IJHSR
ijhighschoolresearch.org
REVIEW ARTICLE

Adolescent Sleep Deprivation and Susceptibility to Later Development of Alzheimer's Disease

Mingwei Ma

Phillips Exeter Academy, 20 Main St, Exeter, NH, 03833, USA; melodyma6@icloud.com

ABSTRACT: Adolescence is a critical period for brain development, and sleep deprivation during this time may lay the groundwork for Alzheimer's disease (AD). AD is a neurodegenerative disorder characterized by memory loss and cognitive decline. Research has shown that sleep loss in older adults potentiates the risk of AD. Interestingly, approximately 80% of teenagers in the U.S. suffer from sleep deprivation. This narrative review paper aims to evaluate how the biological and structural changes induced during sleep deprivation in adolescence affect the susceptibility to AD in later adulthood. In recent years, literature reviews have focused on either the short-term effects of sleep loss during adolescence or the bidirectionality of sleep and AD in older adults. However, due to the difficulty of longitudinal studies across an individual's lifespan, there is a lack of research connecting the two fields. By bridging evidence from both fields, this paper proposes that persistent sleep deprivation during adolescence induces biological and structural changes that may increase the susceptibility to AD development later in life. This review advocates for this crucial gap in research as it may identify an early-life risk factor for AD and point to key public health and policy implications, such as later school start times.

KEYWORDS: Medical and Health Sciences, Neuroscience, Alzheimer's Disease, Sleep Deprivation, Adolescence.

Introduction

Adolescence is a critical period for brain development and growth.[1] The accumulation of sleep debt during this time may increase an individual's susceptibility to Alzheimer's disease (AD) in the future. Sleep deprivation occurs when an individual consistently gets fewer than the recommended hours of sleep for their age. For teenagers, the recommended amount is 8-10 hours of sleep per night, but self-report surveys indicate that approximately 80% of teenagers in the U.S. sleep less than the recommended amount and therefore suffer from sleep deprivation.[2,3] Similar results are found across the globe, in countries like Korea, Brazil, and Taiwan.[4] Contributing to these statistics are both sociological and biological factors. Social factors include academic stress, early school start times, and addictive technology, while biological factors include the circadian rhythm shift due to hormonal fluctuations during puberty.[5] Chronic sleep loss induces short and long-term effects on a teenager's mental health, physical well-being, and brain structure.[6] However, the long-term effects remain understudied. This is due to the difficulty of tracking brain changes over an extended period of time. This limitation is especially challenging during adolescence, when the brain is rapidly undergoing major structural changes and synaptic pruning of neurons.[7]

Emerging evidence from animal and neuroimaging studies shows that sleep loss potentiates the risk of neurodegenerative diseases in older adults. AD is a neurodegenerative disorder characterized by deteriorating memory and cognitive functioning. It is ranked seventh in the United States for leading causes of death among older adults. In addition, the worldwide cost of AD is estimated to reach $2 trillion USD in 2030.[8,9] Decreased sleep quality in older adults is a common aspect of aging. It results in decreased function of the glymphatic system, which is responsible for draining waste proteins from the brain.[10] This causes a build-up of amyloid-beta and tau proteins, increased neuroinflammation, and structural changes in brain regions vulnerable to AD. These consequences of sleep loss are also indicators or biomarkers for AD, reinforcing the idea that sleep loss is a direct risk factor for the pathogenesis of AD.[11]

By bridging two traditionally separate areas of research, this narrative review proposes that persistent sleep deprivation during the adolescent years induces biological and structural changes that may increase the susceptibility to developing Alzheimer's disease in later adulthood. In recent years, extensive studies have been done on either the short-term effects of sleep loss during teenage years or the bidirectionality of sleep and AD in older adults. However, due to the difficulty of longitudinal studies across an individual's lifespan, there is a lack of research bridging the two fields. This review works to generate hypothesized AD mechanistic pathways from adolescence to adulthood for future investigation.

As the number of sleep-deprived teenagers across the globe skyrockets, it becomes increasingly crucial to investigate the long-term neurological effects of chronic sleep loss in adolescence. Addressing this crucial gap in research could potentially identify an early-life risk factor for AD, which has significant public health implications for scientists, doctors, and policymakers. If the hypothesis is proven to be true, then improving sleep duration and quality in adolescents will not only provide immediate benefits like academic performance but may also reduce the risk of future neurodegeneration. In turn, this could lead to decreased death rates due to AD and reduced medical costs. Early implementation of preventive measures, such as later school start times and increased control over technology

DOI: 10.36838/IJHSR812.22

usage, can reduce the number of sleep-deprived adolescents before it is too late.

This paper is organized as follows. First, it discusses the methodology used for this narrative review. Next, it reviews previous research on the causes and effects of sleep deprivation in adolescents, emphasizing its impacts during this critical window of brain development. Then, it examines findings on sleep loss and its specific neurological effects on the brain. The third section provides evidence for the link between the neurological effects of sleep loss and the risk factors of AD in older individuals. The following section analyzes all of the previous evidence to generate hypothesized pathways for the progression from biomarkers induced during adolescence to AD in late adulthood. Finally, the discussion outlines possible early preventive measures for AD, solutions to improve adolescent sleep habits, and ideas for future areas of research.

Methodology

This paper is a narrative review of the research question: How might the biological and structural changes induced by chronic sleep loss during adolescence affect the susceptibility to AD in later adulthood? This paper solely focuses on the issue of sleep deprivation, rather than oversleeping or sleep disorders, due to its higher prevalence among adolescents worldwide. The specific biological and structural changes discussed in this paper refer to the glymphatic system, neuroinflammation, and changes in brain region volume and density. This paper investigates AD in particular because of the urgency to find a cure or prevention, as well as the recent discovery that sleep loss is a direct risk factor for AD.

Databases such as PubMed, Google Scholar, and Science Direct were used to find credible and recent sources. Other sources were obtained by searching through the reference lists of other review articles. This paper considers studies published between 2012 and 2025, with the exceptions of three studies from 1999, 2002, and 2008, as they represent foundational discoveries. Key terms included "adolescent sleep deprivation" and "Alzheimer's disease biomarkers". Key terms also included combinations of phrases from different fields, such as "glymphatic system", "neuroinflammation", "brain region changes", "Alzheimer's pathology", AND "sleep loss". The inclusion criteria were peer-reviewed studies of human or animal models examining the biological consequences of sleep loss or the biomarkers of AD, as well as review articles for a comprehensive background on the topic. Due to the limitations of testing directly on human participants, this paper includes animal studies and evaluates the validity of these studies based on their sample size, methodology, and relevance. The exclusion criteria were studies that focused on sleep disorders or acute sleep loss.

A narrative review approach was taken due to the interdisciplinary nature of this topic, as it bridges two traditionally separate areas of research together. This paper critically analyzes various past empirical research and synthesizes new hypotheses for future research.

Results

Causes and Consequences of Sleep Deprivation in Adolescents:

As the teenage brain undergoes its second major developmental phase, chronic sleep loss disrupts its growth and induces both short- and long-term changes in the individual.[12] A full understanding of the pathways of brain maturation and the impact of sleep debt during this critical period is needed for hypothesizing how early-life sleep loss can potentiate AD in later adulthood.

In recent years, the number of teenagers sleeping less than the recommended 8-10 hours per night is increasing at an alarming rate. This trend is driven by a combination of biological and sociological factors. Adolescence is typically defined as the stage in life between childhood and adulthood, ages 10 to 19. It is characterized by the hormonal fluctuations associated with puberty.[13] These hormonal fluctuations disrupt the circadian rhythm, delaying the natural sleep-wake cycle and making it harder for teenagers to sleep earlier. The circadian rhythm is regulated by a system of internal "clocks" that match up the body's sleep patterns to the 24-hour light-dark cycle.[14] Specifically, the suprachiasmatic nucleus in the hypothalamus receives light from the environment and coordinates bodily functions such as hormone production, temperature fluctuations, and metabolic processes to direct sleep activity.[15] This biological aspect of adolescence naturally reduces sleep duration in teenagers. On top of this innate delay in bedtime, adolescents are exposed to external pressures, such as increased academic stress, early school start times, strenuous after-school activities, and late-night athletic commitments. These pressures can directly cause shorter sleep duration for adolescents. In addition, habits before bedtime, such as high caffeine intake and exposure to technology (social media, video games, television), can disrupt sleep times and decrease sleep quality.[16] The sociological factors can amplify the circadian rhythm shift, increasing the amount of sleep debt per night.

Consequences of chronic sleep loss in adolescents can appear as short-term effects or as long-term effects, summarized in Table 1. Short-term effects of sleep loss are commonly studied through self-report surveys, hormonal assays, and neurocognitive tests. They include increased stress levels, headaches, stomach pain, decreased memory and focus, worsened mental health, decreased cognitive abilities, and mood swings.[17] These consequences can be shown through poor academic performance and burnout.[18] This may lead to even less sleep per night to catch up on school work, forming a bidirectionality between the causes and effects of sleep loss and creating a cycle that leads to chronic sleep deprivation.[18] The long-term consequences of sleep debt are poorly understood, due to the difficulty of longitudinal studies tracking the teenage brain into adulthood. However, growing evidence suggests that chronic sleep loss can lead to obesity, hypertension, mental health disorders, and cognitive decline.[19] Although these long-term effects are unpredictable due to the multi-factorial nature of brain development, it is imperative that we understand them fully.

Table 1: Short- and long-term effects of chronic sleep loss in adolescents.

Table 1. Effects of Chronic Sleep Loss in Adolescents	
Short-term	**Long-term**
Increased stress levels	Obesity
Headaches	Hypertension
Stomach pain	Mental health disorders
Decreased memory and focus	Cognitive decline
Worsened mental health	
Decreased cognitive abilities	
Mood swings	

Adolescence marks the period where the brain undergoes its second major developmental phase.[20] Human longitudinal studies reveal that the brain reorganizes itself during this time by performing key processes.[21] To increase the efficiency of neural processing and communication between brain regions, the brain undergoes synaptic pruning and myelination. Synaptic pruning is the process by which the brain filters and removes unused or weak synaptic connections, and myelination is the process of insulating axons with myelin sheaths to increase the speed of signal conduction.[7,22] The brain also undergoes structural changes. The prefrontal cortex–the part of the brain responsible for executive function, such as impulse control and risk assessment–rapidly develops throughout adolescence.[23] The limbic system, which controls emotions and reward processing, also becomes heightened in reactivity. This causes adolescents to become emotionally sensitive to social and reward stimuli.[24] Lastly, it is crucial to note that the teenage brain is highly plastic, meaning it is very sensitive to environmental factors such as sleep. Accumulation of sleep debt could take advantage of the brain's plasticity during this time and alter the brain's development, leaving long-lasting consequences that carry into adulthood.

This evidence indicates that sleep deprivation due to biological and sociological factors during adolescence can have immediate effects on physical states, mental health, and cognitive function, although the long-term consequences are less understood. The adolescent brain is particularly vulnerable to damage from sleep loss, as it is undergoing major structural and functional changes during this time period. Future research continuing to investigate the long-term effects is crucial for implementing public health policies. In addition, more insight into how exactly the brain changes during its development phase in response to sleep loss will allow us to understand the possible connections to neurodegenerative diseases in the future. The following section will begin to explore this potential link by analyzing the specific neurological effects of sleep deprivation on a molecular and structural level.

Neurological Effects Due to Sleep Loss:

In all individuals, sleep plays a role in critical processes such as memory consolidation, synaptic homeostasis, cognition, sensory processing, critical thinking, and neural restoration.[25] Sleep deprivation disrupts these processes, resulting in significant consequences for the brain and body. This section examines the molecular mechanisms underlying key functions of sleep and how they are impaired by sleep loss.

First, the brain drains waste proteins during sleep in order to maintain tissue and synaptic homeostasis. The glymphatic system is the waste clearance system for excess cerebrospinal fluid (CSF) and other solutes produced by neurons.[26] This system is most active during the third stage of non-rapid eye movement sleep (NREM3) and works to prevent a build-up of waste proteins in the brain by removing them through a network of channels formed by astrocytes.[27] As shown in Figure 2, CSF enters the perivascular space and gets transported by aquaporins to the astrocyte network. As the CSF flows through the astrocytes, it filters out the metabolic waste. The excess CSF and metabolic waste are transported through aquaporins into the perivascular space, where they are excreted from the brain.[28] Sleep loss or poor sleep quality impairs the glymphatic system's function, allowing waste proteins to accumulate and form aggregates such as Tau tangles or amyloid-beta plaques.[29] As waste build-up increases in the brain, the drainage channels become clogged, causing decreased CSF flow in the glymphatic system, creating a toxic cycle (Figure 3).[10] This glymphatic system dysfunction is most commonly seen in older adults, who experience reduced NREM3 sleep due to aging.

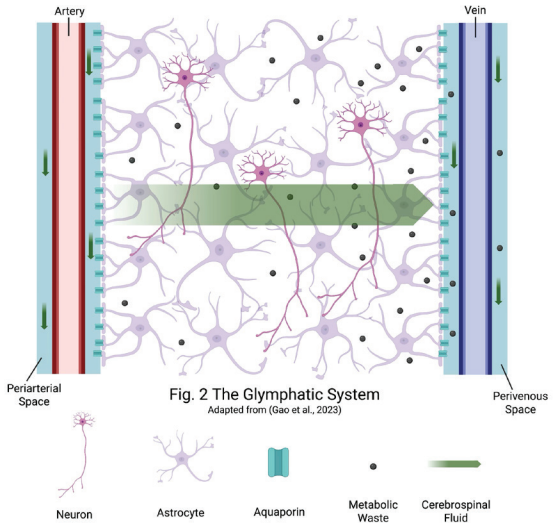

Figure 2: The glymphatic system removes excess CSF fluid and metabolic waste to maintain tissue and synaptic homeostasis.

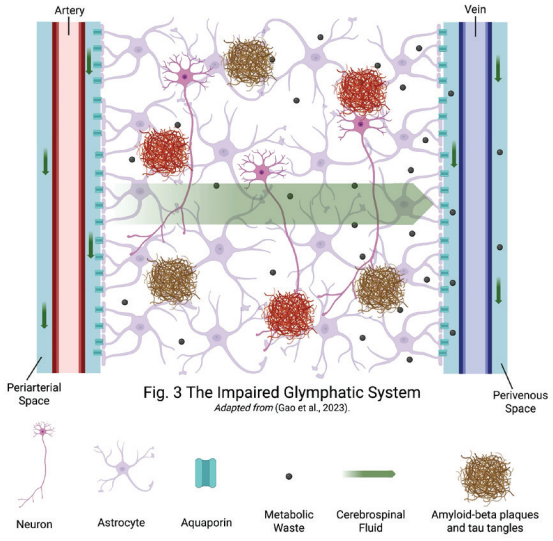

Figure 3: Accumulation of waste proteins leads to an impaired glymphatic system with reduced CSF flow and drainage capabilities.

DOI: 10.36838/IJHSR812.22

Second, the brain's immune system shifts from defensive to maintenance mode during sleep. The brain's immune system–composed mostly of microglia, leukocytes, T-cells, and cytokines–reduces its inflammatory activity and instead focuses on synaptic pruning and memory storage of previous antigens.[30] Although pro-inflammatory cytokines are still present to protect the body from antigens during sleep, the brain also promotes anti-inflammatory cytokines to maintain a balanced neural environment.[30] This mechanism helps to prevent chronic neuroinflammation. Persistent sleep deprivation triggers the production of pro-inflammatory cytokines in the brain, disrupting this balance and causing neuroinflammation.[31] Neuroinflammation–an inflammatory response in the brain–may lead to irreversible consequences such as demyelination of axons, neural tissue damage, disruption of synaptic connectivity, and cognitive decline.[32]

Third, sleep plays a critical role in shaping brain structure through processes like consolidating memory, dendritic spine remodeling, and synaptic pruning. During sleep, the brain has the optimal conditions for memory consolidation, the process of encoding short-term memory into long-term memory.[33] The core of this concept of memory formation is the strength of the synaptic connections relating to this memory, also known as long-term potentiation (LTP).[33] LTP, a form of synaptic plasticity, works in tandem with synaptic pruning, as the latter removes weak neural connections and strengthens strong ones. The loss of sleep impairs the strengthening of these neuronal connections, therefore leading to decreased cognition, memory, and critical thinking.

These findings demonstrate that sleep deprivation impairs numerous neurological processes that occur during sleep, such as waste clearance, immune system maintenance, synaptic pruning, and structural development. Disruption to these essential restorative functions in the brain leads to lasting consequences. Additionally, while current research mostly explores the consequences of insufficient sleep, it would be beneficial for future studies to investigate the consequences of excess sleep or "catch-up" sleep on weekends, especially in teenagers. To answer the research question, the next section will analyze evidence connecting these neurological effects of sleep deprivation to the biomarkers and hallmarks of AD.

Evidence Linking Sleep Deprivation to Alzheimer's Disease:

The overlap between the specific neurological changes discussed above and the pathology of AD suggests that sleep deprivation may be a direct risk factor. Both animal and human studies indicate that the sleep-deprived brain shares key characteristics with brains suffering from AD. These characteristics include accumulation of waste protein aggregates, increased neuroinflammation, and structural changes in vulnerable brain regions. This section analyzes AD pathology and emerging evidence linking it to sleep deprivation. It is worth noting that these studies are focused on the matured adult brain, not the adolescent one. Translating the mechanisms of this link–between sleep loss and adult brains–to adolescent brains is only a speculation and not directly observed.

AD is a neurodegenerative disease that targets the brain's neural connections and results in memory loss. The basis of this cognitive decline involves the decline in activity of the glymphatic system, leading to the accumulation of waste proteins, which induce inflammatory responses and ultimately result in disruption of synaptic activity.[34] AD can be diagnosed by the detection of amyloid-beta and tau protein clumps in the brain through magnetic resonance imaging (MRI) or positron emission tomography (PET).[35] Interestingly, these hallmarks of AD–amyloid-beta aggregates and tau tangles–also appear in sleep-deprived brains, such as older individuals who struggle with entering NREM3 sleep or those who suffer from sleep disorders like insomnia.[36] Researchers investigating the similarity of sleep-deprived brains and AD-affected brains showed that sleep loss acts as a direct risk factor for AD. A 2018 PET study of human participants reveals that after one night of sleep deprivation, the amyloid-beta levels in the right hippocampus and thalamus significantly exceeded the baseline levels of the control group.[37] Another study uses self-reported sleep lengths from human participants and MRI/PET brain scans to analyze amyloid-beta deposition, finding that shorter sleep duration results in greater amyloid-beta burden.[38] In addition, an animal study testing the effects of orexin levels on mice found that sleep deprivation leads to an increased amount of amyloid-beta.[39] This evidence reveals how sleep loss, even just one night, causes the build-up of waste proteins, harming neuron health and synaptic communication.

The accumulation of waste proteins, like amyloid-beta, induces neuroinflammation. Receptor protein LTR2 triggers neurotoxic pro-inflammatory mediators when amyloid-beta binds to it.[40] Neuroinflammation contributes to AD progression through a positive feedback cycle. It increases oxidative stress, degrades neurons, and loses the ability to destroy neurotoxic proteins like amyloid-beta and tau, which in turn triggers more inflammation.[41] Inflammation levels can be measured by miRNA, snippets of non-coding RNA that can act as biomarkers.[42] A human study tracking circulating miRNAs in the blood of participants the morning after a night of no sleep found that two out of the three miRNAs associated with neurodegeneration in AD increased compared to the baseline values.[43] Specifically, this group of researchers found that the levels of miR-127-3p and miR-142-3p, both of which activate inflammation, were greater after a night of no sleep versus a night of sleep. These results further corroborate the idea that sleep loss directly causes inflammation, which in turn causes neurodegeneration.

Taken together, emerging evidence from both human and animal studies indicates that sleep loss is a direct risk factor for AD, as its consequences overlap with the pathology and hallmarks of AD. However, while the neuroscience community is starting to understand the molecular mechanisms of waste protein accumulation and neuroinflammation, little is known about these processes in the sleep-deprived adolescent brain. This research gap may exist due to the recency of the consensus that sleep loss is a direct risk factor for AD, meaning longitudinal studies tracking brains from adolescence to late adulthood have not yet been completed. Due to the lack of direct evidence

connecting sleep deprivation in adolescence to the risk of AD in later adulthood, the following section proposes hypothetical pathways based on current understandings of AD pathology for possible future investigation.

Hypothesized AD Mechanistic Pathways from Adolescence to Adulthood:

Using known evidence of the pathology of AD in adults and the consequences of sleep deprivation, this section works to create extrapolated hypotheses for the possible mechanistic pathways of AD from adolescence to late adulthood.

One pathway involves the impaired glymphatic system. The effectiveness of the glymphatic system is a major concern when considering the long-term neurological consequences of sleep loss in adolescence. As the circadian rhythm shifts back and teenagers fall to the temptation of technology before bedtime, both sleep quantity and quality are compromised. Because the glymphatic system is most active during NREM3 sleep, the fragmented or decreased durations of NREM3 sleep could limit its ability to remove CSF and waste proteins. These proteins, such as amyloid-beta and tau, can cause a build-up in the neurons, which impairs synaptic connections. Persistent sleep deprivation of consecutive nights of sleep loss may cause substantial waste protein accumulation. The glymphatic system may attempt to compensate and work harder to remove these waste proteins during the next NREM3 sleep, but this may backfire and result in a damaged glymphatic system from overactivation. The teenage brain is undergoing rapid brain development, which leaves it very vulnerable to damage during this adolescent period. This impairment and overactivation of the glymphatic system may persist into adulthood. When aging naturally causes an increase in the build-up of neurotoxic proteins, the damaged glymphatic system may not be as effective in removing waste, leading to a faster accumulation of tau or amyloid-beta. This early-life build-up of amyloid-beta and tau aggregates may predispose the brain to faster accumulation of neurotoxic proteins in later adulthood by wearing down the glymphatic system.

A second mechanism is chronic neuroinflammation. The persistent activation of the immune system is a long-term consequence of sleep deprivation in adolescence that may carry into adulthood. A night of sleep loss increases neuroinflammation and results in increased oxidative stress, which impairs neuronal health and synaptic plasticity.[44] Persistent sleep deprivation–common in teenagers due to bad sleep habits and early school start times–causes recurring inflammation in the brain. This chronic neuroinflammation, where microglia cells activate strong immune responses, can damage healthy neurons nearby, including the blood-brain barrier (BBB).[45] The BBB is a selectively permeable membrane between the blood and the interstitium of the brain and acts as a line of defense against foreign antigens.[46,47] During adolescence, the BBB undergoes alterations in its permeability, suggesting that early damage to the barrier in adolescence may decrease the barrier's resilience against antigens in the future.[48] In addition, astrocytes and microglia cells undergo major development during adolescence.48 In late adulthood, the cells may remember the mechanisms for inflammation from previous episodes, resulting in a faster and more aggressive inflammation response when triggered by age-related sleep loss. Due to the brain and immune system's high plasticity during adolescence, chronic inflammation may result in decreased protection against antigens and increased responsiveness or overactivation of immune responses. These consequences may follow into late adulthood, leading to a faster rate of neurodegeneration.

The third pathway involves structural changes in the brain. During periods of sleep loss, brain regions associated with learning, memory, and executive functioning show reductions in volume and activity. Adolescence is when the brain undergoes major growth in key brain regions such as the hippocampus and prefrontal cortex. The hippocampus is responsible for memory consolidation, and the prefrontal cortex is responsible for decision-making and cognition.[49] Sleep deprivation during this stage impacts the growth of these brain regions by reducing grey matter volume, synaptic density, and dendritic spines. As the adolescent brain continues to develop with these limitations, the result may be an adult brain with lower baseline levels of cognition. Human neuroimaging studies have shown that individuals suffering from AD have decreased functioning and volume in the hippocampus and prefrontal cortex, both of which are regions associated with cognition and memory.[50] This early-life underdevelopment of the cognitive functioning regions in the brain may increase the vulnerability to neurodegeneration in later adulthood.

In sum, these three potential pathways, hypothesized from the evidence surrounding glymphatic system function, neuroinflammation, and brain structural changes, suggest that sleep deprivation in adolescence may predispose an individual to AD when older. Future research should acquire more longitudinal data, such as surveys or brain scans about sleep duration and neurodegeneration across lifespans, in order to confirm or deny these hypotheses. With all of this extensive literature review in mind, the paper will discuss the importance of this field and potential research directions.

■ Discussion

This review uses converging evidence from the consequences of sleep loss and pathological characteristics of AD to outline three potential pathways of AD progression: impaired glymphatic system, chronic neuroinflammation, and reduced development of brain regions vulnerable to neurodegeneration. Although this paper analyzes them separately, it's important to note that these three pathways are interconnected in many ways. For example, an impaired glymphatic system leads to the build-up of amyloid-beta and tau proteins, which activate neuroinflammation; inflammation, in turn, hinders cell communication and further reduces glymphatic efficiency.[51] In addition, both the accumulation of waste proteins and inflammation can disrupt brain region development and reduce synaptic density.[51] These three main mechanisms together create a self-perpetuating cycle. On the other hand, human and mouse studies have shown that the accumulation of amyloid-beta proteins results in shortened and disturbed sleep.[52]

DOI: 10.36838/IJHSR812.22

This bidirectional relationship between sleep and AD forms a continuous loop that leads to chronic sleep deprivation.

More attention should be directed to this critical gap in research. Existing studies have established the bidirectional relationship between sleep and AD, yet most of them focus on the aged adult brain, not the adolescent one. The lack of studies investigating the link between sleep loss in teenagers and AD in later life can be attributed to several limitations and reasons. First, there are logistical difficulties in performing longitudinal studies across decades. It is a challenge to find willing participants, ensure these participants are able to perform periodical check-ups, and finish the decades-long experiment until completion. Second, the period of adolescence is a time of big developmental changes in the brain. These neurological changes are unpredictable and different for everybody, making investigating the effects of sleep loss during adolescence hard and inaccurate. Third, the connection between sleep deprivation in adolescence and neurodegenerative diseases may seem weak. Big lifestyle changes can happen between adolescence and late adulthood, such as diet, physical activity, and mental health. These factors may affect the brain more than sleep and complicate the results. It is difficult to determine causality when there are so many factors at play. However, as technology continues to improve, new research methods or laboratory equipment may allow researchers to overcome these limitations. By demonstrating the possibility of chronic sleep loss in adolescence being an early-life risk factor for AD, this paper hopes to invite future research on this topic.

From a public health standpoint, finding an early-life risk factor for AD is critical, as it allows for early preventive measures. Sleep loss in adolescence is a modifiable risk factor, meaning it can be altered through individual and systemic interventions, unlike other risk factors for AD, like genetic predispositions. Public policies such as later school start times and increased control on technology usage can help reduce the number of sleep-deprived adolescents. If the hypothesis is proven to be true, improving sleep duration and quality in adolescents will not only provide immediate benefits like academic performance and mental health, but may also reduce the risk of future neurodegeneration. This leads to reduced medical costs and deaths due to AD, which will increase the quality of life for everyone.

Future research should also consider the role of other factors. For example, certain genes in individuals are found to increase the risk of AD.[53] The role of genetic predispositions to AD in adolescents during sleep deprivation is a promising area for future research. In addition, the long-term effects of "make-up sleep" in teenagers, such as naps or excess sleep on weekends, are also worth investigating. Though this paper focuses on sleep deprivation due to its prevalence among teenagers, the consequences of oversleeping are another concern and can be a future area of research. Lastly, research can investigate how chronic sleep loss during adolescence may increase the susceptibility to other brain disorders or diseases. Examples include Parkinson's disease, multiple sclerosis, stroke, and epilepsy. By bridging two traditionally separate fields of study, this paper opens the possibilities for a wide variety of future research.

■ Conclusion

This review proposes that persistent sleep deprivation during the adolescent years induces biological and structural changes that may increase the risk of developing Alzheimer's disease later in life. By analyzing evidence on the causes and consequences of sleep loss during adolescence, neurological effects on the brain as a result of sleep deprivation, and the role of sleep loss as a direct risk factor of AD, this paper outlines hypothesized mechanistic pathways linking early-life sleep debt to neurodegeneration in later adulthood. The hypothesized pathways are the overactivation of the glymphatic system, chronic neuroinflammation, and reductions in key brain regions associated with cognitive functions. Future research testing the amount of waste protein build-up, neuroinflammation, and structural changes in the adolescent brain after various periods of insufficient sleep, as well as longitudinal data are needed to test these hypotheses. Other variables, such as genetic predisposition to AD and oversleeping, need to be considered as well. By addressing this major gap in research, this paper highlights the potential for identifying an early-life risk factor for AD and its public health policy implications. If the hypothesis is proven to be true, later school start times and increased control over technology could increase the amount of sleep a teenager gets per night and help decrease the susceptibility to AD in later years. Reduced neurodegeneration in the elderly population can reduce medical costs and deaths, and lead to a better quality of life for all involved. Given the sharp increase in the number of sleep-deprived teenagers who will all grow into the elderly population in several decades, public health protocols must be implemented early to prevent neurodegeneration before it is too late.

■ Acknowledgments

This work was supported by Dr. Jorge Avila and Andrew Huckins-Noss from Indigo Research. I attest that the ideas, graphics, and writing in this paper are entirely my own.

■ References

1. Larsen, B.; Luna, B. Adolescence as a Neurobiological Critical Period for the Development of Higher-Order Cognition. *Neurosci. Biobehav. Rev.* **2018**, *94*, 179–195. https://doi.org/10.1016/j.neubiorev.2018.09.005.
2. American Academy of Sleep Medicine. *Teen Sleep Duration Health Advisory - AASM Recommendation*. American Academy of Sleep Medicine – Association for Sleep Clinicians and Researchers. https://aasm.org/advocacy/position-statements/teen-sleep-duration-health-advisory/ (accessed 2025-11-27).
3. National Sleep Foundation. *Teens' Sleep Health and Mental Health Strongly Linked*. National Sleep Foundation. https://www.thensf.org/teens-sleep-health-and-mental-health-strongly-linked/ (accessed 2025-07-26).
4. Leger, D.; Beck, F.; Richard, J.-B.; Godeau, E. Total Sleep Time Severely Drops during Adolescence. *PLOS ONE* **2012**, *7* (10), e45204. https://doi.org/10.1371/journal.pone.0045204.
5. Owens, J. Insufficient Sleep in Adolescents and Young Adults: An Update on Causes and Consequences. *Pediatrics* **2014**, *134* (3), e921–e932. https://doi.org/10.1542/peds.2014-1696.

6. Johri, K.; Pillai, R.; Kulkarni, A.; Balkrishnan, R. Effects of Sleep Deprivation on the Mental Health of Adolescents: A Systematic Review. *Sleep Sci. Pract*. **2025**, *9* (1), 9. https://doi.org/10.1186/s41606-025-00127-w.
7. Cornell, J.; Salinas, S.; Huang, H.-Y.; Zhou, M. Microglia Regulation of Synaptic Plasticity and Learning and Memory. *Neural Regen. Res*. **2021**, *17* (4), 705–716. https://doi.org/10.4103/1673-5374.322423.
8. *Alzheimer's Disease Fact Sheet*. National Institute on Aging. https://www.nia.nih.gov/health/alzheimers-and-dementia/alzheimers-disease-fact-sheet (accessed 2025-07-26).
9. Tay, L. X.; Ong, S. C.; Tay, L. J. *Economic Burden of Alzheimer's Disease: A Systematic Review - Value in Health Regional Issues*. https://www.valuehealthregionalissues.com/article/S2212-1099(23)00094-8/fulltext (accessed 2025-11-27).
10. Nedergaard, M.; Goldman, S. A. Glymphatic Failure as a Final Common Pathway to Dementia. *Science* **2020**. https://doi.org/10.1126/science.abb8739.
11. Sadeghmousavi, S.; Eskian, M.; Rahmani, F.; Rezaei, N. The Effect of Insomnia on the Development of Alzheimer's Disease. *J. Neuroinflammation* **2020**, *17* (1), 289. https://doi.org/10.1186/s12974-020-01960-9.
12. Anastasiades, P. G.; de Vivo, L.; Bellesi, M.; Jones, M. W. Adolescent Sleep and the Foundations of Prefrontal Cortical Development and Dysfunction. *Prog. Neurobiol*. **2022**, *218*, 102338. https://doi.org/10.1016/j.pneurobio.2022.102338.
13. National Academies of Sciences, E.; Division, H. and M.; Education, D. of B. and S. S. and; Board on Children, Y.; Applications, C. on the N. and S. S. of A. D. and I.; Backes, E. P.; Bonnie, R. J. Adolescent Development. In *The Promise of Adolescence: Realizing Opportunity for All Youth*; National Academies Press (US), **2019**.
14. Uccella, S.; Cordani, R.; Salfi, F.; Gorgoni, M.; Scarpelli, S.; Gemignani, A.; Geoffroy, P. A.; De Gennaro, L.; Palagini, L.; Ferrara, M.; Nobili, L. Sleep Deprivation and Insomnia in Adolescence: Implications for Mental Health. *Brain Sci*. **2023**, *13* (4), 569. https://doi.org/10.3390/brainsci13040569.
15. Coomans, C. P.; Ramkisoensing, A.; Meijer, J. H. The Suprachiasmatic Nuclei as a Seasonal Clock. *Front. Neuroendocrinol*. **2015**, *37*, 29–42. https://doi.org/10.1016/j.yfrne.2014.11.002.
16. Owens, J. Insufficient Sleep in Adolescents and Young Adults: An Update on Causes and Consequences. *Pediatrics* **2014**, *134* (3), e921–e932. https://doi.org/10.1542/peds.2014-1696.
17. Medic, G.; Wille, M.; Hemels, M. E. Short- and Long-Term Health Consequences of Sleep Disruption. *Nat. Sci. Sleep* **2017**, *9*, 151–161. https://doi.org/10.2147/NSS.S134864.
18. Evers, K.; Chen, S.; Rothmann, S.; Dhir, A.; Pallesen, S. Investigating the Relation among Disturbed Sleep Due to Social Media Use, School Burnout, and Academic Performance. *J. Adolesc*. **2020**, *84* (1), 156–164. https://doi.org/10.1016/j.adolescence.2020.08.011.
19. Johri, K.; Pillai, R.; Kulkarni, A.; Balkrishnan, R. Effects of Sleep Deprivation on the Mental Health of Adolescents: A Systematic Review. *Sleep Sci. Pract*. **2025**, *9* (1), 9. https://doi.org/10.1186/s41606-025-00127-w.
20. Sisk, C. L.; Foster, D. L. The Neural Basis of Puberty and Adolescence. *Nat. Neurosci*. **2004**, *7* (10), 1040–1047. https://doi.org/10.1038/nn1326.
21. Giedd, J. N.; Blumenthal, J.; Jeffries, N. O.; Castellanos, F. X.; Liu, H.; Zijdenbos, A.; Paus, T.; Evans, A. C.; Rapoport, J. L. Brain Development during Childhood and Adolescence: A Longitudinal MRI Study. *Nat. Neurosci*. **1999**, *2* (10), 861–863. https://doi.org/10.1038/13158.
22. Corrigan, N. M.; Yarnykh, V. L.; Hippe, D. S.; Owen, J. P.; Huber, E.; Zhao, T. C.; Kuhl, P. K. Myelin Development in Cerebral Gray and White Matter during Adolescence and Late Childhood. *NeuroImage* **2021**, *227*, 117678. https://doi.org/10.1016/j.neuroimage.2020.117678.
23. Arain, M.; Haque, M.; Johal, L.; Mathur, P.; Nel, W.; Rais, A.; Sandhu, R.; Sharma, S. Maturation of the Adolescent Brain. *Neuropsychiatr. Dis. Treat*. **2013**, *9*, 449–461. https://doi.org/10.2147/NDT.S39776.
24. Casey, B. J.; Jones, R. M.; Hare, T. A. The Adolescent Brain. *Ann. N. Y. Acad. Sci*. **2008**, *1124*, 111–126. https://doi.org/10.1196/annals.1440.010.
25. Zielinski, M. R.; McKenna, J. T.; McCarley, R. W.; Zielinski, M. R.; McKenna, J. T.; McCarley, R. W. Functions and Mechanisms of Sleep. *AIMS Neurosci*. **2016**, *3* (1), 67–104. https://doi.org/10.3934/Neuroscience.2016.1.67.
26. Iliff, J. J.; Wang, M.; Liao, Y.; Plogg, B. A.; Peng, W.; Gundersen, G. A.; Benveniste, H.; Vates, G. E.; Deane, R.; Goldman, S. A.; Nagelhus, E. A.; Nedergaard, M. A Paravascular Pathway Facilitates CSF Flow through the Brain Parenchyma and the Clearance of Interstitial Solutes, Including Amyloid β. Sci. *Transl. Med*. **2012**, *4* (147), 147ra111. https://doi.org/10.1126/scitranslmed.3003748.
27. Jessen, N. A.; Munk, A. S. F.; Lundgaard, I.; Nedergaard, M. The Glymphatic System – A Beginner's Guide. *Neurochem. Res*. **2015**, *40* (12), 2583–2599. https://doi.org/10.1007/s11064-015-1581-6.
28. Gao, Y.; Liu, K.; Zhu, J. Glymphatic System: An Emerging Therapeutic Approach for Neurological Disorders. *Front. Mol. Neurosci*. **2023**, *16*. https://doi.org/10.3389/fnmol.2023.1138769.
29. Voumvourakis, K. I.; Sideri, E.; Papadimitropoulos, G. N.; Tsantzali, I.; Hewlett, P.; Kitsos, D.; Stefanou, M.; Bonakis, A.; Giannopoulos, S.; Tsivgoulis, G.; Paraskevas, G. P. The Dynamic Relationship between the Glymphatic System, Aging, Memory, and Sleep. *Biomedicines* **2023**, *11* (8), 2092. https://doi.org/10.3390/biomedicines11082092.
30. Besedovsky, L.; Lange, T.; Born, J. Sleep and Immune Function. *Pflüg. Arch. - Eur. J. Physiol*. **2012**, *463* (1), 121–137. https://doi.org/10.1007/s00424-011-1044-0.
31. Asif, N.; Iqbal, R.; Nazir, C. F. Human Immune System during Sleep. *Am. J. Clin. Exp. Immunol*. 2017, *6* (6), 92–96.
32. DiSabato, D. J.; Quan, N.; Godbout, J. P. Neuroinflammation: The Devil Is in the Details. **2016**. https://doi.org/10.1111/jnc.13607.
33. Rasch, B.; Born, J. About Sleep's Role in Memory. *Physiol. Rev*. 2013, *93* (2), 681–766. https://doi.org/10.1152/physrev.00032.2012.
34. Querfurth, H. W.; LaFerla, F. M. Alzheimer's Disease. The New England Journal of Medicine. https://doi.org/10.1056/NEJMra0909142.
35. Scheltens, P.; Blennow, K.; Breteler, M. M. B.; Strooper, B. de; Frisoni, G. B.; Salloway, S.; Flier, W. M. V. der. Alzheimer's Disease. *The Lancet* **2016**, *388* (10043), 505–517. https://doi.org/10.1016/S0140-6736(15)01124-1.
36. Xia, X.; Jiang, Q.; McDermott, J.; Han, J. J. Aging and Alzheimer's Disease: Comparison and Associations from Molecular to System Level. *Aging Cell* **2018**, *17* (5), e12802. https://doi.org/10.1111/acel.12802.
37. Shokri-Kojori, E.; Wang, G.-J.; Wiers, C. E.; Demiral, S. B.; Guo, M.; Kim, S. W.; Lindgren, E.; Ramirez, V.; Zehra, A.; Freeman, C.; Miller, G.; Manza, P.; Srivastava, T.; De Santi, S.; Tomasi, D.; Benveniste, H.; Volkow, N. D. β-Amyloid Accumulation in the Human Brain after One Night of Sleep Deprivation. *Proc. Natl. Acad. Sci. U. S. A*. **2018**, *115* (17), 4483–4488. https://doi.org/10.1073/pnas.1721694115.
38. Spira, A. P.; Gamaldo, A. A.; An, Y.; Wu, M. N.; Simonsick, E. M.; Bilgel, M.; Zhou, Y.; Wong, D. F.; Ferrucci, L.; Resnick, S. M. Self-Reported Sleep and β-Amyloid Deposition in Communi-

DOI: 10.36838/IJHSR812.22

ty-Dwelling Older Adults. *JAMA Neurol.* **2013**, *70* (12), 1537–1543. https://doi.org/10.1001/jamaneurol.2013.4258.
39. Roh, J. H.; Jiang, H.; Finn, M. B.; Stewart, F. R.; Mahan, T. E.; Cirrito, J. R.; Heda, A.; Snider, B. J.; Li, M.; Yanagisawa, M.; de Lecea, L.; Holtzman, D. M. Potential Role of Orexin and Sleep Modulation in the Pathogenesis of Alzheimer's Disease. *J. Exp. Med.* **2014**, *211* (13), 2487–2496. https://doi.org/10.1084/jem.20141788.
40. Liu, S.; Liu, Y.; Hao, W.; Wolf, L.; Kiliaan, A. J.; Penke, B.; Rübe, C. E.; Walter, J.; Heneka, M. T.; Hartmann, T.; Menger, M. D.; Fassbender, K. TLR2 Is a Primary Receptor for Alzheimer's Amyloid β Peptide to Trigger Neuroinflammatory Activation. *J. Immunol. Baltim. Md 1950* **2012**, *188* (3), 1098–1107. https://doi.org/10.4049/jimmunol.1101121.
41. Zhang, W.; Xiao, D.; Mao, Q.; Xia, H. Role of Neuroinflammation in Neurodegeneration Development. *Signal Transduct. Target. Ther.* **2023**, *8* (1), 267. https://doi.org/10.1038/s41392-023-01486-5.
42. van den Berg, M. M. J.; Krauskopf, J.; Ramaekers, J. G.; Kleinjans, J. C. S.; Prickaerts, J.; Briedé, J. J. Circulating microRNAs as Potential Biomarkers for Psychiatric and Neurodegenerative Disorders. *Prog. Neurobiol.* **2020**, *185*, 101732. https://doi.org/10.1016/j.pneurobio.2019.101732.
43. Zhang, L.; Grip, A.; Hjelmqvist, D.; Benedict, C.; Brandão, L. E. M.; Cedernaes, J. Acute Sleep Loss Increases Circulating Morning Levels of Two MicroRNAs Implicated in Neurodegenerative Disease in Healthy Young Men. *J. Cell. Mol. Med.* **2025**, *29* (7), e70523. https://doi.org/10.1111/jcmm.70523.
44. Lv, Y.-N.; Cui, Y.; Zhang, B.; Huang, S.-M. Sleep Deficiency Promotes Alzheimer's Disease Development and Progression. *Front. Neurol.* **2022**, *13*. https://doi.org/10.3389/fneur.2022.1053942.
45. da Fonseca, A. C. C.; Matias, D.; Garcia, C.; Amaral, R.; Geraldo, L. H.; Freitas, C.; Lima, F. R. S. The Impact of Microglial Activation on Blood-Brain Barrier in Brain Diseases. *Front. Cell. Neurosci.* **2014**, *8*, 362. https://doi.org/10.3389/fncel.2014.00362.
46. Kadry, H.; Noorani, B.; Cucullo, L. A Blood–Brain Barrier Overview on Structure, Function, Impairment, and Biomarkers of Integrity. *Fluids Barriers CNS* **2020**, *17* (1), 69. https://doi.org/10.1186/s12987-020-00230-3.
47. Dotiwala, A. K.; McCausland, C.; Samra, N. S. Anatomy, Head and Neck: Blood Brain Barrier. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), **2025**.
48. Brenhouse, H. C.; Schwarz, J. M. Immunoadolescence: Neuroimmune Development and Adolescent Behavior. *Neurosci. Biobehav. Rev.* **2016**, *70*, 288–299. https://doi.org/10.1016/j.neubiorev.2016.05.035.
49. Preston, A. R.; Eichenbaum, H. Interplay of Hippocampus and Prefrontal Cortex in Memory. *Curr. Biol. CB* **2013**, *23* (17), R764–R773. https://doi.org/10.1016/j.cub.2013.05.041.
50. Rao, Y. L.; Ganaraja, B.; Murlimanju, B. V.; Joy, T.; Krishnamurthy, A.; Agrawal, A. Hippocampus and Its Involvement in Alzheimer's Disease: A Review. *3 Biotech* **2022**, *12* (2), 55. https://doi.org/10.1007/s13205-022-03123-4.
51. Cai, Y.; Zhang, Y.; Leng, S.; Ma, Y.; Jiang, Q.; Wen, Q.; Ju, S.; Hu, J. The Relationship between Inflammation, Impaired Glymphatic System, and Neurodegenerative Disorders: A Vicious Cycle. *Neurobiol. Dis.* **2024**, *192*, 106426. https://doi.org/10.1016/j.nbd.2024.106426.
52. Wang, C.; Holtzman, D. M. Bidirectional Relationship between Sleep and Alzheimer's Disease: Role of Amyloid, Tau, and Other Factors. *Neuropsychopharmacology* **2020**, *45* (1), 104–120. https://doi.org/10.1038/s41386-019-0478-5.
53. Krishnamurthy, H. K.; Jayaraman, V.; Krishna, K.; Wang, T.; Bei, K.; Changalath, C.; Rajasekaran, J. J. An Overview of the Genes and Biomarkers in Alzheimer's Disease. *Ageing Res. Rev.* **2025**, *104*, 102599. https://doi.org/10.1016/j.arr.2024.102599.

Author

Mingwei Ma is a high school junior at Phillips Exeter Academy in New Hampshire interested in the intersection of neuroscience, public health, and biomedical engineering.