The Sleepless Brain: Linking Sleep Disruption to Inflammation and Neurodegeneration in Alzheimer's Disease

Presented by Tobbie Berrian

in partial fulfillment of the requirements for completion of the
Health Science Scholars honors program in the
College of Natural Sciences at
The University of Texas at Austin

Spring 2026

Thesis Supervisor:

Kathy Richards, Ph.D.
Nursing
The University of Texas at Austin

Second Reader:

Laura Fonken, Ph.D.
Pharmacology & Toxicology
The University of Texas at Austin

Texas ScholarWorks Statement

I intend to submit a copy of this thesis to the Texas ScholarWorks (TSW) Repository. For more information on the TSW, please visit https://repositories.lib.utexas.edu/.

The Sleepless Brain: Linking Sleep Disruption to Inflammation and Neurodegeneration in Alzheimer's Disease

Tobbie Berrian 12/5/25

Table of Contents

Acknowledgements

First and foremost, I would like to thank my thesis mentor, Dr. Kathy Richards at the University of Texas at Austin Department of Nursing, for the support she has provided throughout the entire thesis creation process. Her feedback, guidance, and knowledge in the field of sleep and Alzheimer's disease have been invaluable during my writing and especially my research periods. My secondary reader, Laura Fonken at the University of Texas Pharmacology & Toxicology department, also made invaluable suggestions that played a major role in the creation of this thesis. I would also like to thank Dr. Stacia Rodenbusch as well as my TA Alec Ainsworth of the College of Natural Sciences Honors Department for making an incredibly challenging process manageable, rewarding, and especially thought-provoking. The amount of thought she has put into running her class and the entire honors thesis process is evident. Finally, I would like to thank the many supporters I have in my life: my family, friends, and classmates who have encouraged me and continued to push me throughout this process.

Abstract

Alzheimer's disease (AD), accounting for approximately 60–70% of major neurocognitive disorders, remains the leading cause of dementia worldwide, yet key mechanisms underlying its onset and progression remain unresolved. However, now scientists believe that a major component of AD progression might have been overlooked throughout decades of research: sleep. Increasing evidence suggests that chronic sleep disruption contributes to neuroinflammation, a process strongly implicated in the development and progression of AD. However, the precise causal pathways, timing, and magnitude of this relationship remain unclear due to a lack of properly collected data.

This thesis synthesizes current neuroscientific and clinical literature to examine how sleep disturbances influence neuroinflammatory processes and how these interactions may contribute to AD pathology. By integrating findings from multiple studies regarding sleep, sleep medicine, and known AD pathology, this project evaluates whether improving sleep quality may represent a meaningful strategy for reducing neuroinflammation and slowing or preventing disease progression. In addition to reviewing experimental and clinical research, the discussion is informed by observational insights drawn from the author's experiences working and volunteering in hospice care, where sleep disturbances and circadian rhythm disruptions are frequently observed among patients with advanced neurodegenerative disease.

This thesis argues that sleep should be considered a modifiable risk factor in AD and that improving sleep quality may help maintain neurobiological resilience by regulating inflammatory responses in the brain. If proven, this link could provide a strong basis to push for public health strategies aimed at sleep hygiene or new clinical recommendations for screening sleep disorders in at-risk populations.

Keywords: Alzheimer's Disease, sleep, neuroinflammation, neurodegeneration, sleep medicine, sleep research, public health, disease prevention, dementia

Introduction

What if one of the simplest ways to slow Alzheimer's disease (AD) doesn't come from a million-dollar drug, but from a good night's sleep? AD is a progressive brain disorder that falls under the category of dementia, slowly destroying memory and thinking skills, eventually making it difficult to carry out even simple daily tasks. Despite affecting more than six million Americans and accounting for roughly two-thirds of all major neurocognitive disorder diagnoses, its precise causes remain largely ambiguous. AD has become a major public health challenge due to its increasing prevalence and the absence of a cure. Over the last several decades, research has made significant advances in identifying hallmark pathologies, including amyloid-β plaques, tau neurofibrillary tangles, and widespread neuroinflammation, but these discoveries have simultaneously revealed the daunting complexity of the disease. With the lack of a cure, scientists and healthcare professionals alike have switched to attempting to find some way to prevent the onset or slow down the progression of AD pathology.

As scientists attempt to untangle the mechanisms that drive AD, one of the most surprising threads gaining attention is a behavior so ordinary that it is often dismissed in both clinical practice and daily life: sleep. Despite the American Academy of Sleep Medicine and the Sleep Research Society recommending that adults sleep at least 7 hours a night, over one-quarter of adults do not meet this recommendation with sleep disturbances affecting an estimated 14.5% of older adults (Adjaye-Gbewonyo et al., 2022). This issue is further amplified by modern societal trends, including increased screen exposure, circadian rhythm disrupting work schedules, and chronic stress, all of which contribute to widespread sleep disruption across a lifespan. Despite the proven importance of sleep's role in AD pathology, it remains surprisingly

overlooked in both clinical practice and research. This oversight stems partly from the common misconception that sleep is simply a passive resting state. In reality, sleep is an active, highly orchestrated physiological process critical to maintaining healthy brain function. Unlike heavy pharmacological interventions, sleep represents a low-risk, non-invasive, and widely accessible target, making it uniquely suited for preventive and early-stage intervention strategies.

Disruptions to sleep, whether through shortened duration, poor quality, or circadian rhythm disruption, have been associated with widespread consequences, including increased systemic inflammation, impaired glymphatic clearance of metabolic waste, and dysregulation of common immune pathways (Cao et al., 2024). With inflammation, glymphatic dysfunction, and immune dysregulation each playing documented roles in amyloid and tau accumulation, researchers have begun to explore whether sleep disturbances may play a more central role in disease development and progression than previously thought. Since neuroinflammation is a central feature of AD pathology, understanding what drives or exacerbates it is crucial (Akiyama et al., 2000). Growing evidence suggests that sleep loss may be one such driver: insufficient sleep promotes activation of microglia and astrocytes, elevates pro-inflammatory cytokines, and disrupts the brain's ability to regulate immune responses (Irwin et al., 2019). Are sleep disturbances an early driver of pathological inflammation that contributes to AD onset? Or are they emerging symptoms of neurodegeneration that further accelerate inflammatory processes in a vicious cycle? Resolving these questions requires a clearer, more integrated understanding of how sleep and inflammation interact. However, generating such clarity has proven difficult.

A major challenge in understanding how sleep interacts with AD comes from the often-underappreciated biological consequences and methodological limitations inherent to studying sleep loss. Animal studies allow precise control of sleep variables but cannot fully replicate

human pathology, while human studies offer greater ecological validity but often rely on indirect measures of sleep or inflammation. Rather than representing flaws, these differences reflect the complexity of studying sleep and neuroinflammation across biological levels. Because of this, the field benefits from careful synthesis that brings these diverse findings into conversation. This thesis aims to integrate these perspectives to clarify how sleep loss may influence inflammatory processes relevant to AD pathology.

This thesis synthesizes current research to identify the mechanisms linking sleep loss to neuroinflammation in Alzheimer's disease and evaluates whether improving sleep can meaningfully slow or prevent disease progression. Despite growing evidence that poor sleep amplifies inflammatory signaling and accelerates hallmark AD pathology, existing research remains fragmented across different models and methodologies, leaving the field without a unified explanation of how these processes interact. To address this gap, the first section of this thesis reviews the biological functions of sleep with a focus on its role in immune regulation. The next section summarizes key inflammatory mechanisms involved in AD pathology. I then synthesize findings from both human and animal studies to evaluate how sleep disturbances may trigger or exacerbate neuroinflammatory responses. The final section examines whether targeting sleep through behavioral or clinical interventions has the potential to slow AD-related inflammation or disease progression.

Background

Sleep

Despite being a universally known biological necessity, over time, sleep has resisted reduction to a single known function. Although it may appear passive, sleep is one of the most complex and tightly regulated processes in the human body. Because sleep cannot be attributed to a single area of the brain, researchers struggled until the late 19th century to make any significant breakthroughs in sleep research. Scientists found that sleep was caused by the interactions between specific brain structures, including the hypothalamus, the thalamus, the basal forebrain, and the brainstem (Falup-Pecurariu et al., 2021). Although researchers were able to identify the neural correlates of sleep, its precise biological functions continue to be actively investigated. Many speculate that in animals, sleep serves as a foundational process essential for maintaining health, cognition, metabolism, and immune regulation (Ramar et al., 2021). Another discovery made possible by the creation of the electroencephalogram in the 1930s was the existence of different stages of sleep. Scientists were able to recognize multiple distinct sleep stages, including rapid eye movement (REM) and non–rapid eye movement (NREM) sleep, determining the neurophysiological landmarks of each. While normal sleep supports essential neural and immune functions, growing evidence suggests that insufficient or fragmented sleep alters these processes in biologically meaningful ways. Understanding what happens when normal sleep is disrupted is therefore critical to appreciating sleep's role in brain health.

Sleep Deprivation

Sleep deprivation refers to a state in which an individual fails to obtain adequate sleep in duration, quality, or continuity to support normal physiological functioning. This deprivation can appear in many different forms, such as acute, meaning only for a single night or brief period, or chronic, a much longer-lasting conundrum. A defining feature of aging is that as humans age, we become more susceptible to disturbances and *less efficient sleepers* due to disruptions between sleep oscillations like slow waves and spindles (Helfrich et al., 2018). Older adults experience changes in sleep quality and architecture with age due to a combination of neurobiological alterations and structural changes in brain regions responsible for sleep regulation (Mander et al., 2017). As a result, insufficient sleep is both common and often underrecognized in older adults, especially those at risk for neurodegenerative disease. According to Peter-Derex et al. (2015), "The prevalence of obstructive sleep apnea increases with aging, but it seems that patients with AD are at even higher risks, with 40%-70% of patients having five or more apneas-hypopneas per hour of sleep" (p. 32). These changes classify sleep deprivation not merely as a lifestyle choice, but as a chronic physiological stressor with cumulative effects on brain function (Fernandes et al., 2017).

Via experimentation in the early 20th century, European clinicians noticed that patients with disturbed sleep exhibited impaired attention, slowed thinking, reduced memory performance, and emotional dysregulation (Schulz, 2022). These observations were made far before the development of advanced neuroimaging technology, meaning that the link between sleep and cognition is robust enough to be detected without advanced tools, suggesting that the relationship between sleep and cognition reflects a fundamental biological process rather than a subtle or incidental effect. These findings are consistent with the research from today as well,

Killgore (2010) used experimental studies on sleep deprivation and found robust impairments in attention, executive function, and memory, even in healthy adults. Beyond its effects on cognition, sleep deprivation exerts a profound influence over immune regulation in the brain, particularly through mechanisms of neuroinflammation.

Neuroinflammation

Neuroinflammation refers to the immune response within the central nervous system (CNS) and plays a critical role in maintaining neural homeostasis under normal physiological conditions. Compared to peripheral inflammation, neuroinflammation is a process primarily driven by microglia and astrocytes, which are the resident immune glial cells in the brain responsible for maintaining the neural environment and responding to injury. In a healthy human brain, this process is strictly regulated and supports synaptic remodeling, debris clearance, and tissue repair. However, when neuroinflammation becomes chronic or dysregulated, it risks shifting from a protective mechanism to a major contributor of cognitive impairment, altering synaptic integrity, and neuronal resilience. Increasing evidence suggests that sleep could possibly be a key modulator of neuroimmune activity, with insufficient or disrupted sleep altering inflammatory signaling pathways in ways that promote sustained microglial activation and elevated proinflammatory cytokine release (Fernandes et al., 2017). Understanding how sleep deprivation influences neuroinflammatory processes provides an essential mechanistic link between disrupted sleep and downstream neurodegenerative risk.

Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized clinically by declining memory, cognition, and functional independence, and biologically by widespread synaptic loss and neuronal degeneration. Within the context of chronic neuroinflammation, AD represents a neurodegenerative disorder in which immune activation plays a central and increasingly recognized role. While most of the research into AD has been primarily concerned with amyloid-β plaques and tau neurofibrillary tangles, the idea that these hallmark pathologies develop within a broader context of sustained neuroimmune dysregulation has become increasingly popular. Both post-mortem and in vivo studies consistently demonstrate elevated reactivity of microglia and astrocytes triggered by injury, increased expression of pro-inflammatory cytokines, and altered immune signaling across affected brain regions, further indicating that neuroinflammation is a central feature of the disease (Twarowski et al., 2023). In this context, elevated reactivity of microglia refers to the switch from a more maintenance or surveillance role of these cells into a far more responsive role.

It should be noted that many of the inflammatory pathways implicated in AD progression overlap with those influenced by sleep and circadian regulation (Zielinski et al., 2022). Despite extensive research into each of these domains independently, sleep, neuroinflammation, and Alzheimer's disease are often examined in isolation rather than as interacting biological systems. Given that sleep disturbances are highly prevalent in aging populations and often emerge years before cognitive decline, understanding how disrupted sleep may contribute to inflammatory processes relevant to AD pathology has become a worthwhile endeavor. While no single pathway fully accounts for the complexity of Alzheimer's disease, situating AD within the broader context of sleep-dependent immune regulation provides a biologically plausible

framework for understanding how modifiable physiological processes may intersect with long-term brain health.

Sleep Disturbances in Alzheimer's Disease

Sleep disturbances are among the most common and distressing non-cognitive symptoms of Alzheimer's disease (AD), affecting both patients and their caregivers. These disruptions can manifest in multiple forms, from insomnia and sleep fragmentation to alterations in sleep architecture and circadian rhythm dysregulation. Growing evidence suggests that these disturbances aren't just secondary symptoms but instead integral to the pathophysiology and progression of AD (Howell et al., 2023).

Different Types of Sleep Disturbances in AD

People with Alzheimer's disease experience a myriad of sleep abnormalities, many of which intensify as the disease progresses. Insomnia and sleep fragmentation are particularly prevalent amongst the community, with patients exhibiting difficulty initiating and maintaining sleep. These disruptions contribute to reduced total sleep time as well as impaired sleep efficiency, further exacerbating cognitive decline. Another type of sleep disturbance commonly found in AD patients is the reduction in slow-wave sleep (SWS): the deeper restorative stage critical for memory consolidation and neural repair (Peter-Derex et al., 2015). Decreased SWS in AD patients correlates with impaired clearance of neurotoxic metabolites, most importantly including amyloid-β, from the brain's interstitial space. REM, or rapid eye movement, sleep disturbances are also a common landmark of AD. Research has shown that patients often exhibit diminished REM duration, increased REM latency, and decreased REM density, all of which are

associated with deficits in emotional regulation and learning (Wang et al., 2016). One of the final ways that sleep is disturbed in AD patients has to do with circadian rhythm disruptions. These disruptions, often manifesting as advanced sleep phase syndrome or irregular sleep–wake patterns, stem from neurodegeneration in the suprachiasmatic nucleus (SCN) and impaired melatonin secretion, leading to fragmented nighttime sleep and excessive daytime somnolence or sleepiness (Peter-Derex et al., 2015).

Beyond the literature, these sleep disturbances are readily observable in clinical and caregiving settings. Through my years working and volunteering in hospice care, I have witnessed firsthand the profound disruption of the sleep–wake cycle in patients with AD. Many patients exhibited a striking reversal of normal circadian rhythms, sleeping for extended periods during the day and becoming increasingly alert, restless, or agitated in the late afternoon and evening, a phenomenon commonly described as sundowning. These nighttime periods were often marked by confusion, emotional distress, and heightened caregiver burden, showcasing the real-world consequences of circadian dysregulation described in the literature. While anecdotal, these experiences highlight how sleep disturbances in AD extend beyond measurable changes in sleep architecture to meaningfully affect patient wellbeing and quality of life, further reinforcing the clinical relevance of disrupted sleep and circadian rhythms in disease progression.

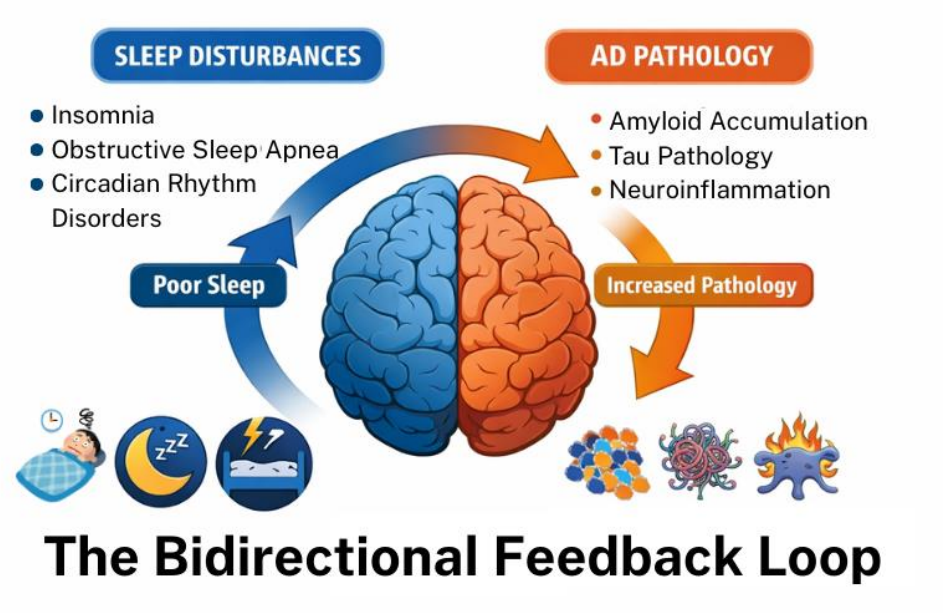
How AD Pathology Disrupts Sleep

A big breakthrough made in recent years when discussing the underlying pathology of AD, is how it directly interferes with sleep-regulating neural systems. One key mechanism is amyloid-β accumulation in sleep-regulating brain regions, including the hypothalamus and

brainstem nuclei responsible for arousal and sleep initiation (Wang et al., 2020). These deposits disrupt neuronal communication, contributing to the wake–sleep imbalance commonly seen across the world in AD patients. In addition, neurodegeneration of hypothalamic and brainstem structures such as the locus coeruleus also create difficulties in both the initiation and maintenance of sleep. This neurodegeneration is compounded by cholinergic and monoaminergic dysfunction, which disturbs neurotransmitter balance essential for *sleep vs wake* regulation (Ferreira-Vieira, 2016). The loss of cholinergic neurons in the basal forebrain, a core feature of AD, is particularly implicated in REM abnormalities.

The Bidirectional Feedback Loop

The reason sleep is such an important factor to investigate when discussing AD is the inherent feedback loop created between the two variables. Sleep and AD pathology exist in a self-reinforcing, bidirectional feedback loop that accelerates neurodegeneration. On one hand, sleep loss increases amyloid burden and neuroinflammation, as insufficient SWS impairs glymphatic clearance (Irwin et al., 2019). Chronic sleep deprivation can also promote microglial activation and the release of pro-inflammatory cytokines, potentially further exacerbating neural damage. On the other hand, AD pathology itself further degrades sleep architecture by damaging sleep-regulatory circuits and altering neurochemical signaling (Baril et al., 2024). This circular interaction establishes a vicious cycle in which disturbed sleep promotes AD pathology, which in turn worsens sleep disruption, ultimately accelerating cognitive decline and neurodegenerative progression.



Inflammation: The Mediator Between Sleep and Alzheimer's Disease

In recent years, inflammation has emerged as a possible biological mechanism linking sleep disruption to Alzheimer's disease (AD). While acute inflammatory responses are often looked at as essential for maintaining neural health, chronic neuroinflammation is now being recognized as a central contributor to neurodegeneration.

Neuroinflammation in Alzheimer's Disease

Neuroinflammation, similar to sleep deprivation, is a defining feature of AD pathology. Postmortem and neuroimaging studies consistently demonstrate chronic activation of microglia and astrocytes in the AD brain, particularly surrounding amyloid-β plaques and tau tangles. Importantly, inflammatory responses in AD are not uniform or static; microglial activation can initially serve compensatory and protective roles, including the clearance of toxic protein

aggregates (Wilcock, 2012). While these glial cells may initially function to mitigate pathology, prolonged or dysregulated activation leads to excessive release of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). Over time, this sustained inflammatory state contributes to synaptic dysfunction and widescale neuronal loss. It should also be known that similar to sleep loss, inflammation is not just a consequence of neurodegeneration; rather, it actively participates in disease progression (Wilcock, 2012). Chronic inflammatory signaling amplifies amyloidogenic processing of amyloid precursor protein and promotes tau hyperphosphorylation, reinforcing core pathological hallmarks of AD.

Effects of Sleep Loss on Inflammatory Processes

Sleep deprivation induces inflammation through multiple biological pathways with effects observed at both the cellular and molecular levels, mostly involving microglial activation. Under normal conditions, microglia play a protective role by clearing debris and supporting synaptic maintenance. However, sleep loss shifts microglia toward a chronically activated, pro-inflammatory state, characterized by exaggerated immune responses and reduced capacity for repair (Cao et al., 2024). This heightened microglial reactivity increases the brain's susceptibility to neuronal injury and disrupts synaptic homeostasis. Sleep deprivation promotes the release of pro-inflammatory cytokines like IL-6 or TNF-α. In fact, both experimental and clinical studies demonstrate that insufficient sleep elevates systemic and central levels of these cytokines, reflecting an upregulation of innate immune signaling (Fernandes et al., 2017; Irwin et al., 2019). Both Fernandes et al. (2017) and Irwin et al. (2019) work together beautifully to explain how sleep works to regulate inflammatory processes with Fernandes explaining how it happens, while

Irwin shows that it happens in humans and explains why it matters clinically. Most of the work from Fernandes et al. (2017) centers on how sleep disruption increases pro-inflammatory cytokines, while Irwin et al. (2019) provides clinical confirmation in humans proving that targeting sleep disturbance might have benefits on several factors, providing significant gains in reducing the Alzheimer's disease risk profile.

Another way that sleep disturbances have been discovered to affect inflammatory cascades is through oxidative stress and neuronal injury. Prolonged wakefulness increases the metabolic demand in neurons while simultaneously reducing antioxidant defenses, leading to the accumulation of reactive oxygen species. This oxidative burden damages cellular membranes, proteins, and DNA, triggering additional inflammatory responses and promoting neuronal vulnerability (Akiyama et al., 2000; Cao et al., 2024). Over time, oxidative stress and inflammation act synergistically to accelerate neurodegenerative processes.

Clinical and Theoretical Implications

Understanding inflammation as a mediator between sleep and Alzheimer's disease has important implications for both prevention and intervention. If sleep disruption contributes to neuroinflammation and subsequent AD pathology, then improving sleep quality may represent a viable strategy to reduce inflammatory burden and slow cognitive decline. Interventions targeting sleep disorders may offer neuroprotective benefits by restoring immune balance and reducing chronic inflammation.

The Benefits of Neuroinflammation in Alzheimer's Disease

As mentioned earlier, neuroinflammation is often characterized as a pathological driver of Alzheimer's disease (AD); however, this perspective oversimplifies a fundamentally adaptive

biological process. In the healthy brain, inflammatory signaling plays an important role in maintaining neural integrity by supporting tissue repair and responding to injury or infection. Rather than being inherently negative, neuroinflammation becomes pathological only when its regulation and resolution are impaired (Wilcock, 2012). Wilcock (2012) challenges the traditional view of neuroinflammation as inherently detrimental, instead she demonstrates that inflammatory responses can play protective roles. Understanding when inflammation turns from good to bad is essential for interpreting the role of inflammation in AD and for contextualizing how sleep disruption may shift inflammation from a protective act to a harmful one.

Neuroinflammation as an Adaptive and Protective Response

Under non-pathological conditions, the brain maintains a tightly regulated immune environment to preserve homeostasis. Microglia, the immune cells of the brain, are continuously surveying neural tissue and responding rapidly to disruptions in homeostasis. When pathological stimuli such as amyloid-β accumulation arise, microglia become activated and initiate an inflammatory response designed to restore balance to said neural environment (Twarowski et al., 2023). This response includes processes like phagocytosis of toxic proteins and removal of damaged synapses. It should be noted that these early microglial responses also shape astrocytic behavior by acting as key signals driving the polarization of astrocytes, another key glial cell found in the neural environment. According to Kakkar et al. (2025), astrocytes adopt two major neuronal phenotypes: the A2 neuroprotective phenotype, which supports synaptic repair, neurotrophic signaling, and metabolic homeostasis, and the A1 neurotoxic phenotype, which is associated with neuronal injury. In early stages of AD, microglial signaling favors A2 astrocytic polarization, reinforcing the compensatory role of neuroinflammation. While in this phase,

activated microglia can limit amyloid burden through clearance mechanisms and support synaptic remodeling in response to neuronal stress. Pro-inflammatory cytokines released during acute immune activation also play roles in neuroplasticity, cell survival signaling, and tissue regeneration (Kakkar et al., 2025). From this perspective, inflammation represents an essential defense mechanism rather than an immediate pathological issue.

Failure of Resolution and the Transition to Pathology

As reported by Attiq et al. (2025), the pathological consequences of neuroinflammation come not from its activation, but from its persistence. “Chronic activation of astroglia and microglial cells promotes loss of neurons, memory, and impaired learning capacity, leading to neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis” (p. 2). In a healthy system, inflammatory responses are followed by phases of resolution that downregulate immune activity and restore homeostasis. In AD however, this resolution process becomes progressively impaired. Multiple factors like aging and genetic susceptibility work to compromise the brain’s ability to terminate inflammatory signaling once the initial threat has been addressed, causing microglia to remain in a chronically activated state. Rather than clearing amyloid buildup efficiently, these cells become less effective at debris removal while continuing to propagate inflammatory signals promoting a shift toward the A1 astrocytic phenotype (Kakkar et al., 2025). This maladaptive state contributes to synaptic loss, neuronal dysfunction, and amplification of amyloid and tau pathology. Thus, neuroinflammation in AD reflects failure of immune regulation rather than excessive immune activity per se.

Implications for Alzheimer's Disease Progression

This distinction between adaptive and maladaptive neuroinflammation has significant implications for understanding AD progression. It helps explain why broad anti-inflammatory therapies have shown limited success in clinical trials; suppressing immune activity indiscriminately may interfere with essential protective functions. The challenge lies in preserving beneficial inflammatory responses while preventing their chronic dysregulation. Sleep, circadian rhythms, and metabolic health play critical roles in coordinating immune activation and resolution. Notably, the importance of regulation rather than suppression is mirrored in sleep research. Arjmandi-Rad et al. (2022) talks in depth about how short-term or acute sleep deprivation can potentially exert beneficial effects by promoting neurogenesis, synaptic plasticity, and reducing neuroinflammation and oxidative stress, whereas chronic sleep disturbances tend to exacerbate AD pathology through increased neuroinflammation. When these regulatory systems are intact, inflammation supports neural resilience; however, when they fail, as seen in chronic sleep deprivation, neuroinflammation becomes self-sustaining and neurotoxic. Understanding this shift is essential for identifying therapeutic strategies aimed at restoring resilience rather than merely suppressing symptoms.

Sleep: The Main Modifiable Risk Factor in Alzheimer's Disease

While factors like age, genetic predisposition, and biological sex remain the strongest risk factors for Alzheimer's disease (AD), these variables are inherently non-modifiable. As a result, they offer limited opportunities for prevention or early intervention. On the other hand, sleep represents a rare and uniquely modifiable risk factor as it is both biologically influential and

behaviorally modifiable across the lifespan. Framing sleep disruption as a modifiable risk factor reframes its role in AD from a passive symptom of the disease or downstream consequence to an active contributor to disease vulnerability and progression.

The Early Appearance of Sleep Disturbances

A growing body of evidence suggests that sleep disturbances often emerge years, and in some cases decades, before the onset of clinically detectable cognitive impairment (Howell et al., 2023). REM Sleep Behavior Disorder (RBD) is a sleep disorder characterized by loss of normal REM muscle paralysis and is relevant to AD because it is strongly associated with neurodegenerative diseases. According to data collected by Howell et al. (2023), longitudinal cohort studies demonstrate that many patients with isolated RBD will eventually develop a defined neurodegenerative disorder, supporting the idea that RBD precedes diagnosis and that conversion towards cognitive decline happens over time. This correlational relationship is critical, as it pushes the idea that sleep disruption is not merely a byproduct of neurodegeneration, but instead a potential early indicator of pathological processes already underway. Unlike overt cognitive symptoms, sleep alterations may serve as a subtle but measurable sign of declining neural resilience, offering a valuable window for intervention during preclinical or early stages of the disease which will be discussed later in this thesis.

Although REM sleep behavior disorder provides one well-documented example of sleep abnormalities preceding neurodegenerative disease, it represents only one component of a broader spectrum of sleep disturbances observed in aging populations. Insomnia, obstructive sleep apnea, circadian rhythm disorders, and movement-related sleep disorders such as restless

legs syndrome or periodic limb movement disorder can all significantly alter sleep architecture (Richards et al., 2026). Each of these conditions contributes to sleep fragmentation, reduced slow-wave sleep, and physiological stress responses that may promote neuroinflammatory processes associated with Alzheimer's pathology.

Modern Behavioral Influences on Sleep Deprivation

The significance of sleep as a modifiable risk factor is further emphasized by its influence on multiple converging pathways implicated in AD pathology. Adequate sleep supports immune regulation while facilitating glymphatic clearance of metabolic waste products. When sleep is chronically disrupted, these protective processes become compromised, leading to a myriad of AD causing conditions. Importantly, this vulnerability does not come solely from acute sleep loss, but from the cumulative burden of long-term sleep insufficiency or circadian misalignment, factors that are increasingly prevalent in modern societies for numerous reasons (Chattu et al., 2018).

Not only are these patterns of insufficient sleep increasingly prevalent in modern societies but they often begin early in life. As Grandner et al. (2021) states, "Existing evidence suggests that Americans trade sleep hours for work or leisure hours (10) and that this trade-off is exacerbated by modern sedentary lifestyles and use of electronic media at night" (p. 569). This sleep trade appears quite early in life as discussed by Chattu et al. (2018), "Although the need for sleep among adolescents has been determined to be about 9.25 h per day, there are still many adolescents who obtain less sleep than they actually need, thus creating a chronic sleep debt" (p. 3). With the definition of adolescents falling between 16 and 19 years old in the study referenced, there was an estimated 10.4% prevalence of behaviorally induced, meaning not

caused by a medical condition, insufficient sleep syndrome amongst high school students in Norway (Chattu et al., 2018). These findings suggest that chronic sleep debt is not merely a condition of aging, but a lifelong behavioral pattern that may compound neurobiological vulnerability over decades. Viewed longitudinally, insufficient sleep beginning in adolescence may represent the earliest stage of cumulative risk exposure for neurodegenerative disease, showcasing potential long-term impact of early interventions promoting healthy sleep behaviors.

Sleep Optimization as a Public Health Strategy

Viewing sleep through a risk-modification lens also highlights its role in maintaining neurobiological resilience rather than simply preventing damage. Resilience, in this context, refers to the brain's capacity to adapt to stressors, resolve inflammation, and maintain functional integrity despite ongoing challenges such as aging or genetic risk. Sleep plays a central role in orchestrating these adaptive responses by regulating immune activation and promoting inflammatory resolution. When sleep is preserved, neuroinflammation can remain tightly controlled and adaptive; when sleep is disrupted, inflammatory responses are more likely to become prolonged and maladaptive, accelerating neurodegenerative processes.

The concept of sleep as a modifiable risk factor is particularly compelling given the limited success of pharmacological approaches aimed at reversing established AD pathology. Despite extensive efforts to target amyloid-β and tau directly, disease-modifying therapies have yielded slight clinical benefits at best. In contrast, interventions aimed at improving sleep quality are comparatively low-risk, cost-effective, and easily scalable. Although improving sleep alone is unlikely to halt AD, it may meaningfully reduce disease burden by slowing pathological

progression and restoring immune balance (Lee et al., 2020). In fact, research has already proven this idea in other animals; Lee et al. (2020) reports that optogenetic rescue of Slow Wave Activity (SWA) successfully halted the amyloid accumulation and restored intraneuronal calcium levels in mice leading to a more ideal neural environment. While caution is necessary when interpreting animal models, these findings reinforce the mechanistic plausibility that restoring sleep architecture, particularly SWA, may directly influence pathological trajectories.

Viewing sleep from this perspective also carries important implications for public health and preventative medicine. Sleep disturbances are common, often underdiagnosed, and frequently dismissed as benign consequences of aging or mere effects of lifestyle. Recognizing sleep disruption as a modifiable risk factor for AD highlights its clinical significance and supports earlier screening and intervention. Addressing sleep problems in midlife or early old age may offer an opportunity to reduce long-term neurodegenerative risk before irreversible damage has occurred. Conceptualizing sleep as a modifiable risk factor aligns with a broader shift in AD research, from attempting to reverse advanced pathology toward creating methods that promote resilience and prevention. Rather than targeting isolated molecular endpoints, improving sleep targets upstream regulatory systems that influence inflammation. This reframing sets the stage for intervention-focused strategies, positioning sleep optimization not as a supplementary concern, but as a central pillar in efforts to mitigate neuroinflammation and slow Alzheimer's disease progression.

Strategies to Improve Sleep & Reduce Neuroinflammation

If sleep disruption contributes to sustained neuroinflammation and accelerates Alzheimer's disease (AD) pathology, then improving sleep quality represents a logical and potentially powerful intervention strategy. Unlike genetic risk or chronological aging, sleep architecture is modifiable through behavioral and clinical approaches. Importantly, the goal of sleep-focused interventions is not merely to increase total sleep time, but to restore the structural and physiological features of sleep, like slow wave sleep (SWS) and circadian alignment, that regulate immune activity and support neural repair. By targeting sleep as a regulatory system rather than a passive state, interventions may reduce inflammatory signaling and promote neurobiological resilience.

Behavioral Interventions and Sleep Hygiene

Behavioral modification remains the most accessible and scalable strategy for improving sleep. According to Baranwal et al. (2023), "In addition to treating coexistent intrinsic sleep disorders, the best treatment for long-term sleep improvement is optimal sleep hygiene, defined as behavioral and lifestyle interventions that can promote better sleep" (p. 60). Sleep hygiene practices like consistent sleep–wake timing, reduction of evening light exposure, limitation of caffeine and alcohol intake, and the establishment of a stable and consistent pre-sleep routine have all demonstrated measurable improvements in sleep continuity and efficiency (Baranwal et al., 2023). Although these interventions may appear simple, their physiological impact is significant. Regular sleep timing reinforces circadian rhythm stability, which may in turn regulate inflammatory gene expression and cytokine release patterns.

Cognitive Behavioral Therapy for Insomnia (CBT-I) has also emerged as a particularly effective non-pharmacological intervention (Koffel et al., 2018). Clinical trials have shown that CBT-I can improve sleep latency while enhancing overall sleep quality in both general and older adult populations. Given the relationship between fragmented sleep and elevated inflammatory markers, improving sleep consolidation through CBT-I may indirectly reduce systemic and central inflammatory signaling. Furthermore, CBT-I avoids many of the adverse cognitive side effects associated with sedative medications, making it especially relevant for populations at risk for neurodegenerative disease. According to Koffel et al. (2018), despite the treatments proven effectiveness in improving sleep outcomes and reducing the risks associated with reliance on hypnotics, CBT-I is a treatment that is heavily under prescribed due to factors such as systemic barriers, patient barriers, and insufficient screening for sleep issues. As such, expanding access to CBT-I may represent an important public health strategy for reducing the burden of sleep-related and neurodegenerative disorders.

Enhancing Slow-Wave Sleep

Since reduced SWS is strongly associated with heightened neuroinflammation, recent strategies aimed at enhancing SWS have become of particular interest to many researchers. Preclinical evidence further supports the therapeutic potential of targeting this specific sleep stage. Lee et al. (2020) demonstrated that optogenetic restoration of slow-wave activity in an Alzheimer's disease mouse model successfully reduced amyloid burden and normalized intracellular calcium dysregulation, suggesting that enhancing physiologic SWS may directly influence disease-relevant pathology rather than merely improving subjective sleep quality. Pharmacological strategies have also been investigated, though with caution. Certain agents,

such as low-dose sedative-hypnotics or melatonin receptor agonists, may improve sleep continuity; however, their long-term effects on slow-wave architecture and cognitive outcomes remain unclear. Broad suppression of neural activity does not necessarily replicate the restorative qualities of physiological sleep. Therefore, future therapeutic development must distinguish between sedation and biologically restorative sleep.

Circadian Rhythm Stabilization

The disruption of the natural circadian rhythm was one of the most prevalent issues I faced during my time volunteering in hospice work. Patients would choose to be awake all night causing issues for themselves and staff and sleep throughout most of the day, usually waking with an unusual burst of energy in the late afternoon showcasing a reversal of natural circadian rhythms. My theory for why this behavior was so widespread in patients that I was able to see, besides the natural effects of AD, has to do with faults created by many of the nursing homes I visited. Australian neuroscientist Kim et al. (2022) speaks about how entrainment of the circadian rhythm occurs mostly due to external environmental signals and is largely done via regular exposure to light during the day and darkness at night. With patients spending most of their time bedridden in a dark room during the day with nothing but a small TV in the area, circadian rhythm disruption is almost a guarantee.

Circadian rhythm disruption (CRD) is another modifiable contributor to neuroinflammation and AD progression. Even though the link between circadian rhythms and neurodegeneration is not fully understood, it is believed that the fragmented sleep-wake cycle in AD patients can be partially attributed to two major mechanisms: the degeneration of the suprachiasmatic nucleus (SCN), and reduced melatonin secretion (Leng et al., 2019). Internationally trained epidemiologist Dr. Leng (2019) states, “If circadian dysfunction is a risk

factor contributing to the development of neurodegenerative diseases, one of the appealing testable hypotheses is that restoring regular circadian rhythms might prevent or halt the progress of these diseases as well as mitigating their related symptoms" (p. 9). Essentially, if a solution to fix CRD can be found after sufficient testing, then it might play a large role in the prevention of AD. One of the easiest circadian rhythm treatments comes from the idea that these rhythms remain responsive to environmental cues, particularly light exposure. Vasey et al. (2021) speaks on how artificial light used in bright light therapy has been shown to be able to train the human circadian rhythm; however, they follow up by stating that more investigation is needed to prove its effectiveness in a variety of clinical scenarios.

Nevertheless, strategies like bright light therapy, timed morning sunlight exposure, and structured daily activity have been shown to cause improvements in sleep consolidation and daytime alertness in older adults and individuals with dementia preventing this inversion of sleep schedules. By strengthening circadian entrainment, these interventions may reduce nighttime wakefulness and mitigate the inflammatory consequences of circadian misalignment. Additionally, maintaining consistent meal timing and physical activity schedules can reinforce peripheral clock synchronization, further stabilizing inflammatory gene expression patterns.

Physical Activity and Exercise

Regular physical activity is one of the most consistently supported lifestyle interventions for both sleep quality and neuroinflammatory regulation. Aerobic exercise has been shown to improve sleep efficiency and reduce sleep onset latency while also causing anti-inflammatory effects through reductions in systemic cytokine levels and improvements in metabolic regulation. Evidence from a large network meta-analysis of 35 randomized controlled trials conducted by

Faizul Hasan et al. (2022), involving more than 3,500 participants demonstrated that multiple exercise modalities had the ability to significantly improve sleep quality in older adults, with combined endurance training and walking producing some of the strongest improvements. During my own experiences visiting patients in nursing home settings, physical therapy sessions were often described as the highlight of the day. For some patients, this enthusiasm stemmed from enjoyment of the exercise itself, while for others it was more of a break from the monotony of daily routines within long-term care environments.

It should be noted that not all forms of exercise cause identical cognitive benefits. According to a network meta-analysis done by Huang et al. (2022), resistance exercise has the highest probability of being the most effective exercise type for slowing cognitive decline among patients with cognitive impairment, especially for patients with dementia while multicomponent exercises were the most effective in protecting cognition in patients with mild cognitive impairments. These findings suggest that exercise prescriptions should be tailored to disease stage, with multi-component approaches potentially serving a preventative role in the general population. Additional factors, including exercise timing, may further influence outcomes, with morning activity appearing to produce more favorable effects than evening exercise. In aging populations, moderate-intensity aerobic exercise has also been associated with improved cognitive performance and increased hippocampal volume (Singh et al., 2025). When combined with improved sleep, these effects may compound to enhance neural resilience. Despite the numerous upsides of physical exercise for AD patients and the general public, it should be mentioned that due to the consequences of later stage dementia, some patients might find themselves bedridden and unable to exercise underscoring the need for early intervention and alternative supportive strategies for maintaining cognitive and physiological health.

Pharmacological Sleep Aids

While lifestyle interventions such as physical activity and sleep hygiene should remain first-line strategies, pharmacological treatments may sometimes be necessary to manage sleep disturbances in older adults and patients with neurodegenerative diseases. One of the most recommended options is melatonin, a hormone naturally produced by the pineal gland that regulates circadian rhythms. Supplemental melatonin has been shown to improve sleep onset and circadian alignment in older adults and may provide modest benefits for patients with dementia. According to a study done by Blackman et al. (2021), melatonin significantly reduced sleep latency and decreased frequency of sleep to wakefulness transitions, leading to less fragmented sleep. Because melatonin works by reinforcing natural sleep signaling rather than sedating the brain directly, it is generally considered one of the safer sleep aids for long-term use.

Certain prescription medications may also improve sleep in clinical settings but must be used cautiously. For example, orexin receptor antagonists, such as suvorexant, promote sleep by inhibiting wakefulness signaling pathways in the brain rather than broadly depressing central nervous system activity. In fact, a study done by Lucey et al. (2023) revealed that Suvorexant use acutely decreased tau phosphorylation and amyloid-β concentrations in the central nervous system, leading many to believe that Suvorexant, a drug approved by the United States Food and Drug Administration (USFDA) for insomnia, may have potential as a repurposed drug for the prevention of Alzheimer's disease. Overall, this class of medications may help improve sleep continuity while minimizing some of the cognitive side effects associated with older sedative drugs. However, not all medications that induce sleep are beneficial for cognitive health. Over-the-counter antihistamines such as diphenhydramine, also known as Benadryl, are frequently

used as sleep aids but are generally discouraged in older adults. These drugs possess anticholinergic properties, meaning they block acetylcholine signaling in the brain. Because acetylcholine plays a critical role in memory and cognitive function, long-term use of anticholinergic medications has been associated with increased risk of cognitive impairment and dementia (Gott et al., 2024). As a result, while such medications may produce sedation, they do not promote restorative sleep and may ultimately worsen neurological outcomes. When medication is necessary, treatments that support natural sleep regulation and minimize anticholinergic or cognitive side effects are generally preferred.

A growing area of interest in sleep medicine has been the use of non-traditional supplements to improve sleep outcomes in patients. A double-blind, placebo-controlled study conducted by Langade et al. (2021), examined the pharmacological impact of Ashwagandha root extract on sleep. The results demonstrated significant improvements in multiple sleep parameters among both healthy individuals and those with insomnia, with more pronounced effects observed in the insomnia group. The study confirms that Ashwagandha root extract can improve sleep quality and can help in managing insomnia, although its downstream effects on neuroinflammatory processes and cognitive outcomes in Alzheimer's disease remain unclear and require more testing.

Addressing Sleep Disorders in Clinical Populations

Beyond lifestyle modification, identifying and treating clinical sleep disorders as soon as possible represents yet another lens to view the situation through. Obstructive sleep apnea (OSA) and restless legs syndrome are both prevalent in older adults and are associated with cognitive decline, but the ability to properly diagnose each disease as quickly as possible is a drastically

undervalued component when talking about the prevention of further downstream consequences. Early screening for sleep disorders in midlife and early older adulthood may therefore represent an underutilized avenue for risk reduction. Rather than treating sleep disturbances as secondary symptoms of aging, proactive identification and management may help preserve cognitive function and reduce inflammatory burden before significant neurodegeneration occurs.

Integrating Sleep into Preventative Alzheimer's Disease Strategies

While no single intervention is likely to prevent Alzheimer's disease in isolation, optimizing sleep represents a biologically plausible and clinically feasible strategy for reducing cumulative neuroinflammatory stress. Importantly, sleep improvement should not be conceptualized as a cure, but as a resilience-enhancing intervention capable of modifying disease trajectory. When implemented alongside other protective factors, like cognitive engagement or metabolic regulation, sleep optimization may form a central pillar of multidimensional disease prevention. Ultimately, I believe the growing recognition of the regulatory role of sleep in immune balance and neurodegeneration supports a paradigm shift in AD research and clinical practice. Rather than focusing exclusively on downstream pathological markers, targeting upstream systems such as sleep and circadian rhythm may provide a more holistic and sustainable approach to reducing neuroinflammatory burden and preserving cognitive function across the lifespan.

Limitations of the Research

Despite the growing body of literature examining the relationship between variables like sleep, neuroinflammation, and Alzheimer's disease (AD), several methodological and

translational limitations remain that complicate interpretation of the findings used in this thesis. While the evidence collectively supports the idea that sleep disturbances influence inflammatory pathways and may contribute to neurodegenerative progression, inconsistencies in study design and measurement techniques make it difficult to establish definitive causal relationships. Recognizing these limitations is essential for contextualizing the conclusions drawn throughout this thesis and for identifying directions for future research.

Methodological Limitations in Existing Literature

One of the most significant limitations in this field is the heavy reliance on correlational data. Many human studies examining sleep disturbances and AD pathology rely on observational designs or retrospective sleep assessments. While these approaches are valuable for identifying associations between sleep quality, inflammatory biomarkers, and cognitive decline, they cannot definitively determine causality.

Another methodological challenge arises from the frequent use of mixed human and animal models. Animal studies, particularly those involving transgenic mouse models of AD, have provided valuable insights into the biological mechanisms linking sleep loss to neuroinflammation and synaptic dysfunction. These models allow researchers to manipulate sleep architecture, genetic pathways, and inflammatory signaling in ways that would be impossible or unethical in human participants. However, the translation of these findings into human physiology is not always straightforward. Rodent sleep architecture differs substantially from human sleep patterns, and the progression of amyloid pathology in animal models often occurs on accelerated timelines compared to the decades-long development of AD in humans. As

a result, findings from animal experiments may overestimate or oversimplify the biological effects observed in human populations.

Another troubling complication lies in the inconsistency of sleep measurement methods across studies. Sleep quality and duration can be assessed through a range of approaches, like subjective questionnaires or actigraphy, a non-invasive technique used to assess cycles of activity and rest. While questionnaires are convenient and widely used in large population studies, they rely heavily on self-report and may be influenced by recall bias or misperception of sleep duration. Actigraphy offers an objective estimate of sleep–wake patterns through wearable devices, but it lacks the precision needed to identify specific sleep stages such as slow wave sleep or rapid eye movement sleep. Polysomnography remains the gold standard for measuring sleep architecture, yet it is expensive, time-intensive, and often conducted in controlled laboratory settings that may not reflect natural sleep behavior. These variations in measurement techniques contribute to discrepancies in reported findings and limit the ability to directly compare results across studies.

Risks and Limitations of Pharmacological Interventions

Pharmacological approaches to improving sleep also introduce additional complexities, particularly within populations already affected by cognitive impairment. Many commonly prescribed sleep medications can produce side effects such as sedation, confusion, impaired balance, or increased fall risk, all of which may be especially problematic for individuals with AD. Certain over-the-counter medications, particularly first-generation antihistamines with anticholinergic properties, may further exacerbate cognitive impairment by interfering with neurotransmitter systems essential for memory and learning. The reason this is important is

because of the idea that even when pharmacological sleep aids successfully increase total sleep time, they do not always replicate the biological characteristics of restorative sleep, such as enhanced SWA or coordinated glymphatic clearance processes. This distinction highlights an important limitation in the therapeutics: inducing sedation is not necessarily equivalent to restoring the complex physiological functions of natural sleep. As a result, pharmacological strategies must be approached with caution, and future research will need to prioritize interventions that preserve or enhance normal sleep architecture rather than simply promoting unconsciousness.

Implications for Future Research

Taken together, these methodological and translational limitations highlight the need for more rigorous and standardized research approaches in the study of the relationship between sleep, neuroinflammation, and Alzheimer's disease. Future investigations on this topic would benefit from longitudinal designs that integrate objective sleep measurements and inflammatory profiling across extended timeframes. Despite these challenges, the convergence of evidence across multiple fields suggests that sleep remains a promising area for preventative intervention. Addressing the limitations identified in current research will be essential for translating this growing body of knowledge into effective clinical strategies aimed at reducing neuroinflammation and slowing the progression of AD.

Conclusion

Alzheimer's disease (AD) remains one of the most pressing neurological challenges of the twenty-first century. Despite decades of research and billions of dollars invested in

pharmaceutical development, effective disease-modifying treatments remain limited. Much of the traditional focus in AD research has centered on targeting downstream molecular hallmarks such as amyloid-β plaques and tau tangles. While these pathological features are undeniably central to the disease process, the findings synthesized throughout this thesis suggest that upstream physiological systems, like sleep regulation and neuroimmune balance, play a far more influential role in shaping the environment in which these pathologies develop. Taken together, the evidence reviewed in this thesis supports the central claim that sleep disruption contributes to neuroinflammation and may meaningfully accelerate the progression of Alzheimer's disease.

Sleep is increasingly recognized not merely as a passive state of rest but as a dynamic biological process essential for maintaining neural homeostasis. During healthy sleep, particularly during slow-wave sleep, the brain engages in a series of restorative functions designed to protect itself, and when sleep becomes fragmented or chronically disrupted, these restorative mechanisms are compromised. As demonstrated across both experimental and clinical research, sleep deprivation can trigger microglial activation, increase pro-inflammatory cytokine production, and impair the clearance of neurotoxic proteins such as amyloid-β. Over time, these disruptions create an environment in which neuroinflammation becomes sustained rather than adaptive, ultimately contributing to neuronal injury and cognitive decline. In this way, sleep functions as a critical regulator of the inflammatory processes that underlie neurodegenerative disease. Perhaps the most significant implication of this relationship is that sleep represents one of the few modifiable risk factors in the context of AD by being both biologically influential and behaviorally modifiable throughout the lifespan. Even though improving sleep alone is unlikely

to eliminate the risk of Alzheimer's disease, it may meaningfully alter the trajectory of neuroinflammatory processes that contribute to its development.

Currently, sleep disturbances are often dismissed as benign aspects of aging or treated only after significant cognitive impairment has already emerged. However, the evidence reviewed in this thesis suggests that sleep abnormalities frequently appear years, and in some cases decades, before the onset of clinically detectable dementia. Integrating sleep assessment into routine neurological screening, cognitive risk profiling, and preventative healthcare models may therefore offer a valuable opportunity for earlier intervention. Identifying chronic sleep disruption in midlife or early older adulthood could allow clinicians to implement behavioral or therapeutic strategies that reduce inflammatory burden before irreversible neurodegeneration occurs. In this sense, sleep should be considered not only a symptom of neurological disease but also a measurable biomarker of neural resilience. At the same time, the findings discussed throughout this thesis highlight an emerging public health concern: sleep itself is declining as a societal norm. Modern lifestyles increasingly prioritize productivity over all at the expense of sufficient sleep duration and quality. Large segments of the population routinely obtain less sleep than recommended, often beginning in adolescence and continuing throughout adulthood. If sleep disruption indeed contributes to inflammatory dysregulation and neurodegenerative vulnerability, these societal trends may carry long-term neurological consequences. Addressing sleep health at the population level, through methods like education or changes in workplace policy, may become a meaningful component of future AD prevention strategies.

While the current body of evidence provides compelling support for the sleep–neuroinflammation connection, important questions remain unanswered. Future research will require large-scale longitudinal studies capable of tracking sleep architecture and cognitive outcomes over extended periods of time. Such studies would help clarify the directionality of the relationship between sleep disturbances and neurodegeneration while identifying critical windows during which intervention may be most effective. Advances in technology may also play a critical role in shaping the future of this field. Wearable sleep monitoring devices and digital health platforms now allow researchers to collect continuous sleep data across large populations in real-world environments. When combined with emerging artificial intelligence and machine learning tools, these data streams may enable the development of personalized sleep profiles capable of predicting neurodegenerative risk. Such approaches could transform sleep monitoring from a diagnostic tool into a proactive strategy for identifying individuals who may benefit from early intervention.

Ultimately, the relationship between sleep, neuroinflammation, and AD underscores a broader shift in neuroscience from focusing solely on irreversible pathology toward understanding the physiological systems that maintain resilience in the aging brain, and there is sufficient evidence that sleep lies at the center of this framework. Protecting and restoring healthy sleep may represent one of the most accessible and impactful strategies for preserving cognitive health across one's lifespan. Although AD remains a complex condition, the evidence reviewed throughout this thesis suggests that its trajectory may not be entirely predetermined. By recognizing sleep as a key biological regulator and a modifiable behavioral factor, researchers and clinicians alike may begin to reframe AD not solely as an unavoidable decline, but as a

condition whose risk and progression can be influenced through earlier intervention and preventative care.

References

Adjaye-Gbewonyo, D., Ng, A., Black, L. (2022). Sleep Difficulties in Adults: United States, 2020. (436). https://dx.doi.org/10.15620/cdc:117490

Akiyama, H., Barger, S., Barnum, S., Bradt, B., Bauer, J., Cole, G. M., Cooper, N. R., Eikelenboom, P., Emmerling, M., Fiebich, B. L., Finch, C. E., Frautschy, S., Griffin, W. S. T., Hampel, H., Hull, M., Landreth, G., Lue, L.-F., Mrak, R., Mackenzie, I. R., McGeer, P. L., O'Banion, M. K. (2000). Inflammation and Alzheimer's disease. *Neurobiology of Aging, 21*(3), 383–421. https://doi.org/10.1016/S0197-4580(00)00124-X

Arjmandi-Rad, S., Ebrahimnejad, M., Zarrindast, MR., Vaseghi, S. (2022). Do Sleep Disturbances have a Dual Effect on Alzheimer's Disease? *Cellular and Molecular Neurobiology, 43*, 711-727. https://doi.org/10.1007/s10571-022-01228-1

Attiq, A., Afzal, S., Raman, H., Ahmad, W. (2025). Neuroinflammation to neurodegeneration: Boulevard of broken nerves. *International immunopharmacology*, *161*, 115015. https://doi.org/10.1016/j.intimp.2025.115015

Baranwal, N., Yu, P. K., & Siegel, N. S. (2023). Sleep physiology, pathophysiology, and sleep hygiene. *Progress in cardiovascular diseases*, *77*, 59–69. https://doi.org/10.1016/j.pcad.2023.02.005

Baril, A.-A., Picard, C., Labonté, A., Sanchez, E., Duclos, C., Mohammediyan, B., Breitner, J. C. S., Villeneuve, S., Poirier, J. (2024). Longer sleep duration and neuroinflammation in at-risk elderly with a parental history of Alzheimer's disease. *Sleep, 47*(6). https://doi.org/10.1093/sleep/zsae081

Blackman, J., Swirski, M., Clynes, J., Harding, S., Leng, Y., & Coulthard, E. (2021).

Pharmacological and non-pharmacological interventions to enhance sleep in mild cognitive impairment and mild Alzheimer's disease: A systematic review. *Journal of sleep research*, *30*(4), e13229. https://doi.org/10.1111/jsr.13229

Cao, D., Zhao, Y., Wang, Y., Wei, D., Yan, M., Su, S., Pan, H., Wang, Q. (2024). Effects of sleep deprivation on anxiety-depressive-like behavior and neuroinflammation. *Brain Research, 1836*, 148916. https://doi.org/10.1016/j.brainres.2024.148916

Chattu, V. K., Manzar, M. D., Kumary, S., Burman, D., Spence, D. W., & Pandi-Perumal, S. R. (2018). The Global Problem of Insufficient Sleep and Its Serious Public Health Implications. *Healthcare (Basel, Switzerland), 7*(1), 1. https://doi.org/10.3390/healthcare7010001

Falup-Pecurariu, C., Diaconu, Ș., Țînț, D., & Falup-Pecurariu, O. (2021). Neurobiology of sleep (Review). *Experimental and Therapeutic Medicine, 21*, 272. https://doi.org/10.3892/etm.2021.9703

Ferreira-Vieira, T. H., Guimaraes, I. M., Silva, F. R., & Ribeiro, F. M. (2016). Alzheimer's disease: Targeting the Cholinergic System. *Current neuropharmacology, 14*(1), 101–115. https://doi.org/10.2174/1570159x13666150716165726

Fernandes, G. L., Araújo, P., Tufik, S., & Andersen, M. L. (2017). The role of IL-6 and STAT in sleep and neuroinflammation. *Clinical Immunology, 180*, 58–59. https://doi.org/10.1016/j.clim.2017.04.004

Grandner, M. A., & Fernandez, F. X. (2021). The translational neuroscience of sleep: A contextual framework. *Science (New York, N.Y.)*, *374*(6567), 568–573. https://doi.org/10.1126/science.abj8188

Gott, J. A., Stücker, S., Kanske, P., Haaker, J., & Dresler, M. (2024). Acetylcholine and

metacognition during sleep. *Consciousness and cognition*, *117*, 103608. https://doi.org/10.1016/j.concog.2023.103608

Hasan, F., Tu, Y. K., Lin, C. M., Chuang, L. P., Jeng, C., Yuliana, L. T., Chen, T. J., & Chiu, H. Y. (2022). Comparative efficacy of exercise regimens on sleep quality in older adults: A systematic review and network meta-analysis. *Sleep medicine reviews*, *65*, 101673. https://doi.org/10.1016/j.smrv.2022.101673

Helfrich, R. F., Mander, B. A., Jagust, W. J., Knight, R. T., Walker, M. P. (2018). Old Brains Come Uncoupled in Sleep: Slow Wave-Spindle Synchrony, Brain Atrophy, and Forgetting. *Neuron, 97*(1), 221 - 230. https://doi.org/10.1016/j.neuron.2017.11.020

Howell, M., Avidan, A. Y., Foldvary-Schaefer, N., Malkani, R. G., During, E. H., Roland, J. P., McCarter, S. J., Zak, R. S., Carandang, G., Kazmi, U., & Ramar, K. (2023). Management of REM sleep behavior disorder: An American Academy of Sleep Medicine clinical practice guideline. *Journal of Clinical Sleep Medicine, 19*(4). https://doi.org/10.5664/jcsm.10424

Huang, X., Zhao, X., Li, B., Cai, Y., Zhang, S., Wan, Q., & Yu, F. (2022). Comparative efficacy of various exercise interventions on cognitive function in patients with mild cognitive impairment or dementia: A systematic review and network meta-analysis. *Journal of Sport and Health Science, 11*(2), 212–223. https://doi.org/10.1016/j.jshs.2021.05.003

Irwin, M. R., Vitiello, M. (2019). Implications of sleep disturbance and inflammation for Alzheimer's disease dementia. *The Lancet Neurology, 18*(3), 296–306. https://doi.org/10.1016/S1474-4422(18)30450-2

Kakkar, A., Singh, H., Singh, BK., Kumar, A., Mishra, AK., Chopra, H. (2025).

Neuroinflammation and Alzheimer's disease: Unravelling the molecular mechanisms. *Journal of Alzheimer's disease: JAD*, *108*(1), 19–41. https://doi.org/10.1177/13872877251374353

Killgore, W. (2010). Effects of sleep deprivation on cognition. *Progress in Brain Research, 185*, 105-129, https://doi.org/10.1016/B978-0-444-53702-7.00007-5

Kim, J. H., Elkhadem, A. R., & Duffy, J. F. (2022). Circadian Rhythm Sleep-Wake Disorders in Older Adults. *Sleep medicine clinics*, *17*(2), 241–252. https://doi.org/10.1016/j.jsmc.2022.02.003

Koffel, E., Bramoweth, A. D., & Ulmer, C. S. (2018). Increasing access to and utilization of cognitive behavioral therapy for insomnia (CBT-I): a narrative review. *Journal of general internal medicine*, *33*(6), 955–962. https://doi.org/10.1007/s11606-018-4390-1

Langade, D., Thakare, V., Kanchi, S., & Kelgane, S. (2021). Clinical evaluation of the pharmacological impact of ashwagandha root extract on sleep in healthy volunteers and insomnia patients: A double-blind, randomized, parallel-group, placebo-controlled study. *Journal of ethnopharmacology*, *264*, 113276. https://doi.org/10.1016/j.jep.2020.113276

Lee, Y. F., Gerashchenko, D., Timofeev, I., Bacskai, B. J., & Kastanenka, K. V. (2020). Slow Wave Sleep Is a Promising Intervention Target for Alzheimer's Disease. *Frontiers in neuroscience*, *14*, 705. https://doi.org/10.3389/fnins.2020.00705

Leng, Y., Musiek, E. S., Hu, K., Cappuccio, F. P., & Yaffe, K. (2019). Association between circadian rhythms and neurodegenerative diseases. *The Lancet. Neurology*, *18*(3), 307–318. https://doi.org/10.1016/S1474-4422(18)30461-7

Lucey, B. P., Liu, H., Toedebusch, C. D., Freund, D., Redrick, T., Chahin, S. L., Mawuenyega,

K. G., Bollinger, J. G., Ovod, V., Barthélemy, N. R., & Bateman, R. J. (2023). Suvorexant Acutely Decreases Tau Phosphorylation and Aβ in the Human CNS. *Annals of neurology*, *94*(1), 27–40. https://doi.org/10.1002/ana.26641

Mander, B. A., Winer, J., Walker, M. (2017). Sleep and Human Aging. *Neuron, 94*(1), 19-36. https://doi.org/10.1016/j.neuron.2017.02.004.

Peter-Derex, L., Yammine, P., Bastuji, H., Croisile, B. (2015). Sleep and Alzheimer's disease. *Sleep Medicine Reviews, 19*, 29–38. https://doi.org/10.1016/j.smrv.2014.03.007

Ramar, K., Malhotra, R. K., Carden, K. A., Martin, J. L., Abbasi-Feinberg, F., Aurora, R. N., Kapur, V. K., Olson, E. J., Rosen, C. L., Rowley, J. A., Shelgikar, A. V., & Trotti, L. M. (2021). Sleep is essential to health: an American Academy of Sleep Medicine position statement. *Journal of Clinical Sleep Medicine, 17*(10), 2115–2119. https://doi.org/10.5664/jcsm.9476

Richards, K.C., Fry L., & Ye, L. (in press). Sleep in long-term care settings. In M.H. Kryger, T. Roth, and W..C. Dement (Eds.). Principles and practice of sleep medicine (8th ed.) Elsevier.

Richards, K. C., Fry, L.M. Lozano, A.J., Ji, W., Morrison, J.D., Britt.K.C., Bliwise, D.L, Gooneeratne, N.S., & Hanlon, A.L. (2025). Treatment of restless legs syndrome improves agitation and sleep in persons with dementia. Journal of the American Medical Directors Association, 26(1), 45–52. https://doi.org/10.1016/j.jamda.2025.105485

Schulz, H. (2022). The history of sleep research and sleep medicine in Europe. *Journal of Sleep Research, 31*(4). https://doi.org/10.1111/jsr.13602

Singh, B., Bennett, H., Miatke, A., Dumuid, D., Curtis, R., Ferguson, T., Brinsley, J., Szeto, K.,

Petersen, J. M., Gough, C., Eglitis, E., Simpson, C. E., Ekegren, C. L., Smith, A. E., Erickson, K. I., & Maher, C. (2025). Effectiveness of exercise for improving cognition, memory and executive function: a systematic umbrella review and meta-meta-analysis. *British journal of sports medicine*, *59*(12), 866–876. https://doi.org/10.1136/bjsports-2024-108589

Twarowski, B., & Herbet, M. (2023). Inflammatory Processes in Alzheimer's Disease—Pathomechanism, Diagnosis and Treatment: A Review. *International Journal of Molecular Sciences, 24*(7), 6518. https://doi.org/10.3390/ijms24076518

Vasey, C., McBride, J., & Penta, K. (2021). Circadian Rhythm Dysregulation and Restoration: The Role of Melatonin. *Nutrients*, *13*(10), 3480. https://doi.org/10.3390/nu13103480

Wang, C., & Holtzman, D. M. (2020). Bidirectional relationship between sleep and Alzheimer's disease: Role of amyloid, tau, and other factors. *Neuropsychopharmacology, 45*(1), 104–120. https://doi.org/10.1038/s41386-019-0478-5

Wang, P., Wing, Y. K., Xing, J., Liu, Y., Zhou, B., Zhang, Z., Yao, H., Guo, Y., Shang, Y., & Zhang, X. (2016). Rapid eye movement sleep behavior disorder in patients with probable Alzheimer's disease. *Aging Clinical and Experimental Research, 28*(5), 951–957. https://doi.org/10.1007/s40520-015-0382-8

Wilcock D. M. (2012). A changing perspective on the role of neuroinflammation in Alzheimer's disease. *International journal of Alzheimer's disease*, *2012*, 495243. https://doi.org/10.1155/2012/495243

Zielinski, M. R., & Gibbons, A. J. (2022). Neuroinflammation, sleep, and circadian rhythms. *Frontiers in Cellular and Infection Microbiology, 12*, 853096.

https://doi.org/10.3389/fcimb.2022.853096

Author Biography

I grew up in Belton, Texas, and graduated from Lake Belton High School. Coming from a family involved in the medical field, I developed an early interest in healthcare and biological sciences. This interest eventually led me to pursue a Bachelor of Science in Neuroscience at The University of Texas at Austin, where I also completed a minor in Social and Behavioral Sciences. During my time at UT, I was an active member of the Health Science Scholars Honors organization and spent all three years performing as a member of the Longhorn Band, an experience that greatly shaped my undergraduate career and sense of community on campus.

Outside of the classroom, I have volunteered with Amedisys Healthcare since the winter of 2022, beginning during my senior year of high school. My experiences working with hospice patients played a meaningful role in shaping my academic interests, particularly my curiosity about neurodegenerative disease and how they relate to sleep. After graduating from UT Austin, I plan to take a gap year working as an Emergency Medical Technician while shadowing physicians in a military hospital as I prepare to apply to medical school. Through these experiences, I hope to continue developing both the scientific understanding and compassionate perspective that inspired the research presented in this thesis.