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Impact of Sleep on the Risk of Cognitive Decline and Dementia

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Abstract

Purpose of review—Trouble falling or staying asleep, poor sleep quality, and short or long sleep duration are gaining attention as potential risk factors for cognitive decline and dementia, including Alzheimer's disease (AD). Sleep-disordered breathing (SDB) has also been linked to these outcomes. Here, we review recent observational and experimental studies investigating the effect of poor sleep on cognitive outcomes and AD and discuss possible mechanisms.

Recent findings—Observational studies with self-report and objective sleep measures (e.g., wrist actigraphy, polysomnography) support links between disturbed sleep and cognitive decline. Several recently published studies demonstrate associations between sleep variables and measures of AD pathology, including cerebrospinal fluid measures (CSF) of Aβ and positron emission tomography (PET) measures of Aβ deposition. In addition, experimental studies suggest that sleep loss alters CSF Aβ dynamics, that decrements in slow-wave sleep may decrease the clearance of Aβ from the brain, and that hypoxemia characteristic of SDB increases Aβ production.

Summary—Findings indicate that poor sleep is a risk factor for cognitive decline and AD. Although mechanisms underlying these associations are not yet clear, healthy sleep appears to play an important role in maintaining brain health with age, and may play a key role in AD prevention.

Keywords

sleep; apnea; cognitive decline; dementia; amyloid

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Kristine Yaffe has served on data safety monitoring boards for Takeda and the NIH, and received honoraria from Novartis and Pfizer.

Introduction

Older adults with dementia exhibit significant sleep disturbance, including shorter sleep duration and fragmented sleep (1-3), altered circadian rest/activity patterns (1), and elevated rates of sleep-disordered breathing (SDB) (4, 5). While these findings have traditionally been interpreted to represent consequences of diseases like Alzheimer's disease (AD), investigators have begun to examine whether sleep disturbances may also contribute to the risk of AD (6). A causal association between poor sleep and AD could be of critical importance to AD prevention because effective interventions exist to improve sleep (7). Here, we review recent studies supporting the notion that poor sleep contributes to cognitive decline and dementia, with a particular focus on AD. We focus on reports of insomnia symptoms (difficulty falling asleep, staying asleep, and poor sleep quality), short and long sleep duration, objective measures of these variables, and SDB. Because REM sleep behavior disorder is generally viewed as a marker of specific neurodegenerative diseases (8, 9) rather than a potential cause, we excluded it from this review.

Prospective Studies of Sleep and Cognitive Outcomes

Recent prospective studies demonstrate links between various aspects of sleep and cognitive outcomes using self-report measures (e.g., questionnaires) or objective sleep measures. The latter include polysomnography (PSG; the gold standard for assessment of sleep) and actigraphy (a method of estimating sleep/wake patterns by recording movement over multiple days using a device typically worn on the wrist) (10).

Three recent European studies focused on self-reported sleep and cognitive outcomes. In a rare study of midlife sleep (mean age = 52) and cognitive impairment and dementia 18 to 26 years later in >2,300 Finnish twins, Virta et al. found that reports of short (<7 hours) and long (>8 hours) sleep duration, poor sleep quality, and use of hypnotic medications >60 days per year were associated with lower cognitive composite scores; long sleep was associated with roughly 1.8 times the odds of developing AD, measured by receipt of an AD medication (11**). Some associations differed by participant characteristics, including apolipoprotein e (APOE) ε4 allele status, sex, and age, indicating that poor sleep may differentially affect cognition in different populations.

In 214 non-demented Swedish adults aged ≥75 years, Hahn et al. found that reports of a persistent decrease in normal sleep depth or duration (a binary variable) were associated with ~70% to 100% greater odds of incident all-cause dementia and AD measured by a clinical exam nine years later, after adjustment for demographic variables and either lifestyle variables or vascular risk factors (12). Results were no longer significant after adjustment for depressive symptoms or physical function, respiratory problems, and pain. Importantly, depressive symptoms explained associations between change in sleep and cognitive outcomes.

In a large study of >17,000 older adults from the Survey of Health, Ageing and Retirement in Europe, Sterniczuk et al. collected data on four sleep variables (sleeping problems and fatigue in past 6 months, sleep medication use, and “recent trouble sleeping or a change in pattern”), created a composite “sleep disturbance index” of those items, and examined their

association with self- or proxy-reported dementia or AD within approximately 4 years (13). They found that higher scores on the index were associated with a 23% greater odds of dementia or AD after accounting for demographic variables, BMI, and baseline cognitive performance; results were similar with the individual sleep items as predictors.

Two recent studies of sleep and cognition measured sleep with actigraphy. This objective sleep measure is particularly useful in studies of sleep, aging, and cognition because self-report sleep measures do not necessarily correlate with objectively measured sleep, and discrepancies between these modes of assessment may be more pronounced among older adults with cognitive impairment (14, 15). Blackwell et al. studied the association of self-reported and actigraphic sleep with cognitive decline over almost 3.5 years in >2,800 older men (16*). They found that poorer actigraphic sleep efficiency (i.e., spending a lower proportion of time in bed asleep) and a greater number of long wake intervals were associated with greater decline in global cognitive function; long wake episodes also were associated with decline in executive function. Self-reported poor sleep quality, measured by a score >5 on the Pittsburgh Sleep Quality Index (PSQI; a sleep questionnaire (17)) was associated with greater decline in executive function (16*). There was no association between sleep duration and cognition. Lim et al. reported that, among 737 older adults without dementia at baseline, those with significant actigraphic sleep fragmentation (in the 90th percentile) had an increased risk of incident AD; greater sleep fragmentation also predicted more rapid cognitive decline (18**).

Besides altered sleep amounts or poor sleep quality, SDB has also been identified as a potential cause of cognitive impairment. Yaffe et al. studied 298 older women and found that SDB (apnea-hypopnea index; AHI ≥15) was associated with 1.9 times the odds of mild cognitive impairment (see below) or dementia five years later (vs. AHI <15) (19). Building on this work, Chang et al., found in a study of >8,000 middle-aged and older patients in a Taiwanese national health database, that compared to those without a medical record SDB diagnosis, patients with SDB had 1.7 times the odds of a medical record dementia diagnosis over 5 years (20**). In sex-stratified analyses, this association was statistically significant in women but not in men, and in age-stratified adjusted analyses, the association was stronger in those aged 50-59 compared to younger or older patients. In adjusted analyses further stratified by age and sex, men aged 50-59 years with SDB had 6 times the odds and women aged ≥70 years had 3 times the odds of dementia, but there was no significant association between SDB and dementia in men or women from other age groups.

Taken together, these observational studies provide further support for associations of disturbed sleep with poor cognitive outcomes, including dementia. Findings from two suggest interactions by age, sex, or APOE genotype (11, 20). While these findings require replication, if these associations are causal, prevention efforts may exert somewhat different effects when applied at different ages or in different populations. Each study has methodological strengths (e.g., objective or repeated sleep measures, long follow-up), but these tended not to overlap within studies, limiting the strength of causal inferences that can be made. In addition, depression or its symptoms may be important mediators or confounders of the association between sleep variables and dementia and should be

considered in these studies (12). However, not all studies clearly addressed the role of depression.

Observational Studies of Sleep and AD Pathology

Importantly, recent observational studies have identified links between sleep variables and AD pathology, measured by AD biomarkers or on autopsy. Ju et al. showed in a cross-sectional study of 142 cognitively normal middle-aged and older adults, that those with a lower level of cerebrospinal fluid (CSF) Aβ42 (i.e., indicating greater Aβ burden) had poorer actigraphic sleep efficiency and greater WASO (21*). Similarly, Spira et al. conducted a cross-sectional study of 70 community-dwelling participants in the Baltimore Longitudinal Study of Aging who completed self-report sleep measures and [^{11}C]-Pittsburgh compound B positron emission tomography (PiB PET) amyloid imaging (22*). They found that self-reported shorter sleep duration and poorer sleep quality both were associated with greater Aβ burden according to a cortical (i.e., global) measure of PiB uptake, and a measure of uptake in the precuneus—a region in which Aβ aggregates early in the AD course (23).

Two studies suggested that sleep variables interact with the APOE genotype to affect AD-related outcomes. Lim et al. showed in 698 non-demented older adults who completed wrist actigraphy, that better sleep consolidation (i.e., lower levels of sleep fragmentation) moderated the association between APOE ε4 genotype and cognitive decline, incident AD, and post-mortem density of neurofibrillary tangles. Specifically, the association between the ε4 allele and these outcomes was stronger among persons with more fragmented sleep (24*). Osorio et al. studied links between SDB, measured by home sleep testing, and AD biomarkers in 95 older adults with normal cognition (25). They found that SDB (AHI 5-14.99 for mild SDB, AHI >15 for moderate to severe SDB) was associated with levels of CSF Aβ42 and phosphorylated and total tau, but that associations differed in magnitude, direction, and significance by APOE status (i.e., ε2+, ε3+, or ε4+).

These important studies complement those linking poor sleep to cognitive decline and dementia by demonstrating associations of sleep variables with measures of AD pathology. However, each was cross-sectional or measured AD pathology at one timepoint, so we cannot infer whether this pathology causes or results from poor sleep. Aβ deposition may be a cause and a consequence at different points in the AD course, or disturbed sleep and Aβ plaques may have a shared cause (26). The use of AD biomarkers is important because they help elucidate the pathology that might link poor sleep to cognitive outcomes, and because they are evident early in the AD course, a time at which prevention may still be feasible (27). Prospective observational studies are needed to better understand the temporal order of sleep disturbance and AD biomarkers and evaluate potential opportunities for prevention.

Experimental Studies of Sleep and AD Biomarkers

Experimental studies provide the most compelling evidence of causal associations, but typically are performed in animals. Kang et al. showed that Aβ levels in interstitial fluid (ISF) increase with time spent awake and that sleep deprivation (SD) increases Aβ deposition in an AD mouse model (28). Recent investigations also suggest that perturbed sleep increases AD risk. Di Meco et al. found in another mouse model of AD that chronic

SD impaired both cued recall and spatial memory (29*). While they found no effect of SD on soluble Aβ levels from the whole brain, SD altered tau phosphorylation and increased insoluble tau. In a rare experimental study of sleep and AD biomarkers in humans, Ooms et al. found that sleep deprivation eliminated a normally occurring morning decrease in Aβ in CSF among middle-aged men reporting normal sleep (30*).

Xie et al. performed a provocative study in this domain (31**). They found in mice that both naturally occurring slow wave sleep (SWS) and general anesthesia increased brain interstitial space, resulting in a flushing of this space by CSF that increased clearance of exogenous Aβ that was injected into the cortex (31**). The authors proposed that sleep may serve to clear toxic metabolites such as Aβ peptides through this system.

Finally, a study examined the effect of chronic intermittent hypoxia—one of the primary consequences of SDB—on AD pathology. Shiota et al. examined the effect of hypoxia on Aβ in an AD mouse model and cultured cells (32*). *In vivo* exposure to 8 weeks of intermittent hypoxia significantly increased the amount of Aβ42 in brain tissue; it increased the proportion of neurons with intracellular Aβ but did not increase Aβ plaques. Similarly, exposure of Aβ precursor protein-expressing cells *in vitro* to intermittent hypoxia increased Aβ in the medium. Findings from these experiments support the plausibility of causal associations between poor sleep and AD biomarkers in human observational studies.

Mechanisms Linking Sleep to Poor Cognitive Outcomes or AD Pathology

Several mechanisms may account for observed associations of poor sleep with cognitive decline and AD pathology. Two recent studies suggest that sleep loss leads to neuronal damage that could mediate cognitive decline. Cross et al. used proton magnetic resonance spectroscopy (MRS), a neuroimaging technique that measures brain metabolites, to examine cross-sectional associations between the PSQI (Global Score and subscales) and N-acetylaspartate (NAA; an index of neuronal health) and myo-inositol (mI; a measure of gliosis/neuronal injury) in the hippocampus and thalamus of healthy older adults (33*). They found that poorer sleep quality and lower sleep efficiency were associated with higher mI in the hippocampus, suggesting that sleep loss may adversely affect this structure, which is central to memory. Additionally, Zhang et al. found in mice that exposure to extended wakefulness caused damage to locus ceruleus neurons that are critical to cognitive function by deactivating sirtuin type 3, a protein important to cell metabolism (34*). Conversely, brain aging may negatively affect cognition by undermining SWS. Mander et al. argued, based on relevant findings in older adults with normal cognition, that medial prefrontal cortex atrophy in this population may contribute to cognitive decline by limiting SWS and subsequently interfering with sleep-dependent memory consolidation (35).

Regarding links of sleep loss to Aβ, Xie et al. showed that SWS increases Aβ clearance from the brain, and that sleep loss may therefore enhance Aβ aggregation (31). To explain their findings linking sleep loss to changes in Aβ, Kang et al. (28) invoked findings that wakefulness increases synaptic strength, which sleep—particularly SWS—then serves to downregulate (36, 37). They referred to *in vivo* and *in vitro* studies demonstrating that increases in neuronal activity enhance Aβ production (38-40), and argued that sleep loss may alter Aβ levels through wake-related increases in synaptic strength. Further research is

needed to evaluate these mechanisms, especially the one described in a single study by Xie et al. (31).

SDB causes hypoxemia and sleep fragmentation, both of which may lead to cognitive decline and Aβ deposition. SDB interferes with sleep-dependent memory consolidation, which may mediate its effect on cognition (41). By limiting SWS, SDB may also contribute to Aβ deposition through the mechanisms described above (28, 31). Further, hypoxemia may upregulate hypoxia-inducible factor-1 (HIF-1), ultimately leading to greater cleavage of amyloid precursor protein by β- and γ-secretase and greater Aβ production (42-44). SDB and sleep loss both are associated with increases in inflammation (45, 46), which is itself associated with cognitive decline (47) and thought to contribute to AD pathology (48). Inflammation may mediate associations between sleep disturbance and both cognitive decline and AD biomarkers (16, 19).

Conclusion

Recent studies provide further support for sleep disturbance as a potential cause of cognitive decline, dementia, and AD pathology. More research is needed, including prospective human studies with objective sleep measures, AD biomarkers, and cognitive measures. While we focused on sleep as a contributor to AD, poor sleep and AD pathology likely share a synergistic relationship: poor sleep may facilitate Aβ deposition, which in turn worsens sleep, and so on (26). Population aging will dramatically increase AD prevalence (49, 50), and because no cures exist, delaying or preventing AD is imperative to reducing its burden (51). As evidence for poor sleep as an AD risk factor grows, educating clinicians about this and the importance of safely promoting healthy sleep may play a useful role in AD prevention.

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Abbreviations

Aβ	amyloid beta
AD	Alzheimer's disease
AHI	apnea-hypopnea index
APOE	apolipoprotein e
CSF	cerebrospinal fluid

ISF	interstitial fluid
mI	myo-inositol
MRS	magnetic resonance spectroscopy
NAA	N-acetylaspartate
PiB PET	Pittsburgh compound B positron emission tomography
PSG	polysomnography
PSQI	Pittsburgh Sleep Quality Index
RBD	rapid eye movement sleep behavior disorder
SD	sleep deprivation
SDB	sleep-disordered breathing
SWS	slow wave sleep
WASO	wake after sleep onset

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* of special interest

** of outstanding interest

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Key points

- Recent studies with objective and self-report sleep measures support sleep disturbance as a risk factor for cognitive decline and Alzheimer's disease in older adults.
- Observational studies in humans are beginning to identify associations between sleep parameters and Alzheimer's disease biomarkers, even among individuals without clinical dementia.
- Experimental studies suggest that sleep loss and hypoxia (a consequence of sleep-disordered breathing) affect Alzheimer's disease biomarkers.
- Maintenance of healthy sleep may be an important avenue for prevention of dementia.