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Sleep disorders and the risk of stroke

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Abstract

Introduction: Stroke is a major cause of disability and death in the United States and across the world, and the incidence and prevalence of stroke are expected to rise significantly due to an aging population. Obstructive sleep apnea, an established independent risk factor for stroke, is a highly prevalent disease that is estimated to double the risk of stroke. It remains uncertain whether non-apnea sleep disorders increase the risk of stroke.

Areas covered: This paper reviews the literature describing the association between incident stroke and sleep apnea, REM sleep behavior disorder, restless legs syndrome, periodic limb movements of sleep, insomnia, and shift work.

Expert Commentary: Trials of CPAP for stroke prevention in sleep apnea patients have been largely disappointing, but additional trials that target populations not yet optimally studied are needed. Self-reported short and long sleep duration may be associated with incident stroke. However, abnormal sleep duration may be a marker of chronic disease, which may itself be associated with incident stroke. The relationship between non-apnea sleep disorders and incident stroke deserves further attention. Identification of specific non-apnea sleep disorders or sleep problems that convey an increased risk for stroke may provide novel targets for stroke prevention.

Keywords

sleep-disordered breathing; sleep apnea; stroke; restless legs syndrome; REM sleep behavior disorder; sleep duration

1. Introduction

Stroke is a major cause of disability and death in the United States and across the world. The incidence and prevalence of stroke are expected to rise significantly due to an aging

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Declaration of interest

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population. Sleep apnea is an established independent risk factor for stroke that is estimated to confer an approximately two-fold increased risk [2]. Sleep apnea is highly prevalent in the United States, with moderate-to-severe sleep apnea now estimated to affect approximately 17% of men and 9% of women aged 50–70 years [3]. Worldwide prevalence estimates of obstructive sleep apnea in adults range from 9 to 38% [4].

The evidence for an association between individual non-apnea sleep disorders and incident stroke is less robust. However, a 2013 retrospective study of 94,160 subjects (47,080 of whom had a non-apnea sleep disorder by International Classification of Diseases [ICD] codes for specific disorders of sleep of nonorganic origin and sleep disturbances) used Taiwan's National Health Insurance Research Database from 1997 to 2001 to investigate the association between non-apnea sleep disorders and incident stroke. In this study, the non-apnea sleep disorder group had a 20% greater risk of incident ischemic stroke than the control group after adjustment for age, gender, and comorbidities (aHR [adjusted hazard ratio] 1.19; 95% confidence interval [CI], 1.14–1.24) [*5].

Here we will review the evidence that supports a causal relationship between sleep apnea and incident stroke. We will discuss the relationship between incident stroke and non-apnea sleep disorders including long and short sleep duration, insomnia, restless legs syndrome (RLS), periodic limb movements of sleep (PLMs) rapid eye movement (REM) sleep behavior disorder, and shift work. We will briefly discuss the current state of neurotherapeutics to prevent stroke related to sleep disorders and sleep problems. Finally, we will provide our opinion about important future directions for research needed to further clarify the relationship between sleep disorders and the risk of stroke.

2. Sleep apnea and risk of stroke

Sleep apnea is a common condition manifesting with repeated apneas and hypopneas during sleep. Sleep apnea is associated with an increased risk of stroke in the general population [**6], as well as in subgroups of patients including the elderly [7] and those with coronary artery disease [8]. A 2014 meta-analysis by Li et al investigated the effect of obstructive sleep apnea (OSA) on incident ischemic and “hemorrhagic stroke” across ten prospective community-based, population-based, or clinic-based studies [**2]. Across all studies and including patients with and without a history of prior stroke, OSA was associated with a two-fold increased risk of incident stroke (relative risk [RR] 2.10; 95% CI, 1.5–2.93). Another 2014 meta-analysis of five prospective studies (two of which were included in the Li et al meta-analysis) found a similar association between OSA and risk of stroke (RR=1.94; 95% CI, 1.29–2.92) [9].

The largest of the studies included in the Li et al meta-analysis was the 2010 community-based Sleep Heart Health Study (SHHS) [**6]. The SHHS was the first prospective study to report sex-stratified analyses of the relationship between OSA severity and incident stroke. In this study, 5422 participants > 40 years without a history of stroke underwent baseline polysomnography (PSG) and were followed for a median of 8.7 years. Incident ischemic stroke was observed in 85 (3.5%) of 2462 men and in 108 (3.6%) of 2960 women. In unadjusted analysis, the obstructive apnea/hypopnea index (OAH) was associated with

incident ischemic stroke in both men and women. After adjustment for age, race, body mass index (BMI), smoking status, systolic blood pressure, use of anti-hypertensive medications, and diabetes, men in the highest OAH quartile (19.1 to 64.5) as compared to the lowest (OAH 0 to <4.1) showed an almost three-fold increased risk of incident stroke (hazard ratio [HR] 2.86; 95% CI, 1.10–7.39). Men in quartiles II (OAH 4.1 to <9.5) and III (OAH 9.5 to 12.1) in comparison to those in quartile I did not show a significantly higher risk of stroke (QII HR 1.86; 95% CI, 0.67–5.12 and QIII HR 1.86; 95% CI, 0.70–4.9). After adjustment in men, the risk of incident ischemic stroke increased with higher OAH quartiles ($p=0.016$ for linear trend). After adjustment in women, the relationship between OAH and incident ischemic stroke was less robust and non-significant, with an HR of 1.34 in quartile II (95% CI, 0.76–2.36), 1.20 in quartile III (95% CI, 0.67–2.16), and 1.21 in quartile IV (95% CI, 0.65–2.24). In addition, the test for linear trend in women was not significant ($p=0.693$). However, in women with an OAH ≥ 25 , a statistically significant 2% increase in stroke HR was observed for each one-unit increase in OAH.

The reason for the differing results in men versus women in SHHS is unclear. The authors suggested several possibilities, including insufficient power (albeit not supported by post-hoc power calculations); an increase in sleep apnea prevalence in women over time with initially negative PSG leading to initial misclassification; a greater contribution from competing risk factors such as diabetes, hypertension, and smoking than from sleep apnea; and differences in vascular and cardiac responses to sleep apnea-related stress in women versus men.

Somewhat divergent from the results of SHHS are the results of a Spanish prospective observational study (not included in the two aforementioned meta-analyses) of 967 women without a prior history of stroke and with baseline PSG or respiratory polygraphy obtained for suspected OSA [10]. In this study, a strong association between incident stroke and AHI ≥ 10 was observed in women not treated with continuous positive airway pressure (CPAP) (aHR 6.44; 95% CI, 1.46–28.32) when compared to those with AHI < 10 after adjustment for age, BMI, hypertension, type 2 diabetes, and atrial fibrillation [10]. Interestingly, in adjusted analysis, women with AHI ≥ 10 who were treated with CPAP, as compared to women with AHI < 10, had no increased risk of incident stroke (aHR 1.31; 95% CI, 0.26–6.59). The authors concluded that the strong association between AHI and incident stroke observed in untreated women in their study, as compared to in SHHS, was related to a higher median AHI in their subjects (24 in the untreated group and 43 in the CPAP group) compared to the median OAH in SHHS subjects (6.9 in women without stroke).

Additional studies have sought to clarify whether OSA may be associated with certain subtypes of stroke, such as cardioembolic stroke, large vessel atherosclerotic stroke, or small vessel ischemic disease (lacunar stroke). In a case-control study of 53 consecutive subjects who had an ischemic stroke within one year of a preceding PSG, cardioembolic stroke (as defined by The Trial of Org 10172 in Acute Stroke Treatment [TOAST] classification system) was more common in individuals with OSA (defined as AHI > 10) than in those without (72% versus 33%, $p=0.01$) [11]. While the prevalence of atrial fibrillation was higher in the OSA group than in the control group (59% versus 24%, $p=0.01$), the authors reported that the association between OSA and cardioembolic stroke remained significant

even after controlling for atrial fibrillation (odds ratio [OR] 4.5, $p=0.03$). A retrospective cohort study of 334 subjects with atrial fibrillation and a baseline PSG found a higher prevalence of first-time ischemic stroke after a mean 4.4 years of follow-up in patients with OSA (defined as AHI ≥ 5) than in patients without OSA (25.4% versus 8.2%; $p=0.006$), with a dose-response relationship observed between AHI and incident stroke ($p=0.005$) [12]. On the other hand, a larger study of 17,375 patients with atrial fibrillation in the Taiwan National Health Insurance Research Database found no evidence of increased risk of stroke in 133 subjects with OSA compared to 17,242 without OSA during an average 2.5 years of follow-up [13].

The mechanism(s) by which obstructive sleep apnea independently increases stroke risk remain(s) unclear. Drawing conclusions about underlying pathophysiology is complicated by common established risk factors for both entities, such as hypertension and age. Suggested potential mechanisms include increased daytime [14] and nocturnal [14,15] sympathetic tone, potentially leading to increases in nocturnal blood pressure and arrhythmia. Impaired cerebral autoregulation in response to changes in blood pressure may also play a role [16]. Intermittent hypoxia may directly damage cerebral parenchyma and vasculature [17] or promote atherogenesis [18,19]. In addition, a relationship between OSA and hypercoagulability may exist [20,21]. Finally, long obstructive sleep apneas may lead to stroke via right-to-left shunting and paradoxical embolism [22]. Evaluation of patient-level PSG data may help clarify the specific physiological mechanisms that convey an increased risk of stroke in OSA.

Fewer studies have investigated the association between central sleep apnea (CSA) and incident stroke. CSA is associated with incident atrial fibrillation, an important risk factor for ischemic stroke [23]. A prospective cohort study in Spain followed 394 subjects aged 70 years with baseline PSG and without previous stroke for a median of six years [7]. During this period, 20 incident ischemic strokes were observed. Whereas the obstructive apnea index was not associated with incident ischemic stroke, the central apnea index (CAI) was higher in subjects with incident ischemic stroke (mean CAI 9.48 versus 2.60, $p=0.014$). After adjustment for atrial fibrillation and sex, CAI ≥ 3 was associated with three times the risk of incident ischemic stroke (aHR 3.08; 95% CI, 1.3–7.5). However, it should be noted that a CAI ≥ 5 is used as the threshold in many sleep laboratories. Furthermore, the authors did not describe how many subjects had Cheyne-Stokes respiration with CSA, a breathing pattern commonly observed in individuals with heart failure.

Current American Heart Association/American Stroke Association (AHA/ASA) primary stroke prevention guidelines recommend that providers consider screening all patients for sleep apnea through detailed history, including structured questionnaires, physical examination, and, if indicated, PSG [24].

Few studies have investigated the incidence of recurrent stroke in patients with OSA and a prior history of stroke or transient ischemic attack (TIA) [25,26]. A prospective cohort study of 91 patients with prior stroke or TIA, 61 (67.7%) of whom were found to have sleep-disordered breathing, found recurrent TIA or stroke was 50% more common in the SDB patients compared to the non-SDB patients (OR 1.52; 95% CI, 1.06–2.14) after two years of

follow-up [25]. No difference was observed between the SDB and non-SDB subjects in age, smoking, hypertension, BMI, ischemic heart disease, cardiac arrhythmias, diabetes mellitus, or hypercholesterolemia.

Sleep apnea is highly prevalent after stroke, with estimates as high as 70% [27,28]. Given this high prevalence and the strength of the evidence that the treatment of sleep apnea improves outcomes in the general (non-stroke) population, current American Heart Association/American Stroke Association (AHA/ASA) secondary stroke prevention guidelines recommend that providers consider a sleep study in patients who have had an ischemic stroke or TIA [29].

3. Sleep duration and risk of stroke

3.1. Incident stroke

Long sleep duration is associated with diabetes mellitus and coronary heart disease, and short sleep duration is associated with diabetes mellitus, hypertension, and coronary heart disease [30]. A number of population-based cohort studies have investigated the association between self-reported sleep duration and incident stroke. Most of these studies examined the relationship between sleep duration and combined incident ischemic and “hemorrhagic stroke” [31–36].

A 2015 meta-analysis of twelve prospective studies with over 500,000 participants examined the association between self-reported short sleep duration and risk of stroke [31]. Sleep duration of < five to six hours was associated with a 15% increased risk of incident stroke (RR 1.15; 95% CI, 1.07–1.24) compared to six to eight hours with no evidence for heterogeneity across studies. Not included in this meta-analysis is a population-based study in the Augsburg region of Germany that followed 17,604 subjects aged 25 to 74 for a mean of 14 years and found that sleep duration of five hours compared to seven to eight hours was associated with a trend toward increased risk of stroke in men (aHR 1.36; 95% CI, 0.95–1.94) but not women (aHR 0.68; 95% CI, 0.40–1.18) after adjustment for potential confounders [32].

A 2010 prospective study of 1,268 adults with hypertension found that subjects who reported a sleep duration of < 7.5 hours, as opposed to 7.5 hours, had a two-fold increased risk of incident stroke (HR 2.21; 95% CI, 1.30–3.76) [37]. In addition, in a subset of 932 subjects who had brain magnetic resonance imaging (MRI) scans, sleep duration of <7.5 hours versus 7.5 hours was associated with a 2.5 times increased risk of silent cerebral infarction (HR 2.52; 95% CI, 1.43–4.57).

Like short sleep duration, long sleep duration has also been associated with incident stroke in cohort studies. The aforementioned 2015 meta-analysis of twelve prospective studies with over 500,000 participants also examined the association between self-reported long sleep duration and risk of stroke [31]. Sleep duration of eight to nine hours was associated with a 45% increased risk of incident stroke (RR 1.45; 95% CI, 1.30–1.62) compared to six to eight hours, although there was significant among-study heterogeneity ($I^2=54\%$; $p=0.003$). Not included in this meta-analysis is the aforementioned population-based German study

that found a trend after adjustment toward increased incident stroke risk in men, but not women, who reported ten hours of sleep per day (aHR 1.38; 95% CI, 0.98–1.94). [32]

The outcomes of incident ischemic stroke and “hemorrhagic stroke” were analyzed separately in a large population-based study of sleep duration in 95,023 Chinese adults followed for a mean of 7.9 years [38]. In this study, reported sleep duration of six to eight hours was the referent. For neither men nor women was sleep duration < six hours or sleep duration > eight hours associated with incident ischemic stroke. Sleep duration > eight hours was strongly associated with incident “hemorrhagic stroke” in women (aHR 3.58; 95% CI, 1.28–10.06) but not men (aHR 1.38; 95% CI, 0.77–2.45).

Taken together, the results of these studies suggest a possible association between self-reported long sleep duration and incident stroke, with a possible disproportionate fraction of “hemorrhagic stroke.” As discussed above, self-reported short sleep duration has also been associated with incident stroke in cohort studies. However, confounding is a concern, as abnormal sleep duration, especially long sleep duration, may be a marker of chronic disease, which may itself be associated with incident stroke.

Future studies of sleep duration and stroke incidence should report results separately for men versus women and for ischemic stroke versus intraparenchymal hemorrhage and should carefully account for potential confounders.

3.2. Sleep duration and stroke mortality

Short sleep duration is distinct from chronic insomnia, which will be discussed later, in that lifestyle choices or elimination of environmental barriers can improve sleep duration. In insomnia, the problem is that - despite an effort to obtain more sleep, to obtain an adequate amount of sleep, or to obtain refreshing sleep - the patient is unable to do so. A number of cohort studies have investigated the association between self-reported sleep duration and combined ischemic and “hemorrhagic stroke” mortality [39–41]. The large Multiethnic Cohort Study conducted in Los Angeles and Hawaii followed 135,685 adults aged 45 to 75 years for a mean of 12.9 years [39]. Self-reported sleep duration nine hours as compared to seven hours was associated with an approximately one-third increased risk of stroke mortality for both men (HR 1.35; 95% CI, 1.03–1.75) and women (HR 1.39; 95% CI, 1.06–1.83). No association between sleep duration and stroke mortality was seen for men or women at five hours, six hours, or eight hours of sleep. A Japanese cohort study of 49,256 adults aged 40–79 found similar results, though risks for men and women were not reportedly separately [41]. An increased risk of stroke mortality was seen in subjects reporting nine (aHR 1.30; 95% CI, 1.06–1.60) and ten (aHR 1.51; 95% CI, 1.24–1.85) hours of sleep per day compared to those reporting seven. On the other hand, another Japanese cohort study of 11,325 adults with a mean follow-up of 8.2 years found no association between sleep duration and stroke mortality in men and found a trend toward an association between stroke mortality and sleep duration only for women reporting six to 6.9 hours of sleep per night (aHR 3.2; 95% CI, 1.0–10.5) [40].

A few studies have reported ischemic and “hemorrhagic” stroke mortality separately [42–44]. A 2009 Japanese community-based cohort study followed almost 100,000 adults aged

40 to 79 years for a median of 14.3 years [42]. Men who slept ten hours in comparison to those who slept seven hours had a 58% higher risk of ischemic stroke mortality (aHR 1.58; 95% CI, 1.19–2.12) and a trend toward a higher risk of “hemorrhagic stroke” mortality (aHR 1.56; 95% CI, 0.99–2.45). Women who slept eight hours in comparison to those who slept seven hours had a trend toward increased ischemic stroke mortality (aHR 1.29; 95% CI, 1.00–1.67). Women who reported ten hours had a substantially (almost 2.5 times) increased risk of ischemic stroke mortality (aHR 2.37; 95% CI, 1.70–3.32). No association was seen between sleep duration and “hemorrhagic stroke” mortality for women.

A Chinese population-based cohort study followed 63,257 adults aged 45 to 74 for a mean 14.7 years [43]. Subjects who reported five hours of sleep and nine hours of sleep, in comparison to those who reported seven hours, had an increased risk of ischemic stroke mortality (aHR 1.37, 95% CI, 1.12–1.68 and 1.68, 95% CI, 1.36–2.06 respectively). No association was seen between sleep duration and “hemorrhagic stroke” mortality. Sex-specific findings were not reported.

Finally, a 2016 Japanese population-based cohort study followed 27,896 adults 35 years during 16 years of follow-up [44]. Subjects who reported nine hours of sleep in comparison to those reported seven hours had a 65% increased risk of ischemic stroke mortality (aHR 1.65; 95% CI, 1.16–2.35), in keeping with the results of the aforementioned studies. The association between nine hours of sleep and ischemic stroke mortality was of larger magnitude and reached statistical significance in women (aHR 2.07; 95% CI, 1.30–3.27) compared to men (aHR 1.34; 95% CI, 0.88–2.05). Women who reported eight hours of sleep per day had a three-fourths increased risk of ischemic stroke mortality (aHR 1.75; 95% CI 1.13–2.68) whereas men did not (aHR 1.03; 95% CI, 0.70–1.54). Self-reported sleep duration of six hours was associated with a two-thirds decreased risk of “hemorrhagic stroke” mortality in men (aHR 0.31; 95% CI, 0.16–0.64) but no decreased risk in women (aHR 1.04; 95% CI, 0.61–1.76). No other associations between sleep duration and “hemorrhagic stroke” mortality were observed.

Taken together, these results suggest an increased risk of ischemic stroke mortality in men and women who sleep nine hours per day, with the effect potentially more pronounced in women. Although a potential protective effect of short sleep duration on “hemorrhagic stroke” mortality was seen in men in the 2016 Japanese study, this finding was not observed in men in the 2009 Japanese study.

A joint consensus statement from the American Academy of Sleep Medicine and the Sleep Research Society suggests that seven to nine hours of sleep are appropriate “to support optimal health in adults” [45].

3.3. Sleep duration and special populations

The prospective Women’s Health Initiative observational study followed 93,175 postmenopausal women for a mean of 7.5 years [46]. Compared to women who reported seven hours of sleep per night, an increased risk of ischemic stroke was observed in women who reported eight hours (HR 1.24; 95% CI, 1.04–1.47) and nine hours (HR 1.70; 95% CI, 1.32–2.21). A study of a bi-ethnic stroke population in Corpus Christi, Texas, found no

difference in pre-stroke sleep duration between Mexican American and non-Hispanic white stroke patients [47].

4. Non-apnea sleep disorders and risk of stroke

4.1. REM sleep behavior disorder

Most studies of the association between REM sleep behavior disorder (RBD) and stroke included subjects post-stroke, limiting conclusions about directionality. However, a 2017 Chinese community-based cohort study of 12,000 subjects examined the association of probable REM sleep behavior disorder (pRBD) and incident stroke [48]. Probable REM sleep behavior disorder was established using a validated RBD questionnaire. Stroke incidence was evaluated through ICD-10 codes and medical record review. Subjects were free of stroke and Parkinson's disease at the start of the study and were followed prospectively for three years. Analyses were adjusted for multiple potential confounders including self-reported sleep duration. Compared to subjects without pRBD, subjects with pRBD had a greater risk of developing incident ischemic stroke (HR 1.93; 95% CI, 1.07–3.46) and “hemorrhagic stroke” (HR 6.61; 95% CI, 2.27–19.27).

The authors offered several possible explanations for the increased risk of stroke in pRBD patients, including disturbed sleep leading to autonomic and metabolic consequences. The increased risk of “hemorrhagic stroke” in particular was thought potentially secondary to common antecedents between RBD and cerebral amyloid angiopathy, a common cause of intraparenchymal (and subarachnoid) hemorrhage in the elderly.

4.2. Restless legs syndrome

Whether an independent association exists between RLS and incident ischemic stroke remains unclear. RLS is often, at least in published studies, comorbid with OSA, which complicates the interpretation of study data. In addition, RLS and ischemic stroke may share risk factors. A questionnaire-based study of 4000 men living in Sweden found that subjects who met criteria for RLS had 2.5 times the odds of reporting heart problems when compared to those without RLS (OR 2.5; 95% CI, 1.4–4.3) [49]. There was also a trend toward an association between RLS and hypertension (OR 1.5; 95% CI, 0.9–2.4).

A prospective cohort study using data from the Women's Health and Physicians' Health studies followed 29,756 female health professionals 45 years old and 19,182 male physicians 40 years old; subjects were asked to report incident stroke during follow-up [50]. No association was seen between a history of RLS per the International Restless Legs Syndrome Study Group (IRLSSG) rating scale on questionnaire and stroke for male or female subjects. An analysis of two European population-based prospective cohort studies – the Dortmund Health Study with 2.1 years of follow-up and Study of Health in Pomerania with 4-years of follow-up – had a combined total of 5620 participants and found no significant association between RLS (per the IRLSSG criteria recorded in face-to-face interview) and incident stroke [51].

On the other hand, a ten-year cohort study of 1,986 men aged 55 to 69 in South Wales, UK, found a two-thirds increased risk of incident ischemic stroke in men who reported restless

legs, compared to those who did not, on the Wisconsin sleep questionnaire (aHR 1.67; 95% CI, 1.07–2.6) after adjustment for potential confounders [52]. Among 1093 end-stage renal disease patients followed for a mean of 3.7 years, in comparison to subjects without RLS, an approximately 2.5 times increased risk of incident stroke was observed in subjects with moderate RLS (aHR 2.42; 95% CI, 1.50–3.90) and severe RLS (aHR, 2.64; 95% CI, 1.49–4.91) per the IRLSSG rating scale recorded in face-to-face interview [53].

One study involved examination of MRI scans from 26 subjects with RLS (by self-reported IRLSSG diagnostic criteria) and 241 controls. No significant difference in silent infarction or large subcortical lesions was seen between the RLS cases and the controls, though the study was underpowered [54]. Another study compared the MRI scans from 53 patients with RLS per IRLSSG <10 years duration, 44 patients with RLS >10 years duration, and 74 normal controls [55]. The mean age was similar among the three groups, and AHI was similar between the RLS <10 years and >10 years groups. Each subject's MRI scan was scored for small vessel disease area and volume by a masked investigator. Mean small vessel disease area and volume were higher in subjects with RLS > 10 years compared to controls and compared to subjects with RLS < 10 years. No difference was seen between mean small vessel disease area and volume between controls and subjects with RLS < 10 years.

4.3. Periodic limb movements of sleep

Periodic limb movements of sleep (PLMs) are highly prevalent and more common in individuals with RLS. A relationship between PLMs and cerebrovascular disease has been hypothesized, and a number of indirect associations lend support to a possible relationship. PLMs are associated with increased blood pressure [56–58] and heart rate [57–59] during sleep. Increased blood pressure with PLMs has been found both in patients with RLS [60] and without RLS [56]. In addition, PLMs may be associated with left ventricular hypertrophy in patients with RLS [61] and with a higher prevalence of atrial fibrillation in patients with mild sleep-disordered breathing [62].

In one study of 30 patients with first minor stroke or high-risk TIA, each subject underwent polysomnography with grading of PLM severity [63]. PLM severity was found to be positively associated with white matter disease burden by CT/MRI, even after adjustment for several potential confounders. A prospective cohort study of 2911 community-based elderly men with PLM measurement by in-home PSG followed subjects for four years to ascertain the outcomes of coronary heart disease, cerebrovascular disease, peripheral artery disease, and all-cause cardiovascular disease.[64] After adjustment for numerous potential confounders, neither periodic limb movement index (average number of PLMs per hour of sleep) nor periodic limb movement arousal index was associated with incident stroke or TIA. However, the study may have been underpowered. A relationship was observed between all-cause cardiovascular disease and the periodic limb movement index (p for trend=0.0249) and the periodic limb movement arousal index (p =0.0317) in men without hypertension.

Ultimately, a prospective study of a large sample of patients with and without PLMs will be required to establish whether PLMs are an independent risk factor for stroke [65].

4.4. Shift work

Results from cohort and case-control studies examining the relationship between shift work and incident stroke have been mixed, with some suggesting a relationship [66,67] and others not [68]. One cohort study of 80,109 female nurses found a 4% increased risk of incident ischemic stroke for every five years of rotating night shift work (HR 1.04; 9% CI, 1.01–1.07, *p* value for trend = 0.01) after adjustment for numerous potential confounders including BMI and smoking [66]. In a prospective cohort study of approximately half a million Finnish men, shift work, in comparison to regular day hours, was associated with an increased risk of death from cerebrovascular disease [67].

4.5. Insomnia

Insomnia is difficulty initiating or maintaining sleep accompanied by daytime consequences and not attributable to environmental circumstances or inadequate opportunities for sleep [69]. Some definitions have included a complaint of non-restorative sleep. Either way, insomnia differs from short sleep duration, which is often attributable to environmental circumstances or lifestyle choices that reduce the opportunity for adequate sleep. A patient with chronic insomnia usually has underlying psychological, physiological, or psychophysiological features that promote the condition and could have an impact on stroke risk. Insomnia has been associated with incident cardiovascular events in several studies [70–72], but few studies have specifically reported on incident cerebrovascular disease. One study to examine the association between insomnia and incident stroke was a repeated survey-based study of 17,604 German men and women aged 25 to 74 followed for a mean of 14 years [32]. Subjects were asked about symptoms of insomnia at a baseline interview. In unadjusted analysis, trouble falling asleep was associated with incident stroke (HR 1.59; 95% CI, 1.24–2.05). However, after adjustment for numerous potential confounders, the association was not significant (aHR 1.17; 95% CI, 0.90–1.52). Similarly, before adjustment, difficulty staying asleep was associated with a 78% increased risk of incident stroke (HR 1.78; 95% CI, 1.46–2.17). In adjusted analysis, no association was seen (HR 1.06; 95% CI, 0.87–1.30). In the aforementioned Welsh study of men aged 55–69 years followed for ten years, a 75% increased risk of incident ischemic stroke was observed in men who reported insomnia, versus those who did not, on the Wisconsin sleep questionnaire (aHR 1.75; 95% CI, 1.02–3.01) [52]. Overall, whether an association exists between self-reported insomnia and incident stroke remains uncertain.

5. Treatment of sleep disorders for prevention of stroke

5.1. Hypnotics

A study using data from the Taiwan National Health Insurance Research Database investigated the relationship between zolpidem prescription and subsequent ischemic or “hemorrhagic” stroke [73]. After adjustment for age, gender, coronary artery disease, diabetes, hypertension, and hyperlipidemia, the odds ratio for stroke was 30% higher in individuals exposed to zolpidem than those not (aOR 1.32; 95% CI, 1.26–1.38), with increasing odds per mg/year of exposure (*p* value for trend <0.0001). The American Academy of Sleep Medicine (AASM) guidelines make no strong recommendations for pharmacologic treatment of insomnia [69].

5.2. Continuous positive airway pressure

Trials of CPAP for OSA have sometimes been limited to subjects without sleepiness, given that adherent use of CPAP is proven to be effective for sleepiness and equipoise may not exist for randomization of sleep patients in the general population to a control group. The 2016 Sleep Apnea Cardiovascular Endpoints (SAVE) trial is the largest study to date to address the efficacy of CPAP in prevention of cardiovascular events [**74]. In this 89-site study, 2,717 adults aged 45 to 75 with coronary artery disease or cerebrovascular disease and moderate-to-severe sleep apnea (at least 12 oxygen saturation drops by at least four percentage points per hour) were randomized to CPAP versus usual care. Participants assigned to CPAP averaged 3.3 hours of CPAP use per night. No difference was observed in stroke incidence (a secondary endpoint and component of the primary endpoint) between the CPAP group (5.0%) and the usual care group (5.1%) after a mean follow-up of 3.7 years.

These results of SAVE emerged in the context of limited CPAP adherence in the treatment group and an Asian-predominant study population that may limit generalizability, though no significant heterogeneity between China- versus non-China subjects was observed. Moreover, SAVE excluded subjects with severe daytime sleepiness and those with recent stroke. However, the results of SAVE are in keeping with previous smaller randomized controlled trials that found no association between CPAP treatment and incident hypertension [75] and cardiovascular events [75,76].

5.3. Other

Treatment for RLS commonly consists of behavioral modifications, dopamine agonists, or alpha-2-delta calcium channel ligands. AASM guidelines note that pramipexole and ropinirole use are supported by a high body of evidence level and a favorable harm/burden assessment [**77]. No convincing evidence exists to suggest that treatment of RLS with these agents is associated with an increased or decreased risk of stroke. Pharmacologic treatment of RBD often consists of melatonin or low-dose clonazepam, both of which are given level B recommendations by the AASM guidelines [**78]. As with RLS, no convincing evidence exists to suggest that treatment of RBD with these agents is associated with an increased or decreased risk of stroke.

6. Expert Commentary

Sleep disorders and stroke are highly prevalent and consequential illnesses with bidirectional relationships worthy of dedicated study. In this review, we have narrowed our attention to the relationships between a number of sleep disorders or problems and incident stroke.

The association between obstructive sleep apnea and subsequent incident stroke is well-established, though which among several suspected pathophysiologic mechanism(s) may be most salient remains uncertain. Evaluation of patient-level PSG data from large prospective cohort studies, retrospectively or prospectively, may help clarify going forward the specific physiological mechanisms through which OSA may increase risk for ischemic stroke (e.g. desaturations or arousals). However, we cannot assume that standard PSG necessarily assesses the most important variables that mediate influences between sleep, sleep apnea,

and stroke. Regardless, its ready availability makes patient-level PSG data an attractive area for further study.

In addition, future studies of both apnea and non-apnea sleep disorders should report incident ischemic stroke and intraparenchymal hemorrhage separately to help clarify the mechanisms underlying the associations. Ultimately, randomized clinical trials could provide the most definitive proof that OSA causes or contributes to ischemic stroke.

To date, randomized trials of CPAP for stroke prevention in OSA patients have been largely disappointing, though lack of power and limited CPAP adherence have diminished confidence in their results. Future trials may target subgroups of patients who may be more likely to benefit from PAP therapy, such as those who are more likely to adhere to PAP therapy, are older, have had a recent stroke, or report longer sleep duration. New technological options including telemedicine may promote CPAP adherence and allow for a more robust assessment of CPAP efficacy.

In addition to OSA, CSA is an area deserving of further research, particularly given its association with heart disease and other medical comorbidities that may increase the risk of stroke. Of course, the lower prevalence of CSA as compared to OSA can make it more challenging to study. Contrary to many clinicians' impressions, CSA is much less common than OSA among patients with ischemic stroke.

Among the non-apnea sleep disorders and problems, long and short sleep duration appear to be associated with incident stroke based on available evidence. However, confounding by underlying chronic illness may better explain the association.

The relationship between non-apnea sleep disorders or problems and incident stroke deserves further attention. Further evidence that conditions associated with sleep disruption but not hypoxia increase stroke risk could help to distinguish between these two high-level, branch-point pathways by which OSA may influence stroke risk. Clinical impact could also be substantial, in that the identification of specific non-apnea sleep disorders that convey an increased risk for stroke may ultimately result in enhanced screening or even empiric treatments for patients with those conditions. At present, the establishment of healthy sleep has not been thoroughly investigated as a potential novel strategy for primary and secondary stroke prevention.

7. Five-year view

During the next five years, we speculate that – despite challenges to the medical research funding climate in many countries including the United States – efforts to advance understanding of how sleep disorders influence stroke risk will grow. Despite considerable progress in recent decades on reduction of incident stroke, an aging population and the unique impact of stroke on disability will motivate exploration for potential answers.

Obstructive sleep apnea remains undiagnosed for most affected patients, and as more evidence accumulates about its likely impact on incident stroke, motivation will intensify to develop new effective approaches to diagnosis and treatment. Such approaches will need to

be proven cost-effective, given the magnitude of the public health challenges associated with both OSA and stroke.

At the time of this writing, a large randomized controlled trial – Sleep for Stroke Management And Recovery Trial (Sleep SMART) – is on course to be funded in the United States by the National Institute for Neurological Disorders and Stroke. Sleep SMART will be executed at approximately 110 sites nationwide, through StrokeNet, over a period of five years. The primary hypotheses to be tested are that treatment of OSA with PAP after ischemic stroke or high-risk transient ischemic attack 1) will reduce the likelihood of secondary stroke, acute coronary syndrome, or death within the subsequent six months and 2) will improve recovery at three months. Subjects most likely to tolerate PAP will be enrolled, and telemedicine will be used to standardize approaches across sites and to optimize adherence to therapy. If results are positive, this trial could provide the strongest evidence yet that OSA raises the risk for incident stroke.

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Key Issues

- Stroke is a major cause of disability and death in the United States and across the world, and the incidence and prevalence of stroke are expected to rise significantly due to an aging population.
- Obstructive sleep apnea, an established independent risk factor for stroke, is highly prevalent in the United States and abroad and is estimated to confer an approximately two-fold increased risk of stroke.
- Self-reported short and long sleep duration may be associated with incident stroke, although abnormal sleep duration, especially long sleep duration, may be a marker of chronic disease, which may itself be associated with incident stroke.
- Trials of CPAP for stroke prevention in sleep apnea patients have been largely disappointing. Future trials may target subgroups of patients who may be more likely to benefit from PAP therapy and may harness evolving technology to improve PAP adherence.
- The relationship between non-apnea sleep disorders (such as restless legs syndrome and REM sleep behavior disorder) and incident stroke deserves further attention. Identification of specific non-apnea sleep disorders or sleep problems that convey an increased risk for stroke may provide novel targets for stroke prevention.