marker depicts the overall rate from included studies (square data markers) and 95%CI

Study name	Statistics for each study					Odds ratio and 95% CI	Relative weight
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value		
Nakanishi et al[34]	1.310	0.823	2.086	1.137	0.255		71.09
Yamamoto et al (1)[24]	1.570	0.722	3.412	1.139	0.255		25.56
Yamamoto et al (2)[28]	5.060	0.591	43.303	1.480	0.139		3.34
	1.435	0.970	2.125	1.805	0.071		

0.01   0.1   1   10   100

No ALI   ALI

Figure S3. Forest plots of studies with confounder-adjusted analysis assessing association between a non-dipping pattern and CMB. A diamond data marker depicts the overall rate from included studies (square data markers) and 95%CI

Study name	Statistics for each study					Odds ratio and 95% CI	Relative weight
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value		
Henskens et al[25]	1.430	0.378	5.411	0.527	0.598		7.70
Staals et al[26]	1.070	0.692	1.655	0.304	0.761		71.71
Kwon et al[31]	1.280	0.567	2.887	0.595	0.552		20.60
	1.135	0.785	1.642	0.674	0.501		

0.01   0.1   1   10   100

No CMB   **CMB**