

Alzheimer's disease: What's sleep got to do with it?

Research has linked sleep disturbances to dementia and cognitive decline in older adults,¹⁻⁴ but it has not been able to determine the causal relationship between sleep and Alzheimer's disease (AD). Do sleep traits, such as poor sleep quality and sleep duration, affect the development of AD or does AD alter sleep? The theories are not mutually exclusive, but if the first is true, sleep may be an important modifiable risk factor in the slowing and prevention of AD.

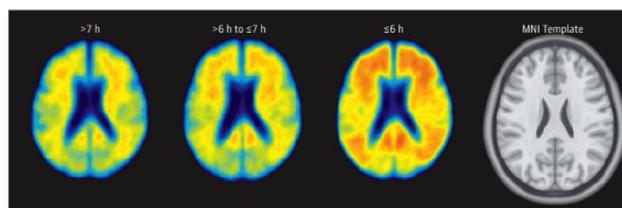
Does sleep quality affect beta-amyloid deposition?

A build-up of beta-amyloid in the brain is a hallmark sign of AD. To see if there is a link between sleep and beta-amyloid pathology, Spira and colleagues⁵ studied a cross-section of adults from the neuroimaging sub-study of the Baltimore Longitudinal Study of Aging. Seventy adults between 52 and 91 years of age (mean age = 76) answered questions on the length and quality of their sleep. Beta-amyloid burden was measured using Pittsburgh compound-B, a tracer that binds to beta-amyloid deposits in the brain, and positron emission tomography. They found that sleep traits associated with greater amyloid build-up included:

- Shorter sleep duration (Figure 1).
- Poor sleep quality.

This is the first published study that shows an association between sleep and beta-amyloid burden in community-dwelling older adults. However, the study did not determine whether poor sleep was the cause of elevated beta-amyloid or if greater beta-amyloid concentration caused poor sleep.

Figure 1. Unadjusted Distribution Volume Ratios of Pittsburgh Compound B Positron Emission Tomography Images by Sleep Duration. (Beta-amyloid increases as color changes from blue to red.)



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Which comes first, beta-amyloid or poor sleep?

To better understand the relationship between beta-amyloid and sleep, Virta and colleagues⁶ looked at sleep characteristics during midlife and their relationship to late-life cognitive impairment. The pathogenesis of AD develops over a long period that can begin as early as 10-15 years before the first clinical symptoms appear, so examining sleep patterns in middle-age subjects, before pathological changes might be expected, could further our understanding of the sleep/AD relationship. Researchers studied sleep duration, sleep quality, and use of hypnotics in 2,336 middle-aged (mean age = 52.3 years) twins. Twenty years later (mean time = 22 years), investigators assessed the subjects' cognitive function and found that lower cognitive scores were found in individuals who reported the following:

- Short (<7 hours) or long (>8 hours) hours of sleep at midlife compared to 7-8 hours per day.
- Poor sleep quality.
- Use of hypnotics for 60 or more days per year.

The sleep survey was completed before preclinical AD pathology would be expected to develop, so researchers concluded that their findings support the hypothesis that sleep quality and/or duration impact the development of AD.

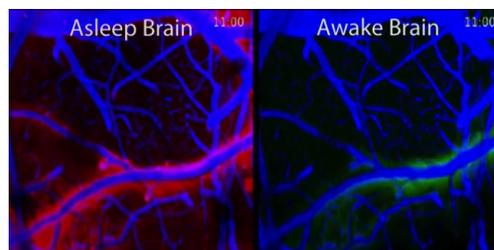
Is a good night's sleep the answer?

Current thought is that the build-up of beta-amyloid in the brain is due to overproduction, reduced clearance, or both. Excess beta-amyloid ends up in the interstitial spaces of the brain. The concentration of beta-amyloid in interstitial and cerebrospinal fluid varies, depending on whether a person is asleep or awake: beta-amyloid concentration dips during sleep and peaks during consciousness.^{7,8} This suggests that sleep/wake patterns affect fluctuations in beta-amyloid concentration.

Rodent studies recently uncovered a mechanism for clearing toxic waste from the brain. A paravascular pathway, called the glymphatic system, removes the brain's "garbage" by moving large amounts of cerebrospinal fluid (CSF) quickly through the brain and sweeping the waste from interstitial spaces.⁹ Xie and colleagues¹⁰ used florescent imaging to compare this CSF influx in the brains of awake, sleeping, and anesthetized mice. They found that sleep changes the cellular structure of the brain and plays a critical role in beta-amyloid clearance. Their findings included:

- Space between neurons increased 60% during sleep and anesthesia, resulting in an increased exchange of CSF and interstitial fluid (Figure 2).
- CSF influx into the interstitial space in awake mice was only about 5% of the CSF influx in sleeping or anesthetized mice.
- Sleeping and anesthetized mice cleared twice as much beta-amyloid from their brains as conscious mice.

Figure 2. CSF flow in the brain of a mouse while asleep (red) and awake (green).



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These findings suggest that sleep helps the brain dispose of metabolic waste that accumulates while awake.

Further studies in other cohorts are needed before we can say poor sleep promotes AD pathology. If similar results are found, sleep length and quality could be early, modifiable risk factors, and interventions to improve sleep or maintain healthy sleep may help prevent or slow AD.

For more information

On the glymphatic system: www.urmc.rochester.edu/news/story/index.cfm?id=3584

On sleep and the glymphatic system: www.urmc.rochester.edu/news/story/index.cfm?id=3956

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