# Predictive Effects of Quality and Duration of Sleep on Cognition and CSF Biomarkers

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Abstract

Current literature on the effects of sleep on cognition has shown conflicting results regarding the effects of long and short sleep duration. Using previously collected data from the Vanderbilt Memory & Aging Project, this study explored the association between sleep and cognitive functioning and cerebrospinal fluid biomarker components of Alzheimer's disease pathophysiology in older adults with normal cognition and mild cognitive impairment. Sleep quality was hypothesized to be a better predictor of cognitive functioning and cerebrospinal fluid biomarkers. The sample consisted of 66 older adults, with a mean age of 73.29. Half of the sample had mild cognitive impairment, while the other half had normal cognition. Results showed no significant predictive effects of either sleep quality or sleep duration on either cognitive measures or cerebrospinal fluid biomarker levels. However, results did show some sleep quality x diagnosis interaction effects for information processing speed, executive function and amyloid-beta levels, and sleep quality x sleep duration interaction for global cognition and amyloid-beta levels.

# Predictive Effects of Quality and Duration of Sleep on Cognition and CSF Biomarkers

Alzheimer's disease (AD) and other forms of dementia are prevalent among the elderly, with AD affecting 11% percent of individuals age 65 and over and 32% of adults age 85 and over (Alzheimer's Association, 2014). This progressive and debilitating disease targets the brain and causes problems with cognition, predominantly memory. In the beginning stages of the disease, adults with AD have mild cognitive problems, often forgetting conversations and events or repeating questions. As the disease progresses, the person with AD will begin forgetting friends and family, get lost in familiar places, and may need assistance with personal care. In the final stages, individuals with AD are unable to recognize their family or friends, remember details of their lives, or care for themselves (Alzheimer's Association, 2014).

AD is preceded by mild cognitive impairment (MCI). MCI is characterized by slight decline in cognitive abilities that, while noticeable, do not significantly compromise the individual's ability to perform activities of daily living. The presence of MCI increases the risk of later developing AD; however, some people with MCI never progress to dementia (Albert et al., 2011). Unfortunately, there is no cure for or treatment that prevents MCI or AD. Once the degradation of the brain and cognition begins, there is little that can be done to ameliorate or even cease progression. AD research has focused on finding protective and risk factors for the disease so that older adults can work to preserve their cognition. Lifestyle factors are among the risk factors that have been studied for dementia, for instance examining the effects of sleep on the brain.

AD is characterized by abnormal deposits of amyloid-β (Aβ) and tau protein in the cerebrospinal fluid (CSF) (Jack et al., 2013). Aβ is a peptide fragment, usually either 40 or 42 amino acids long, that is cleaved from the β-amyloid precursor protein (APP) (Selkoe, 2000).

The amyloid hypothesis of AD states that accumulation of Aβ in the brain, which occurs as a result of changes in the generation and clearance rates, is the central early event that drives AD pathogenesis, including the formation of neurofibrillary tangles, synapse loss, and the death of neurons (Tanzi & Bertram, 2005). Mutations in APP genes cause an altered breakdown of APP, which leads to the increased production of Aβ42. As Aβ levels rise in the brain, the naturally sticky Aβ forms insoluble plaques (Selkoe, 2000). As levels of Aβ42 and Aβ40 in the brain rise, however, levels of Aβ42 in CSF decrease. This may occur because the aggregation of Aβ42 into plaques impairs the clearance of the Aβ42 from the brain into the CSF (Spies, Verbeek, van Groen, & Claassen, 2012).

Tau is a naturally occurring protein in the brain whose primary function is stabilizing microtubules (Lee et al., 2005). Phosphorylation of tau occurs most often during the development of the fetal brain, with neurons in the adult at a much lower tau phosphorylation state (Ballatore, Lee, & Trojanowski, 2007). However, changes in the shape of tau observed in the early stages of AD are thought to make tau more vulnerable to abnormal phosphorylation. (Schraen-Maschke et al., 2008). Increased states of phosphorylation cause the tau to disengage from the microtubules, which causes the concentration of unbound tau to rise. Because of this increase, the tau is more likely to misfold and aggregate into neurofibrillary tangles (Ballatore, Lee, & Trojanowski, 2007). The number of neurofibrillary tangles in the brain has been correlated with level of dementia, and the overexpression of neuronal tau in mice was associated with the degradation of axons in the brain and spinal cord (Lee et al., 2005).

*Sleep and Cognition*

Sleep is an important biological process that has been connected to AD and cognitive decline with age. The National Sleep Foundation recommends that adults have seven to eight

hours of sleep per night (Hirshkowitz et al., 2015). Regardless of the presence of dementia or cognitive impairment, sleep disturbances increase with age, including decreased Stage 3, 4, and REM sleep in adults over the age of 60. Sleep efficiency, which was defined by Redline et al., (2004) as the percentage of time asleep during the time in bed, also decreases with age (Redline et al., 2004). A population-based study by Merlino and colleagues (2010) found that, among adults over the age of 65, 84.7% reported insomnia, 30.6% excessive daytime sleepiness, and 26.2% snoring or sleep apnea.

Sleep disturbances may also affect cognition in older adults. Benedict and colleagues (2014) showed a positive association between self-reported sleep disturbances and a higher risk of developing dementia. Longer sleep duration, sleep latency, and poor sleep efficiency correlated with cognitive problems, most prominently executive and visuospatial functions (Shin et al., 2014). Poor sleep quality was also associated with deficits in working memory, attentional set shifting, and abstract problem solving in older adults. In addition, poor sleep quality was associated with functional symptoms of depression, such as decreased concentration and motivation (Nebes et al., 2009). Furthermore, research suggests that improvements in sleep could, in turn, improve cognition. Treatment for three months with a first time continuous positive airway pressure (CPAP), often used to treat obstructive sleep apnea, increased the gray matter volume in the brain, most significantly in the hippocampus and frontal lobe. Increases in gray matter volume were in turn associated with improved cognition, with improvement in verbal and visuospatial memory, attention, and executive functioning (Canessa et al., 2011).

Studies of sleep duration and cognition have shown conflicting results. While most agree that long sleep times, considered to be greater than the recommended maximum of 8 hours, correlate with cognitive dysfunction, studies differ on the effect of short sleep times, considered

to be less than the recommended minimum of 7 hours. Faubel and colleagues (2009) reported a decrease on scores of cognitive measures as sleep time increased from 7 to 11 hours, with no significant effect for the shorter sleep time of 7 hours. Loerbroks, Debling, Ameling, and Stürmer (2010) found that only sleep times of greater than 9 hours were associated with lower cognitive scores. A study by Keage and colleagues (2012), on the other hand, found that sleep times of less than 6.5 hours were associated with increased risk of cognitive decline, and Kronholm and colleagues (2009) demonstrated associations between both short and long sleep duration and cognitive functioning, as well as tiredness and fatigue. These differing results could suggest that the effect of sleep on cognition might stem from quality of sleep rather than duration. This explanation is further supported by studies that have shown associations between cognition and sleep disturbances but not cognition and sleep duration (Blackwell et al., 2006; 2011).

*Sleep and AD Pathology*

Studies have also shown associations between sleep problems and the pathology associated with AD, providing more biological information on how sleep can affect cognition. A theory proposed by Lucey and Bateman (2014) suggest an Aβ diurnal pattern in which concentrations of Aβ40 and Aβ42 in CSF fluctuated by 25% over a 24-hour time period, with clearance of Aβ40 and Aβ42 occurring during nocturnal periods. Lucey and Batemen propose that sleep problems such as decreased sleep efficiency and decreased slow wave sleep affect the Aβ40, Aβ42, and total Aβ deposits in the brain by disrupting this Aβ diurnal pattern. During normal sleep, slow wave sleep causes synaptic activity, which increases the clearance of Aβ42 from the brain by the interstitial fluid (ISF). However, with the disruption of sleep and especially slow wave activity, the synaptic activity decreases, and the Aβ42 in the brain is not properly

cleared and instead deposits as plaques. Another study by Kang and colleagues (2009) suggests the Aβ40 levels in ISF, which assists in clearing Aβ40 from the brain, are regulated by the sleep-wake cycle and orexin, a neuropeptide that regulates arousal and wakefulness. Levels of Aβ40 in ISF in sleep-deprived mice were significantly higher than levels of Aβ40 in ISF in non-sleep-deprived mice. Furthermore, decreased levels of Aβ40 in ISF were more highly correlated with non-REM sleep than REM sleep in mice (Kang et al., 2009). Manipulation of sleep in mice showed that there was increased Aβ40 plaque formation during periods of prolonged sleep deprivation, while treatment with an orexin receptor antagonist that increased sleep slowed Aβ40 plaque formation (Kang et al., 2009).

Sleep can also have an effect on levels of p-tau and t-tau. A study by Liguori and colleagues (2014) showed that levels of t-tau in CSF positively correlated with increases in the first stage of sleep and negatively with decreases in deep sleep. Levels of p-tau were also positively correlated with increases in the first stage of sleep. Increased levels of p-tau and t-tau were also associated with increased levels of orexin (Liguori et al., 2014). Sleep disturbances due to sleep-disordered breathing were also associated with increases in t-tau and p-tau, and sleep deprivation increased levels of insoluble t-tau in CSF (Spira, Chin-Edinboro, Wu, & Yaffe, 2014).

*Glymphatic System*

The recently discovered glymphatic system provides one explanation as to why sleep may affect CSF levels of AD biomarkers. Throughout most of the body, lymphatic vessels are responsible for clearing waste from tissues. However, in the brain, the glymphatic system assists in removal of possibly neurotoxic waste products from the brain, including Aβ and tau (Iliff & Nedergaard, 2013). The system consists of three parts: a CSF influx route, an ISF clearance

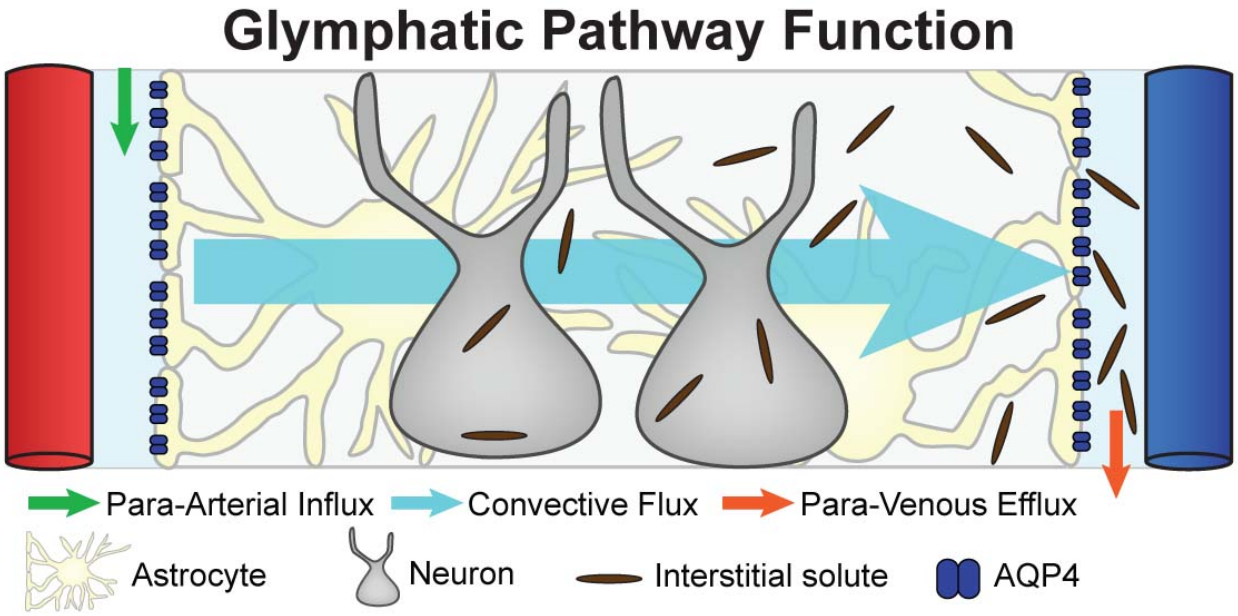


Fig. 1. Model of the glymphatic pathway. CSF enters through perivascular spaces, removes solutes via an exchange with ISF, and ISF leaves through paravenous spaces. This image is credited to Jeffrey J. Iliff and is in the public domain.

route, and an exchange between the CSF and ISF routes (Nedergaard, 2013) (Fig. 1). The CSF influx travels through the perivascular space surrounding arteries and exchanges with ISF, which is facilitated through water channels called aquaporin 4 (AQP4). The convective flow during the exchange drives waste products of neurons, including Aβ and tau, toward the veins (Jessen, Munk, Lundgaard, & Nedergaard, 2015). The ISF and waste products travel through the paravenous space until it reaches the lymphatic system in the neck, where the waste products are then removed from the brain (Nedergaard, 2013). A study by Iliff and colleagues (2012) showed that the glymphatic system clears 40-80% of large proteins, including Aβ40. The glymphatic system works mainly during sleep, with suppressed function during wakefulness (Jessen, Munk, Lundgaard, & Nedergaard, 2015).

Research into effects on the glymphatic system has shown how a lack of proper sleep can affect AD biomarker concentrations in the brain. Xie and colleagues (2013) found that the ISF concentration of Aβ40 increased in wakefulness and decreased during sleep. The changes in Aβ

concentration resulted from changes in the volume of the interstitial space, with a 60% increase in interstitial space associated with natural sleep or anesthesia. Furthermore, influx of CSF is increased during sleep, possibly due to the increase in interstitial space volume. Iliff and colleagues (2012) showed that decreased function of the glymphatic system in APQ4-null mice led to a 55% decrease in soluble Aβ40 clearance when compared to clearance in wild-type mice.

Suppressed function of the glymphatic pathway also increases tau levels. Research by Iliff and colleagues (2014) found that TBI, a possible risk factor for dementia, impairs the glymphatic pathway in mice by approximately 60%, thus suppressing the removal of p-tau from the brain. A comparison of AQP4-null and wild-type mice further showed that AQP4-null mice had much higher levels of p-tau in the brain after TBI than wild-type mice, likely due to the impairment of the glymphatic system (Iliff et al., 2014). Furthermore, impairment of glymphatic function in this study also resulted in decreased motor and cognitive function, again shown by worse functional outcome in AQP4-null mice (Iliff et al., 2014). This research suggests that one explanation for increased risk of dementia after TBI is the impairment of the glymphatic pathway and resulting increase in tau levels. The impairment of the glymphatic system increases tau levels because of reductions in neurotoxin clearance (Lucke-Wold et al., 2015). When sleep is disrupted, extracellular spaces do not enlarge, which decreases glymphatic clearance of proteins and neurotoxins. Hyperphosphorylated tau is then able to accumulate, leading to the neurofibrillary tangles characteristic of AD and other tauopathies (Lucke-Wold et al., 2015).

*Limitations*

A major limitation of the current literature is that the sleep measures used vary greatly. Measures of sleep duration, sleep quality, and sleep disturbances have all been used in research studies to represent sleep. Several studies, including those by Macey and colleagues (2002) and

Osorio and colleagues (2014), have even used specific sleep problems such as obstructive sleep apnea and sleep-disordered breathing, respectively, as measures of sleep hygiene. In using only one measure to determine sleep hygiene, however, researchers are missing potentially useful information by ignoring other areas in which sleep can be impaired. This limitation is especially prominent when reviewing the literature, as the different aspects of sleep can have different effects on cognition and CSF biomarkers. Previous studies (Blackwell et al., 2006; 2011) have shown that two different measures of sleep – duration and disturbances – show different associations with cognition, where duration was not correlated with cognition but increased measures of sleep disturbances, such as sleep efficiency and latency, were associated with impaired cognition. The use of different sleep measures in these studies could account for discrepancies in the literature. While these studies have been helpful in determining the effects of sleep on cognition and CSF biomarkers, a more comprehensive measure of sleep hygiene should be used to examine which aspects of sleep have an effect on AD. Further discrepancies might be due to differences in the accuracy of methods of sleep measurement.

*Research Goals*

The goal of this research study was to examine how sleep duration and quality relate to neuropsychological functioning and CSF biomarkers of AD among participants with normal and impaired cognition. In doing so, I addressed some of the limitations of previous studies. First, I used the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), a comprehensive self-report sleep measure that reports, among others, sleep duration, sleep disturbances, and sleep quality. In using an inventory that queries several different measures of sleep hygiene, I had a more complete assessment of sleep hygiene rather than focusing on only one factor. Second, my sample size consisted of both participants who are

cognitively normal controls or have MCI, allowing me to compare the associations with sleep hygiene for impaired and normal cognition.

Furthermore, I examined more closely whether sleep quality or sleep duration is a better predictor of these variables using a multiple regression analysis. As previously stated, results from studies, such as Faubel et al. (2009) and Keage et al. (2012), reported differing results as to whether short sleep duration is associated with cognition, prompting the theory that it might be sleep quality, and not sleep duration, that truly affects cognition. Since these studies are observational, I tested association rather than causation. However, by using a measure for sleep that reports both sleep quality and sleep duration, I hoped that I would be able to further examine and compare the associations of sleep quality and duration with cognition and CSF biomarkers.

Because sleep duration and sleep quality are correlated with one another, I expected to find that both are associated with cognition and CSF biomarker levels. However, I hypothesized that sleep quality would be a better predictor of cognition and CSF biomarkers than sleep duration, because I predicted that quality would have a stronger effect than duration. In addition, for the PSQI measures, shorter sleep is considered worse and has a higher subscore. As shown in previous research, shorter sleep was not always associated with lower cognitive scores. Furthermore, I predicted that, in comparing participants with MCI and participants with normal cognition, those with MCI would show stronger associations between poorer sleep and poorer cognition scores, decreased levels of Aβ42, and increased levels of p-tau.

## Methods

### *MAP Study*

This study analyzed data collected from the Vanderbilt Memory & Aging Project (MAP). MAP examines the relation between vascular health and brain health using neuropsychological,

neuroimaging, and proteomic markers of cerebrovascular disease and AD. Data from MAP will identify early identification strategies, risk reduction, and possible treatment targets for AD and related memory disorders. MAP is a longitudinal study; however, the current study only utilized baseline visit data, including sleep hygiene scores, neuropsychological assessment scores, and CSF biomarker levels. The baseline visit data was collected from September 2012 to November 2014.

*Participants*

Participants in the study included 66 older adults taken from the larger MAP sample who have available data on sleep hygiene, neuropsychological assessment scores, and CSF biomarker levels. Half of these adults met criteria for mild cognitive impairment (MCI) based on the diagnostic guidelines of Albert and colleagues (2011), while the other half consisted of adults who were deemed to be cognitively normal through a comprehensive eligibility visit, which included a neuropsychological protocol. Exclusion criteria includes participants without a reliable research proxy; participants with a major psychiatric illness, such as schizophrenia; neurological illness, such as multiple sclerosis, or head injury with a loss of consciousness of more than five minutes; participants with a diagnosis of heart failure; and participants who are unable to undergo MRI testing.

*Sleep Hygiene*

Sleep hygiene was measured using the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The PSQI is a self-report index that measures sleep hygiene over the past month. The questionnaire consists of twenty-one questions separated into seven subsections: duration of sleep, sleep disturbance, sleep latency, day dysfunction due to sleepiness, sleep efficiency, overall sleep quality, and medication needed to sleep. From each

section, a subscore is derived ranging from 0 to 3, and the seven subsections are added together to create a total score ranging from 0 to 21. A participant with a score of 5 or below is considered to have good sleep hygiene, while a participant with a score of above 5 is considered to have poor sleep hygiene. I used the subscores for sleep duration and sleep quality on the PSQI.

*Cognition*

Cognition was measured through a comprehensive neuropsychological protocol. The assessment included global cognition as well as three domains: learning and memory, information processing, and executive function. Global cognition was measured using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al, 2005). Learning and memory was assessed using the California Verbal Learning Test-II (CVLT-II) (Delis, Kramer, Kaplan, & Ober, 2000), which is a strong predictor of early cognitive decline (Bilgel et al., 2014). Information processing was assessed using the Wechsler Adult Intelligence Scale-IV (WAIS-IV) Coding (Wechsler, 2008), which is a strong predictor of progression of cognitive decline (Parikh et al., 2015). Executive function was assessed using the Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference Test, which is associated with impairments in instrumental activities of daily living in older adults (Jefferson, Paul, Ozonoff, & Cohen, 2006), and the D-KEFS Number-Letter Switching (Delis, Kaplan, & Kramer, 2001), which is a strong predictor of functional status in older adults (Mitchell & Miller, 2008; Bell-McGinty, Podell, Franzen, Baird, & Williams, 2002).

*Cerebrospinal Fluid Biomarkers*

MAP participants were asked if they would participate in an optional lumbar puncture for cerebrospinal fluid (CSF) acquisition. The CSF collected was tested in batch by board-certified laboratory technicians blinded to clinical information. They tested for Aβ1-42 (INNOTEST® β-

AMYLOID$_{(1-42)}$) and tau phosphorylated at threonine 181 (p-tau; INNOTEST® PHOSPHO-TAU$_{(181P)}$) levels using commercially available enzyme-linked immunosorbent assays (Fujirebio, Ghent, Belgium) (Palmqvist et al., 2014).

*Data Analysis*

To begin, I ran descriptive statistics on the sample to understand participant characteristics, such as demographics (e.g., age, sex, race, education), sleep duration and quality, neuropsychological performances, and CSF biomarker levels. I used a multiple regression analysis to determine whether sleep quality or sleep duration is a better predictor of cognition scores and CSF biomarker levels. The predictor variables were the PSQI subscores of sleep quality and sleep duration. The cognitive outcome variables included the total score of MoCA as a global cognition measure, the short delay free recall score (SDFR) and long delay free recall (LDFR) score of CVLT-II as memory measures, the WAIS-IV Coding total score as a processing speed measure, and the total time in seconds for D-KEFS Color-Word Interference Test and D-KEFS Number-Letter Switching as executive function measures. The CSF biomarker outcome variables were level of p-tau and Aβ42. The scores for Aβ42, p-tau, D-KEFS Color-Word Interference, and D-KEFS Number-Letter Switching were converted to approximate a normal distribution using a log transformation. One regression model was run per outcome variable for eight total models.

Covariates include age, education, body mass index (BMI), and depressed mood as assessed by the Geriatric Depression Scale (GDS). The covariates were chosen based on their association with either cognition or sleep. Age is associated with cognition, such that as age increases, there is a graduate rate of cognitive decline even among cognitively normal older adults (Wilson, Leurgans, Boyle, Schneider, & Bennett, 2010). Age is also associated with sleep,

with sleep disturbances increasing with age and sleep efficiency decreasing with age (Redline et al., 2004). Older adults also commonly report insomnia, excessive daytime sleepiness, and snoring or sleep apnea (Merlino et al., 2010). Education is also associated with cognition, with low education levels relating to faster cognitive decline in older adults (Bosma et al., 2003). High BMI is associated with decreased sleep duration, as well as poorer sleep quality and excessive daytime sleepiness (Beccuti & Pannain, 2011). People with depression have more difficulty falling asleep and more awakenings during sleep, as well as a higher comorbidity of sleep disorders, such as obstructive sleep apnea. They also have decreased slow-wave sleep and increased REM sleep (Medina, Lechuga, Escandón, & Moctezuma, 2014).

I first used an F-test to determine whether the relationship between the predictor variables and the outcome variable was statistically reliable, meaning that the regression model with the predictor variables has a better fit than a model with no predictor variables. I then used R-squared to determine how the predictors accounted for each outcome variable. I compared the beta coefficients for each independent variable to determine which had a greater predictive effect on the dependent variable. Since eight regression analyses were run, I used the Bonferroni correction to adjust the p-value for multiple comparisons (i.e., 0.05/8=0.006). I also tested for multicollinearity of the predictor variables using variance inflation factors (VIF).

For the third part of my study, which examined how diagnosis affects the relationship between sleep quality and duration and cognition and CSF biomarkers, I tested a three-way interaction using a backward elimination regression analysis. A p-value of 0.05 was used for the interaction analyses. I looked at sleep quality and sleep duration and used diagnosis of MCI or normal cognition as an interacting variable to determine the significance of its interaction with the predictor variables.

# Results

## *Participant Characteristics*

Table 1.
Descriptive Statistics, Mean (SD)

| | Total Participants (n = 66) | NC (n = 33) | MCI (n = 33) |
|---|---|---|---|
| Age (years) | 73.29 (6.15) | 73.79 (5.39) | 72.79 (6.88) |
| Sex (% male) | 76% | 88% | 67% |
| Race (% white) | 97% | 97% | 97% |
| Education (years) | 15.64 (2.98) | 16.64 (2.58) | 14.64 (3.05) |
| Diagnosis (% NC) | 50% | - | - |
| BMI ($kg/m^2$) | 27.80 (3.79) | 27.38 (3.34) | 28.22 (4.19) |
| GDS | 3.29 (3.06) | 1.94 (1.92) | 4.64 (3.40) |
| PSQI Duration | 0.59 (0.82) | 0.67 (0.82) | 0.52 (0.83) |
| PSQI Quality | 0.76 (0.77) | 0.79 (0.65) | 0.73 (0.89) |
| A-beta 42 (mg/L) | 555.85 (248.66) | 619.12 (242.52) | 492.58 (241.92) |
| P-tau (mg/L) | 63.61 (26.20) | 56.06 (21.30) | 71.15 (28.69) |
| MoCA | 24.85 (3.17) | 26. 36 (2.19) | 23.33 (3.30) |
| CVLT-II SDFR | 6.83 (3.86) | 9.12 (3.12) | 4.55 (3.11) |
| CVLT-II LDFR | 7.24 (4.19) | 9.55 (3.58) | 4.94 (3.45) |
| D-KEFS CWI ** (s) | 68.50 (22.99) | 60.82 (13.97) | 76.18 (27.50) |
| WAIS-IV Coding | 53.47 (12.85) | 57.21 (11.42) | 49.73 (13.27) |
| D-KEFS NLS*** (s) | 111.48 (59.31) * | 87.09 (28.30) | 136.63 (71.76) * |

* data missing from one participant
** D-KEFS Color Word Interference
*** D-KEFS Number-Letter Switching

As shown in Table 1, participants had a mean age of 73.29 years (S.D. 6.15) and a mean education of 15.63 years (S.D. 2.98). Of the sample, 97% were Caucasian and 76% were male. 50% of the sample had a diagnosis of MCI. Participants had a mean BMI of 27.80 (S.D. 3.79) and a mean GDS score of 3.29 (S.D. 3.06).

## *Cognition and Sleep Quality and Duration*

The predictive effects of sleep quality and duration on cognition were analyzed using a multiple regression analysis, with the PSQI subscores of sleep quality and sleep duration as the

predictor variables and covariates for age, education, BMI, and depressed mood. For each of the six cognition scores used, a multiple regression analysis was run with the cognition score as the outcome variable. VIF for sleep duration and sleep quality were 1.455 and 1.659, respectively. Since VIF were less than 10, I concluded there was no multicollinearity between the predictor variables.

For the D-KEFS Color-Word Interference Test, a significant regression model for the predictors of sleep duration and quality was found ($F$ (6, 59) = 3.271, $p$ = 0.045), with change in $R^2$ = 0.090; of note this significant finding did not survive the more stringent p-value threshold for multiple comparison correction. Sleep quality was a significant predictor of D-KEFS Color-Word Interference Test score for a p-value of 0.05 but not for a p-value of 0.006 adjusted for multiple comparisons ($\beta$ = 0.366, $p$ = 0.018), but sleep duration was not ($\beta$ = -0.270, $p$ = 0.061), as shown in Table 2.

Table 2.
Predictor Effects for Cognition Outcomes

| | Sleep Predictor | β | p |
|---|---|---|---|
| MoCA | Duration | 0.040 | 0.303 |
| | Quality | 0.068 | 0.484 |
| CVLT-II SDFR | Duration | -0.179 | 0.232 |
| | Quality | 0.205 | 0.198 |
| CVLT-II LDFR | Duration | -0.220 | 0.143 |
| | Quality | 0.122 | 0.441 |
| D-KEFS CWI | Duration | -0.270 | 0.061 |
| | Quality | 0.366 | 0.018 * |
| WAIS-IV Coding | Duration | 0.139 | 0.328 |
| | Quality | -0.169 | 0.266 |
| D-KEFS NLS | Duration | -0.174 | 0.221 |
| | Quality | -0.095 | 0.532 |

* significant at p = 0.05, but not at p = 0.006 adjusted for multiple analyses

No significant regression models for sleep duration and sleep quality predictors were found for MoCA ($F$ (6, 59) = 0.311, $p$ = 0.734), CVLT-II SDFR ($F$ (6, 59) = 1.059, $p$ = 0.353),

CVLT-II LDFR ($F$ (6, 59) = 1.101, $p$ = 0.339), WAIS-IV Coding ($F$ (6, 59) = 0.753, $p$ = 0.475), or D-KEFS Number-Letter Switching ($F$ (6, 59) = 1.767, $p$ = 0.180). As shown in Table 2, no significant effects were found for either predictor.

*CSF Biomarkers and Sleep Quality and Duration*

The predictive effects of sleep quality and duration on cognition were analyzed using a multiple regression analysis, with the PSQI subscores of sleep quality and sleep duration as the predictor variables and covariates for age, education, BMI, and depressed mood. For the levels of Aβ42 and p-tau, separate multiple regressions were run with the CSF biomarker level as the outcome variable. VIF for sleep duration and sleep quality were 1.455 and 1.659, respectively. Since VIF was less than 10, I concluded there was no multicollinearity between the predictor variables.

No significant regression models for sleep duration and sleep quality predictors were found for either Aβ42 ($F$ (6, 59) = 2.192, $p$ = 0.121) or p-tau ($F$ (6, 59) = 2.893, $p$ = 0.063). As shown in Table 3, no significant effects were found for either predictor.

Table 3.
Predictor Effects for CSF Biomarker Outcomes

| | Sleep Predictor | β | p |
|---|---|---|---|
| Aβ42 | Duration | 0.080 | 0.585 |
| | Quality | 0.231 | 0.142 |
| p-tau | Duration | -1.336 | 0.187 |
| | Quality | -0.169 | 0.284 |

*Interaction Effect of Diagnosis for Cognition Scores*

The interaction effect of diagnosis for cognition scores was analyzed with a three-way interaction between diagnosis, sleep quality, and sleep duration, using a backward elimination multiple regression analysis to eliminate interactions that were not significant at $p$ = 0.05. The

covariates remained the same as in the multiple regression analyses, and one model was run for each of the cognition scores for a total of eight models.

The final models for all cognition outcome variables had significant regression equations, as seen in Table 4.

Table 4.
Final Model Regressions for Interaction of Sleep Quality, Sleep Duration, and Diagnosis for Cognition Outcomes

| | F | df | p | $R^2$ |
|---|---|---|---|---|
| MoCA | 5.866 | 8, 57 | <0.0005 | 0.452 |
| CVLT-II SDFR | 8.090 | 7, 58 | <0.0005 | 0.532 |
| CVLT-II LDFR | 6.522 | 7, 58 | <0.0005 | 0.440 |
| D-KEFS CWI | 3.806 | 8, 57 | 0.001 | 0.348 |
| WAIS-IV Coding | 2.921 | 8, 57 | 0.008 | 0.291 |
| D-KEFS NLS | 4.022 | 7, 57 | 0.001 | 0.331 |

There was only a significant predictive effect of diagnosis for CVLT-II SDFR ($\beta$ = -0.712, $p < 0.0005$), CVLT-II LDFR ($\beta$ = -0.675, $p < 0.0005$), and D-KEFS Number-Letter Switching ($\beta$ = 0.424, $p = 0.002$), with no significant interaction effects.

D-KEFS Color-Word Interference ($\beta$ = 0.841, $p = 0.041$) and WAIS-IV Coding ($\beta$ = -0.858, $p = 0.045$) had only a significant interaction effect of sleep quality and diagnosis (Fig. 2 and 3), with no significant predictive main effects.

The final model for MoCA had a significant interaction effect of sleep duration and sleep quality ($\beta$ = -0.610, $p = 0.015$), indicating that associations with poor global cognition scores might occur when both sleep quality and sleep duration are poor. There was also a significant predictive effect of diagnosis ($\beta$ = -0.337, $p = 0.005$) and sleep duration ($\beta$ = 0.262, $p = 0.032$).

*Interaction Effect of Diagnosis for CSF Biomarker Levels*

The interaction effect of diagnosis for CSF biomarkers levels was analyzed with a three-way interaction between diagnosis, sleep quality, and sleep duration, using a backward

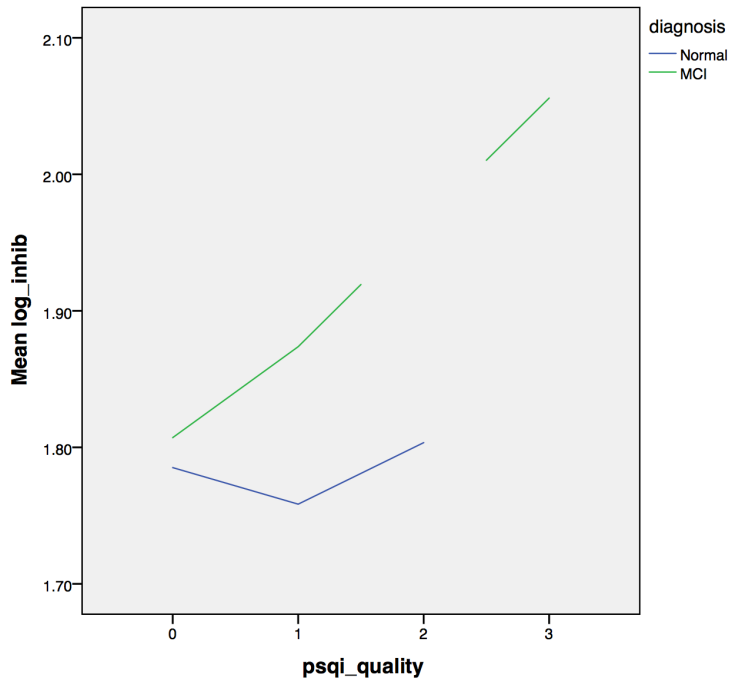


Fig. 2.
Interaction Effects of Diagnosis and Sleep Quality for D-KEFS Color-Word Interference.
As sleep quality scores increase, indicating a decrease in sleep quality, scores for the D-KEFS Color-Word Interference test increase for participants with MCI. This increase is not seen for participants with normal cognition, which indicates that sleep has a greater association with D-KEFS Color-Word Interference scores for participants with MCI.

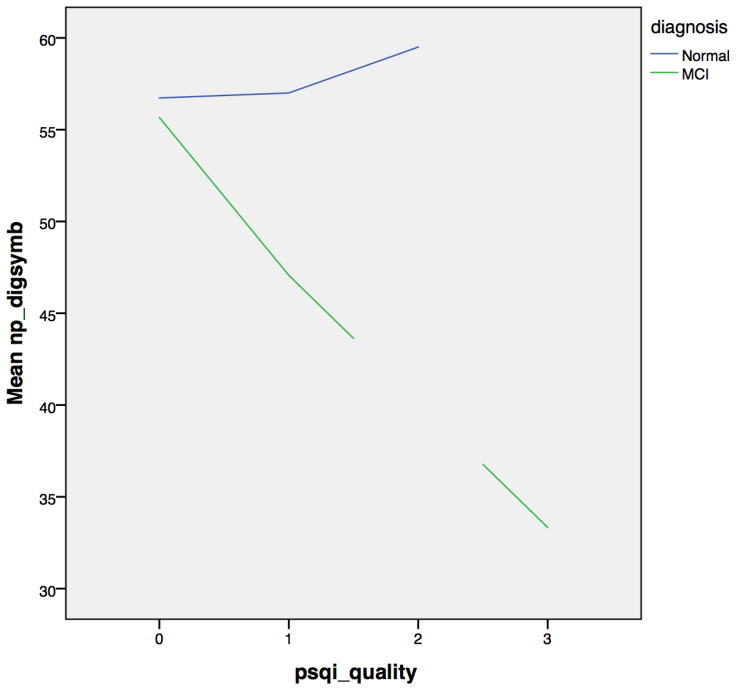


Fig. 3.
Interaction Effects of Diagnosis and Sleep Quality for WAIS-IV Coding.
As sleep quality scores increase, indicating a decrease in sleep quality, the scores for the WAIS-IV Coding test decrease for participants with MCI. This decrease is not seen for participants with normal cognition, which indicates that sleep has a greater association with WAIS-IV Coding scores for participants with MCI.

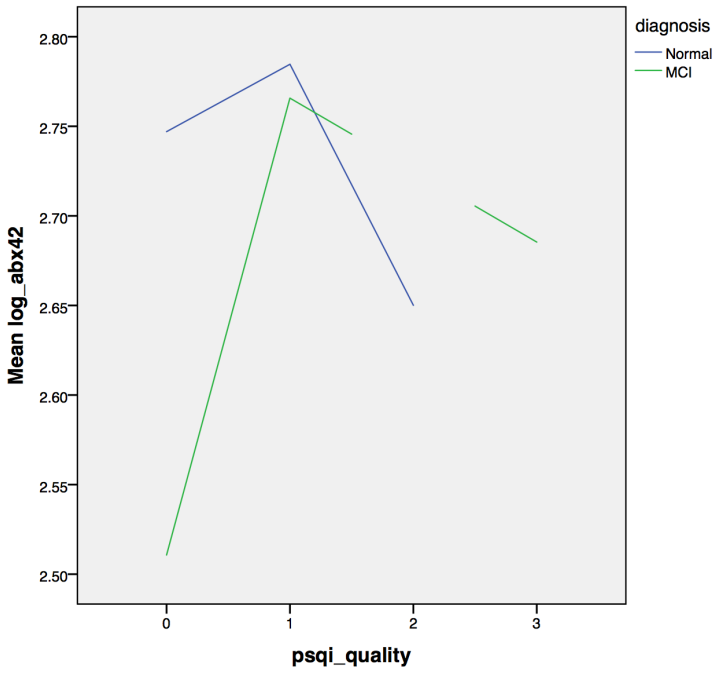


Fig. 4.
Interaction Effects of Diagnosis and Sleep Quality for Aβ42.
The level of Aβ42 is lower for participants with MCI than for participants with normal cognition at the score of good sleep quality (0). However, an increase in the sleep quality score, indicating a decrease in sleep quality, shows a much smaller difference in Aβ42 levels for participants with MCI and normal cognition.

elimination multiple regression analysis to eliminate interactions that were not significant at $p$ = 0.05. The covariates remained the same as in the multiple regression analyses, and one model was run each for Aβ42 and p-tau.

The final models for both CSF biomarker outcome variables had significant regression equations, as seen in Table 5.

Table 5.
Final Model Regressions for Interaction of Sleep Quality, Sleep Duration, and Diagnosis for CSF Biomarker Outcomes

| | F | df | p | $R^2$ |
|---|---|---|---|---|
| Aβ42 | 2.494 | 9, 56 | 0.006 | 0.322 |
| p-tau | 3.285 | 7, 58 | 0.005 | 0.284 |

For Aβ42, there was a significant interaction of sleep duration and quality ($\beta$ = -0.827, $p$ = 0.005), indicating that associations with lower levels of Aβ42 might occur when both sleep quality and sleep duration are poor, and a significant interaction of sleep quality and diagnosis ($\beta$ = 1.126, $p$ = 0.011) (Fig. 4). There was also a significant predictive effect of diagnosis ($\beta$ = -

0.478, $p = 0.007$) and sleep duration ($\beta = 0.619$, $p = 0.007$). For p-tau, the only significant effect was for diagnosis ($\beta = 0.461$, $p = 0.001$).

## Discussion

The purpose of this study was to determine whether sleep quality or sleep duration was a better predictor of cognition and CSF biomarker levels in older adults with normal cognition and MCI. No significant predictive effects of sleep duration or sleep quality were found for any of the outcome variables in the multiple regression analyses, although sleep quality was found to be a significant predictor of D-KEFS Color-Word Interference when the p-value was not adjusted for multiple comparisons. With the three-way interaction using a backward elimination multiple regression analysis, several significant effects were found for the different tests. The most common significant effect was a main effect of diagnosis, while common interaction effects were the interaction of sleep quality and diagnosis and the interaction of sleep duration and sleep quality.

The lack of association found between sleep duration and quality and cognition scores and CSF biomarker levels is contrary to previous literature. Studies such as Blackwell and colleagues (2006) and Keage and colleagues (2012) report associations between cognition and sleep quality and cognition and sleep duration, respectively, and Kang and colleagues (2009) and Liguori and colleagues (2014) show associations between sleep and Aβ and p-tau, respectively. One explanation for the discrepancy could be the low percentage of variance explained by sleep even in studies when sleep was a significant predictor of cognition. In a study done by Kronholm and colleagues (2009), the regression model showed that sleep only accounted for 2.6% of the variance in objective cognitive tests and 10.8% of the variance in subjective cognition tests. In this study, even when the regression equation was significant by $p < 0.05$, although not with the

p-value adjusted for multiple analyses, the variance in the outcome variable explained by sleep quality and duration was only 9%. The regression equation for D-KEFS Color-Word Interference did show that sleep quality was a significant predictor for sleep at $p < 0.05$, while sleep duration was not. This supports the hypothesis that sleep quality has a greater effect on cognition than sleep duration. However, since the predictive value of sleep quality was not significant at a p-value adjusted for multiple analyses, and since the D-KEFS Color-Word Interference was the only model that showed any possibly significant outcomes, the significance at $p < 0.05$ suggests a Type I error.

The interaction effects between sleep quality and diagnosis found for D-KEFS Color-Word Interference, WAIS-IV Coding, and Aβ42 support the hypothesis that the relationship between sleep quality and cognition scores and CSF biomarker levels was more affected by diagnosis than that of sleep duration. This is supported by a study done by Kim and colleagues (2011), which examined the effects of sleep quality on cognition in participants with normal cognition and MCI. They found that impaired sleep quality due to sleep apnea syndrome and decreased slow wave sleep had a significantly predictive effect on cognition of participants with MCI. These findings suggest that impaired sleep could be a risk for increased cognitive decline among older individuals who are already suffering from cognitive impairment.

As opposed to showing an interaction between diagnosis and sleep, the final model for the MoCA and Aβ42 outcome variables showed a significant interaction between the sleep duration and sleep quality subscores. My original hypothesis was that sleep quality, rather than sleep duration, drove the association of sleep with cognition. However, the interaction effect between sleep duration and sleep quality suggests that the association could come from a combination of both measures of sleep. A study by Kronholm and colleagues (2006) showed that

tiredness and fatigue were common in both short and long-range sleepers, suggesting that sleep quality and sleep duration are associated with one another. It could be that an individual needs both good sleep duration and good sleep quality to obtain the full positive effects of sleep and retain cognitive abilities.

Although limitations of the existing literature were addressed, this study also had several limitations of its own. First, the PSQI measure of sleep, while comprehensive and valid, was self-reported. Self-reported measures can be unreliable, and this unreliability was an especially prominent concern among participants who have memory deficits. Although the participants in this study only had MCI, and not AD, there was a greater chance that their answers on any self-report measure were compromised by cognitive difficulty recalling accurate information (Chen & Lin, 2014). Future research studies could use other more expensive and time-consuming methods of sleep measurement, such as actigraphy or polysomnography, which are more valid and reliable measures of sleep. Another limitation to this study was the smaller sample size of 66 participants. Small sample sizes can affect the power and significance of the results. A study with low statistical power can make it difficult to observe an effect. Furthermore, low power decreases the chance that a statistically significant effect is a result of a true effect (Button et al., 2013). The small sample size further limited the study when the participants were subdivided into groups (for example, MCI and normal control). Furthermore, this study did not address the effects of sleep hygiene on AD. Since significant effects were found for the interaction between diagnosis and sleep quality and duration, it is possible that sleep could have a different effect on AD. Future studies could compare the effects of sleep quality and duration between normal control, MCI, and AD groups of participants. Further research could also examine other reasons for discrepancies within the existing literature on the effects of sleep duration. The effect of sleep

quality and sleep duration is only one possible explanation for these disparities. An interaction between sleep quality and sleep duration, or other measures of sleep hygiene, such as sleep efficiency or sleep latency, might also be a reason for discrepancies in the literature.

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