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Editorial

Editorial

Longer sleep duration in Alzheimer's disease progression: a compensatory response?

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The relationship between sleep duration and Alzheimer's disease (AD) progression is a topic of ongoing research and debate in the scientific community. An increasing body of evidence suggests that individuals with excessively long and/or short sleep durations have an increased risk of AD, all-cause dementia, or cognitive decline [1–4]. This U- or J-shaped relationship, particularly with regard to long sleep duration, is intriguing and has spurred various hypotheses regarding the underlying mechanisms. One such hypothesis posits that longer sleep duration reflects a compensatory response employed to counteract neuroinflammation associated with neurodegeneration [5]. This hypothesis finds support in animal research indicating a sleep-promoting role for pro-inflammatory cytokines [6, 7] as well as in human studies demonstrating associations between long sleep duration and elevated inflammatory markers [8].

In the current issue of *SLEEP*, the study by Baril et al. has made a significant contribution to the understanding of this compensatory hypothesis [9]. The PREVENT-AD cohort [10], which enrolled individuals with a parental or multiple-sibling history of sporadic AD and therefore greater genetic risk of developing AD, offers an excellent opportunity to investigate sleep patterns around the expected age of AD onset (EYO). Noteworthy aspects of this study include the evaluation of AD biomarkers and inflammatory cytokines in cerebrospinal fluid (CSF), actigraphy measurement of sleep, and a comprehensive cognitive assessment. This dedicated design facilitated the objective examination of sleep characteristics during periods when AD pathologies accumulate [11] and neuroinflammation is anticipated to intensify. Additionally, it allowed for an investigation of how the relationship between sleep and neuroinflammation varies according to AD biomarker and cognitive status.

With approximately 200 older adults without dementia, Baril et al. discovered that "proximity to, or exceeding, parental age of AD onset" was linked to longer sleep duration (i.e. > 8 hours) and a "hypersomnia sleep profile" as determined by principal component analysis conducted on various actigraphy-derived sleep metrics. They also found that longer sleep duration and the hypersomnia sleep profile were associated with elevated neuroinflammatory impacts in a subset of participants with CSF. In subsequent subgroup analyses, they found that the association between the hypersomnia sleep profile and neuroinflammation was only significant in "those with an EYO<5" (meaning those who were close to or even exceeded their parental age at onset) or those with better cognitive performance. Considering these findings, the study presents a compelling scenario wherein the neuroinflammation process, occurring proximate to EYO amidst a significant accumulation of AD pathologies, "might promote the elongation of sleep as a compensatory mechanism" to mitigate adverse effects on, or potentially "protecting," cognitive function.

A lingering question remains: is extended sleep driven by inflammation, AD pathology, a combination, or another factor? A previous study demonstrated that self-reported sleep duration "increased progressively throughout the years before clinical AD onset [12]." Another study found that frequent daytime napping was associated with preclinical AD [13]. Rest-activity fragmentation (that increases with napping) was found to be significantly correlated with CSF pTau181/ amyloid-β42 ratio [14]. Additionally, a recent study suggested that daytime sleep became longer and more frequent with aging, and the aging effect showed a significant trend of accelerating during AD progression [15]. A prior animal study reported degeneration of wake-promoting neurons due to neuronal and neurotransmitter loss associated with tau pathology [16], leading to difficulties staying awake. These observations support the notion that AD pathology may contribute to the dysfunction of maintaining wakefulness and, thus, resulting in longer sleep duration. However, conflicting results also exist. For example, in cognitively normal adults, amyloid deposition, as assessed by decreased CSF amyloid-β42, was associated with

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reduced sleep quality but not total sleep time at night [13]. In support of inflammation as a driver of longer sleep duration, previous research in rodents shows that pro-inflammatory cytokines can promote sleep [17]. Associations between greater sleepiness with CSF interleukin-6, a pro-inflammatory biomarker in humans have also been reported [18]. Therefore, to confirm the interpretation, it is imperative for future research to identify the underlying causes of the longer sleep duration in these individuals who are potentially in a preclinical stage of AD but nearing symptom onset.

Several studies reporting a U-shaped relationship have measured sleep 5–10 years prior to cognitive testing. In a study of middle-to-old age adults with approximately 25 years of follow-up, self-reported short sleep duration, but not long sleep duration, was associated with an increased risk of cognitive impairment [19], further implying a confounding factor of the timing of sleep monitoring relative to the onset of symptomatic AD. Nevertheless, these associational studies, including the study by Baril et al., have limited capacity to infer causation [20]. Further evidence, ideally from randomized clinical trials, is required to disentangle whether long sleep duration represents a byproduct or coincident symptom of neurodegenerative processes, or a resilience or protective factor that assists in maintaining cognitive function despite a higher impact of pathology.

It is also important to note that previous findings in human studies exhibit significant heterogeneity and inconsistency regarding the relationship between sleep duration and inflammatory markers [5]. The reasons for longer sleep duration can be more complex, involving a cascade of biological and physiological changes. For example, neurofunctional changes in the central circadian pacemaker have been demonstrated in individuals with AD [21], suggesting that the circadian network is vulnerable to AD pathology. The AD hallmark, amyloid-β, shows a diurnal pattern which is ablated in AD [22]. A vast body of observational findings also suggests that circadian disruptions may occur early in the course of AD processes [14, 23–26]. Circadian dysfunction may lead to sleep disruptions and poor sleep quality, and it is plausible that longer sleep duration or time in bed is a compensatory opportunity for adequate sleep and sleep-related restorative and homeostatic mechanisms [27–29].

While Baril et al. have taken a significant step forward, their findings warrant external replications. Another notable limitation lies in the caution required when implementing and interpreting sleep scoring based on actigraphy [30]. Ideally, future research should utilize more accurate assessments of sleep such as wearable electroencephalogram-based sleep monitors. Also, based on the range of EYOs, most participants should be amyloid-positive if they have AD and not another disease process. However, amyloid status of the participants was not reported despite the availability of CSF t-tau/Aβ42 and CSF p-tau181/Aβ42 ratios. Additionally, daytime sleep (napping) was excluded from analysis, which is a significant weakness since daytime napping is strongly correlated to hypersomnia, naps can contribute substantially to total (over the 24-hour-day) sleep time, and naps may reduce nighttime sleep quality and duration.

This study carries important implications for future research. For instance, the finding that long sleep duration was specifically linked to neuroinflammation in individuals exhibiting better cognitive function suggests that long sleep duration might denote a resilience phenotype in the presence of underlying pathologies. The identification of resilience factors in AD should be one of the prioritized future endeavors. In this context, digital phenotyping, such as the hyposomnia profile derived from actigraphy in this study, may offer a distinct advantage and represent a significant edge over existing efforts in this field based on costly and complicated imaging modalities [31–33]. Additionally, the complex interplay between sleep and neurodegenerative processes warrants further investigations to systematically understand the underlying pathways [24]. Integrating data across multiple levels, from cellular to organismal, systems biology approach holds promise in this regard, as this approach may better identify the intricate mechanisms that involve numerous biological and/or physiological processes.

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Data Availability

Data sharing is not applicable to this editorial as no new data were created or analyzed.

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