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Sleep Extension and Stable Sleep Schedules in Older Adults

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DEDICATION

"The ultimate lesson all of us have to learn is unconditional love, which includes not only others but ourselves as well" (Dr. Elisabeth Kübler-Ross). I dedicate this work to my son, Jacob, for teaching me the meaning of true unconditional love. He makes all of this worthwhile.

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ABSTRACT

There is consistent evidence demonstrating a "U-shaped" association between sleep duration and mortality, as well as several morbidities, such as increased systemic inflammation, decreased cognitive performance, and mood disturbances. Much of the information on long sleep is epidemiological in nature. The present study examined the associations between sleep duration and extension on mood, inflammation, and cognition. Ten (50-79 y) healthy adults who report sleeping 6-8 h were assessed on cognitive, emotional, and inflammatory measures in a cross-over design. Following a baseline week, participants were randomized to one of two three-week treatments: (1) a control treatment of habitual time in bed; and (2) a sleep extension treatment, in which participants extended their time in bed 2 hours longer than their median baseline time in bed. After 1 week of recovery, participants repeated the 1-week baseline and crossed over to the other treatment. Cognitive function was assessed after the first baseline and after each treatment. Sleepiness, fatigue, depression, anxiety, blood pressure, and heart rate were assessed weekly. Inflammation, glucose, and cholesterol were assessed following both treatments. As expected, sleep disturbance was associated with increased blood pressure and heart rate and negative changes in mood. Unexpectedly, more total sleep time was associated with improved blood pressure and heart rate. Total sleep time

and sleep disturbance was not associated with cognition, or clinician-administered mood assessments. The results of the study have important public health relevance, as it provides more insight on the associations of sleep duration on physiological health.

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List of Abbreviations

BDI-II ..... Beck Depression Inventory II

BMI ..... Body Mass Index

BP ..... Blood Pressure

BPMT ..... Block Pattern Memory Task

BSS ..... Beck Scale for Suicide Ideation

CDC ..... Center for Disease Control

CRP ..... C-Reactive Protein

EEG ..... Electroencephalography

EMG ..... Electromyography

ESS ..... Epworth Sleepiness Scale

HAM-A ..... Hamilton Anxiety Rating Scale

HAM-D ..... Hamilton Depression Rating Scale

HDL ..... High-Density Lipoproteins

HR ..... Heart Rate

IDO Indoleamine-2, 3-dioxygenase

IL-6 ..... Interleukin-6

LDL ..... Low-Density Lipoproteins

LMC ..... Lexington Medical Center

LTP ..... Long-Term Potentiation

MAF ..... Multidimensional Assessment of Fatigue

NSAID ..... Non-Steroidal Anti-Inflammatory

PAI-1 ..... Plasminogen Activator Inhibitor

PCA ..... Principal Components Analysis

PHQ-9 ..... Patient Health Questionnaire-9

PSG ..... Polysomnography

PVT ..... Psychomotor Vigilance Test

REM ..... Rapid Eye Movement

SAD ..... Seasonal Affective Disorder

SAFTEE ..... Systematic Assessment for Treatment and Emergent Events

SB5 ..... Stanford Binet Intelligence Scales, Fifth Edition

SMT ..... Sentence Memory Task

SOL ..... Sleep Onset Latency

STAI ..... State Trait Anxiety Scale

TIB ..... Time in Bed

TMT ..... Trail Making Test

TNF-α ..... Tumor Necrosis Factor - alpha

TST ..... Total Sleep Time

CHAPTER 1

INTRODUCTION

Sleep Extension and Stable Sleep Schedules in Older Adults

Popular opinion reflects the notion that much of society is chronically sleep deprived and should sleep as long as possible when given the chance. Epidemiological studies have clearly shown negative associations with extreme sleep duration, and many experimental studies have shown negative effects of sleep restriction. However, it has become apparent that sleeping longer is much more hazardous than previously thought, and is associated with increased risk of mortality. Longer sleep duration is also related to several morbidities, negatively affecting individuals both physiologically and psychologically. The current study will examine the impact of increased sleep duration on depression, inflammation, and cognitive performance in healthy, older adults.

1.1 ASSOCIATION OF SLEEP DURATION WITH MORTALITY AND MORBIDITY

More than 50 epidemiologic studies over a span of 50 years have consistently shown a "U-shaped" relationship between sleep duration and mortality. The associations have demonstrated progressively increased mortality associated with short sleep (≤ 6 hours; hr) and long sleep (≥ 8 hr), with approximately 7 hours of sleep per night being the optimal sleep duration for survival (Amagai et al., 2004; Hublin, Partinen, Koskenvuo, & Kaprio, 2007; Kripke, Garfinkel, Wingard, Klauber, & Marler, 2002; Lan, Lan, Wen, Lin, & Chuang, 2007; Patel et al., 2004; Tamakoshi & Ohno, 2004). Additionally, Ferrie

et al., (2007) found that changes in sleep duration, as in, decreased sleep and increased sleep durations, were associated with increased mortality risk. Some studies have found an increased risk of mortality with just long sleep duration, but not short sleep duration (Cohen-Mansfield & Perach, 2012).

Several meta-analyses have found increased all-cause mortality in both short and long sleepers (Cappuccio, D'Elia, Strazzullo, & Miller, 2010; Gallicchio & Kalesan, 2009). The relationship between sleep duration and mortality has been demonstrated in studies of millions of participants and in several different countries, with follow-up testing as long as 10-20 years. Additionally, these studies have statistically controlled for over 30 potential covariates, such as age, sex, obesity, depression, smoking, and cardiovascular health. It appears that older adults may be more vulnerable to the sleep duration extremes (Youngstedt & Kripke, 2004).

Similar U-shaped associations have been found between sleep duration and several morbidities, such as depression (Tamakoshi & Ohno, 2004), cardiovascular disease (Ayas, White, Manson, et al., 2003), diabetes (Ayas, White, Al-Delaimy, et al., 2003), stroke (Qureshi, Giles, Croft, & Bliwise, 1997), obesity (Taheri, Lin, Austin, Young, & Mignot, 2004), poor lipid profile (Kaneita, Uchiyama, Yoshiike, & Ohida, 2008; Williams, Hu, Patel, & Mantzoros, 2007), impaired cognitive function (Ferrie et al., 2011; Kronholm et al., 2009; Schmutte et al., 2007; Xu et al., 2011), and inflammation (Dowd, Goldman, & Weinstein, 2011; Grandner et al., 2013; Patel et al., 2009; Williams et al., 2007). Some studies have shown associations between morbidities, such as cardiovascular disease, in short sleepers, but not long sleepers (Hoevenaar-Blom, Spijkerman, Kromhout, van den Berg, & Verschuren, 2011). Much of the evidence for

the associations between sleep duration and mortality, as well as morbidities, is epidemiological in nature. Therefore, randomized controlled trials are needed to shed more light on the impact of sleep duration, or more specifically, long sleep duration. Youngstedt and Kripke's (2004) interpretation of Minino and Smith's (2001) Center for Disease Control (CDC) 2000 National Vital Statistics Report was that long sleep would be the fourth leading cause of death in the United States if it were truly the cause of the associated mortality. As a result, long sleep could be a greater risk to mortality than diabetes (Youngstedt & Kripke, 2004).

1.2 LONG SLEEP: A NEGLECTED RISK FACTOR

Considering the growing epidemiological evidence, the risks associated with long sleep may be as great as, if not greater, than the risks of short sleep (Youngstedt & Kripke, 2004). Some studies have found that a greater proportion of adults report sleeping 8 hours or greater per night, as compared to adults reporting sleeping 6 hours or less. This trend suggests that long sleep, or long time in bed (TIB), might be a greater societal risk than short sleep (Kripke et al., 2002). The potential risks related to long sleep, or long time in bed, have largely been ignored, in contrast to the vast literature on the risks of short sleep, sleep loss, and sleep debt (Balkin & Badia, 1988; Cohen, Doyle, Alper, Janicki-Deverts, & Turner, 2009; Karine Spiegel, Leproult, & Van Cauter, 1999; Van Dongen, Maislin, Mullington, & Dinges, 2003). Banks and Dinges (2007) completed a review on recent studies of sleep restriction; they noted that the experimental studies that restricted sleep found significant negative health effects on metabolic and endocrine functions, as well as increased inflammatory responses.

A few arguments drive the skepticism that long sleep could be harmful. First, there is debate whether we are actually a sleep deprived society; it is a popular belief that a longer sleep duration is healthy and normal. Second, when asked to report total sleep time (TST), individuals tend to erroneously report the time they spent in bed instead of time physically sleeping (Hublin et al., 2007). Additionally, there is always a risk of bias in self-reported measures, as individuals may be influenced by societal demands when responding to survey questions about sleep (Bliwise & Young, 2007). Third, there must be some underlying confounding mechanism that explains the relationship between long sleep and mortality and morbidity (Qureshi et al., 1997). Finally, many sleep researchers debate the association between long sleep and mortality and morbidity by arguing that no plausible mechanisms have been found to explain how long sleep could be hazardous (Foley, 2004; Knutson & Turek, 2006; Stamatakis & Punjabi, 2007). Interestingly, Foley (2004) expresses the need for randomized controlled trials in order to further research the potential mechanisms to explain the association between long sleep and mortality and morbidity. Foley (2004), Knutson and Turek (2006), and Stamatakis and Punjabi (2007) all acknowledge that epidemiological evidence is not causal and can only provide limited information. Each of these arguments will be further discussed in more detail.

1.3 ARE WE A SLEEP DEPRIVED SOCIETY?

According to the National Institutes of Health's Commission on Sleep Disorders Research (1993), modern industrialized societies are dangerously sleep-deprived. Some evidence suggests that average sleep duration has decreased since industrialization, possibly due to artificial light (Ekirch, 2001; Webb & Agnew, 1975), time restraints, and choosing to do other activities instead of sleep (L. Hale, 2005; Webb & Agnew, 1975).

Bliwise (1996) also reported that fatigue and tiredness has increased in the past few decades, and argued that Americans do not consider sleep to be important, and therefore do not prioritize it. Other population trends have paralleled the proposed decrease in sleep duration, such as increased diabetes (Spiegel, Knutson, Leproult, Tasali, & Van Cauter, 2005) and increased obesity (James, 2008). Increased expenditure of energy or increased stress may explain some of these trends (Taheri et al., 2004). However, there is conflicting evidence to suggest that, in the past 30 years, there has not been a decrease in sleep duration, or at least not a rise in individuals reporting less than 6 hours of sleep per night (Knutson, Van Cauter, Rathouz, DeLeire, & Lauderdale, 2010; Rowshan Ravan, Bengtsson, Lissner, Lapidus, & Björkelund, 2010). For example, Bin, Marshall, & Glozier (2012) recently completed a systematic review, examining self-reported sleep duration from the 1960s to 2000s. They concluded that there has been no consistent decrease in sleep duration across 15 countries in the 40-year span (Bin et al., 2012). Indeed, for many countries, there was an increase in sleep.

When not given time restraints, individuals tend to increase their sleep on weekends or in experimental laboratory settings (Webb & Agnew, 1975). However, this behavior may be an individual taking advantage of the situation, instead of signifying an attempt to rectify sleep debt. For example, extending sleep when given the option may be more similar to overeating on occasion. Individuals who report that they are less likely to sleep longer to replace sleep and are more likely to extend sleep due to pleasure or boredom and idleness (Palmer & Harrison, 1983). There is no consistent evidence that shows that sleeping 8 hours or more per night leads to better health, sleep, mood, quality of life, or even fewer accidents. Instead, impairments in mood, health, sleep, and quality

of life are reported in individuals who sleep more than 8 hours per night (D. E. Ford & Kamerow, 1989; Hartmann, Baekeland, & Zwilling, 1972).

1.4 LONG TOTAL SLEEP TIME OR LONG TIME IN BED?

When comparing self-reported sleep time to objective data, such as actigraphy, it appears that the total sleep time reported by older adults may actually be more indicative of time in bed (Kline et al., 2010). Kline et al. (2010) also report that, compared to objective data, self-reported long sleepers tend to overestimate their total sleep time by about 60 minutes. This overestimation is also found in average sleepers (Diane S. Lauderdale, Knutson, Yan, Liu, & Rathouz, 2008; Silva et al., 2007). Time in bed is more modifiable than altering total sleep time; spending less time in bed (i.e. restricting sleep) may potentially decrease the risk of mortality and morbidity (Youngstedt & Kripke, 2004).

Time in bed and total sleep time are highly correlated, and it is probable that individuals who report sleeping longer in epidemiological studies truly are sleeping longer. Patel, Blackwell, Ancoli-Israel, and Stone (2012) found that self-reported long sleepers not only spend more time in bed, but do indeed sleep longer objectively than self-reported average sleepers, as confirmed by both actigraphy and polysomnography (PSG). As mentioned previously, there are significant risks associated with objectively longer sleep (Kripke, Langer, Elliott, Klauber, & Rex, 2011; van den Berg et al., 2008), and associations of increased risk of mortality have been found in studies that discriminated between time in bed and total sleep time (Gale & Martyn, 1998; Kojima et al., 2000; Kripke et al., 2011). Much of the epidemiological evidence is based on self-reports, but corroborating self-reports through the use of objective measurement, such as

actigraphy, would increase the validity and integrity of the data and can provide more valid and reliable information on the hazardous effects of long sleep.

1.5 ALTERNATIVE EXPLANATIONS FOR MORTALITY/MORBIDITY ASSOCIATION WITH LONG SLEEP

The associations of long sleep with mortality and morbidity found in epidemiological studies might be explained by multiple psychobiological and sociobehavioral factors. These factors include sleep fragmentation (Lan et al., 2007; Youngstedt & Kripke, 2004), poor sleep quality (Lan et al., 2007), sleep apnea (Bliwise, King, & Harris, 1994; Qureshi et al., 1997), daytime sleepiness (Bliwise et al., 1994), depression (Patel, Malhotra, Gottlieb, White, & Hu, 2006), low socioeconomic status ([SES]; (Hale, 2005; Lauderdale, 2006; Patel et al., 2006), unemployment (Kronholm, Härmä, Hublin, Aro, & Partonen, 2006), race (Lauren Hale & Do, 2007; Lauderdale, 2006), and low physical activity (Hublin et al., 2007; Morgan, 2007; Taheri et al., 2004). Many of the factors are also associated with significant health problems; long sleep could indicate declining health (Youngstedt & Kripke, 2004).

Epidemiological studies attempt to statistically control for factors that are believed to influence the relationship between long sleep and mortality and morbidity. It can be argued that perhaps not all the factors are controlled for sufficiently. Additionally, the interactions between correlated variables may not be statistically examined in an efficient manner. One major concern for control of some of the factors in epidemiological studies is how specifically it may impact long sleep. For example, if long sleepers tend to be less physically active (Hublin et al., 2007; Morgan, 2007; Taheri et al., 2004), then controlling for exercise could underestimate the effects of long sleep on

mortality. In order to provide more evidence on how long sleep may be hazardous, randomized controlled trials are needed. Additionally, randomized controlled trials help solve the issue of difficult to control confounding factors found in epidemiological research and would provide more evidence on the potential hazardous nature of long sleep.

1.6 EXPERIMENTAL STUDY OF SLEEP EXTENSION

Sleep extension has not been studied rigorously in the sleep field. A few studies were completed in the late 1960's and early 1970's that examined sleep extension in healthy young men (Globus, 1969; J. M. Taub & Berger, 1969; Taub & Berger, 1973). In a recent study of young adults, we asked participants to increase their sleep by 3 hours per night for one week (Reynolds, Bowles, Saxena, Fayad, & Youngstedt, 2014). Although limited by a small sample size, we found increased symptoms of depression and anxiety, as well as increased systemic inflammatory markers in individuals who extended sleep, compared to those who maintained their normal sleep patterns. To date, the Reynolds et al. (2014) study is the most comprehensive randomized controlled study that has examined the effects of sleep extension.

The current trend is to use sleep extension as an intervention for individuals who are habitually sleep deprived in order to improve specific health conditions, such as blood pressure (Haack, Serrador, & Cohen, 2013), obesity (Cizza et al., 2010), fasting insulin sensitivity (Leproult, Deliens, Gilson, & Peigneux, 2014), cognitive performance (Lucassen et al., 2014), and food desirability (Tasali, Chapotot, Wroblewski, & Schoeller, 2014). However, no studies to date have been published examining the effects of sleep extension in habitually normal sleeping older adults. In order to fully understand the

impact of longer sleep, it is important to complete randomized controlled trials. Additionally, it is important to examine sleep extension in different age groups, as the effects of extended sleep may impact age groups differently.

1.7 HOW MIGHT LONG SLEEP BE HAZARDOUS?

It can be posited that excessive amounts of all healthful behaviors, such as exercise, caloric intake, and exposure to sunlight, could be hazardous. Several mechanisms explain how long sleep, or spending more time in bed, could be hazardous (Youngstedt & Kripke, 2004). Physically spending more time in bed could be harmful to health, as significant impairments in insulin insensitivity and cardiovascular function have resulted from just minimal bed-rest of 2 (Schneider et al., 2009) to 5 (Hamburg et al., 2007) days of bed-rest. Additionally, long sleep has been associated with lower levels of daytime physical activity and more sedentary behavior (Hublin et al., 2007).

Long sleep is correlated with increased sleep fragmentation; poor health outcomes have also been associated with sleep fragmentation in experimental studies (Horner, 1996; Stepanski, 2002). There is also an association between lipid levels and long sleep, with long sleep potentially leading to abnormal cholesterol levels, or dyslipidemia (Kaneita et al., 2008; van den Berg et al., 2008). Another mechanism by which long sleep is harmful is that extended time in bed is correlated with decreased light exposure, and light exposure is highly related to depression (Bhattacharjee, 2007). Additionally, individuals who sleep longer are exposed to a shorter photoperiod, or day-length, and decreased exposure to light could disrupt the circadian pacemaker and perpetuate long sleep duration (Aeschbach et al., 2003). An altered photoperiod has been associated with mortality in several species (Gordon, 1998). Lethargy and grogginess are commonly

reported by long sleepers and excessive sleeping (Globus, 1969; Hartmann et al., 1972; J. M. Taub & Berger, 1969; John M. Taub & Berger, 1973) and may actually indicate underlying depression, cognitive impairment, and/or cytokine imbalance caused by excessive sleeping.

1.8 LONG SLEEP AND INDIVIDUAL MECHANISMS

1.8.1 Long sleep and inactivity. Long sleep has been associated with sedentary behavior and low levels of daytime physical activity (Hublin et al., 2007). This association could be explained by long sleepers making less time for physical activity and instead opting for more sedentary behaviors, such as watching television (Basner et al., 2007). The association between long sleep and lower daytime physical activity levels could also be explained by feelings of lethargy commonly reported by long sleepers and excessive sleeping (Globus, 1969; Hartmann et al., 1972; J. M. Taub & Berger, 1969; John M. Taub & Berger, 1973).

Only one extra hour per day of sedentary behavior, such as watching television or using a computer, has been associated with adverse health effects, such as metabolic syndrome (Ford, Kohl, Mokdad, & Ajani, 2005). Bed-rest studies have shown significant impairments in insulin sensitivity and cardiovascular function after just 2 days (Schneider et al., 2009) and 5 days of bed rest (Hamburg et al., 2007). More prolonged bed-rest elicits profound deficits in bone density, muscle function, systemic inflammation, and insulin resistance (Brower, 2009), as well as mood disturbances (Ishizaki et al., 2002). Associations have been made between lipid levels and long sleep, with long sleep potentially leading to abnormal cholesterol levels, or dyslipidemia (Kaneita, Uchiyama, Yoshiike, & Ohida, 2008; van den Berg et al., 2008).

1.8.2 Long sleep and sleep fragmentation. Long sleep is associated with increased sleep fragmentation (Youngstedt & Kripke, 2004). Additionally, long sleepers tend to report more body aches and pains compared to shorter sleepers (Hartmann et al., 1972), which suggests that long sleepers experience more pain due to sleep disruption. Increased sleep fragmentation has been associated with poor health outcomes in experimentally induced sleep fragmentation (Horner, 1996; Stepanski, 2002), as well as epidemiologic research (Bennett, Barbour, Langford, Stradling, & Davies, 1999). For example, increased sleep fragmentation is associated with degraded mood and decreased cognitive performance (Bonnet, 1985, 1986; Stepanski, 2002). Furthermore, van den Berg et al. (2008) found an association between unhealthy cholesterol levels and long sleep, and posited that sleep fragmentation and longer time in bed explain this association in older adults. Disrupted sleep may even play a part in predicting mortality (Dew et al., 2003).

Sleep fragmentation is usually defined as arousal during sleep that results in increased electroencephalography (EEG) frequency of at least 3 seconds, as an increase even at this level is correlated with significantly increased daytime sleepiness. Other definitions also include an electromyography (EMG) amplitude increase (Stepanski, 2002). The Sleep Continuity Theory attempts to explain how fragmented sleep impacts daytime function. In order for sleep to be restorative, an individual must sleep consecutively (uninterrupted) for a minimum of 10 minutes (Bonnet, 1985, 1986). Carskadon, Brown, and Dement (1982) found that older adults tend to have substantially more fragmented sleep, and the decreased continuity of sleep was highly correlated with daytime well-being.

The effects of sleep fragmentation mimic those of sleep deprivation (Stepanski, 2002). In fact, it is argued that sleep fragmentation actually results in partial sleep deprivation, which leads to increased daytime sleepiness. Sleep debt may be accrued as stage one sleep is increased in combination with decreased total sleep time. This argument is also fueled by the notion that stage one sleep may not be as restorative as other stages of sleep (Stepanski, 2002). As a further explanation, even though an individual may spend more time in bed and have a greater total number of hours of sleep, sleep fragmentation results in decreased consecutive minutes of sleep. The decrease of depth and continuous waking essentially leads to sleep loss, as well as symptoms that are commonly associated with sleep deprivation.

Impairments in cognitive performance are found in studies of disrupted sleep (Bonnet, 1985, 1986). A few hypotheses attempt to explain the relationship between long sleep and cognitive performance. Fatigue and tiredness, which are reported in sleep extension, (Taub & Berger, 1969; Taub & Berger, 1973) long sleepers (Hartmann et al., 1972), and excessive sleeping (Globus, 1969), may indicate that spending more time in bed is not beneficial. Poor sleep quality is also believed to be the culprit that leads to impaired cognitive performance (Xu et al., 2011). Another hypothesis attempting to explain impaired cognitive performance is that prolonged elevation of plasma melatonin levels in the daytime (Aeschbach et al., 2003) could inhibit memory formation (Kronholm et al., 2009; Rawashdeh, de Borsetti, Roman, & Cahill, 2007).

Dew et al. (2003) found that specific sleep parameters predicted the probability of mortality in older adults. They argued that a plausible explanation is that disrupted sleep could indicate dysfunction in brain regions associated with thalamocortical circuits,

which are responsible for maintaining sleep. Additionally, evidence may suggest that changes in the immune system are modulated by sleep disturbances (Dew et al., 2003).

1.8.3 Long sleep and inflammation. Recent evidence has shown that inflammation may serve as a mediator of the association of long sleep with mortality (Penninx, Milaneschi, Lamers, & Vogelzangs, 2013). Several studies have shown an association between long sleep duration and increased levels of inflammation (Dowd et al., 2011; Grandner et al., 2013; Patel et al., 2009; Williams et al., 2007). Longer sleep duration may affect cytokines that are important for regulating inflammation. Increased levels of proteins and cytokines, such as C-reactive protein (CRP) and interleukin-6 (IL-6), are associated with an increased risk of diseases such as diabetes and cardiovascular disease. Since sleep duration may be involved in the regulation of these cytokines, these associations may potentially have a significant impact on long-term health (Patel et al., 2009). Moreover, increased levels of IL-6 and CRP in older adults have been correlated with increased risk of mortality (Harris et al., 1999). It is important to understand the physiology of inflammation and how sleep may affect these processes, especially in older adults.

Elevated systemic inflammation is a response to infection and/or tissue damage; elevations in proteins and cytokines such as CRP and IL-6, respectively, without infection or tissue damage are considered abnormal and increase the risk of developing diseases such as cardiovascular disease and diabetes. A dysregulated inflammatory response may result from the activation of the immune system in this abnormal circumstance. In response to a perceived threat, pro-inflammatory cytokines (such as IL-6 and tumor necrosis factor [TNF]-α) are produced. Anti-inflammatory cytokines are

called into action to reduce pro-inflammatory cytokines by attenuating production or working at the receptor level. Then, acute phase proteins (such as CRP) are synthesized, leading to the systemic inflammatory response (Penninx et al., 2013).

The direction of the relationship between long sleep duration and increased inflammation is not clearly understood. It is important to recognize that understanding the causal nature of the relationship relies on experimental study to determine whether increased inflammation causes or is caused by long sleep duration. Long sleep may directly cause increased inflammation in that cytokine expression may be impacted by the more frequent awakenings and increased sleep fragmentation (Dowd et al., 2011). However, it is also posited that cytokines may have a direct effect on the brain and predispose an individual to longer sleep durations, since cytokines, such as IL-6, tend to induce sleep. Additionally, an increase in sleep duration may correspond with declining health and the aging process in individuals over 60 (Dowd et al., 2011).

Dowd et al. (2011) recently conducted a study examining self-reported sleep duration and levels of inflammatory biomarkers and found that higher levels of IL-6 were associated with longer sleepers in the Taiwanese population. There was no significant relationship between short sleep and higher inflammation levels. Since this was a prospective study, it was concluded that the relationship between long sleep and increased inflammation was not due to acute illness, but to physiological processes that are expressed in a longer time period (Dowd et al., 2011). In a recent study, researchers also found an association between long sleepers and increased levels of CRP, as well as no association between short sleep duration and CRP after adjusting for medical and

sleep comorbidities (Grandner et al., 2013). Higher levels of both CRP and IL-6 have been found in long sleepers (Patel et al., 2009).

Conversely, Matthews et al. (2010) found that shorter sleep durations, as measured by PSG, were associated with higher levels of CRP in African Americans and higher plasminogen activator inhibitor (PAI-1) in Chinese individuals. Unfortunately, the authors did not examine the relationship between longer sleep duration and biomarkers of inflammation due to the small sample of individuals who reported sleeping greater than 8 hours per night. However, they found interesting relationships between other sleep characteristics and biomarkers of inflammation: in initial models, sleep disordered breathing, sleep continuity, and quality were associated with coagulation and levels of inflammation (Matthews et al., 2010).

Increased levels of TNF-α and IL-6 are reported in individuals with disorders who exhibit excessive daytime sleepiness (Papanicolaou, Wilder, Manolagas, & Chrousos, 1998; Vgontzas et al., 1997), such as individuals with sleep apnea (Vgontzas et al., 1997). Individuals with sleep disordered breathing, like sleep apnea, may spend more time in bed in order to make up for fragmented sleep (Taheri et al., 2004). Moreover, lethargy and grogginess, as reported in sleep extension (Taub & Berger, 1969; Taub & Berger, 1973), long sleepers (Hartmann et al., 1972), and excessive sleeping (Globus, 1969), may indicate cytokine imbalance (Papanicolaou et al., 1998; Vgontzas et al., 1997). Evening levels of inflammatory biomarkers in addition to slow wave sleep have been shown to predict fatigue (Thomas, Motivala, Olmstead, & Irwin, 2011). Long time in bed may lead to increased sleep fragmentation and decreased sleep depth (Youngstedt & Kripke,

2004). Furthermore, decreased sleep depth, as in less slow wave sleep, is correlated with both daytime fatigue and increased inflammation (Thomas et al., 2011).

There is clear evidence that inflammation has strong correlations with sleep depth, sleep quality, and sleep duration, as well as physiological symptoms such as fatigue. Additionally, increased levels of inflammation have been associated with cognitive decline (Gimeno, Marmot, & Singh-Manoux, 2008; Weaver et al., 2002). Inflammation has also been associated with other morbidities, such as mood disorders. Recent evidence has shown correlations between inflammation and anxiety (Vogelzangs, Beekman, de Jonge, & Penninx, 2013), as well as depression (Penninx et al., 2013).

1.8.4 Long sleep and mood/emotion. Depression and sleep disturbances have high rates of co-occurrence (Tsuno, Besset, & Ritchie, 2005), and depression is associated with long sleep duration (Breslau, Roth, Rosenthal, & Andreski, 1996; Ferrie et al., 2011; Ford & Kamerow, 1989; Hartmann et al., 1972; Tsuno et al., 2005). In their meta-analysis on sleep and depression, Tsuno et al. (2005) discussed some of the most common alterations in sleep architecture found in individuals with depression, including impaired sleep efficiency and decreased sleep depth. Additionally, individuals with depression were more likely to have higher levels of rapid-eye movement (REM) sleep, such as shortened REM sleep latency and increased density of eye movements during REM sleep (Tsuno et al., 2005).

The relationship between sleep and psychiatric disorders, such as depression and anxiety, is complex. The direction of this relationship is not well understood, however, we do have correlational evidence of the relationship between sleep and mood disorders. Studies have consistently shown that sleep disturbances predict major depressive

episodes (Breslau et al., 1996; Tsuno et al., 2005). Gillespie et al. (2012) conducted a twin study and examined the relationship between measures of self-reported disrupted sleep and symptoms of depression and anxiety. They found an interesting age-difference trend: the relationship between disrupted sleep and anxiety and depression was reciprocal in older women, whereas, in younger women, anxiety and depression were associated with disrupted sleep. The relationship in men was not as clear (Gillespie et al., 2012). The combination of sleep abnormalities, such as shortened REM sleep latency and reduced slow wave sleep, may be more strongly associated with mood disorders (Tsuno et al., 2005). Interestingly, Ford and Kamerow (1989) found that individuals who reported hypersomnia of longer durations had a higher chance of reporting major depression than those who experienced a recent episode of hypersomnia. Moreover, individuals whose hypersomnia was alleviated still had a higher risk of reporting depression (Ford & Kamerow, 1989).

As mentioned earlier, lethargy and grogginess are reported following sleep extension, (Taub & Berger, 1969; Taub & Berger, 1973) in long sleepers (Hartmann et al., 1972), and following excessive sleeping (Globus, 1969), and may contribute to depression. Light exposure may be another mechanism by which sleep and depression are related. Less exposure to light is associated with depressed mood (Bhattacharjee, 2007). Individuals who sleep longer are exposed to a shorter photoperiod, and this decreased exposure to light could disrupt the circadian pacemaker and perpetuate long sleep duration (Aeschbach et al., 2003).

Moreover, an altered photoperiod has been associated with mortality in several species (Gordon, 1998). Individuals with seasonal affective disorder (SAD) are more

likely than other subtypes of depression to report hypersomnia. Additionally, there is evidence that supports the hypothesis that individuals with SAD have circadian phase delay, as exposure to bright light in the morning is used as a treatment to cause phase advance (Bhattacharjee, 2007; Tsuno et al., 2005). Furthermore, Bhattacharjee (2007) argued that some forms of depression may be a result of a depressed individual's out of sync circadian clock with the sleep-wake cycle. Depressive symptoms may lead to impairments in cognition, as associations between cognitive decline and depression in older adults have been well-established (Bielak, Gerstorf, Kiely, Anstey, & Luszcz, 2011).

1.8.5 Long sleep and cognitive impairment. Recent epidemiological studies show an interesting relationship between sleep duration and cognitive functioning. More specifically, many of the recent studies examined the impact of short and long sleep durations on fluid intelligence. Fluid intelligence is described as the ability to reason and think abstractly in new situations and environments, and is related to performance in higher-order cognitive tasks (Heitz, Unsworth, & Engle, 2005). Working memory tasks demonstrate an individual's ability to control attention, which is a construct of fluid intelligence. The executive control is also considered a construct of attention and related to fluid intelligence (Heitz et al., 2005). Inhibition (including interference control and selective attention), working memory, and cognitive flexibility make up the three core executive functions (Diamond, 2013).

Poor quality of sleep may derange metabolic and endocrine function, which in turn would result in cognitive dysfunction (Jelicic et al., 2002; Spiegel et al., 1999). Nebes, Buysse, Halligan, Houck, and Monk (2009) utilized tasks measuring working

memory, inhibition, and attention through N-back, Stroop, and Trail-Making, respectively, and found that sleep latency and efficiency were correlated with cognitive performance. Other sleep-related factors, such as daytime sleepiness and napping, are associated with cognitive impairment. These sleep-related factors could be due to other disorders; for example, in patients with sleep apnea, breathing pauses during sleep may cause repeated anoxia, leading to cerebral white matter change and subsequent cognitive decline (Xu et al., 2011).

Studies examining both verbal and non-verbal memory in older adults demonstrated memory impairments in relation to sleep duration. Verbal short-term and general memory impairments were found in older adults sleeping longer than 8 hours after controlling for covariates, such as depression, medication, and age, (Schmutte et al., 2007; Xu et al., 2011). Mograss, Guillem, and Stickgold (2010) conducted a study examining face recognition and sleep duration and found that long sleepers failed to retain the old information in face recognition tasks. Interestingly, long and average sleepers demonstrated a positive correlation in terms of accuracy in face recognition tasks and sleep duration, although short sleepers demonstrated a negative correlation and higher accuracy compared to both average and long sleepers. The researchers suggested that the short sleepers accumulated NonREM (Rapid Eye Movement) slow-wave sleep more rapidly at the beginning of the night, resulting in better performance in the face recognition tasks compared to average and long sleepers. It is suggested that the transition and duration of the stages of sleep are related to memory consolidation and potentiated networks, explaining the short sleepers' faster reaction times and better memory performance (Mograss et al., 2010).

Disrupted sleep may cause sleepiness, which may result in reduced vigilance; this reduced vigilance may in turn negatively influence executive functioning (Blackwell et al., 2011). Long sleepers have demonstrated decreased performance in vigilance tasks (Blackwell et al., 2011; Taub, Globus, Phoebus, & Drury, 1971; Taub & Berger, 1969) and tend to make more omissions in cognitive tasks (Mograss et al., 2010; Taub & Berger, 1969). Younger and older adults long sleepers also demonstrate decreased psychomotor speed and cognitive functioning related to verbal memory (Kronholm et al., 2009).

Cognitive aging is the notion that not everyone experiences the same rate of cognitive decline (Ferrie et al., 2011). Ferrie et al. (2011) found as much as a 3-8 year increase in cognitive aging when measuring cognitive functioning in older adults who slept greater than 8 hours per night. Faubel et al. (2009) found that individuals who slept 11 hours or more per night demonstrated a 10-year increase in age on a mental status exam, even after adjusting for confounds such as sleep apnea and health-related quality of life. Additionally, associations were discovered between sleep fragmentation and mental status scores related to memory and naming (Blackwell et al., 2011).

Blackwell et al. (2006) found that objectively measured sleep was related to poorer cognition, but not total sleep time. The researchers found that higher sleep latency in women was associated with higher risk of cognitive impairment, as was higher wake after sleep onset; these results suggest that disturbance of sleep, rather than sleep quantity, may affect cognition (Blackwell et al., 2006). Moreover, sleep quality, timing, and amount are all potential contributors to individual variability in age-associated cognitive impairment (Nebes et al., 2009). Nebes et al. (2009) suggested different

mechanisms, such as cortical atrophy, white matter pathology, and reductions in neurotransmitter binding, which may explain the age-associated individual differences in cognitive decrements.

It can be posited that longer sleep duration may be caused by cognitive deficits, however, longitudinal studies are able to show changes in sleep duration, which provides evidence that this reverse causality is unlikely (Ferrie et al., 2011). Another plausible hypothesis is that decreased cognitive performance may be due to internal factors deteriorating the brain, which is reflected in sleep duration and efficiency in cognitive processing (Kronholm et al., 2011). Other theories for poor cognitive performance in longer sleepers include the following: fatigue or tiredness, as individuals who sleep longer may not be benefiting from the additional time in bed; some underlying neurological disease; passive way of life (Kronholm et al., 2009); and prolonged elevation of plasma melatonin levels in the daytime (Aeschbach et al., 2003), which could inhibit memory formation (Kronholm et al., 2009; Rawashdeh et al., 2007).

1.9 RELATIONSHIPS BETWEEN MECHANISMS

Associations between longer duration of sleep and individual factors, such as inflammation, mood/emotion, and cognitive impairment, have been established in the literature. It is important to note that not only are there correlations between longer sleep duration and physiological and psychological factors, many of the factors are intercorrelated. For example, inflammation is related to mood and emotion, as well as cognitive performance; cognitive performance is also associated with mood and emotion. However, the causative nature and interactions of these relationships is not well understood.

1.9.1 Inflammation and emotional/mood disturbances. Systemic inflammation is related to pain and discomfort, and both inflammation and physical pain are associated with emotional or mood disturbances. When investigating the psychological differences between long and short sleepers, Hartmann et al. (1972) found that long sleepers tended to have more complaints of body aches and pains, as well as mild to moderate neurotic issues. They reported that long sleepers were worriers and more likely than short sleepers to be anxious and mildly depressed (Hartmann et al., 1972). Studies examining patients with inflammatory diseases have found associations between pain, depression, and sleep disturbances (Li, Zhang, Zhu, Du, & Huang, 2012; Wolfe, Michaud, & Li, 2006). Additionally, studies in the general population have shown that poorer quality of sleep is correlated with depression (Sayar, Arikan, & Yontem, 2002).

There is a growing body of evidence showing associations between depression and increased systemic inflammation. More specifically, research shows that there is an association between depression and up-regulated inflammatory responses, such as increased acute phase reactive proteins and pro-inflammatory cytokines. A possible mechanism by which pro-inflammatory cytokines impact mood is through the induction of the indoleamine-2, 3-dioxygenase (IDO) enzyme by pro-inflammatory cytokines. IDO catalyzes the synthesis of kynurenine, which is a metabolite that comes from dietary tryptophan. Since tryptophan is necessary for the synthesis of serotonin and melatonin, the resulting depletion of tryptophan might contribute to symptoms of depression (Penninx et al., 2013).

Furthermore, IDO activation increases the synthesis of tryptophan catabolites (TRYCATs), an *N*-methyl-D-aspartate (NMDA) agonist. Higher levels of TRYCATs,

which have been reported in depressed patients, may disturb neurotransmitter responses along glutamatergic pathways, causing hippocampal damage. This damage could contribute to symptoms of depression. Higher levels of TRYCATs in depressed patients have also been associated with somatic health complaints, such as pain (Penninx et al., 2013). In a recent review, Penninx et al. (2013) found that individuals with atypical depression, marked by hypersomnia, fatigue, and mood reactivity, had higher levels of inflammation compared to other types of depression. It could be posited that individuals with atypical depression experience increased inflammation due to spending more time in bed, which could also explain the increased fatigue and hypersomnia. Long time in bed may lead to increased sleep fragmentation and decreased sleep depth (Youngstedt & Kripke, 2004), which is correlated with both daytime fatigue and increased inflammation (Thomas et al., 2011).

There is an association between anxiety and increased systemic inflammation. A recent study found that men who had a current anxiety disorder also had increased CRP levels, and both men and women with late onset of anxiety displayed low-grade systemic inflammation. The relationship between increased inflammation and anxiety could be explained by confounds such as poor lifestyle behaviors, subclinical cardiovascular disease preceding both inflammation and anxiety, or immune dysregulation. However, it is unclear of the causal direction of immune dysregulation (Vogelzangs et al., 2013). Additionally, Li et al. (2012) found an association between poor sleep and increased symptoms of depression, anxiety, and pain in individuals with ankylosing spondylitis, a chronic inflammatory disease. Poor sleep, caused by sleep disruption, fragmentation, or restriction, causes increased sensitivity to pain, or hyperalgesia. Since the pain threshold

is lowered and the pain signals are amplified, patients experience increased attention to pain and further disrupted sleep (Li et al., 2012). Other confounding factors contributing to the relationship between inflammation and mood include the interaction between inflammation, mood, and cognitive function.

1.9.2 Inflammation and cognitive function. Increased levels of inflammation have been associated with cognitive decline in older adults (Gimeno et al., 2008; Weaver et al., 2002). As previously discussed (see "Inflammation and emotional/mood disturbances"), the impact of the depletion of tryptophan, which is needed for the synthesis of melatonin and serotonin, could impact both depression (Penninx et al., 2013) and memory. Individuals who sleep longer may have prolonged elevation of plasma melatonin levels in the daytime (Aeschbach et al., 2003), which could inhibit memory formation (Kronholm et al., 2009; Rawashdeh et al., 2007). Inflammation in the hippocampus may lead to deficits in learning and memory (Monje, Toda, & Palmer, 2003); hippocampal long-term potentiation (LTP) is considered to be a cellular model for learning and memory (Bellinger, Madamba, Campbell, & Siggins, 1995). One theory, primarily an Alzheimer's disease model, attempts to explain why inflammatory cytokines have a negative impact on LTP: the theory proposes that β-amyloid protein-induced secretion of IL-6 is increased after a self-amplifying neurometabolic cascade and results in neuronal injury (Weaver et al., 2002).

In an attempt to further understand how inflammation in the hippocampus is related to LPT, Bellinger et al. (1995) placed electrodes in the dentate gyrus granule cell layer and the dentate molecular layer of mice with detectable levels of IL-6 gene expression, and those with no gene expression. LTP was elicited and evoked potentials

in hippocampal slices were examined. It was discovered that the transgenic mice had significantly reduced dentate mean LTP. It has been postulated that, in cognitive disorders associated with viral infection, IL-6 could be a contributing factor since IL-6 has been shown to reduce NMDA-mediated toxicity in the hippocampus. One hypothesis as to why LTP is reduced is that IL-6 may inhibit NMDA receptor function or NMDA-mediated second messenger systems. Bellinger et al. (1995) suggested that short- and long-lasting neuronal plasticity can be disrupted by the over-expression of cytokines, which could lead to a profound impact on cognitive function. Furthermore, inflammation not only inhibits neurogenesis, it has also been found that neurogenesis can be restored if inflammation is blocked (Monje et al., 2003).

Gimeno et al. (2008) found that both CRP and IL-6 are associated with low cognitive performance and decline in older adults. More specifically, associations were found of CRP with inductive reasoning and vocabulary, whereas IL-6 was related to fluency. One explanation for these results is that the differences in cognitive function are due to activation of different regions in the brain; for example, the prefrontal cortex is involved with inductive reasoning, the frontal and temporal lobe is related to tasks of verbal fluency, and the left front lobe is involved with verbal ability (Gimeno et al., 2008). Moreover, Weaver et al. (2002) also conducted a longitudinal study and reported that IL-6 predicted increased risks for cognitive decline at follow-up visits. The researchers found that high levels of IL-6 were associated with poorer baseline cognitive function (Weaver et al., 2002). A recent study discovered a negative correlation between IL-6 levels and cognitive performance in depressed and healthy older adults; recall ability

and encoding ability decreased as IL-6 levels increased (Elderkin-Thompson, Irwin, Hellemann, & Kumar, 2012).

1.9.3 Emotional/mood disturbances and cognitive function. Associations between cognitive decline and depression (Bielak et al., 2011), as well as anxiety (Bunce, Batterham, Mackinnon, & Christensen, 2012), in older adults have been well-established. As many researchers question the causal direction of cognitive decline and depression, Bielak et al. (2011) used temporal models over a 15 year period to conclude that symptoms of depression predicted declines in perceptual speed in older adults. The analysis was repeated after removing participants who possibly had dementia, and the same pattern was found. However, when Bunce et al. (2012) removed possible dementia and mild cognitive impairment data, their initial significant associations of depression symptoms and cognitive variables became insignificant. Interestingly, the associations between anxiety and cognitive variables increased in strength. There are several hypotheses that attempt to explain the relationship between depression and dementia, and include changes in inflammation in the brain, increased cortisol production that causes hippocampal atrophy, vascular disease, and decreased nerve growth factor (Bunce et al., 2012).

Although the potential presence of dementia complicates the relationship between cognition and depression, other mechanisms have been suggested for the link between cognition and depression. For example, it is hypothesized that an individual with declining cognitive abilities may react to this awareness of declining ability by developing symptoms of depression. It is also proposed that depression may be a risk factor for decreased cognitive performance (Singh-Manoux et al., 2010). Singh-Manoux

et al. (2010) suggested that the depression as a risk factor for cognitive decline may explain the results of their study, which found an association between depression and decreased cognitive ability in older adults. However, in contrast to other proposed hypotheses, vascular disease was not shown to be a factor in the relationship between depression and cognitive ability (Singh-Manoux et al., 2010).

It has already been established that there are associations between levels of systemic inflammation and cognitive performance. Elderkin-Thompson et al. (2012) make the case that memory encoding performance can be predicted by biomarkers of inflammation (e.g. IL-6), and that poor performance can be mistaken for mild cognitive impairment or dementia. It is suggested that this immunologic imbalance could result in inaccuracies in determining older adults' cognitive abilities (Elderkin-Thompson et al., 2012). Sleep is also a factor in terms of cognition and mood disturbances, especially in older adults. Depressive symptomatology may be a mediating variable in terms of cognitive decline in older adults who experience sleep disturbances (Jelicic et al., 2002).

1.10 TIME IN BED EXTENSION IN OLDER ADULTS

Age-related changes in sleep duration are likely related to age-related changes in the circadian sleep-wake rhythm (Prinz, Vitiello, Raskind, & Thorpy, 1990). Even with these changes in sleep duration, many older adults voluntarily tend to spend more time in bed as a result of compensating for age-related sleep disturbances (Carskadon et al., 1982; Prinz et al., 1990) or simply out of habit (Youngstedt et al., 2009). Furthermore, (Carskadon et al., 1982) found that older adults tend to have substantially more fragmented sleep, and the decreased continuity of sleep was highly correlated with daytime well-being. There is evidence that sleep restriction benefits overall well-being

and sleep quality, improving both sleep depth and continuity (Hoch et al., 2001), and may ultimately lead to reducing mortality and morbidity associated with long sleep (Youngstedt et al., 2009). Even with evidence of the potential hazardous effects of long sleep or long time in bed in older adults, there are still conflicting opinions on the associations.

On the other hand, extending time in bed could beneficially facilitate more sleep. Associations have been found between increased pro-inflammatory responses elicited by sleep disturbances resulting in loss of sleep (M. R. Irwin, Carrillo, & Olmstead, 2010; M. R. Irwin, Wang, Campomayor, Collado-Hidalgo, & Cole, 2006). These associations may be the mechanism by which poor sleep quality or sleep loss accelerates morbidity in aging. Because of this evidence of short sleep and its relationship to increased inflammation, it is plausible that extending sleep may result in decreased inflammation. Older adults may be more vulnerable to the risks of extreme sleep durations, such as short sleep, as older adults have shown the highest mortality rates related to sleep duration (Youngstedt & Kripke, 2004).

However, it is plausible that sleep extension may have hazardous effects on older adults. It has been demonstrated that healthy adults with reduced sleep efficiency and prolonged sleep latency had a two-fold elevated risk of mortality compared to normal sleepers (Dew et al., 2003). Additionally, extension of sleep could produce greater sleep fragmentation, mimicking sleep loss. Disordered sleep, in association with a decrease in sleep depth, is associated with increased inflammation (Irwin et al., 2004). Aging is correlated with increased nocturnal wakefulness (Bliwise, 1993) and increased time in

bed (Hoch et al., 2001; Prinz et al., 1990), potentially leaving older adults even more vulnerable to risks of mortality and morbidity.

1.11 CONCLUSION

Long sleep, or long time in bed, is associated with mortality and several morbidities. It is clear that older adults may be more vulnerable to the effects of long sleep duration. Although the mechanisms for which long sleep is hazardous are unclear, randomized controlled trials will provide more light on the impact of experimentally extending sleep in older adults. The results of an experimental study of sleep extension have important public health relevance, as extended sleep could contribute to mortality and poor health in older adults. Due to the growing evidence of the harmful effects of long sleep duration, it was hypothesized that increased sleep duration would predict unhealthier physiological measures, decreased mood state, and declined cognitive performance. Additionally, it was hypothesized that increased sleep disturbances would predict unhealthier physiological measures, decreased mood state, and declined cognitive performance.

CHAPTER 2

METHODS

2.1 DESIGN OVERVIEW

Following a baseline week, participants were randomized to one of two three-week treatments: (1) a control treatment, in which participants followed a fixed schedule in which their time-in-bed (TIB) was the same as their median baseline TIB; and (2) a sleep extension treatment, in which participants were asked to follow a fixed sleep schedule in which their TIB was 2 hours longer than their median baseline TIB. After 1 week of recovery, participants repeated the 1-week baseline and crossed over to the other treatment. Measures were subjected to a principal components analysis (PCA) to reduce cases to adjust for the overlapping variance among similar measures. The factor scores generated from the PCA were used in multiple linear regression analyses in order to generate associations between sleep and the physiological and psychological variables.

2.2 PARTICIPANTS AND SCREENING

Fourteen older (50-79 y), healthy adults who reported sleeping 6-8 h were randomized in the crossover study. Three participants dropped out of the study due to schedule changes and/or time constraints. Ten older adults (1 male; M=64.90±4.82 years) completed the study and were assessed on cognitive, emotional, and inflammatory

measures in a cross-over design (median sleep vs. sleep extension). See Figure 2.1 for an enrollment summary of the participants enrolled on the study. Participants were recruited via word-of-mouth, flyers, advertisements, retirement communities, and University of South Carolina press releases. Participants who completed our ongoing study of sleep restriction in older adults were notified about the study. Individuals who were excluded from our ongoing study, who might have met the inclusion criteria of the proposed study, were notified about the study.

The first screen occurred via a phone interview to establish that prospective participants were between 50-79 years of age, reported good health (no significant health conditions), and that they normally slept between 6-8 hours per night. Interested participants who met the age, health, and sleep requirements were invited to the laboratory to complete questionnaires to further determine eligibility. Exclusions included recent shiftwork (previous 2 months) or transmeridian travel (previous 4 weeks) or plans of either during the study period; moderate depression [(Patient Health Questionnaire (PHQ-9) $\geq$ 10; (Kroenke, Spitzer, & Williams, 2001; Kroenke, Spitzer, Williams, & Löwe, 2010)] suicidality [(Beck Scale for Suicide Ideation (BSS) >11; Beck, Kovacs, & Weissman, 1979)]; cognitive impairment [(Mini-Mental State Examination (MMSE) $\leq$ 26; Cockrell & Folstein, 1988); use of hypnotics or other medications to promote sleep; any medical, neurologic, or psychiatric illness causing long sleep; factors associated with significant changes in inflammation (a key outcome variable), including several medical disorders (e.g., rheumatoid arthritis), medications (e.g., steroids) current smoking, an obese body mass index (BMI >33), and greater than 3 hours of moderate to vigorous exercise per week.

Prospective participants who met the initial criteria were invited to the laboratory for further study orientation and to sign a written informed consent form approved by the University of South Carolina Institutional Review Board. Prospective participants were interviewed about their sleep, health, and behavioral patterns (i.e. self-reported usual sleep patterns, mental health, general health, etc.), and completed questionnaires (PHQ-9 and BSS) in order to rule out any of the previously mentioned exclusion criteria. In order to ensure that participants had the necessary level of cognitive function, the MMSE (exclusion for score of ≤ 26; Cockrell & Folstein, 1988) was administered. For further screening, Imran Iftikhar, MD, a sleep physician and Associate Professor of Medicine at the University of South Carolina School of Medicine, performed an interview to screen for sleep disorders. Demographics were collected at the time of consent, and a list of all medications taken was requested. See Figure 2.2 for a flowchart of the screening appointments.

2.3 BASELINE

A 1-week baseline before each treatment assessed pre-treatment measures, and also served as a final screen to establish that the participants slept 6-8 hours. Participants were excluded if actigraphic TIB was outside of the 6-8.5 hour range. During baseline, participants were asked to follow their usual sleep-wake schedules.

2.4 EXPERIMENTAL TREATMENTS AND RANDOMIZATION

Following baseline, participants were randomly assigned to one of two, 3-week treatments: (1) extended TIB, or (2) fixed TIB: Median Sleep. The randomization was stratified by median duration of actigraphic baseline (< 7 vs. ≥ 7 h). Following

randomization, participants completed 5-point Likert scale questions regarding their expectancy of experiencing changes in sleep, mood, daytime alertness, and health.

2.4.1 Extended TIB condition. In the extended TIB treatment, participants were asked to follow a fixed sleep schedule, in which their time in bed (TIB) was 2 hours longer per night than their actigraphic median TIB during the baseline week. This was accomplished by advancing bedtime, delaying arising time, or some combination of these changes in accordance with the preferences and sleep tendencies of each participant. For example, delaying arising time was favored for a participant who preferred to sleep longer in the mornings.

2.4.2 Fixed sleep condition. In the fixed sleep treatment, participants were asked to follow a fixed sleep schedule, in which their TIB was the same as their median TIB during the baseline week. This treatment served as a control for a fixed TIB, believed to be beneficial, as well as for behavioral artifacts, such as expectancy, Hawthorne, and demand effects.

2.5 CROSS-OVER DESIGN

After completion of the baseline and 3-week study, participants completed a 1-week recovery period to avoid carry-over effects. Participants then underwent a second 1-week baseline and were crossed-over to the other treatment: participants who were initially randomized to the extended TIB group then underwent the fixed TIB treatment; participants who were initially randomized to the fixed TIB group then began the extended TIB treatment. Baseline and treatment measures were repeated as described previously.

2.6 MEASURES

Table 2.1 displays the time points in which each assessment occurred. Each of the 3-week treatments was preceded by a one-week baseline. Cognitive measures were assessed at the first baseline and after each treatment condition. Clinician-administered mood measures were assessed after each baseline and treatment condition. Blood pressure, heart rate, sleepiness, depressive symptoms, and anxiety symptoms were assessed weekly. Inflammation, glucose, and cholesterol measures were assessed following both treatment conditions.

2.6.1 Sleep and sleepiness assessment. Throughout each baseline and each 3-week treatment, participants wore wrist actigraphic monitors (Phillips Respironics Actiwatch Spectrum device) for continuous assessment of sleep-wake patterns. Participants were given the option to continue wearing the actigraphy device during the 1-week recovery period. For those who continued to wear the device, wrist actigraphic recordings were maintained during the recovery period to ensure participants maintained pre-experiment sleep patterns.

Illumination recording allowed estimates of TIB accurate to 1 minute. Advantages of actigraphy are the applicability to home settings and the larger number of nights that can be recorded, which improves the stability of estimates in the presence of night-to-night variability. Actigraphy, which is a highly validated and reliable alternative to laboratory polysomnography (PSG), is a cost-effective alternative PSGs. For longer-term studies, daily sleep estimation with actigraphy may be preferable to PSG recording, which typically is restricted to 1 or 2 nights. Total sleep time (TST), TIB, sleep fragmentation index, sleep efficiency, and sleep onset latency (SOL) were also assessed.

Actigraphic algorithms calculated sleep fragmentation index as the sum of the percentage of mobile bouts and percentage of immobile bouts less than 1 minute to the number of immobile bouts. Sleep efficiency was calculated by the actigraph as the percentage of time spent asleep within the TIB interval.

In a daily morning sleep diary, participants reported time in bed, wake time, quality of sleep, etc. To measure subjective sleepiness, participants completed the Epworth Sleepiness Scale (ESS; Johns, 1991) at the end of each baseline week and each treatment week. Higher scores on the ESS represent increased level of daytime sleepiness. The Multidimensional Assessment of Fatigue (MAF) Scale (Belza, Henke, Yelin, Epstein, & Gilliss, 1993) was used to measure fatigue at the end of each baseline week and each treatment week. Higher scores on the MAF indicate increased level of fatigue.

2.6.2 Cognitive assessment. At the initial baseline and at the end of each 3-week treatment, working memory, sustained attention, and executive function were assessed with a cognitive performance battery, which consisted of verbal and non-verbal working memory tasks, Psychomotor Vigilance Test (PVT), Stroop Test (Stroop, 1935), and the Trail Making Test (TMT). The Stanford-Binet Intelligence Scale, 5th edition (SB5; Roid, 2003) includes two working memory tasks: Block Pattern Memory Task (BPMT), which tests nonverbal working memory, and the Sentence Memory Task (SMT), which tests verbal working memory. Composite scores were obtained by scoring both the verbal and nonverbal tasks, but individual scores were determined to compare verbal and nonverbal working memory ability. One advantage of the SB5 is that it contains a sample of normative data from older adults (85+ years). In order to maintain the integrity of the

tests, the SB5 working memory assessments were administered by two blinded clinical psychology doctoral students, Katherine Knies and Betsy Davis. The clinical students were supervised by Dr. M. Michele Burnette, Ph.D.

Additionally, working memory was also assessed using the valid and reliable Automated Reading Span (verbal working memory) and Automated Operation Span tasks (nonverbal working memory; Unsworth, Heitz, Schrock, & Engle, 2005). The Automated Reading Span task requires participants to read sentences while also trying to remember strings of unrelated letters; the overall test score and errors (speed and accuracy) were recorded. The total score comprised the sum of all the correctly recalled sets of letters. The Automated Operation Span task requires participants to solve math equations while also remember letters; the scoring for this task was the same as the scoring for the Automated Reading Span task.

The PVT, which is sensitive to aging and changes in sleep (Drummond et al., 2005), was used to assess changes in reaction time associated with state dependent changes in sustained attention. Participants used the PVT device to press a button as quickly as possible when each visual stimulus was presented. Sustained attention measured via changes in psychomotor vigilance has a compelling history in the extended sleep literature (Blackwell et al., 2011; Kronholm et al., 2011; Taub, Globus, Phoebus, & Drury, 1971; Taub & Berger, 1973). Metrics that were assessed included median reaction time (RT), the fastest 10% of responses, the slowest 10% of responses, the number of response "lapses" (RT > 500 ms), and standard deviation of responses.

The Stroop Color-Word Test (Stroop, 1935) is a reliable and useful tool used in psychology. The basic paradigm of the Stroop test consists of a basic task (e.g. reading

names of colors presented in blank ink) and comparing the performance on the basic task with performance on a comparable task where a habitual response is suppressed (e.g. reading names of colors presented in various ink colors, incongruent to the color name). The increased time needed to complete the comparable task compared to the basic task is called the "Stroop interference effect," and is considered to be a measure of executive functioning and cognitive control and flexibility (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006). The Stroop test is used in many areas of sleep research, including long sleep duration (Nebes et al., 2009), sleep deprivation (Cain, Silva, Chang, Ronda, & Duffy, 2011; Tucker, Whitney, Belenky, Hinson, & Van Dongen, 2010), sleep restriction (Philip et al., 2012), sleep fragmentation (Ferri et al., 2010), obstructive sleep apnea (Lee et al., 2011), narcolepsy (Moraes, Rossini, & Reimão, 2012), and insomnia (Spiegelhalder, Espie, Nissen, & Riemann, 2008). Interference was measured by subtracting the average time of the first two subtasks completion from the average time of third subtask completion (Interference = [(Stroop I + Stroop II) / 2] – Stroop III; Valentijn et al., 2005; Van der Elst et al., 2006). Reaction times and errors were also evaluated.

The TMT (part A) requires participants to draw lines (trails) in order from randomly placed circles numbers (1 to 2 to 3, etc.). Part B requires participants to draw lines (trails) alternating between numbers and letters (1 to A to 2 to B to 3 to C, etc.). The TMT (part B) has been shown to be highly sensitive to cognitive aging and is a valid measure of executive function (Oosterman et al., 2010). The TMT (part B) has been used in several studies of sleep duration (Blackwell et al., 2011; Nebes et al., 2009) and sleep

quality (Blackwell et al., 2006). Reaction times of trail-making completion were evaluated.

2.6.3 Depression, anxiety, and mood assessment. During both baselines**,** and at the end of each treatment, participants were assessed with the clinician-administered Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959) and Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960). The HAM-A and HAM-D were administered by blinded clinical psychology students, who were under the supervision of a licensed psychologist.

At the end of each baseline period, and the end of each treatment week, participants completed the self-administered Beck Depression Inventory (BDI-II; Beck et al., 1996) and the Spielberger State Trait Anxiety Inventory (STAI Form Y-1; Spielberger, 1989). The Beck Scale for Suicide Ideation (BSS; Beck et al., 1979) was administered if a participant indicated suicidal thoughts on the on the BDI-II. No participants indicated suicidal thoughts on the BDI-II. With the emergence of moderate depression (BDI $\geq$26 or HAM-D $\geq$20), moderate anxiety (HAM-A $\geq$ 21), and/or significant suicide ideation (BSS>11), the participant was to be discharged from the experiment and referred to appropriate care at the Psychology Services Center at the University of South Carolina. No participants demonstrated moderate depression, anxiety, or suicide ideation at any point in the study (including screening).

Additionally, participants completed a daily diary consisting of Likert scale questions pertaining to mood. Participants rated how they felt the previous day; a score of zero represented "normal" mood, -3 represented "low" mood, and +3 represented "elated" mood. Significant impairment (consistent "low" ratings) would have activated

further assessment, possible termination, and referral for care; however, no participants indicated significant impairment on any mood measures.

2.6.4 Symptoms assessment. At each baseline and the end of each 3-week treatment, symptoms were assessed with the Systematic Assessment for Treatment and Emergent Events (SAFTEE; Moynihan, 1983), which is a checklist adaptation of a comprehensive National Institute of Mental Health interview used to detect and monitor the side effects of treatments. Ninety-four individual symptoms are grouped into 17 SAFTEE-defined categories, such as head, eyes, chest, etc. The SAFTEE was used in order to determine no adverse effects of treatment during the study. No adverse effects were reported during the study.

2.6.5 Physiological measures. At the end of each 3-week intervention, participants underwent a 12-hr fast and blood draw (7 ml) to obtain lipid levels (lipoprotein, low-density lipoprotein, very low-density lipoprotein, and triglycerides), glucose, and an inflammation marker (CRP). Fasting blood draws were conducted at the Lexington Medical Center's (LMC) Clinical Pathology Laboratory in West Columbia, SC. The LMC laboratory collected, processed, stored, and analyzed samples.

Following a 10-minute seated resting period, systolic and diastolic blood pressure, as well as heart rate, were recorded at the beginning of each weekly appointment with an Omron RS8 automatic wrist blood pressure monitor. The Omron RS8 device is a validated, easy to use blood pressure monitoring device (Takahashi, Yoshika, & Yokoi, 2013). At the beginning of each participant's weekly appointment, the device was placed on the participant's non-dominant wrist below the ulna wrist bone, per the manufacturer's instructions. The participant sat quietly for 10 minutes, without legs or ankles crossed.

After 10 minutes, the blood pressure and heart rate readings were recorded, and then repeated after 2 minutes. If an error or large difference occurred between the two readings (i.e. >10 units), the reading was taken a third time. The averages of the recordings were reported.

2.6.6 Marker of inflammation. CRP was assayed at LMC's Clinical Pathology Laboratory in West Columbia, SC, after each treatment period. Recent infection/illness resulted in interpolation of data based on group values (n=2; see "Data Screening"). Participants were carefully screened for alcohol consumption, smoking history, body mass index (BMI), physical activity, and use of medications (antidepressants, statins, and non-steroidal anti-inflammatory drug (NSAID; O'Connor et al., 2009; O'Connor & Irwin, 2010), as these factors may impact inflammatory marker results.

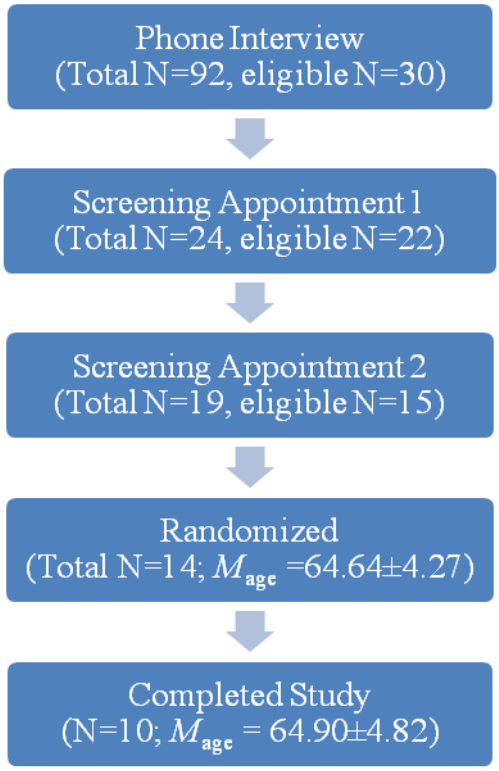

Figure 2.1. Study Enrollment at Flow Chart. Mean age and standard deviation are reported for the randomized and completed stages.

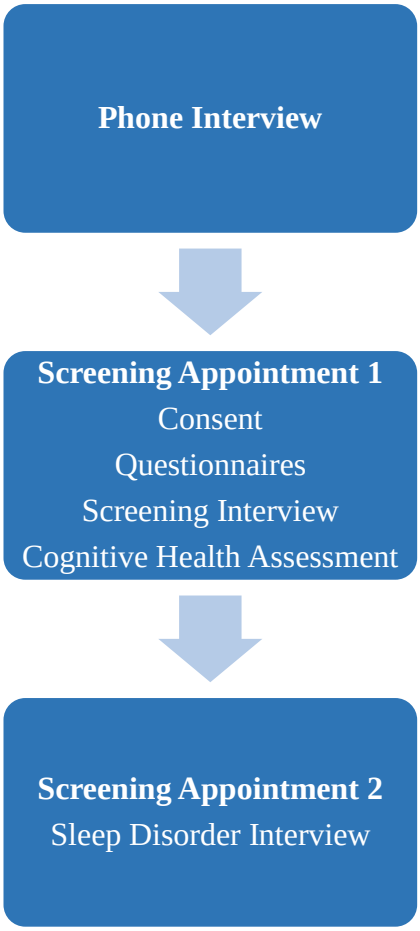

Figure 2.2. Screening Process Flow Chart. Screening process began a phone interview to ensure general inclusion criteria are met (age, sleep, etc.); first screening appointment included consent, questionnaires (Patient Health Questionnaire ≥ 10, Beck Scale for Suicide Ideation >11), screening interview (questions regarding health and behavior), and cognitive health assessment (Mini-Mental State Examination ≤ 26); second screening appointment included interview with sleep physician to screen for sleep disorders.

Table 2.1. Assessments Measured at each Time Point

Experimental Measures during Baseline and Treatment Groups Cross-Over Study; Recovery week occurs during Week 5.

Baseline		Treatment (Control vs. Sleep Extension)		
	Follow-Up Appts.		Follow-Up Appts.	Condition Follow-Up 1
Daily Week 1	End Week 1	Daily Weeks 2-4	End Week 2-4	End Week 4
Actigraphy	Cognitive Battery	Actigraphy	Sleepiness	Blood Draw
Sleep Diary	Sleepiness	Sleep Diary	Fatigue	
Mood Diary	Fatigue	Mood Diary	Depression*	Cognitive Battery
	Depression*		Anxiety	
	Anxiety		BP HR	Symptoms
	Symptoms			
	BP HR			

Baseline		Treatment (Control vs. Sleep Extension)		
	Follow-Up Appts.		Follow-Up Appts.	Condition Follow-Up 2
Daily Week 6	End Week 6	Daily Weeks 7-9	End Week 7-9	End Week 9
Actigraphy	Sleepiness	Actigraphy	Sleepiness	Blood Draw
Sleep Diary	Fatigue	Sleep Diary	Fatigue	
Mood Diary	Depression*	Mood Diary	Depression*	Cognitive Battery
	Anxiety		Anxiety	
	Symptoms		BP HR	Symptoms
	BP HR			

Note. Sleepiness (weekly): Epworth Sleepiness Scale (ESS); Depression: Beck Depression Inventory (BDI-II; weekly), Hamilton Depression Rating Scale (HAM-D; end of each baseline and end of each treatment); Anxiety: State Trait Anxiety Scale (STAI; weekly), Hamilton Anxiety Rating Scale (HAM-A; end of each baseline and end of each treatment); Cognitive Battery (end of first baseline and end of each treatment): Block Pattern Memory Task (BPMT), Sentence Memory Task (SMT), Automated Reading Span Task, Automated Operation Span Task, Trail Making Test (TMT), Psychomotor Vigilance Test (PVT), Stroop Test; Symptoms (end of each baseline and end of each treatment): Systematic Assessment for Treatment and Emergent Events (SAFTEE); BP (blood pressure) and HR (heart rate) assessed weekly; *Beck Scale for Suicide Ideation administered after screening if participant indicates suicidal thoughts on BDI-II

CHAPTER 3

RESULTS

Means and standard deviations for screening data are available in Appendix A. Means and standard deviations for raw and transformed data are available in Appendix B. In order to determine if time in bed (TIB) and total sleep time (TST) were extended, *t*-test comparisons were completed on the actigraphic variables. These comparisons are available in Appendix C. Additionally, principal components analyses (PCA) were completed on each set of independent and dependent variables in order to identify the distinct contributions of variance of each set of measures to the constructs of interest. Our constructs of interest were Sleep, Physiological Health, Cognition, and Mood. Multiple linear regressions were completed to determine predictive tendencies of the independent variables.

3.1 DATA SCREENING

Prior to analysis, sleep, cognitive, mood, and physiological measures were screened for equipment errors, accuracy of data entry, missing values, outliers, and fit between their distributions and the assumptions of multivariate analysis (including skewness and kurtosis) using SPSS. Actigraph malfunction resulted in the loss of one week of an individual's sleep data from the last habitual sleep week condition. The sleep data for the week were replaced by the mean from the same participant's two other habitual sleep weeks (week 7 and 8). Actigraph computational error resulted in

consistent underestimation of SOL data, therefore, SOL data were removed from analyses. Missing values of two participants for the SB5 at baseline and for the end of the habitual sleep condition were replaced by mean scores of participants during the same condition and in the same condition order. Due to test malfunction, not enough data from the Automated Operation Span task were recovered for analysis. More specifically, the task did not run correctly on the programming platform and generated an error, which did not allow the participant to complete the task. Therefore, this test was dropped from further analysis.

Missing values of one participant for the HAM-A and HAM-D for the end of the habitual sleep condition were replaced by mean scores of participants during the same condition and in the same condition order (unique subject from actigraphic data). The single missing value of one response on the BDI was replaced by the mean response to the other BDI questions for that week. Two participants reported infections during the blood draw at the end of the second condition; the two corresponding CRP cases were found to be univariate outliers. The average of the CRP values of all participants in the same condition and in the same condition order was calculated and substituted for those values.

All raw data were examined for univariate outliers. Cases were considered to be univariate outliers if the values that were greater than 3 or less than -3 standard deviations from the mean. Out of the 100 cases of blood measures data, no additional outliers were identified with these criteria. Out of 400 sleep data cases, eight cases met these criteria and were replaced with mean values of participants in the same condition. Out of the 300 cognitive data cases, three cases met these criteria and were replaced with mean values of

participants in the same condition. Out of the 320 cases of sleepiness and mood data, four outliers were identified as univariate outliers with these criteria and were replaced with mean values of participants in the same condition. Out of 240 blood pressure and heart rate cases, one outlier was identified as a univariate outlier with these criteria and was replaced with mean value of participants in the same condition. Out of 80 clinician-administered mood assessments, one outlier was identified as a univariate outlier with these criteria and was replaced with mean value of participants in the same condition. Out of the total data set, less than 1.4% of all data were removed.

To improve pairwise linearity and to reduce the extreme negative skewness and kurtosis, CRP, Stroop Interference scores, and PVT mean scores were logarithmically transformed. Additionally, to reduce positive skewness in LDL and heart rate measures, the data were square root transformed. BDI, STAI, ESS, and MAF difference scores were computed by subtracting baseline values from weekly data due to extreme skewness and kurtosis. TMT A, TMT B, PVT number of lapses, and SB5 Sentence Memory Task violated the assumptions of skewness and kurtosis, but would not normalize with any transformation attempt (i.e. square root, log transformation, etc.). Appendix D contains all of the transformed histograms to demonstrate correction of normality.

3.2 DATA REDUCTION: PCA

Given the small number of participants and the large number of measures with overlapping variance, principal components analysis was used to extract components describing unique portions of the data from the sleep, physiological, cognitive, and mood measures. Reducing the variables minimized the impact of Type II errors by multiple comparisons. Tables of correlation matrices that demonstrate overlapping relationships

between the raw measures are presented in Appendix C. PCA generates factor scores for each individual case, which represent the estimates of the values that would be produced if the constructs could be directly measured. These factor scores were then used for the multiple linear regression analyses. Additional analyses of raw data would have been inappropriate and duplicate analyses, increasing the risk of Type II errors. Clinician-administered assessments (HAM-A and HAM-D), blood pressure, and heart rate were not subjected to the PCA analyses due to measurements being taken at different points than other mood and physiological data. These data were directly subjected to multiple linear regressions.

3.2.1 Sleep components. The actigraphic measures (TST, sleep fragmentation, and sleep efficiency) were subjected to a PCA using ones as prior communality estimates. In order to compare the actigraphic measures to the physiological data, which was not collected at baseline, PCA was performed on the actigraphic measures without the baseline data. However, the cognitive and mood data contained baseline measures. To render the actigraphic data comparable to those dependent variables, a second PCA was performed including the baseline data. Although the loadings varied slightly between the two extractions, the same components were obtained from both analyses.

Actigraphic measures of all condition weeks except for baseline data were subjected to a PCA using ones as prior communality estimates. The principal axis method was used to extract the components, and this was followed by a promax (oblique) rotation with Kaiser normalization. The rotation was converged in 3 iterations. Only the first two components displayed eigenvalues greater than 1, and the results of the scree test also suggested that only the first two components were meaningful. Combined,

components 1 and 2 accounted for 85% of the total variance. Measures and corresponding factor loadings are presented in Table 3.1. In interpreting the component matrix, a measure was said to load on a given component if the factor loading was .50 or greater for that component, and was less than .50 for the other. Using these criteria, four measures were found to load on the first component (sleep fragmentation, WASO, number of awakenings, and sleep efficiency), which was subsequently labeled the Disturbance component. The Disturbance component represents disruptions of sleep; as the factor scores increase for this component, it represents increasingly disrupted sleep. Only one measure loaded on the second component (TST), so it was labeled TST. These factors were used only for the physiological data collected from the blood draws, which were collected after each condition ended and not during any baseline conditions.

Actigraphic measures with baseline data were subjected to a PCA using ones as prior communality estimates. The principal axis method was used to extract the components, and this was followed by a promax (oblique) rotation with Kaiser normalization. The rotation was converged in 3 iterations. Only the first two components displayed eigenvalues greater than 1, and the results of the scree test also suggested that only the first two components were meaningful. Combined, components 1 and 2 accounted for 85% of the total variance. Measures and corresponding factor loadings are presented in Table 3.2. In interpreting the component matrix, a measure was said to load on a given component if the factor loading was .50 or greater for that component, and was less than .50 for the other. Using these criteria, four measures were found to load on the first component (sleep fragmentation, WASO, number of awakenings, and sleep efficiency), which was subsequently labeled the Disturbance

component. The Disturbance component represents disruptions of sleep; as the factor scores increase for this component, it represents increasingly disrupted sleep. Only one measure loaded on the second component (TST), so it was labeled TST.

3.2.2 Physiological components. Physiological measures, with the exception of blood pressure data and heart rate, were subjected to a PCA using ones as prior communality estimates. Blood pressure data and heart-rate were collected at different time points than the rest of the data, which would have skewed the analysis based variability related to the collection times. The principal axis method was used to extract the components, and this was followed by a promax (oblique) rotation with Kaiser normalization. The rotation was converged in 3 iterations. Only the first two components displayed eigenvalues greater than 1, and the results of the screen test also suggested that only the first two components were meaningful. Combined, components 1 and 2 accounted for 65% of the total variance.

Measures and corresponding factor loadings are presented in Table 3.3. In interpreting the component matrix, a measure was said to load on a given component if the factor loading was .44 or greater for that component, and was less than .43 for the other. Using these criteria, three measures were found to load on the first component (CRP, glucose, and HDL), which was subsequently labeled the Cardiovascular Risk component. The Cardiovascular Risk component represents risk of a cardiovascular event; as the factor scores increase for this component, it represents increased risk of a cardiovascular event. Two measures loaded on the second component (Trig and LDL), which was labeled the Lipid Profile component. As scores increase for the Lipid Profile

component, it represents a higher cholesterol levels and higher risk of developing heart disease.

3.2.3 Cognition components. Eight cognition measures were subjected to a PCA using ones as prior communality estimates. The principal axis method was used to extract the components, and this was followed by a promax (oblique) rotation with Kaiser normalization. The rotation was converged in 5 iterations. Only the first three components displayed eigenvalues greater than 1, and the results of the scree test also suggested that only the first two components were meaningful. Combined, components 1, 2, and 3 accounted for 75% of the total variance.

Measures and corresponding factor loadings are presented in Table 3.4. In interpreting the rotated factor pattern, a measure was said to load on a given component if the factor loading was .50 or greater for that component, and was less than .50 for the other. Using these criteria, three measures were found to load on the first component (TMT parts A and B, and Stroop Interference scores), which was subsequently labeled the Executive Control (assisted with motor sequencing) component. The Executive Control component represents control of executive functions; as the factor scores decrease for this component, it represents increased control of executive functions. Three measures also loaded on the second component (Automated Reading Span, number of PVT lapses, and PVT reaction time), which was labeled the Vigilance component. The Vigilance component represents concentration ability; as the factor scores decrease for this component, it represents increased ability to concentrate on a task. Factor scores were reversed scored in order to provide a more comprehensible relationship. Two measures also loaded on the third component (SB5 Block Pattern Memory Task and SB5

Sentence Memory Task), which was labeled the Working Memory component. The Working Memory component represents working memory capacity; as the factor scores increase for this component, it represents increased working memory capacity.

3.2.4 Mood and sleepiness components. Mood and sleepiness measures were subjected to a PCA using ones as prior communality estimates. The principal axis method was used to extract the components, and this was followed by a promax (oblique) rotation with Kaiser normalization. The rotation was converged in 3 iterations. Only the first two components displayed eigenvalues greater than 1, and the results of the scree test also suggested that only the first two components were meaningful. Combined, components 1 and 2 accounted for 70% of the total variance.

Measures and corresponding factor loadings are presented in Table 3.5. In interpreting the rotated factor pattern, a measure was said to load on a given component if the factor loading was .50 or greater for that component, and was less than .50 for the other. Using these criteria, two items loaded on the first component (STAI and BDI), which was labeled the Mood component. The Mood component represents subjective feelings of current mood state; as the factor scores decrease for this component, it represents more negative mood states. Two items were found to load on the second component (ESS and MAF), which was subsequently labeled the Sleepiness component. The Sleepiness component represents subjective feelings of sleepiness and fatigue; as the factor scores increase for this component, it represents increased subjective feelings of sleepiness and fatigue.

3.3 STATISTICAL ANALYSES

The major manipulation in the study was TIB. In order to examine the effects of TIB on sleep, a paired samples *t*-test was performed comparing the normal and sleep extension groups' actigraphic TIB data to verify the manipulation. The TIB statistically significantly increased from 484.86±16.44 min in the normal sleep condition to 555.06±33.59 min during the sleep extension condition, $t(9)=-8.746$, $p<.0001$. Figure 3.1 shows the average TIB in minutes for each group and Figure 3.2 shows the cross-over nature of the study for TIB. Additional information and analysis of TST is reported in Appendix C.

3. 4 LINEAR REGRESSION RESULTS

Using the factor scores for each case that were generated from each PCA, multiple linear regressions were performed to exam associations of physiological, cognitive, and mood data with the Disturbance component scores and TST. Linear regressions were also performed on transformed clinician-administered mood assessments (HAM-A and HAM-D), blood pressure, and heart rate data.

3.4.1 Physiological components. Two multiple linear regressions were performed to assess Cardiovascular Risk and Lipid Profile components from the Disturbance component and TST. The baseline data were not included sleep PCA components because baseline physiological data were not collected. These variables did were not significantly associated with Cardiovascular Risk, $F(2, 19)=2.499$, $p=.112$, $R^2=.227$ or Lipid Profile, $F(2, 19)=01.640$, $p=.223$, $R^2=.162$.

3.4.2 Cognition components. Three multiple linear regressions were performed to examine associations of Executive Control (Motor Planning), Vigilance, and Working

Memory components with TST and the Disturbance component. The baseline data were included in the TST and Disturbance data. These variables did not were not significantly associated with Executive Control ($F(2, 29)=.191$, $p=.827$, $R^2=.014$), Vigilance ($F(2, 29)=1.074$, $p=.356$, $R^2=.074$), or Working Memory, ($F(2, 29)=1.542$, $p=.232$, $R^2=.103$). There were not enough participants to utilize order effects in an analysis. The cognitive variables on the sleep variables had no impact when the baseline data were covaried from the analysis.

3.4.3 Mood and Sleepiness components. Two multiple linear regressions were performed to assess the association of the Mood (Emotional State) component with TST and the Disturbance component. The baseline data were included in the TST and Disturbance data. These associations approached statistical significance $F(2, 59)=2.879$, $p=.064$, $R^2=.092$. The Disturbance component added statistically significantly to the prediction, $p=.022$. See Figure 3.3 for the scatterplot representing the relationship between the Disturbance and Mood components. These variables did not statistically significantly Sleepiness ($F(2, 59)=.976$, $p=.383$, $R^2=.033$).

3.4.4 Clinician-administered mood assessments. Two multiple linear regressions were performed to predict anxiety and depressive symptoms (HAM-A and HAM-D, respectively) from TST and the Disturbance component. The baseline data were included in the TST and Disturbance data. These variables did not statistically significantly predict anxiety ($F(2, 19)=.071$, $p=.932$, $R^2=.008$) or depressive symptoms ($F(2, 19)=.167$, $p=.848$, $R^2=.019$).

3.4.5 Blood pressure and heart rate. Three multiple linear regressions were performed to predict systolic blood pressure, diastolic blood pressure, and heart rate from

TST and the Disturbance component. The baseline data were included in the TST and Disturbance data. These variables statistically significantly predicted systolic blood pressure, $F(2, 79)=7.404$, $p=.001$, $R^2=.161$. The Disturbance component added statistically significantly to the prediction, $p=.0004$. See Figure 3.4 for the scatterplot representing the relationship between the Disturbance component and the systolic blood pressure. These variables statistically significantly predicted diastolic blood pressure, $F(2, 79)=4.977$, $p=.009$, $R^2=.114$. TST and the Disturbance component added statistically significantly to the prediction, $p=.016$ and $p=.031$ (Figures 3.5 and 3.6), respectively. These variables statistically significantly predicted heart rate, $F(2, 79)=3.671$, $p=.030$, $R^2=.087$. TST and the Disturbance component added statistically significantly to the prediction, $p=.047$ and $p=.050$ (Figures 3.7 and 3.8), respectively.

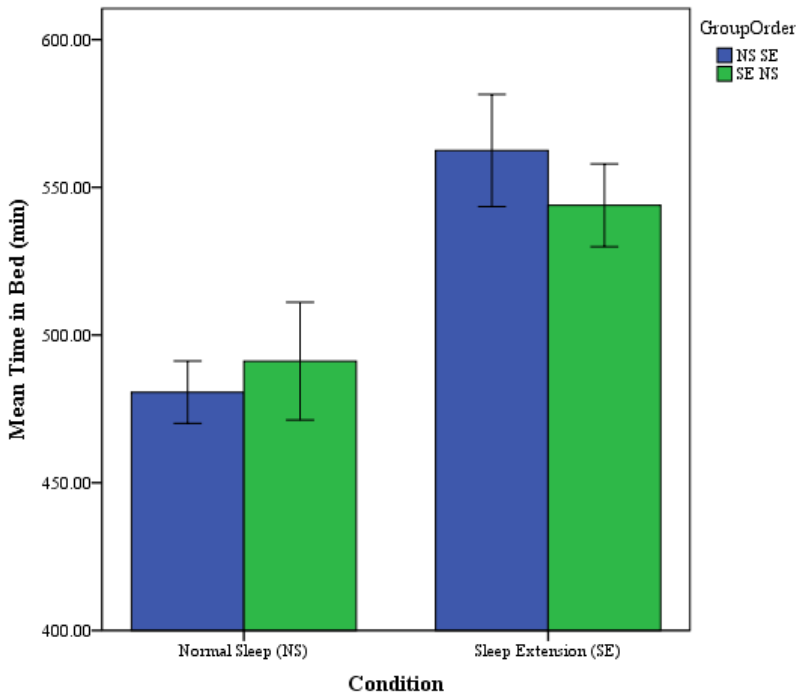

Figure 3.1. Time in Bed for each Condition. Time in Bed (TIB), as measured in minutes, for each condition. Blue bar represents condition order of normal sleep (NS) followed by sleep extension (SE); green bar represents condition order of SE followed by NS. Error bars represent standard error.

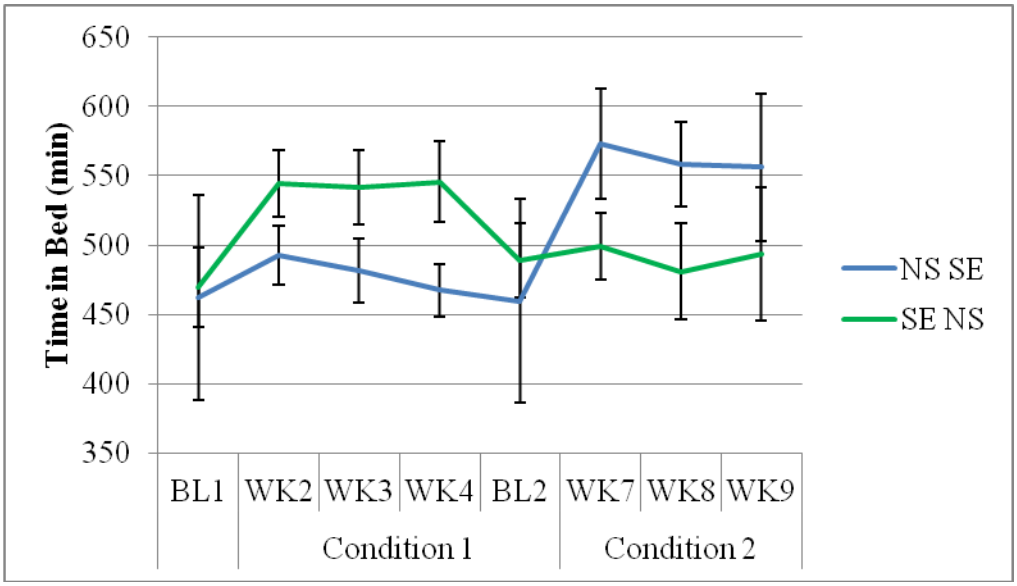

Figure 3.2. Time in Bed for each Week. Time in Bed (TIB), as measured in minutes, for each Baseline (BL) and week (WK) per condition. Blue line represents condition order of normal sleep (NS) followed by sleep extension (SE); green line represents condition order of SE followed by NS. Error bars represent standard error.

Table 3.1. Factor Loadings for Sleep Measures without Baseline

Table shows sleep measures and corresponding factor loadings. Actigraphic data do not include baseline data.

Measures	Component 1 (Sleep Disturbance)	Component 2 (TST)
Total Sleep Time	.057	.994
Sleep Efficiency	-.872	.315
Number of Awakenings	.906	.197
Sleep Fragmentation	.816	.041
Wake after Sleep Onset	.941	.056

Table 3.2. Factor Loadings for Sleep Measures with Baseline

Table shows sleep measures and corresponding factor loadings, with baseline data included.

Measures	Component 1 (Sleep Disturbance)	Component 2 (TST)
Total Sleep Time	.053	.985
Sleep Efficiency	-.922	.306
Number of Awakenings	.862	.136
Sleep Fragmentation	.797	.156
Wake after Sleep Onset	.944	.046

Table 3.3. Factor Loadings for Physiological Measures

Table shows physiological measures and corresponding factor loadings.

Measures	Component 1 (Cardiovascular Risk)	Component 2 (Lipid Profile)
C-Reactive Protein	.720	.125
Glucose	.895	-.207
High-Density Lipoprotein	-.444	-.434
Triglycerides	.314	.654
Low-Density Lipoprotein	-.273	.923

Table 3.4. Factor Loadings for Mood and Sleepiness Measures

Table shows the depression, anxiety, sleepiness, and fatigue difference scores and corresponding factor loadings.

Measures	Component 1 (Mood)	Component 2 (Sleepiness)
Sleepiness (ESS)	-.123	.892
Fatigue (MAF)	.183	.661
Depression (BDI)	.894	-.033
Anxiety (STAI)	.838	.038

Note. Epworth Sleepiness Scale (ESS); Multidimensional Assessment of Fatigue (MAF), Beck Depression Inventory II (BDI II), State-Trait Anxiety Inventory (STAI).

Table 3.5. Factor Loadings for Cognitive Measures

Table shows the cognitive measures and corresponding factor loadings.

Measures	Component 1 (Executive Control)	Component 2 (Vigilance)	Component 3 (Working Memory)
TMT A Total Time	.961	.105	.120
TMT B Total Time	.928	-.099	.008
Stroop Interference Score	.581	.389	-.120
PVT Log Reaction Time	.232	.844	-.114
PVT Number of Lapses	.015	.871	-.031
Rspan Score	-.467	.621	.263
SB5 BPMT	.143	-.052	.889
SB5 SMT	.040	-.045	.830

Note. Trail Making Test (TMT), Psychomotor Vigilance Task (PVT), Automated Reading Span (Rspan), Stanford-Binet 5 (SB5), Block Pattern Memory Task (BPMT), Sentence Memory Task (SMT).

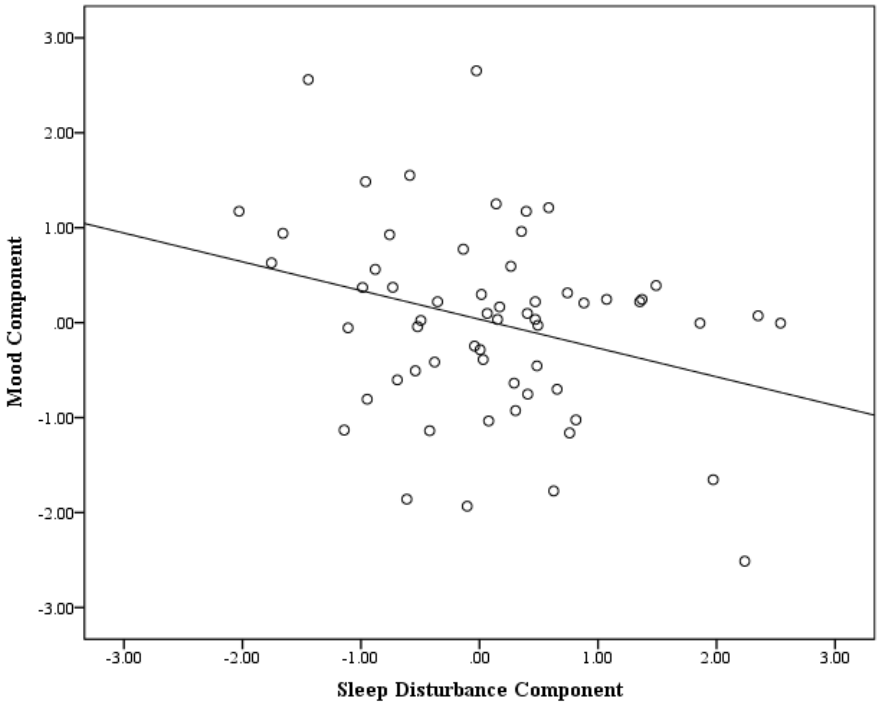

Figure 3.3. Scatterplot of Mood and Sleep Disturbance Components. No outliers (±3 standard deviations from mean) were identified in regression analysis.

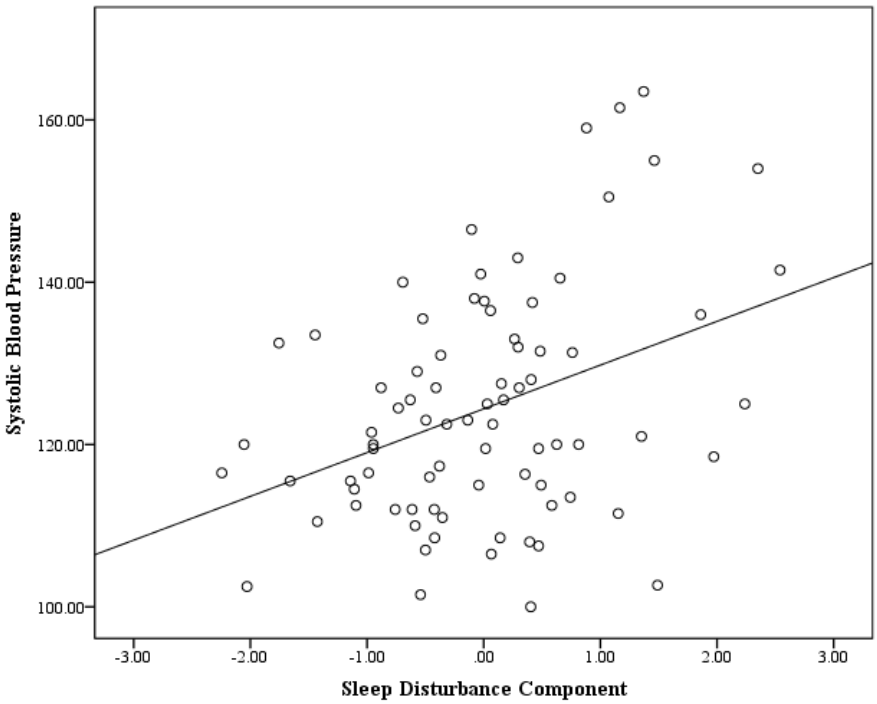

Figure 3.4. Scatterplot of Disturbance Component and Systolic Blood Pressure. No outliers (±3 standard deviations from mean) were identified in regression analysis.

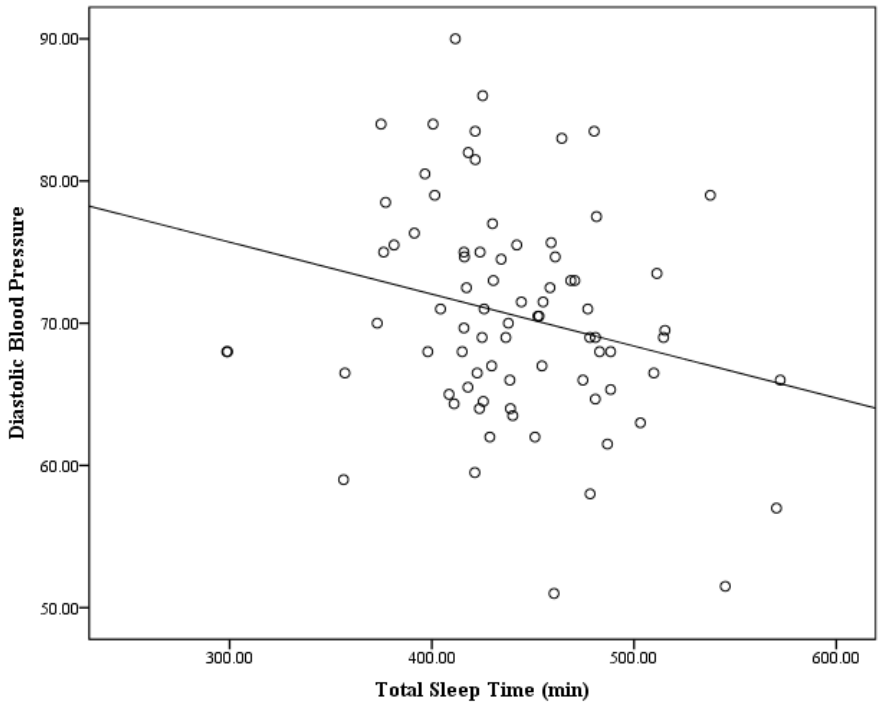

Figure 3.5. Scatterplot of Total Sleep Time and Diastolic Blood Pressure. No outliers (±3 standard deviations from mean) were identified in regression analysis.

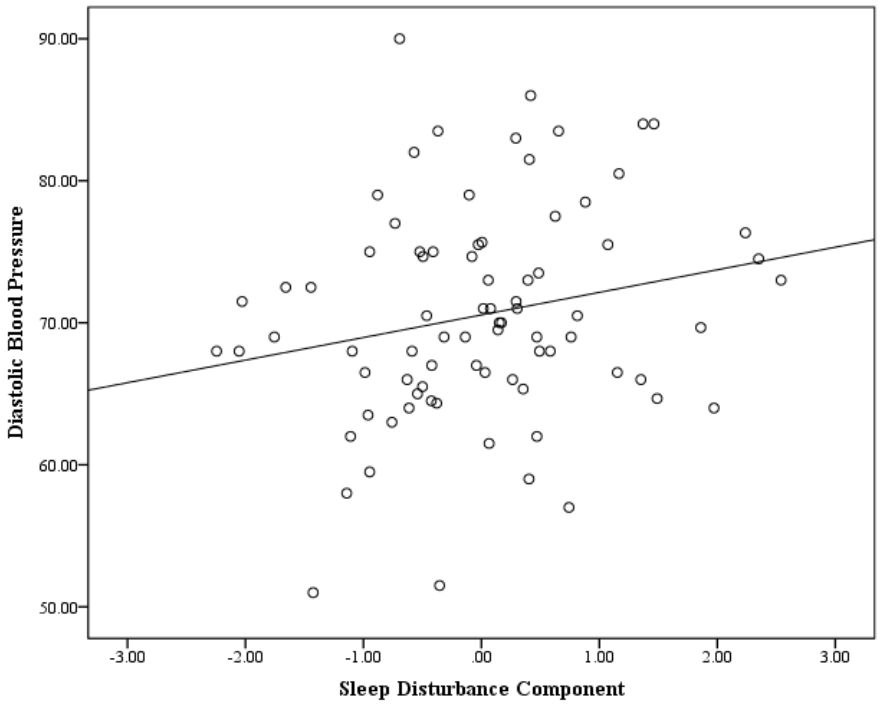

Figure 3.6. Scatterplot of Disturbance Component and Diastolic Blood Pressure. No outliers (±3 standard deviations from mean) were identified in regression analysis.

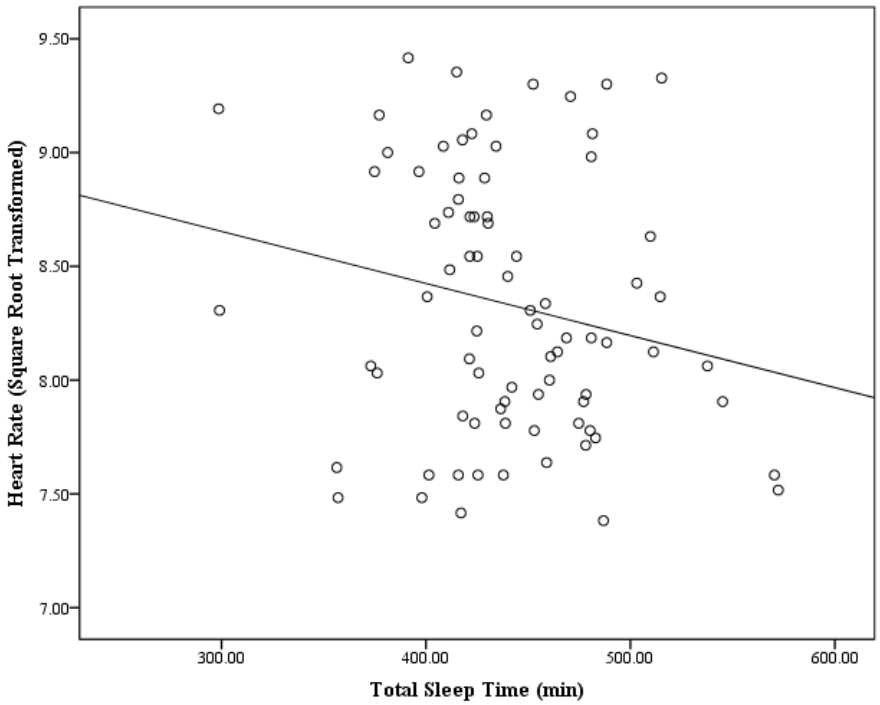

Figure 3.7. Scatterplot of Total Sleep Time and Heart Rate. No outliers (±3 standard deviations from mean) were identified in regression analysis.

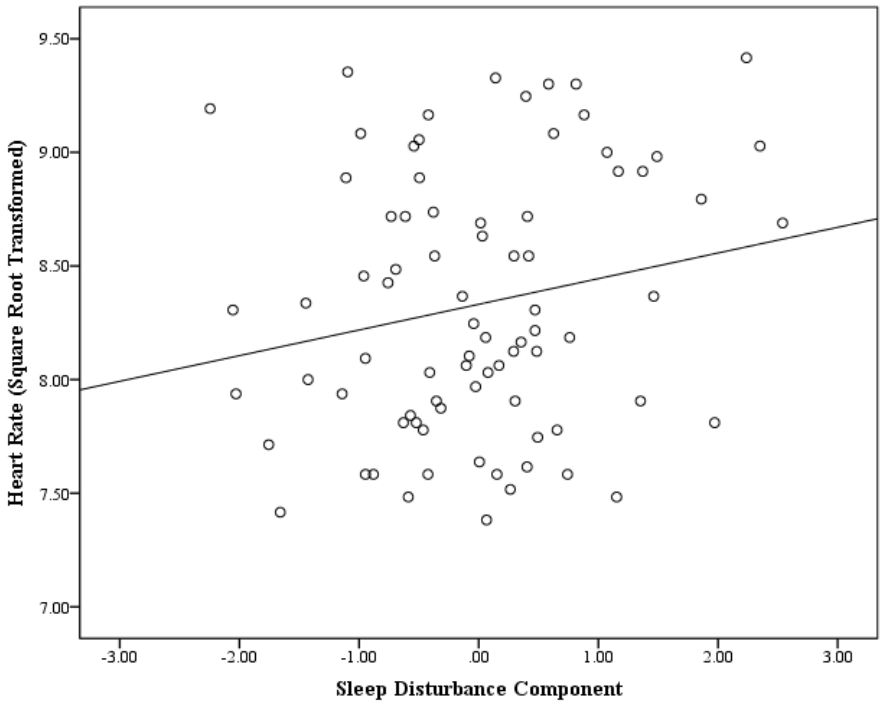

Figure 3.8. Scatterplot of Disturbance Component and Heart Rate. No outliers (±3 standard deviations from mean) were identified in regression analysis.

CHAPTER 4

DISCUSSION

The goal of this study was to examine the association of sleep duration with multiple outcomes in older adults. In a randomized controlled trial, healthy, older adults were asked to spend 2 extra hours in bed per night during a sleep extension condition. Participants also completed a habitual sleep condition. Physiological, cognitive, and mood measures were taken throughout the study. Epidemiological studies have clearly shown negative associations with long sleep duration, including associations with several morbidities and increased mortality. Due to the growing evidence of the harmful effects of long sleep duration, it was hypothesized that greater sleep duration would be associated with unhealthy levels of physiological measures, decreased mood state, and cognitive performance. Additionally, it was hypothesized that more sleep disturbance would be associated with unhealthy levels of these variables.

As expected, participants were able to spend additional time in bed. Participants spent approximately 70 additional minutes in bed attempting to sleep. Participants also increased their total sleep time approximately 50 minutes compared to their habitual sleep time. Although participants were not able to extend their sleep to the full 2 hours, other sleep extension studies have shown significant differences in sleep quality and sleepiness in as little as 14 minutes of increased sleep time (Cizza et al., 2014). These results were consistent with our pilot data, in which we found statistically significant increases in total

sleep time after asking participants to spend more time in bed attempting to sleep (Reynolds et al., 2014).

Comparisons between treatments were not feasible due to the small sample size. Additionally, due to the large number of measures with overlapping variance, principal components analysis was a better fit for data reduction as a preliminary analysis. After the measures were reduced, linear regressions were used in order to predict physiological, cognitive, and mood measures from the sleep data. Although the data sample was too small to make pre vs. post comparisons, clear patterns emerged when examining the data. Computing linear regressions to predict physiological, cognitive, and mood measures was more feasible for the study design and smaller sample size.

Although group comparisons were not feasible, it was clear that the results were not consistent with the hypothesis that more sleep duration would be associated with worse physiological health and cognitive performance. Unexpectedly, TST had a more positive association with blood pressure and heart rate. Higher levels of TST were associated with decreased diastolic blood pressure and heart rate. Even though epidemiological evidence suggests otherwise, experimental study of sleep extension had not yet been conducted in older adults. It is possible that sleep extension in older adults is not harmful, as previously suggested. One potential explanation is that the older adults who participated in the study were not sleeping at their optimal level and had obtained a sleep debt. Three weeks of extended sleep may have relieved that debt and resulted in improved physiological health.

Unexpectedly, TST and sleep disturbances did not predict any associations of cardiovascular risk, lipid profile, executive function, vigilance, working memory,

sleepiness, or clinician-administered mood assessments. It is important to note that these null results could imply that increased sleep duration may be neither harmful nor helpful to certain aspects of physiological, psychological, or emotional health. It can be posited that these null results provide evidence that normal-sleeping older adults without significant health conditions, who increase their total sleep time, do not benefit in these specific aspects of health. However, a larger sample size is needed in order to make concrete conclusions.

As expected, sleep disturbances impacted mood and blood pressure. Sleep disturbances had a negative impact on mood, systolic blood pressure, diastolic blood pressure, and heart rate. As sleep became increasingly disturbed, diastolic blood pressure, systolic blood pressure, and heart rate increased. Additionally, higher levels of sleep disturbance were associated with changes to a more negative mood. These results are consistent with sleep disturbance studies, including those examining individuals with sleep apnea, restless leg syndrome, and other conditions that are associated with increased disruption of sleep. Additionally, as sleep time increased, sleep disturbances also increased. These results are consistent with the literature on sleep extension.

A major limitation of this study is the small sample size. The small sample size limits the statistical analysis and conclusions that can be made from the data. However, according to Comrey and Lee (1992), a sample size of 200 cases is considered "fair," 300 as "good," and 500 as "very good" for factor analysis. Since the sleep, cognitive, and mood data consisted of at least 300 cases, these were considered "good." Due to the limited number of cases for the physiological data (100 cases), caution should be made regarding conclusions derived from the analysis of this set of data. Additionally, only

four participants were randomized to the sleep extension condition first, which was not enough for order comparisons against the six participants who were randomized to the habitual sleep condition first.

Another limitation and interesting observation is the potential order effects. As seen in Figure C.2, participants who were randomized to the sleep extension condition first were able to extend their sleep longer than those who were randomized to the habitual sleep condition first. However, it is possible that, with a greater sample size in this condition, the data would be more similar to the opposing group. If there are indeed order effects, it may be beneficial to conduct a future study examining these effects. Since there have been no other cross-over studies of sleep extension in older adults, additional studies are needed to determine if this is the most appropriate design for a sleep extension study. Additionally, future cross-over studies should carefully examine the length of the recovery period. It is also possible that the recovery period of 1 week may need to be extended in future studies if evidence is found for carry-over effects.

The current study is the most comprehensive sleep extension study in older adults to date. Although limited by small sample size, patterns in the data emerged that were explained by rest and sleep disturbance components. This study was the first of its kind to use the cross-over research design for sleep extension in older adults, which provided interesting information in terms of order effects. Future randomized controlled trials should examine longer duration (i.e. more than 3 weeks) in sleep extension studies in order to determine to what extent older adults may or may not benefit from extension of sleep duration.

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APPENDIX A – SCREENING DATA

Table A.1. Descriptive Statistics for Screening Data

Means and standard deviations for screening and demographic data.

Measure	(N=24, 3 Male)
Age	
M	65.71
SD	5.55
Body Mass Index	
M	27.20
SD	4.09
Subjective Total Sleep Time (hours)	
M	7.14
SD	0.78
Patient Health Questionnaire-9	
M	1.13
SD	1.26
Beck Scale for Suicide Ideation	
M	0.00
SD	0.00
Mini Mental State Exam	
M	28.58
SD	1.10
Expectations Questionnaire	
M	13.88
SD	2.52

APPENDIX B – DESCRIPTIVE STATISTICS OF RAW AND TRANSFORMED DATA

Means and standard deviations reported for raw sleep data (Table B.1), physiological (Table B.2), blood pressure and heart rate data (Table B.3), mood data (Table B.4), and cognition data (Table B.5).

Table B.1. Descriptive Statistics for Raw Sleep Data

Means and standard deviations for raw sleep data.

Sleep Measures	Normal Sleep (N=30)	Sleep Extension
Time in Bed		
M	484.86	555.06
SD	27.82	35.49
Total Sleep Time		
M	424.88	475.11
SD	28.87	49.72
Number of Awakenings		
M	22.49	27.32
SD	5.47	4.87
Sleep Efficiency (%)		
M	88.30	87.37
SD	3.41	2.68
Sleep Fragmentation (%)		
M	25.97	29.78
SD	5.59	4.68
Wake after Sleep Onset		
M	44.53	55.35
SD	14.39	11.76

Table B.2. Descriptive Statistics for Physiological Data

Means and standard deviations for raw and transformed physiological data.

Physiological Measures	Normal Sleep (N=10)	Sleep Extension
C-Reactive Protein (log10)		
M	0.11	0.06
SD	0.39	0.36
Glucose		
M	92.70	92.30
SD	6.17	6.11
Triglycerides		
M	70.40	75.20
SD	11.10	17.69
High-Density Lipoprotein		
M	74.10	73.30
SD	20.72	14.65
Low-Density Lipoprotein (sqrt)		
M	9.95	9.97
SD	2.19	1.80

Table B.3. Descriptive Statistics for Blood Pressure and Heart Rate Data.

Means and standard deviations for raw blood pressure and transformed heart rate data.

Blood Pressure and Heart Rate	Normal Sleep (N=30)	Sleep Extension
Systolic		
M	124.14	123.56
SD	15.30	13.59
Diastolic		
M	70.68	69.39
SD	7.49	7.11
Heart Rate (sqrt)		
M	8.34	8.37
SD	0.53	0.65

Table B.4. Descriptive Statistics for Mood and Sleepiness Data

Means and standard deviations for transformed mood and sleepiness data.

Mood Scores	Normal Sleep	Sleep Extension
Beck Depression Inventory II (n=30)		
M	0.00	-0.57
SD	1.84	1.65
State-Trait Anxiety Inventory (n=30)		
M	1.70	-0.11
SD	6.37	5.10
Epworth Sleepiness Scale (n=30)		
M	0.33	0.53
SD	2.56	1.83
Multidimensional Assessment of Fatigue (n=30)		
M	0.69	-0.55
SD	4.64	4.31
Hamilton Anxiety Inventory (n=10)		
M	-0.22	-0.60
SD	2.00	2.07
Hamilton Depression Inventory (n=10)		
M	-0.32	-0.50
SD	0.94	1.72

Table B.5. Descriptive Statistics for Cognitive Data

Means and standard deviations for raw and transformed cognitive data.

Cognitive Measures	Normal Sleep (N=10)	Sleep Extension
Stroop Interference (log)		
M	1.52	1.55
SD	0.14	0.08
Trail Making Test A (s)		
M	34.46	29.51
SD	18.98	13.72
Trail Making Test B (s)		
M	85.04	74.39
SD	63.99	41.54
Psychomotor Vigilance Test (log)		
M	2.47	2.47
SD	0.07	0.06
Psychomotor Vigilance Test Number of Lapses		
M	2.30	1.30
SD	3.89	3.13
Automated Reading Span Score		
M	30.50	36.20
SD	21.46	22.04
Stanford-Binet 5 Block Pattern Memory Task		
M	18.70	18.50
SD	2.91	2.76
Stanford-Binet 5 Sentence Memory Task		
M	20.18	19.60
SD	2.15	1.84

APPENDIX C – COMPARISONS OF RAW DATA

A paired samples *t*-test revealed that actigraphic TST statistically significantly increased from 424.88±24.49 min in the normal sleep condition to 475.11±43.43 min during the sleep extension condition, $t(9)=-6.327$, $p<.001$. Figure 1 shows the average TST in minutes for each group. Figure 2 shows the cross-over nature of the study for TST for each week of the study. Additional t-tests of raw data are shown for sleep data (Table C.1), physiological data (Table C.2), mood data (Table C.3), and cognitive data (Table C.4). Correlation matrices are shown for the raw sleep data (Table C.5), raw physiological data (Table C.6), raw mood and sleepiness data (Table C.7), and raw cognitive data (Table C.8).

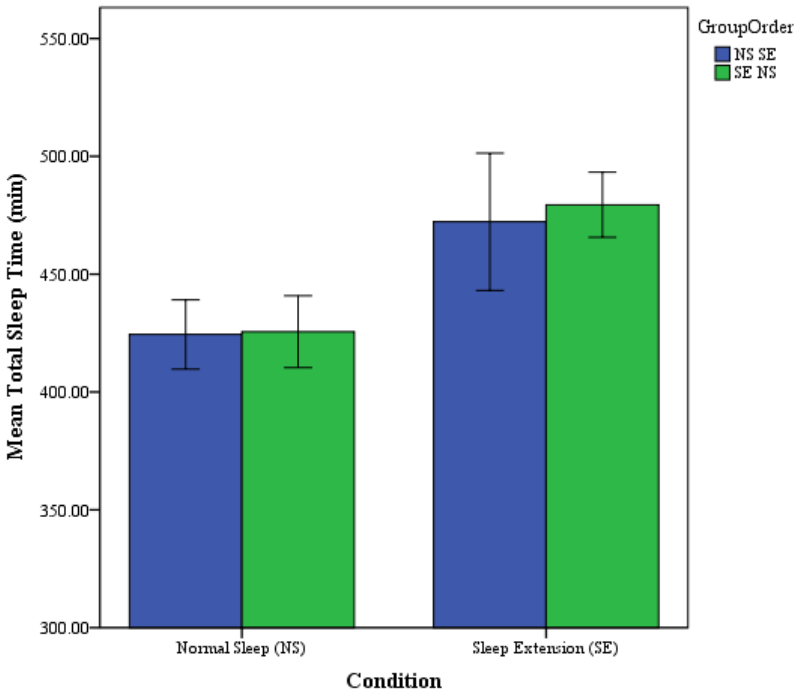


Figure C.1. Total Sleep Time for each Condition. Blue bar represents condition order of normal sleep (NS) followed by sleep extension (SE); green bar represents condition order of SE followed by NS. Error bars represent standard error.

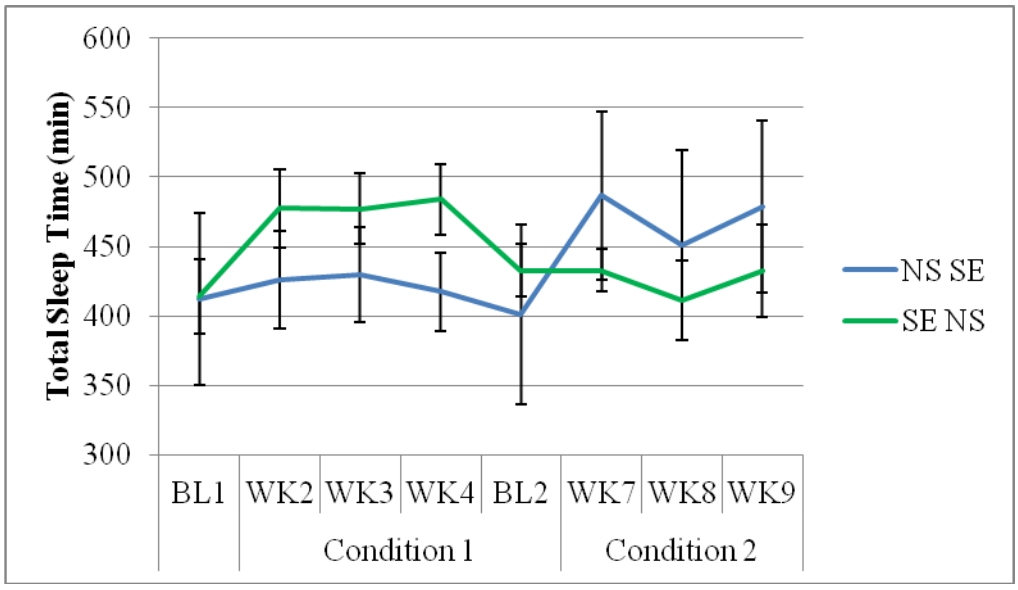


Figure C.2. Total Sleep Time for each Week. Total sleep time, as measured in minutes, for each Baseline (BL) and week (WK) per condition. Blue line represents condition order of normal sleep (NS) followed by sleep extension (SE); green line represents condition order of SE followed by NS. Error bars represent standard error.

Table C.1. Raw Sleep Data Comparisons

T-tests for raw sleep measurements.

Sleep Measures					
Sleep Measures	*T*	df	P-Value	*M*	*SE*
TIB	-8.527	58	0.000	-70.199	8.23283
TST	-4.786	58	0.000	-50.2357	10.49674
Awakenings	-3.614	58	0.001	-4.83167	1.33702
Sleep Efficiency	1.164	58	0.249	0.92133	0.79154
Sleep Fragmentation	-2.86	58	0.006	-3.80467	1.33031
WASO	-3.19	58	0.002	-10.8217	3.39237

Note. Time in bed (TIB), total sleep time (TST), wake after sleep onset (WASO)

Table C.2. Raw Physiological Data Comparisons

T-tests for raw physiological measurements.

Physiological Measures					
Physiological Measures	t	Df	P-Value	M	SE
CRP	0.276	18	0.786	0.047	0.169
Glucose	0.146	18	0.886	0.400	2.745
Trig	-0.727	18	0.477	-4.800	6.603
HDL	0.100	18	0.922	0.800	8.024
LDL	-0.026	18	0.979	-0.024	0.896

Note. C-reactive protein (CRP), high-density lipoprotein (HDL), low-density lipoprotein (LDL).

Table C.3. Raw Blood Pressure and Heart Rate Data Comparisons

T-tests for raw blood pressure and heart rate measurements.

Blood Pressure and Heart Rate Measures					
Blood Pressure and Heart Rate Measures	t	Df	P-Value	M	SE
Systolic	0.156	58	0.876	0.583	3.736
Diastolic	0.681	58	0.499	1.283	1.885
Heart Rate	-0.159	58	0.874	-0.024	0.152

Table C.4. Raw Mood Data Comparisons

T-tests for raw mood measurements.

Mood Difference Scores					
Mood Difference Scores	t	df	P-Value	M	SE
BDI	1.255	58	0.215	0.567	0.452
STAI	1.212	58	0.230	1.807	1.490
ESS	-0.348	58	0.729	-0.200	0.575
MAF	1.075	58	0.287	1.243	1.157
HAMA	0.418	18	0.681	0.380	0.909
HAMD	0.291	18	0.775	0.180	0.619

Note. Beck Depression Inventory II (BDI), State-Trait Anxiety Inventory (STAI), Epworth Sleepiness Scale (ESS), Multidimensional Assessment of Fatigue (MAF), Hamilton Anxiety Inventory (HAM-A), Hamilton Depression Inventory (HAM-D).

Table C.5. Raw and Transformed Cognitive Data Comparisons

T-tests for raw and transformed cognitive measurements.

Cognitive Measures					
Cognitive Measures	T	df	P-Value	M	SE
Stroop Interference Score (log)	-0.741	18	0.468	-0.037	0.050
Trail Making Test A	0.669	18	0.512	4.955	7.405
Trail Making Test B	0.442	18	0.664	10.652	24.124
PVT Mean Responses (log)	-0.02	18	0.984	-0.001	0.028
PVT Number of Lapses	0.634	18	0.534	1.000	1.578
Automated Reading Span Score	-0.586	18	0.565	-5.700	9.729
SB5 BPMT	0.158	18	0.876	0.200	1.268
SB5 SMT	0.648	18	0.525	0.580	0.895

Note. Psychomotor vigilance test (PVT), Stanford-Binet 5 (SB5), Block Pattern Memory Task (BPMT), Sentence Memory Task (SMT).

Table C.6. Raw Sleep Data Correlation Matrix

Table shows correlation matrix of raw sleep data.

	TST	Sleep Efficiency	Number of Awakenings	Sleep Fragmentation	WASO
TST					
Sleep Efficiency	.170				
Number of Awakenings	.191	-.688**			
Sleep Fragmentation	.186	-.628**	.589**		
WASO	.160	-.863**	.788**	.666**	

Note. Total Sleep Time (TST), Wake after Sleep Onset (WASO); *, $p<.05$; **, $p<.01$

Table C.7. Raw Physiological Data Correlation Matrix

Table shows correlation matrix of raw physiological data.

	CRP	Glucose	Triglycerides	HDL	LDL
CRP					
Glucose	.277				
Triglycerides	.234	.253			
HDL	-.461*	-.297	-.321		
LDL	-.032	-.136	.373	-.196	

Note. C-reactive protein (CRP), high-density lipoprotein (HDL), low-density lipoprotein (LDL); *, $p<.05$.

Table C.8. Raw Mood and Sleepiness Data Correlation Matrix

Table shows correlation matrix of raw mood and sleepiness data.

	ESS	MAF	BDI	STAI	Daily Mood
ESS					
MAF	.615**				
BDI	.298**	.371**			
STAI	.236*	.375**	.586**		
Daily Mood	-.132	-.100	-.174	-.218	

Note. Epworth Sleepiness Scale (ESS); Multidimensional Assessment of Fatigue (MAF), Beck Depression Inventory II (BDI II), State-Trait Anxiety Inventory (STAI); *, $p<.05$; **, $p<.01$

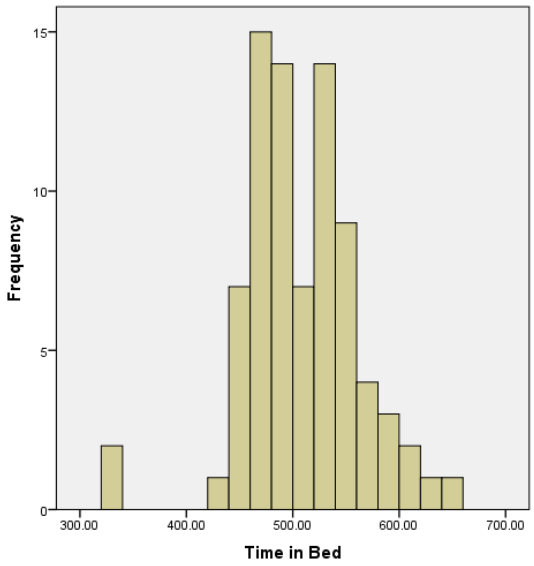
Table C.9. Raw Cognitive Data Correlation Matrix

Table shows correlation matrix of raw cognitive data.

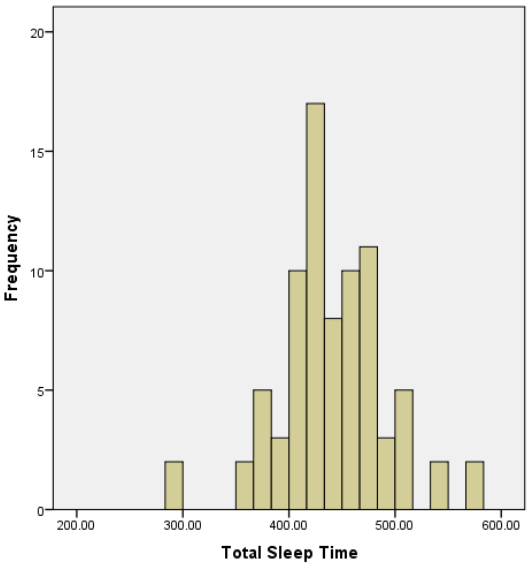
	TMT A	TMT B	Stroop Int.	PVT Log RT	PVT Lapses	Rspan	SB5 BPMT	SB5 SMT
TMT A								
TMT B	.722**							
Stroop Int.	.578**	.647**						
PVT Log	.463*	.344						
RT			.477**					
PVT Lapses	.224	.110	.328					
				.730**				
Rspan	-.226	-.243	-.064	.253	.261			
SB5 BPMT	.123	-.199	-.040	.049	.133	.290		
SB5 SMT	-.128	-.327	-.431*	-.041	-.086	.154	.345	

Note. Trail Making Test (TMT), Stroop Int. (Stroop Interference), Psychomotor Vigilance Task (PVT), reaction time (RT), Automated Reading Span (Rspan), Stanford-Binet 5 (SB5), Block Pattern Memory Task (BPMT), Sentence Memory Task (SMT); *, $p<.05$; **, $p<.01$

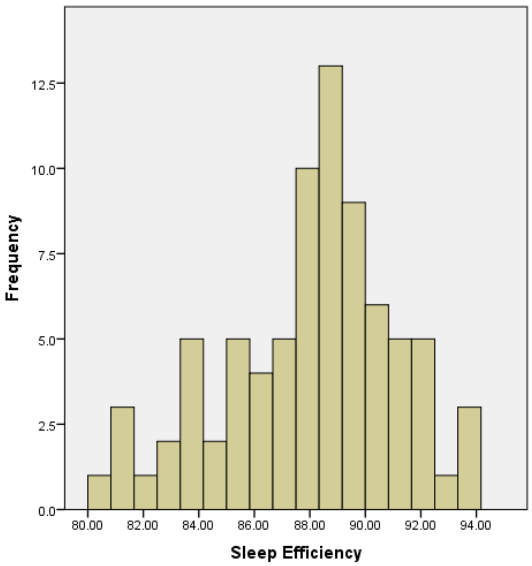
APPENDIX D – HISTOGRAMS OF RAW AND TRANSFORMED DATA



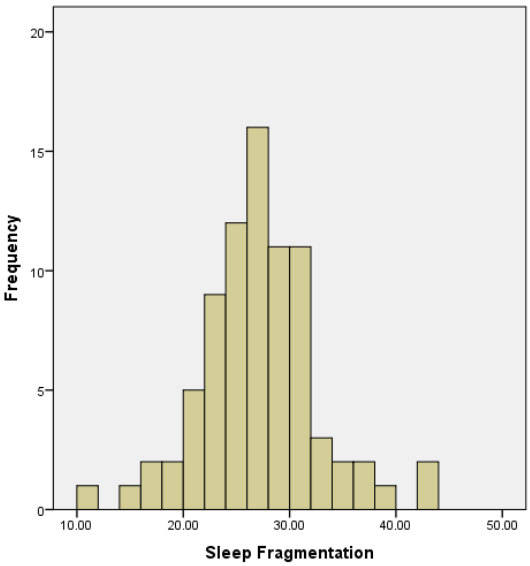
a.



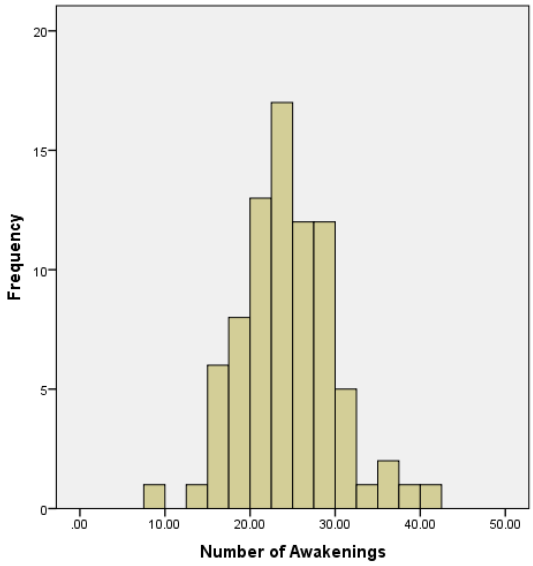
b.



d.

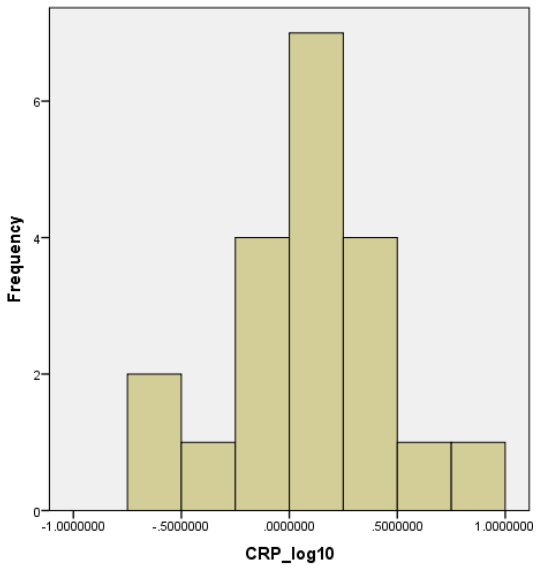


e.

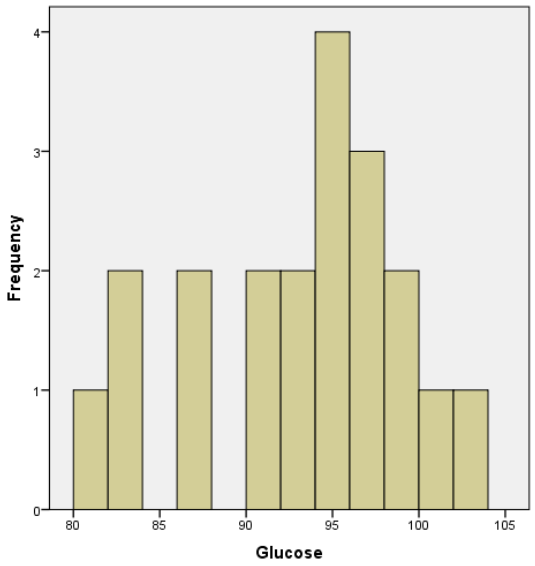


f.

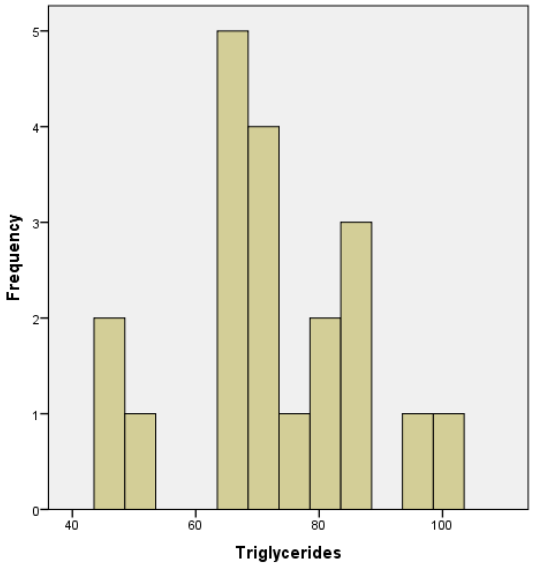
Figure D.1. Histograms of Raw Sleep Data. Histograms include time in bed (a), total sleep time (b), sleep efficiency (c), sleep fragmentation (d), and number of awakenings (f) raw data.

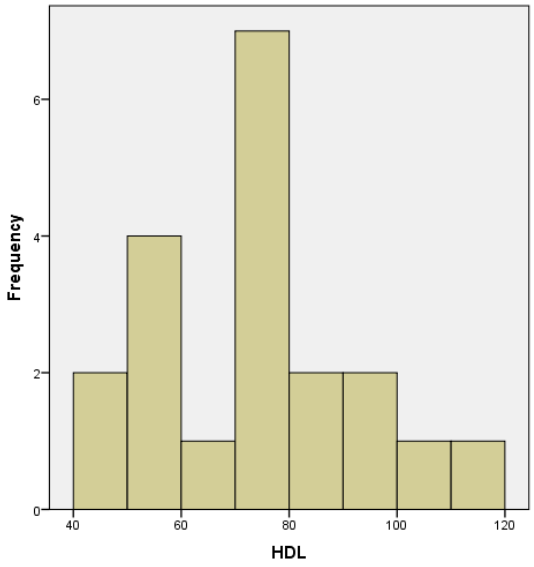


a.



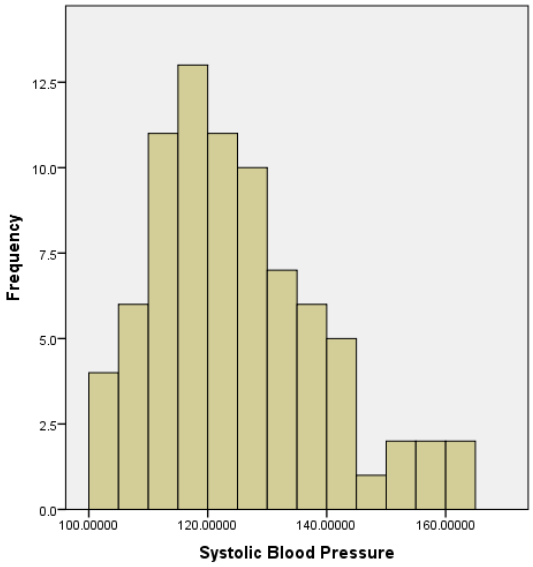
b.

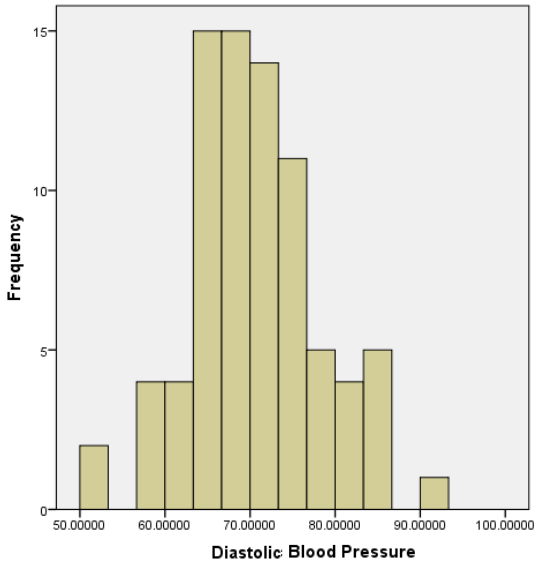




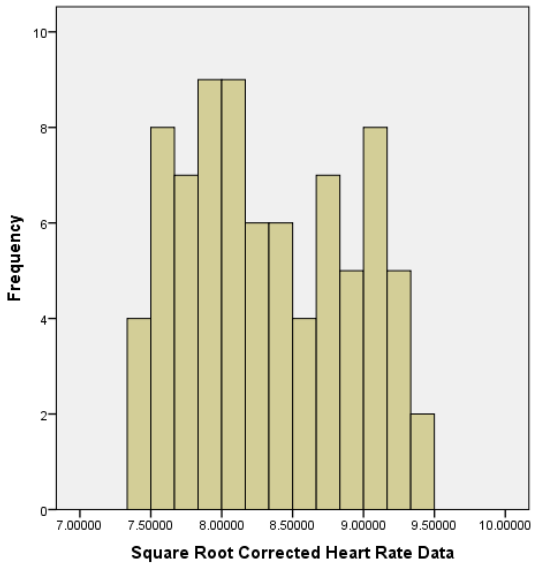
c. d.

Figure D.2. Histograms of Raw and Transformed Physiological Data. C-reactive protein (CRP, a) log transformed and raw glucose (b), triglycerides (c), and high-density lipoproteins (HDL, d) data.



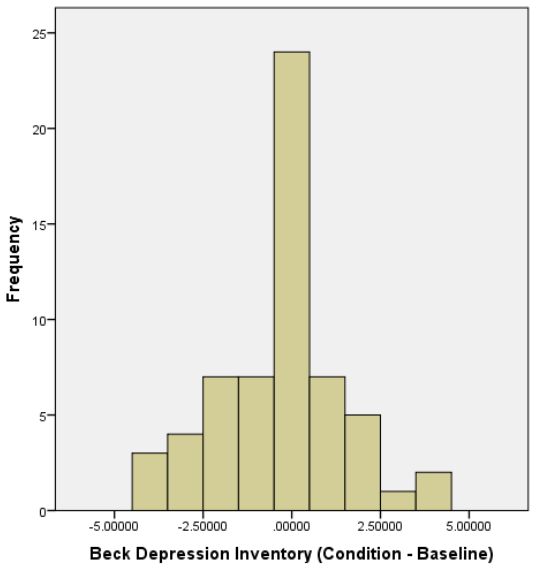


a. b.

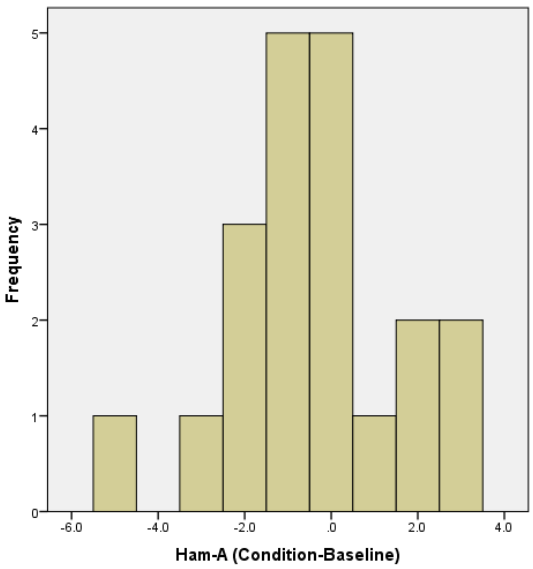


c.

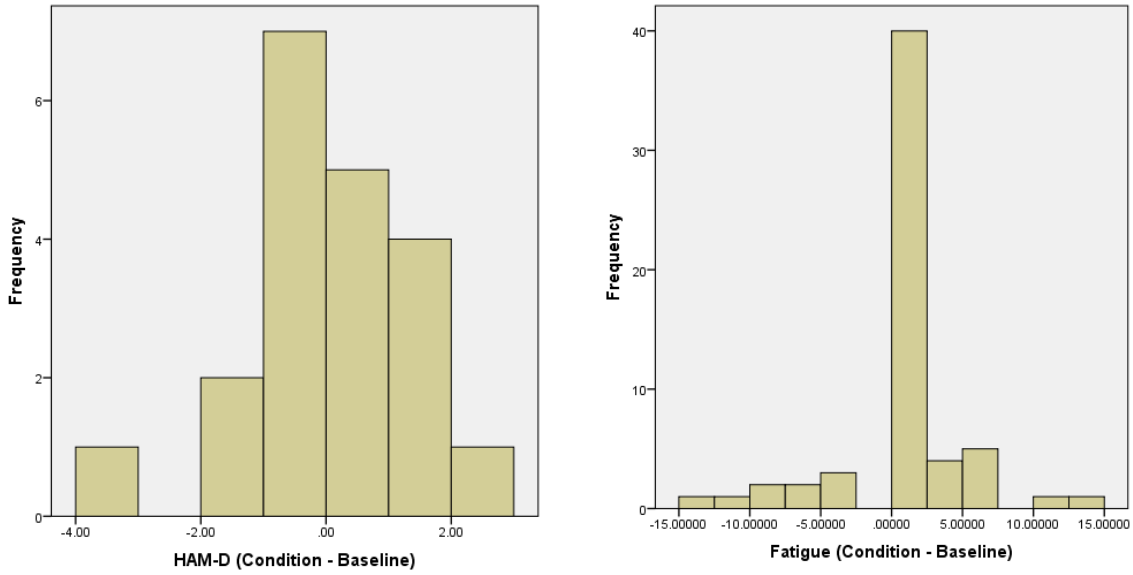
Figure D.3. Histograms of Blood Pressure and Heart Rate Data. Histograms of raw systolic (a) and diastolic (b) blood pressure and square root transformed heart rate data (c).



a.

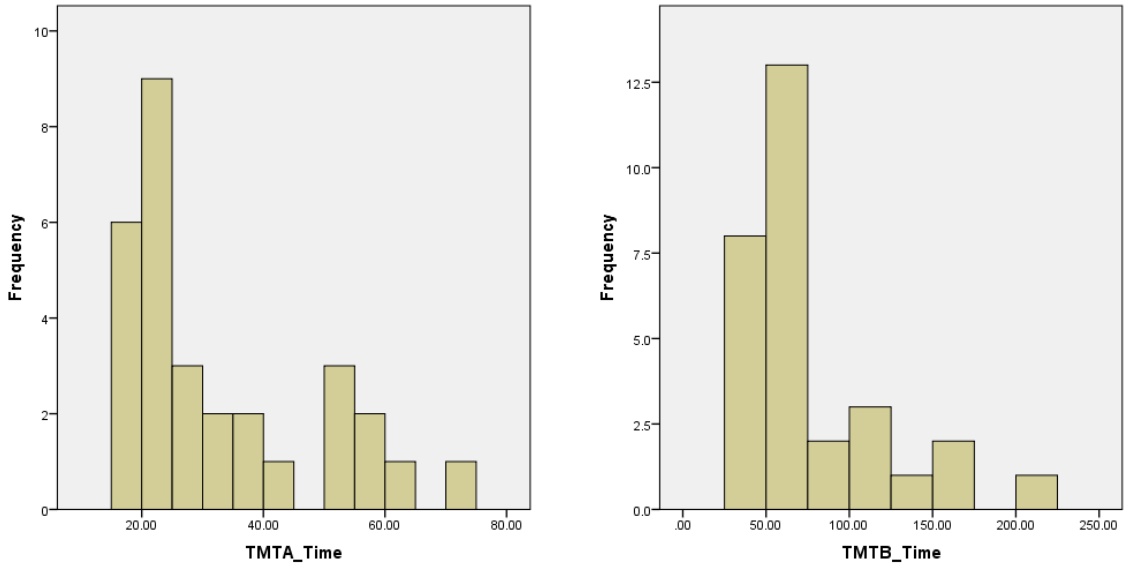


b.

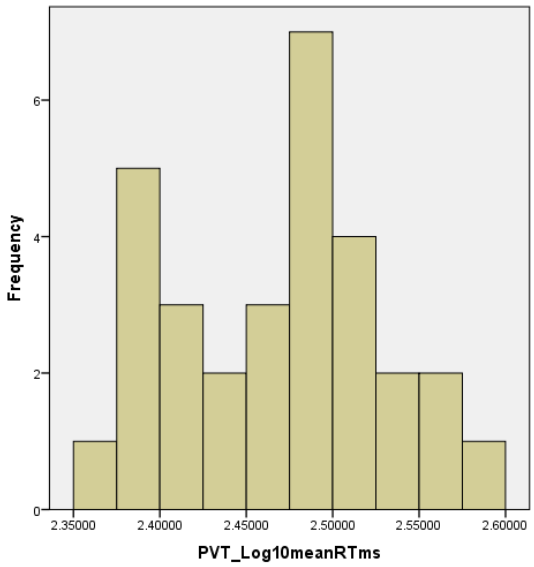


a. b.

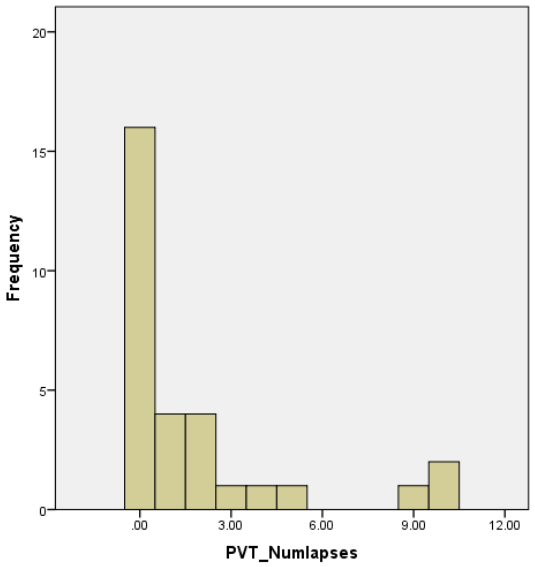
Figure D.4. Histograms of Transformed Mood Data. Mood and fatigue data include Beck Depression Inventory II (a), Hamilton Anxiety Rating Scale (HAM-A, b), Hamilton Depression Rating Scale (HAM-D, c), Multidimensional Assessment of Fatigue (d).



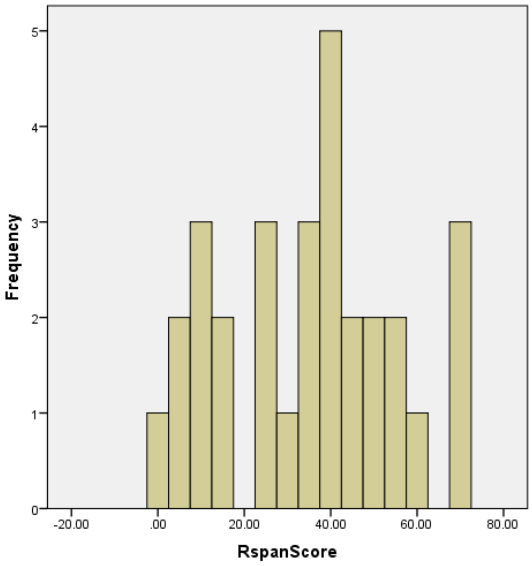
a. b.



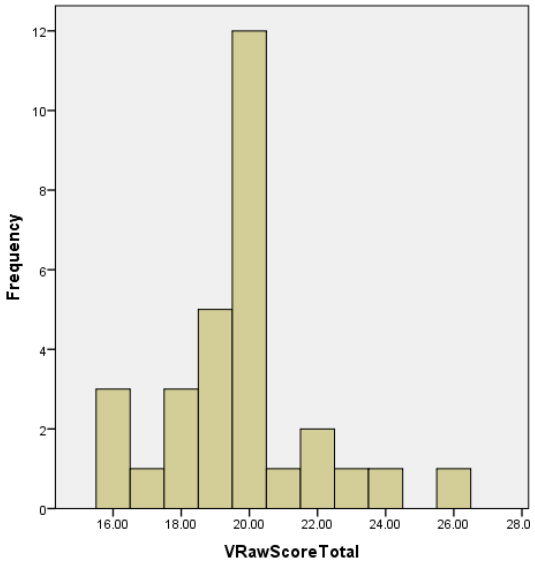
c.



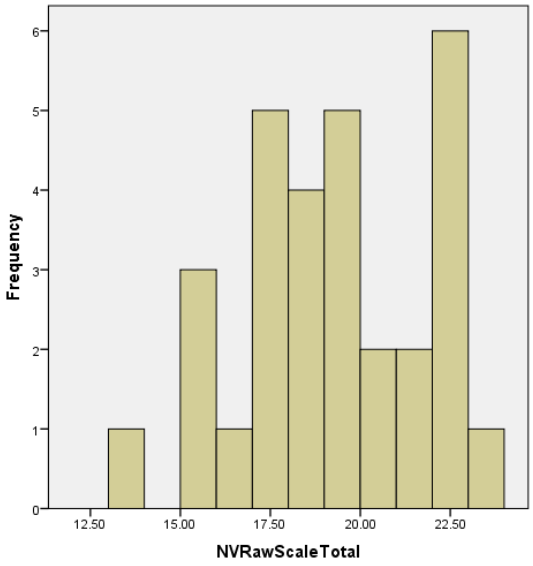
d.



e.



f.



g.

Figure D.5. Histograms of Cognitive Data. Histograms for Trail Making Test A (TMT-A, a), Trail Making Test B (TMT-B, b), log transformed psychomotor vigilance test (PVT, c), PVT number of lapses (d), Automated Operating Reading Span (Rspan, e), Stanford-Binet 5 (SB5) Verbal (V) Raw Score (f), SB5 Nonverbal (NV) Raw Score (g) data.