

Review

Sleep Loss and Alzheimer's Disease: Mechanisms, Risk Factors, and Cognitive Consequences—A Narrative Review

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Abstract

Sleep loss is increasingly recognized as a potentially modifiable factor in cognitive aging and Alzheimer's disease (AD). Evidence supports a bidirectional relationship in which sleep disruption may both reflect early AD-related neurodegenerative changes and contribute to disease progression. This narrative review thematically synthesizes peer-reviewed evidence on the biological mechanisms, sleep-related risk factors, and cognitive consequences linking sleep and AD. Particular attention is given to glymphatic dysfunction, amyloid- β and tau pathology, circadian dysregulation, neuroinflammation, oxidative stress, impaired proteostasis, and synaptic dysfunction. The review also considers clinically relevant sleep phenotypes, including insomnia, obstructive sleep apnea, excessive daytime sleepiness, circadian rhythm disturbance, and reduced slow-wave sleep, as well as their potential effects on memory, attention, executive function, and learning. Although current evidence does not establish that sleep interventions alone can prevent AD, sleep health should be regarded as an important component of brain health, early risk assessment, and dementia risk reduction.

Keywords: sleep loss; Alzheimer's disease; dementia; amyloid-beta; tau pathology; glymphatic system; neuroinflammation; cognitive decline



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1. Introduction

Sleep is increasingly recognized as an important contributor to brain health, cognitive aging, and susceptibility to neurodegenerative disease. Current evidence supports a complex, bidirectional relationship in which sleep disruption may reflect early Alzheimer's disease (AD)-related changes while also contributing to biological processes associated with disease progression [1,2]. Sleep disturbances are common, can often be identified in routine practice and may be amenable to intervention. Sleep assessment may therefore be valuable not only for symptom management in individuals with established disease but also for risk reduction, early identification, and supportive care at different stages of neurodegeneration [1,3,4].

Alzheimer's disease is a progressive neurodegenerative disorder marked by gradual cognitive deterioration and characteristic pathological changes in the brain. Its underlying

pathology includes amyloid- β ($A\beta$) deposition, tau accumulation, synaptic dysfunction, neuroinflammation, and progressive neuronal loss, which may ultimately lead to impairments in episodic memory, executive function, behavior, daily functioning, and independence [3]. These pathological processes may develop years before the clinical onset of dementia. Sleep disturbances are also common during the preclinical and prodromal stages of AD. Symptoms such as insomnia, sleep fragmentation, excessive daytime sleepiness, and circadian rhythm disruption are frequently observed in older adults and in individuals with mild cognitive impairment (MCI) or AD, but they may also precede measurable cognitive decline [1,4]. Normal sleep supports several processes that are directly relevant to AD pathogenesis. These include memory consolidation, emotional regulation, immune and metabolic balance, synaptic remodeling, mitochondrial recovery, and removal of metabolic waste products [5]. Slow-wave sleep (SWS), also referred to as N3 sleep, is the deepest stage of non-rapid eye movement (NREM) sleep and is particularly important in this context. SWS is characterized by synchronized cortical slow oscillations and is strongly implicated in hippocampal-neocortical memory consolidation, synaptic homeostasis, and glymphatic clearance [5,6]. In a healthy brain, the alternating states of wakefulness and sleep create a rhythm between information acquisition, synaptic activity, restoration, and clearance. When sleep becomes shortened or fragmented, this balance is disturbed, potentially increasing exposure of neurons to metabolic stress and reducing the efficiency of restorative mechanisms.

Sleep architecture also changes with aging. Older adults commonly experience lighter sleep, reduced sleep efficiency, more nocturnal awakenings, earlier sleep timing, less SWS, and greater daytime sleepiness [2,7]. Although these changes are not necessarily pathological, they may increase vulnerability to age-related and neurodegenerative processes. In individuals with genetic susceptibility, vascular risk factors, depression, chronic stress, or early AD pathology, age-related changes in sleep may further increase the risk of cognitive decline, limit the brain's capacity for metabolite clearance, memory consolidation, and maintenance of cognitive health [2,6].

The relationship between sleep and AD is therefore unlikely to be explained by a single mechanism. Rather, disrupted sleep influences AD through several interacting pathways. In parallel, early $A\beta$ and tau deposition may damage sleep-wake regulatory circuits, leading to further sleep fragmentation and circadian instability. This creates a self-reinforcing cycle in which sleep loss and neurodegenerative pathology amplify each other over time [7–9].

A practical challenge in this field is that the term “sleep loss” covers several related but distinct phenomena. It may refer to reduced total sleep duration, repeated nocturnal awakenings, low sleep efficiency, reduced SWS, circadian misalignment, untreated sleep apnea, or poor subjective sleep quality [5]. These phenotypes may share common consequences, but they are not biologically identical. For example, sleep apnea is characterized by intermittent hypoxia and vascular stress, whereas insomnia often involves hyperarousal and difficulty maintaining stable sleep. Circadian disruption changes the timing of sleep and biological rhythms even when sleep duration is not severely reduced [5,7]. Recognizing this heterogeneity is essential for interpreting the literature and for translating evidence into clinical practice.

This narrative review aims to summarize and critically discuss current evidence on the relationship between sleep loss and AD, with particular emphasis on underlying biological mechanisms, sleep-related risk factors, and cognitive consequences. Sleep disturbances are common, clinically observable, and potentially modifiable. A clearer understanding of how disrupted sleep contributes to neurodegenerative vulnerability may support earlier

identification of at-risk individuals and inform preventive, diagnostic, and supportive strategies to preserve cognitive health with aging.

2. Materials and Methods

This article was designed as a narrative review. Relevant peer-reviewed literature was identified through searches of major biomedical databases, including PubMed/MEDLINE, Scopus, and Google Scholar. Search terms included combinations of: "sleep loss," "sleep deprivation," "sleep disturbance," "sleep disorders," "slow-wave sleep," "circadian rhythm," "glymphatic system," "amyloid-beta," "tau pathology," "neuroinflammation," "cognitive decline," "mild cognitive impairment," "dementia," and "Alzheimer's disease." These terms were selected to capture both clinical sleep disorders and mechanistic pathways that may connect sleep disruption with AD biology.

Priority was given to recent reviews, systematic reviews, meta-analyses, umbrella reviews, clinical studies, and experimental studies published mainly between 2016 and 2026. Older foundational studies were also included when they were considered important for explaining core mechanisms, such as amyloid- β dynamics, tau pathology, glymphatic clearance, sleep architecture, synaptic plasticity, and autophagy. Articles were selected based on their relevance to the topic, scientific quality, and contribution to the conceptual understanding of the sleep-AD relationship. Because the aim was interpretative synthesis rather than quantitative estimation, the emphasis was placed on studies that clarified mechanisms, clinical associations, risk groups, or cognitive outcomes.

The evidence was organized thematically rather than quantitatively. First, mechanisms linking sleep loss to Alzheimer's disease were grouped into major biological domains, including A β accumulation, tau pathology, glymphatic dysfunction, circadian rhythm disruption, neuroinflammation, oxidative stress, synaptic dysfunction, and impaired autophagy. Second, epidemiological and clinical evidence was summarized to identify sleep-related risk factors and vulnerable populations. Finally, studies addressing cognition were integrated to explain how insufficient or disrupted sleep may contribute to deficits in memory, attention, executive function, and progression toward cognitive impairment.

Because this is a narrative review, no formal systematic review protocol, PRISMA-based selection process, meta-analysis, or structured risk-of-bias assessment was performed. Instead, the review provides an interpretative synthesis of the available evidence and highlights clinically relevant mechanisms and implications for prevention, early detection, and supportive management. Figure 1 and graphical abstract were generated using OpenAI's AI image-generation tool and subsequently reviewed and edited by the authors for scientific accuracy.

3. Mechanisms Linking Sleep Loss to Alzheimer's Disease

3.1. Amyloid- β Accumulation

A β accumulation is a central event in AD and reflects an imbalance between production, aggregation, and clearance [8,9]. A β peptides are generated from amyloid precursor protein through sequential enzymatic cleavage, and aggregation-prone species, particularly A β 42, can oligomerize and form extracellular plaques. Although plaques are the most visible neuropathological feature, soluble A β oligomers are considered especially neurotoxic because they impair synaptic transmission and long-term potentiation, promote oxidative stress, and activate inflammatory responses [10,11]. The sleep-wake cycle may influence this process because neuronal activity, interstitial metabolite concentrations, and clearance efficiency differ between wakefulness and sleep.

Sleep loss may contribute to A β accumulation through converging mechanisms. Wakefulness is associated with higher neuronal and synaptic activity, which can enhance interstitial A β release, whereas sleep, especially NREM sleep and SWS, supports the clearance of extracellular metabolites [12,13]. During consolidated sleep, slow oscillations are linked to coordinated neural, vascular, and cerebrospinal fluid dynamics that facilitate metabolite removal [13–16]. Consequently, when sleep is shortened or fragmented—especially regarding the depletion of slow-wave activity—the physiological window for removing extracellular A β is significantly compromised. Sustained disruption of these clearance dynamics may facilitate the accumulation and oligomerization of soluble amyloid peptides, ultimately accelerating the development of amyloid plaques.

This relationship is supported by both clinical and experimental research. Studies in humans demonstrate that acute sleep deprivation elevates A β burden or disrupts normal A β dynamics, while sleep loss has been shown to increase A β levels within brain cerebrospinal fluid (CSF) and interstitial fluid [16–19]. Furthermore, sleep deprivation in mouse models of AD can accelerate the accumulation of A β , impair sleep microarchitecture, and lead to maladaptive recovery sleep [17]. These observations indicate that sleep disturbances do not simply co-occur alongside amyloid pathology but instead may actively drive early molecular alterations. Conversely, the accumulation of amyloid may damage the neural networks that control sleep, resulting in diminished sleep quality and a subsequent reduction in clearance efficiency. Therefore, amyloid biology illustrates a clear bidirectional feedback loop operating between AD pathology and sleep quality.

3.2. *Tau Pathology*

As a key neuropathological feature of Alzheimer's disease (AD), tau pathology demonstrates a stronger correlation with cognitive deterioration and neuronal impairment than amyloid plaque accumulation [20]. The microtubule-associated protein tau is responsible for maintaining the stability of axonal transport and neuronal microtubules under physiological conditions. Pathological transformations cause tau to undergo abnormal phosphorylation, detach from microtubules, misfold, and form paired helical filaments that aggregate into neurofibrillary tangles. These alterations severely compromise cytoskeletal structure, synaptic transmission, axonal transport, and intercellular communication [21]. Given that tau pathology propagates through interconnected anatomical networks, variations in extracellular tau secretion and neuronal activity significantly impact the course of the disease [21,22].

The progression of AD is heavily influenced by this factor, and it appears that it may be driven by both immediate and long-term consequences of sleep loss. During periods of wakefulness, elevated neuronal activity triggers a corresponding rise in the extracellular release of tau. Consequently, sleep deprivation can elevate tau concentrations within the interstitial fluid and cerebrospinal fluid, a shift that may enhance the propagation of pathological tau throughout interconnected neural networks [22,23]. This mechanism is highly critical because tau pathology typically advances along a well-defined anatomical pathway, initiating in medial temporal structures like the entorhinal cortex and hippocampus prior to spreading into association cortices. Because these specific brain regions are vital for supporting spatial orientation, episodic memory, higher cognitive processing, and semantic function, repeated sleep disturbances that increase extracellular tau availability might actively accelerate the spread of neurodegeneration through networks crucial for maintaining cognitive health [24].

Clinical evidence further links sleep disruption to alterations in tau-related biomarkers. Acute sleep deprivation has been associated with changes in total and phosphorylated tau concentrations in cerebrospinal fluid and plasma, while recurrent sleep loss may promote tau phosphorylation through oxidative stress, neuroinflammation, kinase dysregulation, and impaired proteostasis [22,25,26]. Reduced NREM sleep and lower slow-wave activity have also been associated with greater tau pathology in older adults and individuals at increased risk of AD [27]. These findings indicate that sleep architecture, rather than sleep duration alone, may be particularly relevant to tau-related neurodegeneration and cognitive decline.

This relationship is also bidirectional. Tau deposition within sleep-wake regulatory regions, including the locus coeruleus, basal forebrain, hypothalamus, and brainstem, may contribute to sleep fragmentation and disruption of SWS and REM sleep [28–30]. Degeneration of arousal- and sleep-regulating neurons can destabilize transitions between sleep and wakefulness, increase nocturnal awakenings, and promote daytime sleepiness. In turn, impaired sleep continuity may reduce tau clearance and synaptic recovery, thereby perpetuating the interaction between tau pathology and sleep disturbance.

3.3. Glymphatic Dysfunction

The glymphatic system is a glia-dependent, brain clearance network that facilitates cerebrospinal fluid (CSF) influx along periarterial spaces, exchange with interstitial fluid (ISF) within the brain parenchyma, and subsequent solute efflux through perivenous and meningeal lymphatic pathways. This system contributes to the removal of A β , tau, and other potentially neurotoxic metabolites. Its efficiency depends on arterial pulsatility, the structural integrity of perivascular spaces, and the polarized expression of aquaporin-4 (AQP4) channels at astrocytic endfeet [31–35]. Glymphatic transport is functionally linked to meningeal lymphatic drainage toward the deep cervical lymph nodes, indicating that cerebral waste clearance is mediated by an integrated glymphatic-meningeal lymphatic axis rather than by a single isolated pathway [32,33]. This clearance network is highly relevant to AD, as its dysfunction may favor the retention of soluble A β and tau, promote neuroinflammation and vascular injury, and contribute to progressive disruption of cerebral homeostasis [35].

Glymphatic activity is strongly modulated by sleep and appears to be most efficient during NREM sleep, particularly during SWS. During this state, reduced noradrenergic tone, coordinated neural and vascular oscillations, and lower resistance to fluid movement are thought to facilitate CSF-ISF exchange [13,31,34]. Sleep loss may impair this process through several converging mechanisms. Prolonged wakefulness reduces the time spent in the physiological state most conducive to clearance, whereas sleep fragmentation and reduced SWS may disrupt the oscillatory dynamics that support perivascular fluid transport. Aging, vascular stiffening, diminished arterial pulsatility, inflammation, blood-brain barrier dysfunction, circadian disruption, and loss of perivascular AQP4 polarization may further compromise glymphatic efficiency [31–35]. Accordingly, sleep duration alone may not adequately reflect clearance capacity, as apparently sufficient sleep may remain physiologically ineffective when it is fragmented, shallow, or deficient in slow-wave activity.

Experimental evidence indicates that cerebral clearance depends on sleep architecture and quality, not only duration. In AD models, impaired recovery sleep and abnormal norepinephrine oscillations are associated with reduced clearance and greater A β accumulation [17]. Glymphatic dysfunction may also contribute to a self-reinforcing cycle in which impaired removal promotes A β and tau accumulation, while protein deposition, astrocytic dysfunction, neuroinflammation, and vascular remodeling further disrupt CSF-ISF exchange [32,33,35].

Human studies also support the role of sleep in glymphatic clearance. In cognitively healthy adults, normal sleep was associated with higher morning plasma A β and tau concentrations than sleep deprivation, consistent with greater overnight transport from the brain to the circulation [36]. However, human evidence remains limited and largely indirect. Glymphatic dysfunction should therefore be considered a plausible and potentially modifiable component of AD pathophysiology, although its causal role requires confirmation in longitudinal and interventional studies.

3.4. Circadian Rhythm Disruption

Synchronization of environmental cues, particularly light, with the suprachiasmatic nucleus allows the circadian system to coordinate daily rhythms in hormone secretion, body temperature, immune function, metabolism, sleep-wake regulation, and neuronal activity. Both aging and progressive neurodegeneration weaken this temporal framework, resulting in characteristic signs such as nighttime wakefulness, fragmented rest patterns, lowered daytime vitality, and severe diurnal somnolence [37–39]. Clinically, individuals diagnosed with AD frequently manifest this internal misalignment through flattened amplitudes in their rest-activity cycles, irregular schedules, frequent daytime napping, and heightened agitation during the evening hours [40].

Circadian disruption may promote AD pathology by disturbing the daily regulation of A β and tau metabolism, reducing melatonin signaling, increasing oxidative stress, altering immune responses, and impairing glymphatic clearance [37,40]. Circadian rhythms help organize physiological processes into appropriate time windows. When these rhythms are weakened or misaligned, metabolic and inflammatory signals may occur at inappropriate times, and sleep may become less consolidated. This may reduce the restorative value of sleep even when total sleep time appears adequate.

Human studies suggest that fragmented rest-activity rhythms may precede MCI or dementia and are associated with subsequent A β pathology and poorer cognitive outcomes [40,41]. Irregular sleep timing and poor sleep continuity have also been linked to reduced hippocampal volume and poorer cognition in older adults [42]. These findings support circadian abnormalities as potential early markers of AD risk rather than merely late symptoms of dementia. From a clinical standpoint, evaluating circadian function is essential because targeted interventions, such as optimizing light exposure, maintaining consistent sleep-wake cycles, engaging in physical activity, and establishing structured daytime routines, can help stabilize biological rhythms in vulnerable individuals.

3.5. Neuroinflammation and Glial Activation

Neuroinflammation is another pathway through which sleep disruption may contribute to AD progression. Sleep loss can activate microglia and astrocytes, shifting these cells from homeostatic functions toward pro-inflammatory signaling and increased cytokine release, with adverse effects on synapses and neurons [43–45]. Inflammation may therefore act not only as a consequence of pathology but also as a mediator of responses to A β , tau, oxidative stress, and synaptic injury.

Microglial activation contributes to A β clearance and the removal of damaged cellular material. Although this response may initially be protective, persistent or dysregulated activation can impair the process, promote excessive synaptic pruning, and increase inflammatory signaling and neuronal injury. NF- κ B and NLRP3 inflammasome pathways are implicated in this transition [46]. Sleep loss may therefore favor a shift from adaptive immune surveillance toward chronic neuroinflammation that supports neurodegeneration.

Astrocytes link sleep and AD through their roles in synaptic regulation, metabolic support, blood-brain barrier integrity, and AQP4-dependent glymphatic clearance [47]. Sleep loss may impair these functions, reducing waste removal and increasing inflammatory stress. Interactions between astrocytes and microglia may further disrupt glial maintenance of neuronal homeostasis and repair. AD should therefore be understood not only as a disorder of protein aggregation but also as a disease of altered neuronal-glial communication [44,47].

3.6. Oxidative Stress, Synaptic Dysfunction, and Impaired Plasticity

Sleep loss may increase oxidative stress by disrupting the balance between reactive oxygen species and antioxidant defenses [48]. Neurons are particularly susceptible because of their high metabolic demands, lipid-rich membranes, and reliance on mitochondrial function. Sleep supports cellular repair, metabolic regulation, and antioxidant activity; recurrent deprivation may therefore damage proteins, lipids, mitochondrial enzymes, and DNA, increasing susceptibility to neurodegeneration [48–50].

Mitochondrial dysfunction is likely to mediate these effects. Sleep deprivation can reduce mitochondrial efficiency, impair ATP production, and increase reactive oxygen species, thereby compromising synaptic transmission and plasticity [49,50]. The hippocampus and prefrontal cortex are particularly affected because of their roles in memory, attention, working memory, and executive function [51,52]. In AD, sleep loss may further reduce the functional reserve of these regions, increasing the likelihood that underlying pathology becomes clinically apparent.

Sleep loss can disrupt synaptic homeostasis. During normal sleep, synaptic strength is recalibrated after wake-related activity [53]. Experimental studies indicate that sleep deprivation impairs long-term potentiation, alters dendritic spine density, and disrupts signaling required for synaptic function [51,54]. These changes may underlie deficits in learning, attention, and executive control. With aging or AD-related pathology, repeated impairment of synaptic plasticity may have cumulative effects, limiting memory consolidation and maintaining neural networks in a state of metabolic and synaptic stress.

3.7. Autophagy and Proteostasis

Autophagy is a key intracellular degradation pathway that removes damaged organelles, misfolded proteins, and protein aggregates, thereby maintaining neuronal proteostasis [55]. Neurons are especially dependent on these mechanisms because of their longevity, high metabolic activity, and limited regenerative capacity. Inefficient removal of damaged cellular components can therefore increase cellular stress and compromise synaptic function [56].

Sleep loss may further impair proteostasis by increasing metabolic and oxidative stress while reducing intracellular protein clearance. This process complements glymphatic dysfunction: autophagy removes damaged intracellular components, whereas the glymphatic system clears extracellular waste. Disruption of both pathways may create a combined burden of increased metabolite production and reduced clearance, thereby compromising neuronal homeostasis.

Experimental evidence suggests that autophagic dysfunction in sleep-wake regulatory circuits may emerge early in AD. In AD mouse models, sleep disruption preceded advanced cognitive impairment and was associated with autophagic burden in the hypothalamus and locus coeruleus [57]. Experimental enhancement of autophagy improved recovery sleep, indicating that the sleep-autophagy axis may represent a potential therapeutic target [57]. Table 1 summarizes the main mechanisms that link sleep loss to AD.

Table 1. Main mechanisms linking sleep loss to Alzheimer's disease.

Mechanism	Effect of Sleep Loss	Relevance to Alzheimer's Disease	Cognitive/Clinical Consequence
Amyloid- β accumulation	Reduced clearance, increased interstitial A β	Promotes amyloid plaque formation	Higher AD vulnerability
Tau pathology	Increased extracellular tau and phosphorylation	Facilitates tau spread and neuronal dysfunction	Memory decline
Glymphatic dysfunction	Reduced waste clearance during disrupted sleep	Impaired removal of A β and tau	Neurodegenerative burden
Circadian disruption	Altered sleep-wake timing and hormonal rhythms	May precede MCI/dementia	Poorer cognitive outcomes
Neuroinflammation	Microglial and astrocytic activation	Synaptic and neuronal injury	Cognitive impairment
Oxidative stress and synaptic dysfunction	Mitochondrial stress, impaired plasticity	Reduced hippocampal/prefrontal function	Impaired memory and executive function
Impaired autophagy/proteostasis	Reduced clearance of damaged proteins	Protein aggregation	Disease progression

4. Risk Factors and Vulnerable Groups

Several sleep-related conditions may increase the risk of AD or serve as early indicators of cognitive and neurodegenerative change. Although different sleep disorders may share consequences such as sleep fragmentation, impaired metabolic clearance, inflammation, and poorer cognition, they represent distinct phenotypes with different underlying mechanisms and clinical implications. Their effects should therefore not be generalized or interpreted solely according to total sleep duration.

Insomnia is characterized by persistent difficulty initiating or maintaining sleep, early-morning awakening, or non-restorative sleep accompanied by daytime impairment. Meta-analytic evidence associates insomnia with an increased risk of dementia and AD, although estimates vary according to study design, symptom definition, and insomnia subtype. Insomnia may contribute to cognitive decline through physiological and cognitive hyperarousal, increased sympathetic and hypothalamic-pituitary-adrenal axis activity, reduced sleep continuity, and loss of restorative NREM sleep. Persistent insomnia also frequently coexists with depression, anxiety, chronic stress, pain, cardiometabolic disease, and medication use, which may independently influence cognition and confound the observed relationship with dementia [58,59]. Evidence is particularly heterogeneous when insomnia is defined only by subjective symptoms, suggesting that insomnia accompanied by objectively short sleep duration may represent a biologically distinct and potentially higher-risk phenotype [59].

OSA has a different pathophysiological profile. Recurrent upper-airway obstruction produces intermittent hypoxia, repeated arousals, intrathoracic pressure changes, sympathetic activation, oxidative stress, endothelial dysfunction, and vascular injury. These processes may impair attention and executive function while also promoting blood-brain barrier disruption, neuroinflammation, cerebral small-vessel disease, and reduced clearance of A β and tau [60,61]. Meta-analytic and biomarker studies suggest that OSA is associated with increased risk of cognitive impairment and AD, although the strength of this association varies and many studies have not used polysomnography to confirm the diagnosis [61,62]. OSA may therefore affect cognition through both neurodegenerative and vascular pathways, distinguishing it from insomnia-related hyperarousal. Continuous pos-

itive airway pressure may improve sleepiness and some cognitive outcomes, but evidence that it modifies AD biomarkers or slows disease progression remains insufficient, particularly because adherence is variable and long-term randomized studies are limited [62].

Circadian rhythm disruption refers to weakened, irregular, or misaligned timing of sleep-wake behavior and other physiological rhythms. It may occur even when total sleep duration is apparently adequate. Reduced daytime light exposure, irregular routines, shift work, low physical activity, and age-related weakening of the suprachiasmatic system may diminish circadian amplitude and alter the temporal regulation of melatonin, metabolism, immune activity, and A β and tau dynamics. In older adults and individuals with AD, circadian disruption may manifest as irregular sleep timing, increased daytime napping, nocturnal wakefulness, reduced daytime activity, or evening behavioral disturbance. Rest-activity rhythm abnormalities may precede overt cognitive symptoms, although they may also reflect early degeneration of circadian and arousal-regulating networks. Circadian instability should therefore be regarded as both a possible risk marker and a potential consequence of neurodegeneration rather than as an interchangeable measure of insufficient sleep [63,64].

Excessive daytime sleepiness is best considered a clinical manifestation rather than a single sleep disorder. It may result from OSA, insufficient or fragmented sleep, sedating medications, depression, circadian dysregulation, or early degeneration of wake-promoting neural systems. Longitudinal studies have associated persistent or emerging daytime sleepiness with greater dementia risk and increased cerebral A β accumulation, but reverse causation remains a major concern because early AD pathology may itself impair arousal networks [65–67]. Excessive daytime sleepiness should therefore prompt investigation of its underlying cause rather than being interpreted independently as a direct causal factor for AD.

Reduced SWS represents a sleep-structure phenotype that may occur with aging, insomnia, OSA, or neurodegenerative disease. Reduction in SWS may therefore impair restorative sleep even when total sleep duration is within the recommended range. Prospective evidence has linked greater loss of SWS with incident dementia, while experimental studies suggest alteration of A β and tau dynamics [6,16,27]. Unlike OSA, reduced SWS does not necessarily involve intermittent hypoxia, and unlike insomnia, it may remain clinically unrecognized without polysomnography or validated physiological monitoring. This distinction reinforces the importance of assessing sleep quality and structure rather than relying exclusively on self-reported sleep duration.

These phenotypic differences have implications for individualized risk assessment and prevention. Evaluation should identify the predominant disturbance and its likely mechanism: hyperarousal and maladaptive sleep behavior in insomnia; intermittent hypoxia and vascular stress in OSA; temporal misalignment in circadian disorders; an underlying sleep, medical, or neurological cause in excessive daytime sleepiness; and impaired restorative sleep in reduced SWS. Management should then be phenotype-specific, including cognitive behavioral therapy for insomnia, diagnostic sleep testing and appropriate respiratory therapy for suspected OSA, structured light exposure and regular activity-sleep schedules for circadian disruption, and investigation of reversible causes of daytime sleepiness. In older adults, treatment decisions should also account for frailty, multimorbidity, medication burden, vascular risk, mood symptoms, and cognitive status [68,69]. Sleep assessment is therefore most appropriately incorporated into a broader, individualized dementia risk-reduction strategy rather than treated as a uniform or isolated exposure. The principal sleep-related risk factors differ in their underlying mechanisms and should not be interpreted as interchangeable exposures. Their main characteristics and clinical implications are summarized in Table 2.

Table 2. Main sleep-related risk factors and their relevance to AD.

Sleep-Related Factor	Predominant Mechanisms	Relevance to AD and Cognitive Decline	Clinical Assessment or Management
Insomnia	Hyperarousal, reduced sleep continuity, loss of restorative NREM sleep, stress-system activation	Associated with increased risk of cognitive decline and dementia, although findings vary by insomnia subtype and measurement method	Clinical history, validated questionnaires, sleep diary, CBT-I
Obstructive sleep apnea	Intermittent hypoxia, repeated arousals, oxidative stress, endothelial dysfunction, vascular injury	May contribute to cognitive impairment through both neurodegenerative and vascular pathways	Polysomnography or home sleep testing; positive airway pressure therapy when indicated
Circadian rhythm disruption	Circadian misalignment, reduced melatonin signaling, altered metabolic and immune rhythms	May precede cognitive symptoms or reflect early degeneration of circadian regulatory networks	Actigraphy, sleep-wake diary, assessment of light exposure and daily routines
Excessive daytime sleepiness	Fragmented sleep, sleep apnea, medication effects, depression, circadian dysfunction, degeneration of arousal systems	Associated with dementia risk, but reverse causation is an important concern	Investigation of underlying sleep, neurological, psychiatric, and medication-related causes
Reduced slow-wave sleep	Impaired restorative sleep, reduced synaptic recovery, altered metabolite clearance	Associated with changes in A β and tau dynamics and with incident cognitive impairment	Polysomnography or validated physiological monitoring
Short or fragmented sleep	Increased wake-related neuronal activity, reduced clearance, impaired memory consolidation	May increase susceptibility to cognitive decline, particularly when persistent	Sleep history, actigraphy, sleep diary, assessment of contributing disorders
Shift work or irregular sleep timing	Circadian misalignment, chronic sleep restriction, metabolic and vascular stress	Potential contributor to long-term cognitive and cardiometabolic risk	Occupational history, stabilization of sleep timing, light and activity scheduling
Vulnerable populations	Genetic susceptibility, vascular risk, depression, multimorbidity, frailty, low cognitive reserve	May modify the effect of sleep disturbance on cognitive outcomes	Individualized multidomain risk assessment

5. Cognitive Consequences of Sleep Loss

Sleep loss affects cognition through both immediate neurophysiological disruption and longer-term changes in neural plasticity and brain integrity. Acute sleep deprivation impairs alertness, sustained attention, processing speed, working memory, inhibitory control, reasoning, and decision-making [52,68]. Performance is particularly affected in vigilance and executive tasks, with slower reaction times, reduced accuracy, and greater intra-individual variability. Repeated partial sleep restriction may produce cumulative deficits and attenuate the performance gains normally associated with practice and learning, even when the degree of sleep loss appears modest [52,68]. The magnitude of these effects varies across individuals and may be influenced by age, genetic factors, baseline brain structure, cognitive reserve, and the duration and pattern of sleep disruption [69–71].

Sleep disruption can impair both memory encoding and post-learning consolidation, thereby affecting episodic and spatial memory, associative learning, and the acquisition of new information [51,53,54,69]. Experimental evidence further indicates that sleep deprivation disrupts hippocampal synaptic plasticity, reduces dendritic spine density, and interferes with the formation and maintenance of learning-related synaptic connections [51,54,69]. These alterations overlap with cognitive domains affected during the early stages of MCI and AD. Consequently, insufficient or fragmented sleep may produce cognitive symptoms that resemble early neurodegeneration while also potentially contributing to its progression.

In older adults, observational studies have linked poor sleep efficiency, prolonged sleep latency, nocturnal awakenings, irregular rest-activity patterns, and excessive daytime napping with poorer memory, executive function, and processing speed [68]. However, findings vary according to whether sleep is assessed by self-report, actigraphy, or polysomnography, and total sleep duration alone is not consistently associated with cognitive performance. Sleep continuity and architecture may therefore provide more informative measures than time spent asleep. Age-related differences in the cognitive response to sleep loss have also been reported, although results are inconsistent and may partly reflect compensatory effort, task characteristics, baseline cognitive ability, or survivor bias [68,69].

Sleep-related cognitive changes are also associated with structural and functional alterations in the brain. Reduced SWS has been linked to lower cortical and subcortical gray matter volumes, greater white matter hyperintensity burden, and an increased risk of incident dementia [6]. Sleep deprivation may further impair long-term potentiation, synaptic homeostasis, and functional connectivity within hippocampal, prefrontal, and frontoparietal networks that support memory, attention, and executive control [51,54,69,70]. Although evidence from developmental studies cannot be directly extrapolated to older adults, it demonstrates that prolonged sleep disruption can interfere with the maturation and organization of prefrontal networks, underscoring the broader importance of sleep for maintaining neural circuitry across the lifespan [70].

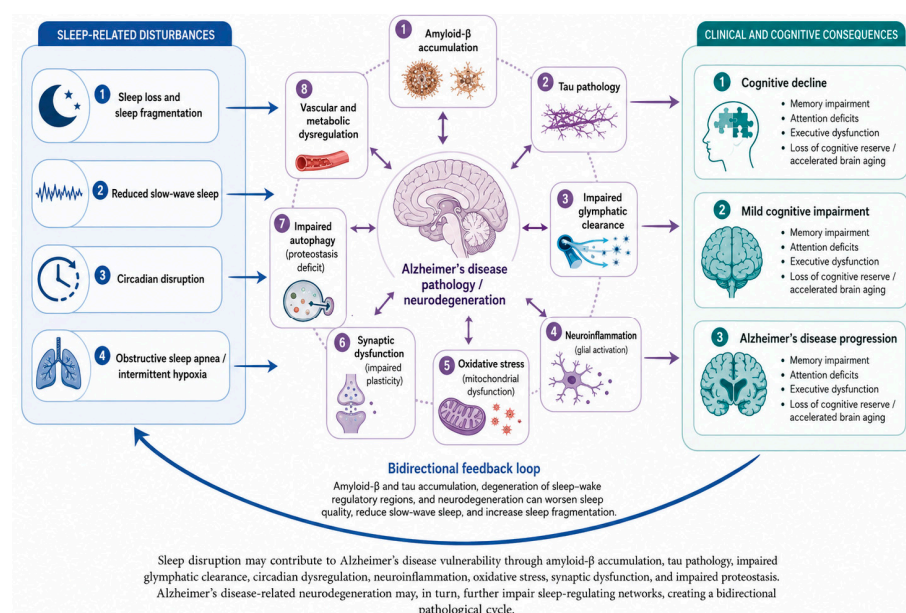
Cognitive reserve may partly explain why individuals exposed to comparable sleep disturbances show different levels of cognitive impairment. Educational attainment, occupational complexity, intellectually stimulating activities, and other reserve-related factors may support more efficient or flexible use of neural networks when sleep or neuropathological changes compromise brain function [71]. Available evidence suggests that higher cognitive reserve may attenuate the cognitive effects of reduced SWS, disturbed sleep continuity, and sleep disorders such as obstructive sleep apnea. Conversely, healthy sleep may itself contribute to the maintenance of cognitive reserve. However, the evidence remains limited and heterogeneous, and cognitive reserve should be regarded as a potential moderator rather than as complete protection against the effects of chronic sleep disruption or AD pathology [70,71].

The clinical course of sleep-related cognitive impairment depends on its duration, underlying cause, and interaction with age-related and pathological processes. Cognitive deficits following acute sleep deprivation are often transient and may improve after adequate recovery sleep. In contrast, chronic sleep fragmentation or recurrent sleep restriction, particularly in older adults with vascular risk factors, reduced cognitive reserve, or preclinical AD pathology, may be associated with more persistent decline. Recovery sleep may not fully reverse the effects of repeated disruption when sleep architecture remains abnormal or when molecular and structural changes have already developed [69]. Interindividual variation should also be considered, as sensitivity to sleep loss differs substantially [70]. Sleep loss affects several interrelated cognitive domains, although the magnitude and persistence of impairment vary according to age, baseline cognitive function, sleep phenotype, and duration of disruption. The main effects are summarized in Table 3.

Table 3. Cognitive consequences of sleep loss.

Cognitive Domain	Typical Effects of Sleep Loss	Potential Mechanisms	Clinical Relevance
Attention and vigilance	Slower reaction time, lapses in attention, reduced accuracy, greater performance variability	Reduced cortical alertness and impaired arousal regulation	May affect daily safety, driving, medication use, and task completion
Working memory	Reduced ability to retain and manipulate information	Prefrontal dysfunction and impaired network connectivity	May resemble early executive impairment
Episodic memory	Impaired encoding, consolidation, and retrieval of newly learned information	Hippocampal dysfunction, reduced SWS, impaired synaptic plasticity	Overlaps with cognitive domains affected early in MCI and AD
Executive function	Reduced inhibition, planning, reasoning, cognitive flexibility, and decision-making	Prefrontal cortical dysfunction and disrupted frontoparietal networks	May impair independence and complex daily activities
Learning	Slower acquisition and reduced benefit from repeated practice	Impaired long-term potentiation and synaptic remodeling	Repeated sleep restriction may produce cumulative deficits
Processing speed	Slower responses and reduced efficiency	Reduced alertness and impaired neural communication	Can worsen performance across multiple cognitive tasks
Emotional and behavioral regulation	Irritability, poorer emotional control, increased stress reactivity	Disrupted prefrontal-limbic regulation	May indirectly worsen cognitive performance and quality of life
Long-term cognitive trajectory	Greater risk of cognitive decline in some longitudinal studies	Interaction among sleep fragmentation, vascular injury, inflammation, and neurodegenerative pathology	Associations are clinically relevant but do not by themselves establish causality

From a clinical perspective, sleep complaints should neither be dismissed as nonspecific consequences of aging nor interpreted automatically as evidence of dementia. Careful assessment is required to determine whether cognitive symptoms are related to insufficient sleep, insomnia, sleep-disordered breathing, circadian disruption, medication use, depression, an underlying neurodegenerative process, or a combination of these factors. Identification and treatment of modifiable sleep disturbances may improve quality of life, although evidence that such interventions prevent AD or alter its progression remains insufficient [71]. The resulting bidirectional relationship is summarized in Figure 1.

**Figure 1.** Bidirectional relationship between sleep loss and Alzheimer's disease pathology.

6. Clinical and Preventive Implications

Sleep health should be regarded as an integral component of cognitive health. In clinical practice, sleep concerns in middle-aged and older adults warrant systematic assessment, particularly when they coexist with cognitive symptoms, mood disorders, cardiometabolic disease, vascular risk factors, or a family history of dementia. More precise sleep phenotyping may improve risk assessment and treatment selection, because different phenotypes are not biologically equivalent and are unlikely to respond to the same intervention. Their distinction may therefore support more individualized prevention and management strategies [72,73]. A comprehensive sleep history should include sleep duration and timing, sleep-onset latency, nocturnal awakenings, snoring or witnessed apneas, daytime sleepiness, napping, variability in sleep schedules, and the use of caffeine, alcohol, prescribed medications, over-the-counter preparations, and other substances. Information provided by family members or care partners may be particularly valuable when cognitive impairment limits the reliability of self-report [73].

Validated instruments can complement clinical assessment. The Insomnia Severity Index and Pittsburgh Sleep Quality Index may be used to characterize insomnia symptoms and perceived sleep quality, whereas the Epworth Sleepiness Scale assesses subjective daytime sleepiness [74–76]. The STOP-Bang questionnaire may help identify individuals at increased risk of obstructive sleep apnea, although screening results require confirmation through appropriate diagnostic evaluation [77]. Sleep diaries provide prospective information on sleep timing, continuity, and variability, while actigraphy can support the assessment of sleep-wake patterns and circadian rhythm disturbances [78,79]. Polysomnography is indicated when sleep-disordered breathing is suspected and may also be appropriate in selected cases involving periodic limb movements, atypical or potentially harmful parasomnias, or clinically relevant alterations in sleep architecture [80]. The choice of assessment method should be guided by the predominant sleep phenotype, cognitive status, comorbidities, accessibility, and the individual's ability to complete the procedure.

Management should target the underlying sleep disorder rather than sleep duration alone. Interventions may include sleep-related education, regular sleep-wake schedules, appropriately timed light exposure, physical activity, and treatment of coexisting depression or anxiety [81]. Cognitive behavioral therapy for insomnia (CBT-I) is recommended as a first-line treatment and can be delivered in person, digitally, or via telehealth. A 2026 randomized controlled trial showed that a seven-week app-based program significantly reduced insomnia severity, improved sleep continuity, and achieved remission in 48% of participants compared with 18% of controls [82]. However, the study focused on adults with subthreshold to moderate insomnia and did not evaluate AD-related outcomes.

Cognitive behavioral therapy for insomnia (CBT-I) may also support clinically supervised reduction in sleep-related medications and substances. In a 2026 retrospective cohort study, telehealth CBT-I combined with individualized gradual dose reduction improved insomnia symptoms, sleep quality, and sleep efficiency, while decreasing use of several sedative medications and substances [83]. The results are encouraging, although the observational design limits conclusions about causality.

OSA requires a distinct treatment pathway because its effects are mediated not only by sleep fragmentation but also by intermittent hypoxia, sympathetic activation, oxidative stress, inflammation, and vascular injury [72]. Continuous positive airway pressure (CPAP) remains the standard treatment for clinically significant OSA and may improve sleep continuity, oxygenation, daytime alertness, and cardiovascular outcomes. Preliminary evidence also suggests potential cognitive benefits in people with AD-related mild cognitive impairment and OSA, although these findings should be interpreted cautiously [84].

Circadian rhythm disturbance should be addressed through regular sleep-wake timing, appropriately timed light exposure, daytime physical activity, and reduction in prolonged or irregular daytime napping [72,73]. Management may also require modification of environmental cues and daily routines, particularly for people living with MCI or dementia. Interventions should be adapted to individual sensory, mobility, occupational, cultural, and caregiving circumstances. For people with more advanced cognitive impairment, simple and consistent routines may be more feasible than complex behavioral programs.

Pharmacological sleep aids should be used cautiously in older adults because sedative medications may impair cognition, increase fall risk, and alter sleep architecture [85]. These risks may be greater in people living with MCI or dementia because of reduced cognitive reserve, frailty, polypharmacy, and altered drug metabolism. Non-pharmacological interventions are therefore generally preferable as first-line strategies when possible. When medication is required, treatment should be individualized, reviewed regularly, and directed toward the underlying sleep disorder rather than limited to symptom suppression. Abrupt discontinuation of long-term hypnotic medication should be avoided, and gradual dose reduction should be coordinated with the prescribing clinician [83,85].

Nutritional and anti-inflammatory approaches, including omega-3 fatty acids, have been proposed as adjunctive strategies because of their potential effects on neuroinflammation, synaptic function, and amyloid processing [86,87]. However, current evidence does not establish these approaches as treatments for insomnia or as effective interventions for preventing AD. Their role should therefore be presented cautiously and considered within a broader strategy that includes sleep regularity, physical activity, cardiovascular and metabolic risk management, social and cognitive engagement, and treatment of mood disorders [87].

Sleep disturbance should neither be interpreted as evidence of AD nor presented as a single causal determinant of dementia. Current intervention studies primarily support improvements in insomnia symptoms, sleep quality, daytime functioning, and selected cognitive outcomes. Evidence that sleep treatment prevents AD or slows established neurodegeneration remains limited. Sleep optimization is therefore best incorporated into an individualized, multidomain approach to cognitive health [82–84].

7. Limitations

This review has several limitations. As a narrative review, it did not follow a prospectively registered protocol, PRISMA-based selection process, quantitative synthesis, or structured assessment of risk of bias and evidence certainty. Study selection was guided by relevance to the conceptual synthesis, and selection bias cannot be excluded. The findings should therefore be interpreted as a critical integrative overview rather than as a definitive causal or quantitative estimate of the association between sleep loss and AD. Although this approach allows integration of experimental, biomarker, epidemiological, and clinical evidence, it does not permit pooled effect-size calculation or formal comparison of evidence certainty across outcomes.

The evidence base is also methodologically heterogeneous. Studies differ in design, population characteristics, follow-up duration, definitions of sleep loss, and AD-related outcomes. Sleep has been assessed using different methods, while outcomes range from short-term cognitive performance to cerebrospinal fluid biomarkers, neuroimaging findings, mild cognitive impairment, and dementia. These measures are not interchangeable and may reflect distinct biological processes. Moreover, sleep disorders involve overlapping but different mechanisms. Generalizing across these phenotypes may therefore obscure clinically relevant differences in risk and treatment response.

The strength of evidence also varies across mechanisms. Several biomarker studies examined the effects of one night or a brief period of experimentally induced sleep deprivation on amyloid- β or tau concentrations [16,18,22,25]. Although these studies demonstrate acute biological responsiveness, they cannot establish that transient changes lead to sustained protein accumulation, neurodegeneration, or clinically manifest AD. Likewise, much of the evidence regarding glymphatic dysfunction, glial activation, autophagic impairment, and disruption of sleep-regulating circuits derives from animal models or experimental settings [13,17,31,39,52]. Their relevance to chronic, naturally occurring sleep disturbances in heterogeneous aging populations therefore remains uncertain.

Causal direction is difficult to determine. Cross-sectional studies cannot establish whether sleep disturbance precedes AD pathology or reflects early neurodegeneration. Prospective studies improve temporal inference but remain vulnerable to reverse causation, as amyloid and tau pathology may begin years before cognitive symptoms and disrupt the locus coeruleus, basal forebrain, hypothalamic, and brainstem systems involved in sleep-wake regulation [28–30]. Sleep disturbance may therefore act simultaneously as a risk marker, an early manifestation of disease, and a potential contributor to further progression, supporting a bidirectional rather than strictly unidirectional model.

Residual confounding is another concern. Sleep disturbances commonly coexist with depression, anxiety, chronic stress, pain, obesity, diabetes, hypertension, cardiovascular disease, medication use, reduced physical activity, and multimorbidity. These factors may independently affect sleep, cognition, vascular health, inflammation, and dementia risk. Genetic susceptibility, including APOE ϵ 4 status, cognitive reserve, socioeconomic circumstances, and access to healthcare may further contribute to between-study variation.

Finally, evidence that treating sleep disturbance prevents AD or slows established neurodegeneration remains limited. Improvements in insomnia or obstructive sleep apnea may benefit sleep quality, daytime functioning, mood, attention, and quality of life, but should not be equated with disease modification. Intervention studies are often small, heterogeneous, or of limited duration and do not consistently include longitudinal AD biomarkers or dementia-incidence outcomes. Sleep assessment and treatment should therefore be viewed as part of a broader strategy for brain health rather than as evidence that sleep intervention alone can prevent AD. Large longitudinal studies and randomized controlled trials using standardized sleep phenotyping, objective adherence measures, cognitive outcomes, and AD-specific biomarkers are needed to clarify causality and therapeutic relevance.

8. Conclusions

Current evidence supports a bidirectional relationship between sleep disturbance and AD. Sleep disruption may emerge during the early stages of neurodegeneration while also contributing to processes that accelerate cognitive and pathological decline. It should therefore be viewed neither as an isolated cause nor solely as a consequence of AD, but as part of a broader interaction among aging, vascular and metabolic health, circadian regulation, and neurodegenerative change.

The clinical significance of this relationship lies in the modifiable nature of many sleep disorders. Although it remains uncertain whether improving sleep can prevent AD or alter its progression, identifying and treating insomnia, obstructive sleep apnea, circadian disruption, and other sleep disturbances may improve daytime functioning, mood, quality of life, and cognitive performance. Future longitudinal studies and randomized trials should determine whether sustained improvements in sleep can influence AD biomarkers, cognitive trajectories, or dementia incidence.

Sleep assessment and management should be incorporated into broader strategies for healthy aging and dementia risk reduction. Promoting healthy sleep across the lifespan represents a practical low-risk approach to supporting brain health with aging.

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Abbreviations

The following abbreviations are used in this manuscript:

A β	Amyloid- β
AD	Alzheimer's disease
CSF	Cerebrospinal fluid
CBT-I	Cognitive behavioral therapy for insomnia
MCI	Mild cognitive impairment
NREM	Non-rapid eye movement
OSA	Obstructive sleep apnea
SWS	Slow-wave sleep

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