# IMPACT OF SLEEP DISORDERS AND DISTURBED SLEEP ON BRAIN HEALTH

A Scientific Statement from The American Heart Association

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# STROKE COUNCIL PROFESSIONAL EDUCATION COMMITTEE

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# SLEEP AND SLEEP DISTURBANCES

# WHAT IS SLEEP?

SLEEP IS A BIOBEHAVIORAL STATE CHARACTERIZED BY CHANGES IN BRAIN ELECTRICAL ACTIVITY THAT MANIFEST AS ALTERED CONSCIOUSNESS, REDUCED SENSORY RESPONSIVENESS, AND DECREASED MUSCLE TONE.



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# SLEEP ARCHITECTURE: STAGES

| | EEG Pattern | Typical Duration | 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 sec in duration) and K complexes (sharp, biphasic delta waves, > 5 sec). | 45% of total sleep time. | Spindles implicated in synaptic plasticity and memory consolidation. K-complexes maintain sleep and memory consolidation. |
| **Stage N3 (NREM) (also: Slow Save Sleep)** | 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. Saw tooth 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. |



Abbreviations: EEG - electroencephalogram, NREM - non-rapid eye-movement, REM - rapid eye movement

# SLEEP DURATION

| | Thresholds for Adults | Comments |
|---|---|---|
| **Sufficient Sleep** | **7-9 hours of sleep per night for adults aged 18-64, and 7-8 hour per night for older adults.** | **Associated with optimal health for most adults.** |
| **Short Sleep Duration** | **Less than 7 hours of self-reported sleep per Night.** | **Associated with weight gain, diabetes, hypertension, cardiovascular disease, poorer acute cognitive function.** |
| **Long Sleep Duration** | **More than 9 hours of self-reported sleep per night.** | **Associated with depression, polypharmacy, numerous morbidities and mortality.** |

Recommendations listed here are based on the Centers for Disease Control and Prevention. However, some other organizations and publications define short and long duration using different durations.

# COMMON SLEEP DISTURBANCES

| | Definitions | Thresholds for Abnormality | 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, though some diagnostic criteria specify a minimum length of sleep onset duration (≥ 30 min) or periods of waking after sleep onset (≥ 30 min at least three times per week). | Associated with elevated sympathetic CNS activity, systemic inflammation and hypothalamic-pituitary-adrenal axis dysregulation, as well as increased risk of mood and anxiety disorders, weight gain, diabetes, hypertension, stroke, and dementia. |
| **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 sec. | 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 (e.g., genetic), extrinsic (e.g., 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. |

This table does not include all sleep disorders and disturbances. The focus is on disorders that have been most directly linked to brain health. Abbreviations: EEG - electroencephalography

# SLEEP-DISORDERED BREATHING (sleep disorders)

| | Definitions | Thresholds for Abnormality | Comments |
|---|---|---|---|
| **Obstructive Sleep Apnea (OSA)** | AHI 5-15 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<br>Mild: AHI 5-15<br>Moderate: AHI 15-30<br>Severe: AHI >30 | Severe OSA 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/or 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 (CAI) ≥ 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 CAI often also experience obstructive events. |
| **Sleep-Related Hypoventilation** | Polysomnography shows elevated carbon dioxide levels during sleep (e.g., end-tidal carbon dioxide tension or Transcutaneous carbon dioxide) >55 mmHg for >10 min) or an increase in >10 mmHg compared to an awake supine value to a value >50 mmHg 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 |



Abbreviations: AHI – Apnea-hypopnea index (defined as the number of obstructive apneas, or episodes of complete upper airway obstruction, and/or hypopneas, or partial airway obstruction, per hour of sleep, CAI – Central Apnea Index

# BRAIN HEALTH

# WHAT IS BRAIN HEALTH?

ALTERATIONS IN "BRAIN HEALTH" ENCOMPASS THE SPECTRUM OF SUBCLINICAL TO CLINICAL DISEASE.

THESE CAN INCLUDE:

- CEREBROVASCULAR IMAGING CHANGES
- CLINICALLY APPARENT STROKE
- COGNITIVE DECLINE
- DEMENTIA



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# LONGSTANDING VASCULAR DISEASE CAN ADVERSELY IMPACT BRAIN HEALTH IN MANY WAYS

- Clinically apparent ischemic stroke and intracerebral hemorrhage
- "Subclinical" silent infarcts, white matter hyperintensities (leukoaraiosis), cerebral microbleeds, enlarged perivascular spaces, cerebral atrophy
  - These are associated with long-term sequelae including cognitive decline and dementia, impaired gait, and increased stroke risk
- Comorbid Alzheimer's Disease (AD) and AD-related dementias: AD and the vascular contributions to cognitive impairment and dementia are common dementia subtypes

# ASSESSING BRAIN HEALTH

## CLINICAL ASSESSMENTS

- Clinical signs for stroke
- Cognitive measures
- Psychiatric evaluation

## ADDITIONAL TESTING

- Neuroimaging
- Blood testing, including neurofilament light chain, a marker of axonal injury
- Cerebrospinal fluid biomarkers
- Indictors for underlying Alzheimer's Disease pathology, specifically:
  - Amyloid-β (Aβ) or tau positron emission tomography
  - Blood or cerebrospinal fluid phosphorylated tau or Aβ levels

# NORMAL PHYSIOLOGY OF SLEEP AND BRAIN HEALTH

# SLEEP AND MEMORY CONSOLIDATION

## SLEEP PLAYS A CENTRAL ROLE IN OPTIMIZATION OF COGNITIVE PERFORMANCE

- Important for attention, executive function, and short-term memory (particularly cognitive processes that rely heavily on the prefrontal cortex)
- Strengthening and promoting preserved recent learning, including episodic and procedural memory
- Integrating REM (rapid eye movement) and NREM (non-REM) for memory consolidation – relocating new, unstable memories from the hippocampus to the neocortex where they are more durable

- Older adults may experience deficits in the consolidation of episodic memories due to aging-related deterioration of brain structure, sleep quality, and concomitant comorbidity.

# “SYNAPTIC HOMEOSTASIS”

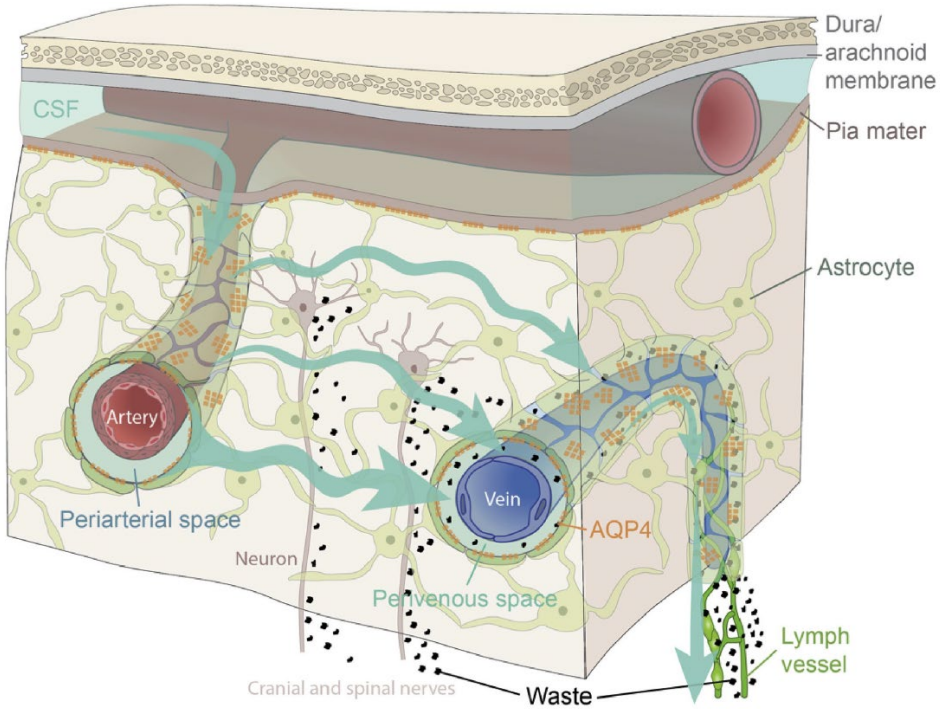
## A LEADING HYPOTHESIS FOR MECHANISMS INVOLVED IN SLEEP-DEPENDENT MEMORY CONSOLIDATION:

- In wakefulness, learning is associated with selective changes in synapse number and strength in relevant circuits
- With cumulative learning throughout wakefulness, net increases in synaptic density and strengths increase throughout the brain – a process not sustainable long-term
- “Synaptic homeostasis” holds that slow-wave activity during NREM (non-rapid eye movement) sleep downregulates synaptic strengths proportionately across all synapses, effectively normalizing synaptic strengths throughout the brain
- The advantage of such daily recurrent homeostatic downregulation of synaptic strengths is retention of energetic efficiency without compromising fidelity of synaptic neurotransmission

# GLYMPHATIC SYSTEM

## AN ALTERNATE PATHWAY IMPLICATED IN BRAIN HEALTH

- A perivascular transit passageway for cerebral spinal fluid (CSF) to exchange with interstitial fluid, facilitating waste removal including Aβ and tau protein.
  1) CSF enters into the peri-arterial channels via vascular pulsatility/vasomotion
  2) Aquaporin-4 channels on the glia end-feet facilitate efficient perivascular CSF exchange for waste clearance
  3) Glymphatic waste egresses via peri-venous channels, and 'hot spots' along dural venous sinuses serve as bridges between the glymphatic system and lymphatic vasculature in the dura
  4) Glymphatic waste disposal depends on sleep state, with enhanced glymphatic activity during N3 sleep and under certain anesthetic regimens




Iliff et al., Trans Med Sci, 2012; Benveniste & Nedergaard, Current Biology in Neurobiology, 2022



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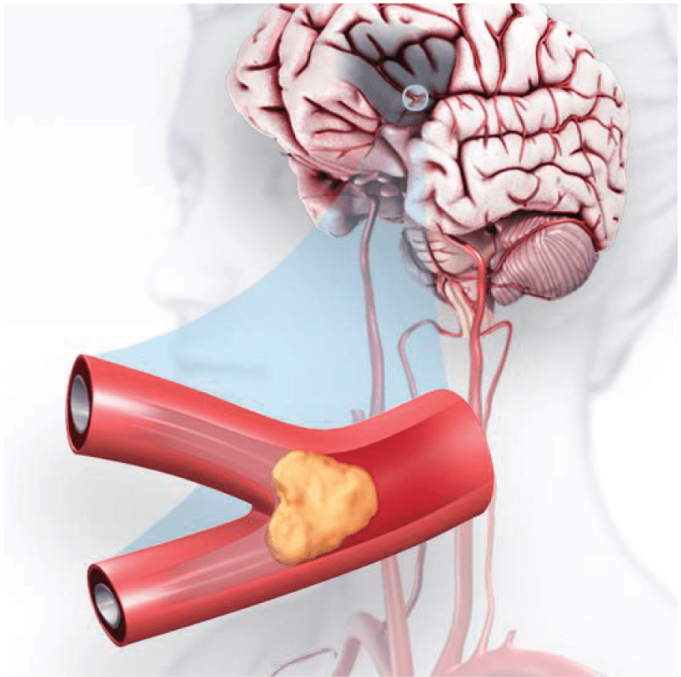
# EPIDEMIOLOGY: ASSOCIATIONS OF SLEEP WITH BRAIN HEALTH

# SLEEP AND STROKE

## SLEEP DISTURBANCES AND DISORDERS ARE ASSOCIATED WITH INCREASED STROKE RISK

- Obstructive Sleep Apnea
  - Stronger association in men
  - Stronger association with higher Apnea-Hypopnea Index in both men and women
- Long sleep duration
- Short sleep duration
- Insomnia





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# SLEEP AND SILENT CEREBROVASCULAR DISEASE

## SLEEP DISTURBANCES AND DISORDERS ARE ASSOCIATED WITH SUBCLINICAL MARKERS OF VASCULAR BRAIN INJURY

- Obstructive Sleep Apnea
  - Associated with higher odds of white matter hyperintensities (in addition to lacunar infarcts) on MRI
  - Associated with decreases in cerebral blood flow in medial temporal regions, reversible with CPAP treatment
- Insomnia
  - Linked to lower integrity of white matter fibers connecting subcortical nuclei and the prefrontal cortex
- Short sleep duration
  - Predicted white matter hyperintensities in the parietal region
  - Less N3/Slow Wave Sleep was associated with higher white matter hyperintensity volumes and lower cortical gray matter volumes

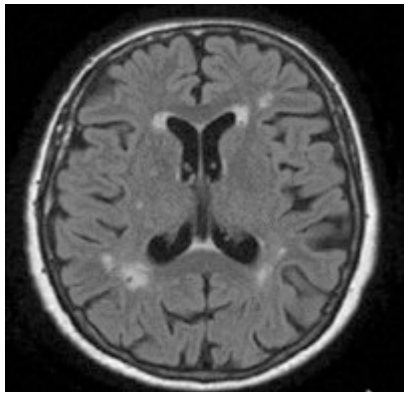

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Image: Moroni et al., Circulation: Cardiovascular Imaging. 2020.

# SLEEP AND ALZHEIMER'S DISEASE (AD) AND AD-RELATED DEMENTIAS (ADRDS)

## SLEEP DISTURBANCES AND DISORDERS ARE ASSOCIATED AD AND ADRDS

- Obstructive Sleep Apnea
  - Dementia, including specifically AD
  - Mild cognitive impairment
  - Cerebral spinal fluid and blood-based biomarkers of Aβ and tau
  - Heightened inflammation
  - Hippocampal volume loss
- Insomnia
  - Dementia

- **Short sleep duration/Long sleep duration**
  - Dementia
  - Aβ deposition
  - Smaller brain volumes
- **Impaired circadian rest/activity rhythms**
  - **Mild cognitive impairment**
  - **Dementia**
  - Aβ deposition
  - Medial temporal lobe atrophy

# METHODOLOGICAL CONSIDERATIONS

## STUDY DESIGN, MEASUREMENT, AND CONFOUNDING COMPLICATE EVALUATION OF LITERATURE ON SLEEP AND BRAIN HEALTH

- Study design considerations
  - Accounting for reverse causation – disease pathology may be present for years before clinical symptoms manifest
  - Accounting for simultaneous assessment of sleep and dementia in older adults – sleep and circadian disorders may be a manifestation of underlying pathology
  - Diverse patient populations to increase generalizability
- Measurement considerations
  - Accounting for more multiple sleep phenotypes
  - Accounting for varying assessment methods, cut points, and definitions
  - Incorporating repeated measures of sleep throughout adulthood
- Confounding considerations
  - Accounting for common factors among dementia and sleep disorders including genetics and vascular risk factors
  - Accounting for important covariates
  - Adequate power, sample-size estimates

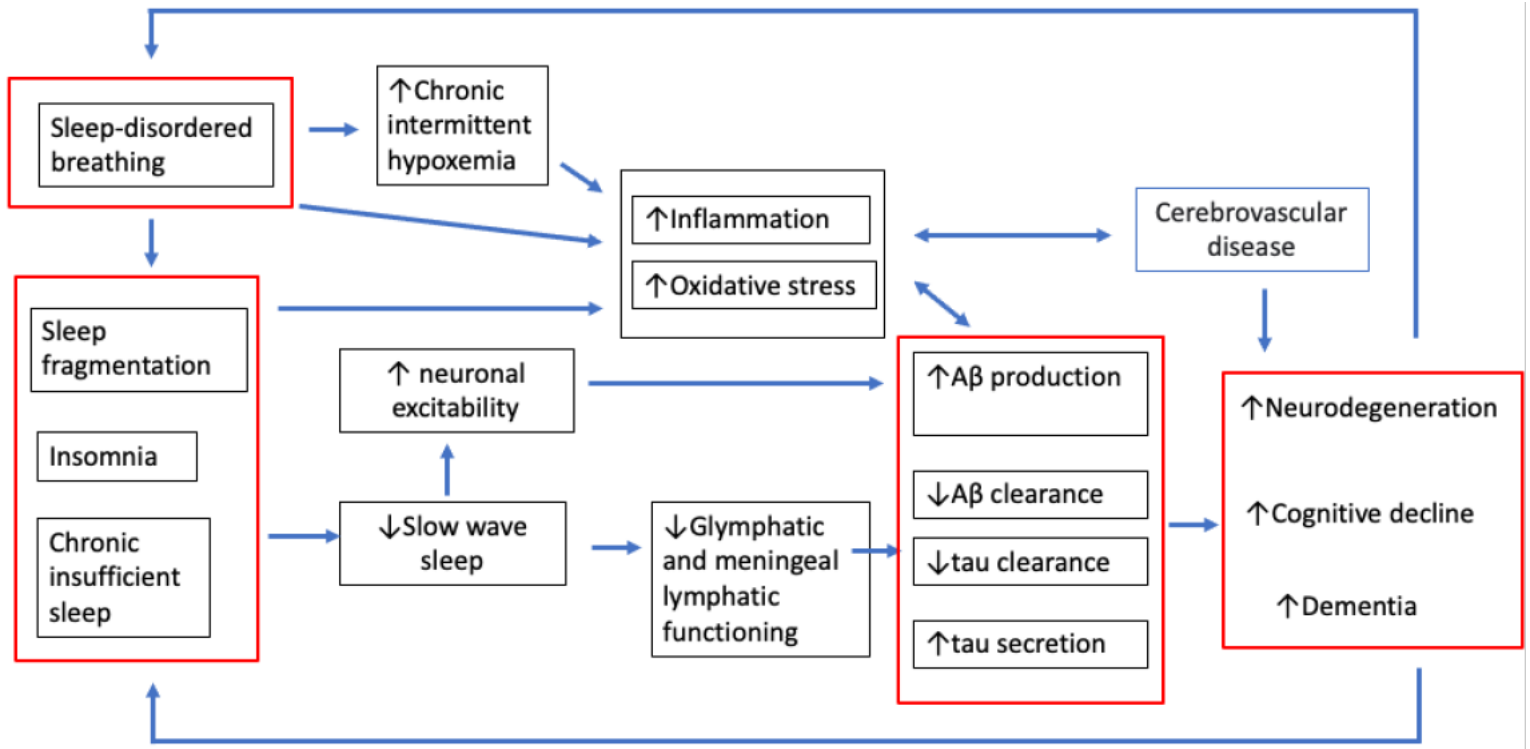
# MECHANISMS FOR THE IMPACT OF SLEEP DISORDERS AND DISTURBANCES ON BRAIN HEALTH

# TRADITIONAL VASCULAR RISK FACTORS AS MEDIATORS

- Vascular risk factors may confound sleep/brain health associations
- Sleep disorders can contribute to the development of cardiovascular risk factors
  - Including obesity, hypertension, diabetes, dyslipidemia, ischemic heart disease, and atrial fibrillation
  - Mechanisms include pro-inflammatory pathways, autonomic nervous system dysfunction, alterations in 24-hour blood pressure profiles, carotid and coronary atherosclerosis, reduced Stage N3 sleep
- Sleep disorders can lead to alterations in cerebral autoregulation, hypercoagulability, increased shunting through a patent foramen ovale, endothelial dysfunction, sympathetic hyperarousal and sleep fragmentation
- Timing of sleep in relation to stroke risk, possible circadian rhythmicity of stroke

# DISTURBANCES IN SYNAPTIC HOMEOSTASIS

- Stage N3 sleep may protect against neurodegenerative disease and support brain recovery after stroke
  - Excessive neuronal activity can increase Aβ production and tau release
  - Sleep deprivation in experimental rat models impairs axonal sprouting, synaptogenesis, and motor recovery after stroke




Concepts adapted from: Xie et al., Science 2013; 342(6156): 373-377; Shokri-Kojori et al., Proc Natl Acad Sci USA 2018; 115(17): 4483-4488; Eide & Ringstad. Brain Res 2021; 1772: 147669; and Eide et al., Brain 2021; 144(3): 863-874.

Mechanisms through which sleep disorders may lead to dementia.



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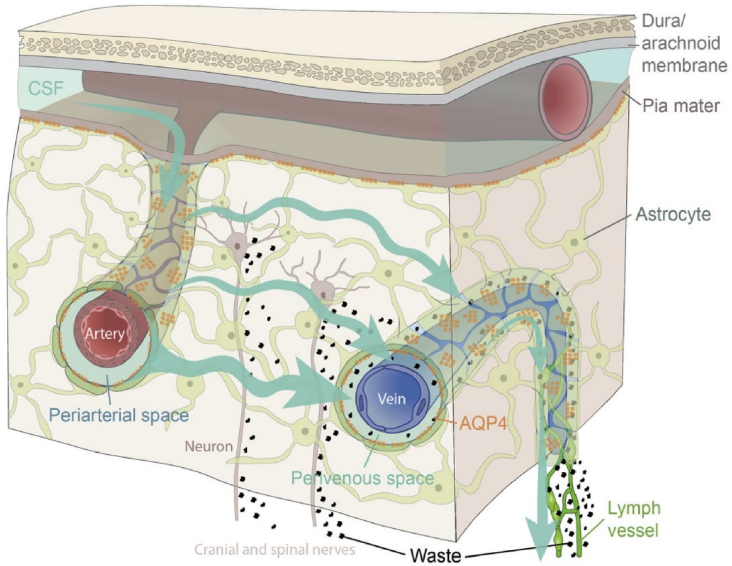
# GLYMPHATIC DYSFUNCTION

- Sleep disturbances or disorders may reduce efficiency of glymphatic clearance of neurotoxic metabolites
- Glymphatic clearance efficiency is optimized in deeper stages of sleep
  - Stage N3 sleep is associated with reduced central noradrenergic tone and increased interstitial fluid volume fraction
  - Glymphatic transport function is dependent on body posture and under circadian control
- Glymphatic dysfunction is associated with aging, sleep deprivation, in neurodegenerative disease states including Alzheimer's Dementia, cerebral small vessel disease, cerebral amyloid angiopathy, Parkinson's Disease, and normal pressure hydrocephalus.

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# MOLECULAR MECHANISMS OF ALZHEIMER'S DISEASE (AD)

- Lower cerebral spinal fluid Aβ is found in the morning, however this is attenuated by prolonged wakefulness.
- Endothelial cells mediating blood-brain barrier dysfunction, important for Aβ clearance, are under circadian control.
- Truncated forms of tau, leading to increased tau peptides, are found in cerebrospinal fluid in sleep-deprived humans.
- Overnight  sleep deprivation may promote tau phosphorylation isoforms found in early stages of AD.
- Other factors increasing Aβ and tau include intermittent hypoxia, sleep fragmentation, intrathoracic pressure swings, stress, depression, disrupted circadian rhythms, or increased oxidative stress and inflammation
- Sleep deprivation and obstructive sleep apnea may also increase release of other proteins associated with non-AD neurogenerative pathways

# IMPORTANCE OF SLEEP IN PEOPLE WITH IMPAIRED BRAIN HEALTH

# POST-STROKE RECOVERY

- Insomnia, sleepiness, and long-duration of sleep are common among stroke patients
- Stroke patients have poorer sleep efficiency, shorter total sleep time, and different sleep architecture (including lower percentage of slow wave sleep), compared to control patients
- Lower sleep efficiency, less total sleep time, less Stage N3 sleep, longer rapid eye movement (REM) sleep latency, and lower REM percentages are associated with worse post-stroke clinical outcomes including functional status and memory
- In the inpatient rehabilitation setting, greater sleep time, sleep efficiency, Stage N2 percentage, and REM percentage are associated with improvement in ability to perform activities of daily living
- Obstructive Sleep Apnea identified after stroke is associated with worse functional and cognitive outcomes, and increased stroke recurrence and mortality
  - Pilot trials of CPAP suggest benefit in neurologic and cognitive outcome
  - Sleep SMART (NCT03812653) and RISEUP (NCT04130503) are ongoing trials

# SLEEP DISORDERS IN INDIVIDUALS WITH DEMENTIAS

- Patients with Alzheimer's Disease (AD) commonly experience difficulty falling asleep, nighttime awakenings, and daytime sleepiness
- Patients with AD and AD-Related Dementias (ADRD) experience circadian rhythm disorders
- Sleep disorders in AD/ADRD patients portend more severe cognitive and neuropsychiatric symptoms, poorer quality of life, higher caregiver burden, earlier institutionalization, and increased mortality
- Sleep-focused clinical trials have largely excluded patients with dementia
  - Uncertainty remains regarding the risks associated with sleep therapies
  - The clinical relevance and impact of Obstructive Sleep Apnea treatment is unknown in this patient population

# PREVENTION AND TREATMENT

# OPTIMIZING SLEEP TO PRESERVE BRAIN HEALTH

- The "Life's Essential 8" 2022 AHA Presidential Advisory highlights the potential role of sleep duration in preventing cardiovascular health
- Reducing prevalence of Obstructive Sleep Apnea may also prevent adverse brain outcomes
- Novel approaches are needed to preserve brain health through non-vascular pathways, including optimizing memory consolidation and synaptic homeostasis, reducing sleep fragmentation, regulating daily rhythmicity, and identifying means to enhance Stage N3 sleep and/or glymphatic waste clearance
- Modifiable risk factors for poor brain health seem most impactful at earlier stages in life




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# TREATMENT OF SLEEP DISORDERS TO PROTECT BRAIN HEALTH

- CPAP to treat Obstructive Sleep Apnea may improve neurologic function, quality of life, depression, language, and cognition
  - Study results are mixed, and follow-up durations have been short
  - Adherence to CPAP is difficult for stroke survivors but may predict greater improvements in brain health outcomes
  - More rigorously conducted, long-term clinical trials are needed to investigate treatment of Obstructive Sleep Apnea and dementia
- Insufficient evidence also remains to determine the effect of treatments for other sleep disorders and cognitive decline
- 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

# REDUCING DISPARITIES IN SLEEP AND BRAIN HEALTH

## SOCIAL DETERMINANTS OF HEALTH PROVIDE AN ESSENTIAL CONTEXT FOR OPTIMIZING AND PRESERVING BRAIN HEALTH

- Individuals of low socioeconomic status, who identify from within a racial/ethnic minority group, or who experience specific neighborhood-level factors, have higher likelihood of poor sleep quality, quantity, and sleep disorders
- Individuals from racial/ethnic minority group backgrounds are more likely to have sleep-related chronic illness and disproportionate sleep loss
- There are considerable health equity concerns regarding diagnosis, and access and adherence to treatment of sleep disorders involving multi-level social determinants of health

# REDUCING DISPARITIES IN SLEEP AND BRAIN HEALTH

## MULTI-LEVEL INTERVENTIONS ARE NEEDED TO REDUCE SLEEP DISPARITIES

- Individual and family levels
- Neighborhood and broader sociocultural context
- Access to care
- Advocacy
- Interdisciplinary efforts among sleep specialists, non-sleep specialist physicians, advanced practitioners, nurses, public health practitioners, educators, the media, payors, public interest groups, and others

# FUTURE DIRECTIONS

# FUTURE DIRECTIONS FOR SLEEP AND BRAIN HEALTH

| |
|---|
| Interventional |
| Identify scalable interventions to enhance aspects of sleep (e.g., duration, slow-wave activity) that may benefit brain health |
| Identify populations (e.g., based on age, sex, race, ethnicity, socio-economic status, biomarkers, comorbidity, genetics) who are most at risk of adverse brain outcomes in the face of poor sleep so that future RCTs can be targeted |
| Conduct RCTs (including the very old as well as patients with dementia) to determine whether the treatment of prevalent sleep disorders, such as insomnia and obstructive sleep apnea, as well as short, fragmented, and irregular sleep improve 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 mechanisms. |
| 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 interacts 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 neurodegenerations |
| 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 non-respiratory 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 measures as well as neurodegeneration |
| Increase the use of sleep-dependent tasks instead of traditional cognitive testing during wakefulness |