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Is sleep disruption a risk factor for Alzheimer's disease?

Arthur Cassa Macedo[a], Sara Balouch[b] and Naji Tabet[b]

Author Note

[a]University of Sussex, Brighton, England, UK.

[b]Centre for Dementia Studies, Brighton & Sussex Medical School, Brighton, England, UK.

Correspondence concerning this article should be addressed to Dr Sara Balouch, Room 101, Trafford Centre for Medical Research, Brighton & Sussex Medical School, University of Sussex Campus, Falmer, Brighton, East Sussex, BN1 9RY; Tel +44-1273-872691; Email: s.balouch@bsms.ac.uk

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Abstract

Sleep disturbances are routinely encountered in Alzheimer's disease (AD) and affect about 25-40% of patients in the mild-to-moderate stages of the disease. In many, sleep pathology may represent a symptom of the underlying neurodegeneration. However, a history of sleep disruption occurring years prior to onset of cognitive symptoms could represent a potential risk factor for AD. The aim of the present narrative review was to evaluate current evidence linking sleep disturbances with AD development and to understand the mechanisms that may contribute to this.

Although the mechanisms by which poor sleep may contribute to AD genesis is not fully understood, emerging evidence linking disturbances in the sleep wake cycle with Aβ deposition is shedding light on the relationship between sleep pathology and the subsequent development of AD. Aβ burden appears to be enhanced by sleep-wake cycle disruptions and is suspected as being an important mechanism by which sleep disruptions contribute in AD development. Other mechanisms triggered by sleep disruption may also be involved in AD development, such as brain hypoxia, oxidative stress, circadian activity rhythms disturbances, overexpression of orexins and blood brain barrier impairment. Further understanding of the link between sleep disturbances and future development of AD is still needed before sleep disturbances are clearly marked as a preventable risk factor for AD. In these circumstances, early lifestyle interventions to help increase the quantity and quality of sleep may have a favorable outcome on decreasing the incidence of AD and this needs to be investigated further.

Keywords: Alzheimer Disease; Dementia; Sleep; Sleep wake disorders; Risk factors.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive impairment [1] and considered the main cause of dementia, accounting for up to 70% of cases [2]. In 2010, the number of people affected by dementia worldwide was estimated to be 35.6 million, and this figure is expected to double every 20 years [3]. The increasing number of cases, closely related to the increase in human life expectancy, and the absence of a cure for AD turns this disease into a major global health problem.

The main pathological hallmarks of AD are the diffuse deposition of extracellular amyloid-β (Aβ) plaques across the brain parenchyma, the aggregation of hyperphosphorylated tau protein into intracellular neurofibrillary tangles (NFT) and neuronal loss [4-6]. The accumulation of results from an imbalance between its production and clearance, which is a key early step in the pathogenesis of AD and begins 10-20 years before the appearance of cognitive symptoms – this period is known as the preclinical stage of AD [7].

Risk factors for AD include advanced age [8-10], inherited genetic mutations in three genes ($_{A\beta}$PP, PSEN1 and PSEN2) [11-13], allele apolipoprotein E (APOE) ε4 [14-16], lack of aerobic cardiovascular exercise [17], high blood pressure [18], tobacco use [19] and hypercholesterolemia [20], among others. Recently, growing evidence suggests that sleep disruption could also be a risk factor for AD. The focus of this narrative review is to highlight the evidence for sleep disruption as a possible risk factor for AD and describe the various physiological pathways on how sleep disruption could lead to AD.

Sleep Disturbance as a Characteristic of AD

Sleep disturbances are routinely encountered in patients with AD and affect 25-40% of the patients presenting with mild-to-moderate stages [21]. Several sleep disorders commonly

affect AD patients and these include insomnia, diminished duration of night-time sleep, increased nocturnal awakenings and enhanced daytime sleep [22]. AD patients also present with changes in their sleep architecture that include reduced duration of rapid eye movement (REM) sleep stage bouts [23, 24], enhanced duration of stage N1 of non-REM sleep and decreased K complexes and sleep spindles [2].

Associations between Sleep Disruption and AD

Sleep disturbance in AD may represent a symptom of the progressing underlying neurodegeneration. However, the association between AD and sleep disturbances also raises questions about a possible causal role for sleep impairment in AD pathogenesis. In essence, sleep impairment may represent a risk factor for the disease. In support of this hypothesis, studies show that both self-reported sleep problems [25-27] and rest fragmentation at night [28] increase the risk of developing dementia, including dementia caused by AD.

A cross-sectional study conducted by Spira et al. studied 70 community-dwelling subjects using self-report sleep measures and [11C]-Pittsburgh compound B positron emission tomography (PiB PET) amyloid imaging [29]. They found a greater Aβ burden associated with both self-reported shorter sleep duration and poorer sleep quality [29]. Mander et al. [30] also used PiB PET to image brain Aβ deposits in 98 older adults. They compared the amyloid burden with sleep scores obtained from both the Epworth Sleepiness Scale (ESS) and the Medical Outcomes Study (MOS) Sleep Scale. Greater amyloid deposition in brain regions typically affected in AD was associated with self-report of less adequate sleep, more sleep problems and greater somnolence.

Another cross-sectional study of 142 cognitively normal middle-aged and older adults showed that lower CSF $A\beta_{42}$ levels, which indicate greater Aβ deposition, were associated with

poorer actigraphic measured sleep efficiency and higher frequency of waking episodes after sleep onset (WASO) [31]. However, despite evidence from these cross-sectional studies, it remains difficult to infer with certainty that poor sleep is a contributor to AD pathogenesis. Notwithstanding this difficulty, the reported association between Aβ deposition and sleep disturbances prior to development of AD is of note and may shed light on possible mechanistic role for sleep dysfunction as a risk factor for AD.

Prospective studies also demonstrate associations between several aspects of sleep and AD. Hahn et al. [25], for example, conducted a study with 214 Swedish participants without dementia, aged ≥75 years at baseline and showed that the ones presenting with diminished self-reported sleep depth or duration were approximately 70-100% more likely to be affected by all-cause dementia and AD, measured by clinical evaluation 9 years later [25]. Lim et al. [28] showed, in a study with 737 cognitively unimpaired older adults, that significant actigraphic sleep fragmentation measured during 10 days was associated with enhanced risk of developing AD at 6-year follow-up.

Sterniczuck et al. [26], on the other hand, developed a "sleep disturbance index" that included four variables (sleep medication use, sleeping problems and fatigue in past 6 months, and "recent trouble sleeping or a change in pattern"). Using the index, they studied more than 17,000 older adults and analyzed its association with the presence of self-reported dementia or AD approximately 4 years later. Higher indices were linked to 23% greater odds of dementia or AD, even after demographic variables, body mass index, and baseline cognitive performance had been accounted for [26].

Lim et al., on the other hand, used wrist actigraphy to measure sleep consolidation in 698 cognitively unimpaired older adults. People presenting with higher levels of sleep fragmentation showed a stronger association of APOE ε4 genotype with cognitive decline, post-mortem density of neurofibrillary tangles and incident AD [32].

Physiological Pathways of Sleep Disruption Leading to AD

Aβ levels and the sleep-wake cycle. Studies so far reveal that Aβ levels in both mice [33] and humans [34] fluctuate along the sleep-wake cycle in a diurnal pattern. Kang et al. [33] used in vivo cerebral microdialysis to measure Aβ concentration in the brain interstitial fluid (ISF) of mice exposed to a 12h light: 12h dark cycle. It was demonstrated that the Aβ levels present a diurnal oscillation, being higher while the mice were awake (during the dark phase) and lower when they were asleep (during the light period) [33]. In animals, the diurnal oscillation observed in Aβ is also shown by other substances produced by neurons, such as lactate, whose variation is in phase with Aβ levels oscillation [35, 36].

Measurements of Aβ levels in the cerebrospinal fluid (CSF) were also assessed in humans and corroborated the previous findings, as long as a diurnal variation was also observed. However, there was a phase delay of approximately 6 hours most likely due to the CSF being collected from the lumbar compartment, thus Aβ from the ISF needs time to reach this point [33, 34]. Therefore, it seems that Aβ concentration (both in humans and rats) varies within the sleep-wake cycle, and disruption of sleep can affect this fluctuating pattern. In fact, the levels of Aβ can variate up to 30% from the highest to the lowest concentration across the day [34]. Findings revealing that a change of 25-40% in Aβ production can either protect or accelerate the development of AD [37, 38], suggesting that sleep disruption may potentially play an important role in contributing to AD pathogenesis.

Aβ release is a process regulated by neuronal activity [35, 39, 40]. The enhancement of neuronal firing causes the increase in Aβ release and, consequently, concentration in the ISF [40, 41]. During the wake and REM sleep phases, the firing frequency of the neurons is high, while during the slow wave sleep (SWS), cortical neurons overall activity is decreased [42].

Sleep disturbances and Aβ aggregation. The default mode network (DMN), which includes the precuneus, medial prefrontal and lateral parietal brain regions, is sorely affected by SWS disruptions. This network is most active when there is no task being performed. Due to its intense neuronal activity, it is more prone to suffer with amyloid deposition [43], which has been confirmed by imaging techniques [35, 44]. Normally, sleep diminishes the activity of the components of DMN, as well as the connectivity between them and with other structures [45, 46]. On the other hand, poor-quality sleep causes an enhancement in DMN connectivity and consecutive activity (when compared to high-quality sleep). Thus, Aβ release increases along with the tendency for Aβ plaque formation [47].

Sprecher et al. [48] demonstrated the complex relationship between Aβ burden and sleep disturbance. They found that β-amyloid deposition within medial prefrontal cortex (mPFC) was significantly correlated with the disruption degree in NREM (non-rapid eye movement) SWA (slow wave activity) generation. Moreover, reduced NREM SWA is associated with the impairment in both overnight memory consolidation and hippocampal-neocortical memory transformation, which could be a possible indirect mechanism by which Aβ burden impairs the memory domain in AD.

Sleep also appears to play a role in Aβ clearance from the brain. This has only been shown in a mouse study, however, where an increase of 60% in the brain extracellular space volume and in the volume of extracellular fluid was observed during sleep. The probable mechanism underlying this volume increase is a change in the cell volume of astrocytes, which occurs due to an alteration in the adrenergic signaling during sleep [49-52]. The Aβ clearance is also known to be two-fold faster during sleep [49], mainly because an acceleration in the ISF-to-CSF bulk flow and in the blood brain barrier (BBB) transport [49, 53]. The BBB transport can be increased both directly (via upregulation of LRP1, transporter that allows Aβ

to pass through the BBB) or indirectly through the increase in glymphatic bulk flow [54-56]. Impaired sleep appears to be an important factor for diminished Aβ clearance and, consequently, increased Aβ concentrations in the brain, which enhances the tendency of Aβ accumulation.

The above findings are supported by research showing that sleep deprivation causes an enhancement in Aβ deposition in the APPSWE and APPSWE/PS1DE9 mouse models that are characterized by the development of significant amyloid plaques [33]. On the other hand, following the increase in sleep promoted by treatment with the orexin antagonist almorexant, an attenuation in Aβ plaque burden was observed [33]. In humans, a study showed that CSF Aβ concentration decreases following a night of sleep, while after sleep deprivation, this concentration was shown to increase [57]. Additionally, Aβ burden was found to be greater in community-based older adults with self-reported inadequate quantity and quality in sleep [29].

However, another study showed that the diurnal oscillation in the ISF Aβ levels stopped occurring in a given brain region after amyloid plaques become present [36]. But, active immunization with Aβ before the formation of amyloid plaques prevented Aβ deposition and the lack of diurnal pattern, revealing a causal role of Aβ [36]. The same was found for humans with presenilin mutations: those who had no amyloid deposition, according to imaging techniques, presented with normal diurnal oscillation in Aβ levels, while those who presented with amyloid plaques showed a mitigation in the diurnal pattern of CSF Aβ levels [36]. Thus, these data suggest that Aβ aggregation disrupts the sleep-wake cycle and diurnal fluctuation of Aβ. In essence, poor sleep can lead to increased Aβ levels and subsequent deposition; accumulated Aβ disrupts further normal sleep mechanisms resulting in potential worsening of sleep pathology which is routinely encountered in AD patients.

The lack of diurnal oscillation caused by the accumulation of amyloid plaques may be due to sequestration of Aβ in those plaques or to an alteration in the neuronal firing pattern.

The sequestration of Aβ by amyloid plaques, mainly of the $A\beta_{42}$ isoform, results in reduced clearance of Aβ, compromising its diurnal oscillation [1]. Furthermore, the disruption of SWS caused by sleep disturbances, as mentioned before, leads to a lack of deactivation of the DMN and enhancement in CSF Aβ levels during sleep period, when they were supposed to fall, counteracting the diurnal variation pattern [46].

Sleep disturbances and the blood brain barrier (BBB). He et al. [58] conducted a study with a mice chronic sleep restriction (CSR) model and showed that CSR decreased endothelin-1 and the expression of tight junction proteins. The 2-deoxy-glucose uptake by the brain was diminished through a downregulation of the glucosetransporter 1 (GLUT1) expression in cerebral microvessels of the BBB. Additionally, impairment of BBB permeability was observed. Endothelial and inducible nitric oxide synthase were also decreased, whereas the cyclooxygenase-2 related inflammation increased, reflecting endothelial damage. These alterations, combined with comorbid medical conditions, could lead to permanent damage to the BBB and contribute to neurodegeneration.

Orexins and Alzheimer's disease pathology. Orexins are neuropeptide hormones with several central [59] and peripheral roles [60] that have been shown to be involved in Aβ dynamics regulation [33]. Orexins play a role in wakefulness maintenance and prevent undesirable transitions into sleep [61], as presented by orexin knock-out mice and narcoleptic patients [62-66]. In mice, chronic overexpression of orexins led to non-REM sleep fragmentation and REM sleep suppression during day time [67]. Additionally, the consequences of sleep deprivation and orexin modulation over Aβ pathology have also been studied in both wild mice and human APP transgenic mice, whose characteristic is the expression of a mutated form of human amyloid precursor protein (*hAPP*). The results showed

that ISF Aβ concentration was enhanced by chronic sleep deprivation and orexin infusion, whereas amyloid plaque deposition was reduced by dual orexin receptor antagonist [33].

Oxidative stress induced by extended wakefulness. Zhang et al. examined the metabolic responses of short and long-term sleep loss over the Locus Ceruleus Neurons (LCn) of young adult mice. LCns activity reaches high levels during wakefulness and falls greatly in NREM sleep, while during REM sleep it becomes quiescent [68]. Enhanced neuronal activity across wakefulness requires an increase in their ATP production and consequently more O_2^- generation [69]. The nicotinamide adenine dinucleotide-dependent deacetylase sirtuin type 3 (SirT3) upregulates antioxidant mechanisms to protect neurons against oxidative stress [70, 71], but Zhang et al.'s findings point to the fact that those mechanisms are effective in short-term wakefulness. When wakefulness is extended for many consecutive night shifts, SirT3 activity diminishes, and oxidative stress is observed. Along with metabolic unbalance, LCn degeneration occurs, in part due to apoptosis. Cumulative loss of LCns could then result of recurrent episodes of extended wake and lead to cognitive impairment. Moreover, LCns damage could also accelerate neurodegeneration, as shown in previous studies with animal models of AD and PD [72-74].

Hypoxia induced by sleep disordered breathing (SDB). Emamian et al. showed, in a meta-analysis, that patients with AD present a risk five-fold higher of having obstructive sleep apnea (OSA) than cognitively normal individuals of similar age [75]. Additionally, Haba-Rubio et al. assessed the sleep and cognitive function of 580 individuals aged >65 years using validated questionnaires and polysomnography. Cognitive impaired individuals were shown to present with higher sleepiness scores and more disrupted sleep. These results were associated with the severity of the SDB-induced intermittent hypoxia [76].

OSA is characterized by nocturnal intermittent hypoxemia derived from partial or complete upper airway obstruction episodes occurring across sleep [77]. Many studies point OSA as a possible reversible cause of dementia [78-80]. Sleep-disordered breathing was significantly associated with an earlier age of onset of mild cognitive impairment (MCI – a preclinical stage of AD) and AD by a longitudinal cohort study [81]. Additionally, community-dwelling women affected by OSA were shown to present a higher risk of developing MCI or dementia [82]. It has also been demonstrated that OSA is associated with enhanced CSF levels of Aβ42 and phosphorylated tau in older adults presenting with the APOε3/3 alleles [83].

Bu et al. [84] compared serum Aβ and P-tau 181 levels in OSA patients and individuals with simple snoring. Aβ40, Aβ42 and total Aβ levels were considerably higher in OSA patients, whose severity of OSA and the consequent hypoxia was positively correlated with those levels. Moreover, they found greater P-tau 181 levels in participants affected by OSA. These data suggest that chronic intermittent hypoxia is associated to enhanced Aβ levels.

Chronic hypoxia leads to downregulation, in neurons, of the expression of ADAM10, a candidate protein for α-secretase which is essential to the processing of APP through the non-amyloidogenic pathway [85]. On the other hand, the level and activity of β-secretase (BACE-1), an enzyme that participates of the breakdown of APP through the amyloidogenic pathway, are both increased by the upregulation of hypoxia-inducible factor 1α (HIF-1-α) caused by hypoxia [86-88]. Additionally, zinc metalloproteinase neprilysin (NEP), an enzyme that cleaves Aβ, is downregulated by hypoxia [89]. Taken together, these data suggest that hypoxia may enhance Aβ levels by increasing its generation and diminishing its breakdown.

Tau-protein hyperphosphorylation was also shown to be induced by hypoxia in mice by activating kinases which phosphorylate tau (such as glycogen synthase kinase 3 beta, mitogen-activated protein kinase and cyclin-dependent kinase 5) and inactivating the protein phosphatase 2A (PPA2), an enzyme that dephosphorylate tau [90, 91]. Furthermore, chronic

hypoxia can also accelerate tau pathology via calpain-mediated tau hyperphosphorylation [92, 93].

Circadian activity rhythms and risk of Alzheimer's disease. Other circadian disturbances rather than sleep disruptions were also suggested as a potential risk factor for AD development. AD patients are commonly affected by some circadian disturbances, including reduced amplitudes and phase delay of circadian variation in core body temperature and activity [94]. Tranah et al. [95] measured circadian activity rhythms by wrist actigraphy in 1282 healthy community-dwelling older women (mean age 83 years), which were also clinically evaluated and classified approximately 5 years later according to their cognitive status (normal, MCI, dementia). They found that circadian activity rhythms were prospectively associated with incident dementia or mild cognitive impairment (MCI). Older women presenting with diminished activity rhythms were more likely to develop dementia or MCI. Lower amplitude, a delayed timing of peak activity and a less robust rhythm showed consistent association with development of dementia or MCI, independent of the sleep fragmentation and sleep duration.

Based on these findings, activity rhythm abnormalities could be a prognostic factor of enhanced risk for dementia and MCI in older, cognitively healthy community-dwelling women. Further studies are necessary to confirm the direct causal relationship between circadian rhythm disturbances and MCI/dementia and to establish if interventions that prevent circadian rhythm disturbances could delay the onset of MCI/dementia. Potential interventions include physical activity and light exposure [96-102], strengthen circadian activity rhythms, and improve sleep synchronization in older adults [102-106].

Sleep Disturbances in other Neurodegenerative Disorders

Finally, sleep disturbances are not specific to AD. There appears to be a two-way cause-effect link between sleep disruption and other neurodegenerative disorders too. Sleep disturbances are usually found as non-motor manifestations of Parkinson's Disease (PD) [107]. Studies suggest that sleep disturbances presented by patients with PD, such as NREM sleep irregularities on EEG and sleep spindle alterations correlate with increased risk for developing dementia [107, 108]. Additionally, the onset of motor symptoms of Parkinsonism in PD and Dementia with Lewy Bodies (DLB) appears to be preceded by REM sleep Behavior Disorder (RBD) in many years [109-112]. Eventually, sleep disturbances with nighttime sleep disruptions are frequently encountered in DLB [113].

Patients affected by vascular dementia (VaD), in turn, suffer with sleep-wake cycle disruption and diminished sleep efficiency [114]. Furthermore, recent studies indicate that sleep disruptions, mainly excessive daytime sleepiness, seem to show a strong correlation with higher predictive power for subsequent VaD [115]. Moreover, sleep disturbances characterized by enhanced nocturnal activity, excessive daytime sleepiness and reduced morning activity have all been reported in patients with Frontotemporal Dementia [109, 116-118]. These findings suggest that perhaps sleep disruption is a risk factor for dementia in general and not solely Alzheimer-type dementia.

Conclusions

In this review we have presented evidence that clearly demonstrates how disturbances in the sleep cycle may contribute to the etiology of AD through various different physiological pathways. This suggests that sleep disturbance is a preventable risk factor for AD.

Early interventions in patients presenting with disrupted sleep cycles, regardless of the cause, are necessary to both improve the quality of life of the individual and to avoid the

consequences of a dysregulated sleep, which may include an acceleration of the progression of AD (see Ooms and Ju for a review on treatment in dementia [119]).

The timely management of sleep disorders is an important potential strategy to prevent or at least delay the onset of AD. Although many studies support the relationship between sleep impairment and AD pathogenesis, the extent of the role of sleep in the causality of this disease is not yet clear. Further studies are needed to understand fully the correlation between sleep disturbances and AD, such as prospective studies using polysomnography - the gold standard for the measurement of sleep disturbances. Prospective studies investigating the effects of improving the quality of sleep in AD onset are also necessary to determine the role of sleep disturbances in AD onset. Nevertheless, the association between sleep disturbance and Aβ deposition (and possibly tau) provides a credible mechanistic pathway. Understanding the mechanisms that may link a history of sleep impairment with the subsequent development of AD will be crucial in helping with prevention. The emerging data about sleep as a potential risk factor for AD will highlight the need for future assessment of pharmacological and non-pharmacological interventions to optimize treatment of sleep disorders specifically in relation to AD prevention.

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Conflict of Interest/Disclosure Statement

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