Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Sleep (deficit/excess)

Evidence Summary

Sleep deficit and excess are consistently associated with Alzheimer's disease, cognitive impairment, and many age-related diseases. Slow wave sleep (SWS) appears particularly important for memory.

Neuroprotective Benefit: Poor sleep is associated with many diseases, including Alzheimer's. However, this relationship may be bi-directional, and causality is difficult to ascertain.

Aging and related health concerns: Studies suggest that short and long sleep are risk factors for mortality and age-related diseases. As with the evidence for Alzheimer's disease, however, causality is unclear.

Safety: Sleep deficit and excess are consistently associated with many ailments. The optimal amount for adults is 7-8 hours per night.

What is it?

Sleep is divided into stages and alternates between non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. A full night of sleep is important because these stages are not distributed equally throughout the night. The earlier part of the night is largely NREM sleep, while REM sleep increases later in the night. The importance of NREM sleep for the consolidation of memory is well-known. The function of REM sleep is less understood, although it is the period of time that we dream. Sleep is controlled by our circadian rhythm by both cell-intrinsic mechanisms and system-wide mechanisms. Lack of sleep or excess sleep is associated with many age-related diseases. However, whether poor sleep habits cause these diseases or is caused by these diseases is less well-understood.

Neuroprotective Benefit: Poor sleep is associated with many diseases, including Alzheimer's. However, this relationship may be bi-directional, and causality is difficult to ascertain.

Types of evidence:

- Multiple meta-analyses based on multiple cross-sectional and prospective cohort studies
- Biomarker studies of sleep and Alzheimer's pathology
- Many preclinical studies

Human research to suggest prevention of dementia, prevention of cognitive decline, or improved cognitive function?

The effects of sleep on health occur over a long time frame. Therefore, most studies are observational (rather than RCTs) which comes with the usual confounding factors including the direction of causality, co-morbidities associated with both poor sleep and Alzheimer's, and other factors such as socio-demographic or lifestyle factors. For the following studies, short sleep is usually defined as <6 hours and long sleep >9 hours. 7-8 hours of sleep is optimal for health outcomes.

General cognitive function

A meta-analysis of 26 cross-sectional studies suggest that both short and long sleep are associated with a 42% and 61% increased risk of poor cognitive function, respectively (Lo et al, 2015). The cognitive domains most affected include executive function, verbal memory, and working memory capacity. Wickens et al, (2015) reported that short-term sleep deprivation affects simple task performance more than complex task performance.

Sleep problems and risk of Alzheimer's disease

A meta-analysis of observational studies suggested that sleep problems in general (including sleep time, quality, and sleep apnea) are associated with a 55% increased risk for Alzheimer's disease and a 278% increased risk for preclinical Alzheimer's disease. It reports that 15% of Alzheimer's disease cases may be attributable to sleep problems (Bubu et al, 2017).

Sleep duration and risk of Alzheimer's disease

Sleep duration is also a risk factor for Alzheimer's disease and dementia. A meta-analysis of 3 prospective cohort studies reported that long sleep was associated with a 42% increased risk of dementia (Kim et al, 2016) while a meta-analysis of 5 prospective cohort studies reported that short sleep was associated with a 53% increased risk of dementia (de Almondes et al, 2016).

Studies have been criticized for not fully controlling for sociodemographic, lifestyle factors, and comorbidities (such as depression and cardiovascular disease) that are themselves risk factors for Alzheimer's disease. After controlling for these factors in a prospective cohort, Chen et al (2016) reported that short sleep was significantly associated with a 36% increased risk of MCI/dementia but long sleep was non-significantly associated with a 27% increased risk of MCI/dementia.

Change in sleep patterns and risk of Alzheimer's disease

In a prospective cohort study over 10 years, Westwood et al (2017) reported transitioning to sleeping >9 hours was associated with a 143% increased risk of all-cause dementia and a 120% increased risk of clinical Alzheimer's disease while those who always slept >9 hours were not at an increased risk.

Alzheimer's disease biomarkers and sleep in healthy individuals

Human research suggests that decreased sleep quality and impaired sleep duration in both cognitively healthy middle aged-and elderly individuals is associated with biomarkers of Alzheimer's disease such as CSF amyloid-beta or greater brain amyloid-beta from PET imaging (Ju et al, 2013; Brown et al, 2016; Drogos et al, 2016; Sprecher et al, 2015; Spira et al, 2013). Since amyloid beta may accumulate in the brain decades before clinical symptoms develop, determining whether poor sleep *causes or is caused by* Alzheimer's-like pathology is difficult. Given the consistent association between sleep duration and cognitive impairment or Alzheimer's disease, there is a strong rationale for optimizing sleep duration throughout life.

Human research to suggest benefits to patients with dementia:
Interestingly, using actigraphy data to assess sleep, one study of 208 Alzheimer's patients reported that Alzheimer's disease severity is not associated with total sleep time, and that Alzheimer's patients slept longer than would be expected for an elderly individual of the same age (Leger et al, 2017). However, studies suggest that sleep quality (such as sleep efficiency and sleep fragmentation) is correlated with severity of Alzheimer's disease (Leger et al, 2017; Liguori et al, 2014).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Many mechanisms could explain why lack of sleep may lead to cognitive impairment or Alzheimer's disease.

Slow-wave sleep
A hallmark of aging is a decrease in slow wave sleep (SWS) during non-REM sleep (NREM). Reduced SWS is seen in patients with MCI and can also predict beta-amyloid levels in healthy individuals (Mander et al, 2015; Mander et al, 2016; Westerberg et al, 2012).

The glymphatic system
The glymphatic system is a mechanism to recycle the interstitial fluid (ISF – the fluid surrounding brain cells). It consists of the cerebral spinal fluid (CSF) of the brain ventricles, the ISF, and the perivascular spaces (the space surrounding cerebral blood vessels). The CSF acts as a 'sink' for solutes in the brain ISF, and the perivascular spaces mediate much of the transfer between these two compartments.

While awake, transfer between these two compartments is reduced by ~95%. However, during sleep, the ISF spaces increase by ~60%, and the ISF flows through the perivascular spaces into the CSF. Rodent studies suggest that amyloid beta and tau can be cleared by this mechanism, and, in fact, amyloid beta in rodent brains is increased during the waking hours and decreases after sleep. Interestingly, this clearance mechanism decreases in rodents with age (Simon and Iliff, 2016). This suggests that impaired sleep may decrease the clearance of amyloid beta from the brain.

Synaptic Homeostasis Hypothesis (SHY)
SHY posits that learning occurs during waking hours, leading to a net increase in synaptic strength, and that during sleep there is a net decrease in synaptic strength. This net decrease increases the signal-to-noise ratio of neuronal communication so that the strongest and most important synapses developed during the day (our important memories) are easier to access in the future.

Rodent studies suggest that markers of synapses increase during the day and decrease after a night's sleep. Electron microscope data confirms that during the day there is a net increase in the number of synapses and that only the strongest synapses are retained after a night's sleep. Further electrophysiological evidence and structural evidence support this hypothesis (Tononi and Cirelli, 2014; de Vivo et al, 2017).

Importantly, evidence from humans and animals suggests that this global decrease in synaptic strength occurs during SWS. In addition, increasing SWS leads to an increase in memory retention (Tononi and Cirelli, 2014). Although no studies have confirmed that a decrease in SWS in Alzheimer's leads to memory impairment, this remains a distinct possibility.

Memory consolidation

One of the primary functions of sleep is the consolidation and transformation of memory. Initially, memories are encoded in the hippocampus – a region of the medial temporal lobe of the brain. Rodent studies suggest that during sleep the neurons that encoded particular memories are reactivated and strengthened. Sleep is also important for the transfer of memories from the hippocampus to other areas of the brain, where they are placed into long-term storage and integrated with existing memories. Therefore, long-term sleep deficit may reduce the strength and integration of memories which may lead to cognitive deficits (Dudai et al, 2015).

Co-morbidities

Short and long sleep may be associated with a number of other diseases, such as cardiovascular disease, diabetes, and obesity that are themselves risk factors for Alzheimer's disease (see below).

APOE4 interactions:

Using actigraphic data in elderly individuals without dementia, every 1-standard deviation of sleep improvement attenuated the effect of ApoE4 allele on the risk of incident Alzheimer's with up to 6 years of follow up (HR 0.67; 95%CI 0.46-0.97) (Lim et al, 2013). ApoE4 itself may decrease sleep duration and efficiency in healthy older adults (Drogos et al, 2016).

Aging and related health concerns: Studies suggest that short and long sleep are risk factors for mortality and age-related diseases. As with the evidence for Alzheimer's disease, however, causality is unclear.

Types of evidence:

- Meta-analyses on risk of mortality, cardiovascular disease, diabetes, and obesity

Longevity:

Sleep disruption is common in elderly and is often associated with various age-related diseases and mortality. A cross-sectional study using polysomnography data showed that as individuals aged, sleep efficiency, sleep time, and REM sleep decreased; also, the latency of REM sleep increased and quality of stage N2 (SWS) sleep decreased (Mazzotti et al, 2014). A meta-analysis of 35 studies and 1,526,609 individuals reported that short sleep and long sleep were dose-dependently associated with a greater risk of mortality. These relationships were also seen for individuals without CVD or cancer at baseline (Shen et al, 2016). Mortality risk also increased in meta-analyses of prospective cohorts in adults and elderly with short sleep (~10%) and long sleep (~30%) (Cappuccio et al, 2010; Silva et al, 2016).

As with the studies on dementia, it is difficult to separate out causality; however, studies that exclude individuals that died within a few years after baseline measures find similar results suggesting that sleep might be an independent predictor of all-cause mortality.

Cardiovascular disease (CVD)

Associations between sleep duration and morbidity/mortality from CVD are mixed. A meta-analysis of prospective studies in patients without baseline CVD (17 studies, 311,260 subjects) reported that insomnia was associated with a 33% increased risk of CVD mortality, a 41% increased risk of myocardial infarction, and a 28% increased risk of chronic heart disease (Li et al, 2014, Sofi et al, 2014).

However, a meta-analysis in elderly patients reported that long sleep was associated with a 43% increased risk of CVD mortality, while short sleep was associated with a *non-significant* 18% increased risk (Silva et al, 2016). Another prospective study of 241,949 adults 45 and up (avg. age ~61) reported that, after excluding individuals with baseline illness and adjusting for baseline health state, short sleep was not associated with incident CVD but long sleep was associated with a 29% increased risk of incident CVD (Holliday et al, 2013).

Why these meta-analyses have divergent results is unclear. One possible conclusion could be the different study designs and inclusion criteria. Additionally, Holliday et al (2013) controlled for general health status. If sleep is associated with a general decrease in health, controlling for CVD at baseline might not sufficiently control for individuals that may have other related co-morbidities (such as diabetes). In addition, Li et al (2014) and Sofi et al (2014) used insomnia, rather than sleep duration, as a defining characteristic which includes difficulty falling asleep and restless sleep which may have changed the outcome.

Diabetes

Sleep is also associated with risk of type 2 diabetes. A meta-analysis of 10 studies reported that short sleep and long sleep were associated with a 28% and 48% increased risk of diabetes, respectively (Cappuccio et al, 2010). In another meta-analysis, each hour decrease in sleep from 7 hours resulted in a 9% increased risk of developing diabetes while each hour increase of sleep was associated with a 14% increased risk (Shan et al, 2015). In addition, even after adjusting for baseline health, <6 hours of sleep was associated with a 29% increased risk of developing diabetes (Holliday et al, 2013).

Obesity

Sleep is also associated with risk of obesity. A meta-analysis of 11 prospective studies reported a 25% increased risk for short sleep duration but no increased risk for long-sleep duration (Wu et al, 2014). Chronic sleep restriction leads to alterations in levels of appetite-regulating hormones, such as leptin and ghrelin, and is also associated with reduced physical activity (possibly due to low day-time energy).

Safety: Sleep deficit and excess are consistently associated with many ailments. The optimal amount for adults is 7-8 hours of sleep per night.

There is no evidence that 7-8 hours of sleep causes any harm. However, certain sleep drugs that individuals use to get 7-8 hours of sleep may be associated with their own risk factors.

Research underway:

Many studies are underway examining the relation of sleep to Alzheimer's disease and other aging-related diseases.

Search terms:

Pubmed:

Sleep (meta-analysis, systematic review) + aging, Alzheimer, mortality, longevity, cardiovascular, diabetes, obesity

Sleep + apoe