Stroke

AHA SCIENTIFIC STATEMENT

Impact of Sleep Disorders and Disturbed Sleep on Brain Health: A Scientific Statement From the American Heart Association

Rebecca F. Gottesman, MD, PhD, FAHA, Chair; Pamela L. Lutsey, PhD, MPH, FAHA, Vice Chair; Helene Benveniste, MD, PhD; Devin L. Brown, MD, MS; Kelsie M. Full, PhD, MPH; Jin-Moo Lee, MD, PhD; Ricardo S. Osorio, MD; Matthew P. Pase, PhD; Nancy S. Redeker, PhD, FAHA; Susan Redline, MD, MPH; Adam P. Spira, PhD; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; and Council on Hypertension

ABSTRACT: Accumulating evidence supports a link between sleep disorders, disturbed sleep, and adverse brain health, ranging from stroke to subclinical cerebrovascular disease to cognitive outcomes, including the development of Alzheimer disease and Alzheimer disease–related dementias. Sleep disorders such as sleep-disordered breathing (eg, obstructive sleep apnea), and other sleep disturbances, as well, some of which are also considered sleep disorders (eg, insomnia, sleep fragmentation, circadian rhythm disorders, and extreme sleep duration), have been associated with adverse brain health. Understanding the causal role of sleep disorders and disturbances in the development of adverse brain health is complicated by the common development of sleep disorders among individuals with neurodegenerative disease. In addition to the role of sleep disorders in stroke and cerebrovascular injury, mechanistic hypotheses linking sleep with brain health and biomarker data (blood-based, cerebrospinal fluid-based, and imaging) suggest direct links to Alzheimer disease–specific pathology. These potential mechanisms and the increasing understanding of the "glymphatic system," and the recognition of the importance of sleep in poststroke recovery, as well, support a biological basis for the indirect (through the worsening of vascular disease) and direct (through specific effects on neuropathology) connections between sleep disorders and brain health. Given promising evidence for the benefits of treatment and prevention, sleep disorders and disturbances represent potential targets for early treatment that may improve brain health more broadly. In this scientific statement, we discuss the evidence supporting an association between sleep disorders and disturbances and poor brain health ranging from stroke to dementia and opportunities for prevention and early treatment.

Key Words: AHA Scientific Statements ■ brain ■ cerebrovascular disorders ■ dementia ■ sleep apnea syndromes ■ sleep disorders

As the population ages, more adults will experience stroke, cognitive impairment, and dementia. Thus, identifying potential modifiable risk factors for poor brain health is increasingly critical. Sleep disturbances and disorders are common in aging adults and are linked to poor brain health through epidemiological data and supported by plausible biological mechanisms (Figure 1).[1–5] As a result, sleep disorders and disturbances represent an opportunity for potential prevention or treatment to reduce the burden of poor brain health in the population. This scientific statement will address these disturbances of sleep, including sleep disorders such as sleep-disordered breathing (SDB) and other sleep disturbances and disorders, as well, where sleep patterns may be abnormal, and will summarize known relationships with distinct brain health outcomes and identify priorities for future research.

SLEEP AND SLEEP DISTURBANCES

Sleep and Sleep Stages

Sleep is a biobehavioral state characterized by changes in brain electrical activity that manifest as altered consciousness, reduced sensory responsiveness, and decreased muscle tone.[6–8] Key metrics used to

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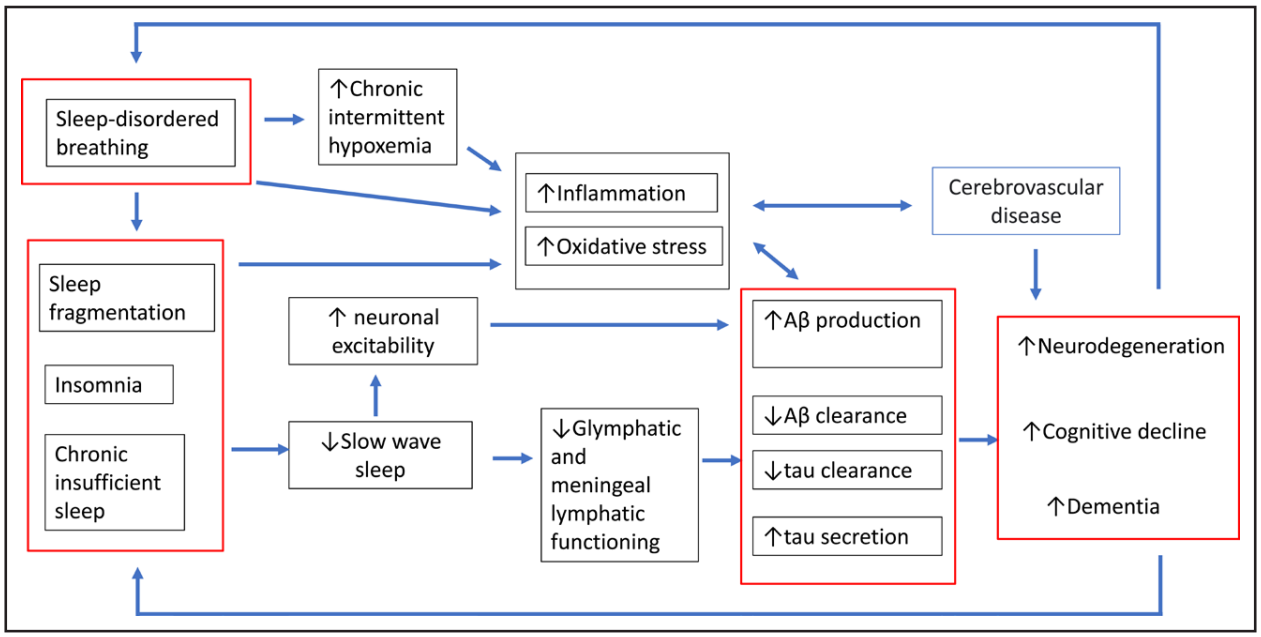

Figure 1. Mechanisms through which sleep disorders may lead to dementia.[1–5]
Aβ indicates β-amyloid protein.

quantify sleep architecture and duration are described in Table 1. The 2 main sleep states are non–rapid eye movement sleep and rapid eye movement (REM). Non–rapid eye movement sleep includes 3 sleep stages (N1, N2, and N3) defined by distinct patterns of neurophysiological activity. Sleep stages occur across cycles that are ≈120 minutes in duration, resulting in 4 to 6 cycles per night. The Centers for Disease Control and Prevention recommends 7 to 9 hours of sleep per night for adults 18 to 64 years of age and 7 to 8 hours per night for older adults.[9] Intrinsic and external stimuli that cause arousals can disturb the underlying structure of sleep, referred to as sleep architecture. Sleep architecture varies across the life span, with reduced sleep quality, including greater fragmentation and light sleep and significant reductions in N3 (slow-wave) and REM sleep, and quantity at older ages and among people with morbidities.

Sleep Disorders and Disturbed Sleep

Multiple sleep disturbances affect brain health. These include disorders such as SDB and unhealthy patterns of sleep duration, continuity, timing, and circadian rhythms that disturb sleep but may not result from specific sleep disorders. This scientific statement focuses on those disturbances that are most pertinent to brain health, which are summarized and defined in Table 2. We note that there are other forms of sleep disorders and disturbances that we do not discuss because they are not clearly linked to brain health (eg, restless leg syndrome). Obstructive sleep apnea (OSA) is the most common form of SDB and results in intermittent hypoxia and sleep fragmentation. OSA is diagnosed on the basis of the presence of symptoms and measures of respiratory events and oxygen saturation from overnight polysomnography (PSG), which yields the apnea-hypopnea index (AHI), a rate of apneic or hypopneic events per hour of sleep, along with other important indicators of SDB. Central sleep apnea is identified when the predominant respiratory event type is "central" (ie, lacking significant airflow limitation and showing reduced or absent respiratory effort).

BRAIN HEALTH

Alterations in brain health encompass the spectrum of subclinical to clinical disease, including cerebrovascular imaging changes, clinically apparent stroke, cognitive decline, and dementia. Long-standing vascular disease can adversely affect brain health in multiple ways, of which stroke or cerebral hemorrhage are the most clinically apparent. Subclinical cerebrovascular disease, including silent infarcts, white matter hyperintensities (leukoaraiosis), cerebral microbleeds, enlarged perivascular spaces, and cerebral atrophy, is associated with long-term sequelae, including cognitive decline and dementia,[10] impaired gait,[11] and increased stroke risk.[12] Alzheimer disease (AD) and AD-related dementias (ADRDs) encompass many pathophysiological conditions that can be comorbid. AD and the vascular contributions to cognitive impairment and dementia are the most common dementia subtypes.

Brain health can be assessed by clinical signs (for stroke), cognitive measures, and psychiatric evaluation, but

Table 1. Definitions Used to Characterize Sleep Architecture and Duration

Sleep architecture			
Stages of sleep	**EEG pattern**	**Typical duration in adults**	**Interpretation**
Stage N1 (NREM)	Low-voltage amplitude, mixed-frequency activity, presence of theta activity, slow rolling eye movements and vertex waves.	<5% of total sleep time	Transition from wake, lightest sleep stage. Increased duration in disorders associated with poor sleep quality.
Stage N2 (NREM)	Presence of sleep spindles (bursts of 11–15 Hz frequency band activity, 0.5 and 2 s in duration) and K complexes (sharp, biphasic delta waves, >5 s).	45% of total sleep time	Spindles implicated in synaptic plasticity and memory consolidation. K complexes maintain sleep and memory consolidation.
Stage N3 (NREM) also referred to as slow-wave sleep (SWS)	High amplitude, slow (delta) waves.	25% of total sleep time	"Deepest" sleep; high arousal threshold, making it harder to awake from. Reflects global synchronous neural activity. Linked to hormone and cellular energy regulation, metabolic waste product clearance, immune and autonomic nervous system, cardiovascular and brain health. Declines with aging and in disorders that fragment sleep.
Stage R (REM)	Low amplitude, mixed-frequency EEG with low muscle activity and rapid eye movements. Sawtooth waves present.	25% of total sleep time	High brain metabolic activity and pulse and blood pressure variability. Sleep-disordered breathing may be most severe in REM. Reduced REM associated with reduced declarative memory and emotional regulation and higher mortality, depression. REM duration and timing can be altered by some medications.
Sleep duration			
Duration categories	**Thresholds for adults[9]**		**Comments**
Sufficient sleep	7–9 h of sleep per night for adults aged 18-64, and 7-8 h per night for older adults		Associated with optimal health for most adults.
Short sleep duration	<7 h of self-reported sleep per night*		Associated with weight gain, diabetes, hypertension, cardiovascular disease, poorer acute cognitive function.
Long sleep duration	>9 h of self-reported sleep per night		Associated with depression, polypharmacy, numerous morbidities and mortality.

EEG indicates electroencephalogram; NREM, nonrapid eye movement; and REM, rapid eye movement.

*The recommendations listed here are according to the Centers for Disease Control and Prevention. However, some other organizations and publications define short sleep and long duration using different cut points.

also by imaging, blood, and, in some cases, cerebrospinal fluid (CSF) biomarkers that can help evaluate underlying pathology. Amyloid-β (Aβ) or tau positron emission tomography, or blood or CSF phosphorylated tau or Aβ levels may be indicators of underlying AD neuropathology. Neurofilament light chain, a marker of axonal injury, may indicate nonspecific underlying neurodegeneration.[13]

Of note, many other factors contribute to or may result from adverse brain health (eg, depression,[14] substance abuse, and other aspects of mental health) but are beyond the scope of this scientific statement.

NORMAL PHYSIOLOGY OF SLEEP AND BRAIN HEALTH

Sleep and Memory Consolidation

Sleep plays a central role in the optimization of cognitive performance. Experimental sleep deprivation studies show adverse effects of sleep loss on performance in numerous cognitive domains, including attention, executive function, and short-term memory, with cognitive processes that rely heavily on the prefrontal cortex particularly affected.[15] Memory is among the most studied cognitive domains in relation to sleep, and accumulating literature details how sleep strengthens and promotes preserved recent learning, including episodic and procedural memory.[16] Features of non–rapid eye movement sleep (especially slow oscillations and sleep spindles) and REM sleep play overlapping and complementary roles in the underlying process of memory consolidation in which new, unstable memories are relocated from the hippocampus to the neocortex, where they are more durable.[17] Compared with younger adults, older adults may exhibit deficits in the consolidation of episodic memories, likely due to aging-related deterioration of brain structure and sleep quality and concomitant comorbidity.[17]

Synaptic Homeostasis

The precise cellular/molecular mechanisms involved in sleep-dependent memory consolidation are not clear, although synaptic homeostasis has emerged as a leading hypothesis. During wakefulness, learning is associated with selective changes in synapse number and strength (ie, postsynaptic neuron responsiveness to stimulation by presynaptic neurons) in relevant circuits. Thus, with cumulative learning throughout wakefulness, net increases in synaptic density and strengths increase throughout the brain, a process that is not sustainable over the long term. The synaptic homeostasis hypothesis holds that N3

Table 2. Definitions Used to Characterize Common Disturbances of Sleep and Sleep-Disordered Breathing*

Common disturbances of sleep			
Sleep disturbances	**Definitions**	**Thresholds for abnormality in adults**	**Comments**
Insomnia	A perceived difficulty with sleep initiation, consolidation, duration (staying asleep), or quality, despite an adequate opportunity to sleep, coupled with subsequent daytime impairment.	Based primarily on perceived sleep quality, although some diagnostic criteria specify a minimum length of sleep onset duration (≥30 min) or periods of waking after sleep onset (≥30 min at least 3 times per wk).	Associated with elevated sympathetic central nervous system activity, systemic inflammation, and hypothalamic-pituitary-adrenal axis dysregulation, and increased risk of mood and anxiety disorders, weight gain, diabetes, hypertension, stroke, and dementia, as well.
Sleep fragmentation	Repetitive interruptions of sleep by arousal or periods of wakefulness.	Defined using EEG, autonomic or behavioral markers. On EEG tracing, arousals are identified by "an abrupt shift in EEG frequency lasting ≥3 s."	Fragmented sleep is less restorative, may reduce memory consolidation. Associated with adverse values of numerous brain health markers.
Circadian rhythm disorders	Problems with regularity or timing of the sleep/wake cycle in relation to the external environment (light/dark cycle).	Numerous specific disorders exist, each with its own specific clinical criteria and thresholds. Can be due to intrinsic (eg, genetic), extrinsic (eg, light exposure, travel, shift work) factors, and associated with development (delayed phase) and aging (advanced phase).	Misalignment of the body's internal clock with the light/dark cycle can result in cardiovascular disease and may contribute to or result from neurological disease.
Sleep-disordered breathing (sleep disorders)			
Sleep disorders	**Definitions**	**Thresholds for abnormality in adults**	**Comments**
Obstructive sleep apnea	AHI† ≥5 to 15 with nocturnal symptoms (snoring, snorting, gasping, breathing pauses) or excessive daytime symptoms (sleepiness, fatigue) despite sufficient opportunity to sleep, unexplained by other medical problems; or AHI ≥15 regardless of symptoms.	Normal: AHI <5 Mild: AHI 5–15 Moderate: AHI 15–30 Severe: AHI ≥30	Severe obstructive sleep apnea often associated with sleep fragmentation, reduced N3 and REM sleep, and hypoxemia. Alternative metrics, such as sleep apnea–related hypoxic burden, arousal intensity, sleep apnea–related heart rate changes are emergent predictors of heart disease and mortality.
Central sleep apnea	Polysomnography showing a predominance of central apneas or hypopneas (>50%) with a central apnea hypopnea index ≥5. Central events are identified as an absence of airflow for ≥10 s with no or limited respiratory effort (apneas) or reduction in airflow without airflow limitation and little respiratory effort (hypopneas).	Central Apnea Index ≥5. Clear cutoffs for severity not established.	Often associated with cardiac disease (heart failure, atrial fibrillation), stroke, or opioid use. Often occurs with Cheyne-Stokes respiration (≥3 consecutive central apneas/central hypopneas separated by crescendo and decrescendo change in breathing amplitude). Patients with an elevated Central Apnea Index often also experience obstructive events.
Sleep-related hypoventilation	Polysomnography shows elevated carbon dioxide levels during sleep (eg, end-tidal carbon dioxide tension or transcutaneous carbon dioxide) >55 mm Hg for >10 min or an increase in >10 mm Hg compared with an awake supine value to a value >50 mm Hg for >10 min.	Severity tracks magnitude of sleep-related hypercapnia and hypoxia.	Includes several disorders such as: Obesity hypoventilation syndrome Congenital central alveolar hypoventilation syndrome Idiopathic central alveolar hypoventilation Sleep-related hypoventilation due to a medication or substance Sleep-related hypoventilation due to a medical disorder

AHI indicates Apnea-hypopnea index; EEG, electroencephalogram; and REM, rapid eye movement sleep.
*This table does not include all sleep disorders and disturbances. The focus is on disorders that have been most directly linked to brain health.
†AHI is defined as the number of obstructive apneas (episodes of complete upper airway obstruction) or hypopneas (partial airway obstruction) or both per hour of sleep.

(slow-wave) activity during non–rapid eye movement sleep downregulates synaptic strengths proportionately across all synapses, effectively normalizing synaptic strengths throughout the brain.[18] The theoretical advantage of daily recurrent homeostatic downregulation of synaptic strengths is the retention of energetic efficiency without compromising the fidelity of synaptic neurotransmission. Strong evidence for this hypothesis comes from flies[19] and fish.[20] Although direct evidence in mammals is lacking, there is little reason to believe that this fundamental mechanism is restricted to nonmammals, because sleep behaviors are highly conserved across species.

Glymphatic System

The glymphatic system is an alternate novel and exploratory pathway that may be implicated in brain health. It is modeled as a perivascular transit passageway for CSF to exchange with the interstitial fluid surrounding all brain cells, thereby facilitating waste removal including Aβ and

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tau protein.[21,22] Glymphatic waste clearance is dependent on specialized physiology (Figure 2[23]). First, CSF, driven by vascular pulsatility[24,25] and vasomotion,[26] enters into the periarterial channels. Second, aquaporin-4 water channels expressed on the glia end-feet facilitate efficient perivascular CSF exchange for waste clearance.[21,27] Third, glymphatic waste egresses through perivenous channels,[21] whereas "hot spots" along dural venous sinuses serve as bridges between the glymphatic system and bona fide lymphatic vasculature in the dura.[28–30] Last, a critical feature of glymphatic waste disposal is the dependence on sleep state, with enhanced glymphatic activity during N3 sleep and under certain anesthetic regimens.[1,31]

EPIDEMIOLOGY: ASSOCIATIONS OF SLEEP WITH BRAIN HEALTH

Sleep and Stroke

Several disturbances and disorders of sleep have been linked to greater risk of stroke. In a meta-analysis of 10 prospective studies, moderate-to-severe OSA was associated with a doubling of stroke risk (hazard ratio, 2.02 [95% CI, 1.40–2.90]).[32] In the community-based SHHS trial (Sleep Heart Health Study), which included 5422 participants who experienced 193 incident ischemic stroke events over a median of 8.7 years,[33] the observed association was stronger in men than in women ($P_{interaction}$=0.0009). Among men, the hazard ratio for the highest (AHI ≥19) versus lowest (AHI ≤4) quartile of OSA was 2.86 (1.10–7.39), whereas in women it was 1.21 (0.65–2.24), after accounting for established stroke risk factors. However, in a large clinic-based study, women with OSA (AHI≥10) were observed to have a higher rate of incident stroke than women with a lower AHI.[34]

Both short and long sleep duration have been prospectively associated with greater stroke risk. In meta-analyses, long sleep duration was associated with an ≈45% greater risk of incident stroke.[35,36] In the European Prospective Investigation into Cancer-Norfolk cohort, 346 stroke cases occurred among 9692 stroke-free participants after 9.5 years of follow-up.[35] The adjusted hazard ratio for long sleep (>8 hours) and stroke was 1.46 (95% CI, 1.08–1.98). The association between short sleep duration and stroke has generally been more modest[35,36]; in one meta-analysis the hazard ratio was 1.15 (1.07–1.24).[35] Evidence also supports an association between symptoms of insomnia and greater stroke risk.[37]

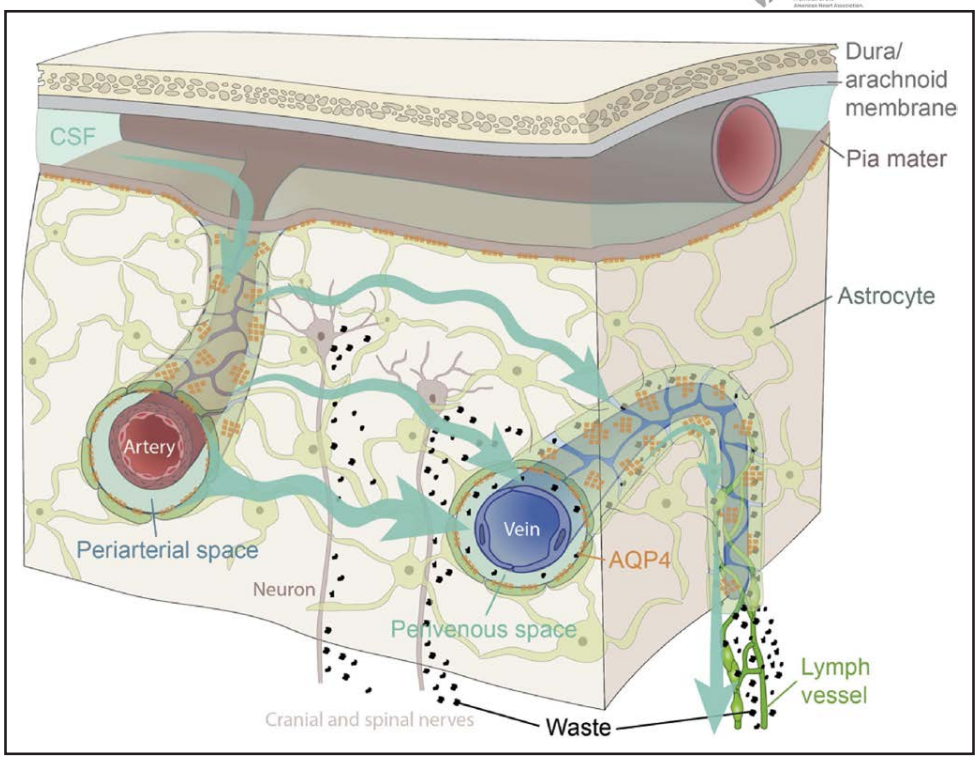

Figure 2. Glymphatic system model of brain waste clearance.
Key components of the glymphatic system model include (1) inward CSF flow along the perivascular channels of penetrating cortical arteries; (2) mixing of CSF with ISF, which involves AQP4 water channels decorating the glial end-feet; (3) vascular pulsatility propels perivascular CSF into the ISF in a bulk flow–driven manner (advective transport). The advective fluid streams (large green arrows) push solute waste in the ISF toward the perivenous channels; (4) CSF-ISF fluid and solute waste drain along the perivenous channels, which merge with meningeal lymphatics and other exit routes; and (5) the function of the system depends on the brain state. AQP4 indicates Aquaporin-4; CSF, cerebrospinal fluid; and ISF, interstitial fluid. Reprinted from Benveniste and Nedergaard.[23]

Sleep and Silent Cerebrovascular Disease

In addition to clinical stroke, sleep disorders have been associated with subclinical markers of vascular brain injury on MRI, often referred to as "silent," given the lack of clear acute neurological changes associated with the development of these lesions.[38] A meta-analysis of mostly cross-sectional observational studies reported that OSA was associated with a higher odds of white matter hyperintensities across 9 studies (odds ratio, 2.13 [95% CI, 1.46–3.66]) and lacunar infarcts across 7 studies (odds ratio, 1.78 [1.06–3.01]).[39] However, caution must be used when making inferences from cross-sectional data because directionality of the association is unclear. OSA is also associated with decreases in cerebral blood flow, particularly in medial temporal regions (theoretically due to endothelial dysfunction, intermittent hypoxia leading to apoptosis or increased oxidative stress and inflammation, impaired autoregulation, effects on cardiac output or sympathetic activity, or some combination of these), and this effect appears to be reversible with continuous positive airway pressure (CPAP) treatment.[40]

Compared with OSA, other sleep disorders have been studied less frequently with respect to MRI markers of vascular brain injury. Relative to healthy sleep, insomnia has been linked with lower integrity of white matter fibers connecting subcortical nuclei and the prefrontal cortex.[41] In addition, in a prospective study, short self-reported sleep duration (≤6 versus 6–8 hours) predicted increased white matter hyperintensities in the parietal region.[42] In one cross-sectional study with in-home PSG, less N3 (slow-wave sleep) was associated with higher white matter hyperintensity volumes and lower cortical gray matter volumes, but not covert brain infarcts.[43]

Sleep and AD/ADRDs

SDB has been associated with AD/ADRDs and with imaging markers often indicative of these pathologies. A 2022 meta-analysis linked OSA to a 34% increased risk of all-cause dementia, 28% increased risk of AD, and 54% increased risk of Parkinson disease dementia; no significant associations were found with "vascular dementia," although only 2 studies with this outcome were included.[44] A seminal study linking OSA to subsequent diagnoses of mild cognitive impairment and all-cause dementia in older women suggested that hypoxemia, rather than sleep fragmentation or shortened sleep duration, accounted for this association, although more studies are needed.[45] OSA has also been linked to CSF and blood-based biomarkers of Aβ and tau, and other possible mechanisms, as well, leading to cognitive impairment, including heightened inflammation that is a hallmark of several neurodegenerative diseases.[46,47] In addition, hippocampal volume loss, an early manifestation of ADRD, has been noted in individuals with OSA.[48]

Other sleep disorders and disturbances have also been associated with dementia risk and biomarkers. Insomnia has been associated with a 53% increase in dementia risk[49]; both short (<7 hours)[50] and long (>9 hours)[51] sleep duration have been linked to at least a doubling in dementia risk; and the use of sleep medications has been associated with a 48% increase in dementia risk.[52] Self-reported shorter sleep duration and poorer quality sleep and actigraphy measures of greater wakefulness after sleep onset and lower sleep efficiency have all been linked to Aβ deposition.[53,54] Greater N3 activity and higher sleep efficiency may protect against increases in brain Aβ accumulation,[55] and less N3 sleep has been associated with smaller brain volumes.[43] Last, less robust and delayed circadian rest/activity rhythms, measured with actigraphy, were associated with subsequent mild cognitive impairment and dementia in a study of older women,[56] and more fragmented and rest/activity rhythms have been tied to brain Aβ deposition and greater medial temporal lobe atrophy.[57,58]

METHODOLOGICAL CONSIDERATIONS

Evaluating the literature on poor sleep and brain health is complicated by issues related to study design, measurement, and confounding by comorbidities and health behaviors. Designing studies to evaluate sleep disorders and disturbances and brain health presents challenges because disease pathology may be present years before clinical symptoms manifest, so reverse causation may be present. During this preclinical period, poor sleep may contribute to disease progression[59] or may be the result of sleep-wake cycle dysregulation caused by dementia-related pathophysiological changes.[60] For example, sleepiness associated with long sleep is associated with epidermal growth factor receptor signaling genes (KSR2 and ERBB4) that are overexpressed in brain tissues and may promote sleep through MAPK/ERK (mitogen-activated protein kinase/extracellular signal–regulated kinase) and RFamide neuropeptide signaling.[61] Studies are needed with sleep measured earlier in the life course, before pathophysiological changes.[62,63] Particular caution should be used when interpreting studies in which sleep and dementia were assessed simultaneously in older adults, because sleep and circadian disorders may be a manifestation of underlying brain pathology, and thus a marker but not a direct cause of dementia risk. Also, few studies have been conducted in racially and ethnically diverse populations, limiting generalizability.

Measurement is also an important consideration. As covered in this scientific statement, many important sleep characteristics have been examined in connection

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with brain health, but studies often focus on a single sleep phenotype (eg, OSA or sleep duration), making it difficult to clarify mechanisms or compare findings across studies, while also limiting inference on how multiple aspects of sleep interact to influence brain health. Furthermore, assessment methods vary across studies,[63] as do the cut points used to define sleep-disordered states. In addition, it is unclear how changes in sleep throughout adulthood affect dementia risk because few studies have repeated measures of sleep from midlife, or even earlier, to late life.[62] Considerations are also needed regarding how markers of brain health are defined. Many epidemiological studies define dementia with electronic health records with high specificity in defining dementia but low sensitivity,[64] and varying cognitive measures are used. Studies incorporating imaging or blood-based biomarkers may enhance evidence of underlying mechanisms, but relatively few longitudinal studies have robust brain biomarker panels (eg, positron emission tomography, Aβ, tau, or neurofilament light chain) in large numbers.

Confounding is also an important threat to validity, because sleep disorders and dementia share risk factors, including genetic (presence of an APOEε4 allele, which infers a high genetic risk of AD, also predicts worse sleep[65]) and vascular risk factors, as well. In some studies, the associations between sleep disorders and disturbances with dementia have been independent of diabetes, obesity, smoking, previous stroke, and depression,[45,66] and in general are robust to vascular risk factor adjustment[50]; in other studies, however, the association with dementia is attenuated when vascular risk factors are considered. It is important to note that some observational studies of sleep and brain health are missing information on important covariates (eg, mental health conditions and comorbid conditions).[67] Last, because much of the epidemiological research on sleep and brain health has been observational, adequately powered randomized controlled trials may be required to determine causality and to rigorously test whether sleep interventions may preserve brain health.[63,68]

MECHANISMS FOR THE EFFECT OF SLEEP DISORDERS AND DISTURBANCES ON BRAIN HEALTH

Traditional Vascular Risk Factors as Mediators

In addition to the potential role of vascular risk factors as confounders of the sleep/brain health association, sleep disorders can contribute to the development of cardiovascular risk factors, including obesity, hypertension, diabetes, and dyslipidemia.[69,70] Common sleep disorders, particularly insomnia[71] and OSA,[69] are associated with an increased prevalence of cardiovascular risk factors, and adequate sleep duration, quality, and regularity are emphasized for optimal cardiovascular health.[70]

Several potential mechanisms link SDB, in particular, with stroke, because OSA can lead to alterations in cerebral autoregulation, hypercoagulability, increased shunting through a patent foramen ovale if present, and endothelial dysfunction, and sympathetic hyperarousal and sleep fragmentation, as well.[72] Timing of sleep in relation to stroke risk may be important, because a circadian rhythmicity of stroke has been noted, with the highest frequency of onset in the morning hours.[73] Although beyond the scope of this scientific statement, this circadian pattern has supported the idea that "wake-up stroke" (stroke deficits identified on awakening) may still represent recent stroke onset and thus may be eligible for acute interventions.[74]

Although some associations are likely bidirectional, longitudinal and mendelian randomization studies support causal associations of disturbed sleep and sleep disorders with concentrations of hemoglobin A1c (a marker of diabetes)[75] and development of ischemic heart disease and atrial fibrillation.[76] Mechanisms include activation of proinflammatory pathways, autonomic nervous system dysfunction, alterations in 24-hour blood pressure profiles (ie, nondipping blood pressure), carotid and coronary artery atherosclerosis,[77] and reduced stage N3 sleep (the sleep stage that appears most cardioprotective).[69] Data from large-scale randomized controlled trials are limited, although treating OSA has been shown to modestly reduce blood pressure[78] and prevent atrial fibrillation.[79,80]

Cerebrovascular disease may also mediate the association between OSA and other sleep disturbances and dementia. For instance, there is a link between OSA and hypertension,[69] a factor that contributes to the progression of cerebral small vessel disease, making it challenging to separate the direct effects of OSA on cognitive decline. The vascular consequences of OSA may also influence brain health through inflammation; for example, one study demonstrated that white blood cell count partially mediated the relationship between OSA and an MRI-based measure of "brain age."[81] Future interventional studies will need to evaluate causal associations and the factors that mediate the relationships between sleep characteristics and brain health, as well.

Disturbances in Synaptic Homeostasis

Given the importance of N3 sleep in synaptic and circuit plasticity, similar mechanisms might protect against neurodegenerative disease and support brain recovery after stroke. Excessive neuronal activity can increase Aβ production and tau release (Figure 1), potentially leading to Aβ deposition and neurofibrillary tangle formation,[5] whereas sleep deprivation in experimental rat models

impaired axonal sprouting, synaptogenesis, and motor recovery after stroke.[82]

Glymphatic Dysfunction

Because the efficiency of the glymphatic system is optimized in the deeper stages of sleep, sleep disturbances or disorders may reduce the efficiency of glymphatic clearance of neurotoxic metabolites (Figure 2[23]). The association between N3 sleep and brain waste egress was explained by reduced central noradrenergic tone leading to an increase in the interstitial fluid volume fraction and thereby more efficient waste transport.[1] Astrocytes, key cells of the glymphatic system, are thought to regulate the sleep-wake cycle through norepinephrine which modulates levels of extracellular ions and thereby the interstitial fluid volume fraction.[83] Glymphatic transport function in sleep is dependent on body posture, and under circadian control peaking during the mid-rest phase. Glymphatic dysfunction has been documented in aging,[22] sleep deprivation,[2,4] and neurodegenerative disease states, including AD,[84] cerebral small vessel disease,[85] cerebral amyloid angiopathy,[86] Parkinson disease, and normal pressure hydrocephalus.[87] Thus, the importance of good sleep in the context of glymphatic waste clearance has emerged as a novel therapeutic target for sustaining brain health.

Molecular Mechanisms of AD

Aβ peptides are natural byproducts of metabolism that are closely associated with neuronal activity,[88] with evidence of high metabolic activity at rest in the regions that more frequently develop Aβ plaques in late life.[89] Sleep promotes opposite effects. In transgenic mice, soluble Aβ levels are lower during sleep, whereas sleep deprivation increases soluble Aβ concentrations in brain interstitial fluid, and chronic sleep restriction accelerates Aβ plaque formation.[90] In humans, CSF Aβ fluctuates in a similar diurnal pattern, with lower CSF Aβ42 levels in the morning,[90] a decrease that is attenuated by prolonged wakefulness.[91] Furthermore, endothelial cells that mediate blood-brain barrier endothelial function, important for Aβ clearance, are under circadian control.[92]

Sleep-mediated changes in tau concentrations are most likely due to altered release rather than increased production, with increased tau peptides corresponding to truncated forms of tau (151–221) found in the CSF of acutely sleep-deprived humans.[93] In addition, overnight sleep deprivation seems to promote tau phosphorylation isoforms that are seen in the earliest stages of AD pathogenesis.[94] Other potential mechanisms for sleep disturbances and disorders to increase Aβ and tau are through the intermittent hypoxia, sleep fragmentation, and intrathoracic pressure swings that are observed in OSA, and increased stress, depression, disrupted circadian rhythms, or increased oxidative stress and inflammation common in normal or pathological aging, as well (Figure 1). Other proteins released with neuronal activity (eg, α-synuclein) or neuroaxonal injury (eg, total tau and NfL) are also increased with sleep deprivation[95] and OSA[96] in humans, suggesting that sleep loss may also promote neurodegeneration through other non-AD pathways. Likewise, APOEε4 may affect sleep by mechanisms that are both dependent and independent of AD pathological change.[97]

IMPORTANCE OF SLEEP IN PEOPLE WITH IMPAIRED BRAIN HEALTH

Poststroke Recovery

Insomnia (38%),[98] sleepiness (10%–15%),[99] and long-duration sleep (35%–40%)[99] are common among patients with stroke. Furthermore, PSG-based studies show that, compared with controls, patients with stroke have poorer sleep efficiency, shorter total sleep time, and different sleep architecture, including a lower percentage of slow-wave sleep.[100] Although not well understood, sleep likely promotes the neural network reorganization and repair that underlie poststroke recovery.[101] Lower sleep efficiency, less total sleep time, and less N3 sleep measured by PSG shortly after stroke hospitalization have been associated with worse neurological status at discharge.[102] Longer REM sleep latency, measured between days 6 and 10 poststroke, was associated with worse functional outcome at 3 months poststroke.[103] Furthermore, lower sleep efficiency and lower REM percentage have been implicated in poorer memory poststroke.[104] Likewise, among patients with stroke in inpatient rehabilitation, greater sleep time, sleep efficiency, N2 percentage, and REM percentage measured by PSG 7 to 10 days after admission were associated with improvement in the ability to perform activities of daily living,[105] consistent with preclinical data emphasizing the importance of sleep in stroke recovery.[82] More research is needed to study the association between sleep and stroke outcomes. These discoveries may open the door for clinical trials to test the potential benefits of optimizing sleep in this population.

Although OSA is common after stroke with a prevalence of ≈70%, central sleep apnea is uncommon after stroke with a prevalence of ≈12%.[106] OSA identified after stroke is associated with worse functional and cognitive outcomes.[107] Likewise, OSA is associated with an increased risk of stroke recurrence and mortality.[108,109] Some pilot trials of CPAP after stroke have suggested the benefit of OSA treatment on neurological and cognitive function, helping to substantiate a possible causal relationship between OSA and worse stroke recovery.[110,111] Therefore, OSA remains a possible treatment target to improve stroke recovery. This hypothesis is being tested

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in ongoing trials such as Sleep SMART (Sleep for Stroke Management and Recovery Trial; NCT03812653) and the RISEUP study (The Recovery in Stroke Using PAP Study; NCT04130503).

Sleep Disorders in Individuals With AD and ADRDs

Among patients with AD, difficulties falling asleep, nighttime awakenings, and daytime sleepiness are commonly reported. Recent meta-analyses found that 26% of people with dementia living at home exhibit a sleep-related disturbance[112] measured by informant report, compared with 38% of those in long-term care[113]; 70% of long-term care residents had poor sleep quality according to actigraphy.[113]

Patients with AD/ADRDs may exhibit significant alterations in the timing of sleep and wake due to circadian rhythm disorders. Sleep problems in this population are predictive of more severe cognitive and neuropsychiatric symptoms, poorer quality of life, higher caregiver burden, early institutionalization, and increased mortality. Although multiple brain regions are involved in the regulation of breathing and sleep/wake states, sleep disorders in AD are believed to occur due to neurodegeneration of the ventrolateral preoptic area and the suprachiasmatic nucleus, and damage to the ascending activating system and respiratory control centers, including the basal nucleus of Meynert, the locus coeruleus, the upper raphe nuclei, the tegmento-pontine reticular nuclei, and adjacent areas, as well.[114]

Sleep-focused clinical trials have largely excluded patients with dementia, and uncertainty remains about the risks associated with sleep therapies when used in AD (although several current medications show promise).[115] Although OSA is 5 times more common in AD than in age-matched controls with a reported prevalence that ranges between 33% and 58%,[116] the clinical relevance and effect of OSA treatment are unknown. Although several small studies, including one with a 3-year follow-up,[117] have shown that CPAP treatment of severe OSA in AD is associated with slower cognitive decline, the largest prospective cohort to date of patients with mild-to-moderate AD who have OSA, but without sleepiness, was not able to demonstrate worse longitudinal outcomes among individuals with both AD and OSA.[118]

Sleep Disorders in Individuals With Other Dementing Disorders

Although beyond the scope of this review, sleep disorders are also important in consideration of other related dementing disorders. REM sleep behavior disorder is pathognomonic for the diagnosis of dementia with Lewy bodies. This condition, in which the typical REM sleep muscle atonia is lost and patients resultantly flail, move, and sometimes injure their bedmates, is likely a consequence of neurodegeneration in the basal forebrain.[119]

PREVENTION AND TREATMENT

Optimizing Sleep to Preserve Brain Health

Improving sleep characteristics at the population level may lead to better brain health outcomes. From a vascular perspective, sleep's potential role in preventing cardiovascular disease was highlighted by the inclusion of optimal sleep duration as the 8th component of cardiovascular health in the 2022 American Heart Association presidential advisory, "Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health."[70] Although the American Heart Association statement focused on sleep duration, improving other aspects of sleep, such as reducing the prevalence of OSA[69] through primordial prevention of obesity, may also prevent adverse brain outcomes. Novel approaches are needed to preserve brain health through nonvascular pathways. For instance, optimizing memory consolidation and synaptic homeostasis during sleep, reducing sleep fragmentation and regularizing daily rhythmicity, and identification of means (behavioral or pharmacological) to enhance N3 sleep or glymphatic waste clearance, or both, have theoretical positive effects on brain health.

It is important to note that modifiable risk factors for poor brain health seem the most effective at earlier stages in the life course. Midlife hypertension and other risk factors appear to have the strongest associations with cognitive decline and dementia,[120,121] although even earlier vascular health is associated with midlife cognition.[122] This scientific statement is focused on brain health in mid-to-late life, in part, because the majority of published data have focused on that portion of the life course. However, optimizing sleep in earlier life stages may also preserve the brain, although additional data to support that hypothesis are needed.

Treatment of Sleep Disorders to Protect Brain Health

It is unclear whether treating sleep disorders mitigates cerebrovascular alterations and brain health. The primary focus has been on treatment of OSA with CPAP. CPAP may improve neurological function,[123] quality of life, depression,[123] language among stroke survivors,[124] and cognition in community-based samples.[125,126] However, evidence is weak, results are mixed, and follow-up durations have been short (typically ≤3 months). Commonly suggested CPAP adherence is at least 4 hours per night, but that level has been difficult to achieve, especially among people with strokes for whom adherence levels are overall low but predict outcomes.[123,127] However, adherence >4 hours per night might lead to greater improvements in brain health outcomes.[128]

The APPLES study (Apnea Positive Pressure Long-Term Efficacy Study) randomly assigned patients with OSA to active versus sham CPAP and found some mild

but transient improvements in some neurocognitive function among those patients with severe OSA.[129] More rigorously conducted long-term clinical trials are needed that investigate the effects of treating OSA (eg, insomnia and short and fragmented sleep) on dementia and ADRD biomarkers. Likewise, although treatments exist for other sleep disorders (eg, cognitive behavioral therapy for insomnia), there is insufficient evidence to demonstrate that such treatments can mitigate cognitive decline,[130] and this remains an important research priority. Moreover, there is a need to understand in which situations sleepiness acts as a risk factor for a treatable sleep disorder rather than a marker of neuropathology. A focus on factors that contribute to treatment response and inclusion of diverse population groups will be essential. There is still clinical equipoise for most sleep-related interventions, so placebo or no-treatment controlled trials may still be appropriate to study these treatments, despite potential ethical considerations with withholding treatment.[131]

REDUCING DISPARITIES IN SLEEP AND BRAIN HEALTH

Social determinants of health provide an essential context for optimizing and preserving cardiovascular health,[70] including brain health. Disparities by indices of social determinants of health in the prevalence of sleep disorders unfortunately exist with individuals of low socioeconomic status or people of underrepresented races and ethnicities having a higher likelihood of poor sleep quantity, quality, and sleep disorders (eg, SDB),[132] with similar observations for other important social determinants of health (eg, neighborhood-level factors, including noise, air. and light pollution, occupational conditions).[133] Furthermore, individuals of underrepresented races and ethnicities are more likely to have sleep-related chronic illness, and disproportionate sleep loss in Black adults versus White adults accounts for some observed disparities in cardiometabolic health.[133] Likewise, there are considerable health equity concerns regarding diagnosis, access to, and adherence to treatment of sleep disorders.[132] Women, Black adults, and Hispanic/Latino adults are often undiagnosed and remain untreated for OSA and other sleep disorders.[133] Multilevel social determinants likely play a role in equitable treatment and treatment adherence.

To reduce sleep disparities at a societal level, multilevel interventions are needed, including those targeting: (1) the individual and family levels (eg, improved screening, referral, and follow-up in primary care and specialty health care settings, targeted sleep promotion education in clinics, daycare centers, schools, lay press, and social media); (2) the neighborhood and broader sociocultural context (eg, improved urban planning to increase green space, and reduce light, noise pollution, and the urban heat island); (3) access to care (eg, home sleep apnea testing, electronic prescribing, integrated services within primary care practices, proactive screening for high-risk patients); and (4) advocacy (eg, insurance coverage for sleep-related services).[132] Improving sleep equity will have broad benefits, likely including reducing disparities in brain health.

Although screening, treatment, and follow-up for sleep disorders are often the domains of physician sleep specialists, efforts to reduce the burden of sleep disorders on brain health require interdisciplinary efforts. These efforts need to be broadly focused on increasing awareness in community and primary care settings, providing supportive

Table 3. Future Directions for Sleep and Brain Health

Interventional
Identify scalable interventions to enhance aspects of sleep (eg, duration, slow-wave activity) that may benefit brain health
Identify populations (eg, on the basis of age, sex, race, ethnicity, socioeconomic status, biomarkers, comorbidity, genetics) who are most at risk of adverse brain outcomes in the face of poor sleep so that future randomized controlled trials can be targeted
Conduct randomized controlled trials (including the very old and patients with dementia) to determine whether the treatment of prevalent sleep disorders, such as insomnia and obstructive sleep apnea, and short, fragmented, and irregular sleep, improves brain health outcomes
Consider novel trial designs or causal modeling frameworks such as target trial emulation from existing observational data to study sleep interventions
Observational
Conduct studies that include deep phenotyping of markers of both sleep and brain health to allow for a deeper understanding of underlying mechanism
Develop better parameters, including possibly incorporation of wearables, to comprehensively evaluate sleep characteristics and brain health in large samples, and over time
Use longitudinal studies and causal frameworks to establish the extent to which changes in sleep across the lifespan drive neurodegeneration and cognitive decline in later life, as well as the precise mechanism by which neurodegeneration disrupts sleep characteristics
Examine how sleep disorders interact with circadian rhythm alterations to affect brain health
Mechanistic/basic and translational
Understand the role of sleep and circadian rhythms on the mechanisms of action of neurodegenerative proteinopathies
Use neuropathological studies to better establish the regulation of sleep and sleep breathing and how they are disrupted by neurodegeneration
Understand the relationship between age-related sleep disorders and impaired learning/memory consolidation
Understand how sleep disorders alter synaptic homeostasis
Learn how hypoxemia interacts with nonrespiratory sleep parameters to affect the pathways of interest
Define drivers of increased glymphatic transport and waste clearance during sleep
Define anatomical pathways and driving forces of solute clearance from the brain
Understand the anatomical and functional coupling between the glymphatic and lymphatic systems in health and disease
Evaluate brain biomarkers or other surrogate measures of sleep and neurodegeneration, as well
Increase the use of sleep-dependent tasks instead of traditional cognitive testing during wakefulness

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care to provide consumer education on treatment strategies, and promoting adherence to treatment. Public health awareness campaigns targeted to groups that may be at highest risk (eg, older adults and those experiencing health inequities) are likely to be helpful in dispelling myths about sleep and sleep disorders and in increasing knowledge and self-efficacy for obtaining treatment. Addressing this problem will take the concerted effort of non–sleep specialist physicians, advanced practice professionals, nurses, public health practitioners, educators, the media, payors, public interest groups, and others.

CONCLUSIONS

Optimal sleep may play a crucial role in preserving brain health. Convergence of evidence from epidemiology, clinical investigations, and basic science all suggest associations. There are numerous distinct pathways mechanistically (eg, Aβ production, glymphatic clearance), yet shared underlying causes that may contribute (eg, aging, vascular risk factors, disruption of blood brain barrier integrity, AD pathology). Future directions are provided in Table 3. Additional research is needed to refine understanding of the physiological and pathophysiological links between sleep and brain health, the epidemiological associations of specific aspects of sleep and various brain health outcomes, and the importance of sleep among people with impaired brain health. Above all, it is necessary to identify opportunities to optimize sleep health and the treatment of sleep disorders to reduce sleep disparities and improve sleep overall. Doing so will require multilevel approaches that have the potential to improve brain health at both an individual and societal level.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Writing Group Disclosures

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Rebecca F. Gottesman	National Institutes of Health, National Institute of Neurological Disorders and Stroke	NIH NINDS Intramural Research Program†	None	None	None	None	None	None
Pamela L. Lutsey	University of Minnesota	NIH (K24 HL159246, grants to her institution)†	None	None	None	None	None	None
Helene Benveniste	Yale School of Medicine	NIH (research support)†; Cure Alzheimer's Fund (research support)*	None	None	None	None	None	None
Devin L. Brown	University of Michigan	NIH (grants to University of Michigan)†; ResMed (in-kind support [providing CPAP and masks for project on which she is a multiple PI])*	None	None	None	None	None	University of Michigan (professor of neurology)†
Kelsie M. Full	Vanderbilt University Medical Center	Alzheimer's Association†; NIA (ADRC funding)†; National Institute of Aging†	None	None	None	None	None	Vanderbilt University Medical Center (assistant professor)†

(*Continued*)

Writing Group Disclosures Continued

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Jin-Moo Lee	Washington University School of Medicine Stroke Center	None	None	None	None	None	None	None
Ricardo S. Osorio	NYU Grossman School of Medicine	None	None	None	None	None	None	None
Matthew P. Pase	Monash University, The Turner Institute for Brain and Mental Health (Australia)	NIA (multi PI on project grant)†; NHMRC (PI on project grant and investigator grant)†; Alzheimer's Association (PI on project grant)†	None	None	None	None	None	None
Nancy S. Redeker	University of Connecticut Schools of Nursing and University of Connecticut School of Medicine	None	None	None	None	None	None	None
Susan Redline	Brigham and Women's Hospital	NIH (multiple grants related to sleep and cognition)†	None	None	None	None	Apnimed, Inc. (unpaid)*; Eli Lilly*; Jazz Pharmaceuticals*	None
Adam P. Spira	Johns Hopkins Bloomberg School of Public Health	NIH (PI, multiple PI, or co-investigator on NIH grants related to this topic)†; Richman Precision Center of Medicine, Dept of Psychiatry and Behavioral Sciences, Johns Hopkins University (PI on a grant from this center related to this topic)†; Johns Hopkins Bloomberg School of Public Health (multiple PI on a grant from Johns Hopkins Bloomberg School of Public Health related to this topic)†; Johns Hopkins University (co-investigator on a grant funded by Johns Hopkins University)†	None	Springer Nature Switzerland AG (guest editing special issues of *Current Sleep Medicine Reports*)*	None	Sequoia Neurovitality*	Sequoia Neurovitality*; Merck*; BellSant, Inc.†	Johns Hopkins Bloomberg School of Public Health (professor)†

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Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Oreste Marrone	National Research Council of Italy	None	None	None	None	None	None	None
Eeeseung Byun	University of Washington	None	None	None	None	None	None	None
S. Justin Thomas	University of Alabama at Birmingham	None	None	None	None	None	None	None
Dong Zhang	University of Iowa	None	None	None	None	None	None	None
Nerissa Ko	University of California San Francisco	None	None	None	None	None	None	None

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