Sleep Medicine Reviews 45 (2019) 54–69

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

The bidirectional impact of sleep and circadian rhythm dysfunction in human ischaemic stroke: A systematic review

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ARTICLE INFO

Article history:
Received 31 May 2018
Received in revised form
8 March 2019
Accepted 12 March 2019
Available online 20 March 2019

Keywords:
Ischaemic stroke
Sleep disorders
Sleep architecture
Circadian rhythms
Systematic review

SUMMARY

Sleep and circadian rhythm disruption are potentially modifiable risk factors and consequences of ischaemic stroke. Pre-clinical evidence suggests a direct effect of sleep and endogenous circadian rhythm dysfunction on lesion volumes and post-stroke recovery. In humans, sleep and stroke literature has focused primarily on obstructive sleep apnoea. However, the bidirectional impact of non-apnoea related sleep disorders, sleep architecture, and endogenous circadian rhythm dysfunction in ischaemic stroke remains unclear. A systematic search of publications in three major databases from inception to August 7 2018 identified 67 studies meeting inclusion criteria. Long sleep duration or sleep disorders significantly increased the risk of ischaemic stroke. Inversely, ischaemic stroke was associated with sleep architectural and endogenous circadian rhythm disruption which were generally associated with post-stroke severity and functional outcome. Importantly, no studies examined direct measures of circadian rhythm dysfunction as a risk factor for ischaemic stroke. Most studies were moderate to high quality. However, methodology and stroke characteristics (e.g., stroke topography, stroke severity) were heterogenous thereby limiting generalisable conclusions. Furthermore, *a priori* neuroimaging outcomes in conjunction with sleep and circadian features were seldom assessed. The clinical pathogenic implications and methodological limitations of studies are discussed, and a research agenda for future studies is outlined.

Introduction

Anecdotally, sleep and circadian rhythm disturbances are common and potentially modifiable sequelae of ischaemic stroke (IS). Sleep-wake pathologies present both a risk factor and consequence of stroke. Chronic sleep and circadian dysfunction activate deleterious pathophysiological mechanisms (e.g., inflammation, autonomic nervous system activation with haemodynamic swings, hypothalamic-pituitary-adrenal axis activation), which may contribute to the pathogenesis of IS [1]. Inversely, lesions to sleep-wake networks and sleep disorders may compromise post-stroke recovery and sleep-potentiated neuroplasticity [2]. Furthermore, the glymphatic system, a pseudo-lymphatic perivascular network driven most efficiently by sleep, is compromised after human IS [3].

In pre-clinical studies, sleep deprivation after IS is associated with increased lesion volumes, and sleep deprivation prior to IS initiates compensatory rebound sleep that is neuroprotective [4,5]. Endogenous markers of circadian rhythms (i.e., melatonin) are suppressed after IS, and exogenous administration of melatonin is neuroprotective [6,7]. However, whether experimental findings translate to heterogeneous human stroke cohorts remains unclear.

Literature investigating stroke-related sleep dysfunction in humans has primarily focused on the impact of obstructive sleep apnoea on stroke risk and outcome [8,9]. In humans, a circadian variation in the timing of stroke onset is characterised by an increased incidence of all-stroke types in the morning (<6AM) and nadir during night-time [10]. However, the cause and neuroanatomical correlates of non-apnoea related sleep and endogenous sleep-potentiated circadian rhythm dysfunction in human IS remain unclear. Thus, the aim of the present review is to investigate

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https://doi.org/10.1016/j.smrv.2019.03.003
1087-0792/

Abbreviations

AHI	Apnoea–hypopnea index
IS	Ischaemic stroke
mRS	Modified Rankin scale
NIHSS	National Institutes of Health Stroke scale
NOS	Newcastle-Ottawa scale
NREM	Non-rapid-eye-movement sleep
PLM	Periodic leg movements
PS	Post-stroke
PSG	Polysomnography
RBD	Rapid-eye-movement behaviour disorder
REM	Rapid-eye-movement sleep
RLS	Restless legs syndrome
SA	Sleep architecture
SE	Sleep efficiency
SL	Sleep onset latency
SWS	Slow-wave-sleep
TIA	Transient ischaemic attack
TST	Total sleep time
WASO	Wake after sleep onset
WMH	White matter hyperintensities

the bidirectionality of non-apnoea sleep and circadian dysfunction in human IS. These aims will be stratified, where possible, to examine associations with post-stroke recovery, stroke topography, and time-course.

Methods

The systematic review was conducted in accordance with preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [11]. The review was registered on the international prospective register of systematic reviews (PROSPERO) database (registration number: CRD42018079498).

Search strategy

The authors developed comprehensive search strategies to identify relevant studies pertaining to sleep architecture, sleep quality or duration, non-apnoea sleep disorders, circadian rhythms, and IS. Searches were conducted across MEDLINE (1946 – 7 August 2018, Ovid); Embase (1974 – 7 August 2018, Ovid); and PsycINFO (1806 – 7 August 2018, Ovid), and the Cochrane central register of controlled trials (CENTRAL) utilising a combination of subject headings and free-text created in collaboration with a clinical librarian. Subject headings were modified as required for translation to each database and included: sleep, circadian rhythms, sleep wake disorders, and stroke, with a broad list of free-text terms addressing sleep architecture, non-apnoea sleep disorders, circadian rhythms, and IS (see Supplementary Figs. S1–3 for search terms).

Non-ischaemic stroke types (i.e., haemorrhagic stroke and transient ischaemic attack) represent 15% of stroke cases and exhibit markedly different pathophysiology, neurological clinical evolution, and functional recovery/outcome [12]. Therefore, studies investigating only haemorrhagic stroke and/or TIA were excluded and considered outside the scope of this review.

Single case reports were not included in the review due to this study design's inherent low statistical validity and the availability of more robust evidence from other observational studies including cohort and case–control studies. Although meta-analyses were referenced to support findings from primary studies, they were excluded in our search strategy to avoid duplicate-inclusion and pooling of unstratified (non-ischaemic) stroke types. As case studies, systematic reviews and meta-analyses were to be excluded from the search results, the search strategy was limited to observational studies and clinical trials using established search filters [13] and the Emtree term "controlled study." There were no date or language restrictions applied. Removal of duplicate studies occurred prior to title and abstract screening. Authors scanned the reference lists of included studies and searched for ongoing trials in the Australian New Zealand clinical trials registry and ClinicalTrials.gov.

Inclusion and exclusion criteria

Inclusion criteria were: observational studies or clinical trials; IS confirmed by CT or MRI; sleep assessed by polysomnography (PSG), actigraphy/accelerometer, or self-reported sleep-wake duration diaries; and circadian rhythm assessed via validated scale, actigraphy, or endogenous melatonin or metabolites (e.g., 6-sulphatoxymelatonin).

Exclusion criteria included: case studies, systematic reviews and meta-analyses; animal or tissue studies; self-reported stroke; homogenous haemorrhagic stroke or TIA cohorts; daytime alertness or sleepiness-specific outcomes only; sleep apnoea-specific outcomes; and indirect or non-sleep related circadian rhythmicity (e.g., shift work, heart rate, alertness).

Papers excluded on the basis of "wrong outcomes" (see Fig. 1) refers to one or more of the following reasons: resting state daytime/awake electroencephalography (EEG); daytime sleepiness or fatigue outcomes only; indirect/proxy measures of circadian rhythms (e.g., pineal calcification, blood pressure, timing of stroke onset); traumatic brain injury or non-ischaemic-stroke potentiated lesions; and sleep apnoea outcomes only.

Study selection

Titles and abstracts of potentially eligible citations were imported into Covidence, a web-based platform used to streamline the production of systematic reviews. EG and EL independently reviewed all titles and abstracts to determine initial eligibility. Full papers of eligible studies were independently assessed by EG and EL for inclusion. To achieve consensus, any conflicts raised between the reviewers were resolved through discussion with AB and/or MH.

Data extraction

Extracted variables were chosen based on the STROBE guidelines used for reporting observational studies [14]. Extracted data included: study identification/details; study design/setting; study demographics; stroke time (assessment administration); sleep or circadian rhythm measurement tool; stroke severity and topography (laterality, lesion location, stroke volume); adjustment variables; summarised and raw outcome data; and study quality assessment information. Data extraction for the entire sample was completed by EG. Twenty-five percent of the sample was randomly selected and independently extracted by EL; agreement ratings between EG and EL were very good (92% for study characteristics and findings, 100% for study quality), and therefore did not warrant additional double-extraction. Missing data, or eligible studies that did not distinguish ischaemic and haemorrhagic stroke data, were requested from study authors. In studies supplying multiple covariate models, the most conservative (i.e., most adjusted variables) were exclusively selected. Confidence intervals (CI) are reported as 95%. Reported percentages are rounded to the nearest

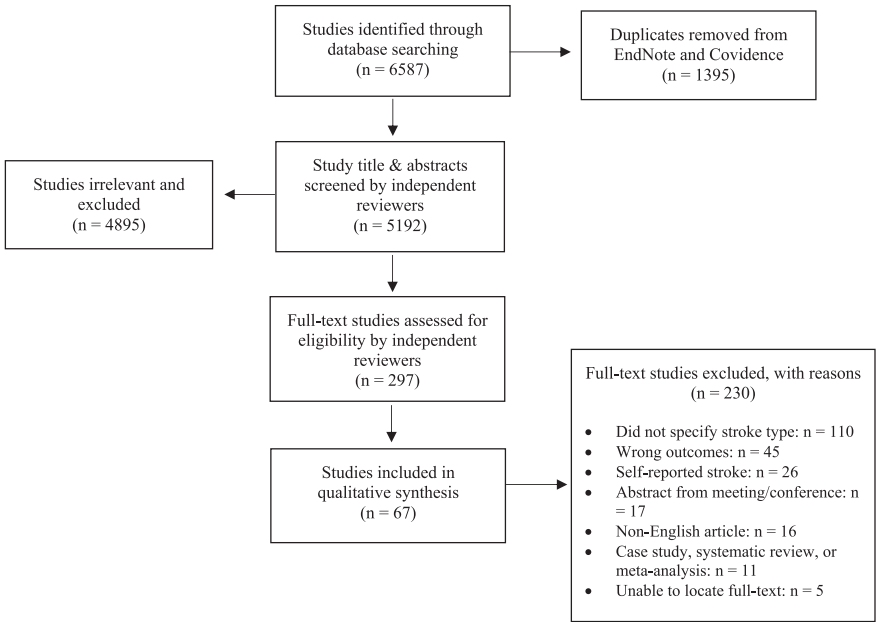

Fig. 1. PRISMA flowchart of study selection. *n* refers to number of studies.

whole number. Raw or summarised statistically significant data are assumed as $p < 0.05$ unless otherwise specified.

Quality assessment

Critical appraisal of methodological quality for cohort and case–control studies was assessed using the Newcastle-Ottawa scale (NOS) [15], and the NOS tool adapted for cross-sectional studies. Studies were rated according to their selection criteria, comparability on the basis of design or analysis, and outcomes or exposures. Case-control and cohort studies were rated on a 1–9 scale. Ratings of 1–3 were scored as "low quality," 4–6 were scored as "moderate quality," and 7–9 were scored as "high quality." The NOS adapted for cross-sectional studies uses a 10-point scale; ratings of 1–3 were scored as "low quality," 4–7 were scored as "moderate quality," and 8–10 were scored as "high quality." Quality assessment scores are summarised in Tables 1–6. A breakdown of study-specific NOS results is presented in Supplementary Tables S1–S3.

Results

A systematic search conducted on August 7, 2018 yielded 6587 citations. After removal of duplicates, 5192 unique citations were included in the title and abstract screening. Subsequently, 297 full-text studies were assessed for eligibility, of which 67 studies were included in the qualitative synthesis. Study characteristics, quality, and findings are summarised in Tables 1–6. Individual study stroke topography, stroke severity, and adjustment variables are reported in Supplementary Tables S4–S9. Refer to Fig. 1 for the complete PRISMA selection process.

Corresponding authors that did not distinguish stroke types were contacted for additional data or clarification if mention of stroke-stratification was included. A total of 43 authors were contacted for additional data and 12 authors responded to the request; six provided stratified data or confirmed exclusive ischaemic stroke samples, and six were unable to provide the requested data.

Study characteristics

All studies were observational. Study quality was generally moderate (58%, n = 39 studies) or high (40%, n = 27 studies). One study was rated as low quality. The 67 included studies were published between 1992 and 2018, with over half published after 2012 and only three studies published before 2000. Sixteen percent of studies included Chinese populations (n = 11), while the other commonest populations were from Japan (n = 8), Switzerland (n = 8), and the United States (n = 7).

Studies were grouped into six categories according to directionality and outcomes: 1) sleep duration on risk of IS, 2) sleep disorders on risk of IS, 3) sleep architectural dysfunction on risk of IS, 4) impact of IS on sleep architecture, 5) impact of IS on sleep disorders, 6) impact of IS on circadian rhythms.

Sleep and circadian rhythm measures

Among studies investigating sleep disorders, 19 of 25 studies (76%) utilised validated diagnostic criteria. Studies investigating sleep duration as a risk factor for IS utilised self-report sleep measures with responses clustered into the following numerical groups: ≤6, 7, 8, 9, and ≥10 h of sleep per night. Sleep architecture and quality was measured via PSG or EEG in 19 of 26 (73%) studies or by validated self-report sleep questionnaires in five of 26 (19%) studies. The remaining two (8%) studies utilised peripheral measures of generalised sleep disturbance (e.g., Nottingham health profile, patient-reported outcomes measurement information system). Circadian rhythms were most commonly assessed through endogenous melatonin serum or urinary melatonin metabolite, 6-sulfatoxymelatonin (6 of 9, 67%). The remaining studies utilised actigraphy (2 of 9, 22%) and a validated self-report chronotype questionnaire (1 of 9, 11%).

Primary findings

The 67 included studies investigated sleep dysfunction as a risk factor for IS (n = 20), and the impact, or consequence, of IS on sleep (n = 38) and circadian rhythms (n = 9). One study was included in

Table 1
Summary of study characteristics and results of studies investigating sleep duration on ischaemic stroke risk.

Author, Year	Study quality (NOS score)	Design, follow-up period, outcome variable	Demographics (study country, gender, age)	Sleep measure	Ischaemic stroke outcome (Total N); Control N	Summary
Chen et al., 2008 [20]	High (7)	Cohort, 7.5 y f/u, IS incidence	USA; female: 100%, range: 50–79 y	Self-report (TST, ≤5, 6, 7, 8, 9, ≥10 h)	1166 (93175); 0	>9h sleep ↑ IS incidence
Eguchi et al., 2010 [24]	Moderate (4)	Cohort, 4 y f/u, IS incidence	Japan; female: 62.4%, mean: 69.9 y	Self-report sleep diary (difference b/w sleep and wake)	517 (932); 0	<7.5 h (vs >7.5 h) sleep ↑ IS incidence
Gianfagna et al., 2016 [22]	High (8)	Cohort, 17 y f/u, IS incidence	Italy; male: 100%, mean: 50.9 y	Self-report (TST, ≤5, 6, 7, 8, 9, ≥10 h)	96 (2277); 0	5 h, >9h sleep ↑ IS incidence
Ikehara et al., 2009 [18]	High (8)	Cohort, 14.3 y f/u, IS death	Japan; male: 56.7%, range: 40–79 y	Self-report (TST, ≤ 4, 5, 6, 7, 8, 9, ≥10 h)	1071 (98634); 0	>10h sleep ↑ IS death
Kakizaki et al., 2013 [19]	High (7)	Cohort, 13 y f/u, IS death	Japan; female: 51.8%, mean: 61.1 y	Self-report (TST: < 6, 7, 8, 9, >10 h)	549 (49256); 0	>10h sleep ↑ IS risk death
Kawachi et al., 2016 [17]	Moderate (6)	Cohort, 16 y f/u, IS death	Japan; female: 51.4%, range: 35–97 y	Self-report (TST, ≤6, 7, 8, ≥9 h)	354 (27896); 0	>9h sleep ↑ IS death
Wen et al., 2016 [23]	High (7)	Case-control, nr, IS incidence	China; male: 54.4%, mean: 64.97 y	Self-report (TST)	223 (880); 547	≥9h sleep ↑ IS incidence
Zhang et al., 2008 [21]	Moderate (5)	Case-control, nr, IS incidence	China; male: 59.6%, mean: 63.5 y	Self-report (TST, ≤ 4, 4–6, 6–8, >8 h)	245 (749); 282	>8h sleep ↑ IS incidence

Abbreviations: b/w = between, d = day(s), f/u = follow-up, h = hours, IS = ischaemic stroke, mo = month(s), NOS = Newcastle-Ottawa scale, nr = not reported, TST = total sleep time, y = year(s).

two sections (Tables 4 and 5) as it measured both sleep disorders and sleep architecture [16]. Thirty-one studies (46%) reported stroke topography, lesion volume, or other relevant neuroimaging measures (see Supplementary Tables S4–S9). Synthesised findings are presented in the following six sections according to directionality and outcomes.

Sleep duration as a risk factor for IS (n = 8)

Seven of eight studies (88%) reported a significant association between long-sleep duration, or ≥8 h of sleep, and IS death [17–19] or incidence [20–23]. Study quality was high (63%, n = 5) to moderate (38%, n = 3). Hazard ratios (HRs) for long sleep duration risk ranged from 1.24 [20] to 3.90 [21]. HRs for sleep duration of >10 h (n = 2 studies) ranged between 1.69 and 2.37 [18,19]. Nine or more hours of sleep (n = 4 studies) was associated with HRs between 1.24 and 1.94 [17,20,22,23]. Eight or more hours of sleep (n = 1 study) was associated with a 3.90-fold increased risk in IS incidence [21]. Inversely, Eguchi and colleagues (2010) reported an increased risk in IS risk in short sleep duration (<7.5 vs >7.5 h of sleep) [24]. All studies (excluding [22], which only adjusted for age) included cerebrovascular risk factors as co-variates. However, only two studies adjusted for depression or depressive symptoms [18,20]. Study characteristics and findings are summarised in Table 1.

Non-apnoea sleep disorders as a risk factor for IS (n = 9)

Non-apnoea sleep disorders, including restless legs syndrome (RLS) [25–27], REM sleep behaviour disorder (RBD) [28], hypersomnia [29], and insomnia [25,30–32] increase the risk of IS. Study quality was moderate (56%, n = 5) to high (44%, n = 4). Sleep-related movement disorders (i.e., RLS and periodic leg movements [PLM]) were associated with a 1.67, 2.04, and 3.89-fold increase in IS risk [25–27]. Insomnia was associated with a 1.19, 1.40, 1.75, and 1.79-fold increase in IS risk [25,30–32]. Participants with chronic insomnia had an increased risk of all-cause stroke compared to those in a remission group [30]. The presence of probable RBD, measured using a validated 13-item self-report questionnaire [33], was associated with a 1.93-fold increase in IS risk after adjusting for sleep measures and other potential confounders [28]. Hypersomnia was associated with a non-significant 1.87-fold increase in IS risk (HR = 1.87, CI: 0.60–5.80) [32]. Study characteristics and findings are summarised in Table 2.

Sleep architecture or quality as a risk factor for IS (n = 3)

No consistent associations were found in a heterogeneous sample of studies investigating sleep architecture [34,35] or sleep quality [36] and risk of IS. Study quality was moderate (66%, n = 2) to high (33%, n = 1). Poor sleep quality, measured using the PSQI, was associated with white matter hyperintensity (WMH) presence and severity (Odds Ratio [OR] = 2.44, CI: 1.26–4.71) [36]. However, no associations were found for silent lacunar infarction [36]. Long sleep duration with blood oxygenation saturation (SpO2) <95% was associated with increased microinfarction (OR = 3.88, CI: 1.10–13.76) [34]. Furthermore, increased slow-wave sleep (SWS) duration was associated with less generalised atrophy (OR = 0.32, CI: 0.10–1.03) [34]. No associations were found between sleep architecture and ischaemic stroke. In a TIA and all-cause stroke sample, patients with the longest nocturnal wake time and highest apnoea–hypopnea index (AHI) had an increased mortality risk (HR = 8.78, CI: 1.1–71.8; HR = 9.71, CI: 1.20–78.29) [35]. However, no statistically significant results were found when data were

Table 2
Summary of study characteristics and results of studies investigating impact of non-apnoea sleep disorders on ischaemic stroke risk.

Author, Year	Study Quality (NOS score)	Design, follow-up period, outcome variable	Demographics (study country, gender, age)	Sleep disorders measure	IS outcome (Total N); control N	Summary
Canivet et al., 2014 [31]	High (7)	Cohort, 11 y f/u, insomnia symptoms prevalence	Sweden; 56.8% female, range: 45-69	4-item self-report questionnaire based on DSM-IV criteria	604 (13617); 0	Insomnia symptoms reported in 51.7% of IS pts, insomnia ↑ risk of all-cause CVD in pts with low socioeconomic status
Chou et al., 2017 [26]	High (7)	Cohort, 5 y f/u, PLM + RLS prevalence	Taiwan; 56.2% male, mean: 57.11 y	ICD-9-CM codes: 327.5 (PLM) and 333.9 (RLS)	137 (3020); 2416	PLM + RLS ↑ IS risk
Elwood et al., 2006 [25]	Moderate (5)	Cohort, 10 y f/u, sleep disturbance prevalence	UK; 100% male, range: 55−69 y	Wisconsin sleep questionnaire	103 (1874); 0	Insomnia ↑ IS, RLS ↑ IS
Frauscher et al., 2010 [79]	Moderate (4)	Case control, RBD prevalence and comorbidities in sleep disorder-PSG confirmed pts	Austria; demographics for RBD-confirmed pts only: 79% male, 57.7 y	PSG, ICSD-2 criteria	1 pontine infarction (34 RBD, 703 total); 0	4.8% (34 of 703) pts diagnosed with RBD, n = 1 with pontine infarction (ns)
Huang et al., 2013 [32]	High (7)	Cohort, 9 y f/u, non-apnoea SD prevalence	Taiwan; 55.1% female. ≤ 35 y: 1%, 35−50 y: 7.6%, 50−65 s: 27.1%, >65 y: 64.4%	ICD-9-CM codes: insomnia (780.5, 780.50, 780.52); hypersomnia (780.54); others (307.4, 780.55−780.56, 780.58−780.59)	9330 (144240); 94160	Insomnia ↑ IS risk, non-apnoea sleep disorders ↑ IS risk
Ma et al., 2017 [28]	Moderate (5)	Cohort, 3 y f/u, RBD prevalence	China; Demographics for total N listed only by RBD group. No RBD group: 81.9% male, mean: 53.9 y. RBD group: 86.9% male, mean: 54.3 y	13-item RBD questionnaire: Hong Kong	136 (12003); 0	RBD ↑ IS risk
Molnar et al., 2016 [27]	High (8)	Cohort, 8 y f/u, RLS incidence	USA; Demographics for total N only. 93% male, mean: 59.8 y	ICD-9-CM code: 333.94	397 (7392); 3696	RLS ↑ IS risk
Wang et al., 2016 [80]	Moderate (6)	Cohort, 85% of pts examined ≤ 3 mo PS, post-stroke depression associations with insomnia	China, 53% male, 68.7 y	Self-report (non-validated)	608 (608); 0	History of insomnia ↑ PS depression
Wu et al., 2014 [30]	Moderate (6)	Cohort, 4 y f/u, insomnia prevalence	Taiwan; Demographics listed only for all stroke types by insomnia status. Insomnia group: 53.5% female, mean: 52 y. Non-insomnia group: 53.0% female, mean: 51 y	ICD-9-CM codes: 780.52, 307.41, 307.42	861 (85752); 64314	Insomnia ↑ IS risk, persistent insomnia vs. remission ↑ IS risk

Abbreviations: d = day(s), f/u = follow-up, ICD-9-CM = International classification of diseases ninth revision clinical modification, IS = ischaemic stroke, mo = month(s), NOS = Newcastle-Ottawa scale, PLM = periodic limb movements, RLS = restless legs syndrome, TIA = transient ischaemic attack, y = year(s).

Table 3
Summary of study characteristics and results of studies investigating sleep quality or sleep architecture on ischaemic stroke risk.

Author, Year	Study quality (NOS score)	Design, follow-up period, outcome variable	Demographics (study country, gender, age)	Sleep measure	Ischaemic Stroke Outcome (Total N); Control N	Summary
Del Brutto et al., 2015 [36]	High (9)	Cross-sectional, SQ in WMH & cerebral small vessel disease	Ecuador; Demographics listed for total N. 59% female, mean: 70 y	PSQI	28 LI, 154 WMH (237); 0	Poor SQ ↑ WMH
Gelber et al., 2015 [34]	Moderate (6)	Case control, PSG time to death 6.4 y, retrospective PSG associations after death	USA; 100% male, mean: 84 y	PSG	68 infarctions (167); 0	> sleep duration + SpO2 <95% ↑ microinfarction; > SWS ↓ generalised atrophy
[a]Ponsaing et al., 2017 [35]	High (8)	Cohort, mean stroke to PSG: 6 d, 19–37 mo f/u period, PSG associations of mortality in IS	Denmark; 63.5% male, mean: 70.25 y	PSG	48 (63); 0	Stratified IS results: no ↑ mortality risk related to PSG variables between IS survivors and non-survivors (*ns*). Non-stratified stroke + TIA results: > AHI and nocturnal wake time ↑ mortality risk

Abbreviations: AHI = apnoea–hypopnea index, IS = ischaemic stroke, d = day(s), f/u = follow-up, ICD-9-CM = International classification of diseases ninth revision clinical modification, mo = month(s), PSQI = Pittsburgh sleep quality index, RLS = restless legs syndrome, SpO2 = blood oxygen saturation, SQ = sleep quality (subjective), SWS = slow-wave sleep (N3), WMH = white matter hyperintensities, y = year(s).
[a] Note: Raw data for IS-stratified results were provided upon request by the corresponding authors and calculated according to study methodology by EG and EL. Study quality NOS scores are based solely on data reported in the original peer-reviewed manuscript.

stratified by ischaemic stroke only [35]. Study characteristics and findings are summarised in Table 3.

Impact of IS on sleep architecture or quality (n = 23)

Sleep architecture and quality is compromised after IS [16,37–54]. Study quality was moderate (74%, n = 17) to high (26%, n = 6). Authors investigating sleep-potentiated stroke recovery found associations between sleep dysfunction and stroke severity or outcome [37,43,47,49,50,52,55]. Thirteen studies (57%) assessed sleep within 14 days after stroke [37,38,40–43,45,47,49,51–54]. Sleep architecture was objectively measured using PSG or high-definition EEG in 17 of 23 (74%) studies. Utilising PSG, sleep architectural variables impacted after IS, when compared to controls, ranged across studies from sleep efficiency (SE) and wake after sleep onset (WASO) [42,44], to total sleep time (TST), SE, non-rapid-eye-movement stage 2 sleep (NREM-2), SWS, and REM [53]. Sleep efficiency was reduced in 65% of studies (n = 11 of 17 studies) utilising PSG. Significant reductions to NREM-1, NREM-2, NREM-3 (SWS), and REM were reported in 12% (n = 2), 41% (n = 7), 35% (n = 6), and 35% (n = 6) of studies, respectively. Study characteristics and findings are summarised in Table 4.

Sleep architectural variables associated with post-stroke (PS) outcome, lesion volume, or topography varied across studies; SWS and REM correlated with stroke severity or functional outcome in five studies [43,44,49,52,53], and stroke topography was associated with sleep quality or architecture in six studies [16,36,43,44,52,53]. IS patients had bilateral reductions in sleep spindles and sawtooth waves [41,47,50]. In both the acute (<10 days) and chronic (3-months) stage of stroke, SWS and theta activity over the contralesional hemisphere were significantly higher in the lateral temporo-parietal-occipital region and contralateral frontocentral region, respectively, which corresponded to the ipsilesional hemisphere [43,44]. Decreased REM percentage was associated with deep (versus superficial) lesions and was an independent predictor of functional outcome [49,52,53]. However, Manconi and colleagues (2014) reported no significant sleep architectural differences between supratentorial and infratentorial strokes [45]. Cortical lesions were associated with worse overall sleep quality [40]. These findings are inconsistent: Chen et al. (2015) reported left hemispheric and anterior circulation infarction associations with poorer sleep quality compared to right-sided and posterior circulation infarction, respectively [16]. In a small sample of mild-to-moderate extra-thalamic stroke, positive post-stroke (PS) outcome was associated with increased sleep efficiency (SE), total sleep time (TST), and NREM-2 sleep [47].

Impact of IS on non-apnoea sleep disorders (n = 16)

Sleep disorders were more common after IS when compared to normative averages or controls [16,29,56–62]. Study quality was mostly moderate (50%, n = 8) to high (44%, n = 7). One study was rated as low quality. Eight (50%) studies examined PS sleep-related movements disorders (n = 5 RLS [61,63–66], n = 3 PLM [56,67,68]; five studies examined PS insomnia [57–59,62,69]; one study examined PS REM sleep behaviour disorder [60]; one study examined PS hypersomnia [29]; one study examined all-cause (non-apnoea) sleep disorders [16]. Time from stroke to sleep assessment ranged significantly across studies from ≤2-days PS [65,67,68], to 3-months post stroke [56,57,59,60]. Study characteristics and findings are summarised in Table 5.

Prevalence of restless legs syndrome (RLS) and periodic limb movements (PLM) after IS (n = 8)

One of six studies (17%) examining PS RLS prevalence included healthy controls [67]. Prevalence across studies ranged from 8% (n = 3) to 33% (n = 10) [56,68]. Four of six studies (67%) reported an RLS prevalence of ≤14.5% [63,65–67]. Two studies reported associations between RLS and PS symptoms or quality of life (QoL); RLS was negatively associated with QoL independent of functional outcome and depression, and stroke symptoms were significantly more severe in RLS patients as measured by the Barthel index and modified Rankin scale [63,64]. Two of three studies including neuroimaging-specific outcomes reported associations between stroke topography and RLS; subcortical strokes (basal ganglia and/or corona radiata lesions) were associated with RLS, and a 17-fold increase in brainstem stroke-potentiated RLS was reported when accompanied with PS sensory symptoms (CI: 1.38–330.77) [65,66].

Among three studies investigating PS PLM, two included control groups and reported a greater quantity of PLMs detected on PSG when compared to healthy controls or TIA [56,67]. Associations between PLM and stroke topography were reported in one study; bivariate correlational analyses revealed that PLM index and lesion

Table 4
Summary of study characteristics and results of studies investigating the impact of ischaemic stroke on sleep architecture and sleep quality.

Author, Year	Study Quality (NOS score)	Design, time of assessment administration, outcome variable	Demographics (study country, gender, age)	Sleep measure	Stroke outcome (Total N); Control N	Summary
Alvarez-Sabin et al., 2017 [81]	High (8)	Cross-sectional; nr, PSG in OSA pts with silent cerebral infarction (SCI) vs controls	Spain; 72.1% male, mean: 64.5 y	PSG	61 (183); 122	SCI SA vs controls: *ns*, OSA ↑ lacunar SCI
Bassetti & Aldrich, 2001 [47]	Moderate (6)	Case control; 11.7 d PS, PSG in acute hemispheric, extra-thalamic stroke vs TIA controls	USA; 66.67% male, mean: 62.1 y	PSG	24 (41); 17 TIA matched	IS SA vs TIA (control): TST min ↓ SE % ↓, N2% ↓, N3-4 ↓. SA in good vs. bad IS outcome: TST ↑, SE % ↑, N2 ↑, sawtooth wave ratio ↑
Chen et al., 2015 [16]	Moderate (5)	Case control; nr, PSG in IS vs controls	China; 64.4% male, mean: 56.6 y	PSG, PSQI, ESS	101 (187); 86	IS SA vs control: TST min ↓, N1% ↓, N3-4% ↓, PSQI ↓, WASO % ↑, ESS score ↑, REM % ↑, SL min ↑, RL min ↑; Thalamic SA vs non-thalamic: N2 ↓, N3-4 ↑, SL ↓; Cerebral infarction SA vs subcortical, brainstem, cerebellum: TST ↓, SE ↓, N3-4 ↓, REM ↓, RL ↓, N1 ↑, SL ↑, WASO ↑
Gokkaya et al., 2005 [46]	Moderate (4)	Case control; 6 mo PS, Nottingham health profile (NHP) scores in IS vs controls	Turkey; 70% male, mean: 58.2 y	NHP	39 (108); 58	Chronic IS NHP sleep domain scores vs controls: ↑ (worse)
Giubilei et al., 1992 [49]	Moderate (5)	Case control; ≤ 5 hr + 3 w PS, PSG changes in acute + chronic IS vs controls	Italy; 55% male, mean: 66.3 y	PSG	18 (28); 10	IS SA vs control: REM min ↓, REM/NREM ratio ↓, REM bouts ↓, WASO ↑; ↓ acute REM correlated with worse PS outcome + severity; deep vs supervision lesions (acute): ↓ REM %
Hermann et al., 2008 [50]	High (7)	Cohort; ≤ 1 mo + 3–6 mo PS + ≥ 1 yr PS; stroke mediated PSG evolution in paramedian thalamic stroke vs controls	Switzerland; 73.9% male, mean: 48.4 y	PSG, spectral EEG analysis (n = 2), self-report sleep duration	46 (58); 12 (peripheral neurological disease controls)	IS SA vs control: N1 ↑, N2 ↓, spindle density ↓; SA + stroke topography PS: unilateral IS ↓ spindle density vs bilateral IS; self-report sleep needs PS ↑ (hypersomnia > in bilateral vs unilateral IS)
Jiang et al., 2013 [39]	Moderate (6)	Case control; ≤ 3 mo PS, PSG in IS + VCIND vs controls	China; 66.67% male, mean: 61 y	PSG, PSQI	48 (152); 48	IS SA vs control: TST ↓, SE ↓, SL ↑, SWS ↓, REM ↓, arousal index ↑, PSQI ↑ (worse)
Karaca, 2016 [48]	Moderate (5)	Cross-sectional; nr, Self-reported SQ in IS vs haemorrhagic stroke	Turkey; 60.9% male, mean: 60.2 y	PSQI	19 (23); 0	IS SQ (mean PSQI) score: 3.0. Regression to estimate PSQI variations: Beck depression inventory score (B = 0.035, CI: 0.004–0.066), comorbidities (B = 0.901, CI: 0.048–1.754)
Katzan et al., 2018 [55]	Moderate (6)	Cohort; median 99 d PS, self-reported sleep disturbance after IS	USA; 54.9% male, mean: 62 y	PROMIS (Patient-Reported Outcomes Measurement Information System)	1195 (1195); 0	IS sleep disturbance scores ↑ (better) vs US population avg (49.2 vs 10.5, p = 0.02); 27.5% of IS pts with meaningfully worse scores (+5 points) vs avg population norms; sleep disturbance associated with worse PS outcome
[a] Klobučníková et al., 2016 [51]	High (7)	Case control, mean 4 d PS; PSG associations with EDS in acute IS	Slovakia; 56.8% male, mean: 68.36 y	PSG, ESS	93 (102); 0	PSG associations for EDS vs no EDS in IS: ↓ REM, ↑ respiratory disturbance index
Manconi et al., 2014 [45]	Moderate (6)	Cohort; admission + 3 mo PS, PSG in supratentorial vs infratentorial IS	Switzerland; 96% male, mean: 64.8 y	PSG	14 supratentorial IS (14 infratentorial IS); 0	Acute IS SA vs chronic: ↓ SE %, SL min ↑, REM latency ↑; Supratentorial IS SA vs infratentorial = *ns*
Muller et al., 2002 [44]	Moderate (5)	Case control; acute + subacute (not specified), PSG in acute hemispheric IS without sleep apnoea vs controls	Switzerland; 60% female, mean: 53 y	PSG	10 (20); 10	IS SA vs controls: WASO min ↑, SE % ↓; Positive correlation b/w SWS + stroke volume (r = 0.79); NREM SWA sleep/wakefulness ratio ↓ in IS vs control + correlated with NIHSS
Pace et al., 2018 [52]	High (8)	Cohort; ≤9 d PS; PSG evolution in IS + associations of functional outcome	Multicentre (Germany, Italy, Switzerland); 71.9% male, mean: 61.2 y	PSG, ESS	153 (153); 0	PSG associations with poor functional (mRS >2) vs good functional outcome (mRS ≤2): ↓ SE, ↓ REM sleep duration, ↑ REM latency, ↑ AHI; ↑ REM latency predictor of worse outcome PS
Poryazova et al., 2015 [43]	Moderate (4)	Case control; ≤ 10 d + ≤ 3 mo PS, HD sleep EEG in acute and chronic hemispheric IS vs controls	Switzerland; 75% male, mean: 52 y	HD EEG	8 (16); 8	Acute + chronic IS SA: ↓ SWS, theta activity, spindle frequency ipsilesionally. SWS correlations: IS severity (NIHSS) + outcome (Barthel index)
Santamaria et al., 2000 [41]	Moderate (5)	Case control; 14 d PS, Sleep spindle in unilateral acute thalamic IS vs controls	Spain; 53.8% female, mean: 67 y	PSG	13 (31); 18	IS SA vs controls: TST min ↓, N2% ↓, time in bed min ↓, bilateral sleep spindle ratios ↓
Siccoli et al., 2008 [42]	Moderate (4)	Case control; ≤ 8 d + ≤ 12 mo PS, PSG & cognition in acute and chronic hemispheric IS vs controls	Switzerland; 64% female, mean: 43 y	PSG	11 (16); 5	Acute IS SA vs. chronic IS or controls: SE % ↓, WASO min ↓

Siengsukon & Boyd, 2009 [82]	Moderate (5)	Case control mean 58.8 mo PS, SQ potentiated off-line motor learning in IS vs controls	USA, 50% female, mean: 62.6 y	Sleep log, PSQI, SSS	40 (80); 40	No significant differences between IS vs control average sleep time, PSQI, SSS (*ns*)
Siengsukon et al., 2015 [83]	Moderate (5)	Case control, ≥6 mo PS, SA potentiated offline motor learning in chronic IS vs controls	USA; 63.3% female, mean: 60.6 y	PSG, PSQI, SSS	20 (10); 30	IS SQ vs controls: no significant differences; SA offline motor learning associations in IS vs controls: ↑ SE, ↓ N3, ↑ REM weakly-to-moderately associated with ↑ offline motor learning (*ns*)
Suh, Choi-Kwon, & Kim, 2014 [40]	High (8)	Cross-sectional; 6.7 d PS, VHSS scores + topography in acute IS	South Korea; 58.9% male, mean: 62.3 y	VHSS, actigraphy (in 54 pts)	282 (282); 0	Multiple regression analysis of factors related to VHSS scores: cortical lesion location, diabetes mellitus, depression; SL: depression; night-time awakenings: depression
[b]Terzoudi et al., 2009 [53]	High (7)	Case control, ≤ 10 d PS, PSG in acute stroke vs controls in relation to outcome + topography	Greece; 64% male, mean: 61.8 y	PSG	45 (78); 16	SA in stroke (excl pts with SDB) vs controls: ↓ TST, ↓ SE, ↓ N2, ↓ SWS; Severe vs mild stroke deficits (NIHSS > 7 vs < 7): ↓ REM, % of N1 + REM negatively associated with stroke severity (NIHSS); ↓ REM % in brainstem, hemispheric, and multiple lesions (vs cerebellar lesions); worse outcome (Barthel index) associated with ↓ REM latency
Vock et al., 2002 [54]	Moderate (5)	Cohort; acute (1−8 d) + subacute (9 −35 d) + chronic (5−24 mo) PS, longitudinal SA evolution in hemispheric IS	Switzerland; 59.2% female,	PSG, sleep diary, ESS	40 (27); 13	IS SA abnormalities vs controls/published norms (no *p* values reported): 67% acute PS, 54% subacute PS, 53% chronic PS; Acute IS SA vs chronic IS: TST ↑, SE ↓, WASO ↑; ↑ self-reported TST, ↑ WASO, ↑ N1, ↓ SE, associated with worse PS outcome (BI or mRS)
Wu et al., 2016 [38]	Moderate (4)	Cohort; 14 d + 3 mo PS, PSG in acute minor thalamic infarction versus controls	China; 70.4% male, mean: 61.4 y	PSG, PSQI, ESS	27 (39); 12	IS SA vs control: SL min ↓, SE % ↓, N2% ↓, N3% ↓
Zhang et al., 2014 [37]	Moderate (5)	Cross-sectional; 2 d + 3 mo PS, SQ in IS vs control	China; 70.3% male, mean: 35.9 y	PSQI	223 (381); 158	IS SQ (PSQI) ↓ vs controls (29.1 vs 47.1), < SQ ↑ 3-mo mRS scores

Abbreviations: AHI = apnea−hypopnea index BI = Barthel index, IS = ischaemic stroke, d = day(s), ESS = Epworth sleepiness scale, f/u = follow-up, ICD-9-CM = International classification of diseases ninth revision clinical modification, mo = month(s), MSLT = multiple sleep latency test, N1-4 = NREM stages 1−4, NHP = Nottingham health profile, NIHSS = National institutes of stroke scale (stroke severity), PS = post-stroke, PSG = polysomnography, PSQI = Pittsburgh sleep quality index, pts = patients, REM = rapid-eye-movement sleep, RL = rapid-eye-movement latency (total time to first REM bout), RLS = restless legs syndrome, SA = sleep architecture, SCI = silent cerebral infarction, SE = sleep efficiency, SL = sleep latency, SpO2 = blood oxygen saturation, SQ = sleep quality, SSS = Stanford sleepiness scale, SWA = slow-wave activity (ratio), SWS = slow-wave sleep (N3), TIA = transient ischaemic attack, VCIND = vascular cognitive impairment-no dementia, VHSS = Verran-snyder-halpern sleep scale, WASO = wake after sleep onset, WMH = white matter hyperintensities, y = year(s).

[a] Raw data for IS-stratified results were provided upon request by the corresponding authors and calculated according to study methodology by EG and EL. Study quality NOS scores are based solely on data reported in the original peer-reviewed manuscript.

[b] Results include both ischaemic stroke and haemorrhagic stroke. Authors reported no statistically significant differences in sleep architecture between either stroke types.

Table 5
Summary of study characteristics and results of studies investigating the impact of ischaemic stroke on non-apnoea sleep disorders.

Author, Year	Study quality (NOS score)	Design, time of assessment administration, outcome variable	Demographics (study country, gender, age)	Sleep measure	Stroke outcome (Total N); controls	Summary
Bassetti et al., 1996 [29]	Moderate (5)	Cohort; 6 pts < 5-weeks PS, 10 pts < 5-mo PS, 2 pts >1-y PS; PSG in paramedial thalamic IS + hypersomnia vs normative data	Switzerland; 83.3% male, age range: 16–60 y	PSG	12 (12); 0	IS + severe hypersomnia vs norms: N1% ↑, N2% ↓, N3-4% ↓, sleep spindles ↓
Benbir, G. & Karadeniz, D., 2012 [67]	High (7)	Case-control; ≤2-d PS, PLM + RLS prevalence in supratentorial IS vs controls	Turkey; 62.9% male, mean: 68.1 y	PSG	35 (70); 35	PLM-index in male IS ↑ vs controls, IS topography + PLMs: *ns*. RLS in IS ↓ vs controls: 14.3% vs. 20%.
Benbir, G. & Karadeniz, D., 2013 [68]	High (8)	Cross-sectional; admission + 3-weeks + 3-mo PS, PLM + RLS prevalence and association with IS outcome	Turkey; 54.2% male, mean: 69.0 y	PSG, International Restless Legs Syndrome Study Group Diagnostic Criteria (IRLSSGC)	24 (All stroke, 2 RLS); 0	8% (n = 2) PS RLS, > arousal-associated PLM-index at admission: ↑ NIHSS, ↓ Barthel scores at 3-mo PS
Boulos et al., 2017a [64]	Moderate (6)	Cohort; 3.9 + 110.4-d PS, RLS after IS and associations with PS QoL	Canada; Total N demographics reported (incl TIA), 51.1% female, mean: 67.4 y	Questionnaire based on IRLSSGC	48 (94); 0	24.4% (n = 23, 10 IS) PS RLS. PS RLS ↓ (worse) QoL vs no RLS. RLS predictor of PS QoL score: baseline OR 0.28 (0.10–0.75), 2–6-month f/u OR 0.14 (0.02–0.82)
Boulos et al., 2017b [56]	High (8)	Cross-sectional; median 51 d PS, PLM and WMH incidence after IS	Canada; Total N demographics listed only, 57% male, mean: 63.7 y	Medical history, RLS diagnostic questionnaire (confirmed by sleep neurologist), PSG	16 (30); 14 (TIA)	IS PLM ↑ vs control, IS PLM-index ↑. PLM index + stroke volume correlated with ↑ WMHs.
Chen et al., 2015 [16]	Moderate (5)	Case-control; nr, PSG confirmed SD after IS vs controls	China; 64.4% male, mean: 56.67 y	PSG, PSQI, ESS	101 (187); 86	IS SD prevalence 77%, PS SD NIHSS ↑ vs no SD
Glozier et al., 2017 [58]	High (8)	Cohort; 28-d +, 6, 12-mo PS, self-reported insomnia after IS and associations with PS functional outcome	Australia; Total N demographics listed by insomnia vs no insomnia: insomnia: 57% male, 70% 46–65 y; no insomnia: 74% male, 79% 46–65 y	Karolinska Sleep Questionnaire	304 (368); 0	PS insomnia prevalence 30–37%, chronic insomnia prevalence 16%, chronic insomnia vs no insomnia: ↑ depression, ↑ anxiety, ↑ disability
Kim et al., 2017 [69]	Moderate (7)	Cohort; acute (not specified), insomnia after acute IS	South Korea; Total N (IS + haemorrhagic stroke) demographics only. 56.85% male mean: 65.63 y	Medical records	8205 (10625); 0	PS insomnia prevalence: IS = 305/8205 (3.8%), haemorrhage = 99/2420 (4.27%)
Lee et al., 2009 [66]	Moderate (6)	Cohort; 1-mo PS, RLS after IS	South Korea; 54% male, mean: 63.9 y	IRLSSGC	137 (All IS, 17 RLS); 0	PS RLS prevalence 12.4% (n = 17); 94% (n = 16) subcortical lesions
Leppavuori et al., 2002 [57]	High (8)	Cross-sectional, 3-mo PS, insomnia after IS	Finland; 50.9%, mean: 70.7 y	DSM-IV criteria	277 (All IS, 157 self-reported insomnia complaints); 0	Self-reported PS insomnia prevalence 57% (n = 157), 37.5% (n = 104) DSM-IV confirmed; pre-existing in 38.6% of IS, de novo in 18.1%. Independent correlates of de novo insomnia: ↑ dementia, ↑ psychotropic drugs, ↑ anxiety, ↑ Barthal index
Medeiros et al., 2011 [63]	Low (3)	Cohort; ≤15 d + 3-mo + 1-y PS, RLS in acute IS stroke and associations with PS outcomes	Brazil; 61.5% male, mean: 64.0 y	PSQI, IRLSSGC	96 (All IS, 12 RLS); 0	PS RLS prevalence 12.5% (n = 12), 100% pre-existing). PS RLS SQ (PSQI) ↓ vs non-RLS. PS (3–12 mo) RLS outcome (Barthel index, mRS) ↓ vs non-RLS
Palomaki et al., 2003 [62]	Moderate (6)	Case-control; ≤14-d + 6, 12, and 18-mo PS, insomnia prevalence after IS and efficacy of mianserin for PS insomnia	Finland; Demographics by treatment condition only. Placebo group: 65.3% males, mean: 54.7 y. Mianserin group: 70.6% males, mean: 55.7 y	Hamilton Depression Scale (3-items related to insomnia), neurologist confirmation if score ≥1	100 (100); 49	PS confirmed insomnia prevalence 51% (n = 51) of stroke patients with confirmed insomnia. PS insomnia ↑ poor life satisfaction. 2-mo placebo treatment ↑ insomnia
Rist et al., 2014 [61]	High (8)	Cross-sectional; nr, self-reported RLS after IS	France; Demographics for total N listed only by RLS group. No RLS: 59.7% female, mean: 71.6 y. RLS: 72.9% female, mean: 71.6 y	3-item self-report questionnaire	88 (1035); 0	PS RLS prevalence: 21% (n = 218). WML ↑ RLS risk
Ruppert et al., 2014 [65]	Moderate (5)	Cross-sectional; <2-d PS, RLS after brainstem IS	France; 60% male, mean aged 62.8 y	IRLSSGC	30 (30); 0	PS RLS prevalence: 10% (n = 3). RLS + topography or severity: ns. RLS + PS sensory symptoms ↑ brainstem IS RLS

Tang et al., 2014 [60]	Moderate (5)	Cohort, 3-mo PS, RBD after IS	Hong Kong: Demographics by RBD status. RBD: 53.8% male, mean: 67.3 y. Non-RBD: 61.3% male, mean: 66.5 y	13-item RBD questionnaire	119 (119); 0	PS RBD prevalence: 10.9% (n = 12). Brainstem IS ↑ RBD. IS volume in non-RBD ↑ vs. RBD
Tang et al., 2015 [59]	High (9)	Cross-sectional; 3-mo PS, insomnia after IS	Hong Kong: 60.4% male, mean: 66.1 y	7-item self-report questionnaire	336 (336); 0	PS insomnia prevalence: 44% (n = 147); PS insomnia associated with ↓ QoL

Abbreviations: IS = ischaemic stroke, clinical modification, d = day(s), ESS = Epworth sleepiness scale, f/u = follow-up, ICD-9-CM = International classification of diseases, mo = month(s), ninth revision, nr = not reported, PS = post-stroke, PSG = polysomnography, PSQI = Pittsburgh sleep quality index, QoL = quality of life, RBD = rapid-eye-movement behaviour disorder, RLS = restless legs syndrome, RLSSGC = International restless legs syndrome study group diagnostic criteria, SpO2 = blood oxygen saturation, SQ = sleep quality (subjective), SWS = slow-wave sleep (N3), WMH = white matter hyperintensities, y = year(s).

volume significantly correlated with increased WMHs [56]. However, in patients with supratentorial IS, no significant associations were found between IS topography and the presence of PLM [67].

Prevalence of insomnia after IS (n = 5)

No studies investigating PS insomnia included control groups. The prevalence of insomnia complaints after stroke ranged between 3.8% and 57% [57,69]. However, among studies utilising validated questionnaires, the prevalence of insomnia was 30%, 37.5%, and 44% [57–59]. No associations between insomnia, IS topography, PS severity or outcome were reported. Independent correlates of insomnia included anxiety and use of psychotropic drugs [57]. Insomnia symptoms were associated with depression and reduced quality of life [59,62]. These findings are supported by Glozier et al. (2017): patients with chronic insomnia (16%) after stroke had a 3.31, 3.60, and 6.75-fold increased rate of anxiety, disability, and depression, respectively [58].

Prevalence of rapid-eye-movement behaviour disorder after IS (RBD) (n = 1)

Tang and colleagues (2014) reported that 10.9% of IS patients had symptoms of rapid-eye-movement behaviour disorder (RBD) using a validated RBD questionnaire [60]. Acute brainstem infarction was a significant independent predictor of RBD (OR = 3.68, CI: 1.17–12.2). Infarct volume was significantly larger in non-RBD patients versus RBD-patients [60].

Impact of IS on circadian rhythms (n = 9)

Among studies measuring endogenous markers of circadian rhythmicity after acute IS (n = 6 studies), all reported significant reductions to melatonin compared to controls [70–75]. Study quality was generally moderate (67%, n = 6). Three studies (33%) were rated as high quality. These findings are consistent for nocturnal serum melatonin [70–75], but not for the urinary melatonin metabolite, 6-sulphatoxymelatonin [72,73]. Circadian rhythm dysfunction was associated with IS severity or functional outcome in four of nine studies (44%) [74–77]. Backward logistic regression analyses revealed that nocturnal melatonin was independently associated with an increased probability of IS [71]. Comparable findings were reported in a PS insomnia sample; nocturnal serum concentrations of melatonin, GABA, and total antioxidants were lower in IS insomnia patients [75]. There was a significant interaction between NIHSS and melatonin that was associated with insomnia [75]. Study characteristics and findings are summarised in Table 6.

Two of three studies utilising actigraphy [77,78] or validated chronotype questionnaire [76] reported significant changes to circadian rhythms after IS. Self-reported chronotype, defined by mid-sleep time on work-free days corrected for sleep deficit on workdays (MSFsc), changed significantly after IS [76]. Changes to MSFsc after stroke were negatively correlated with stroke severity and outcome (NIHSS and mRS at hospital discharge) [76]. Interior circulatory strokes were associated with MSFsc delays, whereas posterior circulatory strokes were associated with advances of MSFsc [76]. Takekawa and colleagues (2007) reported fragmented circadian rhythms in non-ambulatory patients in the acute phase of IS [77]. However, Zuurbier and colleagues (2014) reported no significant associations between lacunar infarctions and actigraphy measured 24-hour circadian fragmentation (intradaily variability) in a large cohort study [78]. Increased white matter lesion volume and cerebral microbleeds were significantly correlated with circadian fragmentation [78].

Table 6
Summary of study characteristics and results of studies investigating the impact of ischaemic stroke on circadian rhythms.

Author, year	Study quality (NOS score)	Design, time of assessment administration, outcome variable	Demographics (study country, gender, age)	Circadian rhythm measure	Stroke outcome (Total N); controls	Summary
Adamczak-Ratajczak et al., 2017 [70]	High (7)	Case control, ≤2-d PS, melatonin in acute IS vs controls	Poland; 100% male, mean: 53 y,	Melatonin serum	8 (29); 10	Melatonin amplitude + mesor ↓ after IS
Atanassova et al., 2009 [71]	High (7)	Cross-sectional matched case–control, 3-d PS, melatonin in acute IS vs controls	Bulgaria; 60.6% male, mean: 58.4 y	Melatonin serum	33 (68); 33	Melatonin ↓, cortisol ↑ after IS
Fiorina et al., 1999 [74]	Moderate (4)	Case control, nr, nocturnal and diurnal melatonin excretion in IS vs controls	Italy; 61.5% male, mean: 64.3 y	Urinary melatonin excretion	13 (18); 5	Nocturnal melatonin ↓, diurnal melatonin ns, after acute (3 d) and chronic (2 w) IS
Kantermann et al., 2014 [76]	Moderate (6)	Cross-sectional, 2-mo PS, chronotype (mid-sleep on work-free d corrected for sleep deficit on workdays; MSFsc) after mild IS	Germany; 62.9% male, mean: 66.3 y	MCTQ	35 (35); 0	Chronotype (MSFsc) ↓ after anterior circulation IS, ↑ after posterior circulation; changes to MSFsc after IS negatively correlated with severity (NIHSS and mRS at discharge): chronotype correlation with IS severity: $r = -0.565$ for NIHSS at discharge, $r = -0.620$ for mRS at discharge
Ritzenthaler et al., 2009 [73]	Moderate (6)	Cohort, <1-d PS, melatonin in IS vs controls	France; 69.3% male, age range: 18–50 y: 22.0%, 51–70 y: 36.2%, >70 y: 41.7%.	Melatonin serum, aMT6S	127 (343); 216	Melatonin ↓ after IS, aMT6S after IS ↓ (ns)
Ritzenthaler et al., 2013 [72]	Moderate (5)	Cohort; <1 d, 5- PS, melatonin in IS vs controls	France; 64.3% male, age range: 27.7–88.5 y (median: 73.1 y)	Melatonin serum, aMT6S	42 (232); 190	Melatonin, aMT6S ↓ after IS
Takekawa et al., 2007 [77]	Moderate (6)	Cohort, <7 d PS, circadian rhythm (actigraphy + rectal temperature) ambulatory vs. non-ambulatory pts after mild IS	Japan; No gender information provided. Mean: 68.4 y	Actigraphy, rectal temperature	50 (50); 0	mRS score ↓ in abberant circadian fragmentation group vs. normals: Admission mRS scores between normal, mild, severe/abberant CR groups: 2.8 vs. 2.9 vs. 4.8
Zhang et al., 2017 [75]	Moderate (5)	Case-control, N/A, melatonin in IS + insomnia vs controls	China; Demographics by inomnia group only. Non-insomnia group: 56% male, mean: 58.9 y. Insomnia group: 52% male, mean: 59.7 y	Melatonin serum, MEQ	25 (50); 25	Nocturnal melatonin, GABA, total antioxidants ↓ after IS (+insomnia) vs. controls; melatonin ↑ NIHSS
Zuurbier et al., 2014 [78]	High (10)	Cohort study, 3 mo PS, circadian fragmentation (actigraphy - intradaily variability) in WML, LI, cerebral microbleeds	Netherlands; 58.1% male, mean: 59.2 y	Actigraphy	43 LI (970); 0	Circadian fragmentation ↑ WML volume + cerebral microbleeds. Circadian fragmentation + LI = ns

Abbreviations: IS = ischaemic stroke, aMT6s = 6-sulphatoxymelatonin (urinary melatonin metabolite), CR = circadian rhythm, d = days, GABA = gamma-aminobutyric acid, LI = lacunar infarction, MCTQ = Munich chronotype questionnaire, MEQ = morningingness-eveningness questionnaire, mo = months, mRS = modified Rankin scale (functional post-stroke outcome), MSFsc = mid-sleep on work-free days corrected for sleep deficit on workdays, NIHSS = National institutes of health stroke scale (stroke severity), ns = non-significant, PS = post-stroke, WML = white matter lesions, y = years.

Discussion

Summary of findings, limitations, and clinical pathogenic implications

To our knowledge, this is the first systematic review to investigate the bidirectional impact of sleep and circadian dysfunction as both a risk factor and consequence of IS. Accumulating data from included studies suggest that chronic sleep dysfunction, characterised by long sleep duration or sleep disorders, significantly increases the risk of IS. Inversely, when compared to controls, IS is associated with sleep and endogenous circadian rhythm disruption which may be associated with IS topography and functional outcome.

We were unable to identify any studies that investigated objective or validated measures of sleep-potentiated circadian rhythm dysfunction as a risk factor for IS. Shift work disorder is a common circadian rhythm disorder and is an independent risk factor for all-cause stroke (RR R: 1.05, CI: 1.01 to 1.09) [84,85]. However, no screened IS studies utilised the only validated shift work disorder questionnaire created by Barger and colleagues (2012) [86].

Despite liberal inclusion criteria, a majority (70%, n = 47) of studies examined sleep and circadian dysfunction *after* IS. Less than 30% of studies reported *a priori* neuroimaging hypotheses (e.g., IS topography, lesion volumes) related to PS outcome or severity. The most well-defined study designs and samples were from large prospective cohort studies investigating sleep duration and sleep disorders as risk factors for IS. Only one study was classified as low quality or as having a high-risk of bias.

Long sleep duration is a risk factor for IS

Prolonged sleep duration, characterised by eight or more hours of sleep per night, was associated with the highest stroke risk. Findings are consistent with recent meta-analyses reporting increased all-type stroke incidence for long versus short sleep duration [87–90]. Despite recent epidemiological evidence suggesting a U-shaped relationship between short sleep duration and all-cause mortality, our sample of studies did not corroborate these associations for short sleep duration and IS risk [22,91,92].

Depression or depressive symptoms were only adjusted for in two studies [18,20]. Given the frequency of hypersomnia and long-sleeping tendencies in individuals with depression, and the frequency of depression after stroke, future studies investigating prospective associations with IS should include depression as a covariate, as well as other psychiatric comorbidities [93]. An important limitation is the widespread use of subjective, self-reported sleep duration, although no studies were classified as having a high risk of bias. The use of objective sleep measures (e.g., accelerometer or PSG) are especially necessary among the elderly and in patients with sleep disorders where misperception of sleep is well recognised [94,95]. Furthermore, the total hours of sleep duration were heterogeneously clustered and not measured as continuous variables. For example, while Giangfagna et al. (2016) grouped sleep duration into "≤5, 6, 7, 8, 9, or ≥10 h", Kawachi and colleagues (2016) used a restrictive "≤6, 7, 8, or ≥9 h" grouping [17,22]. No studies examined IS risk beyond ≥10h, thereby limiting potential findings for extreme sleep duration. Importantly, no studies included neuroimaging correlates of sleep duration risk, which may clarify the neuroanatomical basis of pathological long-sleep duration.

The underlying biological mechanisms supporting the association between chronic long-sleep duration and IS pathogenesis are unclear. One possible explanation may be stroke-related proinflammatory biomarkers such as C-reactive protein (CRP). Habitual long sleep duration is associated with elevations in CRP which have shown to significantly increase the risk of IS [96–98]. Furthermore, epidemiological evidence suggests an association between long-sleep duration and stroke-related risk factors including WMHs, atrial fibrillation, arterial atherosclerosis, and left ventricular masses [99–102]. Whether prolonged sleep duration is an independent causal risk factor for IS, or merely a marker of underlying poor health, remains unclear.

Bidirectional impact of sleep architectural and quality dysfunction in IS

Sleep architecture and self-reported sleep quality is compromised after IS. However, there is insufficient evidence among our sample of heterogenous studies to suggest an association between longitudinal dysfunction to sleep architecture or subjective sleep quality and risk of IS. SWS duration measured in the contralesional hemisphere correlated with stroke volume and outcome. Furthermore, sleep architecture was most severely affected in thalamic and cortical strokes. These findings are consistent with neuroanatomical evidence; thalamocortical projections within the ascending reticular activating system are, in part, responsible for sleep-wake regulation [103].

There are important limitations among these studies. First, no studies included baseline (pre-stroke) polysomnographic characteristics to gauge the causal impact of IS on sleep dysfunction. A majority of studies using PSG also included small samples and did not report or justify effect size calculations. Next, control population types (i.e., TIA vs healthy age and gender-matched controls) were inconsistent across studies. IS populations were also heterogenous; stroke severities, stroke topographies, and PS time-course differed across studies. Thus, the range and degree of sleep architectural disturbance may be attributed to the heterogeneity of infarct locations (topography) and volumes across studies. Furthermore, a majority of studies did not exclude patients taking known sleep architecture altering drugs (e.g., benzodiazepines, GABA agonists, serotonergic antagonists) or patients with *a priori* sleep disorder diagnoses. Finally, the decrease in SE may be due to deleterious environmental stressors associated with acute hospital care; namely, prolonged or insufficient light exposure, white noise, and overnight clinical interactions [104]. Although sleep architecture is compromised after IS, there is insufficient evidence to suggest a causal relationship between IS and sleep architectural dysfunction. Nonetheless, our findings are consistent with a recent review by Duss and colleagues (2017) postulating sleep-potentiated neuroprotection and neuroplasticity after IS [2].

Non-apnoea sleep disorders are risk factors for IS

Non-apnoea sleep disorders increase the risk of IS after controlling for covariates. Sleep-related movement disorders (i.e., RLS and PLM), insomnia, and self-reported RBD were associated with the highest risk. Furthermore, de novo sleep disorders were generally more common after IS when compared to normative averages or controls. However, conclusions for specific sleep disorders cannot be generalised given the small sample of included studies. Studies included relatively young samples (mean age: 55.3 years) with insufficient follow-up periods (mean follow-up period: 5.8 years) to reach peak IS risk (≥65 years). Therefore, underestimation of IS risk is likely.

Prevalence of RLS after IS were in line with upper-ranges of normative averages (10–15%) [105]. However, acute and chronic IS symptoms were significantly more severe in patients with RLS. Topographically, subcortical strokes were associated with RLS,

particularly when accompanied with PS sensory symptoms. These findings are consistent with a recent prospective study showing RLS as a significant predictor of all-type subcortical stroke [106]. Mechanistically, pre-clinical data also support these findings; subcortical basal ganglia nuclei and dopaminergic dysfunction has been implicated in the pathogenesis of RLS [107].

The prevalence or severity of PLM, hypersomnia, insomnia, and RBD were generally greater after IS when compared to controls or normative averages [29,108–110]. Furthermore, brainstem infarction was a significant independent predictor of RBD.

In summary, non-apnoea sleep disorders increase the risk of IS after controlling for covariates. It is well established that sleep disorders contribute to sleep fragmentation, increased nocturnal arousals, and atypical sleep architecture. Thus, the proposed mechanisms for sleep disordered IS pathogenesis include sympathetic hyperactivity, hypothalamic pituitary adrenal axis activation, and deficiencies in central dopaminergic neurotransmission [107,111,112]. Longitudinal sleep-potentiated autonomic dysfunction may increase the prepathological risk of IS, and dysautonomia *after* IS may be exaggerated during sleep thereby obstructing PS recovery [113].

Circadian rhythms are disrupted after acute IS

Melatonin, an endogenous marker of circadian rhythms, is reduced after IS when compared to controls. Diminution of melatonin, and self-reported chronotypic changes, were associated with increased PS severity (NIHSS) and worse functional outcome at discharge (mRS). Importantly, nocturnal melatonin sampling occurred in light-controlled environments, thereby limiting the confounding effects of light exposure on pineal secretion of endogenous melatonin. No studies reported duration, intensity (lux), and wavelength (e.g., blue light, 540 nm) of *daytime* light exposure – hence it was not feasible to determine whether altered circadian function was likely due to a direct impact of IS or secondary to altered environmental light exposure. No studies included pre-stroke or longitudinal measures of melatonin concentrations which limits directional and causal associations between circadian misalignment and IS. Importantly, the impact of potential sleep pathology after IS on circadian rhythmicity was not investigated in studies included in our sample. Circadian rhythm outcomes were not stratified by neuroanatomical IS topography and were heterogenous across studies. Focal suprahypothalamic lesions disrupt slow-wave-sleep potentiated elevations of growth hormone [114]. However, whether melatonin secretion in humans is impacted by focal lesions to the intergeniculate leaflet (which innervate the suprachiasmatic nucleus and pineal gland), or is disturbed as part of diffuse neurovascular injury or altered exposure to Zeitgebers, remains unclear.

The neuroprotective function of melatonin has been established in pre-clinical models of focal and diffuse brain ischaemia [6]. Melatonin initiates free radical scavenging and secondary antioxidant actions which exhibit a daily rhythm and are inhibited by light in humans [115]. In IS, the melatonin rhythm is impaired, with a reduction in nocturnal amplitude or a tendency to phase delay or advance. However, whether these effects are transient or chronically sustained requires further investigation. The radiological impact of varying stroke severities and topographies on melatonin secretion should be further evaluated using novel neuroimaging methods. The interplay of sleep pathology commonly reported after IS should also be measured in conjunction with endogenous circadian rhythm disruption.

Exogenous melatonin treatment in acute animal focal ischaemia has a neuroprotective effect [116]. Transcranial near-infrared light therapy has been implicated in photobiomodulation via normalisation of misaligned circadian rhythms and motor function recovery after embolic stroke in animals [117]. Thus, both exogenous melatonin supplementation and near-infrared light therapy should be assessed in randomised trials in acute human IS given their reported neuroprotective efficacy in pre-clinical models.

Limitations

Given the lack of homogeneity across studies and outcomes, there was limited scope for conducting a meta-analysis. Furthermore, findings from this review cannot be generalised across other stroke types (i.e., haemorrhagic, TIA) or varying stroke topographies given the marked differences in pathophysiology. Whenever possible, study-specific stroke topography and stroke severity characteristics have been reported in supplementary tables. An additional limitation is publishing or reporting biases of only *positive* findings.

The Newcastle Ottawa Scale is widely used and has been validated as a study quality assessment tool for non-RCTs [15]. However, the NOS may not give sufficient weight to validated (i.e., polysomnography) versus less informative or reliable sleep-measurement tools (e.g., actigraphy, sleep diary). It is therefore possible that a study scored as “high quality” utilises inferior sleep-measurement tools if other NOS criteria is met (e.g., exceptional sample size, sample representativeness, controls, and robust statistical methodology). Alternatively, a study utilising polysomnography may be scored as moderate or low-quality if accompanying NOS criteria is not fulfilled.

Finally, 43 screened studies investigating sleep or circadian dysfunction after stroke did not differentiate or stratify results by stroke type (e.g., TIA vs ischaemic vs haemorrhagic). Attempts were made to contact corresponding authors for addition stratified data or clarification. However, response rates were poor (28%, n = 12) and only six (14%) corresponding authors provided stratified data, thereby restricting our sample of included studies.

Conclusions

This systematic review revealed that long sleep duration and sleep disorders increase the risk of developing IS. Inversely, after IS, sleep and endogenous rhythm disruption is common and may be associated with IS severity and outcome. We were unable to identify any studies investigating the impact of longitudinal circadian rhythm dysfunction on IS risk. As evidenced by our study sample's heterogenous methodology, the direct assessment of sleep and circadian rhythms in IS is an emerging field in its infancy. Future studies should standardise sleep and circadian measurement methodology and incorporate *a priori* neuroimaging-specific outcomes. Additional recommendations are outlined in our research agenda.

Author disclosures

Elie Gottlieb reports no disclosures. Elizabeth Landau reports no disclosures. Helen Baxter reports no disclosures. Dr. Emilio Werden reports no disclosures. A/Prof Mark Howard reports no disclosures. A/Prof Amy Brodtmann is on the editorial board of Neurology and International Journal of Stroke.

Study funding

The authors received no specific funding for this work.

Practice points

A systematic review investigating the bidirectional impact of sleep and circadian rhythm dysfunction after ischaemic stroke revealed the following:

1. This literature generally consisted of moderate to high quality studies. However, methodology (e.g., stroke to sleep and circadian assessment times, follow-up periods, measurement tools) and stroke characteristics (e.g., stroke topography, stroke severity) were heterogenous.
2. Long sleep duration and sleep disorders increase the risk of ischaemic stroke. Inversely, when compared to controls, ischaemic stroke is associated with sleep architectural and endogenous circadian rhythm disruption.
3. Post-stroke sleep architectural and circadian rhythm abnormalities may be associated with post-stroke severity and functional outcome.
4. The range and degree of sleep architectural disturbances reported after ischaemic stroke are likely due to varied infarct locations and volumes across studies.
5. There is a major gap in the circadian rhythm and stroke literature; we were unable to locate any studies investigating direct measures of circadian rhythm dysfunction as a risk factor for IS.

Research agenda

Future studies investigating sleep and circadian dysfunction in human ischaemic stroke should address shortcoming described in pre-existing literature and specifically:

1. Longitudinal polysomnographic measurement of objective sleep architecture in conjunction with radiological measures of brain features (location, volume, activity) should be assessed to further establish the causal impact of chronic sleep dysfunction on ischaemic stroke.
2. Direct and objective measures of circadian rhythms should be longitudinally assessed in large prospective cohorts to determine the impact of chronic circadian dysfunction on IS risk.
3. Studies investigating sleep and ischaemic stroke should stratify results by strict delineations of homogenous stroke topography and severity.
4. Observational follow-up periods should be extended to better determine the transient or sustained effects of post-stroke sleep and circadian dysfunction.
5. Future clinical IS sleep research should control for important covariates including depression and other psychiatric comorbidities, stroke severity, stroke topography, and sleep-altering drugs.
6. Future studies investigating circadian rhythms after ischaemic stroke should measure daytime environmental light exposure to determine whether this is the source of altered circadian function post-stroke.
7. Exogenous melatonin supplementation and light therapy should be clinically evaluated in randomised trials of acute ischaemic stroke.

Conflicts of interest

The primary author acknowledges the University of Melbourne Faculty of Medicine, Dentistry and Health Sciences for a Melbourne Research Scholarship supporting a doctoral degree but neither benefited from this systematic review.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2019.03.003.

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