

DISRUPTION OF SLEEP AND CIRCADIAN RHYTHM ORGANIZATION AS RISK
FACTORS FOR DIAGNOSIS OF ALZHEIMER'S DISEASE

by

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DEDICATION

For my grandparents.

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ABSTRACT

Individuals commonly report disrupted nighttime sleep and daytime sleepiness in the early, preclinical, stages of Alzheimer's disease (AD), as well as other dementias. Furthermore, there is accumulating evidence of a bidirectional relationship between sleep disturbance and AD-related neuropathology (i.e., amyloid- β plaques and neurofibrillary tangles). Despite this, increasing age remains the strongest predictor of late-onset sporadic AD. It is unclear how early in the course of AD sleep-related disturbance manifests and what role these changes have in the etiology of the disease. Moreover, the interplay between sleep and age-related changes to health status, as measured by a frailty index, has not been previously explored. The present dissertation examined the relationship between sleep disturbance and overall health status, including more traditional risk factors for AD, in predicting risk of negative health outcomes, (i.e., cognitive impairment, dementia, and mortality) in cognitively healthy people. Analyses were based on epidemiological data from two large multi-national cohorts, namely the Survey of Health, Ageing, and Retirement in Europe, and the Honolulu-Asia Aging Study. The combination of sleep-related items (i.e., a 'sleep disturbance index') was compared to a measure of overall health status (i.e., a 'frailty index'). Results demonstrate that problems with sleep maintenance, as indicated by disrupted nighttime sleep continuity and daytime sleepiness, are risk factors for cognitive impairment and AD/dementia, up to an average of ~6 years before reported diagnosis, even when risks associated with overall health status are taken into account. By contrast, sleep disturbance was unexpectedly found to decrease risk of mortality when controlling for overall health status. Taken together, sleep disturbance is an important symptom early in the course of cognitive decline and dementia. Further work is required to understand the complex interaction between sleep as a restorative function, and frailty, as a measure of physiological vulnerability to adverse outcomes. Continued exploration of the connections between sleep disturbance, frailty, and dementia, could ultimately identify novel biomarkers leading to the earlier and more accurate diagnosis of AD, as well as guide interventions that could delay institutionalization and/or provide better quality care for those with dementia.

LIST OF ABBREVIATIONS USED

3xTg-AD	triple transgenic mouse model of Alzheimer's disease
Ach	acetylcholinesterase inhibitors
AD	Alzheimer's disease
A β	amyloid- β
Apo	apolipoprotein
APP	amyloid precursor protein
AUC	area under the curve
BMI	body mass index
BZD	benzodiazepine
CBT	core body temperature
CBT-I	cognitive behavioral therapy for insomnia
CI	confidence interval
CSF	cerebrospinal fluid
EEG	electroencephalography
FI	frailty index
HAAS	Honolulu-Asia Aging Study
ICU	intensive care unit
LD	light/dark
MCI	mild cognitive impairment
NFT	neurofibrillary tangles
N1/N2/N3	non-REM stages 1-3
OR	odds ratio
PD	Parkinson's disease
ROC	receiver operating curve
SCN	suprachiasmatic nucleus
SDI	sleep disturbance index
SWS	slow wave sleep
SHARE	Survey of Health, Ageing, and Retirement in Europe
VP	vasopressin
VIP	vasoactive intestinal polypeptide

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CHAPTER 1 INTRODUCTION

1.1 Preface

Chapters 1, 2 and 3 have been published. The first author was involved in drafting and revising each manuscript, analysis and interpretation of the data, and preparation of all non-copyrighted figures and tables. Copyright permissions have been obtained (Appendix B.1; C.1; D.1).

Sterniczuk, R., & Rusak, B. (2016). Sleep in relation to aging, frailty, and cognition.

In Fillit, H, Rockwood K, & Young, J. (Ed.), *Brocklehurst's Textbook of Geriatric Medicine and Gerontology* (pp. 108-1-108-6.e2). 8e Elsevier, Philadelphia.

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1.2 Changes to Published Material

- p.9, first paragraph – typo “has” been reported
- p.10 section 1.4.3, second paragraph – typo “periodic”
- p.16 – second and fifth use of “AD” changed to “dementia”
- p.23, second paragraph – last sentence now reads “its long-term effectiveness in older adults has yet to be determined”

1.3 Sleep and Health

Getting adequate sleep and maintaining normal daily sleep-wake rhythms are important to sustaining good lifelong physical and mental health and reducing the risk of disease development. Acute sleep loss leads, for example, to disruption of endocrine function and glucose metabolism (Buxton et al., 2010; Omisade, Buxton, & Rusak, 2010; Spiegel, Knutson, Leproult, Tasali, & Van Cauter, 2005). Chronic sleep loss and daily rhythm disruption also lead to numerous negative long-term health consequences (Knutsson, 2003) including increased risk for obesity (Cappuccio et al., 2008), cardiovascular disease (Puttonen, Härmä, & Hublin, 2010) and type II diabetes (Rüger & Scheer, 2009). In addition, disrupted sleep-wake and circadian rhythms (e.g., as a result of chronic shift or night work) have been linked to an increased risk for developing cancer (Kolstad, 2008; Megdal, Kroenke, Laden, Pukkala, & Schernhammer, 2005; Parent, El-Zein, Rousseau, Pintos, & Siemiatycki, 2012) and for resistance to cancer treatments (Dauchy et al., 2014).

Some of the negative consequences of sleep loss may be related to its impact on immune system function. Disturbed or short sleep weakens immune system function (Gamaldo et al., 2012; Palmblad, Petrini, Wasserman, & Akerstedt, 1979), which can lead to impaired healing and recovery (Adam & Oswald 1984; Evans & French, 1995; & Brown, 2005), as well as inadequate immune system responses to vaccinations (Prather et al., 2012). Increased risk of metabolic diseases, weakened immune responses, and inadequate tissue repair, are in turn associated with accelerated health deficit accumulation, and increasing frailty in older adults (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013; Mitnitski, Song, & Rockwood, 2013).

Sleep has also been shown to be involved in brain plasticity and consolidation of newly acquired information, so disrupted sleep can interfere with learning and memory (Aton et al., 2009; Walker, 2008). Sleep has also been proposed to play an important role in facilitating clearance of metabolic products of neuronal metabolism, including the substance most closely linked to development of Alzheimer's disease, beta-amyloid (Kang et al., 2009; Xie et al., 2013). These physiological effects of sleep loss may be the basis for findings of increased risk for cognitive decline and ultimately for development of Alzheimer's disease in those with sleep problems (Lim et al., 2013; Sterniczuk, Theou, Rusak, & Rockwood, 2013).

1.4 Sleep and Circadian Rhythm Disturbance in Older Adults

Several changes in sleep patterns have been associated with aging, including an advance in the timing of both sleep onset and waking to earlier clock times, more disrupted sleep, reduced slow-wave sleep with more light sleep, and increased daytime napping (Kripke et al., 2005; May, Hasher, & Stoltzfus, 1993; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). As a result, more than 80% of those over 65 report some degree of disrupted sleep (Foley et al., 1995). Older adults also have more difficulty adjusting to changes in daily rhythms resulting from travel or shift work schedules (Monk, 2005). Although the types of sleep shown, degree of sleep continuity (i.e., sleep maintenance or lack of interruption by wake episodes), and the distribution of sleep across the 24 h cycle change with age, total daily sleep time remains relatively stable in healthy aging, with those 60 and over sleeping an average of 6.5-7 hours a day (Foley, Monjan, Simonsick, Wallace, & Blazer, 1999; Quan et al., 2005).

Sleep changes during aging may be related to disruption of sleep-regulatory mechanisms in the brain (Šimić et al., 2009; Sterniczuk, Dyck, Laferla, & Antle, 2010). But it is important to bear in mind that many medical conditions that disrupt nocturnal sleep (and consequently can provoke daytime sleepiness) also increase in frequency with age. These include sleep-related breathing disorders (e.g., sleep apnea), pain syndromes (e.g., arthritis), prostatitis in men, and menopause-related hot flashes in women. In addition, sleep may be disrupted early in the prodromal stages of neurological diseases (e.g., Parkinson's and Alzheimer's diseases; Rothman & Mattson, 2012; Sterniczuk et al., 2013). These and other potential contributors to sleep disruption in aging should be ruled out before considering whether changes intrinsic to sleep-regulatory or circadian mechanisms are implicated in these features (Vitiello, Moe, & Prinz, 2002).

One impact of the circadian system on sleep is to promote sustained waking during the day and sleep at night; a reduction in the strength of this circadian impact can contribute to increased sleep disruption and redistribution of sleep during the 24 h day. There is evidence from both animal model and human studies that the amplitude of oscillation of the circadian pacemaker in the hypothalamic suprachiasmatic nucleus (SCN) is reduced during aging (Hofman and Swaab, 1994; Nakamura et al., 2011; Wu & Swaab, 2007). In addition, the molecular mechanisms responsible for generating these daily rhythms may be disrupted with age (Thome, Coogan, Woods, Darie, & Häßler, 2011). Aging also affects various physiological rhythms that influence sleep, such as body temperature, melatonin secretion, and fluctuations in other neuroendocrine systems (e.g., declining secretion of luteinizing, growth, and thyroid-stimulating hormones; lowered serotonin levels).

1.5 Changes in Sleep Architecture During Aging

1.5.1 Non-REM Sleep

Although older adults spend more time in bed than younger adults, they experience pronounced deterioration in the quality of sleep, as measured by changes to sleep architecture (Ancoli-Israel, Ayalon, & Salzman, 2008; Figure 1.1). Sleep tends to become shallower and lighter with advancing age, and there are fewer sleep spindles and smaller amplitude K complexes observable during non-REM stage 2 sleep (N2), as measured by electroencephalography (EEG). One of the most profound changes observed in older adults is a reduction in the number and amplitude of EEG delta waves, which corresponds to a significant decrease in the percentage of time spent in slow-wave sleep or non-REM stage 3 (N3; formerly divided into stages 3 and 4; Crowley, 2011), or even the virtual absence of this sleep stage in the oldest cohorts (Bliwise, 1993; Ohayon et al. 2004). A meta-analysis of 65 studies demonstrated that there is a significant decrease in total sleep time, sleep efficiency (time spent asleep as a proportion of the time spent in bed), percentage of slow-wave sleep, and REM sleep latency, from young adulthood to about age 60, after which only sleep efficiency appears to continue to decrease. These changes are also accompanied by an increase in the percentage of non-REM 1 (N1) and N2, as well as an increase in sleep latency and time spent awake after sleep onset (Ohayon et al. 2004).

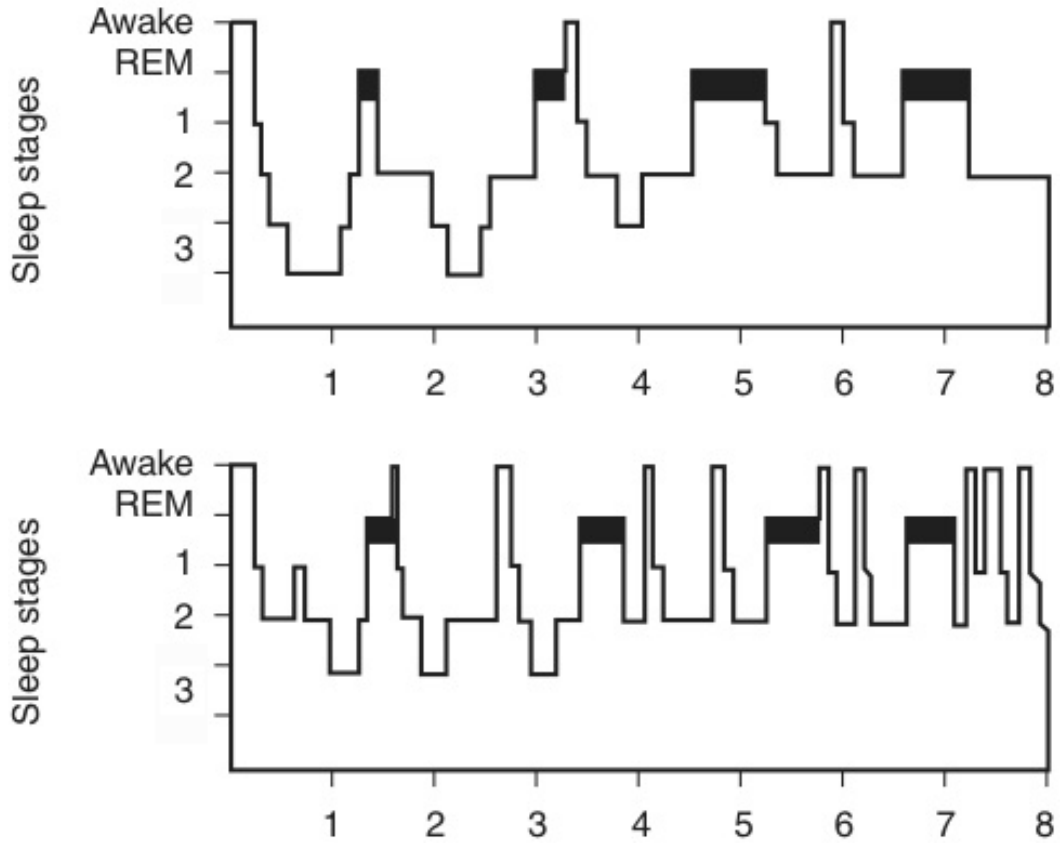


Figure 1.1 Typical distribution of sleep architecture across an 8-hour sleep cycle, in a young adult (top) and an older adult (bottom).

1.5.2 REM Sleep

Many reports have suggested as much as a 50% reduction in REM sleep in older as compared to younger adults (Ohayon et al., 2004; Van Cauter, Leproult, & Plat, 2000). However, when the impacts of mental and physical illnesses are controlled for (Vitiello et al., 2002), the percentage of REM sleep is relatively well preserved from age 60 onward (Ohayon et al., 2004).

1.6 Sleep Disorders in Aging

1.6.1 Late-life Insomnia

Insomnia is usually defined as inadequate or unrefreshing sleep, and is characterized by self-reports of difficulty falling or staying asleep, typically accompanied by increases in sleepiness and functional impairment during the day. It is the most common sleep complaint in most age groups, including among older adults (Kamel & Gammack, 2006; Table 1.1). Complaints of insomnia are often (Foley et al., 1995; Pallesen et al., 2001; Liu & Liu, 2005), but not always (Kim, Uchiyama, Okawa, Liu, & Ogihara, 2000; Pearson, Johnson, & Nahin, 2006), reported to increase with age. Women are more likely to complain of insomnia, especially during and after menopause, and this sex difference appears to increase after age 65. Insomnia symptoms tend to persist over time (Foley et al., 1999; Quan et al., 2005; Mallon, Broman, & Hetta, 2000), with early-morning awakenings and disrupted sleep continuity during the night being highly associated with older age groups; younger adults tend to exhibit greater difficulty initiating sleep.

Table 1.1 Common sleep disorders in older adults.

Sleep disorder	Prevalence	Characteristic features
Late-life insomnia	Up to 50% over 65 years	<ul style="list-style-type: none"> • Difficulty falling or staying asleep • Early morning awakenings • Disrupted sleep continuity at night
Obstructive sleep apnea	Up to 62% over 60 years	<ul style="list-style-type: none"> • 5 or more episodes per hour of reduction or complete cessation of airflow
Periodic limb movements	Up to 45% over 65 years	<ul style="list-style-type: none"> • Involuntary repetitive leg jerks occurring at 20-40 second intervals • Occurs during non-REM sleep
Restless legs syndrome	Up to 35% over 65 years	<ul style="list-style-type: none"> • Irresistible urge to move one's legs due to a restless, "crawling" sensation, or pain • Associated with sleep onset
REM-sleep behavior disorder	0.5% of the general population	<ul style="list-style-type: none"> • Acting out elaborate movements during sleep e.g., punching, kicking, yelling • Occurs during REM sleep

1.6.2 Sleep-disordered Breathing

Sleep-related respiratory disorders encompass those conditions that cause abnormal respiratory events during sleep, ranging from mild snoring to a reduction (hypopnea) or complete cessation of airflow (apnea; Wolkove et al., 2007a). Obstructive sleep apnea is one of the most common sleep disorders and is due to relaxation and subsequent collapse of muscles in the back of the throat, causing obstruction of the upper airway. The increased prevalence of sleep apnea in older adults, which has been reported to be as high as 62% in those over 60 (Ancoli-Israel & Ayalon, 2006), may be due to the increased occurrence of obesity, age-related decline in muscle tone, or impaired pharyngeal sensory detection thresholds. Sleep apnea often goes unrecognized in older adults because the overt symptoms that are reported (i.e., fatigue, daytime sleepiness, morning headache, mood changes, poor concentration or memory loss) tend to be attributed to other comorbidities or to the aging process.

Peaking at age 50-60, snoring is also a frequent complaint of older adults. Interestingly, the prevalence of snoring has been shown to fall after the age of 75, possibly reflecting a survivorship effect. Snoring may be related to various comorbidities (especially obesity and sleep-disordered breathing) that ultimately contribute to premature death in this age group. Narrowing of the upper airway that contributes to snoring is also associated with the many health consequences of sleep-disordered breathing, including hypertension, heart disease and stroke (Koskenvuo et al., 1987; Zamarrón, Gude, Otero Otero, & Rodríguez-Suárez, 1999; Leineweber, Kecklund, Janszky, Akerstedt, & Orth-Gomér, 2004).

1.6.3 Periodic Limb Movements in Sleep/Restless Legs Syndrome

Periodic limb movements are repetitive leg jerks or kicks that occur specifically during sleep. They can range from subtle contractions of ankle or toe muscles to dramatic flailing of the limbs. These movements often occur during N2, resulting in sleep disruption and excessive daytime sleepiness. Its prevalence increases with age and can be found in as many as 45% of community-dwelling older adults (Ancoli-Israel et al., 1991).

Restless legs syndrome is commonly comorbid, and often confused, with periodic leg-movement disorder. It is characterized by uncomfortable, restless, “crawling” sensations in the legs, creating an irresistible urge to move or walk, typically when one first goes to bed. These sensations can contribute to sleep-onset insomnia as well as disrupted sleep. The condition is also more prevalent in older adults, occurring in up to 35% of those over 65, with about twice as many women being affected. Restless legs syndrome has been associated with iron deficiency and abnormal dopaminergic signaling and can be treated with interventions aimed at these features (Dauvillier & Winkelmann, 2013).

1.6.4 REM-sleep Behavior Disorder

REM-sleep behavior disorder involves movement during dreams due to the absence of muscle atonia that normally occurs during REM sleep (Boeve, 2010). Individuals may engage in punching, kicking, yelling or even more elaborate behaviors during REM sleep; the behaviors are often aggressive in nature and cause injury to the sleeper or bed partner. This condition is relatively rare in the general population (0.5%) and it occurs almost exclusively in males over 60 (Olson, Boeve, & Silber, 2000). The etiology of REM-sleep behavior disorder is unclear, but it has been strongly linked to the subsequent development

of neurodegenerative diseases known as synucleinopathies, including Parkinson's disease, Lewy body dementia and multiple system atrophy (Schenck & Mahowald, 2002).

1.6.5 Sleep Disturbance and Comorbidity

Despite the characteristic sleep changes that are experienced by older adults, these typically age-associated sleep disturbances may not be an inevitable part of the healthy aging process, but rather a consequence of other changes that accompany aging. Insomnia in particular, appears to be a major factor contributing to the increase in age-associated sleep complaints (Ancoli-Israel et al., 2008; Wolkove, Elkholy, Baltzan, & Palayew, 2007). However, the decreased ability to fall asleep or maintain sleep once initiated is frequently linked to a comorbid health condition. There is an increased risk for various medical and psychiatric conditions (e.g., depression, diabetes, arthritis, chronic pain, loss of bladder elasticity) during aging, which may indirectly disturb sleep (Ancoli-Israel et al., 2008). In addition, pharmacological treatments for these conditions (e.g., antidepressants, beta-blockers, diuretics, corticosteroids) are often not recognized as factors that may contribute to sleep disturbances. Although one study reported that an extensive health assessment can identify medical conditions that account for most sleep complaints in an older population (Vitiello et al., 2002), an estimated 10 to 16% of community-dwelling adults over 65 still report chronic (primary) insomnia, in the absence of an obvious precipitant (Foley, Ancoli-Israel, Britz, & Walsh, 2004; López-Torres et al., 2012).

1.6.6 Sleep and Frailty

Frailty can be conceptualized as an increasing vulnerability to poor health outcomes (i.e., disability, institutionalization, mortality) as a result of accumulating age-associated declines in physiological systems; as health deficits increase with age, so does frailty (Rockwood, Mogilner, & Mitnitski, 2004; Rockwood & Mitnitski, 2007). Little is known about the relationship between frailty and sleep or about the consequences of sleep disturbance in frail populations (Cochen et al., 2009; Mehra, 2012). In addition, the sparse literature on this topic has focused primarily on community-dwelling older adults (Endeshaw, Unruh, Kutner, Newman, & Bliwise, 2009; Ensrud et al., 2009; Ensrud et al., 2012; Sterniczuk et al., 2013; Vaz Fragoso, Gahbauer, Van Ness, & Gill, 2009).

Daytime drowsiness is associated with a higher level of frailty (Van Fragoso et al. 2009) and older individuals who exhibit poor subjective sleep quality, increased nighttime waking and greater nighttime hypoxemia, have been found to be at higher risk for increasing frailty roughly 3 years later (Ensrud et al., 2012). Those with excessive daytime sleepiness, frequent nighttime awakenings, and sleep apnea may also be at greater risk for mortality up to roughly 3 years later, whereas short sleep duration and prolonged sleep onset latency are not clearly associated with increased frailty or risk of early death (Ensrud et al., 2012). Given that sleep disturbance is associated with poorer health, frail individuals, who are already more vulnerable to the accumulation of stressors, may also be affected by the consequences of sleep impairment to a greater extent than healthy older adults (e.g., responses to sleep medication, the impact of insomnia or other sleep disorders). Alterations to the sleep/wake cycle may have prognostic utility in predicting future decline in health and increasing frailty. If so, then

treating specific sleep disorders in frail adults may reduce the rate of acquisition of deficits and the development of dependency.

1.6.7 Sleep in Critically Ill Older Adults

Patients who are especially susceptible to the adverse effects of accumulating deficits are those in the intensive care unit (ICU). Sleep disturbance and insomnia are common in ICU patients (Freedman, Kotzer, & Schwab, 1999; Simini, 1999), in particular in older individuals (Flaherty, 2008). Sleep disruption has been linked to impaired healing and recovery, and even to increased mortality (Dew et al., 2003; Eddleston, White, & Guthrie, 2000). In addition, up to 41% and 96% of older patients in the general and surgical wards, respectively, are prescribed sedative-hypnotic drugs. As discussed below, these drugs tend to have greater negative effects in older people and may interact adversely with a variety of other medications that may also be prescribed for these individuals. Several analyses have concluded that the risk of adverse health outcomes from sedative agents does not justify the small benefit achieved (Glass, Lanctôt, Herrmann, Sproule, & Busto, 2005; Pandharipande & Ely, 2006). It remains unclear how age and pre-morbid frailty levels affect sleep quality in older adults who are treated in the ICU (Sterniczuk, Rusak, & Rockwood, 2014). Determining how sleep quality in this environment affects health outcomes, such as cognitive decline and mortality, will help provide guidance as to appropriate treatments for vulnerable older patients in this high-risk situation.

1.7 Sleep and Cognition

Sleep deprivation has long been known to have negative consequences for subsequent cognitive performance, including impaired attention, working memory, decision-making and logical reasoning (Lim & Dinges, 2010). There is mounting evidence that sleep disturbance, particularly reduced sleep duration, sleep fragmentation, and sleep-disordered breathing (e.g., obstructive sleep apnea), may play a significant role in the future development of cognitive impairment. Less consistent evidence has been found for a relationship between impaired cognition and insomnia or circadian rhythm dysfunction (Yaffe, Falvey, & Hoang, 2014).

In addition to the disruption of cognitive functions following acute or chronic sleep loss, there is also a large body of evidence demonstrating that sleep loss *after* new learning may impair retention of the learned material or skill, or so-called ‘offline’ improvement. This term refers to the improvement in later performance that occurs during sleep after learning in the absence of any additional practice or waking experience of the task (Stickgold & Walker, 2007; Fogel et al., 2012; Rasch & Born, 2013). There is considerable controversy about which sleep stages are important for enhancing performance and which categories of learning (semantic, motor, sensory, emotional, etc.) may be most influenced by each of these sleep stages.

Enhancement of later performance following sleep has generally been modeled as involving the enhancement or stabilization of neural connections that have been newly formed or strengthened during a waking learning experience. There is evidence at a cellular level in animal models that such strengthening of neural connectivity occurs during sleep (Aton et al., 2014). One view is that the neurochemical profile of the waking brain is

especially suited to acquiring new information, while that of the sleeping brain is biased toward stabilization of already acquired information (Rasch & Born, 2013). Depending on the kind of learning involved, this strengthening process has been attributed to processes occurring during slow-wave sleep, REM sleep or N2.

An alternative view is that waking results in a global strengthening of synaptic connections throughout active areas of cortex, and that sleep down-regulates synaptic strength globally. This process is hypothesized to strengthen memories by making synapses that have been most strongly enhanced more salient, and also to make subsequent learning possible by preventing everyday experiences from saturating the capacity for synaptic potentiation (Tononi & Cirelli, 2014).

1.8 Neurodegenerative Disorders and Sleep

With age, there is an increased risk of neurodegenerative disease, which often includes a lengthy prodromal period that can include impaired sleep. Alterations to the sleep-wake cycle and circadian rhythms have been observed prior to the onset of Parkinson's disease (PD)-related motor symptoms, and appear to signal an increased risk of mild cognitive impairment and dementia, including Alzheimer's disease (AD; Lim, Kowgier, Yu, Buchman, & Bennett, 2013a; Sterniczuk et al., 2013; Tranah et al., 2011), Lewy body dementia (Guarnieri et al., 2012) and possibly frontotemporal dementia (Anderson, Hatfield, Kipps, Hastings, & Hodges, 2009). For example, early stage AD has been characterized by more nocturnal awakenings, sleep/wake fragmentation, and daytime sleepiness, whereas excessive daytime sleepiness and REM sleep behavior disorder tend to be more prominent in those with Lewy body dementia or PD (Guarnieri et al., 2012;

Rothman & Mattson, 2012; Bjørnarå, Dietrichs, & Toft, 2014).

Sleep loss has been implicated in the mechanisms giving rise to AD in several ways (Figure 1.2). Amyloid- β levels and formation of cortical plaques (a key neuropathological feature of the disease) are increased by sleep loss (Kang et al., 2009), and clearance of amyloid- β from the brain is enhanced during sleep (Xie et al., 2013). In addition, aggregation of amyloid- β has been shown to disrupt sleep/wake cycles, suggesting that there is a detrimental reciprocal feedback relation between sleep loss and amyloid levels (Roh et al., 2012). In addition, better sleep quality has been reported to attenuate the risk of dementia in those carrying the apolipoprotein (Apo) $\epsilon 4$ allele (which confers an elevated risk of developing AD) by decreasing neurofibrillary tangle density (Lim et al., 2013b). These findings suggest that enhancement of sleep quality in the elderly and those otherwise at elevated risk of developing AD may be a useful therapeutic strategy for delaying progression to dementia.

Interpreting changes in sleep quality and patterns during aging requires caution. Some changes may be characteristic of healthy aging and may not predict disease development. Other sleep changes may be secondary consequences of disease processes, such as neurodegenerative damage to sleep regulatory systems that occurs during development of PD. Other sleep changes may actually contribute to development of diseases because of the loss of some of the beneficial effects of sleep for brain health and function, such as clearance of amyloid- β . It is not yet clear which of the changes in sleep patterns that are observed during aging fall into each of these categories: normal changes unrelated to health status, changes secondary to brain disease and changes contributing to brain disease development. Detecting connections between altered sleep patterns or sleep

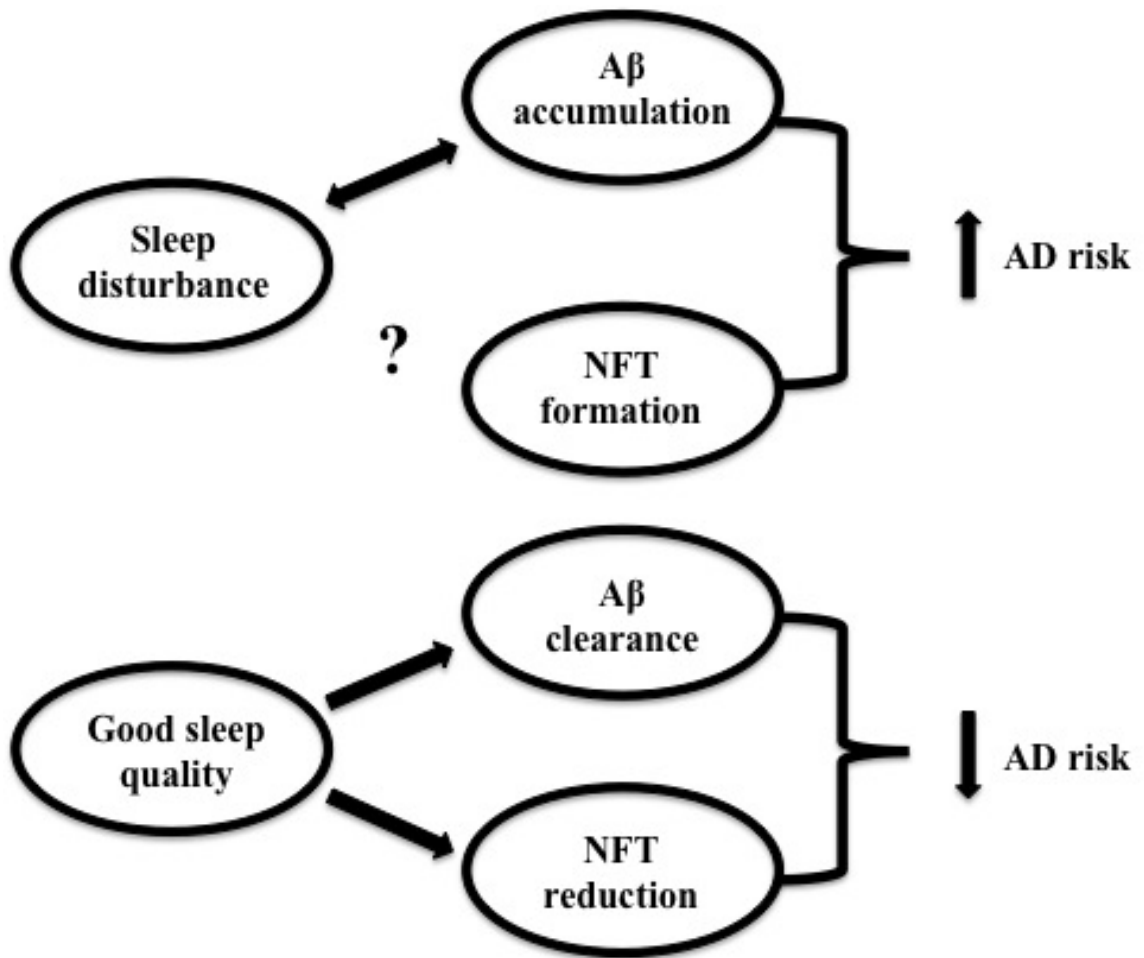


Figure 1.2 Potential mechanisms mediating effects of sleep loss on the development of Alzheimer's disease (AD) neuropathology. A β , amyloid-beta plaques; NFT, neurofibrillary tangles; ?, further work is still needed to establish a relationship.

disorders and disease is made more difficult by the lengthy periods over which neurodegenerative disease symptoms may emerge. Thus, there may be years or even decades between onset of REM sleep behavior disorder symptoms and later development of PD (Postuma, Gagnon, & Montplaisir, 2010).

1.9 Treatment of Sleep Disorders in the Elderly

1.9.1 Behavioral Treatments

Although the elderly often receive pharmacological treatments for sleep problems, including insomnia, there is accumulating evidence suggesting that behavioral approaches may be more effective than medications and should be considered a first-line treatment for this population (Table 1.2).

The most effective behavioral approach to treating sleep disturbance is the use of cognitive behavioral therapy for insomnia (CBT-I). This technique involves addressing unrealistic expectations or misconceptions related to sleep and promoting behaviors that are consistent with good sleep quality while avoiding environmental and internal conditions that tend to disrupt sleep (sleep hygiene). Recommendations for improving sleep hygiene include, but are not limited to: limiting heavy food and drink, especially caffeine and alcohol, near bedtime; exercising no closer than 4 to 8 hours before bedtime; maintaining a routine schedule for sleep and wake times; avoiding or limiting daytime napping; and creating a comfortable sleep environment (good ventilation and temperature, no noise, minimal light exposure, no direct access to a clock; Setiati & Laksmi, 2005). Other educational components include reviewing the influence that medical comorbidities, drugs, and environmental conditions, may have on achieving a good night's sleep.

Table 1.2 Evidence based treatment options for treatment of insomnia.

Nonpharmacological Treatments	Pharmacological Treatments
<ul style="list-style-type: none"> • Cognitive behavioural therapy for insomnia • Cognitive intervention <ul style="list-style-type: none"> ○ Modification of maladaptive or unrealistic thoughts and attitudes related to sleep • Behavioural interventions <ul style="list-style-type: none"> ○ Improvement of sleep hygiene ○ Stimulus control therapy ○ Sleep restriction therapy ○ Relaxation techniques 	<ul style="list-style-type: none"> • Benzodiazepines • Non-benzodiazepines (Z-drugs) • Melatonin or agonists (ramelteon) • Orexin/hypocretin receptor antagonists (suvorexant)

Behaviorally, stimulus control therapy, sleep restriction therapy, and relaxation techniques, are the most often used in addition to the promotion of good sleep hygiene (Neikrug & Ancoli-Israel 2010; Sharma & Andrade, 2012). Stimulus control therapy is based on the idea that poor sleep can result from maladaptive classical conditioning; i.e., the association of being in bed with a variety of non-sleep related behaviors. This treatment involves instructing clients to use their beds strictly for sleep or sex, and not for reading, watching television, using electronic devices, eating, or working. In addition, they must get out of bed if they fail to fall sleep after 20 minutes and only return when they are sufficiently sleepy; this process continues for 20 minutes at a time until they are able to fall asleep.

Sleep restriction therapy is based on enhancing sleep efficiency (i.e., reducing time spent in bed awake, often ruminating about the impact of lack of sleep or other problems) by limiting the time spent in bed to no more than 15 minutes beyond the actual time spent asleep. Once sleep has lengthened to fill the extended period, the allowed time in bed is again increased by 15 min until an adequate sleep duration is achieved. Limiting time in bed may sound counter-intuitive for someone complaining of insomnia; however, this approach is effective because it often switches the individual's perspective from being reluctant to go to bed because of anxiety about falling asleep, to looking forward to being permitted to spend a little more time in bed. This attitude change in combination with an already significant sleep debt can have excellent impacts on sleep quality (Morin et al., 2006; Buysse et al., 2011).

The components of CBT are typically employed together; however, each may stand alone depending on the individual's sleep habits and concerns. Treatment typically takes 6

to 8 sessions, but clinical improvements may not be evident for several weeks (Sateia & Nowell, 2004). Not only are these methods simple to employ, but there is a large body of evidence demonstrating both the effectiveness, and the long-lasting benefits, of CBT-I (Morin et al., 2006), including among elderly patients (Buysse et al., 2011).

1.9.2 Pharmacological Treatments

Because of the number of medical and psychiatric issues that emerge in old age and are treated with pharmacological agents, polypharmacy is very common in this age group. There is typically little consideration given to what effects individual drugs or combinations of drugs may have on sleep in the elderly. Thus, some sleep symptoms that appear in old age may be secondary to drug treatments for other conditions and may be improved by a careful assessment of drug effects on sleep and identification of alternative treatments that may have less impact on sleep. Whenever possible, older adults should take sedating medications near bedtime, while stimulating medications or others that may cause disruption of sleep at night (e.g., diuretics) should be taken during the day.

Several classes of medications are available to treat insomnia and decrease sleep disturbance, including sedative-hypnotics, antidepressants, antipsychotics, antihistamines, and anticonvulsants. Of the sedative-hypnotics, benzodiazepines (BZDs) are the most commonly prescribed medications for sleeping problems. Relative to barbiturates, which are now rarely used as sleep aids, they have a lower risk of toxicity and development of tolerance, but may have harmful effects when taken in conjunction with other sedatives or alcohol.

Different BZDs have different durations of action; those with intermediate or long half-lives are more effective in maintaining sleep throughout the night, but may also cause residual “hangover” effects during the following day. These may include daytime sleepiness, confusion, memory problems and motor problems, which may increase the risk of falls, especially in older people. Discontinuation after prolonged use may trigger rebound insomnia. Thus, these sleep aids are generally recommended for only acute use (up to 4 weeks). A newer class of short-acting non-BZD drugs, so-called ‘Z-drugs’ (zopiclone, zolpidem, zaleplon) have been promoted as having fewer side effects than BZDs, but they actually act on part of the same GABA_A receptors on which BZDs act. There are also reports of amnesic effects and dissociative disorders related to use of these drugs, generally when combined with other nervous system depressants (e.g., alcohol), and they appear to offer few, if any, clinical advantages in efficacy or tolerability in older adults (Bain, 2006). Like BZDs, they are reported to increase the risk of falls and cognitive side effects, so there is little support for their long-term use in this population (Antai-Otong 2006).

1.9.3 Neurohormones

Many studies have evaluated the use of the neurohormone melatonin as a sleep aid. Melatonin is secreted from the pineal gland with a pronounced daily rhythm, rising in the evening about an hour before usual sleep onset and remaining elevated for much of the night phase. There is good experimental evidence that melatonin elevation is a component of the circadian system’s transition to the night phase, and helps to promote sleep onset under appropriate conditions. Although the clinical findings have been mixed in different populations that have been studied, most studies indicate that nightly melatonin

supplementation, alone or combined with magnesium (which also improve measures of insomnia; Abbasi et al., 2012), can reduce sleep onset latency and promote sleep in older adults (Lyseng-Williamson, 2012; Riemersma-van der Lek et al., 2008; Rondanelli et al., 2011), as well as diminish symptoms of REM sleep behavior disorder (McCarter et al., 2013).

Melatonin levels have been reported to decrease in old age (and in some studies much earlier in life; Karasek, 2004; Zhou, Liu, van Heerikhuize, Hofman, & Swaab, 2003a) and some medications also suppress melatonin secretion (e.g., beta-blockers, anti-inflammatories). Although melatonin itself is not a patentable drug, pharmaceutical companies have developed melatonin receptor agonists that are available for treatment of sleep-onset insomnia, such as ramelteon, which shows promise of clinical effectiveness in older adults (Roth et al., 2005). Another drug recently approved by the US Food and Drug Administration for treatment of insomnia (suvorexant) is an antagonist that blocks receptors for the alertness-promoting neurotransmitter orexin (also called hypocretin); its long-term effectiveness in older adults has yet to be determined.

1.10 Key Points

1.10.1 Sleep in Relation to Aging, Frailty, and Cognition

- Sleep disturbance is commonly reported in older individuals, but it is not an inevitable part of healthy aging.
- The most profound changes to sleep architecture in older age include decreased sleep efficiency, increases in N1 and N2, and a reduction in N3.

- Comorbid medical or psychiatric conditions as well as medications and primary sleep disorders can account for most sleep problems in this population.
- Frail older adults may be more vulnerable to the effects of sleep disturbance.
- Disturbed sleep is not only a marker of several neuropsychiatric conditions, but may also contribute to degenerative changes in the brain.
- Sleep is an important factor in the enhancement of cognitive performance, such as learning and memory, but the underlying mechanisms are still not well understood.
- Behavioural interventions should be the first line of treatment when managing sleep disturbances in an older population.

1.11 Summary

Adequate sleep is an integral component of good physical and mental health. Sleep disruptions are more common in older adults, who often show profound changes in sleep architecture, efficiency, and distribution across the 24 h day. Although there are changes in sleep architecture and patterns in older age, many sleep disturbances can actually be attributed to medical or psychiatric conditions or the drugs used to treat these. The relationship between sleep and frailty is not well understood, but excessive daytime sleepiness, frequent nighttime awakenings, and sleep apnea appear to contribute to increasing frailty and have been shown to increase risk of death within a few years. In addition, sleep disturbance may contribute to increased vulnerability for a wide variety of age-associated neurodegenerative disorders. Depending on the disorder, treatment may include pharmacological and/or cognitive-behavioural strategies; however, the latter is recommended as a first line treatment in older adults.

CHAPTER 2

Alzheimer's Disease and the Mistiming of Behavior

2.1 Changes to Published Material

- References added throughout
- p. 26, first paragraph – added “German for time-giver e.g., light”
- p. 29, second paragraph – added “to” and “normally” to fourth sentence; “as well as directly activating the cortex” to the fifth sentence
- p. 30, first paragraph – institutionalized changed to institutionalization
- p. 31, first paragraph – “through out” changed to “throughout”
- p. 32, second paragraph – fourth and fifth sentences changed to “reciprocal firing patterns...sleep in AD.”
- p. 34, first paragraph – “can serve as an early marker” changed to “have been reported as possible early markers”
- p. 35, first paragraph – “within the hypothalamus” removed from fourth sentence
- p. 36, first paragraph – “The decrease in” removed from fifth sentence; “is” changed to “are”
- p.39, first paragraph – “that” changed to “who” in second sentence; third paragraph – “nucleus” changed to “nuclei”
- p. 42 – “progression” removed from second last sentence; “the” removed from last sentence
- p. 47, section 2.6.2 – added “to” to fourth sentence

2.2 Altered Circadian Rhythms

Changes to circadian rhythms in individuals with Alzheimer's disease (AD) are more pronounced than those observed in normal aging. The attenuation of these rhythms may be due to a reduction in environmental zeitgebers (German for "time-giver"; e.g., light), loss of functionality within the circadian clock, or disrupted output from the pacemaker (Wu & Swaab, 2007). Alterations to any of these components at the neurological level may result in the behavioral and physiological disturbances that AD patients exhibit (Antle & Silver, 2005).

2.3 Behavioral Changes

Individuals with AD exhibit prominent behavioral changes in both their sleep-wake and rest-activity patterns (Weldemichael & Grossberg, 2010). AD patients can exhibit bouts of both insomnia and hypersomnia throughout the 24-h day, which are an exaggeration of changes seen in normal healthy aging (Peter-Derex, Yammine, Bastuji, H., & Croisile, 2014). These changes occur more frequently, and with greater severity, particularly in those with moderate to severe AD. In fact, the level of sleep disruption is strongly correlated with dementia severity (Bonanni et al., 2005). Daytime activity levels are lower in AD patients, and activity tends to be more fragmented. Up to 50% of AD patients report fragmentation of their sleep-wake cycle, with daytime napping, increased total sleep time, and early awakenings, being the most common alterations (Lim, Gerstner, & Hotlzman, 2014). However the severity of fragmentation can vary greatly, ranging from a complete loss of rest-activity rhythms, to no disruption at all (see Figure 2.1; Paavilainen et al., 2005). Sleep problems are frequently observed in people

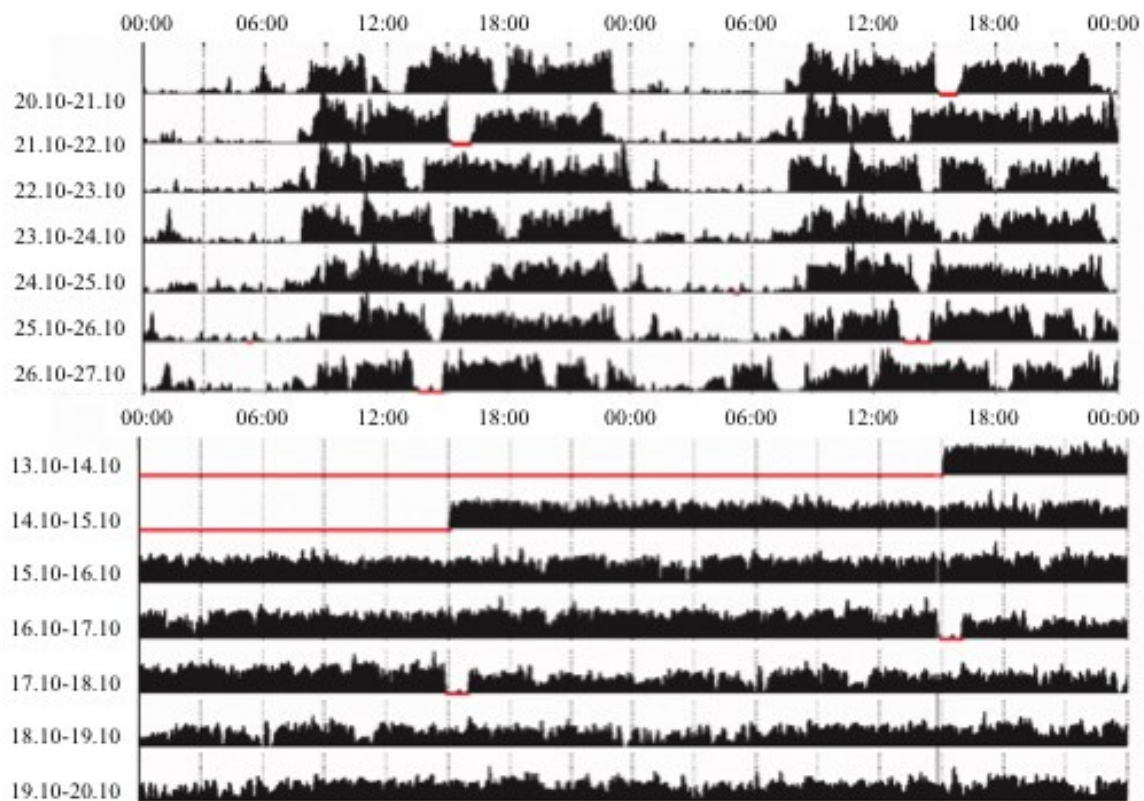


Figure 2.1 Data from actigraphy watches. Top panel: Example of a normal sleep-wake cycle in a nondemented subject with a clear circadian rhythm. Bottom panel: Example of a disrupted sleep-wake pattern in a demented subject, which displays a decreased amplitude, higher frequency of overall activity, and no clear circadian pattern (Paavilainen et al., 2005, Figure 3; Appendix B.3).

exhibiting mild cognitive impairment (the prodromal stage of AD; da Silva, 2015).

Although not fully understood, the declines in sleep indices observed in the preclinical stages of AD may contribute to inadequate memory consolidation and an increased risk of dementia (Tranah et al., 2011).

Environmental conditions appear to play an important role in the severity of altered daytime and nighttime activity levels. Daytime activity levels are higher for AD patients housed at home rather than in an institution, providing evidence for an increase in circadian disruptions due to institutionalization (van Someren et al., 1996). Particularly true of institutionalized patients, there is a rapid cycling between sleep and wakefulness, since most of the 24-h day is spent in bed. Sleep disruption may be so pronounced and fragmented that an individual may not even experience more than one full hour in a sleep state (Jacobs, Ancoli-Israel, Parker, & Kripke 1989; Paavilainen et al., 2005). Increased time spent in bed also contributes to a general decline in health status and has been shown to increase the rate of cognitive deterioration in AD (Wilson et al., 2007). In addition, an increase in pacing behavior is also observed in institutionalized AD patients, which may contribute to circadian disruptions. However, an increase in activity levels through pacing may act as a mechanism to preserve circadian organization, as it keeps an individual active and can promote better health (Cohen-Mansfield, Werner, Marx, & Freedman, 1991; Werth et al., 2002).

Various underlying conditions in AD patients may contribute to the severity of the changes in sleep parameters. Psychiatric comorbidities, such as depression, anxiety and delirium, are common in AD (Zhao et al., 2015), and are important factors contributing to insomnia. In addition, the presence of restless leg syndrome may directly interfere with

sleep onset and increase activity in the evening hours (Ondo, 2014; Venkateshiah & Ioachimescu, 2015). During the daytime, other neurological conditions, such as narcolepsy, Parkinson's disease or dementia, and Lewy body dementia, contribute to hypersomnia in the elderly and may add to excessive daytime sleepiness (Bjørnara et al., 2014; Harper et al., 2004; Wolkove et al., 2007).

Medication use can also interfere with the maintenance of a stable sleep-wake cycle. Medications prescribed for treating AD itself, specifically acetylcholinesterase inhibitors (ChEI), have different effects depending on the timing of administration. Cholinergic stimulation typically causes awakenings and decreases sleep time and efficiency, however this primarily affects non-REM sleep. During REM sleep, the cholinergic system can be enhanced due its increased activity at this time. These effects are visible at doses considerably lower than that needed to treat AD. Because the cholinergic system is responsible for inhibiting sleep-inducing regions during the daytime (i.e., ventrolateral preoptic area), as well as directly activating the cortex, restoring cholinergic functioning via ChEIs during the daytime has the greatest beneficial effect on AD patients. Cholinesterase inhibition before bed tends to interfere with sleep, as well as verbal and spatial memory consolidation (see review Davis & Sadik, 2006).

2.3.1 Sundowning

Although not recognized as a formal psychiatric condition, one frequently reported behavioral disturbance in those with AD is a phenomenon described as “sundowning” (Khachiyants, Trinkle, Son, & Kim, 2011). The term comes from the observation of increased neuropsychiatric symptoms in the late afternoon and/or evening

hours. These behaviors can include agitation, confusion, pacing, yelling, suspiciousness, mood swings, aggression and both visual and auditory hallucinations. Anywhere between 2.4-66% of AD patients can experience this phenomenon, with environmental conditions and cognitive status being important predisposing factors (Khachiyants et al., 2011).

Symptoms also tend to worsen during the fall and winter months, and have been linked to a decrease in the duration and amount of sunlight. “Sundowners” typically exhibit decreased diurnal activity, a higher percentage of nocturnal activity, a higher mesor and amplitude of core body temperature (CBT); as well as a delayed acrophase of both activity and CBT, and these alterations are associated with the severity of “sundowning” (Volicer, Harper, Manning, Goldstein, & Satlin, 2001). These behaviors and shifts in circadian rhythms typically peak in the moderate stage of AD and diminish as the disease progresses. Despite its name, individuals with AD can exhibit “sundowning” symptoms at any time of the day. Finally, certain people tend to be “sundowners” more than others, and this has been related to the number of sedatives that a patient administers daily, as well as the duration of institutionalization (Little, Satlin, Sunderland, & Volier, 1995).

Often these behaviors are a common cause of institutionalization due to increased caregiver stress at home. “Sundowners” are more likely to be demented individuals who have been recently institutionalized and are experiencing a great deal of confusion, especially during the evening hours (Kim, Louis, Muralee, & Tampi, 2005). The appearance of “sundowning” may be due to maladaptive responses to various environmental factors such as nurse shift changes, which cause noise and overstimulation, or the decrease in staff to patient ratio, which may lead to boredom, decreased environmental structure, and distress from diminishing independence

(Khachiyants et al., 2011). As well, afternoon fatigue from higher activity levels in the morning and disturbed nighttime sleep may all contribute to the severity of “sundowning” symptoms. Next to wandering, “sundowning” is the second most common behavioral disturbance in institutionalized dementia patients. Many doubt the existence of this phenomenon however, stating that symptoms such as irritation and confusion may occur at any point in the day/night, and that some individuals show these symptoms through out the whole day with no discernable pattern. Future research is required in order to understand the role of the circadian pacemaker in the occurrence of “sundowning”.

2.4 Physiological Changes

In addition to altered behavioral patterns, AD patients exhibit changes to various aspects of physiology that are under circadian control. Physiological fluctuations may underlie, or contribute to, the disruptions observed with regards to sleep and wakefulness. The most prominent changes include altered sleep architecture, shifted CBT, and diminished melatonin secretion.

2.4.1 Sleep Architecture

Not only does AD create disruptions in one’s sleep-wake cycle, but it also significantly alters sleep architecture (Ancoli-Israel et al., 2008; Prinz et al., 1982). Changes to sleep architecture appear to contribute to an overall decrease in sleep maintenance and efficiency, determined by the ratio of total sleep time to total time in bed. As well, a greater arousal index is also observed in AD patients, characterized by multiplying the number of spontaneous arousals from sleep by the number of hours slept.

Due to an increase in awakenings, both in frequency and duration, there is also an increase in the amount of time spent in stage 1 sleep. It becomes more difficult to differentiate between stages 1 and 2, since sleep spindles and K complexes are much lower in amplitude, shorter in duration, and less numerous. These EEG characteristics diminish as the severity of AD increases. The most consistently reported change in mild to moderate AD is a greater decrease in slow wave sleep (SWS). Not only do sleep spindles and K complexes diminish, but the delta waves characteristic of SWS become virtually eliminated (Bliwise, 1993; Petit, Gagnon, Fantini, Ferini-Strambi, & Montplaisir, 2004; Prinz et al., 1982).

Typically stable in normal aging, the percentage of time spent in REM sleep also significantly decreases in AD (Bliwise, 1993; Prinz et al., 1982). As well, a decrease in the mean REM sleep episode duration is observed. EEG measures show marked slowing of REM rhythms, when compared to wakefulness, as well as control patients, which may make REM sleep a better diagnostic measurement of AD development and severity. REM sleep is dependent upon reciprocal firing patterns between noradrenergic REM-off neurons in the locus coeruleus and cholinergic REM-on neurons in the laterodorsal/pedunculopontine tegmentum (Pal & Mallick, 2007); the integrity of the latter has been particularly implicated in contributing to disrupted REM sleep in AD. The deterioration of these systems, the basal forebrain, raphe nucleus, or reticular formation, may all contribute to altered sleep architecture and abnormal circadian rhythms in AD patients (Weldemichael & Grossberg, 2010).

2.4.2 Core Body Temperature

Numerous studies have examined the effects of AD on CBT because it is a readily obtained endogenous measure of the circadian cycle and one of the best estimates of human circadian phase (Weldemichael & Grossberg, 2010). However, a reliable characterization of CBT can be confounded by various external factors, such as light, body posture and movement, and even social interaction. However, CBT amplitude rhythms are reduced and phase delayed in probable AD patients when compared to younger controls (age 18-32). Interestingly, there tends to be an advance in body temperature seen in normal aging, whereas the opposite is observed in AD with delayed CBT rhythms. Low body temperature may hit its nadir later in the morning (e.g., 6 am), or in extreme cases closer to the afternoon (Harper et al., 2005; Satin, Volicer, Stopa, & Harper, 1995; Volicer et al., 2001). Reduced CBT amplitude may also simply be an artifact of abnormal aging, since normal aging is characterized by a 40% reduction in amplitude, whereas AD patients typically demonstrate a 50% reduction. However, daytime sleepiness is related to increased skin temperature in AD patients and is suggestive of impaired thermoregulation (Most, Scheltens, & Van Someren, 2012).

2.4.3 Melatonin Secretion

Another measurable marker of circadian rhythms is melatonin secretion. Melatonin is produced in a sleep-related manner primarily by the pineal gland. Just as in normal aging (Zhou et al., 2003a), melatonin levels rise during the night and are suppressed at the onset of daylight. The suprachiasmatic nucleus (SCN) exhibits a reduction in melatonin receptors and an altered rhythmicity in their production. Profound

reductions in secretion are observed in AD (see review Wu & Swaab, 2005) and are dependent on the severity of neuronal degeneration (Zhou, Liu, Kamphorst, Hofman, & Swaab, 2003b). As AD neuropathology progresses, cerebrospinal fluid melatonin levels decrease, such that as little as one-fifth of normal melatonin levels may be present in AD patients. Declines in secretion are present at the very earliest stages of neuropathological development and the disappearance of daily melatonin rhythms and decreased cerebrospinal fluid have been reported as possible markers for the first stages of AD (Wang & Wang, 2006).

2.5 Neurological Changes

Distinct neurological changes accompany AD, which are different from those observed in normal aging. The most salient physical change to the brain is progressive cortical atrophy, which is characterized by a narrowing of the gyri and widening of the sulci, as well as atrophy of the hippocampus and dilation of the lateral ventricle Mott & Hulette, 2005). The entorhinal cortex is the first to show a change in volume (Bobinski et al., 1999), and declines of equal magnitude are observed in the hippocampus (Pennanen et al., 2004). The basal forebrain is most severely affected, as it is the primary site of cholinergic innervation. In addition, accelerated temporal lobe volume reduction has been shown to be a better predictor of early AD, which corresponds to long-term memory impairment (Bobinski et al., 1999). Neuronal loss is not characteristic of normal aging, suggesting that alterations to these AD afflicted regions, visible via neuroimaging or biomarkers, may provide early cues to the onset of the disease (Dickerson, Wolk, & Alzheimer's Disease Neuroimaging Initiative, 2011).

In addition to cortical atrophy, there are two distinctive neuropathological hallmarks associated with AD: the accumulation of amyloid- β plaques ($A\beta$) and hyperphosphorylated microtubule-associated tau protein causing neurofibrillary tangles (NFT; Demarin, V., Zavoreo, I., Kes, V. B., & Šimundić, 2011). Plaques first appear in low densities within the basal portions of the frontal, temporal and occipital lobes. Moderate densities appear in the neocortical regions, sparing the sensory and motor areas, which are eventually affected in later stages of AD (Mott & Hulette, 2005). The nucleus basalis of Meynert contains a greater amount of pretangles in women, and is highly affected by AD. The opposite is seen in the infundibular nucleus of the mediobasal hypothalamus, where neurofibrillary tangles are identified in up to 90% of males with AD, versus 8-10% of females. The progression of NFTs occurs in a similar manner, spreading from the entorhinal region to hippocampal formation to the temporal, frontal and parietal cortices, and finally to the primary sensory and motor areas.

Altered sleep-wake patterns may influence the expression of AD neuropathology. For example, chronic sleep deprivation has been shown to significantly increase the level of hippocampal $A\beta$ plaque formation, whereas time spent asleep negatively correlates with the amount of $A\beta$ (Kang et al., 2009). Conversely, increased $A\beta$ neuropathology has been shown to contribute to disrupted sleep-wake cycles (Roh et al., 2012). In addition, endogenous $A\beta$ levels significantly increase during darkness, independent of external lighting conditions, and peak during the evening hours in human subjects (Xie et al., 2014).

2.5.1 The Circadian Pacemaker

Alterations to the SCN have been speculated to be the primary cause for circadian rhythm disruption in AD patients (Wu & Swaab, 2007). The SCN exhibits both NFT formation and rare diffuse plaques, although to a lesser extent than surrounding hypothalamic regions; neuritic plaques do not appear to form within the SCN (Stopa et al., 1999). In addition to AD neuropathology, there is marked neuronal degeneration within the SCN, including a decrease in the volume and total cell count of SCN neurons, suggesting organic deterioration of the circadian oscillator. Levels of vasopressin (VP)-expressing neurons are significantly reduced within the SCN, when compared to those lost in normal aging, which may be due to degeneration of the visual system. VP-expressing neurons are three times lower in AD patients than age and time-of-death matched controls (Liu et al., 2000). However, there does not appear to be significant VP cell loss within surrounding regions such as the paraventricular nucleus or the supraoptic nucleus (Van der Woude et al., 1995). The number of vasoactive intestinal polypeptide (VIP)-expressing neurons also decreases dramatically in presenile AD patients, particularly in females, by about 52% when compared to controls. Both the number and volume of VIP-expressing neurons decline in the SCN in AD patients (Zhou, Hofman, & Swaab, 1995).

Little is known regarding changes to the molecular clockwork of the circadian pacemaker (Thome et al., 2011). It is presumed that altered clock gene and protein expression underlie abnormal circadian oscillations, and in turn may cause the behavioral disruptions observed in AD patients. Variations in the expression of clock genes have been noted between AD patients and controls (Cermakian, Lamont, Boudreau, & Boivin,

2011). Postmortem studies have demonstrated that AD patients that exhibit an altered monoamine oxidase A promoter polymorphism, which plays a role in sleep regulation, appear to be at a greater predisposition to sleep disturbances (Craig, Hart, & Passmore, 2006). Circadian fluctuations of gene expression in the SCN may make the controlled examination of these clock components quite challenging.

Altered input to, and output from, the circadian pacemaker may also contribute to disturbed rhythms in behavior and physiology. Individuals with AD have been shown to exhibit degenerated optic nerves and retinal ganglion cells, making it difficult to transmit photic information to the SCN (Katz, Rimmer, Iragui, & Katzman, 1989). Extra-SCN regions (i.e., pineal gland, bed nucleus of the stria terminalis and cingulate cortex) exhibit rhythmic 24-h expression in *Clock*, *Per1*, *Per2* and *Bmal1* gene expression in AD patients. However, the temporal synchrony is lost between the individual oscillating cells, suggesting that output signals from the SCN are impaired in the disease (Cermakian et al., 2011).

2.5.2 Sleep Regulatory Regions

Brain regions that are involved in regulating sleep are susceptible to AD pathology, especially those that encompass the hypocretin, cholinergic, or serotonergic and noradrenergic signaling systems. Disruption to any of these regions may impair the normal expression and 24-h fluctuation of sleep and wakefulness (Rothman & Mattson, 2012). The accumulation of A β , specifically, has been linked to the dysfunction of these various neurotransmitter systems (see Figure 2.2).

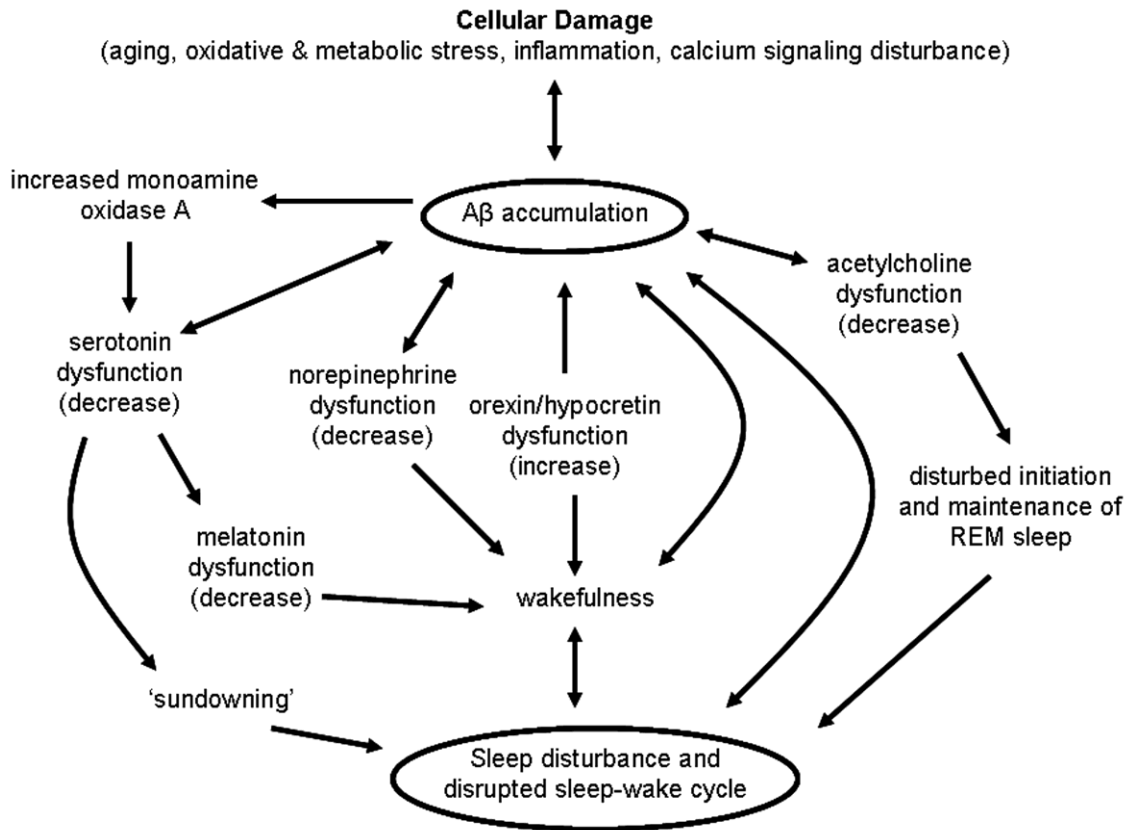


Figure 2.2 Potential pathways of dysfunction that may lead to the development of sleep disturbances in AD patients. Arrow indicates established directionality of the relationship between the accumulation of A β plaques and various neurotransmitter systems. (Adapted from Rothman & Mattson, 2012).

Hypocretins (a.k.a. orexins), are excitatory neurotransmitters secreted from the hypothalamus that promote wakefulness. Individuals who suffer from narcolepsy, or a difficulty in maintaining wakefulness, exhibit decreased levels of hypocretin signaling. Patients with AD exhibit a 40% reduction in the number of hypothalamic hypocretin-1 neurons, as well as a 14% reduction in hypocretin-1 levels in their cerebrospinal fluid (CSF; Fronczek et al., 2012). Patients with increased levels of daytime sleepiness appear to have the lowest concentrations of CSF hypocretin-1. In addition, sleep-wake fragmentation exhibits an inverse relationship with CSF hypocretin levels. As with chronic sleep deprivation, increased hypocretin signaling has also been linked to elevated A β plaque formation (Kang et al., 2009), suggesting that alterations to this system may be directly involved in AD pathogenesis (Slats, Claassen, Verbeek, & Overeem, 2012).

The cholinergic system experiences possibly the greatest deficits in AD (Rehman & Mason, 2001). As mentioned, cholinergic signaling plays an important role in the regulation of sleep. There is a plethora of research demonstrating a loss of cholinergic neurons and decreased choline acetyltransferase activity in AD, particularly in the basal forebrain. Because the initiation and maintenance of REM sleep is dependent upon the cholinergic system, loss of cholinergic neurons is speculated to be one of the main culprits for causing sleep disturbances in AD patients (Montplaisir, Petit, Lorrain, Gauthier, & Nielson, 1995; see review Schliebs & Arendt, 2006).

There are also marked decreases to the noradrenergic and serotonergic systems in AD, which are primarily secreted from the locus coeruleus and raphe nuclei, respectively. Both regions exhibit marked neuronal loss, as well there is a reduction in circulating cortical levels of each neurotransmitter (Nazarali & Reynolds, 1992; Šimić et

al., 2016). Increasing serotonin levels via the prescription of selective serotonin reuptake inhibitors has been shown to improve cognitive function in AD patients, and decrease levels of A β plaques (Cirrito et al., 2011; Mokhber et al., 2014). Because of the behavioral (e.g., emotion, mood, sleep) and psychological (e.g., agitation, confusion, depression) symptoms observed in early AD, and the presence of AD neuropathology in the raphe nucleus at this time, it has been speculated that the brainstem is one of the first regions afflicted by the disease (Šimić et al., 2009). Less understood is the role of the noradrenergic system in AD (Weinshenker, 2008), although profound loss is visible in the hippocampus and may be related to impaired learning and memory. In addition, depletion of norepinephrine causes an increase in A β deposition. It is still unclear, however, whether altered norepinephrine levels are directly involved in sleep disruption and cognitive deterioration in AD (see review Gannon et al., 2015).

2.6 Modeling Alzheimer's Disease

The identification of several genes that are directly linked to AD has allowed for the generation of various animal models that mimic the pathology of human AD, the most commonly used being mouse models. Transgenic animal models permit both a time and cost effective way of characterizing the cellular and biochemical origins leading to the observed abnormalities in AD brains. There are over a dozen AD mouse models, which exhibit amyloid pathology from the overexpression of amyloid precursor protein (APP), but less than half of these express familial AD-associated presenilin mutations and/or tauopathies (Elder, Gama Sosa, & De Gasperi, 2010). Delineating the mechanisms

that underlie AD through these models will aid in the identification of therapeutic targets and the formulation of novel treatments.

2.6.1 Murine Models

Transgenic mouse models of AD are most often chosen for understanding the effects of the disease on circadian rhythms. Currently, two models are available that express both the aggregation of A β and formation of NFT's, namely the triple transgenic mouse model of AD (3xTg-AD) and PLB1 mice. Since review of all the mouse models is beyond the scope of this chapter, only alterations to circadian rhythms in these two models will be summarized here.

Developed in 2003, the 3xTg-AD model was generated by crossing APP_{swe} and human tau_{P301L}, controlled by the murine Thy1 promoter, into a single-cell embryo harvested from mutant PS1_{M146V} knockin mice (Oddo et al., 2003). Intraneuronal A β immunoreactivity is visible in the neocortex at 3 months and in the CA1 region at 6 months. Extracellular A β deposits are first apparent at 6 months, predominantly in layers 4 and 5 of the frontal cortex, and by 12 months in the hippocampus and other cortical regions. In contrast, tau immunoreactivity is first apparent at about 12 months in pyramidal neurons in the CA1 region. Tau-reactive neurons are also found in the amygdala and hippocampus, and an age-related progression towards higher cortical structures is observed. Both A β and tau show age- and regional-dependent formation, with A β manifesting prior to tangles; pathology which is very similar to that seen in human AD patients. By 6 months, synaptic dysfunction and impairment in long-term potentiation are apparent and correlate heavily with memory and cognitive deficits.

Initial findings regarding circadian rhythmicity demonstrated similar total daily activity in these mice at 2 and 6 months, however more recently it was shown that by 4 months of age male 3xTg-AD mice have significantly altered activity patterns. The transgenics exhibit elevated levels of activity during their subjective day, as well as shorter freerunning periods. Diminished percentage of nighttime activity is also visible in the males, although the amplitude of early night activity is increased. Older female mice however, spend less time in an active state during the subjective night (see Figure 2.3; Sterniczuk et al., 2010). However, at 4 months these mice exhibit phase advanced core body temperature rhythms, which by 6 months increase in amplitude (Knight et al., 2012). Thus, there are non-cognitive changes that occur prior to the development AD pathology, specifically extracellular A β , with an exacerbation of disruptions in rhythmicity once extracellular A β depositions are formed. As is observed postmortem in human patients, these mice exhibit diminished VP- and VIP-expression within the SCN prior to the development of NFTs (see Figure 2.4; Sterniczuk et al., 2010) but no difference in the number of retinorecipient gastrin-releasing neuropeptide-expressing cells. No AD neuropathology has been noted in the hypothalamus of these mice. Also, the photic pathway to the SCN does not appear to be affected in these mice since there are no alterations to photic phase shifting ability. These findings suggest that deterioration to the circadian clock may be an early indicator of AD. Understanding these changes may provide useful cues to aid in the early diagnosis of future AD development.

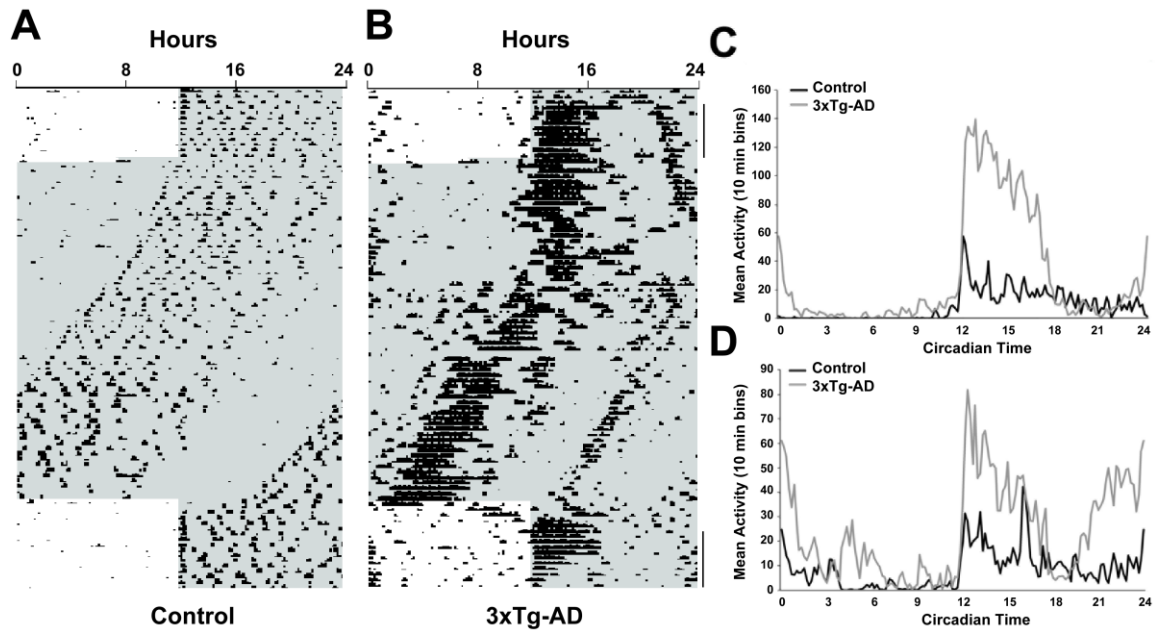


Figure 2.3 Activity patterns of a representative (A) control and (B) 3xTg-AD male mouse over the course of 3 months. (C) A mean activity waveform for all male mice prior to A β pathology (< 6 months of age) for 10 days in a 12:12 LD cycle indicated by the top vertical bar. (D) A mean activity waveform for all male mice post-A β pathology (> 6 months of age) for 10 days in a 12:12 LD cycle indicated by the lower vertical bar. (Sterniczuk et al., 2010, Figure 1).

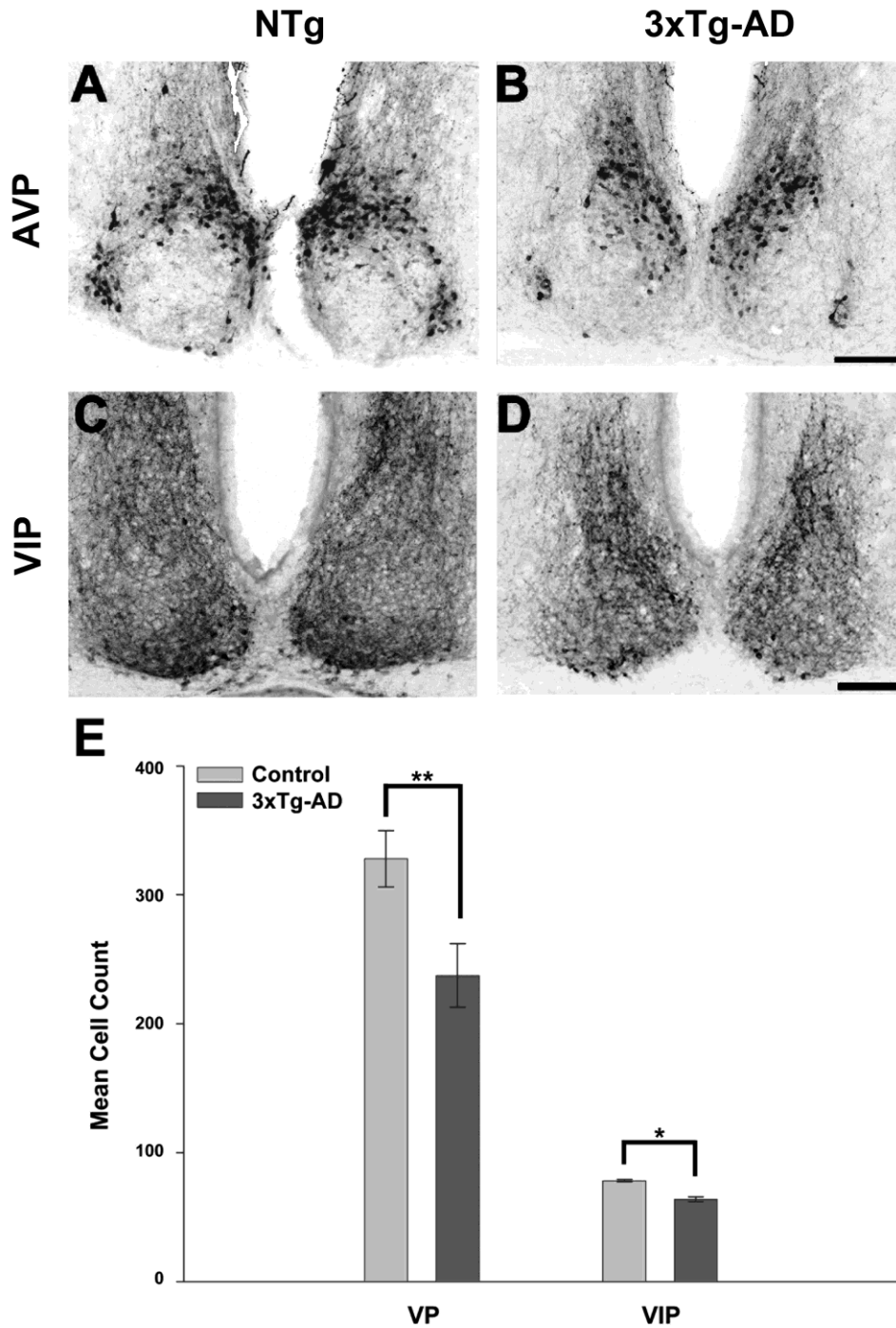


Figure 2.4 Representative SCN tissue slices of (A, B) VP and (C, D) VIP fluorescent immunocytochemistry staining. Male controls (A, C) exhibited significantly more VP- and VIP-containing cells than 3xTg-AD mice (B, D). Scale bar = 100 μ m (E). * Significant at $p < .05$ and ** at $p < .01$. (Sterniczuk et al., 2010, Figure 3).

In 2011 (Platt et al.), the PLB1 model was generated using a single-copy knock-in of mutated APP and Tau. Both proteins are preferentially visible within the hippocampus and cortex, around 5-6 months of age. Much less is known regarding the expression of circadian rhythms in this model. These mice appear to have a normal pattern of circadian activity over the 24 hour day. However, they experience lower levels of activity at 5 months and higher activity at 12 months, which does not reflect the normal decrease in activity due to aging that is observed in wildtypes. In addition, these mice exhibit altered sleep-wake EEG architecture, characterized by increased delta power during wakefulness and REM sleep. A delay in sleep onset and NREM fragmentation is visible at 12 months.

2.7 Chronobiological Treatment of Alzheimer's Disease Symptomology

Depending on the severity of the disease, either an acetylcholinesterase inhibitor or NMDA receptor antagonist, is prescribed to alleviate AD symptoms. Hypnotics are typically prescribed for insomnia and circadian rhythm disorders (Glass et al., 2005), however they quickly lose their effectiveness over time and provide little help for chronic sleeping problems in AD patients (McCleery, Cohen, & Sharpley, 2014). In addition, none of these drugs are capable of regulating the circadian clock and resynchronizing disrupted rhythms. That said, both pharmacological and non-pharmacological approaches have been considered as modulators of the circadian timing system and potential treatments for circadian disruptions in AD (Wu & Swaab, 2007; Deschenes & McCurry, 2009; Weldemichael & Grossberg, 2010).

2.7.1 Melatonin

Due to the observed decrease and dysregulation of melatonin in AD, the most popular pharmacological treatment for circadian disruption is to use melatonin as a chronobiotic. Melatonin has been suggested to be a powerful anti-aging and antioxidant agent by preventing the formation of free radicals (Hardeland, 2013). Decreased levels of melatonin have been found to lead to excessive oxidation and neurotoxicity, resulting in neuronal death. Transgenic mice engineered to exhibit AD pathology demonstrate a reduction in A β generation and tau hyperphosphorylation following melatonin treatment (Cheng, Feng, Zhang, & Zhang, 2006). It can be hypothesized that by supplementing lost melatonin levels, normal sleep-wake rhythms can be restored. There are conflicting results however, as to the efficacy of melatonin replacement. Several recent studies have demonstrated improved sleep quality, and reduced sundowning behavior, nighttime activity, and sleep latency, as well as slower progression of cognitive impairments in AD patients (Brusco, Marquez, & Cardinali, 1998; Cardinali, Brusco, Liberczuk, & Furio, 2002; Wang & Wang, 2006). However, other well-controlled, randomized studies of AD patients, did not find an improvement in sleep-wake rhythms (Serfaty, Kennel-Webb, Warner, Blizard, & Raven, 2002; Singer et al., 2003). The administration of melatonin seems most effective when administered either: before naps during one's wakeful period when melatonin levels are low; or before melatonin levels begin to rise several hours before one's regular bedtime (Touitou & Bogdan, 2006). Overall, the effectiveness of melatonin in alleviating sleep disturbances and circadian dysfunction in AD is still debatable. However, the ability for melatonin to prevent or ameliorate A β and tau

pathology, suggests that melatonin may serve as a potential treatment for AD, and consequently the symptoms that accompany the disease.

2.7.2 Bright Light Therapy

Light, being the most prominent mammalian zeitgeber, has been extensively studied as a nonpharmacological treatment for disrupted sleep-wake rhythms in AD. In theory, presenting a bright light pulse (e.g., 2,000 to 10,000 lux) to an individual with AD, at specific times of the day should result in an advance or delay in activity, and possibly realign one's sleep-wake cycle. Old rats that are exposed to bright light appear to reverse age-related alterations in sleep-wake disturbances, as well as prevent a decrease in the number of VP expressing neurons in the SCN (Hoogendijk, et al., 1996). Although more common in institutionalized residents, AD patients typically receive very little bright light exposure during the day, and light throughout the night may contribute to dysregulation of the sleep-wake cycle. Administering roughly two hours worth of a full-spectrum fluorescent light in the morning to a patient can alleviate sundowning symptoms and improve sleep quality (Ancoli-Israel et al., 2003; Wu & Swaab et al., 2007). This effect is visible when light is approximately 1 meter away, and it does not have to be direct (i.e., it is effective when administered while the person is engaging in other activities). Improvements in daytime sleepiness have also been observed following a bright light pulse in the morning, whereby daytime wakefulness may increase by about 30 minutes in those with dementia (Fetveit & Bjorvatn, 2005). However, vision deteriorates with increasing age and the light presented may not be as effective as it could be upon healthy eyes. As with melatonin, the effectiveness of light therapy is also

inconclusive (Forbes, Blake, Thiessen, Peacock, & Hawranik , 2014; Skjerve, Bjorvatn, & Holsten, 2004).

Others have shown that light exposure during the morning or evening does not improve measures of nighttime or daytime sleep, however roughly a one and a half to two hour delay in the acrophase of circadian rhythms may be observed. Some have suggested that stimulating the SCN as early as possible in the course of AD may contribute to greater stabilization of circadian rhythms, due to some preservation of SCN plasticity. Taken together, the effectiveness of light therapy depends on the severity of AD, as well as the level and duration of illumination one is exposed to.

Combining bright light with melatonin has been shown to have an additive effect by increasing daytime activity and the day-night sleep ratio, when compared to light alone. In addition, this combination can alleviate some of the adverse side effects associated with melatonin (e.g., dysphoric mood) and may even improve cognitive performance in dementia patients.

2.7.3 Structured Environment and Behavioral Modification

Although the findings remain inconsistent, alternative approaches to realigning circadian rhythms have been examined (Deschenes & McCurry, 2009). Creating a structured environment and providing strict guidance to patients with regards to daily behavior, may aid in diminishing the impact that disrupted circadian rhythms have on AD patients. A consistent sleep-wake schedule helps to reinforce time cues and promotes rhythmicity by preventing sleep disturbances at night. This may be done by limiting daytime napping (to a shorter period) and increasing daytime physical activity, as well as

creating a relaxing, ‘sleep friendly’, environment by minimizing noise, light, and the distraction of others (e.g., hospital staff, family members). During the evening hours, it is also important for caregivers to limit patient exposure to activities and events that might disrupt sleep, such as television-viewing (i.e., violent events may be particularly distressing to cognitively impaired individuals). A combination of social activity and low-intensity physical exercise during the morning and afternoon can even increase SWS in older adults. Consistency is key to effective treatment; maintaining regular daytime light exposure, meal times, and daily routines (e.g., avoiding or planning ahead for novelties like family get-togethers) can all help to ease or slow the progression of disruptions in circadian rhythms as well as decrease symptoms of sundowning.

2.8 Conclusion

Recognizing the subtle behavioral, neurological and physiological variations in the developing stages of AD may aid in earlier and more accurate diagnosis. This in turn would guide treatment that is appropriate for restabilizing disturbed circadian rhythms and prevent, or delay, early institutionalization and exacerbation of symptoms. There is no “right” form of treatment for AD. Alleviating symptoms and slowing progression of this disease is based on many factors, such as the type and severity of dementia, as well as visual deterioration and one’s surrounding environment. In most cases, a combination of pharmacological and non-pharmacological treatments are necessary to restore normal functioning (as much as it is possible).

2.9 Dissertation Objectives

Disturbed sleep and abnormal sleep/wake cycles are common among AD patients, even at early stages of the disease; more frequent waking at night and napping during the day are often reported (Lim, et al., 2014; Paavilainen et al., 2005; Witting, Kwa, Eikelenboom, Mirmiran, & Swaab, 1990). There is increasing evidence for a bidirectional relationship between sleep disturbance and AD-related neurological processes (Branger et al., 2016; Hita-Yañez, Atienza, Gil-Neciga, & Cantero, 2012; Kang et al., 2009; Roh et al., 2012; 2014; Sterniczuk et al., 2010; Xie et al., 2013). While A β has been found to increase following sleep restriction, including increased nighttime awakenings in humans (Branger et al., 2016) and acute stimulation of wake-promoting pathways or chronic sleep deprivation, in mice (Kang et al., 2009; Roh et al., 2014), sleep appears to be directly involved in the clearance of this AD-related pathological feature (Xie et al., 2013). Altered sleep/wake activity has been described to occur prior to A β formation (Sterniczuk et al., 2010), and clearance of A β is in turn capable of normalizing sleep/wake cycles (Roh et al., 2012). Furthermore, sleep disturbance has been clinically linked to an increased risk of mild cognitive impairment and dementia diagnosis (Almond et al., 2016; Diem et al., 2015; Hita-Yañez et al., 2012; Ju et al., 2013; Schlosser et al., 2012; Tranah et al., 2011; Tsapanou et al., 2015a,b).

Despite this promising growth of evidence for a direct link between sleep processes and AD pathophysiology, it is not clear whether sleep-related symptoms might allow for the earlier identification of people at increased risk for a diagnosis of AD/dementia, than more traditional measures or modifiable risk factors (Ganguli et al.,

2015; Xu et al., 2015). Nor has it been examined whether sleep is simply a manifestation of poor health status or an important independent predictor of dementia.

There were two overarching goals of this dissertation: (1) to explore whether sleep- and circadian rhythm-related changes occur in preclinical/early AD and dementia; and (2) to examine the relationship between sleep disturbance and overall health status, as measured by a frailty index (FI), in predicting AD/dementia risk, as well as other negative health outcomes (i.e., cognitive impairment, mortality). In order to address these aims, the present dissertation incorporated epidemiological analyses using two large multi-national cohorts, namely the Survey of Health, Ageing, and Retirement in Europe (SHARE, studies 1 and 2; and the Honolulu-Asia Aging Study (HAAS; study 3). Specifically, secondary analyses were designed to address three primary questions: (1) whether sleep disturbance can predict AD and dementia; and if so, (2) what aspects of sleep disturbance are associated with an increased risk for AD and dementia; and (3) how does premorbid health status as measured by a FI impact sleep/wake disturbance as a risk factor for AD/dementia? Additional analyses were conducted to explore the relationships between sleep disturbance and frailty, and risk of other negative health outcomes (i.e., cognitive impairment and mortality).

The findings from these studies are directly relevant to our understanding of the development of AD/dementia, such that results from these analyses will help to determine whether sleep disturbance is simply a manifestation of declining health or a separate process and predictor of AD pathophysiology. This ultimately may help to identify novel biomarkers or develop reliable assessments for the diagnosis of dementia, prior to the manifestations of cognitive decline (e.g., memory impairment). By

recognizing which sleep-related abnormalities are associated specifically with AD, either through clinical assessment or neuroimaging of sleep-associated brain regions, clinicians will be better equipped to differentiate AD from other dementias and neurodegenerative diseases, resulting in more accurate diagnosis of AD at an earlier stage. This in turn will help guide appropriate treatment sooner, with the ultimate goal being to delay institutionalization and promote a greater level of independence, for as long as the disease permits.

2.10 Dissertation Hypotheses

2.10.1 Study 1

As described above, there is increasing support for a unique relationship between sleep disturbance and risk of AD/dementia. These changes appear to occur even prior to typically AD-associated cognitive decline (Almondes et al., 2016; Diem et al., 2015; Ju et al., 2013; Schlosser et al., 2012; Tranah et al., 2011; Tsapanou et al., 2015a,b). Thus, the first hypothesis was that sleep-related factors would predict future reported dementia diagnosis (i.e., after ~4 years) in cognitively healthy community-dwelling participants of the SHARE study. A secondary hypothesis was that combining the several sleep disturbance measures into a sleep disturbance index (SDI) would produce a better fitting model of risk prediction than any factor alone. In addition, incorporating frailty, or overall health status, into the model as a frailty index (FI) would have a synergistic effect on the sleep factors (i.e., the odds ratio was expected to be larger when both indices were added to the model than the ratio produced by either index alone). Since frailty has been linked previously to increased mortality risk (Mitnitski et al., 2005; Rockwood &

Mitnitski, 2007), the prediction is that sleep disturbance symptoms (and the SDI) would predict future dementia, while the FI would predict mortality risk better than the SDI.

2.10.2 Study 2

Since the publication of study 1, additional SHARE data were released (wave 5), which permitted examination of dementia risk after a longer follow-up period (i.e., ~6 years, rather than the ~4 years available earlier). Utilizing only those people who participated in all three waves of data collection, the first hypothesis was that that the results from study 1 would be replicated using the same SDI and FI measures. In addition, we previously reported that people in the SHARE who reported the absence of AD/dementia at baseline, but exhibited ≥ 2 cognitive impairments, had an increased risk of reported AD/dementia after ~4 years, and a greater level of cognitive and functional decline (Sterniczuk, Theou, Rusak, & Rockwood, 2015; Appendix D). Here, the impact of the SDI and FI on risk of negative health outcomes (i.e., cognitive impairment, reported AD/dementia, and mortality) was examined in cognitively healthy participants (i.e., < 2 cognitive impairments at baseline). The hypothesis was that the SDI would be a better predictor of later cognitive impairment and reported AD/dementia in cognitively healthy participants at baseline, compared to the individual sleep factors, while the FI would be a better indicator of mortality risk. Furthermore, given that sleep disturbance has been reported early in the course of dementia in other cohorts (Hita-Yañez et al., 2012; Tranah et al., 2011; Tsapanou et al., 2015a), a secondary hypothesis was that the SDI would be a better predictor of cognitive impairment and dementia risk at ~6 years, compared to the ~4-year follow-up time point.

2.10.3 Study 3

Using a different large multi-national cohort, this study was designed to determine the reliability of the results obtained in studies 1 and 2, and to increase the validity of sleep disturbance and the SDI as a predictor of dementia in cognitively healthy people. Although the SHARE database contains extensive health, social, and socioeconomic data pertaining to aging, it lacks thorough cognitive assessment measures and diagnostic information regarding dementia. As well, only data within a relatively short follow-up time point was available (~6 years). Thus, additional analyses examining sleep-related factors in relation to frailty were conducted on data from the HAAS, a database designed to explore the etiology of dementia. Analyses were conducted on cognitively healthy participants at baseline as assessed by consensus panels (based on neurological and neuropsychological assessment), at ~3, 6, and 10.5 years at follow-up. Given previous reports (Paavilainen et al., 2005; Tsapanou et al., 2015a; Witting et al., 1990), the primary hypothesis was that measures of nighttime sleep disturbance and daytime sleepiness would predict dementia risk in cognitively healthy individuals with a relatively short latency (i.e., < 5 years prior to diagnosis). When combined into an SDI, these factors were expected to be a better predictor of dementia diagnosis than the FI, while the FI was expected to provide a better predictor of mortality risk than the sleep factors, alone or combined.

CHAPTER 3

Sleep Disturbance is Associated with Incident Dementia and Mortality

3.1 Changes to Published Material

- p. 59, section 3.3.1 – “represents the” changed to “consists of”; added: “Participant recruitment occurred via probability sampling using country-specific population data (i.e., census and population registries and/or telephone/address directories; Alcsér et al., 2005). People were excluded if they were incarcerated, hospitalized or out of the country during the time of the survey, unable to speak the country’s language(s), or moved to an unknown address.”
- p. 63, section 3.3.2.3 – added “associated with increasing age and adverse health, covering a wide range of systems and not saturating at a young age. Here, items directly related to sleep disturbance and cognition (i.e., cognitive variables, or the presence of dementia)”
- p. 65, section 3.3.3 – “identifying” changed to “classifying”
- p. 70, section 3.4.7 – “predictive” changed to “classification”; “predictor” changed to “indicator”
- p. 71, first paragraph – “and” added to second sentence and “also” removed
- p. 73, first paragraph – “Our SDI was a strong predictor of dementia when the FI was included in the risk model, albeit only marginally statistically significant ($p = 0.054$).” changed to “the SDI remained only marginally significant when the FI was included in the risk model”
- p. 73, second paragraph – “an overall decline in health or” removed from first sentence

3.2 Abstract

People with Alzheimer's disease (AD) commonly complain of sleep disturbances. It is not known whether sleep-related symptoms permit earlier identification of people at risk for AD or dementia. Secondary analyses of sleep-related measures collected through the Survey of Health, Ageing and Retirement in Europe (SHARE; i.e., sleeping problems, fatigue, taking sleeping medication, and trouble sleeping or a change in pattern) were conducted on those who reported the absence of AD or dementia at baseline. A 'sleep disturbance index' (SDI) using sleep-related measures was created and compared to a frailty index reflecting overall health status. Each sleep measure independently predicted self-reported AD or dementia and mortality within ~4 years. Combined, the SDI was associated with an increased risk of developing AD or dementia (OR= 1.23, 95%CI = 1.11-1.36) and mortality (OR = 1.18, 95% CI = 1.12-1.24), and remained a strong factor for dementia when overall health status was added to the risk model ($p = 0.054$). These findings indicate that sleep disturbance may exist prior to the manifestation of other typical symptoms observed in AD (e.g., memory loss). Sleep-related questions may be useful for screening individuals at risk for dementia and may allow for the earlier detection of AD at the preclinical stage.

3.3 Introduction

Patients with Alzheimer's disease (AD) often suffer from disturbed sleep-wake patterns, including poor sleep continuity and increased activity at night, daytime sleepiness and fragmented activity patterns (Paavilainen et al., 2005; Witting et al., 1990). These alterations are more profound than those observed in normal healthy aging. Time spent in bed, sleep fragmentation (Ancoli-Israel et al., 2004), and an increased propensity to sleep during the day (Bonanni et al., 2005), have been shown to correlate with the degree of dementia. More specifically, the degree to which instrumental activities of daily living are impaired is strongly associated with the level of sleep disturbance (D'Onofrio et al., 2012). Sleep problems frequently contribute to early institutionalization because of the resulting intolerable caregiver burden (Pollack et al., 1991). Institutionalization has been shown to exacerbate sleep-wake disruption (van Someren et al., 1996) and increase the speed of deterioration (Wilson et al., 2007).

Alterations to the sleep/wake cycle may be related to deterioration of the central circadian pacemaker that regulates sleep-wake and other daily rhythms (Hofman & Swaab, 2006; Wu & Swaab, 2007), disruption to genes that regulate circadian rhythms (Thome et al., 2011), and/or to changes in sleep regulatory systems (Šimić et al., 2009). Women with low-amplitude or delayed circadian rhythms at baseline have an increased risk of developing dementia and mild cognitive impairment (a prodromal stage for AD) during the next five years (Tranah et al., 2011). In a mouse model of AD, circadian rhythm abnormalities are detectable before the appearance in the brain of amyloid- β (A β) plaques and neurofibrillary tangles, hallmarks of established AD (Sterniczuk et al., 2010). A β shows daily rhythms in both mice and people, and treatments that reduce sleep

increase deposition of A β in the brains of mice (Kang et al., 2009). Conversely, increased aggregation of A β has recently been shown to disrupt sleep/wake cycles (Roh et al., 2012), suggesting reciprocal impacts between sleep disturbance and A β deposition. In addition, altered sleep architecture (i.e., decreased REM and fragmented slow-wave sleep) is also shown by those with mild cognitive impairment (MCI) who are at a higher genetic risk for AD (Hita-Yanez et al., 2012). These findings suggest that deterioration of the circadian clock and accompanying sleep disturbances may be early indicators of developing AD, and may even contribute to disease progression. Recently, poor sleep quality has been shown to correlate with the level of amyloid deposition in cerebrospinal fluid, in cognitively healthy individuals (Ju et al., 2013). Even so, it has not been shown that sleep disturbance itself predicts development of AD or dementia in otherwise healthy individuals.

We evaluated whether self-reported sleep problems in individuals who do not report AD or dementia at baseline, are early, independent markers of risk for developing AD or dementia over an approximately 4-year period. Individual sleep-related questionnaire items were assessed for their predictive power and a combination of items related to sleep was used to create a sleep disturbance index (SDI). Aging and the accumulation of functional deficits that accompany aging (i.e., the degree of frailty) are strong predictors of the development of AD (Buchman, Boyle, Wilson, Tang, & Bennett, 2007; Panza et al., 2011). We therefore evaluated the risk of dementia in relation to disturbed sleep, frailty and age (Rockwood et al., 2005).

3.4 Methods

3.4.1 Study Population

Secondary analyses were conducted on data from the second (SHARE, release 2.5.0 as of May 24th 2011) and fourth (SHARE, release 1, as of November 30th 2012) waves of the Survey of Health, Ageing and Retirement in Europe (N = 30,038). SHARE consists of non-institutionalized population aged 50 and older and their spouses/partners (independent of age) in participating countries. Participant recruitment occurred via probability sampling using country-specific population data (i.e., census and population registries and/or telephone/address directories; Alcer et al., 2005). People were excluded if they were incarcerated, hospitalized or out of the country during the time of the survey, unable to speak the country's language(s), or moved to an unknown address. Respondents from 12 countries (Austria, Germany, Sweden, Netherlands, Spain, Italy, France, Denmark, Switzerland, Belgium, Czechia, and Poland) who took part in the second and fourth wave of SHARE were chosen for our analyses. We excluded: (1) spouses/partners below the age of 50 (n = 842) and (2) those who reported the presence of AD or dementia at baseline (n = 391), leaving 28,697 participants for analysis (Figure 3.1). Education level was standardized across participants in SHARE according to the ISCED-1997 code. Approval for secondary analyses came from the Research Ethics Committee of the Capital District Health Authority at Halifax, Nova Scotia, Canada.

3.4.2 Health Measures

The major outcome of a diagnosis of AD or dementia (i.e., 0 = absent, 1 = present), was determined by the following question in SHARE's wave 4 questionnaire

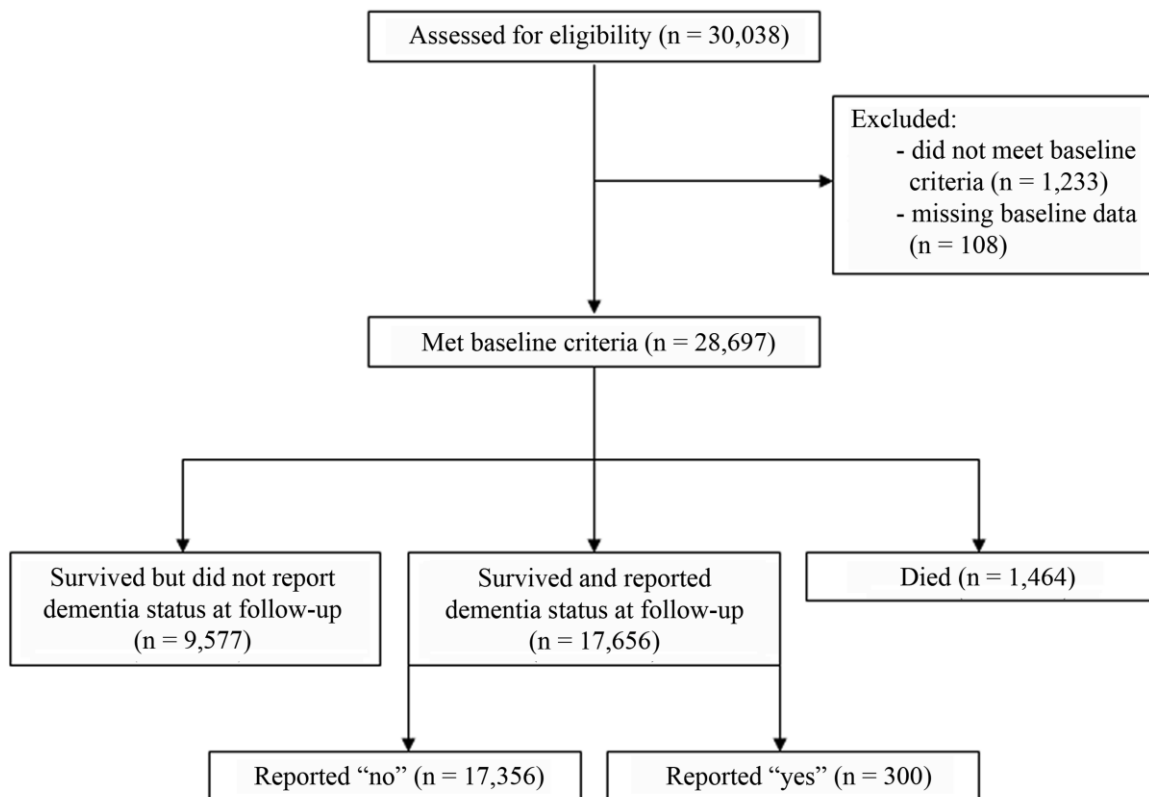


Figure 3.1 Participant flow diagram for the outcome of AD or dementia, and mortality.

“Has a doctor ever told you that you had/Do you currently have any of the conditions on this card? With this we mean that a doctor has told you that you have this condition, and that you are either currently being treated for or bothered by this condition?” The primary option of interest was “Alzheimer’s disease, dementia, organic brain syndrome, senility or any other serious memory impairment”. This health measure was reported by the participants themselves or a proxy respondent (e.g., spouse/partner). Survival was reported by relatives, friends, or neighbours (i.e., died; 0 = no, 1 = yes) after an average of 4.3-years.

3.4.2.1 Sleep Disturbance

A Sleep Disturbance Index (SDI) was created using four sleep-related variables found within the primary 2006 questionnaire, namely ‘bothered by sleeping problems during the past six months’, ‘bothered by fatigue during the past six months’, ‘taking sleep medication for sleeping problems’, and ‘recent trouble sleeping or a change in pattern’. Operationally, any candidate health variable used to create an index should have no more than 5% missing data (Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008). As a result, the variable ‘restless sleep’ was not included in our analyses (~50% missing cases). Only those participants who completed all of the wave 2 sleep measures were included in the analyses (0.9% excluded). The index was calculated by adding the total number of sleep-related impairments (0-4 range). These health measures were reported by the participants themselves and/or by a proxy respondent.

3.4.2.2 Cognitive Performance

The SHARE protocol included performance-based cognitive tests, which were used to generate a cognition score for each participant during each wave. The cognition scores consisted of their performance on tests of temporal orientation (i.e., of date, day, month, year), mathematical ability, verbal fluency, immediate recall, and delayed recall. These tests are sensitive measures for discriminating between cognitively healthy individuals and those with mild cognitive impairment or dementia (i.e., AD; Balthazar, Cendes, & Damasceno, 2007; Martin et al., 2003; Takayama, 2010; Xie et al., 2011). Test scores were coded as either “0”, no deficit in performance, or “1”, a deficit in one’s ability to perform on that cognitive measure. An orientation score of 4 (out of 4) was coded as “0”, whereas a score less than or equal to 3 was coded as “1”. Individuals who are unable to recall all four aspects of time may be exhibiting MCI or be at risk for greater cognitive decline (Xie et al., 2011). A numeracy score greater than or equal to 4 (out of 5) was coded as “0”, whereas a score less than 4 was coded as “1”. Those with MCI exhibit error rates that range from those of healthy control subjects to those with moderate AD; even those who are healthy may make calculation errors (Martin et al., 2003). Therefore, we chose to permit one error on this cognitive measure. Verbal fluency scores greater than or equal to 15 were coded as “0”, whereas scores less than 15 were coded as “1”. The inability to name at least 15 types of animals in one minute may be indicative of MCI or AD (Balthazar et al., 2007). Immediate recall scores greater than or equal to 5 (out of 10) were coded as “0”, whereas scores less than 5 were coded as “1”. The inability to recall at least 5 out of 10 words immediately after their presentation may indicate MCI or AD (Takayama, 2010). Delayed recall scores greater than or equal to 4

(out of 10) were coded as “0”, whereas scores below 4 were coded as “1”. An inability to recall at least 4 out of 10 words after several minutes may also indicate MCI or AD (Takayama, 2010). A single recall score was created using the average of both recoded immediate and delayed recall scores. Those reporting “don’t know” for any of these measures were coded as “1” or impaired. Only those participants who completed all five cognitive tests in wave two were used for the analyses (3.5% excluded). The cognition scores for each wave were calculated by adding the total number of impairments (0-4).

3.4.2.3 Frailty

In keeping with reports that non-traditional risk factors combine to predict dementia (Song, Mitnitski, & Rockwood, 2011) and that cognitive decline in older adults can be predicted most effectively by a general frailty index (FI; Mitnitski, Fallah, Rockwood, & Rockwood, 2011), an FI was included to assay the potentially confounding influence of general health status. The FI was constructed using the deficit accumulation approach, in which a deficit can be any symptom, sign, disease, disability, or laboratory abnormality (Searle et al., 2008). Each deficit was selected according to a standard method (Searle et al., 2008); associated with increasing age and adverse health, covering a wide range of systems and not saturating at a young age. Here, items directly related to sleep disturbance and cognition (i.e., cognitive variables, or the presence of dementia) were excluded, resulting in 53 items (Table 3.1). These measures represent conditions that accumulate with age and were associated with adverse outcomes from the physical health and behavioural risks of the SHARE database (Theou et al., 2013a). Each measure, which a binary, ordinal, or continuous variable, was mapped into a 0-1 interval

Table 3.1 Constructs used to create the sleep disturbance and frailty indices.

List of measures used to construct the Sleep Disturbance Index		
• Fatigue past 6 months	• Sleeping problem last 6 months	• Use of sleep medication
• Recent trouble sleeping		
List of measures used to construct the Frailty Index		
• High blood pressure	• Heart attack	• High cholesterol
• Stroke or cerebral vascular disease	• Diabetes or high blood sugar	• Physical inactivity
• Poor self-rated health	• Have a long-term illness	• In hospital last 12 months
• Have chronic lung disease	• Have asthma	• Have arthritis
• Have osteoporosis	• Have cancer	• Have a stomach or duodenal ulcer
• Have cataracts	• Had a hip or femoral fracture	• Had other fracture
• Have pain in any joint	• Breathlessness	• Have a persistent cough
• Have stomach or intestinal problems	• Wear glasses	• Have poor hearing
• Wear dentures	• Difficulty with biting on hard foods	• Difficulty sitting for about 2 hours
• Difficulty picking up a small coin from a table	• Difficulty stooping, kneeling, or crouching	• Difficulty reaching or extending arm above shoulder level
• Difficulty climbing one flight of stairs without rest	• Difficulty climbing several stairs without rest	• Difficulty pulling or pushing large object
• Difficulty lifting or carrying weight over 10 lbs	• Difficulty getting up from a chair after prolonged sitting	• Difficulty dressing (or putting on shoes and socks)
• Difficulty walking across a room	• Difficulty walking 100 m	• Difficulty bathing or showering
• Difficulty eating or cutting food	• Difficulty getting in or out of bed	• Difficulty using the toilet
• Difficulty using a map	• Difficulty preparing a hot meal	• Difficulty shopping for groceries
• Difficulty making a phone call	• Difficulty taking medication(s)	• Difficulty doing housework
• Difficulty managing money	• Pessimism	• Suicidal
• Feelings of guilt	• Poor appetite	

(e.g. 0, 0.25, 0.5, 0.75, 1). The maximum number of missing variables permitted for each participant was less than 20% of the total number of measures (≤ 10 items). Each participant's FI scores were calculated by dividing the number of recorded deficits by 53 so that, for example, a person in whom 26 deficits were present would have an FI score of $26/53 = 0.49$. In order to compare the FI with the SDI and cognitive score, the FI was divided into five groups with the following cut-off points: 0-0.02, 0.0200001-0.1, 0.1-0.2, 0.2-0.3, and 0.3 or greater.

3.4.3 Statistical Analysis

Independent samples t-tests were used to examine the differences in SDI and FI scores between those who reported the presence vs. absence of AD or dementia, or did not survive, at follow-up (reported as Mean \pm SD). Binary logistic regression was used to estimate the likelihood and 95% confidence intervals (CI) of each sleep variable individually as well as jointly as an index of sleep disruption, in relation to the diagnosis of AD and dementia, and the prediction of mortality. Several covariates (i.e., age, sex, education, body mass index (BMI), and cognition) were used to adjust the risk models for (1-4) each sleep variable, (5) only the SDI, (6) only the FI, (7-10) each sleep variable and the FI, and (11) both the SDI and FI. Receiver operating characteristic (ROC) curves were used to examine the sensitivity and specificity of the SDI and FI in classifying those individuals who would subsequently be diagnosed with AD, dementia, or would not survive after an average of 4.3 years. The area under the curve (AUC) was used to assess statistical significance of the ROC analysis. SPSS (18.0.0, SPSS Inc.) was used to analyze the data. Statistical significance level was set at $p = 0.05$.

3.5 Results

3.5.1 Baseline Demographics and Clinical Characteristics

At baseline, our sample had a mean age of 64.6 years (range 50-104), and women constituted just over half (54.5%) of these individuals. Close to 80% of those sampled had attained a maximal level of upper secondary education (e.g., high school). Only 0.5% reported having attained an advanced research qualification (e.g. PhD). Average BMI was in the lower end of the ‘overweight’ range. When those who reported the presence of AD or dementia at follow-up were selected (n= 300), women constituted a greater percentage (60%; range 50-96), and close to 70% of participants reported having attained a maximal level of lower secondary education (e.g. middle school).

People who reported the presence of AD or dementia after ~4 years, had greater sleep disturbance at baseline than those who did not (did not report dementia: 0.79 ± 1.10 ; reported dementia: 1.22 ± 1.27 ; $p = < 0.001$). People who reported AD or dementia at follow-up also had a higher level of frailty at baseline than those who did not (did not report dementia: 0.14 ± 0.10 ; reported dementia: 0.24 ± 0.14 , $p = < 0.001$). Those who did not survive to follow-up (n = 1,464) also exhibited greater sleep disturbance and a higher level of frailty at baseline, than those who survived (SDI, survived: 0.80 ± 1.11 , did not survive; 1.09 ± 1.26 ; FI, survived: 0.14 ± 0.10 , did not survive: 0.27 ± 0.16 ; Table 3.2)

Table 3.2 Demographic and clinical characteristics of those people who reported AD or dementia versus those who did not, as well as those who survived or died, after an average of 4.3 years, while controlling for age, sex, education, body mass index, and cognition.

	Baseline (n = 28,697)	Reported the absence of AD or dementia (n = 17,356)	Reported the presence of AD or dementia (n = 300)	Survived at follow-up (n = 17,707)	Did not survive at follow-up (n = 1,464)
Age (Mean \pm SD)	64.6 (9.9)	63.7 (9.0)	75.3 (9.1)	63.9 (9.2)	74.6 (10.4)
% women	54.5	55.5	60	55.5	43.8
Education (ISCED code; Mean \pm SD)	2.6 (1.5)	2.7 (1.5)	1.8 (1.3)	2.65 (1.5)	1.98 (1.4)
Body mass index (Mean \pm SD)	26.6 (4.4)	26.63 (4.39)	26.10 (4.72)	26.62 (4.4)	26.21 (5.05)
Cognitive impairments (Mean \pm SD)	1.22 (1.18)	1.11 (1.11)	2.38 (1.31)	1.13 (1.13)	2.09 (1.30)
Impaired activities of daily living (Mean \pm SD)	0.21 (0.77)	0.14 (0.58)	0.62 (1.35)	0.15 (0.61)	0.91 (1.62)
Impaired instrumental activities of daily living (Mean \pm SD)	0.33 (0.99)	0.22 (0.72)	1.25 (1.91)	0.23 (0.77)	1.44 (2.06)
Sleep disturbance index (Mean \pm SD)	.81 (1.12)	0.79 (1.10)	1.22 (1.27)	0.80 (1.11)	1.09 (1.26)
Frailty index (Mean \pm SD)	0.15 (0.11)	0.14 (0.10)	0.24 (0.14)	0.14 (0.10)	0.27 (0.16)
% Fatigue past 6 months	18.3	17.1	28.7	17.3	29.5
% Sleep complaints past 6 months	21.2	21.0	30	21.2	25.8
% Sleep medication for sleep problems	8.5	8	17.7	8.2	15.2
% Trouble sleeping/change in pattern	33.1	32.7	44	33	38.3

Table 3.3 Risk model comparison in the association between reports of AD or dementia diagnosis and mortality after an average of 4.3 years, while controlling for age, sex, education, body mass index, and cognition.

Covariates	Reported AD or dementia (n = 300)			Did not survive (n = 1,464)		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Model 1						
Fatigue past 6 months	1.52	1.25-2.01	< 0.01	1.64	1.42-1.88	< 0.001
Model 2						
Sleep complaints past 6 months	1.44	1.09-1.90	0.01	1.24	1.08-1.43	< 0.01
Model 3						
Sleep medication for sleep problems	1.53	1.09-2.14	0.01	1.40	1.17-1.68	< 0.001
Model 4						
Trouble sleeping/change in pattern	1.49	1.15-1.94	< 0.01	1.32	1.16-1.49	< 0.001
Model 5						
Sleep Disturbance Index	1.23	1.11-1.36	< 0.001	1.18	1.12-1.24	< 0.001
Model 6						
Frailty Index	1.39	1.21-1.59	< 0.001	1.82	1.71-1.95	< 0.001
Model 7						
Fatigue past 6 months	1.17	0.86-1.60	0.31	0.97	0.84-1.13	0.72
Frailty Index	1.35	1.16-1.56	< 0.001	1.83	1.71-1.97	< 0.001
Model 8						
Sleep complaints past 6 months	1.18	0.89-1.58	0.28	0.83	0.71-0.96	0.01
Frailty Index	1.35	1.18-1.56	< 0.001	1.87	1.75-2.00	< 0.001
Model 9						
Sleep medication for sleep problems	1.24	0.87-1.76	0.23	0.95	0.79-1.15	0.60
Frailty Index	1.36	1.18-1.56	< 0.001	1.83	1.71-1.96	< 0.001
Model 10						
Trouble sleeping/change in pattern	1.27	0.97-1.67	0.08	0.94	0.82-1.07	0.33
Frailty Index	1.34	1.17-1.54	< 0.001	1.84	1.72-1.97	< 0.001
Model 11						
Sleep Disturbance Index	1.12	1.00-1.25	0.054	0.95	0.90-1.01	0.10
Frailty Index	1.31	1.12-1.52	< 0.001	1.87	1.74-2.01	< 0.001

3.5.2 Risk Model 1-4: Each Sleep Factor

After controlling for the effects of age, sex, education, BMI, and cognition, we found that all four sleep items, namely reports of ‘being bothered by sleeping problems during the past six months’, ‘being bothered by fatigue during the past six months’, ‘taking sleep medication for sleeping problems’, and ‘recent trouble sleeping or a change in pattern’, independently predicted incident AD or dementia within ~4 years. Similarly, each sleep item was a significant predictor of mortality at follow-up (Table 3.3).

3.5.3 Risk Model 5: Only the SDI

After taking into account age, sex, education, BMI, and baseline cognition, the combined SDI was a statistically significant predictor of AD or dementia (OR = 1.23, 95% CI = 1.11-1.36), and mortality (OR = 1.18, 95% CI = 1.12-1.24; Table 3.3). This model accounted for 19 and 22% of the variance in predicting dementia and mortality, respectively. This model is a good fit to both outcomes, although it is better for predicting dementia (dementia: $\chi^2(8) = 5.53, p = 0.70$; mortality: $\chi^2(8) = 6.87, p = 0.55$).

3.5.4 Risk Model 6: Only the FI

Controlling for age, sex, education, BMI, and baseline cognition, the FI was a significant predictor of AD or dementia (OR = 1.39, 95% CI = 1.21-1.59), and mortality (OR = 1.82, 95% CI = 1.71-1.95; Table 3.3). This model accounted for 19 and 26% of the variance in predicting dementia and mortality, respectively, and demonstrated a very good fit to both outcomes (dementia: $\chi^2(8) = 3.86, p = 0.87$; mortality: $\chi^2(8) = 4.00, p = 0.86$).

3.5.5 Risk Model 7-10: Each Sleep Factor and the FI

After controlling for the same covariates and the FI, none of the individual sleep items were significant predictors of AD or dementia, although a trend is visible with reports of ‘recent trouble sleeping or a change in pattern’ ($p = .08$). A report of “being bothered by sleeping problems during the past six months’ was strongly associated with an increased chance of survival (OR = 0.83, 95% CI = 0.71-0.96; Table 3.3), and demonstrates a good fit to predicting this outcome $\chi^2(8) = 4.09, p = 0.85$. Each model with each individual sleep item, accounts for 19% of the variance in predicting dementia, and 26% in predicting mortality.

3.5.6 Risk Model 11: The SDI and FI

When controlling for age, sex, education, BMI, cognition and FI, the SDI is almost a significant predictor of AD or dementia at follow-up, (OR = 1.12, 95% CI = 1.00-1.25; $p = 0.054$), but not of mortality (OR = 0.95, 95% CI = 0.90-1.01). This model accounted for 19 and 25% of the variance in predicting dementia and mortality, respectively. This model is a great fit to both outcomes (dementia: $\chi^2(8) = 4.90, p = 0.77$; mortality: $\chi^2(8) = 4.61, p = 0.80$; Table 3.3).

3.5.7 ROC

Individually, the SDI and FI exhibit classification accuracy for reports of AD or dementia diagnosis, although the FI is a stronger indicator. The mean AUC for each index (AUC = 0.60, 95% CI 0.57-0.63 for SDI, $p < 0.001$; AUC = 0.71, 95% CI = 0.68-0.74 for FI, $p < 0.001$) is significantly different from 0.5, demonstrating their sensitivity

and specificity in differentiating who will report dementia after ~4 years. The SDI exhibited mild significant accuracy in predicting survival, whereas the FI exhibited much stronger classification accuracy for survival (0.57, 95% CI = 0.55-0.58 for SDI, $p < 0.001$; AUC = 0.73, 95% CI = 0.72-0.74 for FI, $p < 0.001$).

3.6 Discussion

These findings demonstrate that combined indicators of disrupted sleep in otherwise healthy individuals, are associated with a subsequent diagnosis of AD or dementia, independently of cognitive status. Disturbed sleep and disruption to the sleep-wake cycle are well recognized as symptoms of established AD and dementia, here also appear to reflect changes in sleep and/or circadian regulatory mechanisms that occur early in the development of the disease (Sterniczuk et al., 2010). It is also possible that sleep disturbances accelerate the development of AD or dementia, perhaps by affecting neuropathological processes, such as deposition of $A\beta$ (Kang et al., 2009). Of note, combined in a sleep disturbance index, indicators of disrupted sleep are associated with an increased risk of death within ~4 years, however this is no longer the case when overall health status is taken into account. Taken together, these findings are consistent with previous work which link sleep to disease risk and mortality (Cappuccio, D'Elia, Strazzullo, & Miller, 2010; Czeisler, 2011).

Our data must be interpreted with caution. Notably, the SHARE database lacks diagnostic information: AD was not diagnosed, and cognition was not assessed by a standard cognitive measure from which dementia could be diagnosed, nor were neuroimaging or biomarkers employed. Instead, SHARE collected data directly from

participants and/or their proxies; no differentiation between the various types of dementia was made during questioning. For these reasons, we cannot make prevalence or incidence estimates, and so our current analyses are restricted to associations. Using data from the National Population Health Survey and the Canadian Study of Health and Aging, we have previously shown that self-report data may highly underestimate the prevalence of dementia (Thomas et al., 2001). We recognize here that self-reports may differ from those of the proxy; however, excluding information from individuals with greater insight into the presence of abnormalities (e.g., being awake to see and remember sleep disturbance) would decrease the validity of the measures that were examined.

We have however verified that people with a dementia report were more likely to show lower cognitive test scores from the screening tests that were employed; likewise, they were older and had a lower level of education, and a higher proportion had functional impairments in instrumental and personal activities of daily living. Controlling for cognition is a conservative strategy, and helps to reduce the effect of misclassification bias. On the one hand, some people with the exposure (sleep disturbance) did in fact develop dementia at follow-up (but were misclassified as having not done so). Others might have had low baseline cognitive test scores due simply to impaired sleep, but were not otherwise at risk. Although it would clearly be preferable to have verified diagnoses on everyone, knowing that the association persists after accounting for low baseline cognitive test scores lends some confidence to the observed association, thereby motivating further inquiry.

The present analyses are also limited by the relatively short duration of follow-up. Future studies should assess the appearance of sleep disturbances over longer intervals

preceding the diagnosis of AD in order to determine the relation of these symptoms to other symptoms and to the preclinical progression of the illness. These findings should also be replicated in other large cohorts to validate the SDI outside of the SHARE database.

We recently reported that a general decline in health, as assessed by measures that have not traditionally been considered risk factors for AD, is associated with an increase in frailty and in risk for the development of dementia (Song et al., 2011); we have replicated this using the SHARE data. Given that AD typically occurs very late in life, small insults to bodily health and subsequent decline within the functioning of various systems (e.g., cellular, physiological, cognitive, behavioral), commonly accumulate by the time the disease is recognized. Using this deficit accumulation approach, here we demonstrate that small insults within one aspect of physiology, namely sleep, may not increase dementia risk when overall health status is taken into account. However, the additive effects of different sleep-related factors combine to highlight an important role for this system in the development of AD and other dementias; the SDI remained only marginally significant when the FI was included in the risk model. In line with a deficit accumulation approach, we chose to examine the effect of overall health status within this study, even though some of the constructs used to create the FI may be considered high risk factors for AD and dementia (e.g., stroke, diabetes, high blood pressure, etc.); examining the effect of each factor was beyond the scope of our analyses. As we move towards a broader understanding of dementia risk, we need to explain the cumulative effects of risks that are individually small or typically viewed as irrelevant, such as those related to sleep.

A previous study using a much smaller cohort (N = 1,659), did not find a significant relationship between sleep disturbance and increased risk of death (Rockwood, Davis, Merry, MacKnight, & McDowell, 2001). Similarly, we show here that although disturbed sleep and a combination of sleep disturbance factors (i.e., SDI) can increase a person's risk of death, the overall health status of an individual is a stronger determinant of mortality risk. Unexpectedly, an individual report of sleeping problems was associated with a decreased risk of mortality, in a model demonstrating that declining health status increases the chances of death. This may be due to various reasons such as an increased likelihood to seek medical consultation, which could lead to a re-examination of current health status or medications that may have had an adverse effect on health in the long-term. These findings also suggest that some aspects of sleep disturbance may be more strongly associated with increased risk of dementia rather than mortality. Much work is still needed to elucidate whether specific changes in sleep efficiency or sleep patterns are related to adverse health outcomes, or whether a global measure of declining sleep function best predicts these outcomes.

How disturbed sleep comes to be associated with dementia is not entirely clear. Damage to the primary circadian pacemaker in mammals, the SCN, has been proposed to be responsible for abnormal patterns of sleep and waking in AD patients (Wu & Swaab, 2007). The SCN undergoes significant changes in old age (Hofman & Swaab, 2006), but even more profound alterations occur in people with AD, even at younger ages. Depressed levels and daily rhythms of neuropeptides such as vasoactive intestinal polypeptide and vasopressin within the SCN have been observed in both animal models

and human cases of AD (Liu et al., 2000; Zhou et al., 1995) and may occur prior to the development of AD neuropathology (Sterniczuk et al., 2010).

Macular and optic nerve degeneration is a common condition in older individuals and in AD (Guo, Duggan, & Cordeiro, 2010; Hinton, Sadun, Blanks, & Miller, 1986), which could reduce light input from the retina to the SCN. Reduced light input may contribute to disruption of sleep-wake rhythms, because light cycles are critical for synchronizing internally generated rhythms with the external light-dark cycle. Abnormal signaling from the SCN to surrounding regions (Cermakian et al., 2011) and to sleep-regulatory systems may also affect the normal expression of sleep and wakefulness. Relatively little is known about AD-associated changes to cellular and molecular components of the circadian clock (Cermakian et al., 2011), and there is still debate about whether circadian rhythm dysfunction contributes to, or results from, AD pathogenesis and symptomology (Bedrosian & Nelson, 2012; Moghekar & O'Brien, 2012).

The cholinergic system experiences possibly the greatest deficits in AD. Impaired cholinergic neurotransmission contributes to the memory dysfunction visible early in the course of the disease, whereas normal signaling protects neurons from A β accumulation and its toxic effects. Cholinergic signaling plays an important role in the regulation of sleep, particularly in the initiation and maintenance of REM sleep. Loss of cholinergic neurons is speculated to be one of the main culprits for causing sleep disturbances in AD patients (Rothman & Mattson, 2012). It is speculated that functional cholinergic disconnection between brain regions, in conjunction with a hypoxic state, contributes to memory loss in AD (Daulatzai, 2010). Hypoxia due to sleep disordered breathing is closely linked to AD-related memory disturbance; apneas without significant hypoxia are

not associated with an increased risk of dementia (Yaffe et al., 2011). A better understanding of the mechanisms underlying cholinergic dysfunction and AD-associated pathology may lead to novel pharmacological interventions for dementia and the alleviation of sleep related symptoms.

Our data also are relevant to how sleep difficulties might modify risk for health service use in dementia. Extended time in bed and an increase in total sleep time, which often accompanies institutionalization (Brown, Redden, Flood, & Allman, 2009), greatly contribute to the frailty of seniors (Stenholm, Kronholm, Bandinelli, Guralnik, & Ferrucci, 2011). Not only does institutionalization put older individuals at greater risk for functional decline (Covinsky et al., 2003), but it may also exacerbate sleep-wake disruption in AD, when compared to community-dwelling seniors (van Someren et al., 1996). Regular clinical evaluation of sleep disorders in older individuals, or those reporting cognitive impairment, may provide valuable information regarding risk of future cognitive deterioration and dementia development, as sleep-wake fragmentation is strongly associated with cognitive decline (Oosterman, van Someren, Vogels, Van Harten, & Scherder, 2009). It is important to better understand the complex relations among time in bed, sleep duration, sleep quality and sleep-wake cycle regulation during the preclinical and clinical stages of AD and dementia.

3.7 Conclusions

These analyses further support the hypothesis that sleep disturbance plays an important role early in the course of AD and other dementias. Although sleep disturbance is predictive of adverse health outcomes, it was not a stronger risk factor than overall

frailty in our analyses. Nevertheless, it is the case that, compared with elaborate frailty assessments, sleep-related questioning during risk assessment might be a more feasible screening tool for the early detection of dementia. Although sleep disturbance is common in individuals with MCI, it is still unclear as to which of those individuals will develop AD or dementia (Beaulieu-Bonneau & Hudon, 2009), and which component of the sleep disruption is associated with an increased risk. The manifestations of these disruptions in relation to the onset of traditional symptoms of AD (e.g., memory impairment), also remains to be elucidated. Further work in this area may provide valuable information regarding the neurological correlates of disturbed sleep-wake cycles in AD patients, as well as the potential for chronobiological treatment and prevention of AD (Stranahan, 2012). Ultimately, this knowledge could help in producing earlier and more accurate diagnoses, as well as guiding appropriate treatment interventions at the earliest possible stages, in the hopes of preventing or delaying institutionalization.

3.8 SUMMARY OF CHAPTER 3 AND TRANSITION TO CHAPTER 4

In Chapter 3, the concept of a ‘sleep disturbance index’ (SDI) was introduced to examine the impact that cumulative sleep complaints have on dementia and mortality risk in a large multinational cohort. The SDI was then compared to its methodological counterpart, a ‘frailty index’ (FI), or a measure of overall health status using a deficit accumulation approach. Individual sleep items, namely, reports of ‘being bothered by sleeping problems during the past six months’, ‘being bothered by fatigue during the past six months’, ‘taking sleep medication for sleeping problems’, and ‘recent trouble sleeping or a change in pattern’, independently predicted incident AD/dementia and mortality within ~4 years. When these items were combined, the SDI was associated with an increased risk of both negative health outcomes, albeit to a smaller degree. Inclusion of the FI in the model diminished the relative risk of reported AD/dementia associated with sleep disturbance, and the FI was a better indicator of mortality risk. Although these analyses demonstrated that sleep disturbance predicted AD/dementia within a relatively short period of time (< 5 years), poorer overall health status of an individual appeared to be a better predictor, as it was for mortality risk.

In order to replicate and build upon findings from Chapter 3, the following study was designed to explore the risks associated with the SDI and FI for negative health outcomes utilizing the newest release of the SHARE data (i.e., follow-up of an average of 6 years vs. ~4 years). The risks of negative health outcomes (i.e., cognitive impairment, reported AD/dementia, and mortality) were examined by selecting for cognitively healthy participants (i.e., < 2 cognitive impairments) at baseline who did not report the presence

of AD or dementia. Analyses conducted separately from this dissertation were employed when setting this cut point for cognitive function (Sterniczuk et al., 2015; Appendix D.2).

CHAPTER 4

Sleep Disturbance is Associated with Incident Dementia up to 6 years Before

Reported Diagnosis

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4.1 Abstract

Sleep disturbance is a common neuropsychiatric feature of Alzheimer's disease (AD) and dementia that appears even prior to the development of typical symptoms, such as cognitive impairment. Some evidence suggests that sleep disturbance may contribute to the development of AD. Decline in overall health status also predicts development of AD, but how these factors interact is not well understood. Secondary analyses of sleep-related measures collected through the Survey of Health, Ageing and Retirement in Europe (SHARE; i.e., sleeping problems, fatigue, taking sleeping medication, and trouble sleeping or a change in pattern) were conducted on cognitively healthy people who reported the absence of AD or dementia at baseline (N=17,023). Health outcomes included cognitive impairment, reported AD or dementia, and mortality, after an average of 4.3 and 6.2 years. A 'sleep disturbance index' (SDI) using sleep-related measures was created and compared to a frailty index (FI) reflecting overall health status. The SDI was a significant predictor of cognitive impairment and reported AD or dementia at each time point. The SDI continued to be associated with reported AD or dementia at ~6 years in a risk model that included the FI (OR = 1.26, 95% CI = 1.04-1.54; p = 0.02), while the FI was not a significant predictor on its own. Unexpectedly, the SDI was also associated with increased survival at ~6 years (OR = 0.87, 95% CI = 0.77-0.97; p = 0.01) when frailty was taken into account, however this effect was abolished when the interaction effect between the SDI and FI was included in the risk model. Except for reported AD or dementia at ~6 years, the FI was a significant predictor in all other models. These findings add to the evidence demonstrating that sleep disturbance is an early indicator of adverse health outcomes that may be observed sooner than changes to other measures of

overall health status. Screening for the presence of disturbed sleep may be useful for the earlier identification of increased risk of cognitive decline and incident dementia, as well as other negative health outcomes.

4.2 Introduction

It is well established that an acute lack of adequate sleep can impair cognitive performance immediately, including aspects of attention, learning and memory, and executive function (Lim & Dinges, 2010; Rasch & Born, 2013; Stickgold & Walker, 2007). In addition, chronic sleep disruption, including sleep/wake fragmentation, reduced sleep, and sleep-disordered breathing, have been linked to the development of cognitive impairment over the longer term (Yaffe et al., 2014). Most notably, insomnia, including poor sleep continuity and increased nighttime activity, along with daytime sleepiness, are linked to an increased risk of incident dementia (Almondes et al., 2016; Diem et al., 2016; Tranah et al., 2011; Tsapanou et al., 2015a; Sterniczuk et al., 2013), and are among the most commonly reported symptoms of Alzheimer's disease (AD; Paavilainen et al., 2005; Witting et al., 1990; D'Onofrio et al., 2012; You et al., 2015). In addition, there is accumulating evidence that disturbed sleep is also an important indicator of greater cognitive decline (Bonanni et al., 2005) and functional decline in those with dementia (D'Onofrio et al., 2012; Zhao et al., 2016).

The question remains whether disrupted sleep and circadian rhythms contribute to the onset of neurodegenerative processes, or whether early stages of a disease process cause disruptions in sleep and circadian rhythms to appear prior to the emergence of more traditionally recognized disease symptoms (e.g., cognitive impairment in AD, motor dysfunction in Parkinson's disease). The mechanisms that underlie the relationships between disturbed sleep and cognitive impairment or dementia, are unclear (see reviews by Mattis & Sehgal, 2016; Miller, 2015; Musiek et al., 2015; Wu & Swaab, 2007), but may be related to changes within the mechanisms that regulate circadian rhythms and/or

sleep, or to disturbed metabolic functions that are affected by these systems. Sleep/wake rhythm abnormalities are detectable prior to the formation of AD-related amyloid- β (A β) in transgenic mice that develop AD-like conditions (Sterniczuk et al., 2010). People who have a genetic risk of AD display disrupted sleep architecture (Ju et al., 2013), while those with better sleep consolidation have an attenuated genetic risk (Lim et al., 2013). Furthermore, sleep disruption is associated with an increase in the aggregation of A β plaques in both transgenic mice (Kang et al., 2009) and people (Hita-Yañez et al., 2012). Conversely, increased deposition of A β causes disrupted sleep/wake cycles (Roh et al., 2012). These findings demonstrate a reciprocal relationship between sleep disturbance and AD-related neuropathology (i.e., amyloid deposition, neurofibrillary tangle formation).

One increasingly accepted hypothesis regarding aging and health is that the accumulation of a broad range of health-related deficits during aging increases vulnerability for adverse health outcomes, including dementia and increased mortality risk. This accumulation can be operationalized as an overall level of health status or frailty (Rockwood & Mitnitski, 2007). Increasing frailty is associated with a subsequent decline in cognitive performance (Gill et al., 1996; Rolfson et al., 2013), with the frailest people rarely demonstrating improvement in cognition over time compared to their non-frail counterparts (Mitnitski et al., 2011). Additionally, a combination of health-related measures that are otherwise not typically associated with dementia (e.g., a broken hip, the use of dentures) predict an increased risk for the development of AD and dementia up to 10 years later (Panza et al., 2011; Song et al., 2011).

Using self-reported, individual sleep complaints and incorporation of these items into a combined ‘sleep disturbance index’ (SDI), we previously demonstrated that sleep disturbance was associated with future reported incident AD or dementia over ~4 years, in a large multi-national cohort (Survey of Health, Ageing, and Retirement in Europe; SHARE), even when baseline overall health status (i.e., frailty) was included in the risk model (Sterniczuk et al., 2013). We have now analysed the newest release of the SHARE data and took into account the potential impact of baseline differences in cognition (Sterniczuk et al., 2015) in order to explore the predictive power of sleep disturbance and frailty with respect to: (1) cognitive impairment; (2) reported incident AD or dementia, and (3) mortality, over approximately 4- and 6-year time frames. In keeping with a deficit accumulation model, current analyses examined the impact of multiple sleep-related complaints on the risk of adverse health outcomes. Based on previous results (Sterniczuk et al., 2013), we predicted that in cognitively healthy individuals at baseline, sleep disturbance would be a predictor of cognitive decline and dementia, while frailty (overall health status), would be a stronger indicator of mortality risk.

4.3 Methods

4.3.1 Study Population

Secondary analyses were conducted on data from Waves 2 (baseline; 2006-2007), 4 (2010-2012), and 5 (2013) from the SHARE database (releases 2.5.0 as of May 11th 2011, and 1.1.1 as of March 28th 2013, and 1.0.0 as of March 31st, 2015, respectively; N = 27,571), of the Survey of Health, Ageing and Retirement Europe (SHARE). The SHARE database consists of non-institutionalized population aged 50 and older and their

spouses/partners independent of age in 11 participating countries (i.e., Austria, Germany, Sweden, Netherlands, Spain, Italy, France, Denmark, Switzerland, Belgium, Czech). Sampling designs were based on country-specific population data collection and probability sampling (Alcser et al., 2005). Age-eligibility was determined by census and population registries, and/or telephone/address directories. Participants were excluded if they were incarcerated, hospitalized or out of the country during the time of the survey, unable to speak the country's language(s), or moved to an unknown address.

Only those countries that participated in all three waves of data collection were included in our analyses (i.e., 8% excluded). From the second wave, we also excluded (1) spouses/partners below the age of 50 ($n = 787$), (2) individuals who reported a diagnosis of AD or dementia ($n = 348$) and (3) individuals who exhibited impaired performance on 2 or more cognitive domains (i.e., verbal fluency, immediate recall, and delayed recall; $n = 9,208$). Analyses were conducted on 17,023 participants who met inclusion criteria (Figure 1). Education level was standardized across participants in SHARE according to the ISCED-1997 code. Approval for secondary analyses came from the Nova Scotia Health Authority Research Ethics Board at Halifax, Nova Scotia, Canada.

4.3.2 Baseline Health Measures

4.3.2.1 Cognitive Performance

The SHARE protocol included performance-based cognitive tests, which were used to generate a cognition score for each participant during each wave. Cognition

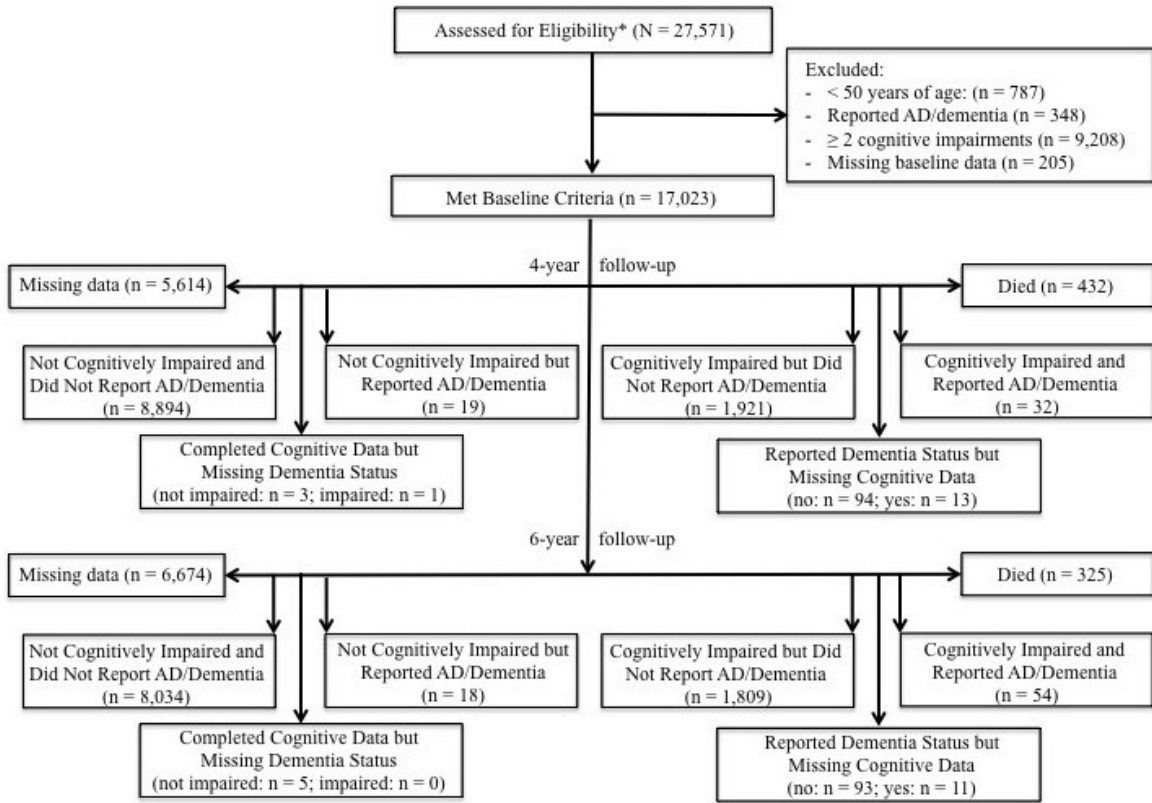


Figure 4.1 Participant flow diagram for the outcomes cognitive impairment, reported AD/dementia, and mortality, after an average of 4.3 and 6.2 years. *8% excluded who did not have data collected in all three waves of data.

scores consisted of performance on tests of verbal fluency, immediate recall, and delayed recall. A detailed description of the coding of these variables and their validation in relation to cognitive and functional decline, including reported dementia, has been reported (Sterniczuk et al., 2013; 2015). Briefly, test scores were coded as either “0”, no deficit in performance, or “1”, a deficit in one’s ability to perform on that cognitive measure. Those reporting “don’t know” for any of these measures were coded as “1” or impaired (i.e., n = 133). The cognition scores for each wave were calculated by adding the total number of impairments across the three measures (0-3). Only those participants who completed all three cognitive tests in Wave 2 were used for the analyses (2.4% excluded) in order to exclude those with existing cognitive impairment before the time points being studied.

4.3.2.2 Sleep Disturbance

As previously reported (Sterniczuk et al., 2013), a ‘Sleep Disturbance Index’ (SDI) was created using four sleep-related variables found within the primary 2006 questionnaire; namely: ‘bothered by sleeping problems during the past six months’, ‘bothered by fatigue during the past six months’, ‘taking medication for sleeping problems’, and ‘recent trouble sleeping or a change in pattern’. Only those participants who completed all of the Wave 2 sleep measures were included in the analyses (1.6% excluded). The index was calculated by adding the total number of sleep-related impairments (0-4 range) to create five levels of sleep problems. These health measures were reported by the participants themselves and/or by a proxy respondent.

4.3.2.3 Frailty

Given that it is well established that a combination of health-related factors, as measured by a frailty index (FI), is an effective predictor of cognitive decline, dementia, and mortality (Armstrong et al., 2016; Rockwood et al., 2005; Rockwood & Mitnitski, 2007; Song et al., 2011), an FI was used as a measure of general health status within these analyses. The FI was constructed using the deficit accumulation approach, in which a health deficit can be any identifiable problem (i.e., symptom, sign, disease, disability, or laboratory abnormality) that represents an acquired condition, which accumulates with age and is related to adverse health outcomes (Searle et al., 2008). Here, 53 items from the physical health and behavioural risks of the SHARE database were selected (Table 1), excluding those related to sleep disturbance and cognition. Each measure was mapped into a 0-1 interval (e.g. 0, 0.25, 0.5, 0.75, 1). The maximum number of missing variables permitted for each participant was less than 20% of the total number of measures (≤ 10 items). Each participant's FI score was calculated by dividing the number of recorded deficits by 53 so that, for example, a person in whom 26 deficits were present would have an FI score of $26/53 = 0.49$. As previously reported (Sterniczuk et al., 2013), the FI was divided into five levels (i.e., 0-0.02, 0.02-0.1, 0.1-0.2, 0.2-0.3, and >0.3), in order to compare it directly with the SDI.

4.3.3 Outcomes

Three major outcomes were examined in data from Wave 4 (~4 years from study onset) and Wave 5 (~6 years), namely: (1) incident cognitive impairment (i.e., impaired performance on < 2 vs. ≥ 2 cognitive measures), (2) self-report, or proxy-report from a

Table 4.1 Constructs used to create the sleep disturbance and frailty indices.

List of measures used to construct the Sleep Disturbance Index		
• Fatigue past 6 months	• Sleeping problem last 6 months	• Use of sleep medication
• Recent trouble sleeping		
List of measures used to construct the Frailty Index		
• High blood pressure	• Heart attack	• High cholesterol
• Stroke or cerebral vascular disease	• Diabetes or high blood sugar	• Physical inactivity
• Poor self-rated health	• Have a long-term illness	• In hospital last 12 months
• Have chronic lung disease	• Have asthma	• Have arthritis
• Have osteoporosis	• Have cancer	• Have a stomach or duodenal ulcer
• Have cataracts	• Had a hip or femoral fracture	• Had other fracture
• Have pain in any joint	• Breathlessness	• Have a persistent cough
• Have stomach or intestinal problems	• Wear glasses	• Have poor hearing
• Wear dentures	• Difficulty with biting on hard foods	• Difficulty sitting for about 2 hours
• Difficulty picking up a small coin from a table	• Difficulty stooping, kneeling, or crouching	• Difficulty reaching or extending arm above shoulder level
• Difficulty climbing one flight of stairs without rest	• Difficulty climbing several stairs without rest	• Difficulty pulling or pushing large object
• Difficulty lifting or carrying weight over 10 lbs	• Difficulty getting up from a chair after prolonged sitting	• Difficulty dressing (or putting on shoes and socks)
• Difficulty walking across a room	• Difficulty walking 100 m	• Difficulty bathing or showering
• Difficulty eating or cutting food	• Difficulty getting in or out of bed	• Difficulty using the toilet
• Difficulty using a map	• Difficulty preparing a hot meal	• Difficulty shopping for groceries
• Difficulty making a phone call	• Difficulty taking medication(s)	• Difficulty doing housework
• Difficulty managing money	• Pessimism	• Suicidal
• Feelings of guilt	• Poor appetite	

spouse/partner, of an AD or dementia diagnosis (i.e., yes or no), (3) and survival (i.e., died or survived) at follow-up. The major outcome of a diagnosis of AD or dementia (i.e., 0 = absent, 1 = present), was determined by the following question in SHARE's Wave 4 and 5 questionnaires, "Has a doctor ever told you that you had/Do you currently have any of the conditions on this card? With this we mean that a doctor has told you that you have this condition, and that you are either currently being treated for or bothered by this condition." The primary option of interest was "Alzheimer's disease, dementia, organic brain syndrome, senility or any other serious memory impairment". This health measure was reported by the participants themselves and/or by a proxy respondent (e.g., spouse/partner). Survival was reported by relatives, friends, or neighbors (i.e., died; 0 = no, 1 = yes) after an average of 4.3 and 6.2 years.

4.3.4 Statistical analysis

Independent samples t-tests were used to examine differences in baseline demographics in relation to: (1) the presence of cognitive impairment, (2) reports of AD or dementia, and (3) mortality, at each follow-up (reported as Mean \pm SD). Binary logistic regression was used to estimate the odds ratio and 95% confidence intervals (CI) of each sleep variable individually as well as jointly as an index of sleep disruption (SDI), in relation to cognitive impairment, reported diagnosis of AD and dementia. Cox proportional hazards regression modeling was used to assess prediction of mortality. Risk models were adjusted for age, sex, education, and body mass index (BMI) in participants deemed cognitively intact at baseline (i.e., Wave 2; < 2 cognitive deficits). Backward stepwise binary logistic regression explored models of best fit for each outcome. SPSS

(18.0.0, SPSS Inc.) was used to analyze the data. Statistical significance level was set at $p = 0.05$.

4.4 Results

4.4.1 Baseline Demographics and Clinical Characteristics

At baseline, our sample had a mean age of 62.2 years (range 50-104), and women constituted just over half (56.2%) of these individuals. The majority of those sampled had attained a maximal level of upper secondary education (70.9%; e.g., high school). Of those remaining, 3.7% reported the completion of some post-secondary non-tertiary education (e.g., college), ~25% reported the completion of a Baccalaureate or Master's degree, and 0.6% reported the attainment of an advanced research qualification (e.g., PhD). Average BMI was in the lower end of the 'overweight' range (Table 4.2).

Those who exhibited cognitive impairment at either follow-up time point were older, had less education, and exhibited a higher BMI, FI, and SDI at baseline. People who reported the presence of AD or dementia at either time point, were more likely to be older, and have a higher SDI and FI at baseline, compared to those who did not. Similarly, those who did not survive to either time point were older, had less education, and also exhibited greater frailty at baseline. More sleep disturbance was apparent in participants who did not survive to ~4 years (Tables 4.2-4.3).

4.4.2 Risk Models 1-4: Each Sleep Factor

After controlling for the effects of age, sex, education, BMI, and cognition, only 'being bothered by fatigue during the past six months', independently predicted cognitive

impairment within ~4 years. It remained a significant predictor at ~6 years, and ‘taking medication for sleeping problems’ was also a significant predictor at that time (Table 4.4). Items ‘being bothered by fatigue during the past six months’ and ‘recent trouble sleeping or a change in pattern’, were predictive of reported dementia at ~4 years, while all items but ‘being bothered by fatigue during the past six months’, were predictive at ~6 years (Table 4.5). Items ‘being bothered by fatigue during the past six months’, as well as ‘taking medication for sleeping problems’, predicted mortality at ~4 years; however, none of the individual sleep items predicted mortality at ~6 years (Table 4.6).

4.4.3 Risk Model 5: Only the SDI

After taking into account age, sex, education, and BMI, the combined SDI was a statistically significant predictor of cognitive impairment and reported AD or dementia at both follow-up time points. The SDI was an indicator of mortality risk only at ~4 years (Tables 4.4-4.6).

4.4.4 Risk Model 6: Only the FI

Controlling for age, sex, education, and BMI, the FI was a significant predictor of cognitive impairment, reported AD or dementia, and mortality, in all risk models at both time points (Tables 4.4-4.6).

4.4.5 Risk Models 7-10: Each Sleep Factor and the FI

After controlling for age, sex, education, BMI, and the FI, only ‘being bothered by fatigue during the past six months’ and ‘taking medication for sleeping problems’

were associated with an increased risk of cognitive impairment, at ~6 years. Items ‘taking medication for sleeping problems’ and ‘recent trouble sleeping or a change in pattern’, were associated with an increased risk of reported dementia only at ~6 years. None of the sleep factors were significant predictors of mortality in models including the FI at either time point; the FI was a significant predictor at both time points in all models (Tables 4.4-4.6).

4.4.6 Risk Model 11: The SDI and FI

When controlling for age, sex, education, BMI, and the FI, the SDI was not significantly associated with cognitive impairment at either time point, but it did predict an increased likelihood of reported AD or dementia; there were no significant interactions between the SDI and FI in these models. The SDI was associated with a decreased risk of mortality at ~6 years (Tables 4.4-4.6). Adding the SDI and FI interaction as a covariate to the model failed to reveal a significant interaction, but resulted in the SDI no longer being a significant predictor of mortality risk. The SDI and FI were moderately correlated ($r = 0.40$), however there was no evidence of multicollinearity amongst the variables. All of the models of best fit retained the FI, except for reported AD or dementia at ~6 years, which retained only age and the SDI. Despite inclusion of the SDI and FI interaction covariate, the SDI remained a significant predictor in the model of best fit for mortality at ~6 years (Table 4.7).

Table 4.2 Demographic and clinical characteristics of people who did or not did not exhibit cognitive impairment, reported AD or dementia or survive, after an average of 4.3 years.*

	Outcome after ~4 years						
	Baseline (n = 17,023)	No Cognitive Impairment (n = 8,916)	Cognitive Impairment (n = 1,954)	Reported the absence of AD or dementia (n = 10,909)	Reported the presence of AD or dementia (n = 64)	Survived at follow-up (n = 11,001)	Did not survive at follow-up (n = 432)
Age (Mean ± SD)	62.23 (8.49)	61.14 (7.68)	66.80 (8.80)	62.13 (8.17)	71.52 (9.14)	62.18 (8.21)	70.11 (9.68)
% women	56.2	58.3	51.4	57.0	53.1	56.9	46.5
Education (ISCED code; Mean ± SD)	3.01 (1.41)	3.21 (1.39)	2.34 (1.34)	3.05 (1.43)	2.73 (1.29)	3.05 (1.43)	2.67 (1.43)
Body mass index (Mean ± SD)	26.35 (4.38)	26.30 (4.29)	26.78 (4.54)	26.38 (4.33)	26.82 (5.63)	26.38 (4.34)	26.38 (4.97)
Sleep disturbance index (Mean ± SD)	0.71 (1.05)	0.70 (1.04)	0.77 (1.09)	0.71 (1.05)	1.13 (1.25)	0.71 (1.05)	0.94 (1.19)
Frailty index, raw (Mean ± SD)	0.12 (0.08)	0.12 (0.08)	0.15 (0.09)	0.12 (0.08)	0.19 (0.11)	0.12 (0.08)	0.20 (0.12)
% Fatigue past 6 months	15.1	14.5	17.0	14.9	28.1	15.0	21.8
% Sleep complaints past 6 months	19.1	18.9	19.4	19.1	28.1	19.1	23.4
% Medication for sleep problems	6.7	6.2	8.6	6.6	12.5	6.7	13.9
% Trouble sleeping/change in pattern	30.3	30	31.7	30.3	43.8	30.4	35.4

*Data are based on people who participated in all three waves of data collection (i.e., Waves 2, 4, and 5).

Table 4.3 Demographic and clinical characteristics of people who did or not did not exhibit cognitive impairment, reported AD or dementia or survive, after an average of 6.2 years.

	No Cognitive Impairment (n = 8,057)	Cognitive Impairment (n = 1,863)	Reported the absence of AD or dementia (n = 9,936)	Reported the presence of AD or dementia (n = 83)	Survived at follow-up (n = 10,034)	Did not survive at follow-up (n = 325)
Age (Mean \pm SD)	60.78 (7.47)	66.21 (8.68)	61.78 (7.98)	69.84 (9.55)	61.85 (8.03)	70.86 (9.72)
% women	58.6	53.5	57.4	61.4	57.5	42.8
Education (ISCED code; Mean \pm SD)	3.25 (1.40)	2.36 (1.37)	3.08 (1.43)	2.82 (1.56)	3.08 (1.43)	2.73 (1.42)
Body mass index (Mean \pm SD)	26.29 (4.36)	26.79 (4.27)	26.39 (4.34)	25.77 (4.50)	26.38 (4.34)	25.91 (4.42)
Sleep disturbance index (Mean \pm SD)	0.68 (1.03)	0.79 (1.12)	0.70 (1.04)	1.17 (1.35)	0.70 (1.05)	0.75 (1.13)
Frailty index, raw (Mean \pm SD)	0.11 (0.74)	0.14 (0.09)	0.12 (0.08)	0.17 (0.11)	0.12 (0.08)	0.18 (0.11)
% Fatigue past 6 months	13.9	17.2	14.5	20.5	14.5	17.5
% Sleep complaints past 6 months	18.6	20.3	18.8	32.5	18.9	18.5
% Medication for sleep problems	5.7	9.6	6.4	19.3	6.5	11.4
% Trouble sleeping/change in pattern	29.8	31.5	30.0	44.6	30.1	27.4

Table 4.4 Risk model comparison for cognitive impairment after an average of 4.3 and 6.2 years (age, sex, education, and body mass index adjusted multivariate models).

Covariates	4.3 years (n = 1,954)			6.2 years (n = 1,863)		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Model 1						
Fatigue past 6 months	1.29	1.12-1.50	< 0.01	1.42	1.22-1.65	< 0.001
Model 2						
Sleep complaints past 6 months	1.03	0.90-1.18	0.63	1.10	0.95-1.26	0.19
Model 3						
Medication for sleep problems	1.17	0.96-1.42	0.13	1.47	1.20-1.80	< 0.001
Model 4						
Trouble sleeping/change in pattern	1.12	0.99-1.25	0.06	1.09	0.97-1.23	0.16
Model 5						
Sleep Disturbance Index	1.06	1.02-1.12	0.01	1.10	1.04-1.16	< 0.001
Model 6						
Frailty Index*	1.17	1.10-1.25	< 0.001	1.23	1.15-1.32	< 0.001
Model 7						
Fatigue past 6 months	1.16	0.99-1.35	0.07	1.23	1.05-1.45	0.01
Frailty Index	1.15	1.07-1.23	< 0.001	1.20	1.11-1.29	< 0.001
Model 8						
Sleep complaints past 6 months	0.94	0.81-1.08	0.35	0.97	0.84-1.12	0.69
Frailty Index	1.18	1.10-1.27	< 0.001	1.24	1.16-1.33	< 0.001
Model 9						
Medication for sleep problems	1.06	0.86-1.29	0.61	1.29	1.05-1.59	0.02
Frailty Index	1.17	1.09-1.25	< 0.001	1.21	1.13-1.30	< 0.001
Model 10						
Trouble sleeping/change in pattern	1.04	0.92-1.17	0.56	0.99	0.87-1.19	0.83
Frailty Index	1.17	1.09-1.25	< 0.001	1.24	1.15-1.33	< 0.001
Model 11						
Sleep Disturbance Index	1.09	0.96-1.08	0.53	1.04	0.98-1.10	0.21
Frailty Index	1.16	1.08-1.25	< 0.001	1.21	1.13-1.30	< 0.001

* Odds ratios for each increment: 0-0.02, 0.02-0.1, 0.1-0.2, 0.2-0.3, and >0.3.

Table 4.5 Risk model comparison for reported AD or dementia diagnosis after an average of 4.3 and 6.2 years (age, sex, education, and body mass index adjusted multivariate models).

Covariates	4.3 years (n = 63)			6.2 years (n = 80)		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Model 1						
Fatigue past 6 months	2.24	1.28-3.93	< 0.01	1.49	0.85-2.61	0.16
Model 2						
Sleep complaints past 6 months	1.68	0.96-2.94	0.07	1.98	1.22-3.21	< 0.01
Model 3						
Medication for sleep problems	1.47	0.69-3.17	0.32	2.36	1.31-4.26	< 0.01
Model 4						
Trouble sleeping/change in pattern	1.92	1.15-3.19	0.01	1.87	1.19-2.95	< 0.01
Model 5						
Sleep Disturbance Index	1.35	1.11-1.65	< 0.01	1.36	1.14-1.63	< 0.01
Model 6						
Frailty Index*	1.82	1.38-2.39	< 0.001	1.48	1.15-1.91	< 0.01
Model 7						
Fatigue past 6 months	1.46	0.79-2.71	0.23	1.10	0.60-2.01	0.77
Frailty Index	1.69	1.26-2.28	< 0.01	1.46	1.11-1.92	< 0.01
Model 8						
Sleep complaints past 6 months	1.19	0.66-2.15	0.56	1.66	0.99-2.76	0.053
Frailty Index	1.77	1.32-2.36	< 0.001	1.37	1.05-1.79	0.02
Model 9						
Sleep medication for sleep problems	1.00	0.46-2.21	0.99	1.90	1.03-3.53	0.04
Frailty Index	1.82	1.37-2.41	< 0.001	1.38	1.06-1.80	0.02
Model 10						
Trouble sleeping/change in pattern	1.49	0.88-2.53	0.14	1.61	1.01-2.58	0.047
Frailty Index	1.72	1.29-2.29	< 0.001	1.38	1.05-1.80	0.02
Model 11						
Sleep Disturbance Index	1.15	0.92-1.44	0.21	1.26	1.04-1.54	0.02
Frailty Index	1.68	1.24-2.27	< 0.01	1.29	0.97-1.71	0.08

* Odds ratios for each increment: 0-0.02, 0.02-0.1, 0.1-0.2, 0.2-0.3, and >0.3

Table 4.6 Risk model comparison for mortality after an average of 4.3 and 6.2 years (age, sex, education, and body mass index adjusted Cox proportional hazards models).

Covariates	4.3 years (n = 432)			6.2 years (n = 325)		
	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Model 1						
Fatigue past 6 months	1.45	1.04-2.03	0.03	1.26	0.94-1.70	0.13
Model 2						
Sleep complaints past 6 months	1.08	0.78-1.48	0.65	1.00	0.74-1.33	0.98
Model 3						
Medication for sleep problems	1.71	1.17-2.50	< 0.01	1.09	0.76-1.57	0.64
Model 4						
Trouble sleeping/change in pattern	1.17	0.89-1.53	0.27	0.96	0.75-1.24	0.75
Model 5						
Sleep Disturbance Index	1.13	1.01-1.27	0.04	1.03	0.93-1.14	0.62
Model 6						
Frailty Index*	1.62	1.40-1.87	< 0.001	1.57	1.39-1.79	< 0.001
Model 7						
Fatigue past 6 months	0.99	0.69-1.41	0.95	0.81	0.58-1.12	0.20
Frailty Index	1.62	1.39-1.90	< 0.001	1.63	1.42-1.88	< 0.001
Model 8						
Sleep complaints past 6 months	0.82	0.59-1.14	0.24	0.75	0.55-1.01	0.06
Frailty Index	1.66	1.43-1.93	< 0.001	1.63	1.43-1.86	< 0.001
Model 9						
Sleep medication for sleep problems	1.24	0.84-1.84	0.29	0.71	0.49-1.04	0.08
Frailty Index	1.59	1.37-1.85	< 0.001	1.64	1.44-1.88	< 0.001
Model 10						
Trouble sleeping/change in pattern	0.93	0.70-1.24	0.63	0.78	0.60-1.01	0.06
Frailty Index	1.64	1.41-1.90	< 0.001	1.62	1.43-1.85	< 0.001
Model 11						
Sleep Disturbance Index	0.98	0.87-1.10	0.71	0.87	0.77-0.97	0.01
Frailty Index	1.64	1.40-1.92	< 0.001	1.70	1.48-1.95	< 0.001

* Odds ratios for each increment: 0-0.02, 0.02-0.1, 0.1-0.2, 0.2-0.3, and >0.3

Table 4.7 Models of best fit for risk model 11, using backward stepwise (conditional) binary logistic regression, for the outcomes of cognitive impairment, dementia, and mortality, at an average of 4.3 and 6.2 years.

Final Step	Variables	OR	Wald	95% CI	<i>p</i>	χ^2
Cognitive Impairment at 4.3 years						
Step 3	Age	1.07	461.43	1.07-1.08	< 0.001	7.57
	Sex	0.62	74.49	0.56-0.69	< 0.001	
	Education	0.66	401.85	0.66-0.69	< 0.001	
	Frailty Index	1.18	26.38	1.11-1.26	< 0.01	
Cognitive Impairment at 6.2 years						
Step 3	Age	1.07	411.22	1.07-1.08	< 0.001	10.26
	Sex	0.66	54.37	0.59-0.73	< 0.001	
	Education	0.66	379.97	0.64-0.69	< 0.001	
	Frailty Index	1.24	40.40	1.16-1.33	< 0.001	
Dementia at 4.3 years						
Step 5	Age	1.11	46.52	1.07-1.14	< 0.01	5.04
	Frailty Index	1.76	18.01	1.36-2.28	< 0.001	
Dementia at 6.2 years						
Step 5	Age	1.12	74.04	1.09-1.15	< 0.001	6.01
	SDI*	1.36	12.02	1.14-1.62	< 0.01	
Mortality at 4.3 years						
Step 4	Age	1.08	93.43	1.06-1.09	< 0.001	218.42
	Sex	0.57	17.84	0.43-0.74	< 0.001	
	Frailty Index	1.64	47.70	1.43-1.89	< 0.001	
Mortality at 6.2 years						
Step 2	Age	1.08	126.58	1.06-1.09	< 0.001	335.72
	Sex	0.44	48.38	0.35-0.55	< 0.001	
	BMI	0.97	4.34	0.94-1.00	0.04	
	SDI*	0.87	6.19	0.78-0.97	0.01	
	Frailty Index	1.71	58.75	1.49-1.96	< 0.001	

*Sleep Disturbance Index

4.5 Discussion

The present analyses are in keeping with our previous work (Sterniczuk et al., 2013), which showed that individual indicators of disturbed sleep in cognitively healthy individuals are associated with an increased risk of cognitive impairment, reported AD or dementia, and mortality. The combination of sleep-related factors also predicted risk of these negative health outcomes. However, a decreased risk of mortality was surprisingly evident at ~6 years, when overall health status (i.e., the FI) was taken into account. Furthermore, while the FI predicted increased risk of all three outcomes (except for reported AD or dementia at ~6 years), the inclusion of frailty within the regression models caused the SDI to no longer be a significant predictor.

Sleep items related to fatigue and sleep medication were most predictive of future cognitive impairment at ~6 years, even after taking into account overall health status. The relationship between fatigue and medication use is unclear in the present study because of a lack of adequate definition of these variables (e.g., how did participants interpret ‘fatigue’; what type of sleep medication did participants use and was fatigue a possible side effect?). Sleep disturbance and fatigue are often symptoms of other health conditions (Ancoli-Israel et al., 2008), so reports of ‘fatigue’ may reflect a primary symptom of another health problem or a secondary symptom of its pharmacological treatment.

The possibility that pharmacological treatments contributed to some of the reported sleep-related symptoms measured in this study is increased by the common use of polypharmacy in this age group, related to the increased likelihood of medical and psychiatric conditions (Robles Bayon & Gude Sampedro, 2014; Maher et al, 2014). Sedative-hypnotics, antidepressants, and antihistamines are commonly prescribed for

insomnia in older adults (McCall, 2004), and are especially concerning because of their impact on cognition (Gray et al., 1999). Risk of cognitive impairment is particularly greater in those who are frail and at high risk of cognitive decline (Robles Bayon & Gude Sampedro, 2014; Gray et al., 1999; Madhusoodanan & Bogunovic, 2004). Physiological and pharmacokinetic differences may make older adults more susceptible to drug-induced adverse events, so special care should be taken when addressing sleep-related concerns in this population.

All of the sleep items were predictive of reported AD or dementia, at one or both time points. In particular, the use of sleep medication and reports of trouble sleeping or a change in sleeping pattern predicted dementia risk at ~6 years, even when overall health status was taken into account. Notably, the FI was a better predictor of AD/dementia at ~4 years in a model with the SDI, which itself was not significant, while the SDI was a better predictor at ~6 years in a model with the FI, which in that case was itself also not significant. This finding is consistent with our earlier report, which only explored outcomes in this cohort at ~4 years (Sterniczuk et al., 2013). These findings suggest that sleep disturbances appear at an early stage of AD/dementia progression and may indicate developing disease in cognitively healthy people (Almondes et al., 2016; Diem et al., 2016; Ortiz-Tudela et al., 2014; Tranah et al., 2011; Tsapanou et al., 2015). These results also suggest that routine clinical questioning about these sleep-related changes (i.e., new onset of fatigue, use of sleep medication, change in sleeping patterns) might provide valuable information about the risk of future cognitive decline in otherwise cognitively intact individuals.

As would be expected (Sterniczuk et al., 2013), the FI, which is based on a deficit accumulation model of aging, was the best indicator of mortality risk (Rockwood & Mitnitski, 2007; Theou et al., 2013b). Unexpectedly, risk modeling showed that the SDI was associated with a *decreased* risk of mortality at ~6 years, when frailty was included in the model. Further examination of this finding however, failed to reveal a significant interaction between the SDI and FI, but resulted in the SDI no longer being a significant predictor; in keeping with our previous report (Rockwood et al., 2001). However, a positive relationship between sleep disturbance and frailty, in relation to mortality risk, was observed. There is extensive epidemiological evidence that both habitual short- and long-sleepers are at elevated risk for a variety of health problems (Badran et al., 2015; Gallicchio & Kalesan, 2009; Shan et al., 2015), as well as all-cause mortality (Cappuccio et al., 2010; Kripke et al., 2011). In one analysis, the increased risks were evident for long-sleepers who were also sedentary, but not for those who were more active, while there was increased risk for short-sleepers regardless of activity level (Bellavia et al., 2013). The observation of reduced mortality risk in those reporting disrupted sleep is unusual and warrants further exploration. Unfortunately, we were limited as to the information available about the sleep variables and about factors such as activity and fitness levels. It is possible that more sensitive and specific measures of sleep disturbance, as well as other health-related factors, could produce a better fitting model to explain these findings.

Notably, we did not calculate an SDI at each successive wave of data collection, thus comparisons between waves and assumptions regarding the dynamics of this health measure in relation to frailty and the outcomes, should be explored in future analyses.

Despite this lack of interval data, taken together, these findings demonstrate that disturbed sleep is associated with adverse health outcomes. Analyses of the impact of sleep variables while accounting for levels of frailty demonstrate that sleep itself is a strong determinant of physical health (Badran et al., 2015; Cappuccio et al., 2010; Kripke et al., 2011; Gallicchio & Kalesa, 2009; Shan et al., 2015). Over longer time frames, other health problems, here captured by an FI, appear to become stronger predictors of adverse outcomes and outweigh the early predictive strength of sleep disturbance. This finding further suggests that changes to a person's sleep/wake cycle, may be an important early indicator of declining health, which becomes more apparent with increasing age.

One way to understand how sleep and circadian systems interact with age-associated cellular processes to cause negative outcomes such as cognitive decline and dementia, is to view each individually minor physiological insult as accumulating over time, to eventually produce detectable clinical deficits. These deficits then manifest as impaired functional capabilities of tissues and organs (e.g., neurodegenerative pathophysiology in the brain; Rockwood & Mitnitski, 2007). In this sense, cognitive impairment can be viewed as resulting from a state of increasing vulnerability due to the gradual increase in deficit damage and a decline of endogenous repair mechanisms (Searle & Rockwood, 2015; Taneja et al., 2016), even if these insults are not typically associated with dementia (Song et al., 2011). In the same way that various physiological system deficits accumulate to determine an individual's level of frailty (or vulnerability to adverse health outcomes), changes specifically to the sleep/wake regulatory system may also result from impairments to multiple mechanisms, which in turn contribute toward an organism's overall level of vulnerability. Furthermore, sleep disturbance is

associated with impaired healing and recovery (Adam & Oswald, 1984; Evans & French, 1995), which may in turn hinder repair processes and accelerate decline (Taneja et al., 2016). Here, disturbed sleep was a better predictor of dementia at an earlier time than overall health status, again suggesting that impairments to the sleep/wake system appear to indicate increasing vulnerability at an earlier stage than what might be captured by other health measures. Clinical interventions designed to improve sleep at the preclinical stage could potentially serve to diminish risk by aiding repair processes (Cardinali et al., 2012; Kang et al., 2009; Xie et al., 2013). That said, we cannot discount the impact of overall health in our risk models, indicating that a systems approach may be more useful in understanding the development of late-life incident dementia rather than searching for a single predictive variable.

There is increasing evidence that altered sleep and circadian rhythms precede and/or contribute to AD-related pathology (Kang et al., 2009; Platt et al., 2011; Sterniczuk et al., 2010) and risk of cognitive decline (Hita-Yañez et al., 2012; Tranah et al., 2011; Tsapanou et al., 2015), and that physiological markers of AD in turn perpetuate sleep disturbances (Roh et al., 2012). Even so, the pathophysiology of this reciprocal relationship is still poorly understood (Ju et al., 2014). Several physiological systems related to sleep have been reported to modulate the expression of AD pathogenesis (Šimić et al., 2016; Sterniczuk & Antle, 2015). Although discussion of these systems is beyond the scope of this paper, pathways include serotonin, norepinephrine, dopamine, orexin, histamine, acetylcholine, and even melatonin; all of which may interact with ongoing cellular damage (e.g., oxidative and metabolic stress, inflammation, impaired calcium signaling, etc.) to produce AD-related pathophysiological changes and

subsequently disturbed sleep/wake patterns. In addition, the circadian clock plays a key role in regulating neuroprotective factors that may defend against these insults, and impaired circadian functioning appears to exacerbate downstream neurodegenerative processes (for review see Musiek et al., 2015).

One of the greatest limitations of our previous analyses (Sterniczuk et al., 2013) was the uncertainty surrounding cognitive health at baseline. Since then, we have attempted to characterize the relationship between cognition, function, and health outcomes in this population (Sterniczuk et al., 2015). Even so, the SHARE study notably lacks diagnostic information related to dementia (e.g., neuroimaging, biomarkers, neuropsychological assessment), and rather collects data directly from participants and/or their proxies. In addition, the line of questioning upon interview did not differentiate between the dementia types (or at least was not recorded), and so we are cautious to not make estimates regarding prevalence but rather focus on describing associations regarding incident dementia in general. Despite these challenges, our attempt to control for cognitive status decreases the chances of misclassification bias, with 34% of participants demonstrating cognitive impairment at baseline but not reporting the presence of AD or dementia; reflecting the underestimation of dementia prevalence that is common in self-reported data (Frank et al., 2011; Thomas et al., 2001).

With advances in medical care, our population is aging at an accelerated rate. However, as more people survive from previously fatal illnesses, there is increasing prevalence of those requiring the long-term management of ongoing disability, including impaired cognition and the debilitating effects of dementia. These age-related conditions in turn require appropriate care and intervention. Long-term outcome studies are still

required to assess whether targeting specific aspects of a disrupted sleep/wake cycle can prevent pathophysiological transitions to dementia. Ideally these interventions would occur at the preclinical (cognitively intact) stage, with changes to one's sleep serving as a readily quantifiable biomarker of disease; how early this needs to occur in disease progression remains to be determined. Given the nature of the problem, such explorations require time and significant resources. However, the potential to even delay the onset of AD by several years has tremendous implications for world health economics, and some would argue even more importantly, on relieving caregiver burden.

4.6 Conclusions

Our current work adds to the growing body of literature demonstrating that there is an important dynamic relationship between sleep disturbance, overall health status, and risk of adverse health outcomes, including cognitive impairment, dementia (Almondes et al., 2016; Porter et al., 2015), and mortality (Cappuccio et al., 2010; Kripke et al., 2011). One way to interpret these findings is to view sleep disturbance as contributing towards the accumulation of physiological insults that over time increase vulnerability to the development of health deficits. In this sense, adequate sleep may be required to aid in repair and recovery mechanisms that prevent the accumulation of negative pathophysiological changes related to cognitive decline and incident dementia.

4.7 SUMMARY OF CHAPTER 4 AND TRANSITION TO CHAPTER 5

Chapter 4 was designed to replicate findings from Chapter 3 over a longer time period; only those who participated in all three waves of data collection were used in the analyses. Findings demonstrated that sleep disturbance is a predictor of cognitive decline in cognitively health people, while the combination of sleep disturbance items is a better indicator of risk for AD/dementia when overall health status is taken into account; this is particularly true at a longer latency to reported diagnosis (i.e., at ~6 years). In addition, disturbed sleep was associated with a decreased likelihood of mortality after overall health status was taken into consideration, again at ~6 years follow-up.

Despite efforts to better control for cognitive status at baseline, the limited cognitive testing that was conducted within SHARE, and the lack of diagnostic examination to determine the presence and type of dementia, may have impacted the findings. Given the absence of these critical pieces of information, the following study was conducted using data from a different epidemiological study in an attempt to better address these issues.

The purpose of this study was to evaluate the findings reported in Chapters 3 and 4 using a different multi-national cohort, the Honolulu-Asia Aging Study (HAAS). The predictive value of the SDI and FI for the risk of cognitive impairment, AD/dementia diagnosis, and mortality was explored, while controlling for cognitive status at baseline. Extensive cognitive and neurological assessments were conducted using this cohort for over a decade, which provided detailed cognitive performance information, and permitted improved diagnostic confidence based on consensus panel dementia ratings.

CHAPTER 5

Sleep Disturbance is Associated with Incident Dementia in Cognitively Healthy

Older Adults

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5.1 Abstract

The present study examined the relationship between sleep disturbance and overall health status, as measured by a frailty index (FI), in predicting cognitive impairment, dementia diagnosis and mortality. Secondary analyses were conducted on cognitively healthy older males who participated in the Honolulu-Asia Aging Study (i.e., examination 4 at baseline; N = 3,852). A 10-item 'sleep disturbance index' consisting of factors related to nighttime insomnia and daytime sleepiness, was compared to a 59-item FI. Only those individuals who scored 80 points or greater on the Cognitive Abilities Screening Instrument (CASI) and did not have a diagnosis of dementia (as determined by a consensus panel) were chosen at baseline. Controlling for age, education, body mass index, and FI, the 'sleep disturbance index' was significantly predictive of incident dementia (n = 62), after an average of 2.9 years. Individual items 'waking up several times at night' and 'sleepy most of the day', increased risk of dementia diagnosis by 3 ~2.5 times, each, in risk models that included the FI; however the FI was not a significant predictor in our dementia risk models. Increasing FI was associated with mortality risk up to 10.5 years, as was greater daily sleep duration (i.e., not waking up early or at night, sleeping more than 8 hours, taking regular naps), but to a shorter latency of ~3 years. Sleep disturbance appears to be an important risk factor in the preclinical stage of incident dementia (i.e., prior to the manifestation of cognitive decline), and can strongly impact an individual's overall health status. Sleep-related questioning should be of particular importance when screening those at risk for dementia and assessing the health of older adults.

5.2 Introduction

Although commonly associated with memory loss and impaired functional ability (McKhann et al., 2011), an increasingly reported feature of Alzheimer's disease (AD) is a disruption to sleep and abnormal daily sleep-wake cycles (Ju et al., 2013; Lim et al., 2014; Paavilainen et al., 2005; Weldemichael and Grossberg, 2010; Witting et al., 1990). Sleep complaints in this population primarily include insomnia, sleep fragmentation, and excessive daytime sleepiness, which are an exaggeration and acceleration of the changes observed in healthy aging. There is accumulating evidence suggesting that sleep disturbance in healthy older adults may be related to the progression of dementia (Tranah et al., 2011; Sterniczuk et al., 2013; Yaffe, Nettiksimmons, Yesavage, & Byers, 2015). Not only is increased daytime sleepiness strongly associated with subjective memory impairment and risk for dementia in healthy older adults (Okamura et al., 2015; Tsapanou et al., 2015a,b), but it is also linked to a greater decline in mental abilities (Bonanni et al., 2005). Poor sleep quality is even linked to increased cortical atrophy in healthy community-dwelling individuals (Sexton, Storsve, Walhovd, Johansen-Berg, & Fjell, 2014).

The mechanisms behind these observations are poorly understood, but one theory is that sleep acts by increasing the space between neurons, resulting in the faster removal of beta-amyloid from the brain, a key neuropathological feature of the disease (Xie et al., 2013). Conversely, sleep loss appears to facilitate beta-amyloid deposition, which may contribute to the more rapid development of AD (Kang et al., 2009). This increase in beta-amyloid has in turn been shown to disrupt sleep/wake cycles (Roh et al., 2012). These findings suggest a strong reciprocal relationship between sleep disturbance and

AD-related neuropathology, as well as cognitive decline (Guarnieri & Sorbi, 2015) and may be linked to deterioration of the circadian clock or other sleep-regulatory brain regions (Sterniczuk et al., 2010; Sterniczuk, Lahsae, Brown, Rockwood, & Rusak, in prep; Wu & Swaab, 2007). However, the existence of a causal relationship between the two is still unclear, as is whether the early screening for sleep-related disruption could serve as a valid and reliable predictor of AD or other dementias and their progression.

Furthermore, risk factors for dementia have been widely reported and vary considerably between individuals (e.g., vascular, inflammation, neurotoxins, psychosocial stress etc.). However, in risk assessment, the impact of each factor is typically small, and may include health factors that are not traditionally associated with dementia or AD (e.g., wearing dentures, experiencing a fracture). There is a growing body of literature showing that when combined, these “deficits” serve as a measure of overall health status or an individual’s level of frailty (Mitnitski & Rockwood, 2015) and are associated with an increased risk for dementia (Katon et al., 2015; Song et al., 2011; Sterniczuk, Theou, Rusak, & Rockwood, in prep). This suggests that, rather than one specific cause, a combination of risk factors accumulate to the point at which repair processes are no longer capable of defending against dementia development (Rockwood, 1997). Most recently, a highly fragmented and unstable sleep wake pattern was linked to increased vascular disease and risk of mortality in older adults (Zuurbier et al., 2015a,b).

Previous analyses using data from the Honolulu-Asia Aging Study (HAAS) demonstrated that daytime sleepiness was strongly associated with the development of incident dementia among Japanese-Americans (Foley et al., 2001). However, the implication of deficit accumulation and the role of frailty in these observations is unclear.

We recently described frailty in relation to mortality in this population (Armstrong, Mitnitski, Launer, White, & Rockwood, 2014), which is in keeping with the well-characterized properties of the frailty index (FI) that are consistent across several studies of populations in developed countries (Mitnitski et al., 2005). As a follow-up to our findings which demonstrated an important role for sleep disturbance in the increased risk for incident dementia, when taking into account frailty (Sterniczuk et al., 2013), along with the observations of others (Foley et al., 2001), the present analyses sought to determine to the relationship between sleep disturbance, frailty and dementia risk (the latter diagnosed by a clinical consensus panel), in initially cognitively healthy HAAS cohort participants.

5.3 Methods

5.3.1 Study Population

Secondary analyses were conducted on data from the HAAS (N = 3,852), which is an extension of the Honolulu Heart Program (HHP), a longitudinal study of heart disease and stroke in Japanese-American men born between 1900 and 1919 who were living on the island of Oahu, Hawaii, in 1965 (88% born in Hawaii; 12% born in Japan; White et al., 1996). World War II service records were used to identify 12,417 possible men for eligibility. HAAS is an informal consortium of epidemiologic studies on dementia in the United States, Japan, and Taiwan. Beginning at the fourth examination (1991-1993; exam 4), participants were screened for dementia in addition to undergoing a standard clinical examination (3,852; 80% of the HHP survivors), and the resulting data served as the baseline for the present analyses. Follow-up examinations were conducted

roughly every 2-3 years: 1994-1996 (exam 5); 1997-1999 (exam 6); 1999-2000 (Exam 7); 2001-2003 (Exam 8); 2004-2005 (Exam 9); and 2008-2009 (Exam 10). To obtain the most cognitively healthy sample at baseline, primary analyses excluded: (1) participants with a Cognitive Abilities Screening Instrument (CASI) score of less than 80 ($n = 1,002$), and (2) participants who met the diagnosis of dementia as determined by a consensus panel at baseline ($n = 226$), leaving 2,725 participants for analysis (Figure 1). Approval for secondary analyses came from the Research Ethics Board of the Capital District [now Nova Scotia] Health Authority at Halifax, Nova Scotia, Canada.

5.3.2 Baseline Health Measures

5.3.2.1 Cognition

The CASI, a validated screening instrument for dementia in the United States and Japan, both in English and Japanese languages, served as a measure of cognitive status. The CASI is a 25-item composite of the Hasegawa Dementia Screening Scale (widely used in Japan), the Folstein Mini-Mental State Examination, and the Modified Mini-Mental State Test. It includes tasks assessing attention, concentration, judgment, orientation, abstraction, short- and long-term memory, language ability, word-list generation, and visual construction (Teng et al., 1994). The score range is 0 to 100. Complete details regarding the cognitive case screening methods for the HAAS and HPP are provided elsewhere (White et al., 1996). Briefly, the first wave of HAAS (exam 4) consisted of a 3-phase dementia-case finding protocol. In phase one, the CASI was used to stratify low scores (< 74) from intermediate (74-81.9) and high scorers (≥ 82). All low scorers along with a random sampling of the other groups were invited for the second

phase. Phase two included a second CASI evaluation, neurological exam, as well as hearing and vision testing. Informant interviews were also conducted using the Informant Questionnaire on Cognitive Decline in the Elderly. Participants with low CASI scores or significant cognitive change as deemed by their informant (scores >3.5), were invited for phase three, as was a random sample of the remaining sample. The third phase included a standard interview, neurological exam, and a neuropsychological assessment. Final diagnoses were established using DSM-III-R criteria, as determined by the study neurologist and at least two other physicians with expertise in geriatric medicine and dementia. Here, for exploratory purposes, cognition at baseline was further stratified according to dementia severity ratings (Meguro et al., 2004; Ross et al., 1997; cognitively healthy: $\text{CASI} \geq 80$, $n = 2,732$; mild cognitive impairment (MCI): $\text{CASI} \geq 74$ and < 80 , $n = 415$; cognitively impaired: $\text{CASI} < 74$, $n = 587$).

5.3.2.2 Frailty Index

As a measure of overall health status, the FI was constructed using a deficit accumulation approach, in which each deficit was selected according to a standard method (i.e., accumulate with age; associated with adverse health outcomes) and included any symptom, sign, disease, disability, or laboratory abnormality (Searle et al., 2008). Items related to sleep disturbance and cognition were excluded, resulting in 59 items (Table 5.1). Responses to each item were mapped into a 0-1 interval (e.g. 0, 0.25, 0.5, 0.75, 1), with “0” indicating the absence of that deficit and “1” indicating its presence. The maximum number of missing variables permitted for each participant was less than 20% of the total number of measures (< 11 items). Each participant’s FI score was

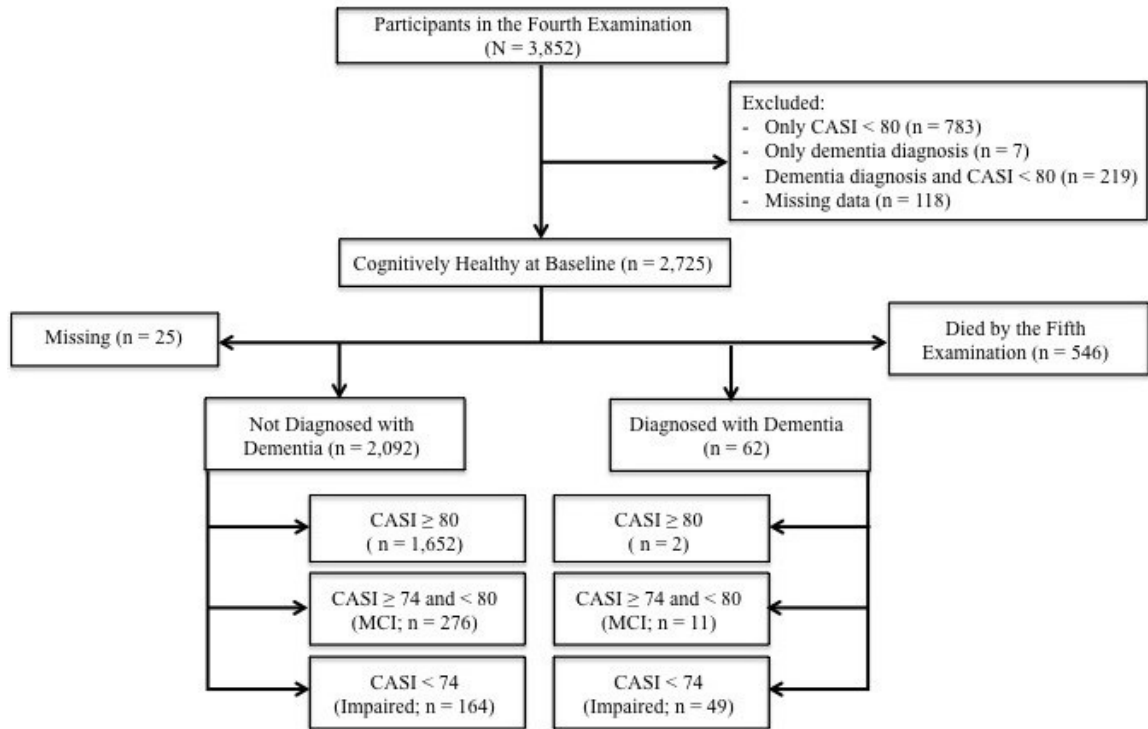


Figure 5.1 Participant flow diagram for cognitive impairment, dementia, and mortality outcomes, after an average of 2.9 years. CASI: Cognitive Abilities Screening Instrument; MCI: mild cognitive impairment.

Table 5.1 Constructs used to create the sleep disturbance and frailty indices.

List of measures used to construct the Sleep Disturbance Index		
• Sleep less than 7 hours	• Sleep more than 8 hours	• Restless sleep
• Wake up several times at night	• Wake up early and can't go back to sleep	• Usually have trouble falling asleep
• Take regular naps	• Sleep most of the day	• Groggy more than half an hour after waking
• Fatigue past 2 weeks		
List of measures used to construct the Frailty Index		
• Heart attack	• High blood pressure	• Hip fracture
• Spine fracture	• Forearm fracture	• Gout
• Gallstones or cholecystitis	• Hepatitis or cirrhosis of the liver	• Diverticulosis or diverticulitis
• Polyps of the large bowel	• Stomach or peptic ulcer	• Thyroid disease
• Prostate problems	• Kidney disease	• Bone disease
• Cancer (except skin)	• Cataract	• Heart disease
• Depression	• Parkinson's disease	• Arthritis
• Hearing problems	• Vision problems	• Impaired speech
• Stroke, cerebral hemorrhage, transient ischemic attack	• Balloon angioplasty	• Pain in wrist or hands
• Stomach resection	• Coronary bypass surgery	• Diabetes
• Pain or discomfort in chest	• Sudden weakness, paralysis of arm/leg	• Sudden tingling or loss or sensation in arm/leg
• Sudden blindness, blurred or double vision	• Bleed or bruise easily	• Sudden dizziness or loss of balance
• Swelling of your feet or ankles	• Phlebitis or varicose veins	• Congestive heart failure
• Angina	• Surgery of arteries of neck	• Surgery of aorta or arteries
• Gastrectomy of stomach	• Surgery on hands	• Unsafe to stand up without using arms
• Difficulty walking ½ mile	• Difficulty walking up 10 steps	• Unable to do heavy work
• Difficulty shopping	• Difficulty preparing own meal	• Difficulty using the phone
• Difficulty paying bills	• Difficulty eating	• Difficulty dressing
• Difficulty bathing	• Difficulty getting to toilet	• Difficulty lifting
• Difficulty reaching out	• Difficulty gripping with hands	

calculated by dividing the number of recorded deficits by 59 so that, for example, a person in whom 29 deficits were present would have an FI score of $29/59 = 0.49$. To simplify interpretation of the results, the FI was arbitrarily grouped into ten groups (0-0.02, 0.03-0.09, 0.1-0.14, 0.15-0.19, 0.20-0.24, 0.25-0.29, 0.30-0.34, 0.34-0.39, 0.4-0.44, and ≥ 0.45), as in our previous analyses (Sterniczuk et al., 2013).

5.3.2.3 Sleep Disturbance Index

Similar to the FI, a Sleep Disturbance Index (SDI) was created using 10 sleep-related variables found within the HAAS Examination 4 Module I form (Table 5.1). Sleep duration was grouped into 3 categories: ≤ 6 hours, 7-8 hours, and ≥ 9 hours. Participants were further coded into one of two groups: short sleepers (≤ 6 hours; '1') or long sleepers (≥ 9 hours; '1'). Those with 7-8 h sleep were coded as '0'. All other factors were coded as either '0' for the sleep problem being absent, or '1' for the sleep problem being present. The maximum number of missing variables permitted for each participant was less than 20% of the total number of measures (< 2 items). The index was calculated using the same procedure as for the FI. The SDI was also grouped into ten groups (0, 0.01-0.09, 0.1-0.19, 0.2-0.29, 0.3-0.39, 0.4-0.49, 0.5-0.59, 0.6-0.69, 0.7-0.79, 0.8-1) for incremental comparison with the FI.

5.3.3 Health Outcomes

There were three outcomes of interest: (1) mild cognitive impairment, (2) diagnosis of AD/dementia, and (3) mortality. As described, MCI was determined using CASI scores (i.e., ≥ 74 and < 80) and was compared to participants who remained

cognitively healthy (i.e., CASI \geq 80). Consensus diagnosis of dementia (i.e., coded as: 0 = absent, 1 = present) was made by the study neurologist and at least two other physicians with expertise in geriatrics and dementia, at Examinations 4 through 8, using the Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, revised criteria for dementia. Date of death was obtained for 90.9% of the sample (i.e., coded as: died; 0 = no, 1 = yes). Outcomes were examined after an average of 2.9 (Exam 5), 6 (Exam 6), and 10.5 (Exam 8) years.

5.3.4 Statistical Analysis

Independent samples t-tests were used to examine the differences in SDI and FI scores between those who exhibited MCI, were diagnosed with AD or dementia, or did not survive, at follow-up (reported as Mean \pm SD). Binary logistic regression was used to estimate the likelihood and 95% confidence intervals (CI) for each sleep variable individually as well as jointly as an index of sleep disruption, in relation to the cognitive impairment and diagnosis of AD and dementia. Cox proportional hazards regression modeling was used to assess prediction of mortality. Covariates: age, education, body mass index (BMI), and FI, were used to adjust the risk models for each sleep variable (models 1-10). Covariates: age, education, and BMI, adjusted risk analysis for the SDI (model 11), the FI (model 12), and a model with both the SDI and FI (model 13). Backward stepwise linear regression examined risk model parsimony, with chi square (χ^2) values having a $p > 0.05$ demonstrating a good fit of the model variables. SPSS (18.0.0, SPSS Inc.) was used to analyze the data. Statistical significance level was set at $p = 0.05$.

5.4 Results

5.4.1 Demographics and Clinical Characteristics

At baseline our sample had a mean age of 76.8 years (range 71-93) and had completed an average of 11.1 years of education. Average BMI fell within the higher end of the ‘normal’ range (23.6). Participants who met criteria for MCI at each follow-up were more likely to be older, have less education, and lower cognition, at baseline (Exam 4; Table 5.2). People with MCI at ~6 years also exhibited higher FI at baseline (Supplemental Table 5.1).

Participants who met the criteria for a diagnosis of dementia at follow-up were more likely to be older, have poorer cognition, and more sleep disturbance at baseline, compared to those who did not meet criteria for dementia after 2.9 (Table 5.2). However, they did not exhibit a higher FI than their dementia-free counterparts; nor were there differences in frailty or sleep disturbance at ~6 and 10.5 years (Supplemental Table 5.2). There were no differences in relation to frailty or sleep disturbance in people with MCI at baseline.

Participants who were less likely to survive at all follow-up time points, tended to be older, have fewer years of education, greater cognitive impairment, a higher BMI, and a higher FI. There was no difference in the number of SDI variables endorsed at baseline by those who did not survive (Table 5.2; Supplemental Table 5.1). People with MCI who died at follow-up were also more likely to higher frailty (Supplemental Table 5.2).

5.4.2 Risk Models 1-10: Individual Sleep Variables

In cognitively healthy participants at baseline, items ‘wake up several times at night’ and ‘sleepy most of the day’ each increased risk of dementia diagnosis by more than 2.5 times, within ~ 3 years, after controlling for the effects of age, education, BMI, and overall health status (Table 5.3). The most parsimonious model of dementia risk included: increasing age, and endorsement of items ‘wake up several times at night’ (Supplemental Table 5.3). None of the risk models were associated with dementia after an average of 6 and 10.5 years (Supplemental Table 5.4; 5.5).

Items ‘wake up several times at night’ and ‘wake up early and can’t go back to sleep’ were associated with a decreased risk of mortality at ~3 years, while sleeping more than 8 hours per night was associated with a 41% increased mortality risk (Table 5.3). The most parsimonious model of mortality risk included: increasing age, lower education, lower BMI, and increasing frailty, as well as decreased reports of ‘wake up several times at night’ and ‘wake up early and can’t go back to sleep’ (Table 5.3). Only the item ‘wake up early and can’t go back to sleep’ was associated with decreased mortality risk at 6 years (Supplemental Table 5.4).

None of the risk models were indicative of MCI at any time point. In those who were categorized as MCI at baseline, reporting to be ‘sleepy for most of the day’ or experiencing ‘fatigue during the past 2 weeks’ were associated with an increased risk for transitioning to dementia within 6 years Supplemental Table 5.5; 5.7). Reporting ‘trouble falling asleep’ decreased mortality risk at ~3 years (Supplemental Table 5.6), while sleeping more than 8 hours increased risk at ~6 years (Supplemental Table 5.7).

5.4.3 Risk Model 11: Only the SDI

Controlling for age, education, and BMI, each unit increase in the SDI was not associated with MCI at any time point, but it predicted a 20% increased risk of dementia diagnosis only after an average of 2.9 years, in cognitively healthy participants at baseline (Table 5.5). The SDI was not a significant predictor of mortality risk at any time point. Also, the SDI was not predictive of dementia or mortality in those categorized as having MCI at baseline.

5.4.4 Risk Model 12: Only the FI

In cognitively healthy people at baseline, FI predicted a decreased likelihood of MCI at ~6 years (Supplemental Table 5.3), but was not associated with dementia diagnosis. Each unit increase in the FI was associated with a 20% increased risk of mortality after ~3 (Table 5.3) and 6 years (Supplemental Table 5.4). The FI was associated with a 36% increased risk of mortality, in people categorized as having MCI at baseline (Supplemental Table 5.8).

5.4.5 Risk Model 13: SDI and FI Combined

When the FI was added to the SDI risk model for dementia diagnosis, the SDI remained a significant predictor and was associated with a 21% increased risk at ~3 years, independent of overall health status (Table 5.3). Conversely, the FI remained a significant predictor of mortality in a model with the SDI, and was associated with a 20% increased risk of death after ~3 and 6 years (Supplemental Table 5.4); the SDI was not associated with MCI or mortality risk in these models. At ~3 years, the best fitting model

Table 5.2

Baseline demographics and clinical characteristics (Mean \pm SD) of cognitively healthy versus mild cognitively impaired participants at baseline, and those cognitively healthy individuals who were or were not diagnosed with dementia, or did not survive, after an average of 2.9 years.

	Baseline		Follow-up Status of Cognitively Healthy People at Baseline					
	Cognitively Healthy (n = 2,725)	Mild Cognitive Impairment (n = 412)	Cognitively Healthy (n = 1,654)	Mild Cognitive Impairment (n = 287)	Not Diagnosed with Dementia (n = 2,092)	Diagnosed with Dementia (n = 62)	Survived (n = 2,154)	Died (n = 546)
Age	76.8 (3.8)	79.0 (4.8)	76.1 (3.5)	77.1 (3.7)	76.4 (3.6)	78.4 (4)	76.4 (3.7)	78.1 (4.3)
Education	11.1 (3.1)	9.3 (2.9)	11.6 (3)	9.8 (2.8)	11.2 (3.1)	10.7 (2.7)	11.2 (3.1)	10.6 (3.0)
CASI	89.3 (4.8)	77.1 (1.7)	88.7 (4.7)	77.3 (1.7)	89.7 (4.8)	86.3 (4.2)	84.8 (9.4)	87.9 (4.6)
BMI	23.6 (3.1)	23.8 (3)	23.8 (3)	24.0 (3.1)	23.8 (3)	23.0 (2.8)	23.8 (3.0)	23.0 (3.2)
FI	0.09 (0.06)	0.09 (0.06)	0.09 (0.06)	0.09 (0.06)	0.09 (0.06)	0.10 (0.07)	0.09 (0.06)	0.10 (0.07)
SDI	3.69 (1.6)	3.72 (1.5)	3.67 (1.57)	3.61 (1.61)	3.67 (1.6)	4.19 (1.9)	3.69 (1.58)	3.70 (1.5)

CASI: Cognitive Abilities Screening Instrument; BMI: Body Mass Index; FI: Frailty Index; SDI: Sleep Disturbance Index

Table 5.3

Risk model comparisons for those cognitively healthy individuals at baseline who met criteria for a diagnosis of dementia or who did not survive, after an average 2.9 years, while controlling for age, education, BMI, and frailty. *Model 11 did not contain the FI; SDI: Sleep Disturbance Index

	Cognitive Impairment (n = 287)			Dementia Diagnosis (n = 62)			Mortality (n = 546)		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Model 1: Sleep < 7 hours	0.98	0.74-1.29	0.86	0.88	0.51-1.54	0.66	0.94	0.76-1.16	0.55
Model 2: Sleep > 8 hours	1.31	0.81-2.11	0.27	1.16	0.45-2.96	0.76	1.41	1.00-1.98	0.05
Model 3: Restless sleep	0.97	0.58-1.62	0.91	0.98	0.36-2.63	0.65	0.94	0.64-1.38	0.74
Model 4: Wake up at night	0.77	0.45-1.31	0.33	2.74	1.38-5.44	< 0.01	0.48	0.29-0.78	< 0.01
Model 5: Wake up early	0.88	0.62-1.25	0.48	1.05	0.55-2.01	0.89	0.70	0.53-0.93	0.01
Model 6: Trouble falling asleep	1.05	0.74-1.49	0.78	1.39	0.75-2.59	0.29	0.82	0.62-1.07	0.15
Model 7: Taking regular naps	0.99	0.75-1.31	0.95	1.51	0.84-2.72	0.17	1.15	0.92-1.43	0.22
Model 8: Sleepy most of day	1.06	0.62-1.82	0.84	2.69	1.28-5.65	< 0.01	1.10	0.75-1.62	0.61
Model 9: Groggy after waking	1.34	0.65-2.70	0.44	1.25	0.30-5.28	0.76	1.13	0.66-1.95	0.65
Model 10: Fatigue past 2 weeks	1.02	0.63-1.67	0.93	1.67	0.74-3.78	0.22	1.08	0.76-1.52	0.68
Model 11: SDI (Models 1-10)*	0.98	0.90-1.07	0.59	1.20	1.03-1.40	0.03	1.01	0.94-1.07	0.89
Model 12: Frailty Index	1.02	0.90-1.16	0.71	1.02	1.02-1.41	0.89	1.22	1.12-1.32	< 0.001
Model 13: SDI	0.98	0.90-1.07	0.67	1.21	1.03-1.43	0.02	0.98	0.92-1.05	0.56
Frailty Index	0.96	0.84-1.10	0.57	0.94	0.72-1.24	0.68	1.20	1.20-1.32	< 0.001

for MCI was age and education, while age and the SDI were the best fit for dementia risk. The most parsimonious model for mortality risk at ~3 years included: age, lower education, lower BMI, and a higher FI (Table 5.9). In people categorized as MCI at baseline, the FI was associated with mortality risk at ~10.5 years (Supplemental Table 5.8).

5.5 Discussion

The current findings add to the growing evidence that sleep disturbance and daytime sleepiness are important associated features in developing dementia, appearing at presymptomatic stages of the developing illness (i.e., prior to the manifestation of cognitive impairment; Almondes et al., 2016; Diem et al., 2016; Sterniczuk et al., 2013; Tranah et al., 2011; Tsapanou et al., 2015a,b). In keeping with previous findings using HAAS data (Foley et al., 2001), the predictive value of sleep-related symptoms, particularly daytime sleepiness, is maintained even when traditional dementia risk factors and overall health status are controlled for. Nighttime sleep disturbance appears to be of particular importance, which is consistent with recent reports that the presence of highly fragmented and unstable sleep wake patterns increases the risk of vascular disease and cognitive impairment in older adults (Luik et al., 2015; Zuurbier et al., 2015a). A combination of sleep-related factors was found to be a better predictor of dementia risk than a combination of health deficits.

These findings are more robust than those in our initial study (Sterniczuk et al., 2013), likely due to a greater level of certainty with respect to cognitive status at baseline and follow-up, and thus greater sensitivity in categorizing participants (i.e., cognitively

healthy vs. MCI). Also in keeping with previous findings (Diem et al., 2016; Sterniczuk et al., 2013; Tranah et al., 2011; Tsapanou et al., 2015a,b), is that sleep-related symptoms were present with a relatively short latency prior to diagnosis (i.e., less than 5 years prior to dementia diagnosis). Interestingly, these relationships were found only in cognitively healthy individuals, suggesting that once someone manifests cognitive impairment, the impact of sleep disturbance is no longer as valuable in predicting further decline (i.e., transitioning from MCI to dementia). Nevertheless, those with cognitive impairment who exhibit excessive daytime sleepiness (and possibly those showing long sleep durations) may transition into dementia more rapidly.

Although increasing levels of frailty have been linked to risk of cognitive decline and dementia (Mitnitski et al., 2011; Song et al., 2011), current analyses did not find a relationship between these variables. Just over a quarter of non-frail individuals do not appear to deteriorate cognitively (Mitnitski et al. 2011). Thus, it is possible that the participants sampled here were ‘healthier’ or less frail to begin with, resulting in a decreased impact on cognitive performance. As expected, the FI was a strong indicator of mortality risk up to 10.5 years, and a better predictor for this outcome than most sleep-related factors or a combination of them. This was most apparent, however, in cognitively healthy individuals, suggesting that the accumulation of health-related deficits prior to cognitive decline is a critical marker of imminent decline in physical functioning. Those who exhibited an increased risk of mortality within the study time frame were also less likely to report early awakenings and night time sleep disruption, and more likely to take regular naps, which is consistent with the impact of longer sleep durations and greater total 24-hour sleep.

There has been some uncertainty surrounding the link between sleep duration and dementia risk. Some have indicated that long sleep duration (≥ 9 hours) is associated with increased risk of dementia and dementia-related mortality (Benito-León, Bermejo-Pareja, Vega, & Louis, 2009; Benito-León, Louis, Villarejo-Galende, Romero, & Bermejo-Pareja, 2014; Chen et al., 2015), as well as the severity of dementia (Fetveit and Bjorvatn, 2006), while others have reported that short sleepers (≤ 5 hours) are more likely to experience cognitive decline within 2 years (Tworoger, Lee, Schernhammer, & Grodstein, 2006). Still others report that both those who sleep less than and greater than 7 hours per night, are at a higher risk of poorer cognition (Gildner, Liebert, Kowal, Chatteriji, & Snodgrass, 2014). Sleep duration was not associated with dementia in the present analyses, which may be due to inconsistencies between diagnostic criteria and covariates used between studies.

Recent changes to the National Sleep Foundation sleep guidelines suggests that 7-8 hours of sleep is optimal for those 65 and older (Hirshkowitz et al., 2015; the “normal” range used in the current study), and chronic deviations outside of this norm are associated with a variety of health problems (Badran et al., 2015; Gallicchio & Kalesa, 2009; Shan et al., 2015), as well as all-cause mortality (Cappuccio et al., 2010). The characteristic U-shaped mortality risk ratios in relation to sleep duration have been noted to be larger when sleep duration is objectively measured (i.e., via actigraphy), rather than when self-reported (Kripke et al., 2011). Interestingly, data collected in such a manner suggests that optimal sleep duration in terms of survival is much shorter than subjective reports have us believe (i.e., 6.5 vs. 6.5-7.5 hours; Kripke et al., 2011). Furthermore, longer sleepers who are also sedentary appear to be at the greatest risk of death, while

increased mortality risk in short sleepers is present regardless of activity levels. These findings suggest an important interaction between sleep duration and physical activity that appears to play a role in mortality risk (Bellavia et al., 2013). This may explain why ‘taking regular naps’ was a predictor of mortality risk in the present analyses. In addition, long sleepers (≥ 9 hours) demonstrated a 41% increased risk of death within a relatively short time span (~ 3 years). However, the impact of physical activity on this finding was not explored. Such future analyses may serve to increase our understanding of the relationships between sleep, frailty, and negative health outcomes.

It is still unclear which physiological changes give rise to sleep symptoms that are also linked to a future diagnosis of dementia. One hypothesis is that changes in neural structures involved in circadian rhythm and sleep regulation, such as the suprachiasmatic nucleus (SCN; the principal circadian pacemaker) or raphe nuclei, underlie the sleep/wake symptoms that appear in dementia and AD (Šimić et al., 2009; Wu and Swaab, 2007). Disruption to any component of the circadian system may result in abnormal sleep patterns (Antle and Silver, 2005). There is some support for this idea from both rodent (Sterniczuk et al., 2010; Sterniczuk et al., in prep) and human studies (Liu et al., 2000; Zhou et al., 1995). For example, reductions in the number of cells in the SCN and in levels of melatonin have been observed in the preclinical stages of AD (Wu et al., 2003), even prior to the development of AD-related neuropathology (Sterniczuk et al., 2010). In addition, the degree of circadian disturbance (e.g., the level and timing of locomotor activity, body temperature) is associated with a variety of AD-related neuropathology (Harper et al., 2005). However, it remains to be elucidated whether sleep and circadian disturbance is a consequence of specific disease-related pathology or if

these disturbances, and/or related physiological abnormalities, contribute to or trigger neurodegenerative processes.

Despite validating and building upon our previous findings (Sterniczuk et al., 2013) with more reliable diagnostic information and a longer duration of follow-up, this study also has limitations. Although participants underwent neurological and neuropsychological consensus assessments, a definitive diagnosis of dementia is not possible until brain tissue is examined post-mortem in relation to clinical evaluations. Unfortunately, HAAS post-mortem neuroimaging and histochemical changes were unavailable to the authors at the time of these analyses. Thus, caution is warranted when interpreting the present findings because confirmation of neurodegenerative disease was not possible. Furthermore, it is unclear which disease-specific processes are associated with the present findings. As well, due to small sample sizes differences between AD and related conditions (i.e., Vascular Cognitive Impairment, Lewy body dementia) were not examined here.

Present findings further suggest that the assessment of sleep quality and quantity in cognitively healthy individuals may provide a simple screening tool for identifying preclinical dementia and AD. Regular clinical evaluation of sleep disorders in older individuals, with or without cognitive impairment, may provide valuable information regarding the risk of cognitive decline or the development of AD and other dementias. Recognizing which symptoms related to disrupted sleep/wake cycles are associated with AD (or other dementias) could help in producing earlier and more accurate diagnoses, as well as guide appropriate treatment interventions at the earliest possible stages.

CHAPTER 6 GENERAL DISCUSSION

6.1 Summary of Main Findings

Using two large multinational cohorts, namely SHARE and HAAS, this dissertation demonstrated several novel findings about the relationships between sleep disturbance, frailty, and risk of negative health outcomes, including cognitive impairment, a diagnosis of AD/dementia and mortality. First, although on its own the SDI was a significant predictor of cognitive impairment in cognitively healthy people, this was not the case when overall health status, or frailty, was taken into account. Similar findings were obtained when cognitive performance was examined using either brief screening measures (i.e., SHARE) or consensus- based diagnostic testing (i.e., HAAS). Furthermore, in models controlling for frailty, reported fatigue and the use of sleep medication, were the best indicators of cognitive impairment (only within the SHARE study), at an average of 6 years follow-up.

Second, disrupted nighttime sleep continuity (i.e., ‘trouble sleeping or change in pattern’; ‘waking up several times during the night’) and daytime sleepiness, were strongly linked to an increased risk of dementia within ~6 years in people who were cognitively healthy at baseline, after taking into account overall health status. This was the case whether the presence of dementia was self- or proxy-reported, or determined by a consensus panel. The combination of sleep items comprising the SDI also predicted AD/dementia when taking into account frailty, with this relationship being apparent at ~3 and 6 year time points, within HAAS and SHARE, respectively. However, the inclusion of the FI diminished the impact of the individual sleep items and the SDI within SHARE at ~4 years.

Finally, fatigue and the use of sleep medication for sleeping problems, as well as the combination of sleep-related items, were associated with increased risk of mortality within ~4 years. When frailty was added to the risk models, only reports of sleeping more than 8 hours per night remained a strong indicator of mortality risk. Despite an increased likelihood of mortality with increasing levels of frailty, at each time point and within each cohort, the SDI was unexpectedly associated with a decreased risk of mortality at ~6 years, with frailty included in the risk model. However, an interaction effect between the SDI and FI resulted in the SDI no longer accounting for a significant amount of variance in the risk model. Even sooner, at ~3 years, reports of waking up several times at night and waking up early and not being able to go back to sleep, specifically diminished mortality risk, even when overall health status was taken into account.

6.2 Overall Conclusions

A few major conclusions can be drawn from the present dissertation based on the three primary questions of interest. First, sleep disturbance is associated with an increased risk of cognitive impairment, AD, and dementia. These findings are in keeping with a growing literature, which demonstrates that disturbed sleep and abnormal circadian rhythms in older adults increases risk for cognitive decline (Almondes et al., 2016; Diem et al., 2015; Hita-Yañez et al., 2012; Schlosser et al., 2012; Tranah et al., 2011; Tsapanou et al., 2015a,b). This conclusion suggests that regular clinical screening for sleep disturbance may provide valuable health information when assessing the risk of developing dementia.

Second, present analyses further indicate that sleep complaints related to disrupted sleep continuity and daytime sleepiness, are most predictive of the development of cognitive decline and risk for AD/dementia. People who have AD typically report difficulty falling asleep and maintaining sleep at night and experience excessive sleepiness during the daytime (Peter-Derex et al., 2015). The manifestation of such symptoms appears to be an early indicator of developing dementia, with present findings demonstrating their appearance up to ~6 years prior to diagnosis in cognitively healthy individuals. These findings further support the conclusion that sleep disruption may precede the onset of cognitive changes that typically characterize AD/dementia by several years.

Third, inclusion of premorbid health status, as assessed by an FI, diminished the effect of sleep complaints on risk of cognitive impairment, as well as prevented sleep from having an impact on AD/dementia and mortality risk at ~4 years within the much larger SHARE cohort; the FI was a significant indicator in each model. This shows that the SDI might not be capturing enough variance, relative to the FI, to better explain risk of negative health outcomes within the SHARE population. More specific and sensitive measures related to sleep disturbance might have created better fitting risk models in those analyses. This became evident within the HAAS data, where more descriptive sleep-related measures were used (i.e., ‘wake up several times at night’ and ‘sleepy most of the day’); each remained a strong predictor when adjusting the models for frailty.

Finally, disturbed sleep appears to diminish risk of mortality, but only after health status is taken into account. However, taking into account the interaction between the SDI and FI prevented the SDI from decreasing mortality risk. Despite the two measures

being moderately correlated with one another ($r = 0.40$), there was no evidence of multicollinearity amongst any of the covariates. Thus, it is unclear as to what might have caused this unusual finding; as noted above more sensitive measures might have better differentiated those who are at risk of poor outcomes. That said, it is apparent from the present findings and the literature, that sleep is an important factor for determining the health of an individual (Badran et al., 2015; Gallicchio & Kalesa, 2009; Shan et al., 2015). It is possible that repair and recovery processes that are facilitated by sleep are disrupted due to inadequate sleep earlier in life, particularly when it is highly fragmented (Zuurbier et al., 2015b). As time progresses, and deficits accumulate, risk of poor outcomes becomes more apparent when health is assessed using a more comprehensive measure of physiological vulnerability (i.e., a frailty index).

6.3 Limitations

Findings from the current dissertation add to our understanding of the relationship between sleep and frailty, and how these health-related measures predict negative outcomes, including dementia; however there are several limitations that warrant further discussion. First and foremost, the present analyses are based on archival data, where the quality and methodology of data collection were beyond our control. Even though *a priori* objectives and hypotheses were established, analyses were limited to the type of data and specific variables that were available.

One common issue with the epidemiological study of sleep is the inconsistency among studies in the variables measured and the inadequate definition of sleep features (Buysse & Ganguli, 2002). Structured interviews that would allow a diagnosis of

insomnia, for example, are not typically conducted within population-based cohort studies (Almondes et al., 2016). Thus, the features labeled ‘insomnia’ vary across studies (e.g., sleep disturbance, trouble sleeping, difficulty falling or staying asleep), as does the phrasing of sleep-related questions, which can make cross-sample comparisons challenging or inappropriate. Notably, the variables used between SHARE and HAAS are inconsistent and poorly defined, particularly within SHARE. For example, what type of ‘sleeping problems’ did participants experience? Did participants interpret ‘fatigue’ as feeling physically exhausted or rather as being sleepy? Which ‘sleep medication’ did participants use, and what did the ‘change in sleeping pattern’ look like? Given the inconsistencies between the SHARE and HAAS sleep-related items, it was difficult to compare the two datasets directly, and thus, conclusions could only be based on general patterns established from the risk models.

One of the most important limitations of the present dissertation is the lack of diagnostic information available, particularly within the SHARE study. Only one question pertaining to dementia was recorded during data collection, which itself was non-specific and all-encompassing (i.e., “Has a doctor ever told you...do you currently have...Alzheimer’s disease, dementia, organic brain syndrome, senility or any other serious memory impairment”). In addition, responses were based on self- or proxy-reports, which are notorious for underestimating the prevalence of MCI and AD (Frank, et al., 2011). The accuracy of responses during interviews may be reduced by disease-related changes to insight and the cognitive abilities required to provide responses (i.e., memory and attention; Farias, Mungas, & Jagust, 2005; Vogel et al., 2004). Informant reports may also be influenced by the lack of awareness of symptoms, for example due to

decreased frequency of contact, or even the caregiver's own mental health problems (e.g., depression; Argüelles, Loewenstein, Eisdorfer, & Argüelles, 2001). Given this issue, it was also not possible to differentiate among dementia types and therefore not feasible to determine whether types of sleep disturbance are uniquely related to particular conditions. In addition, cognitive performance was not tested extensively within SHARE, nor was it examined similarly at each wave of data collection. Because only variables that were explored at each wave were used for analyses within this dissertation, cognitive ability in SHARE may not have accurately reflected impairments that are specific to dementias other than AD.

Due to the lack of extensive cognitive testing, in particular within the SHARE study, it was also difficult to establish criteria for MCI and subsequently examine stochastic processes in cognitive performance in relation to transitions between diagnostic states (healthy vs. MCI vs. dementia). There is also considerable disparity between prevalence and incidence estimates of MCI due to inconsistencies in its definition (e.g., age-associated memory impairment; cognitive impairment no dementia; amnesic MCI; Ward, Arrighi, Michels, & Cedarbaum, 2012). For the purposes of the present dissertation, cognitive performance was used to establish the presence of cognitive impairment, and careful attention was paid to not making claims of MCI as a diagnostic outcome.

One other major difference between SHARE and HAAS is that HAAS only collected data on male participants. Women are more likely to complain of insomnia-related symptoms, especially during and after menopause, and this sex difference increases into older age (Zhang et al., 2006). Difficulty initiating sleep and the use of sleep

medication tend to be more frequently reported in women, while difficulty maintaining sleep and excessive daytime sleepiness are more common in men (Jausse et al., 2011; Middelkoop, Smilde-van den Doel, Neven, Kamphuisen, & Springer, 1996). Thus, some of the inconsistencies between the two datasets may reflect the population demographics. Specifically, it makes sense that reports of waking up several times at night and feeling sleepy most of the day would be associated with dementia in males within HAAS at ~3 years, while sleep-related items were not associated with dementia in models including frailty at ~4 years within SHARE, which was a much larger sample in which more than half the participants were women.

6.4 Future Directions

As it stands, the temporal relationship between sleep and circadian disruption, and the development of AD/dementia, remains unclear (Bedrosian & Nelson, 2012; Moghekar & O'Brien, 2012). Much more work is required to determine whether changes to sleep precede and contribute toward disease-associated pathophysiology or whether sleep symptoms are simply the result of early stage disease processes. One of the greatest unknowns is how early these disruptions manifest in relation to standard cognitive changes that are associated with dementia diagnostic criteria. Recent findings indicate that cognitive impairment may be present in those at risk of AD up to 18 years before diagnosis (Rajan, Wilson, Weuve, Barnes, & Barnes, 2015). However, the majority of population-based cohort studies have examined sleep symptoms in dementia over a relatively shorter time frame (i.e., within ~9 years; Almondes et al., 2016; Yaffe et al., 2014). If sleep abnormalities precede cognitive changes, this would suggest that the

development of sleep disturbance in mid-life might be particularly indicative of dementia risk and should be prioritized in standard clinical exams. Although current analyses did not find any relationships between sleep disruption and dementia at ~10.5 years, those findings were based on a relatively small sample of male participants who met criteria for dementia ($n = 38$). In order to delineate the complexities of these relationships, future work should focus on examining the link between sleep and cognition over a longer period of time (e.g., > 20 years), in multiple large cohorts, and use standardized sleep measures that are clearly defined. Furthermore, clear definitions of sleep complaints will have to address differences between subjective and objective sleep symptoms (e.g., Alameddine, Ellenbogen, & Bianchi, 2015; Ancoli-Israel et al., 2003b; Kripke et al., 2011), with only the former being captured in survey-based studies.

One avenue of growing interest that still requires a great deal of exploration is the impact of sleep on pathophysiological mechanisms involved in AD. The sleep disruption and altered sleep/wake cycles that are characteristic of AD appear to reflect changes in sleep- and circadian-regulatory systems (Mattis & Sehgal, 2016). Direct reciprocal links between sleep deprivation and AD pathogenesis (i.e., the accumulation of A β) have been described (Hita-Yañez et al., 2012; Kang et al., 2009; Roh et al., 2012; Xie et al., 2013). These observations appear to be influenced by genetics and susceptibility to AD (Ju et al., 2013; Lim et al., 2013b) and/or the diminished expression of circadian clock components (Harper et al., 2008; Sterniczuk et al., 2010a; Swaab et al., 1985), as well as AD pathophysiology within sleep-regulatory regions at very early stages of disease (Šimić et al., 2009). Thus, deterioration of the central circadian clock, sleep-regulatory regions, or altered connections between the two systems, may be an early indicator of developing

AD (Wu and Swaab, 2007). Continued research in this area may help elucidate fundamental mechanisms that can identify novel neurochemical targets and treatment approaches for sleep-related symptoms and possibly the progression of AD pathophysiology. Furthermore, the impact that targeting these mechanisms will have on cognition remains to be determined.

Both pharmacological and non-pharmacological treatments for sleep disturbance in people with AD have shown some promise (Wu & Swaab, 2007). Several pharmacological approaches have been examined, including melatonin, which is secreted by the pineal gland and associated with an increase in sleep propensity. However, findings are mixed on its effectiveness, as well as the usefulness of other widely used options (McCleery et al., 2014; Peter-Derex et al., 2015). While there is some evidence that nonpharmacological means, such as bright light at specific times of the day, can improve sleep and strengthen circadian rhythms, even in severe AD (Ancoli-Israel et al., 2003; Wu & Swaab et al., 2007), a recent Cochrane review deemed there to be little evidence in terms of cognitive improvement (Forbes, Blake, Thiessen, Peacock, & Hawranik, 2014). It is unclear whether treating sleeping problems in older adults can prevent or slow cognitive decline, as well as which aspects of sleep disturbance or components of the systems should be targeted to produce the greatest improvements. Furthermore, there are inconsistencies between studies with regards to the timing, dosage, and length of treatments, and how these factors relate to endogenous fluctuations in biological responsiveness to light and melatonin. Given the lack of appropriately designed, randomized, controlled trials, this is an area warranting much more examination.

One other area that is just beginning to be explored is the relationship between cognition and frailty, and whether protecting against declining health status (Armstrong et al., 2016), can improve cognitive performance or even prevent dementia. The literature suggests a reciprocal relationship between frailty and cognitive impairment (Han, Lee, & Kim, 2014; Mitnitski et al., 2011; Robertson, Savva, & Kenny, 2013). One way to understand how sleep and frailty interact to affect cognition is to view the likelihood of cognitive decline as resulting from the build-up of small insults over time. The accumulation of these insults is a product of the rate at which damage arises within a system, and the rate at which that system is capable of repair/removal and recovery from that damage. Obtaining adequate sleep is important for good health and well being (Cappuccio et al., 2008; Hirshkowitz et al., 2015; Kolstad, 2008; Knutsson, 2003; Megdal et al., 2005; Puttonen et al., 2010; R uger & Scheer, 2009), as well as aiding in repair and recovery processes (Adam et al., 1984; Evans & French, 1995); possibly due to in part its impact on immune function (Garnaldo, Shaikh, & McArthur, 2012; Irwin, 2015; Palmbald et al., 1979). Thus, sleep, and its counterpart, physical activity, may be considered important components in modulating the rate at which deficits accumulate and manifest into significant health concerns. This is an emerging area of study that still requires much examination. However, there are potentially profound implications in understanding how sleep impacts frailty, especially if treating sleep problems is protective against negative health outcomes.

6.5 Implications

The purpose of sleep has been explored from many different angles, including adaptive evolutionary perspectives, those related to energy conservation, and in more recent years, its importance in brain plasticity (Frank, 2015). One theory that fits with the present dissertation is that sleep serves an important restorative function, whereby the process of sleep causes clearance of toxins and by-products that accumulate during wakefulness (Mendelsohn & Larrick, 2013), such as AD-related A β aggregates (Xie et al., 2013), which develop following sleep restriction in mice (Kang et al., 2009). These findings suggest that disturbed sleep in cognitively healthy people, as shown here, increases total wake time, which in turn may contribute to the progression of AD-related pathophysiology. Given that sleep disturbance was also found to decrease risk of mortality, other factors likely act to modulate e.g., dementia-associated processes, and determine individual risk of poor outcomes (e.g., diet, exercise, social engagement). The unexpected interactive effect between the SDI and FI demonstrates that further research is still required to understand the relationship between sleep as a restorative function, and frailty as a measure of physiological vulnerability to adverse outcomes.

What these findings imply with respect to our understanding of the role of sleep in dementia etiology ultimately depends on how well sleep and circadian disruption can predict and modify cognitive decline and dementia, in comparison to other identified risk factors (Ganguli et al., 2015; Xu et al., 2015). Notably, there was a great deal of variability in the odds ratios (effect sizes) between individual sleep items and the combined SDI in predicting cognitive impairment and AD/dementia; again, this may be related to inconsistent and poorly defined variables. Even so, although a 20% relative risk may

appear small for example (Chen, Cohen, & Chen, 2010), the implications for informing intervention planning depend on the incidence of dementia within a given cohort, whether other factors impact sleep disturbance as a predictor (e.g., diet, exercise, illness, genetics), and the feasibility of focusing on and administering sleep-related assessments and interventions (e.g., accessibility, required resources).

At minimum, the present data suggest that there is value in simple screening for disruption in sleep continuity and atypical levels of daytime sleepiness and fatigue. Not only might these changes indicate developing health concerns, but they could also serve as specific symptoms to address when developing intervention strategies for people who already have dementia. Sleep disturbance in people with dementia frequently contributes to early institutionalization due to intolerable caregiver burden (Pollak & Perlick, 1991). Long-term care however, often causes a worsening of sleep-wake disruption (Martin & Ancoli-Israel, 2008), and in turn further cognitive deterioration (Wilson et al., 2007). Recognizing which symptoms related to disrupted sleep/wake cycles are associated with AD (or other dementias) could help in producing earlier and more accurate diagnoses through the identification of novel biomarkers, and in turn, guide appropriate treatment interventions at the earliest possible stages. Furthermore, if treating new onset sleep complaints in cognitively healthy adults reduces dementia risk, then the present findings will be that more meaningful; however much work is still required to address this possibility.

Although there are characteristic changes in sleep architecture that occur during normal aging, the onset of sleep complaints in older adults is often linked to other comorbid health conditions (Ancoli-Israel et al., 2008). In fact, careful health assessments

in older adults will most often indicate that sleep complaints are due to the presence of an underlying medical (or psychiatric) condition, rather than being a result of the aging process (Foley et al., 1999; Vitiello et al., 2002). The overall findings from this dissertation indicate that regular clinical evaluation of sleep quality and quantity, and the presence of sleep disorders, in older individuals, with or without cognitive impairment, may provide valuable information regarding the risk of cognitive decline or the development of AD and other dementias.

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APPENDIX A

Supplemental Table 5.1 Demographics and clinical characteristics (Mean \pm SD) of cognitively healthy participants at baseline, in relation to cognition, dementia diagnosis and survival, after an average of 6 and 10.5 years.

	Follow-up Status after 6 Years					
	Cognitively Healthy (n = 1,136)	Mild Cognitive Impairment (n = 240)	Not Diagnosed with Dementia (n = 2,656)	Diagnosed with Dementia (n = 69)	Survived (n = 1,371)	Died (n = 1,009)
Age	75.6 (3.2)	76.6 (3.5)	76.7 (3.8)	78.1 (4.0)	76.5 (3.6)	77.9 (4.2)
Education	11.8 (3.0)	10.1 (2.8)	11.1 (3.1)	11.1 (3.3)	11.3 (3.1)	10.8 (3.0)
CASI	91.5 (4.2)	86.9 (4.0)	89.3 (4.8)	87.7 (4.2)	89.7 (4.8)	88.1 (4.7)
BMI	23.9 (2.8)	24.1 (3.1)	23.6 (3.1)	23.6 (3.5)	23.9 (3.0)	23.2 (3.2)
FI	0.08 (0.06)	0.08 (0.05)	0.09 (0.06)	0.10 (0.07)	0.09 (0.06)	0.10 (0.07)
SDI	3.6 (1.6)	3.7 (1.5)	3.7 (1.6)	3.5 (1.7)	3.7 (1.6)	3.7 (1.6)
	Follow-up Status after 10.5 Years					
	Cognitively Healthy (n = 602)	Mild Cognitive Impairment (n = 146)	Not Diagnosed with Dementia (n = 2,687)	Diagnosed with Dementia (n = 38)	Survived (n = 753)	Died (n = 1,627)
Age	74.9 (2.6)	75.8 (3.0)	76.7 (3.8)	77.6 (4.0)	76.2 (3.3)	77.5 (4.1)
Education	12.0 (3.0)	10.9 (2.9)	11.1 (3.1)	10.8 (3.2)	11.4 (3.1)	10.9 (3.1)
CASI	92.1 (4.2)	88.4 (4.2)	89.3 (4.8)	87.5 (5.0)	90.1 (4.9)	88.6 (4.7)
BMI	24.1 (2.9)	23.9 (2.8)	23.6 (3.1)	23.5 (3.0)	24.1 (3.0)	23.4 (3.1)
FI	0.08 (0.05)	0.08 (0.05)	0.09 (0.06)	0.09 (0.06)	0.08 (0.05)	10.0 (0.07)
SDI	3.6 (1.6)	3.5 (1.5)	3.7 (1.6)	3.6 (1.2)	3.6 (1.6)	3.7 (1.5)

CASI: Cognitive Abilities Screening Instrument; BMI: Body Mass Index; FI: Frailty Index; SDI: Sleep Disturbance Index

Supplemental Table 5.2 Demographics and clinical characteristics (Mean \pm SD) of mild cognitively impaired participants at baseline, in relation to cognition, dementia diagnosis and survival, after an average of 6 and 10.5 years.

	Follow-up Status after 6 Years					
	Cognitively Healthy (n = 21)	Mild Cognitive Impairment (n = 44)	Not Diagnosed with Dementia (n = 390)	Diagnosed with Dementia (n = 22)	Survived (n = 172)	Died (n = 217)
Age	77.4 (4.3)	77.2 (3.9)	79.1 (4.8)	78.4 (5.1)	78.1 (4.6)	80.1 (4.9)
Education	10 (2.5)	9.5 (3.2)	9.2 (2.9)	10.7 (3.3)	9.6 (3.1)	9.1 (2.8)
CASI	78.1 (1.4)	77.8 (1.7)	77.1 (1.7)	77.4 (1.8)	77.2 (1.7)	77.0 (1.6)
BMI	25.2 (3.3)	23.8 (3.0)	23.4 (3.3)	23.5 (2.6)	23.8 (3.2)	23.1 (3.4)
FI	0.07 (0.03)	0.08 (0.04)	0.09 (0.06)	0.10 (0.08)	0.09 (0.06)	0.10 (0.08)
SDI	4.0 (1.1)	3.8 (1.3)	3.7 (1.5)	3.7 (1.7)	3.8 (1.5)	3.6 (1.5)
	Follow-up Status after 10.5 Years					
	Cognitively Healthy (n = 6)	Mild Cognitive Impairment (n = 17)	Not Diagnosed with Dementia (n = 399)	Diagnosed with Dementia (n = 13)	Survived (n = 82)	Died (n = 307)
Age	75.3 (2.3)	75.2 (2.6)	79.0 (4.8)	80.5 (4.9)	77.1 (3.8)	79.8 (4.9)
Education	10 (1.5)	9.3 (2.1)	9.3 (2.9)	7.7 (1.8)	8.9 (2.5)	9.4 (3.0)
CASI	78.2 (1.2)	77.2 (1.7)	77.1 (1.7)	77.4 (1.9)	77.1 (1.7)	77.1 (1.7)
BMI	25.2 (3.5)	24.7 (4.2)	23.4 (3.3)	24.1 (2.6)	24.7 (3.4)	23.1 (3.2)
FI	0.06 (0.03)	0.08 (0.05)	0.10 (0.07)	0.07 (0.05)	0.07 (0.05)	0.10 (0.07)
SDI	3.2 (1.3)	3.9 (1.2)	3.7 (1.5)	4.0 (1.5)	3.8 (1.3)	3.7 (1.6)

CASI: Cognitive Abilities Screening Instrument; BMI: Body Mass Index; FI: Frailty Index; SDI: Sleep Disturbance Index

Supplemental Table 5.3

Models of best fit for risk models 1-10, using backward stepwise (conditional) binary logistic regression, for the outcomes of mild cognitive impairment, dementia and mortality, at an average of 2.9 years.

Final Step	Variables	OR	Wald	95% CI	<i>P</i>	χ^2
Mild Cognitive Impairment						
Step 13	Age	1.07	13.53	1.03-1.11	< 0.001	14.93
	Education	0.79	83.38	0.75-0.83	< 0.001	
Dementia						
Step 12	Age	1.14	17.51	1.07-1.22	< 0.001	5.98
	Wake up several times at night	2.66	7.62	1.32-5.32	< 0.01	
	Sleepy most of the day	2.20	3.89	1.01-4.82	0.049	
Mortality						
Step 8	Age	1.09	44.42	1.07-1.22	< 0.001	11.93
	Education	0.94	12.93	0.91-0.97	< 0.001	
	Body Mass Index	0.94	13.56	0.90-0.97	< 0.001	
	Frailty Index	1.20	14.06	1.09-1.32	< 0.001	
	Sleep more than 8 hours	1.35	2.92	0.96-1.91	0.09	
	Wake up several times at night	0.50	7.42	0.30-0.82	0.01	
	Wake up early and can't go back to sleep'	0.76	3.77	0.57-1.00	0.04	

Supplemental Table 5.4

Risk model comparisons for those cognitively healthy individuals at baseline who met criteria for a diagnosis of dementia or who did not survive, after an average 6 years, while controlling for age, education, BMI, and frailty. *Model 11 did not contain the FI; SDI: Sleep Disturbance Index

	Cognitive Impairment (n = 287)			Dementia Diagnosis (n = 69)			Mortality (n = 1,009)		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Model 1: Sleep < 7 hours	0.90	0.66-1.22	0.50	0.61	0.25-1.44	0.26	1.12	0.93-1.33	0.23
Model 2: Sleep > 8 hours	1.00	0.56-1.78	0.99	0.48	0.70-3.11	0.44	1.20	0.88-1.63	0.24
Model 3: Restless sleep	1.03	0.58-1.82	0.92	1.20	0.26-5.58	0.82	1.05	0.76-1.44	0.79
Model 4: Wake up at night	1.36	0.82-2.25	0.24	6.01	0.68-52.79	0.11	0.62	0.44-0.89	< 0.01
Model 5: Wake up early	0.88	0.61-1.29	0.52	0.42	0.16-1.09	0.07	0.84	0.67-1.05	0.12
Model 6: Trouble falling asleep	1.25	0.86-1.82	0.25	0.74	0.26-2.12	0.58	1.04	0.84-1.30	0.72
Model 7: Taking regular naps	1.17	0.86-1.59	0.33	1.29	0.55-3.02	0.57	1.14	0.95-1.37	0.16
Model 8: Sleepy most of day	1.54	0.92-2.62	0.10	0.34	0.07-1.62	0.18	0.93	0.67-1.29	0.67
Model 9: Groggy after waking	1.11	0.48-2.56	0.81	0.00	0.00	0.99	1.22	0.77-1.94	0.39
Model 10: Fatigue past 2 weeks	1.19	0.70-2.05	0.52	1.16	0.32-4.28	0.82	1.13	0.84-1.51	0.43
Model 11: SDI (Models 1-10)*	1.02	0.93-1.12	0.72	0.90	0.71-1.14	0.37	1.02	0.97-1.08	0.43
Model 12: Frailty Index	0.82	0.70-0.96	0.01	1.00	0.67-1.49	0.99	1.20	1.11-1.29	< 0.001
Model 13: SDI	1.04	0.95-1.15	0.39	0.89	0.70-1.13	0.34	1.00	0.94-1.06	0.95
Frailty Index	0.80	0.68-0.94	< 0.01	1.10	0.71-1.70	0.68	1.20	1.10-1.30	< 0.001

Supplemental Table 5.5

Risk model comparisons for those cognitively healthy individuals at baseline who met criteria for a diagnosis of dementia or who did not survive, after an average 10.5 years, while controlling for age, education, BMI, and frailty. *Model 11 did not contain the FI; SDI: Sleep Disturbance Index

	Cognitive Impairment (n = 146)			Dementia Diagnosis (n = 38)			Mortality (n = 1,627)		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Model 1: Sleep < 7 hours	1.02	0.69-1.51	0.93	0.57	0.21-1.58	0.28	1.02	0.69-1.51	0.93
Model 2: Sleep > 8 hours	1.30	0.65-2.60	0.47	1.63	0.31-8.57	0.56	1.30	0.65-2.60	0.47
Model 3: Restless sleep	0.67	0.30-1.47	0.32	6.75	0.49-92.84	0.15	0.67	0.30-1.47	0.32
Model 4: Wake up at night	0.90	0.44-1.87	0.78	0.60	0.09-4.05	0.60	0.90	0.44-1.87	0.78
Model 5: Wake up early	0.82	0.50-1.34	0.43	0.31	0.09-1.04	0.06	0.82	0.50-1.34	0.43
Model 6: Trouble falling asleep	1.02	0.62-1.70	0.94	0.72	0.17-2.99	0.65	1.02	0.62-1.70	0.94
Model 7: Taking regular naps	0.98	0.66-1.44	0.90	1.14	0.40-3.30	0.81	0.98	0.66-1.44	0.90
Model 8: Sleepy most of day	0.91	0.41-2.02	0.82	1.63	0.35-7.56	0.53	0.91	0.41-2.02	0.82
Model 9: Groggy after waking	1.63	0.70-3.79	0.26	1.57	0.00	1.00	1.63	0.70-3.79	0.26
Model 10: Fatigue past 2 weeks	0.91	0.44-1.88	0.80	2.38	0.22-25.59	0.47	0.91	0.44-1.88	0.80
Model 11: SDI (Models 1-10)*	0.98	0.87-1.10	0.73	0.91	0.63-1.29	0.58	0.98	0.87-1.10	0.73
Model 12: Frailty Index	1.01	0.82-1.24	0.94	0.99	0.65-1.50	0.95	1.01	0.82-1.24	0.94
Model 13: SDI	0.99	0.87-1.11	0.82	0.88	0.61-1.28	0.51	0.99	0.87-1.11	0.82
Frailty Index	0.95	0.76-1.18	0.63	1.11	0.69-1.78	0.67	0.95	0.76-1.18	0.63

Supplemental Table 5.6

Risk model comparisons for those with mild cognitive impairment at baseline who met criteria for a diagnosis of dementia or who did not survive, after an average 2.9 years, while controlling for age, education, BMI, and frailty.

*Model 11 did not contain the FI; SDI: Sleep Disturbance Index

	Dementia Diagnosis (n = 37)			Mortality (n = 140)		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Model 1: Sleep < 7 hours	0.49	0.20-1.20	0.12	0.82	0.48-1.41	0.47
Model 2: Sleep > 8 hours	2.32	0.95-5.69	0.07	1.28	0.62-2.63	0.50
Model 3: Restless sleep	0.87	0.20-3.90	0.86	0.95	0.36-2.55	0.92
Model 4: Wake up at night	0.41	0.05-3.20	0.40	0.56	0.18-1.73	0.31
Model 5: Wake up early	1.29	0.52-3.21	0.58	0.59	0.29-1.17	0.13
Model 6: Trouble falling asleep	1.26	0.51-3.08	0.62	0.41	0.19-0.87	0.02
Model 7: Taking regular naps	0.66	0.31-1.36	0.26	1.62	0.95-2.78	0.08
Model 8: Sleepy most of day	2.76	1.02-7.49	0.05	0.51	0.19-1.39	0.19
Model 9: Groggy after waking	3.09	0.61-15.73	0.18	0.35	0.04-2.84	0.32
Model 10: Fatigue past 2 weeks	0.36	0.05-2.75	0.33	0.70	0.27-1.82	0.46
Model 11: SDI (Models 1-10)*	0.95	0.74-1.21	0.66	0.92	0.78-1.09	0.92
Model 12: Frailty Index	0.95	0.72-1.25	0.70	1.20	1.11-1.29	< 0.001
Model 13: SDI	0.95	0.73-1.23	0.69	0.89	0.75-1.06	0.20
Frailty Index	0.98	0.70-1.36	0.90	1.15	0.93-1.42	0.21

Supplemental Table 5.7

Risk model comparisons for those with mild cognitive impairment at baseline who met criteria for a diagnosis of dementia or who did not survive, after an average 6 years, while controlling for age, education, BMI, and frailty.

*Model 11 did not contain the FI; SDI: Sleep Disturbance Index

	Dementia Diagnosis (n = 22)			Mortality (n = 217)		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Model 1: Sleep < 7 hours	0.93	0.35-2.47	0.88	0.65	0.40-1.07	0.09
Model 2: Sleep > 8 hours	0.79	0.71-3.64	0.77	2.12	1.01-4.47	0.05
Model 3: Restless sleep	0.84	0.15-4.87	0.85	0.70	0.28-1.74	0.44
Model 4: Wake up at night	0.59	0.07-4.82	0.62	0.56	0.22-1.46	0.24
Model 5: Wake up early	0.37	0.08-1.67	0.20	0.66	0.36-1.19	0.17
Model 6: Trouble falling asleep	0.45	0.10-2.03	0.30	0.57	0.31-1.06	0.08
Model 7: Taking regular naps	0.69	0.27-1.74	0.43	1.54	0.94-2.52	0.09
Model 8: Sleepy most of day	3.40	1.12-10.30	0.03	0.67	0.30-1.46	0.31
Model 9: Groggy after waking	1.93	0.23-16.59	0.55	0.53	0.13-2.19	0.38
Model 10: Fatigue past 2 weeks	4.54	1.50-13.78	< 0.01	1.02	0.44-2.39	0.96
Model 11: SDI (Models 1-10)*	0.97	0.71-1.31	0.82	0.95	0.81-1.11	0.48
Model 12: Frailty Index	1.02	0.73-1.42	0.92	1.14	0.96-1.35	0.13
Model 13: SDI	0.95	0.69-1.32	0.78	0.91	0.77-1.07	0.27
Frailty Index	1.05	0.71-1.56	0.81	1.17	0.95-1.44	0.15

Supplemental Table 5.8

Risk model comparisons for those with mild cognitive impairment at baseline who met criteria for a diagnosis of dementia or who did not survive, after an average 10.5 years, while controlling for age, education, BMI, and frailty. *Model 11 did not contain the FI; SDI: Sleep Disturbance Index

	Dementia Diagnosis (n = 13)			Mortality (n = 307)		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Model 1: Sleep < 7 hours	1.59	0.50-5.07	0.44	1.57	0.87-2.83	0.14
Model 2: Sleep > 8 hours	1.17	0.24-5.83	0.85	1.11	0.44-2.77	0.83
Model 3: Restless sleep	1.14	0.11-11.58	0.91	1.04	0.35-3.09	0.95
Model 4: Wake up at night	0.00	0.00	0.99	0.71	0.25-2.01	0.52
Model 5: Wake up early	1.48	0.38-5.78	0.58	1.14	0.57-2.27	0.71
Model 6: Trouble falling asleep	1.70	0.43-6.68	0.45	0.96	0.46-1.97	0.90
Model 7: Taking regular naps	1.86	0.48-7.22	0.37	0.92	0.50-1.68	0.78
Model 8: Sleepy most of day	1.05	0.13-8.70	0.96	0.64	0.26-1.54	0.32
Model 9: Groggy after waking	3.58	0.39-33.17	0.26	2.87	0.35-23.87	0.33
Model 10: Fatigue past 2 weeks	0.00	0.00	0.99	1.67	0.53-5.34	0.38
Model 11: SDI (Models 1-10)*	1.22	0.82-1.81	0.32	1.05	0.86-1.27	0.66
Model 12: Frailty Index	0.73	0.40-1.34	0.31	1.36	1.06-1.76	0.02
Model 13: SDI	1.28	0.85-1.93	0.24	0.97	0.79-1.20	0.79
Frailty Index	0.76	0.40-1.45	0.41	1.41	1.03-1.92	0.03

Supplemental Table 5.9

Model of best fit for risk model 13, using backward stepwise (conditional) binary logistic regression, for the outcomes of mild cognitive impairment, dementia and mortality, at an average of 2.9 years.

Final Step	Variables	OR	Wald	95% CI	<i>p</i>	χ^2
Mild Cognitive Impairment						
Step 4	Age	1.07	14.14	1.03-1.11	< 0.001	8.60
	Education	0.79	81.97	0.75-0.83	< 0.001	
Dementia						
Step 2	Age	1.14	17.40	1.07-1.21	< 0.01	6.01
	SDI*	1.20	4.92	1.02-1.41	< 0.03	
Mortality						
Step 2	Age	1.10	47.94	1.07-1.12	< 0.001	6.33
	Education	0.94	11.32	0.91-0.98	< 0.01	
	Body Mass Index	0.94	13.41	0.90-0.97	< 0.001	
	Frailty Index	1.20	14.60	1.09-1.31	< 0.001	

*Sleep Disturbance Index

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ORIGINAL RESEARCH

Cognitive Test Performance in Relation to Health and Function in 12 European Countries: The SHARE Study



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ABSTRACT

Background

Even subtle impairments on cognitive test scores can be associated with future cognitive decline and dementia. We assayed the relationships between test score impairment and adverse outcomes.

Methods

Secondary analyses were performed on data from non-institutionalized participants, 50+ years of age (N = 30,038), from 12 countries taking part in the Survey of Health, Ageing and Retirement in Europe (SHARE) longitudinal study on aging. At baseline, participants' cognition was tested using verbal fluency, immediate recall, and delayed recall tasks.

Results

Greater levels of cognitive impairment at baseline were strongly associated with future poor health outcomes and functional impairment. Controlling for age, sex and education, those with 1 (OR = 1.58, 95% CI = 1.34–1.87) or ≥ 2 (OR = 2.59, 95% CI = 2.17–3.09) impaired tests at baseline were more likely to die after an average of 40 months compared to individuals with no impairments. After selecting for participants who reported the absence of dementia initially, those with ≥ 2 cognitive impairments at baseline (OR = 3.34, 95% CI = 2.27–4.92) were more likely to report dementia at follow-up compared to those with no impairment.

Conclusions

People with impaired cognitive test scores at baseline are at greater risk to die or develop dementia within four years than their less impaired or unimpaired counterparts.

Key words: Alzheimer's disease, dementia, cognitive impairment, risk factors, longitudinal studies

INTRODUCTION

Cognitive decline and neurodegeneration (including Alzheimer's disease (AD)) are both increasingly common features of aging. Baseline cognition is strongly associated with changes in cognition and functional impairment.⁽¹⁾ Similarly, the risk of institutionalization increases substantially with increasing cognitive and functional impairment. Functional impairment, or physical disability as measured by Instrumental and Basic Activities of Daily Living (IADL; ADL), often proceeds in a hierarchical fashion⁽²⁾ and indeed staging systems based entirely on function correlate well with more general staging schemes.^(3,4) For example, severe dementia, which often manifests as difficulty with three or more ADLs (e.g., bathing, dressing, toileting), is a strong predictor of nursing home admission.⁽⁵⁾ Impairments in IADLs (e.g., telephone use, financial management, housekeeping), which facilitate daily independent living, are often telltale signs of future cognitive decline⁽⁶⁾ and risk of mild cognitive impairment (MCI) or conversion to dementia.⁽⁷⁾ However, the level of cognitive impairment that implies increased risk of further mental or physical decline is not well defined, as it may vary greatly among individuals and populations.

The Survey of Health, Ageing and Retirement in Europe (SHARE) is the first longitudinal study to examine the various health, economic, and social factors that are associated with aging. It currently consists of more than 60,000 people from among the non-institutionalized population aged 50 and older, and their spouses/partners (independent of age), in 20 participating European countries. The cognition-related items included in the SHARE database have been used in some studies,^(8,9,10) but there has not been an analysis of how cognitive status at baseline relates to subsequent adverse health outcomes associated with cognitive decline.

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The first objective of the present analyses was to examine the relationships between cognition and health-related functional capacities (i.e., physical disability and difficulties with IADLs and ADLs) in the SHARE dataset. Secondly, this study examined how performance at baseline on three cognitive tasks relates to three adverse health outcomes at follow-up: dementia, institutionalization, and mortality.

METHODS

Study Sample

Secondary analyses were conducted on data from Waves 2 (baseline; 2006–2007) and 4 (2010–2011) from the SHARE database (releases 2.5.0 as of May 24th, 2011, and 1.1.1 as of November 30th, 2012, respectively; *N* = 30,038; Figure 1). Respondents from 12 countries (Austria, Germany, Sweden, Netherlands, Spain, Italy, France, Denmark, Switzerland, Belgium, Czech Republic, and Poland) who took part in the second and fourth waves of SHARE were chosen for our analyses. Data collection consisted of face-to-face interviews and mail-out surveys. At baseline, we excluded spouses/partners below the age of 50 (*n* = 842) and those individuals who were recorded as being permanently admitted to a nursing home in the last 12 months (*n* = 72). For the analyses examining reports of dementia, we made the same exclusion as above, but also excluded those who reported the presence of AD or dementia at baseline (*n* = 331). Dementia status was not recorded in Wave 1 of SHARE, hence our use of Wave 2 as baseline for these purposes. Health outcomes examined at Wave 4 included reports of AD or dementia, institutionalization, and mortality, after an average of 4 years and 3.6 months. Education level was standardized across participants in SHARE according to the ISCED-1997 code.⁽¹¹⁾ Approval for secondary analyses came from the Research Ethics Board of the Capital District Health Authority at Halifax, Nova Scotia, Canada.

Cognitive Tasks

The SHARE protocol included performance-based cognitive tests,⁽¹²⁾ which were used to generate a cognition score for each participant during each wave, as previously described.⁽¹⁰⁾ Only those cognitive tasks that were conducted in both Waves 2 and 4 were included in the score, namely, performance on verbal fluency, immediate recall, and delayed recall tasks. These tests are sensitive measures for discriminating between cognitively healthy individuals and those with MCI or dementia (i.e., AD).^(2,13,14) Threshold performance scores for being coded as “1” (indicating impairment) were set in relation to scores previously shown to be indicative of MCI or AD, as follows: verbal fluency scores < 15; immediate recall scores < 5; and delayed recall scores < 4 (see Balthazar et al.,⁽¹³⁾ Takayama,⁽¹⁴⁾ and Xie et al.⁽¹⁵⁾ for test details). A single code for recall ability was created by averaging the codes for immediate and delayed recall scores, such that “0” was considered unimpaired and

“0.5” and “1” were considered impaired. Those reporting “don’t know” for any of these measures were coded as “1,” or impaired. Only those participants who completed all three cognitive tests in Wave 2 were used for the analyses (2.3% excluded). The cognition scores for each Wave were calculated by adding the total number of impairments (0–2) and are presented in relation to the number of tests demonstrating impairment, such that each subtest is weighted equally. Cognitive performance was classified as zero (*n* = 11,771), 1 (*n* = 10,423), or 2 impairments (*n* = 6,082).

Functional Capacity

Cognitive status in relation to various measures of functional capacity at baseline was examined, including ADLs, IADLs, mobility, and physical activity. Similar to a previous report,⁽²⁾ cognitive performance was also examined in those with mild, moderate, and severe degrees of ADL and IADL functional impairment (Table 1; scored out of 13; not including the variables measuring mobility and physical activity independent from ADL and IADL questions). Individuals categorized as

TABLE 1.
Categories of functional impairment and corresponding criteria

Category	Criteria	Total Number of Impairments
Mild	<ul style="list-style-type: none"> No impairments with activities of daily living Difficulty with ANY of the following: managing money; making telephone calls; taking medications; using a map to navigate in a strange place 	1-4
Moderate	<ul style="list-style-type: none"> Difficulty with: managing money; making telephone calls; taking medications; AND using a map to navigate in a strange place Impairment with bathing or showering May also exhibit difficulty with ANY of the following: preparation of a hot meal; shopping for groceries or doing work around the house or garden 	5-8
Severe	<ul style="list-style-type: none"> Meets criteria for Moderate functional impairment Difficulty with: preparation of a hot meal; shopping for groceries; AND doing work around the house or garden At least ONE impairment with: dressing; walking across a room; eating; getting in or out of bed; using the toilet 	9-13

“mild” exhibited mild IADL impairment without ADL impairment and were grouped based on difficulty with any of the following: managing money, making telephone calls, taking medications, or using a map to navigate in a strange place. Individuals categorized as “moderate” exhibited difficulty with all of the IADLs in the “mild” group, plus ADLs that required prompts (i.e., impairment with bathing or showering); they may also exhibit difficulty with the preparation of a hot meal, shopping for groceries, or doing work around the house or garden. Individuals categorized as “severe” exhibited severe ADL and IADL impairment which included the same impairment as the “moderate” group, plus they must exhibit difficulty with the preparation of a hot meal, shopping for groceries, and doing work around the house or garden, as well as at least one other ADL impairment (i.e., dressing, walking across a room, eating, getting in or out of bed, or using the toilet).

Dementia, Institutionalization, and Mortality

Diagnosis of AD or dementia (i.e., 0 = absent, 1 = present), was determined by responses to the following question in SHARE’s Wave 2 and 4 questionnaires: “Has a doctor ever told you that you had/Do you currently have any of the conditions on this card? With this we mean that a doctor has told you that you have this condition, and that you are either currently being treated for or bothered by this condition?” The primary option of interest was “Alzheimer’s disease, dementia, organic brain syndrome, senility or any other serious memory impairment”. This health measure was reported by the participants themselves or a proxy respondent (e.g., spouse/partner).

Recent institutionalization status (i.e., 0 = not institutionalized, 1 = permanently institutionalized) was assessed using responses to the following question in Waves 2 and 4: “During the last twelve months, have you been in a nursing home overnight?” Clarifying information for the interviewer when coding responses included: “A nursing home provides all of the following services for its residents: dispensing of medication, available 24-hour personal assistance and supervision (not necessarily a nurse), and room and meals. Permanently means nonstop during the past 12 months”. Response options included: “no”, “yes, temporarily”, and “yes, permanently”. Those who reported being temporarily institutionalized at some point during the past 12 months were coded as not being currently institutionalized. Finally, survival was reported by relatives, friends, or neighbours (i.e., died; 0 = no, 1 = yes).

Statistical Analyses

The first objective was explored using one-way, between-subjects analyses of variance to examine whether at baseline various aspects of functional capacity differed between levels of cognitive impairment; independent samples *t*-tests were used to evaluate such differences for those who did or did not report AD or dementia at baseline. Post-hoc comparisons were

conducted using Games-Howell. Due to potential overestimation of between-groups effects because of the large sample size, eta squared was calculated for the main effects models, and Cohen’s *d* was calculated for the differences in cognition among the mild, moderate, and severe functional performance groups, when possible. For the second objective, binary logistic regression was used to estimate the likelihood and 95% confidence intervals (CI) that 0, 1 or 2–3 cognitive impairments at baseline (Wave 2) predicted future reports of AD or dementia, permanent institutionalization, and mortality at Wave 4. Age, sex, and education were used as covariates to adjust the risk models. Means are reported as \pm the standard deviation. SPSS (18.0.0, SPSS Inc.) was used to analyze the data, with statistical significance set at $p = .05$.

RESULTS

Baseline Demographics

At baseline (Wave 2), our sample had a mean age of 64.7 years (range 50–104), and 54.6% were women. Some 331 reported the presence of AD or dementia, and 16, 46, and 180 of these participants exhibited 0, 1, and ≥ 2 cognitive impairments at baseline. Some 1,508 were recorded as having died at follow-up (Figure 1).

Objective 1: Functional Capacity in Relation to Baseline Cognition and Dementia Status

Higher numbers of cognitive impairments were associated with higher average age, more difficulties with ADLs and IADLs, and more mobility impairments at baseline. Higher levels of cognitive impairment were also associated with lower levels of education and poorer self-perceived health (Table 2). Although these associations were significantly different at each level of cognitive impairment, larger (albeit moderate) effect sizes were associated primarily with differences between those with 1 and ≥ 2 impairments, while there were only small differences between those with 0 and 1 impairment (not reported here).

Functional Impairment Severity for All Participants at Baseline

Non-institutionalized individuals at baseline demonstrated a significant main effect of cognitive performance on functional capacity for those with a mild level of impairment ($F [2, 2108] = 88.28, p < .001; \eta^2 = .08$; Table 3). Post hoc comparisons indicated that in those with mildly impaired function, the number of functional impairments was greater in the participants with ≥ 2 cognitive impairments at baseline, compared to those with 0 or 1 impairment. The effect sizes for comparisons of 1 vs. ≥ 2 ($d = -.42$) and 0 vs. ≥ 2 ($d = -.54$) were much larger than for the comparisons of 0 vs. 1 impairment ($d = -.19$). There was no influence of cognitive performance capacity

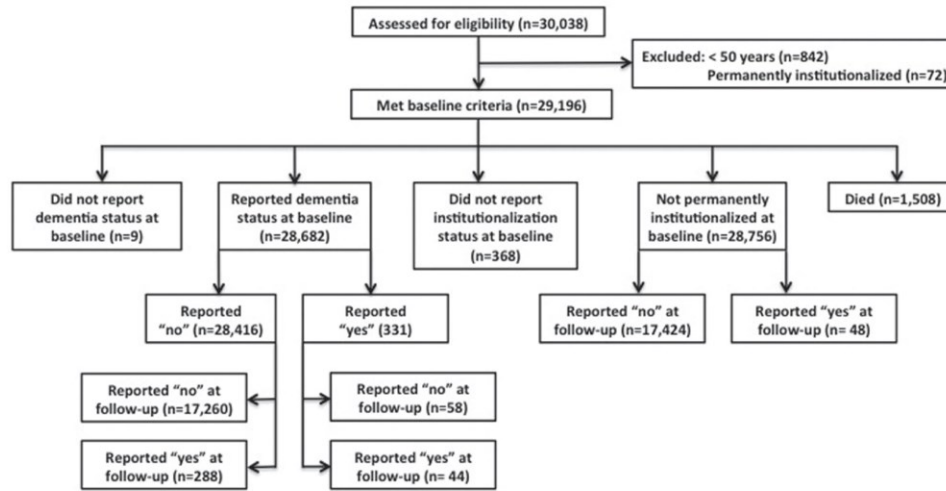


FIGURE 1. Participant flow diagram for baseline and follow-up outcomes: dementia status, institutionalization, and mortality.

TABLE 2.
Functional capacity in relation to cognitive performance and dementia status at baseline (Wave 2)

Health Factors	All (N=30,038)	Number of Cognitive Impairments in Those Non-Institutionalized at Baseline			Reported Dementia Status at Baseline	
		0 (n=11,771)	1 (n=10,423)	≥2 (n=6,082)	Without AD or Dementia (n=28,416)	With AD or Dementia (n=331)
Age (Mean ± SD)	64.3 (10.4)	61.2 (8)	65.1 (9.6)	70.3 (10.5)	64.8 (10.3)	77.6 (9.5)
Education (Mean ± SD; ISCED)	2.6 (1.5)	3.2 (1.4)	2.5(1.4)	1.7 (1.2)	2.5 (1.5)	1.8 (1.4)
Impairments in ADLs (Mean ± SD)	0.2 (0.8)	0.1 (0.4)	0.2 (0.7)	0.5 (1.2)	0.2 (0.7)	2.0 (2.3)
% More than 1 ADL	10.7	4.9	9.1	21.7	9.9	58.3
Impairments in IADLs (Mean ± SD)	0.4 (1.1)	0.1 (0.4)	0.2 (0.7)	0.9 (1.7)	0.3 (0.9)	3.8 (2.7)
% More than 1 IADL	16.4	7.5	13.9	33.9	15.6	81.9
% Self-rated health (very good or excellent health)	26.5	30.6	23.5	8.1	17.4	2.7
% Impaired activities	44.7	36.5	44.3	61.4	44.6	89.7
Impairments in mobility (Mean ± SD)	1.5 (2.3)	0.9 (1.6)	1.4 (2.0)	2.8 (2.9)	1.5 (2.2)	5.0 (3.3)
% Impaired on 1 or more aspects of mobility	46.9	37.3	47.4	65.9	47.0	86.7
% Impaired on 3 or more aspects of mobility	23.3	13.4	21.8	44	23.0	72.5
% Physically inactive	11.6	4.9	9.3	27.1	11.3	58.9
% Problem getting around with a map	7.4	2.4	5.0	18.5	6.6	65.9

TABLE 3.

Number of Cognitive Impairments at Baseline (Wave 2)	Severity of Functional Impairment at Baseline					
	Mild		Moderate		Severe	
	N (%)	M ± SD	N (%)	M ± SD	N (%)	M ± SD
All participants (N=29,196)						
0	342 (1)	1.1±0.4	0	---	1	13
1	656 (2)	1.2±0.5	1	8	7 (0.02)	11.3±1.5
≥2	1,213 (4)	1.6±0.8	24 (0)	7.1±0.6	117 (0.4)	11.9±1.3
Without AD or dementia (N=28,416)						
0	336 (1)	1.1±0.4	0	---	1	13
1	638 (2)	1.2±0.5	1	8	7 (0.02)	11.3±1.5
≥2	1,105 (4)	1.5±0.7	17 (0.05)	7±0.5	76 (0.3)	11.9±1.3
With AD or dementia (N=331)						
0	5 (2)	1.4±0.9	0	---	0	---
1	18 (5)	1.4±0.7	0	---	0	---
≥2	108 (33)	2.2±1.0	7 (2)	7.3±0.8	41 (12)	11.9±1.4

The number of impairments in basic and instrumental activities of daily living (ADLs and IADLs) are shown as M ± SD.

on functional impairment among those with moderate ($F [2, 22] = 2.25, p = .15$) or severe levels of impairment ($F [2, 118] = 1.02, p = .36$).

Participants Chosen by Dementia Status

Participants who reported the presence of AD or dementia exhibited greater functional impairment than those who did not report AD or dementia (Table 2). Those who reported the absence of AD or dementia at baseline also exhibited a significant main effect of cognitive performance on functional capacity in those with mild level of functional impairment ($F [2, 2076] = 68.57, p < .001; \eta^2 = .06$; Table 3). In those with mild functional capacity, the number of functional impairments was greater in the participants with ≥ 2 cognitive impairments at baseline, compared to those with 0 or 1 impairment. There was no effect of cognitive performance on those with moderate ($F [2, 16] = 3.78, p = .07$) or severe functional impairment ($F [2, 78] = 0.98, p = .38$). Similarly, among those with AD or dementia at baseline, poorer cognitive performance was related to worse functional impairment for those with mild functional impairment ($F [2, 128] = 6.46, p < .01; \eta^2 = .09$; Table 3). The effect sizes for comparisons of 1 vs. ≥ 2 ($d = -.66$) and 0 vs. ≥ 2 ($d = -.75$) were much larger than for the comparisons of 0 vs. 1 ($d = -.12$) impairment.

Objective 2: Baseline Cognition in Relation to Health Outcomes

Risk of AD or Dementia

After selecting for individuals who did not report AD or dementia at baseline and taking into account age, sex, and

education in our risk model, those who had ≥ 2 cognitive impairments at baseline (OR = 3.34, 95% CI = 2.27–4.92) were significantly more likely to report AD or dementia after ~4 years, compared to those who did not exhibit any cognitive impairments. A trend towards greater dementia risk was found in those who exhibited 1 cognitive impairment, compared to those with no impairments (OR = 1.45, 95% CI = 0.99–2.14; $p = .06$; Tables 4 and 5).

Risk of Institutionalization

Baseline cognition was not associated with an increased risk of institutionalization in those participants who were recorded as not being permanently institutionalized at baseline (Table 4).

Risk of Mortality

Of the non-institutionalized participants, those who exhibited 1 (OR = 1.58, 95% CI = 1.34–1.87) or ≥ 2 cognitive impairments at baseline (OR = 2.59, 95% CI = 2.17–3.09), were at a greater risk of mortality after ~4 years, than those who did not have impaired test performance (Tables 4 and 5).

DISCUSSION

These analyses are the first to characterize the relationship between cognitive performance, health status, and functional capacity, in the SHARE database. Specific attention was given to Waves 2 and 4 due to the lack of information regarding dementia status in Wave 1. The analyses demonstrate that cognitive performance impairments were strongly related to poorer health status and impaired functional capacity. Those with more than one cognitive impairment were at highest risk, but even one cognitive impairment at baseline predicted

TABLE 4.
Distribution of participants experiencing each outcome, based on cognitive performance at baseline in non-institutionalized individuals, and in those who reported the absence of AD or dementia at baseline.

Outcomes	Number of Cognitive Impairments at Baseline		
	0 N (%)	1 N (%)	≥2 N (%)
	<i>Non-institutionalized at baseline</i>		
Institutionalization (n = 48)	15 (31)	14 (29)	18 (37)
Mortality (n = 1,508)	237 (16)	521 (35)	654 (43)
	<i>Non-institutionalized and without dementia at baseline</i>		
Self-reported dementia diagnosis (n = 288)	42 (15)	83 (29)	153 (53)

TABLE 5.
Logistic regression modeling of baseline cognition (i.e., number of cognitive impairments) in relation to health outcomes at follow-up.

Cognitive Impairments at Baseline	Risk of AD or Dementia			Risk of Institutionalization			Risk of Mortality		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Model 1	Reference category = 0 cognitive impairments								
1	1.45	0.99-2.14	0.06	0.76	0.35-1.61	0.46	1.58	1.34-1.87	<0.001
≥2	3.34	2.27-4.92	<0.001	1.16	0.53-2.56	0.24	2.59	2.17-3.09	<0.001

*Models adjusted for age, sex, and education.

increased risk of adverse health outcomes and impaired functional capacity compared to those without cognitive impairments, and both effects were more pronounced in the group with even mild impairments in IADLs at baseline. The larger effect sizes for those with ≥ 2 cognitive impairments suggest a clinically important difference in impact on health outcomes between this group and those with one or no cognitive impairments.⁽¹⁶⁾ These findings suggest that in otherwise healthy, non-institutionalized individuals, impairments in ≥ 2 cognitive domains may be strongly associated with future cognitive decline (e.g., MCI, AD), poorer health status, and greater functional impairment.

Although SHARE included cognitive tasks that are typically part of standard dementia screening tools (e.g., orientation to time, mathematical ability, verbal fluency, and immediate and delayed recall), not all tasks were measured within each Wave, and those that were did not constitute a comprehensive assessment. However, tasks measuring specific cognitive domains have been shown to stand alone in differentiating healthy individuals from those with MCI or AD.^(13,14) Unfortunately, clinical diagnostic evidence for dementia (e.g., neuropsychological assessment, neuroimaging, biomarkers) was not obtained in SHARE, which constitutes a significant weakness for our analyses. That said, the cognitive domains that were included did provide some insight into the cognitive status of the SHARE sample, and they were shown

here to be highly associated with subsequent dementia reports. In consequence, it seems reasonable to use the measures here to evaluate how dementia might arise over the course of the SHARE study, even if the measures do not allow for more than a broad definition of dementia (cognitive impairment in more than one domain that is sufficiently severe to interfere with social or occupational functioning) to be assayed.

In addition, SHARE data were collected directly from participants and their proxies using the same line of questioning. This increases the consistency among individual respondents, and subsequently the internal validity of the dementia measure. Clinical diagnosis of dementia is a time-consuming process and, even after extensive testing, inconsistent and inaccurate diagnoses based on clinical features remain common.^(17,18) Diagnosis depends both on the diagnostic measures used and especially on the knowledge and experience of the clinician. Consistent self-reporting in surveys such as SHARE avoids this issue, although its weakness is a lack of extensive evaluation.

Various performance-based cognitive tests have been assessed for their utility in identifying those who are at high risk for cognitive decline or dementia and subsequent institutionalization.^(19,20) Of these, the Mini-Mental State Exam (MMSE)⁽²¹⁾ is used most frequently. Impairments on orientation to time, delayed recall (i.e., three-word recall task), and attention in the MMSE are the strongest predictors of conversion to dementia,⁽¹⁴⁾ especially in combination with self- and

informant ratings. Cognitive tasks assessing aspects of recall (i.e., word-list recall) and verbal fluency (i.e., animal naming) have been shown to be sensitive measures for discriminating between cognitively healthy individuals and those with MCI or AD.^(13,14) We sampled both participant and proxy reports, as well as those cognitive measures known to be sensitive to identifying MCI or early AD. In addition, although there are other markers of cognitive status within Wave 2 of the survey (i.e., orientation to time, numeracy), only those tested here were administered during both Waves. Even so, it would seem unnecessary to include additional measures, since those who exhibited more than two impairments were found to be at a very high risk of adverse health outcomes.

Cognition and mental capacity play an important role in determining risk of future adverse health outcomes. Based on our previous findings,⁽²⁾ three clusters of functional impairment (i.e., difficulty with ADLs and/or IADLs) were created, of which, the degree of cognitive impairment was associated with negative health outcomes in the “mild” functionally impaired group. Those exhibiting “moderate” and “severe” functional impairment, however, did not demonstrate a similar relationship between cognitive impairments and health outcomes, suggesting that cognitive performance is not useful in describing outcomes among individuals at later stages of functional decline. Not only is the establishment of clear guidelines for evaluating cognitive capability a valuable tool for aiding in the prediction of negative outcomes, such as dementia and mortality, but it appears also to be an important component in distinguishing healthy individuals from those with declining health status at early stages of functional decline.

SHARE provides an impressively large multinational characterization of health and aging in those over the age of 50. Not only does this database permit the longitudinal examination of the aging process and disease etiology, but it also provides insights into the quality of life and health of those in different nations. Because data collection is ongoing, characterization of cognitive impairments in relation to overall health on measures that are available within the most recent waves of SHARE will serve as a guide for future analyses that incorporate cognition into their models. Future analyses examining cognition in this cohort should take into consideration the clear delineation shown here between cognitive performance associated with future good health versus poor health and cognitive decline (e.g., a risk of MCI or dementia) so as not to exclude from subsequent analyses those who are not at a significant risk of declining health status (i.e., only choosing those with no cognitive impairment at baseline). As additional SHARE data become available, consistencies between measures and performance over an extended period of time may be examined.

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CONFLICT OF INTEREST DISCLOSURES

The authors report no conflicts of interest.

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