The Relationship Between Sleep Deprivation and Alzheimer's Disease Biomarkers: A Literature Review

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Though sleep is widely recognized as a necessity for survival, modern lifestyle patterns have made chronic sleep loss a recurring theme in many adult lives. This literature review explores the biological pathways linking persistent sleep deprivation to Alzheimer's disease (AD) risk and biomarkers. The main goal of this review is to understand how a lack of sleep may be linked to toxic protein buildup and the brain's natural cleanup processes. The methods used to create this literature review were analyzing and reviewing 32 articles from PubMed, ScienceDirect, and Google Scholar, published between 2001 and 2026. The analysis concentrated on how sleep phases, the glymphatic system, and AD biomarkers like amyloid-beta (Aβ) and tau are connected. This analysis suggests that even losing sleep for a night or two is associated with a short-term increase in soluble Aβ. Over the long run, chronic deprivation has been linked in animal models to plaque formation and tau-based tangles. A common theme in the research is that disrupted sleep may impair the glymphatic system, leading to neuroinflammation and cell energy issues (mitochondrial damage). These metabolic failures may create a loop with early-stage brain changes, though actual dementia is not established. With this in mind, sleep and AD seem to have a circular relationship where poor sleep is linked to brain changes that make it harder to have quality sleep. Because sleep habits can be controlled, improving sleep is a logical target for slowing brain aging, though not a proven way to prevent or slow AD.

Introduction

Sleep is often thought of as a time of inactivity and rest, but it is actually a highly complex biological process. It creates a brief state of reduced reaction to surroundings and decreased movement, all while the brain fires in very specific patterns[1]. Every animal needs sleep; going without it for too long can be fatal in animal studies, proving just how essential it is to stay alive[1].

Losing hours of sleep does more than just induce grogginess; a lack of sleep hinders the brain's ability to think and perform. In fact, studies show that staying awake for a full 24 hours can impair performance on a hand-eye tracking task about as much as a blood alcohol concentration of roughly 0.10%[2]. This builds up over time: getting only about 6 hours of sleep a night for two weeks can result in cognitive deficits similar to those of staying awake for an entire night[3]. Restricting sleep even further, to about 4 hours a night for two weeks, can leave a person about as impaired on attention tests as someone who has gone two nights without sleep[3].

While a loss of sleep is harmful in the short term, it becomes more concerning over time when looking at the effect of sleep deprivation on neurological disease. Some neurodegenerative conditions slowly wear down one's memory and thinking skills until common daily activities eventually become impossible[4]. As the disease progresses, it physically alters the brain, causing neurodegeneration and brain tissue shrinkage. The primary reason for this neurodegeneration is the accumulation of tangled and misfolded proteins, specifically amyloid and tau. These proteins spread from cell to cell, corrupting healthy proteins and disrupting neurological balance[4].

Alzheimer's disease threatens global health and is the commonest cause of dementia[4]. Evidence increasingly shows that sleep deprivation is associated with higher Alzheimer's disease risk and with AD biomarkers, possibly by disrupting essential brain maintenance[5,6]. Sleep disturbances are associated with higher risk of the disease and are linked to amyloid protein accumulation, a change linked to cognitive decline[5]. Research shows that even short-term sleep loss can trigger an immediate rise in soluble amyloid in CSF, while long-term sleep deprivation increases plaque formation in mouse models[7,8].

It is important to note that these sleep issues are not all the same. Acute sleep deprivation (one night awake), chronic sleep restriction, insomnia, sleep fragmentation, circadian disruption, and diagnosed sleep disorders such as obstructive sleep apnea can affect the brain in different ways and should not be treated as interchangeable[9]. It is also important to separate Alzheimer's disease risk, preclinical biomarkers (Aβ and tau changes while thinking is still normal), clinical onset, and

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disease progression. A short-term change in a CSF level or a PET signal is not the same as developing Alzheimer's disease or making an existing case worse.

This literature review covers biological mechanisms including protein buildup, tau tangles, inflammation, and oxidative stress (Figure 1). The review is limited to current literature and acknowledges that more long-term human studies are needed to verify whether specific sleep habits can change Alzheimer's disease risk or progression[6,10]. To structure this review, this analysis relies on how pathologists diagnose AD: by looking for clumps of amyloid plaques and tangles of tau proteins[4]. This paper analyzes the idea of a "two-way relationship," meaning that a loss of sleep can allow toxic proteins to accumulate and having too many of those proteins can make it even harder to sleep, creating a destructive cycle[6,11]. Early Alzheimer's-related changes may also impair sleep before memory symptoms appear[12].

Methods

This literature review was conducted to compile existing research, meta-analyses, and clinical studies regarding sleep architecture and brain health. Major scientific and academic databases, such as PubMed, ScienceDirect, and Google Scholar, were used to obtain relevant research data. The revised search was run on August 24, 2026, and was expanded by tracking citations in key reviews already in the original paper. Key terms, such as "sleep deprivation," "Alzheimer's disease," "glymphatic system," "amyloid-beta," and "tau," were used to aid in the search for relevant research articles and data. Articles were selected based on peer-reviewed status, a publication date between 2001 and 2026, and the article's concentration on neurological health plus a sleep exposure and an Alzheimer's-related outcome (risk, biomarkers, imaging, or pathology). One background paper on sleep loss and performance (Dawson and Reid, 1997) falls outside that range. Editorials, news items, and papers with no sleep measure or no AD-related outcome were excluded. The original submission included 11 sources, most of which were reviews. The revised review added primary human and animal studies so that mechanistic claims could be traced to the experiments that produced them. Specific statistics and findings were pulled from the selected papers, including amyloid protein and tau protein levels, cognitive test scores, and brain scans from PET or MRI imaging. For each included primary study, author and year, study design, population or model, sample size, sleep exposure, Alzheimer's-related outcome, main finding, and major limitations were extracted into Table 2.

Findings were synthesized as a narrative review, with human biomarker studies, human imaging studies, animal experiments, and mathematical models discussed separately because they provide different types of evidence. No formal quality-assessment or risk-of-bias tool was used; this is a limitation of the review and is noted in the Discussion. Because the original database search logs were not saved, exact hit counts from the first search could not be reconstructed. Table 1 therefore summarizes source selection for the revised manuscript: 11 original sources, 21 additional records identified by citation tracking and the expanded search, and 32 sources included after eligibility screening.

Results

Sleep comprises 4 distinct stages, with deep sleep, also known as the N3 stage, playing a vital role in neurological health[13,14]. During this stage, the interstitial space in the brain expands, increasing the activity of the glymphatic system, a network that allows the brain to flush toxic solutes more effectively than it can when the body is awake[13,15]. That glymphatic finding comes mainly from mouse experiments[15]; how fully it applies to humans is still being tested[9,16]. As one ages, sleep phases often become disrupted, including the N3 stage. This reduction in deep, slow-wave sleep is associated with a higher burden of harmful proteins and with more severe memory impairment over time[13,14].

Sleep supports brain health by supporting memory integration and plasticity. During a period of rest, the brain stabilizes new memory patterns by processes such as hippocampal neocortical dialogue[13,17]. The brain reestablishes neuronal patterns from the day and consolidates them into long-term memory. Slow-wave sleep, or the N3 stage, supports declarative memory, while REM sleep supports procedural and emotional learning and development[10,17,18].

In addition to memory, sleep is necessary for the function of the glymphatic system. The glymphatic system uses specialized water channels to circulate cerebrospinal fluid through brain tissue[13,15]. This removal mechanism relies on sleep architecture because the interstitial space of the brain expands during rest, allowing a higher clearance rate of metabolic wastes such as Aβ and tau[6,13,15]. Due to neuronal activity's release of amyloid proteins into brain fluid, deep N3 stage sleep is necessary for reducing amyloid release while the glymphatic system flushes away existing waste[6,7,19]. Additionally, sleep supports mitochondrial health by helping the brain to clear the impaired components and synthesize energy[13].

When brain cells fire during daily activity, they naturally produce a waste product called Aβ, which floats in the fluid between neurons[19,20]. Usually, these levels rise and fall on a regular daily schedule[7,21], but staying awake disturbs this rhythm and causes them to accumulate in the short term[7,8]. In healthy middle-aged men, one night of unrestricted sleep was followed by a morning decrease in CSF Aβ42, and one night of total sleep deprivation blocked that decrease; CSF Aβ40

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and tau did not show the same sleep-related change in that trial[8]. Related work measuring overnight CSF amyloid kinetics has also found that sleep loss can raise overnight CSF Aβ[22]. PET scans show that losing just one night of sleep leads to an increase in PET amyloid signal in the right hippocampus and the thalamus, two areas of the brain key for memory that are often affected early in Alzheimer's disease[23]. That study measured a PET signal in 20 healthy adults, not plaque confirmed in brain tissue, and it did not show that one night produced permanent plaques[23]. Some researchers, using a mathematical model, suggest that if the brain does not truly rest during sleep, amyloid production can become imbalanced enough, over a long period, to favor fibril formation[20]. The increased amyloid measured after short-term sleep loss is a change in soluble Aβ or imaging signal. It should not be read as proof that loose amyloid has already clumped into the hard plaques that define Alzheimer's pathology[20,23].

A 2026 meta-analysis of six studies (169 participants without Alzheimer's disease) found that sleep deprivation may transiently raise CSF Aβ, and in some analyses tau, but the authors noted possible publication bias and that tau findings were less consistent until outlier data were removed[24]. Those pooled results support a short-term biomarker response, not a change in who develops Alzheimer's disease or how fast an existing case worsens[24].

Beyond the buildup of Aβ, sleep loss also is associated with higher accumulation of tau. Tau, however, poses a different threat than Aβ production. When tau becomes damaged by chemical changes (hyperphosphorylation), it twists into tangles inside the neurons themselves. These neuron-tau tangles are one of the most common signs linked to Alzheimer's[4]. Studies suggest that sleep loss is linked to these tangles spreading in animal models, since missing deep, N3 stage sleep is linked to higher levels of tau in brain fluid in mice and in a small human CSF sample[14,25]. In mice, interstitial-fluid tau was about 90% higher during normal wakefulness than during sleep and about 100% higher during sleep deprivation; in six adults, CSF tau rose by more than 50% during sleep deprivation. Chronic sleep deprivation also increased tau spreading to connected brain regions in a mouse seeding model[25]. Sleep deprivation has also been shown to alter tau phosphorylation in human CSF and to impair tau-related pathways in AD-model mice[26,27]. Going without quality sleep for too long may hinder the glymphatic system, which normally sweeps away tau before it can disrupt healthy neurological networks[4,13,15]. On top of that, sleep loss triggers an inflammatory neurological response. When sleep is insufficient, the brain's immune cells (microglia and astrocytes) activate and swarm around amyloid clumps[4,6]. Though these cells attempt to clean up the waste at first, keeping them in a state of constant activation, due to a lack of sleep, backfires, creating chronic neuroinflammation where inflammatory neurological chemicals make it even harder for the brain's clearance systems to operate[6,13].

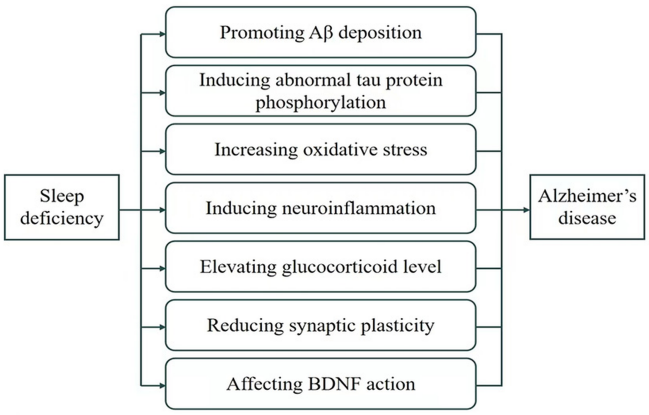


Figure. 1 Proposed biological pathways connecting sleep loss to Alzheimer's disease biomarkers and, in animal models, pathology. The figure shows sleep deficiency leading to amyloid buildup, abnormal tau phosphorylation, oxidative stress, neuroinflammation, higher glucocorticoid levels, reduced synaptic plasticity, and changes in BDNF action. The arrow to "Alzheimer's disease" is a proposed endpoint from the source figure. In this review, the amyloid, tau, and neuroinflammation pathways are supported by human CSF/PET biomarker studies and by mouse pathology studies; the other boxes are proposed mechanisms in the schematic and are not claimed here as proven causes of clinical Alzheimer's disease. Reproduced from Lv et al. under a Creative Commons Attribution (CC BY) license[10].

The sleep–amyloid relationship also runs in the other direction. In APP transgenic mice, the sleep–wake cycle and the day–night rhythm of interstitial Aβ were normal before plaques formed. After plaques formed, sleep deteriorated and the Aβ rhythm disappeared; immunizing mice against Aβ42 restored both. Young people with familial Alzheimer's mutations showed a similar pattern: CSF Aβ still oscillated if amyloid PET was negative, but that oscillation was attenuated after plaques were present[11]. Cognitively normal adults who already have biomarker evidence of amyloid also have worse sleep efficiency, even after age, sex, and APOE ε4 are taken into account[12]. Reduced NREM slow-wave activity, especially in the 1–2 Hz range, has also been associated with greater tau pathology on PET in older adults who were mostly still cognitively normal; that study was cross-sectional, so it cannot show which came first[14]. Earlier imaging work likewise linked Aβ deposition with disrupted human NREM slow waves and weaker overnight memory consolidation[28].

Discussion

Chronic sleep loss is associated with Alzheimer's disease biomarkers and, in animals, with greater pathology. It has not

Table 1 PRISMA-style summary of source selection for the revised review. Exact original database hit counts could not be reconstructed because those search logs were not saved.

Stage	Records
Identification	Original manuscript sources, n = 11; additional records from citation tracking of included reviews and an expanded PubMed/ScienceDirect/Google Scholar search on 24 August 2026, n = 21
Screening	Non-peer-reviewed items and papers outside 2001–2026 excluded
Eligibility	Papers with no sleep exposure or no Alzheimer's-related outcome excluded; reviews retained only for background, figure adaptation, or when they pointed to primary experiments
Included	32 sources in the revised reference list (primary studies, meta-analyses, and background reviews)

Table 2 Summary of key included studies. For each study, the table records design, population or model, sample size, sleep exposure, the Alzheimer's-related outcome and compartment measured (blood, CSF, PET, interstitial fluid, or tissue), the main finding, whether the change was shown to last or reverse, and major limitations.

Study	Design / sample	Sleep exposure	AD-related outcome	Main finding	Duration / reversal	Major limitations
Kang et al., 2009 [7]	Mouse microdialysis; APP mice; 10 healthy young men	6 h acute deprivation; 21 d restriction; orexin antagonist	ISF Aβ (mice); CSF Aβ (humans); plaques (mice)	ISF Aβ higher during wake and deprivation; chronic restriction increased plaques in mice; antagonist reduced plaques	Acute ISF Aβ fell when mice slept again; plaques = chronic mouse finding	Plaques are mouse-only; human n = 10, no plaques
Ooms et al., 2014 [8]	RCT; 26 healthy men aged 40–60, no AD	1 night total deprivation vs unrestricted sleep	CSF Aβ42, Aβ40, tau (CSF)	Sleep: morning CSF Aβ42 fell $\sim$6%. Deprivation blocked that fall. Aβ40 and tau unchanged	Overnight; not followed for plaques	Men only; 1 night; extra night CSF draws in the deprivation group
Shokri-Kojori et al., 2018 [23]	Within-subject PET; 20 healthy adults	1 night total deprivation vs rested sleep	PET amyloid signal (18F-florbetaben), right hippocampus and thalamus	PET signal increased after one night awake	Not shown to be permanent plaques	
Holth et al., 2019 [25]	Mouse ISF; 6 human CSF; tau-seeding mice	Acute deprivation; 28 d deprivation; chemogenetic wake	ISF/CSF tau; tau spread in mice	ISF tau $\sim$90–100% higher with wake/deprivation; human CSF tau $>$50% higher; greater spread to locus coeruleus in mice	Acute CSF/ISF change over hours; spread = 28 d in mice	Human tau n = 6; spread is a mouse seeding model
Roh et al., 2012 [11]	APP/PS1 mice; familial AD CSF (n = 4/group)	Natural sleep–wake before vs after plaques	ISF/CSF Aβ rhythm; sleep amount	After plaques, sleep and Aβ rhythm broke; Aβ immunization restored them in mice	Rhythm lost after plaques; restored by immunization in mice	Familial AD; small human groups
Lucey et al., 2019 [14]	Cross-sectional; adults $>$60; 38 PET, 104 CSF	Habitual sleep, forehead EEG	NREM slow-wave activity vs tau/amyloid PET and CSF	Less 1–2 Hz slow-wave activity associated with more tau pathology	Association only; direction unknown	Cannot prove sleep loss came first
Gosch Berton et al., 2026 [24]	Meta-analysis; 6 studies, 169 people without AD	Acute or chronic sleep deprivation	CSF Aβ40, Aβ42, t-tau, p-tau	Pooled CSF Aβ rose; tau less consistent until outliers removed	Described as transient biomarker change	Small study set; possible publication bias
Hoore et al., 2020 [20]	Mathematical model	Modeled sleep–wake effects on Aβ	Soluble vs fibrillar Aβ (model)	Model predicts long-term fibril risk if soluble Aβ production stays high	Simulation, not a measured human outcome	Not an experiment in people or animals

been shown in people to be a proven cause of Alzheimer's progression. Quality sleep is immensely important for the regulation of toxic proteins, such as Aβ and tau [4,6]. Just one night of total sleep deprivation is associated with an immediate jump in soluble amyloid levels in CSF, while getting regular, steady sleep keeps these numbers more stable [6,8,10]. By allowing neurological clearance systems, such as the glymphatic system, to help flush toxic proteins out, steady, quality sleep may help limit Aβ from bonding into plaques and tau proteins from forming tangles in animal models [4,7,15]. Those plaque and tangle outcomes have not been demonstrated after a single night of sleep loss in humans [23,24].

When sleep is consistently lost, the body creates and accumulates a "sleep debt" that impairs brain function and may increase the risk of longer-term neurological harm [3,6]. This loss of sleep does not only relate to amyloid plaque formation in mice [7]; it also disrupts a brain cell's generation of energy by damaging a cell's mitochondria. By disrupting the clearance of cellular debris, as discussed earlier, sleep deprivation increases the risk of neuroinflammation, where accumulated

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waste releases inflammatory chemicals that further harm brain cells and cognitive function[6,13]. With this in mind, both acute sleep loss and long-term deprivation create neurological vulnerability by letting amyloid and tau accumulate in extracellular fluid at rapid rates without removal[6,24].

The main objective of this literature review was to trace how sleep relates to early disease stages, and the research shown suggests that cognitively normal adults with amyloid biomarkers often have worse sleep, which can appear in the hidden, preclinical phase of Alzheimer's[10,12]. A lack of quality sleep is associated with higher soluble amyloid levels, which may create a neurological environment more vulnerable to plaques over time[6,8]. The research reviewed indicates that without the deep downtime that sleep provides, the brain's baseline chemistry shifts, which models predict could favor plaque formation if the imbalance lasts long enough[20]. Losing deep, slow-wave sleep (N3 stage) and REM sleep is associated with worse cognitive decline and with higher tau pathology in older adults[10,14]. Ultimately, this creates a cycle where accumulated amyloid disrupts quality sleep, and a lack of quality sleep is linked to further toxic protein accumulation[6,10,11].

Observational studies also link sleep-disordered breathing, sleep fragmentation, and self-reported poor sleep with later cognitive impairment or with amyloid on imaging. Those studies estimate risk; they do not prove that fixing sleep will slow Alzheimer's disease, and they can be confounded by age, depression, cardiovascular disease, medications, apnea, physical activity, genetic susceptibility (including APOE $\varepsilon 4$), and existing cognitive impairment[9,29–31].

Adopting healthy sleep habits, such as maintaining consistent sleep–wake cycles, is key to keeping neurological balance while possibly warding off short term and long term brain damage[20]. Simple routine sleep hours and regular physical activity daily are practical ways that may support the clearance of Aβ and tau build up, in turn supporting cerebrovascular health[13]. Those habits are reasonable for general health. They have not been proven in clinical trials to prevent or slow Alzheimer's disease[9]. On a societal scale, changes such as starting high school classes later in the morning have been discussed as a way to improve adolescent sleep, but that idea has not been shown to change long-term Alzheimer's risk[9]. For medical treatments, options like melatonin or orexin receptor drugs have been studied mainly for sleep. In mice, a dual orexin receptor antagonist reduced Aβ plaques[7]; small melatonin studies in mild cognitive impairment have shown only modest effects on test scores, and long-term trials on progression to Alzheimer's are lacking. These drugs should not be described as proven Alzheimer's treatments[6,32]. Even natural sunlight at the right times can help reset the body's circadian rhythm, promoting a more organized sleep schedule[1].

Though the link between sleep issues and Alzheimer's is supported by biomarker and animal data, additional long-term studies on human neurological function are still needed to prove if a change in sleep habits can stop or slow the progression and development of Alzheimer's disease[6,10]. Future studies focusing on specific sleep patterns and architecture markers, such as the analysis of brain wave changes, may give researchers a deeper insight into early neurobiological biomarkers for Alzheimer's disease.

This review has several limitations. No formal quality or risk-of-bias tool was used. Many human studies are small, short, and done in people who do not have Alzheimer's disease. Glymphatic clearance is best shown in rodents, so those findings should be applied to humans with caution. Human, animal, imaging, and modeling studies were mixed in the original draft; they are separated more clearly here, but residual overlap remains. Conflicting or mixed findings, including weaker tau results in the 2026 meta-analysis, show that biomarker changes can be temporary and are not always clinically meaningful.

Conclusion

Improving sleep hygiene is a practical and important way to protect short term and long term neurological health. By addressing sleep issues before any memory or cognitive symptoms begin, it may be possible to reduce strain on brain clearance systems. Less sleep deprivation could lower the overall risk of further biomarker change, but it has not been shown to lower the progression of Alzheimer's disease. That possibility still needs clinical trials.

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