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The Relationship Between Sleep Quality and Motor Function in Hospitalized Older Adult Survivors of Critical Illness

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By

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of the requirements for the degree of
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Dedication

I formally dedicate this dissertation, and my future career in scientific research, to my forever-faithful God, whose relentless loving-kindness had uplifted my spirits throughout what would have otherwise been an arduous journey. "*For I know the plans I have for you*," declares the LORD, "*plans to prosper you and not to harm you, plans to give you hope and a future*" (Jeremiah 29:11).

I also dedicate this dissertation to hardworking women who have persevered despite disadvantaged backgrounds and/or extenuating circumstances to become research scientists.

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List of Abbreviations

ICU	Intensive care unit
TST	Total sleep time
SE	Sleep efficiency
WASO	Wake after sleep onset
SL	Sleep latency
NA	Number of awakenings
REM	Rapid eye movement sleep
NREM	Non-rapid eye movement sleep
OSA	Obstructive sleep apnea
USF	University of South Florida
TGH	Tampa General Hospital
NIH	National Institutes of Health
GST	NIH Toolbox Motor Battery Grip Strength Test
PDT	NIH Toolbox Motor Battery 9-Hole Pegboard Dexterity Test
SBT	NIH Toolbox Motor Battery Standing Balance Test
FICAT	NIH Toolbox Cognition Battery Flanker Inhibitory Control and Attention Test
DCCST	NIH Toolbox Cognition Battery Dimensional Change Card Sort Test
SS	NIH Toolbox Emotion Battery Sadness Survey
FAS	NIH Toolbox Emotion Battery Fear-Affect Survey
PIT	NIH Toolbox Sensation Battery Pain Intensity Test

APACHE	Acute Physiology and Chronic Health Evaluation III
PSQI	Pittsburgh Sleep Quality Index

Abstract

The primary, descriptive aim of this dissertation was to describe the nighttime sleep quality of previously mechanically ventilated older adult patients within 24-48 hours of transfer out of the intensive care unit (ICU) to a medical-surgical floor. The secondary, exploratory aim was to examine the relationships between post-ICU sleep efficiency (SE) and wake after sleep onset (WASO) with grip strength in previously mechanically ventilated older adult patients within 24-48 hours of transfer out of the ICU.

The study included 30 adults ages 65 and older (11 women, 19 men; age 71.37 ± 5.35, range 65-86 years), who were functionally independent at home prior to hospitalization, mechanically ventilated during their ICU stay, and were within 24-48 hours of transfer out of ICU to a medical-surgical floor at Tampa General Hospital, a level 1 trauma center. Subjects wore an actigraph monitor on the dominant wrist (Actiwatch Spectrum) to monitor sleep over two consecutive nights. Parameters of post-ICU sleep quality included total sleep time (TST), sleep efficiency (SE), wake after sleep onset (WASO), sleep latency (SL), and number of awakenings (NA). The outcome measure of motor function was dominant hand grip strength, assessed by the National Institutes of Health Toolbox Motor Battery Grip Strength Test. Sleep data collected between nighttime hours (9:00 PM to 9:00 AM) on both nights were analyzed. For the descriptive aim, means for each sleep parameter and clinical characteristics were reported. For the exploratory aims, multiple regression analyses examined the individual associations between mean sleep parameters (SE and WASO) and grip strength.

Study subjects had a mean SE of 63.24 ± 3.88% and spent 135.39 ± 9.94 minutes awake after sleep onset. The mean TST among subjects was 7.55 ± 2.52 hours, ranging from 2.02 to 10.84 hours of sleep, out of the 12 hours of total time in bed. A total of 6 (20%) subjects slept less than 5 hours each night, and a total of 6 (20%) subjects slept greater than 10 hours each night. The mean SL among study subjects was 42.57 minutes, and ranged from 0.0 to 237.75 minutes. Overall, subjects' average NA was 78.28 ± 26.39, ranging from 35 to 136 awakenings.

In multiple regression analysis, SE was significantly and negatively associated with grip strength, after adjusting for potential confounding factors. The model predictors explained 80.8% of the variance in grip strength, [R^2 = .808, F(10, 15) = 6.324, p = .001]. Higher SE independently predicted worse grip strength (β = -0.326, p = .036). Further, among the tertiles of subjects with moderate or high TST (sleep duration ≥ 6 hours, n = 23), there remained a significant, negative association between SE and grip strength. The predictors explained 73.7% of the variance in grip strength, [R^2 = .737, F(5, 15) = 8.416, p = .001]. Higher SE independently predicted worse grip strength among the subset of subjects with moderate or high sleep duration (β = -0.296, p = .046). Among the two quartiles of subjects with moderate-high or high WASO (≥ 120 minutes spent awake after sleep onset, n = 16), there was a significant, negative association between WASO and grip strength, after adjusting for covariates. The model indicated that the predictors explained 91.4% of the variance in grip strength [R^2 = .914, F(6, 8) = 14.134, p = .001]. Greater WASO independently predicted worse grip strength (β = -0.276, p = .04). Finally, the effects of sex and preexisting obstructive sleep apnea (OSA) on grip strength were individually examined. Higher SE independently predicted worse grip strength among male subjects (β = -0.353, p = .039), as did preexisting OSA (β = -0.493, p = .033).

In summary, objectively measured sleep quality was disturbed among previously mechanically ventilated, hospitalized older adults, even after transfer out of ICU to a medical-surgical floor. Longer TST and greater SE predicted worse grip strength among these frail patients who were previously independent, community dwelling older adults. Among the subjects with more severely fragmented sleep, WASO also independently predicted weaker grip strength. As poor grip strength is an indicator of ICU-acquired weakness, optimal sleep duration and less sleep disturbances may be crucial in prevention of worse functional outcomes and new institutionalization. Additional research is needed to discern the temporality of associations between sleep quality and motor function among older adult survivors of critical illness.

Chapter One: Introduction

Critically ill patients ages 65 and older admitted to an intensive care unit (ICU) have the highest age-specific incidence of mechanical ventilation (Carson, Cox, Holmes, Howard, & Carey, 2006). Approximately 40% of critically ill patients in the ICU require mechanical ventilation (Wunsch et al., 2013). It is estimated that over 50% of mechanically ventilated ICU patients are older than 70 years of age, and of those, over 40% are older than 80 years of age (Cohen & Lambrinos, 1995; Somogyi-Zalud, Zhong, Hamel, & Lynn, 2002).

Sleep disruption is one of the most frequent complaints from ICU patients; poor sleep has been identified as one of the most severe symptoms among survivors of critical illness. Among patients interviewed within 3 days after ICU discharge, 61% reported sleep deprivation and 7% rated insomnia as their worst experience in the ICU (Simini, 1999). Disrupted sleep was the second most stressful factor described by ICU patients in one study (Nelson et al., 2001). These sleep disturbances manifest during the patients' courses of illness within the ICU, and may persist for an extended period after ICU care and even beyond hospital discharge (Rotondi et al., 2002). A longitudinal research study of critical care survivors revealed persistent sleep disturbances in up to 44% of survivors up to 3 months after discharge (Eddleston, White, & Guthrie, 2000). Although numerous studies featuring non-pharmacological interventions have been tested to promote sleep in the ICU, their beneficial effects for the critically ill are limited, and do not specifically address elderly patients (Hu et al., 2015).

Sleep patterns among older adults markedly differ from those of their younger counterparts in the repeated and frequent interruptions of sleep with sustained periods of

wakefulness (Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). Community-dwelling older adults experience significant sleep disturbances, and these are positively correlated with chronic diseases and medical conditions (Foley, Ancoli-Israel, Britz, & Walsh, 2004). Daytime sleepiness poses increased risks for total mortality and cardiovascular mortality among older adults, especially in women (Newman et al., 2000). Subjective complaints of daytime sleepiness and inadequate sleep time have been associated with increased health care utilization (Kapur et al., 2002) and depression (Jaussent et al., 2011) among community-dwelling older adults. Nonetheless, older adults are often poorly represented or excluded from randomized controlled trials of sleep studies. Thus, sleep disturbances in a community-dwelling older adult may be drastically different from those experienced by older adults admitted to an acute hospital setting, let alone hospitalized older adults who were mechanically ventilated while in the ICU (Bloom et al., 2009).

Moreover, up to 90% of older adult ICU patients are discharged from the hospital with at least one geriatric syndrome (Tang, Tang, Hu, & Chen, 2016). Geriatric syndromes may include delirium, falls, frailty, or decline in functional ability (Inouye, Studenski, Tinetti, & Kuchel, 2007). Older adults in the ICU and after discharge from the ICU are at very high risk of developing new or worsened functional decline. Studies suggest that up to 40% of adult ICU patients may experience ICU-acquired weakness (Appleton, Kinsella, & Quasim, 2014). The long-term consequences of critical illness are growing in importance, as the older adult population increases the necessity for critical care, and the mortality rate after surviving critical illness decreases (Needham et al., 2012). The proportion of older adult survivors of critical illness who develop motor and physical impairments remains unknown; these impairments have

recently been recognized as a component of post-intensive care syndrome among patients of all ages (Elliott et al., 2014; Needham et al., 2012).

Physical function is a prognostic clinical outcome for hospitalized older adult patients. Survivors of critical illness experience muscle wasting and an associated decrease in functional ability (Puthucheary et al., 2013), which may have serious health implications for older adults. Hospitalized older adults with lower levels of mobility and less independence in performing activities of daily living had higher risks of functional decline, new institutionalization, and mortality (Brown, Friedkin, & Inouye, 2004; Covinsky, Justice, Rosenthal, Palmer, & Landefeld, 1997). Higher admission grip strength may be associated with better likelihood of hospital discharge disposition to home (Kerr et al., 2006).

Statement of the Problem

Sleep disruption is one of the most frequent complaints from ICU patients. To date, there has not been a descriptive study of the post-ICU sleep quality of hospitalized older adults who were previously mechanically ventilated. Moreover, there has not been a study that explored the relationship between post-ICU sleep quality and motor function within the 24-hour timeframe of transfer out of the ICU.

Purpose of the Study

A thorough approach to understanding functional outcomes among older adult survivors of critical illness requires examination of sleep quality and its relationship to motor function. An understanding of these relationships may provide scientific knowledge necessary to advance clinical practice and improve outcomes for older ICU survivors. A descriptive and exploratory approach is appropriate for integrating what is known about sleep quality and its relationship to motor function in older adult ICU survivors. Building on the existing research base of sleep and

motor function among hospitalized older adult survivors of critical illness will advance the field's understanding of their long-term outcomes. This study described the sleep quality of previously mechanically ventilated older adult patients immediately after ICU transfer to a medical-surgical floor. It also examined the relationship between post-ICU sleep efficiency and sleep fragmentation, and motor function as measured by grip strength. Further, data on selected additional variables will be presented as part of this study for future analyses. A conceptual map of the relationships central to the study is presented below in Figure 1.

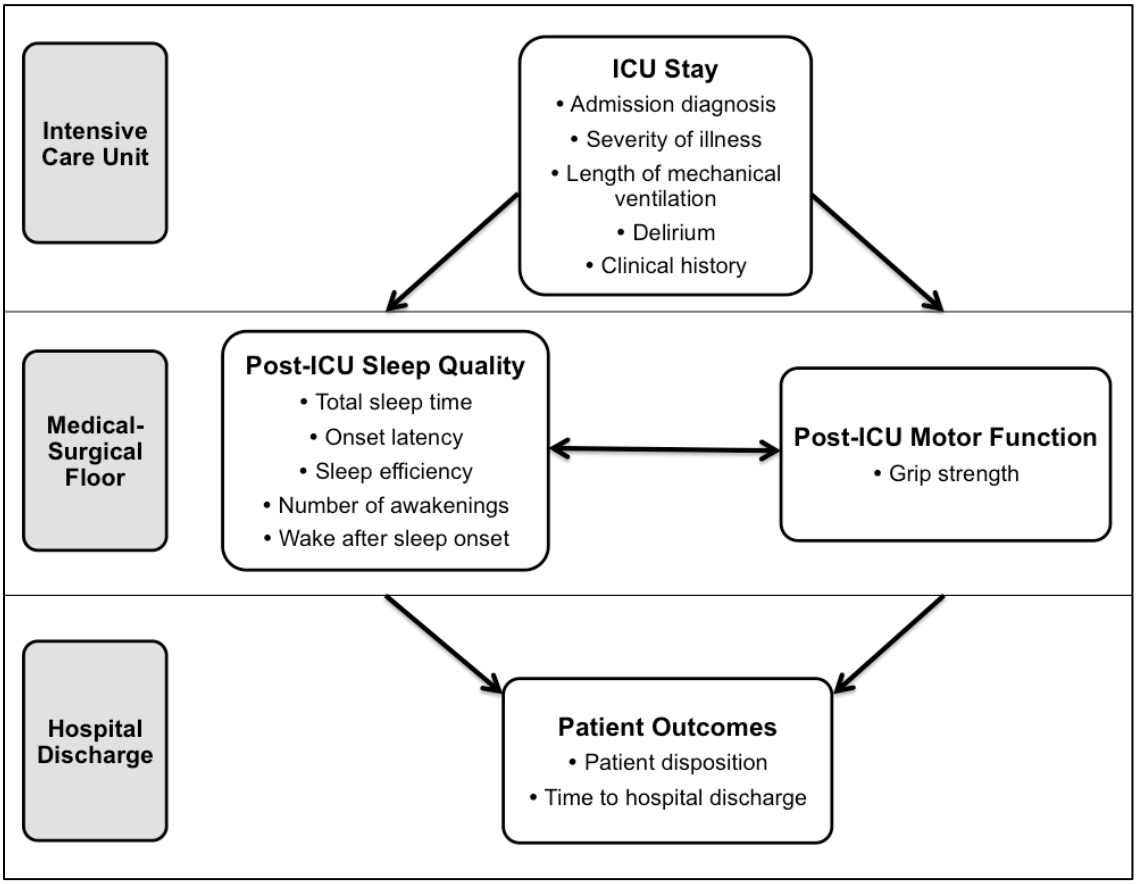

Figure 1. Hypothesized Relationships Between Variables

Specific Aims

The main objectives of this study are two-fold. The study aims and hypotheses are presented below and summarized in Table 1 and Figure 2.

Aim 1: Describe the post-ICU nighttime sleep quality of previously mechanically ventilated older adult patients within 24-48 hours of transfer out of the ICU.

Hypothesis 1: Subjects' nighttime sleep quality, as defined by total sleep time (TST), sleep efficiency (SE), wake after sleep onset (WASO), sleep latency (SL), and number of awakenings (NA), will be abnormal and disturbed at 24-48 hours of transfer out of the ICU.

Aim 2a: Explore the relationship between post-ICU SE and grip strength in previously mechanically ventilated older adult patients within 24-48 hours of transfer out of the ICU.

Aim 2b: Explore the relationship between post-ICU WASO and grip strength in previously mechanically ventilated older adult patients within 24-48 hours of transfer out of the ICU.

Hypothesis 2a: There is a direct, significant, positive relationship between post-ICU SE and grip strength among these older adult subjects.

Hypothesis 2b: There is a direct, significant, negative relationship between post-ICU WASO and grip strength among these older adult subjects.

Table 1. Study Design

Aim	**Objective**	**Design**	**Variables**	**Data Collection Time Points**
Aim 1	Describe the post-ICU nighttime sleep quality of previously mechanically ventilated, older adult patients within 24-48 hours of transfer out of the ICU	Descriptive, cross-sectional	• Sleep quality: TST, SE, WASO, SL, NA	• Actigraphy (2-night observation) within 24-48 hours of transfer out of ICU to a medical-surgical floor
Aim 2	Explore the relationship between post-ICU sleep efficiency, wake after sleep onset, and grip strength in mechanically ventilated, older adult patients within 24-48 hours of transfer out of the ICU	Cross-sectional, exploratory	• Sleep efficiency and fragmented sleep: SE, WASO • Motor function: grip strength	• Actigraphy (2-night observation) within 24-48 hours of transfer out of ICU to a medical-surgical floor • NIH Toolbox Motor Battery Grip Strength Test within 24-48 hours of transfer out of ICU to a medical-surgical floor

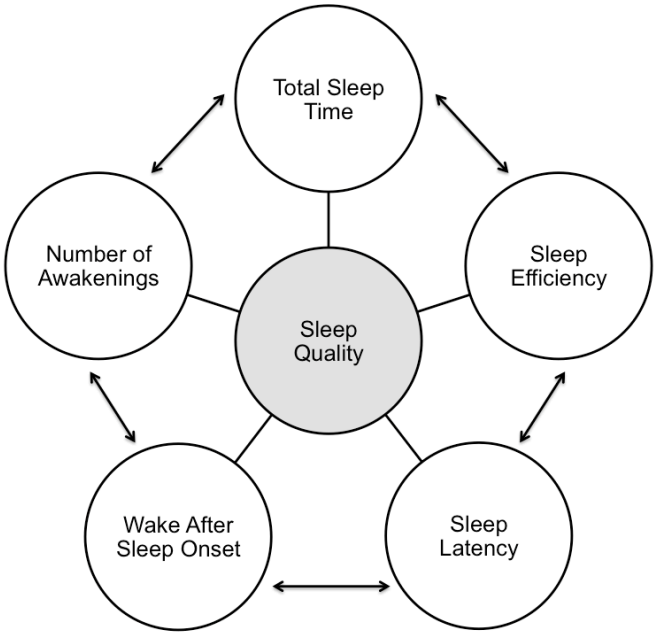

Figure 2a. Primary Descriptive Study Aim

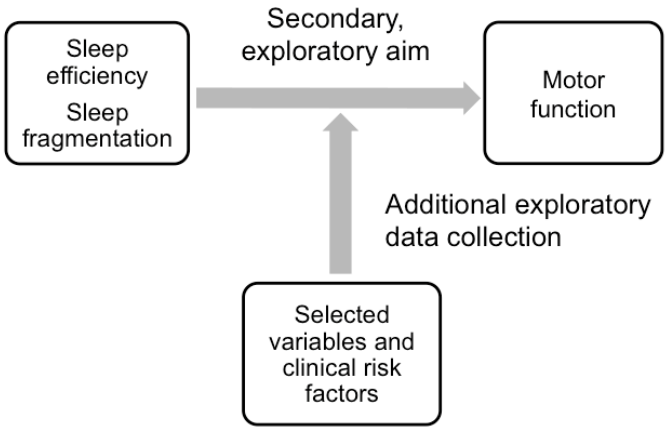

Figure 2b. Secondary Exploratory Study Aim

Definition of Relevant Terms

Sleep Quality. In this study, nighttime sleep quality will be characterized by: total sleep time, sleep efficiency, sleep latency, wake after sleep onset, and number of awakenings. Total sleep time (TST) is the number of minutes spent in sleep stages N1, N2, N3, and REM. Sleep efficiency (SE) is the TST multiplied by 100, divided by total time in bed. Sleep latency (SL) is

the time from lights out until the first epoch of sleep occurs. Wake after sleep onset (WASO) is the number of minutes of wake after first sleep, but before the final awakening. Number of awakenings (NA) is the number of arousals in 15-second epochs or more from the end of SL until lights on.

Sleep Efficiency. Sleep efficiency (SE) is the total sleep time multiplied by 100, divided by total bed time.

Sleep Fragmentation. Wake after sleep onset (WASO) is a measure of sleep fragmentation. Wake after sleep onset (WASO) is the number of minutes spent awake after first onset of sleep, but before the final awakening.

Motor Function. Motor function is the ability to use and control muscles and movements. It is a complex physiologic process and requires the integration of multiple systems, including the neuromuscular, neurosensory, musculoskeletal, and cardiopulmonary systems. (Reuben et al., 2013).

ICU-Acquired Weakness. ICU-acquired weakness, with documented polyneuropathy, myopathy, or both, can be sub-classified. Critical illness polyneuropathy refers to ICU-acquired weakness with electrophysiological evidence of an axonal polyneuropathy. Critical illness myopathy refers to ICU-acquired weakness with myopathy that is documented electrophysiologically or histologically. Critical illness neuromyopathy refers to electrophysiological or histologic findings of both critical illness polyneuropathy and critical illness myopathy (Kress & Hall, 2014).

Grip Strength. Strength is defined as the ability to resist gravity and provide substantial force in movement, with or without resistance. Strength includes the muscular capacity to

produce the force and power necessary to maintain posture, initiate movement, or control movement via the musculoskeletal system (Reuben et al., 2013).

Significance to Nursing

The results of this study will describe the sleep quality of previously mechanically ventilated older adult patients immediately following the transition of care out of the ICU to a medical-surgical floor. The results will also emphasize the influence of sleep quality on post-ICU motor function, as measured by grip strength, among older adult patients upon transfer out of the ICU. An understanding of poor sleep quality, and its relationship to motor dysfunction among older adult patients who are transferred out of ICU, will enable the development of innovative interventions to improve sleep during the early recovery period of acute critical illness. This study will provide a foundation for hospital providers and registered nurses to establish practice standards to ensure optimal sleep quality and motor function in older adult survivors of critical illness.

Chapter Two: Review of the Literature

The review of the literature first emphasizes the conceptual framework and its theoretical underpinnings, and subsequently highlights the main variables of this study: sleep quality, sleep efficiency, sleep fragmentation, motor function, and grip strength.

Conceptual Framework

Hypothesized mechanisms of the relationship between sleep and motor function.

The exact physiologic importance that sleep has in healthy individuals, let alone critically ill ICU patients, is still uncertain. The relationship between post-ICU sleep quality and motor function may be partially mediated by hormonal patterns resulting from sleep disturbances, and subsequent reductions in protein synthesis and increases in protein degradation.

Sleep has been identified as a restorative process for healing, with vital circadian variations in protein synthesis and cellular division, and with peak activity during sleep. Not only does more prolific cellular division occur during sleep, but cells require less than half the time to divide during sleep than when awake (Krachman, D'Alonzo, & Criner, 1995).

Hormonal responses by the endocrine system occur as a result of sleep disturbances. These can be partitioned into two complementary responses: a decrease in anabolic hormones leading to decreased protein synthesis, and an increase in catabolic hormones leading to increased protein degradation. This theoretical model is illustrated below in Figure 3.

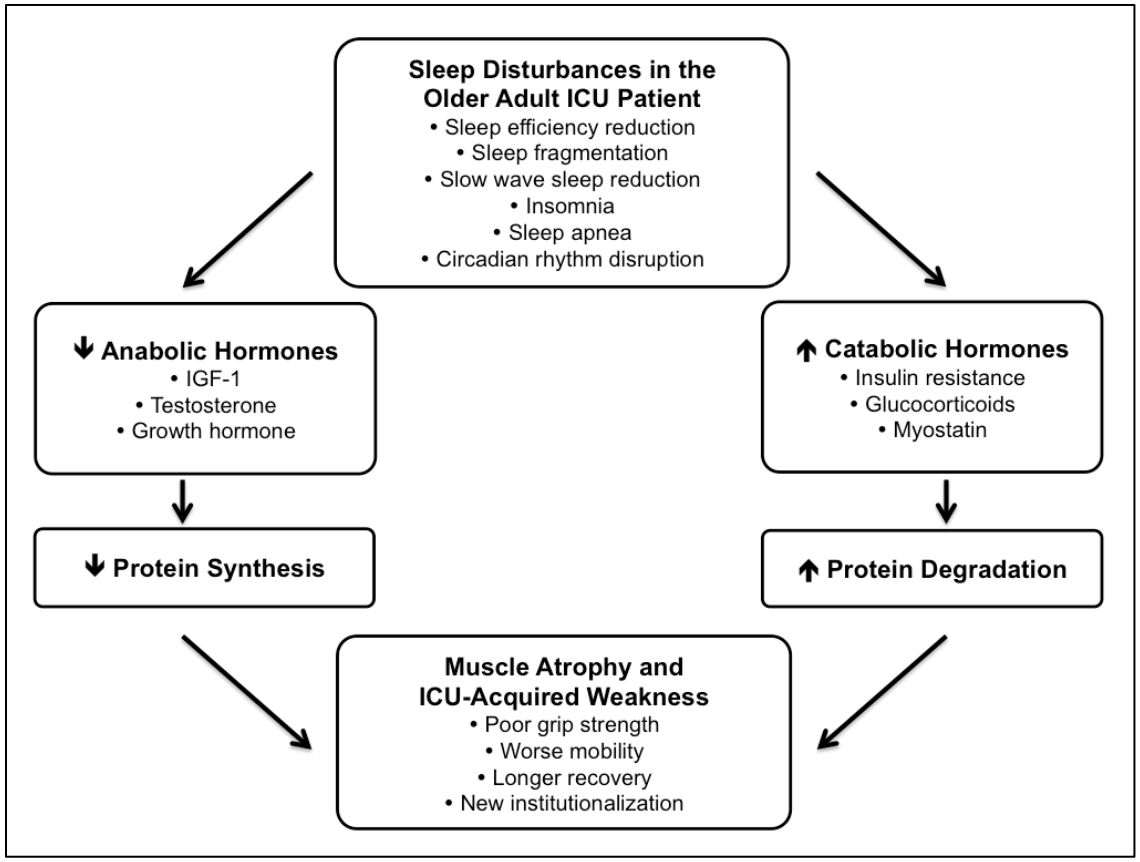

Figure 3. Theoretical Underpinnings of Relationship between Sleep Disturbances and ICU-Acquired Weakness

IGF-1. Insulin-like growth factor (IGF-1)-mediated signaling is elemental in promoting protein synthesis (Sandri, 2008). In muscle, the binding of IGF-1 to its receptor stimulates the activation of phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt) (Dattilo et al., 2011). This is mostly mediated by the stimulation of protein translation via regulation of mammalian target of rapamycin (mTOR). The Akt/mTOR pathway is up-regulated in muscle hypertrophy and is down-regulated in muscle atrophy (Bodine et al., 2001). Therefore, the mTOR pathway promotes protein synthesis (Dattilo et al., 2011). In addition, the phosphorylation and activation of ribosomal kinase S6K1 by mTOR is vital. The mTOR-S6K1 axis may control several fundamental cellular processes, including transcription, translation,

protein and lipid synthesis, as well as cell growth and size (Magnuson, Ekim, & Fingar, 2012; Reiling & Sabatini, 2006).

Testosterone. Testosterone mediates its anabolic properties by binding to cytoplasmic androgen receptors, which migrate to the nucleus, up-regulate transcription, and stimulate protein synthesis. In contrast, low testosterone can indirectly inhibit transcription and protein synthesis by promoting the activity of a protein, REDD1, which in turn blocks the protein synthesis activity of mTOR (White et al., 2013; Wu et al., 2010). Sleep-associated fluctuations occur in nocturnal testosterone, with circulating testosterone levels peaking during sleep and falling upon awakening (Andersen & Tufik, 2008).

Growth hormone. As adults age, the secretion rate of growth hormone markedly decreases in older adults (Finkelstein, Roffwarg, Boyar, Kream, & Hellman, 1972). Previous studies have found a positive, temporal relationship between slow wave sleep and secretion of growth hormone (Gronfier et al., 1996; Van Cauter, Leproult, & Plat, 2000). The stimulation of protein synthesis by growth hormone occurs over a relatively short period of time; growth hormone has a day-by-day role in the regulation of muscle protein dynamics (Fryburg, Gelfand, & Barrett, 1991). Growth hormone leads to protein anabolism by promoting amino acid availability to form proteins instead of amino acid oxidation, without altering proteolysis (Welle, Thornton, Statt, & McHenry, 1996). The anabolic effects of growth hormone are further mediated by its stimulation of IGF-1 production.

Insulin resistance. Previous studies have revealed that among sleep-deprived healthy adults, the acute insulin response to glucose is significantly lower, indicating a relationship between decreased sleep, impaired glucose tolerance, and increased insulin resistance (Spiegel, Knutson, Leproult, Tasali, & Van Cauter, 2005; Spiegel, Leproult, & Van Cauter, 1999). Sleep-

disordered breathing, such as in obstructive sleep apnea (OSA), is also independently associated with increased insulin resistance (Punjabi et al., 2004). Insulin resistance may cause muscle loss via mechanisms that involve the suppression of PI3K and Akt signaling. Suppression of PI3K/Akt leads to the activation of proteolytic systems, such as caspase-3 and the ubiquitin-proteasome pathway, causing protein degradation (X. Wang, Hu, Hu, Du, & Mitch, 2006).

Glucocorticoids. In skeletal muscle, glucocorticoids decrease the rate of protein synthesis and increase the rate of protein breakdown, contributing to muscle atrophy. The severity and the mechanism for the catabolic effect of glucocorticoids may differ with age; glucocorticoids cause more severe atrophy in older age (Schakman, Gilson, & Thissen, 2008). The catabolic action and stimulatory effect of glucocorticoids on muscle protein degradation result from the activation of the major cellular proteolytic systems: the ubiquitin-proteasome system, the lysosomal system, and the calcium-dependent system (Hasselgren, 1999). With regard to the effect of sleep on glucocorticoids, even a partial sleep loss induces the stress response and consequently increases plasma cortisol levels (Leproult, Copinschi, Buxton, & Van Cauter, 1997).

Myostatin. Increases in glucocorticoid levels due to sleep deprivation may up-regulate REDD1, activate the ubiquitin-proteosome system, and up-regulate myostatin expression (Dattilo et al., 2011). Expression of myostatin, a negative regulator of skeletal muscle growth, further reduces protein synthesis and promotes muscle atrophy by increasing protein degradation (McPherron, Lawler, & Lee, 1997).

The impact of sleep disturbances on muscle atrophy, poor motor function, and ICU-acquired weakness may be observed in older adult survivors of critical illness, and may be explained in part by the aforementioned theoretical underpinnings.

Sleep Disturbances in Community-Dwelling Older Adults

Researchers conclude that poor sleep quality in the elderly is largely the result of underlying comorbidity, as well as changes in circadian rhythmicity, effects of pharmacological treatments, sleep-disordered breathing disorders such as OSA, and sleep disorders such as REM sleep behavior disorder (Ancoli-Israel, Ayalon, & Salzman, 2008). While the total amount in hours of sleep may not change for older adults, sleep quality does change with age. Sleep tends to be shallow, fragmented, and variable in duration in middle-aged and elderly adults compared to young adults. Sleep analysis of older adults compared to younger adults have shown that older adults have less deep sleep or slow-wave sleep, and less rapid eye movement (REM) sleep (Ancoli-Israel et al., 2008). Studies examined in a large meta-analysis that included only elderly participants did not find changes in percentage of slow-wave sleep. Rather, it remained relatively constant from age 60 to the mid-90s, although sleep efficiency continued to decrease with advanced age (Ohayon et al., 2004). Sleep fragmentation is common in older adults; increased sleep fragmentation is less restorative than consolidated sleep (Lim et al., 2016; Stepanski, 2002).

Among community-dwelling older adults, obesity, heart disease, stroke, diabetes, lung diseases, and arthritis were independently associated with having one or more sleep problems almost nightly. Sleep problems may include difficulty falling asleep and staying asleep, snoring, breathing pauses, restless legs or daytime sleepiness (Foley et al., 2004). There also appears to be a close tie between poor sleep quality and cognitive impairment. Community-dwelling older adults with cognitive impairment have higher sleepiness scores, as well as significantly longer stage N1 sleep and shorter stage N3 and REM sleep, as well as lower sleep efficiency and higher WASO (Haba-Rubio et al., 2017). In community-dwelling older women, longer sleep duration

and greater sleep fragmentation are associated with poorer cognitive performance in a subset of cognitive domains (Spira et al., 2017). Moreover, excessive daytime sleepiness and insomnia are independent risk factors for depressive symptoms in the elderly (Jaussent et al., 2011). Poor sleep quality is independently associated with physical impairment and disability among community-dwelling older adults (Chien & Chen, 2015). Interestingly, a U-shape relationship between self-reported sleep duration and sarcopenia has been identified in community-dwelling older adults, especially among female older adults (Hu et al., 2017). Community-dwelling older women with disturbed sleep also have an increased risk of hospitalization, which can be partially attributed to demographic characteristics, worse health status, and comorbid conditions (Paudel et al., 2017).

Sleep Disturbances in Critically Ill Older Adults

A large number of the patients admitted to the ICU have acute life-threatening exacerbations of an underlying illness that may be associated with sleep disturbances. For example, the presence of diseases such as COPD and congestive heart failure have been associated with poor sleep quality (Krachman et al., 1995). Sleep while in the ICU has been characterized as severely fragmented and may be evenly distributed between day and night; ICU patients may experience prolonged time spent in stage N1 sleep, decreased time spent in stages N2, N3, and REM sleep, and increased arousals and awakenings (Weinhouse & Schwab, 2006).

Reasons for sleep deprivation during recovery from illness and injury in the ICU are multifactorial. Major contributing factors in this critically ill population are type and severity of underlying illness, pathophysiology of acute illness or injury, surgical pain, and perhaps most importantly, the ICU environment itself. Sleep architecture was found markedly abnormal in critically ill patients, with the vast majority of sleep being superficial (NREM stages 1 and 2),

with very little deep or restorative NREM stages 3 and 4 and REM sleep (Friese, 2008). An early descriptive study of adult patients in a respiratory ICU (Hilton, 1976) found a significant decrease in TST, with only 50% of sleep occurring during the night. Night sleep was characterized by extreme fragmentation, an overrepresentation of stage 1 and NREM sleep (49% of TST), reduced or absent slow wave sleep and REM sleep (3.6% of TST), almost nonexistent NREM stage 4 sleep (0.1% of TST), and circadian rhythm abnormalities.

Sleep disturbances in older ICU patients may be worse than in their younger counterparts. Because sleep quality and recovery capacity varies with increasing, the extent to which sleep disturbance affects recovery in older adult ICU patients remains unclear, as does the nature of poor sleep, especially in the oldest of old (Sterniczuk, Rusak, & Rockwood, 2014). Recovery and prognosis may be worse for older ICU patients who experience more severe sleep disturbances. In fact, recent evidence points towards an interaction between sleep, delirium, and mortality in critically ill patients (Pulak & Jensen, 2016).

Sleep Disturbances in Hospitalized Older Adults

Older adults with more severe illness are less physically active during hospitalization. In contrast to studies conducted among the community-dwelling elderly, older inpatients who slept more were not more active. This highlights the greater propensity for sleep while older adults are hospitalized than while healthy in the community (Beveridge et al., 2015).

Previous studies have revealed that newly hospitalized elderly inpatients have brief and highly fragmented sleep, and experience high noise levels and bright lights (Missildine, Bergstrom, Meininger, Richards, & Foreman, 2010; Vinzio, Ruellan, Perrin, Schlienger, & Goichot, 2003). A study using actigraphy sleep data concluded that hospitalized adult patients slept significantly less on the medical-surgical floor than their self-reported baseline sleep. Mean

sleep efficiency when hospitalized was also low, with over half of the patients' nightly sleep falling below the normal lower boundary of 80% sleep efficiency recommended for adults (Yoder, Staisiunas, Meltzer, Knutson, & Arora, 2012). These sleep disturbances may be exacerbated in older inpatients experiencing pain or depressive symptoms (Dzierzewski et al., 2015). Delirium is also associated with poor sleep among hospitalized elders. Among a sample of hospitalized older adults, more severe sleep-wake cycle disturbances were highly associated with delirium, regardless and independent of whether or not the patient had a history of dementia (Fitzgerald et al., 2017).

Motor Function in Hospitalized Older Adults

Hospitalization may decrease motor function. Researchers found that, among community-dwelling, disabled older women who were hospitalized, 33% of the women experienced functional decline. Older age, frailty, length of stay and higher education were associated with functional decline among these women (Boyd et al., 2009).

Grip strength is a strong predictor of hospitalization and mortality, independent of muscle mass, comorbidities, and inflammatory biomarkers (Legrand et al., 2014). Among hospitalized older adults and surgical patients, poor handgrip strength often predicts postoperative complication. However, other adverse outcomes may include longer length of hospital stay, future functional decline, institutionalization, and mortality (Bohannon, 2001). Handgrip strength is also a significant predictor of cause-specific and total mortality among older disabled women (Rantanen et al., 2003).

Grip Strength and ICU-Acquired Weakness in Hospitalized Older Adults

ICU-acquired weakness may occur in up to 40% of ICU survivors and is described clinically as documented polyneuropathy, myopathy, or both. Independent predictors of ICU-

acquired weakness may include female sex, duration of mechanical ventilation, use of corticosteroids, and dysfunction of 2 or more organs (De Jonghe et al., 2002). Survivors of critical illness may experience residual ICU-acquired weakness and consequent activity limitations for years post-discharge (Zorowitz, 2016). About 25% of critically ill patients who require prolonged mechanical ventilation develop ICU-acquired weakness (De Jonghe et al., 2002; Jolley, Bunnell, & Hough, 2016). A previous study showed that at three months post-ICU admission, mechanically ventilated patients with ICU-acquired weakness had significantly weaker hand grip strength and significantly shorter 6-minute walk distance than those without (Fan et al., 2014). Handgrip strength on dynamometry was independently associated with hospital mortality in a study of ICU patients who were mechanically ventilated for at least five days (Ali et al., 2008). This acquired and persistent weakness carries important implications for the older adult survivor of critical illness.

Sleep and Grip Strength in Older Adults

Research suggests that there is an association between sleep efficiency of less than 80% and WASO of greater than 90 minutes with poor differences in grip strength and gait speed in older community-dwelling males (Dam et al., 2008). One prospective cohort study of community-dwelling older women with five years' follow-up observed independent associations between three sleep parameters (TST, WASO, and SE) and decline in grip strength (Spira et al., 2012). The findings in this cohort study indicated that shorter TST, greater WASO, and lower SE are risk factors for functional decline in community-dwelling older women. Another study of community-dwelling older women showed that greater WASO was associated with worse performance on motor function measures such as gait speed, but not handgrip strength (Goldman et al., 2007). A similar study of community-dwelling elders concluded that sleep efficiency and

WASO were associated with knee extension strength, but not with grip strength (Kim, Yoshida, Sasai, Kojima, & Kim, 2015). However, these studies only included relatively healthy samples of older adults, not a sample of hospitalized elders who have survived critical illness and were mechanically ventilated.

Summary

The physiological mechanisms underlying the relationship between poor sleep quality and motor function are not well understood. Decreased sleep efficiency and increased sleep fragmentation may lead to poor motor function via complementary hormonal responses involving anabolic and catabolic pathways, leading to decreased protein synthesis and increased protein degradation. Previous studies have linked sleep disturbances to poor motor function among community dwelling older adults. The sleep quality of older adult survivors of critical illness upon transfer out of the ICU has not yet been described in the literature, nor has its relationship to motor function been studied while still acutely ill and hospitalized in the medical-surgical inpatient setting. This study examined sleep quality and motor function among a sample of hospitalized older adult survivors of critical illness and explored how these variables are interconnected.

Chapter Three: Methods

This chapter presents the dissertation study methods, which are organized into the following sections: design, setting, sample, measures, procedures and data analysis. The aims of the dissertation study were: to describe the post-ICU nighttime sleep quality of previously mechanically ventilated, older adult patients within 24-48 hours of transfer out of the ICU, and to explore the relationship between post-ICU nighttime sleep quality and motor function in mechanically ventilated, older adult patients within 24-48 hours of transfer out of the ICU.

Design

This study utilized a descriptive design for the primary aim and an exploratory design for the secondary aim. Overall, this study was a prospective, cross-sectional study.

Setting

Subject recruitment and enrollment were conducted at Tampa General Hospital (TGH) in Tampa, Florida. One of the largest hospitals in the state of Florida, TGH is licensed for 1,011 patient beds. According to 2014 data, approximately three-fourths of admissions are white, one-fifth are African-American, and over one-fifth are Hispanic. TGH is the greater Tampa Bay area's only Level 1 trauma center and one of just four burn centers in Florida, with a total of 225 beds assigned to critical care patients. TGH medical-surgical inpatient units include the following: 3H1 Cardiovascular Telemetry, 5A1/5A2 Medical Cardiology, 6A1/6A2/7A2 Complex Medicine, 6C1 Acute Care of the Elderly, 6K4/6K5 Specialty Surgery, 7A1 Joint Replacement, 7C1/7C2 Surgical Oncology, 7F1/8F1/9F1 Transplant, 8A1/8A2 Primary Care,

8C1/8C2 Orthopedic/Surgery Trauma, 9A1/9A2 Neuroscience, and 9C1 Vascular Surgical Acute Care. Characteristics of TGH inpatients are presented in Table 2 below.

The 2015 estimated population in Hillsborough County, Florida was over 1.3 million and is expected to grow by 6.8% by 2020. The populations of other races and of Hispanics are expected to grow substantially in the next five years (18.0% and 12.7%, respectively). The population of adults ages 65 and older in Hillsborough County alone is expected to grow by about 22.3% by 2020. Hillsborough County residents aged 65 and older are more like to live below poverty level (11.3%) compared to all Florida residents aged 65 and older (10.2%).

Table 2. Demographic Characteristics of TGH Inpatients Compared to the Hillsborough County Population (2014)

Demographic Characteristics	Hillsborough County, FL	TGH Inpatients
Gender		
Male	48.7%	43.9%
Female	51.3%	56.1%
Ethnicity		
Hispanic or Latino	26.5%	22.8%
Not Hispanic or Latino	73.5%	77.2%
Race		
American Indian/Alaska Native	0.6%	0.6%
Asian	4.0%	0.6%
Native Hawaiian/Pacific Islander	0.1%	0.1%
Black/African American	17.5%	20.8%
White	75.3%	73.8%
More than two/Other/Unknown	2.5%	4.1%

Sample

A total of 30 study subjects, ages 65 and older, who were functionally independent prior to hospital admission, required mechanical ventilation while in ICU, and within 24-48 hours of transfer out of the ICU to a medical-surgical floor, were recruited between November 2017 and January 2018.

Inclusion criteria. Subjects ages 65 and older who were previously mechanically ventilated while in the ICU, and were within 24-48 hours post-ICU transfer to a medical-surgical

floor, were eligible for this study. Additionally, subjects must have been previously community-dwelling adults ages 65 years or older, and speak English fluently.

Exclusion criteria. Potential subjects who were originally admitted from a long-term care facility, assisted living facility, or skilled nursing facility, or those who received around-the-clock private care at home, were excluded from this study. These subjects were excluded so as to best represent a population of previously healthy, community-dwelling older adults who were suddenly admitted with potentially life-threatening critical illness or injury, and required new mechanical ventilation while hospitalized in the ICU. This exclusion criterion was based on the subjective report of the subject's baseline functional ability. Additional exclusion criteria were imminent death, active palliative care orders, and documented medical history of pre-existing dementia on chart review.

Tables 3 and 4 show the expected target sample with expected demographics. The study procedures adhered to the nondiscriminatory policies of University of South Florida: no one was excluded on the basis of gender, race, ethnicity, socioeconomic status, religion, or sexual orientation. A question on race/ethnicity included five categories for data on race, based on federal (National Institutes of Health, NIH) classification of research subjects: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White. There were two categories for data on ethnicity, in alignment with NIH classification of research subjects: "Hispanic or Latino" and "Not Hispanic or Latino." Study participants could choose to select more than one race.

Table 3. Expected Sample of Enrolled Subjects

Characteristics	TGH Inpatients	Expected Sample
Gender		
Male	43.9%	N = 13
Female	56.1%	N = 17
Ethnicity		
Hispanic or Latino	22.8%	N = 7
Not Hispanic or Latino	77.2%	N = 23
Race		
American Indian/Alaska Native	0.6%	N ≤ 1
Asian	0.6%	N ≤ 1
Native Hawaiian/Pacific Islander	0.1%	N ≤ 1
Black/African American	20.8%	N = 6
White	73.8%	N = 22
More than two/Other/Unknown	4.1%	N = 1

Table 4. Targeted/Planned Enrollment

Targeted/Planned Enrollment: Number of Subjects			
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	4	3	7
Not Hispanic or Latino	13	10	23
Ethnic Category: Total of All Subjects	17	13	30
Racial Categories	**Females**	**Males**	**Total**
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	3	7
White	13	10	23
Racial Categories: Total of All Subjects	17	13	30

Measures. The key variables, measures, and data collection time points are outlined in Table 5 and further described below.

Sleep quality. Actigraphy objectively measured sleep quality. An actigraph is a small, lightweight, monitoring device that can be worn on the subject's limb for two consecutive nights. While the established gold standard for analysis of sleep architecture remains full polysomnography, this is not feasible for an overnight observation period in the hospitalized, previously mechanically ventilated, older adult patient who was transferred within the last 24-48 hours from the ICU to a medical-surgical floor. Full polysomnography requires additional leads for electroencephalographic monitoring, movement of all limbs, eye movements, video monitoring, and presence of a certified sleep technician (Ancoli-Israel et al., 2003). Sleep quality

was measured by wrist actigraphy and was characterized by: total sleep time (TST), sleep latency (SL), sleep efficiency (SE), number of awakenings (NA), and wake after sleep onset (WASO) (Geyer, Talathi, & Carney, 2009). The start of actigraphy sleep recording is referred to as lights out. The end of the sleep recording is referred to as lights on. Total bed time is the entire span of time from lights out to lights on. SL is the time from lights out until the first epoch of sleep occurs. TST is the number of minutes in stages N1, N2, N3, and REM. NA is the number of wakes or arousals in 1-minute epochs or more from the end of onset of sleep latency until lights on. SE is the total sleep time multiplied by 100, divided by total bed time. WASO, a measure of sleep fragmentation, is the number of minutes of wake after first sleep but before the final awakening.

Motor function. Motor function was measured using the NIH Toolbox Motor Battery Grip Strength Test, which has been extensively tested among community-dwelling older adults. Subjects' motor function was assessed with this objective measure while still hospitalized, within 24-48 hours after transfer from ICU to a medical-surgical floor. The NIH Toolbox Motor Battery includes 5 subdomains of motor ability (dexterity, strength, balance, gait speed, and endurance), which have been tested and validated for safety and feasibility in adults up to age 85 (Reuben et al., 2013). The NIH Toolbox Motor Battery Grip Strength Test (GST) of handgrip dynamometry tests for the outcome variable of upper-extremity dominant hand grip strength in this study. Normative reference values for isometric strength of hand grip among community-dwelling adults ages 60 years and older have been previously established in the literature (McKay et al., 2017).

Table 5. Key Variables and Data Collection

Key Concepts and Variables	**Measures**	**Data Collection Time Points**		
		ICU Stay (Retrospective Chart Review)	**Within 24-48 Hours of Transfer to Floor** (Study Enrollment)	**Hospital Discharge** (Prospective Chart Review)
Post-ICU nighttime sleep quality	Actigraphy: • Sleep efficiency • Wake after sleep onset • Total sleep time • Sleep latency • Number of awakenings		X	
Post-ICU motor function	NIH Toolbox Motor Battery: • Grip Strength Test		X	
Additional Variables Collected for Future Analyses	**Measures**	**Data Collection Time Points**		
		ICU Stay (Retrospective Chart Review)	**Within 24-48 Hours of Transfer to Floor** (Study Enrollment)	**Hospital Discharge** (Prospective Chart Review)
ICU delirium	Documentation of delirium by provider	X	X	
Post-ICU geriatric syndromes and survivorship	NIH Toolbox Motor Battery: • 9-Hole Pegboard Dexterity Test • Standing Balance Test		X	
	NIH Toolbox Cognition Battery: • Flanker Inhibitory Control and Attention Test • Dimensional Change Card Sort Test		X	
	NIH Toolbox Emotion Battery: • Sadness Survey • Fear-Affect Survey		X	
	NIH Toolbox Sensation Battery: • Pain Intensity Test		X	
Patient outcomes	Patient disposition at discharge			X
	Time in days to hospital discharge			X
Selected Other Biological and Clinical Variables	**Measures**	**Data Collection Time Points**		
		ICU Stay (Retrospective Chart Review)	**Within 24-48 Hours of Transfer to Floor** (Study Enrollment)	**Hospital Discharge** (Prospective Chart Review)
Demographic characteristics	Age, sex, race/ethnicity, level of education		X	
Subjective baseline sleep quality	Pittsburgh Sleep Quality Index (PSQI) global score		X	
Subjective baseline physical function	Katz Index of Independence in Activities of Daily Living		X	
Admitting diagnosis	Primary problem on chart review	X		
Severity of illness on ICU admission	Acute Physiology and Chronic Health Evaluation (APACHE) III	X		
Length of mechanical ventilation	Documented history on chart review	X		
Length of ICU stay	Documented history on chart review	X		
Multiple ICU readmissions	Documented history on chart review	X		
Multiple re-intubations	Documented history on chart review	X		
Risk of obstructive sleep apnea	Stop-Bang Questionnaire		X	
History of obstructive sleep apnea	Documented history on chart review	X		
History of neurological disorder or injury	Documented history on chart review	X		
History of depression	Documented history on chart review	X		
History of anxiety	Documented history on chart review	X		
Administration of sleep-promoting medications	Documented history on chart review		X	
Administration of pain-relieving medications	Documented history on chart review		X	
Current functional status	Documentation by rehabilitation therapy team		X	

Key Variables

Nighttime sleep quality data on TST, SE, WASO, SL, and NA were collected via wrist actigraphy during a 2-night observation period, within 24-48 hours of the subject's transfer out of ICU to a medical-surgical floor. Acceleration counts were collected in 15-second epochs to record subjects' sleep during this 2-night observation period, from 9:00 PM to 9:00 AM throughout both days and nights. The nighttime sleep quality data were averaged over both nights for each subject.

Objective data on motor function were collected utilizing the NIH Toolbox Motor Battery Grip Strength Test. The Grip Strength Test utilizes handgrip dynamometry for upper-extremity strength. This test of motor function was administered within 24-48 hours of the subject's transfer out of ICU to a medical-surgical floor.

Related Variables Collected for Future Analyses

Data on selected tests from the NIH Toolbox were also collected as part of this study for pilot data in future studies and for later publications. Other selected tests administered from the NIH Toolbox Motor Battery included the 9-Hole Pegboard Dexterity Test (PDT) and the Standing Balance Test (SBT) (Reuben et al., 2013). Selected tests from the NIH Toolbox Cognition Battery included the Flanker Inhibitory Control and Attention Test (FICAT) and the Dimensional Change Card Sort Test (DCCST) to assess attention and cognitive flexibility, respectively (Weintraub et al., 2013). Selected tests from the NIH Toolbox Emotion Battery included the Sadness Survey (SS) and the Fear-Affect Survey (FAS) to evaluate self-reported symptoms of depression and anxiety, respectively (Salsman et al., 2013). The Pain Intensity Test (PIT) from the NIH Toolbox Sensation Battery was also included to assess self-reported pain (Cook et al., 2013).

The subject's admitting diagnosis, severity of illness on ICU admission (Acute Physiology and Chronic Health Evaluation, APACHE III) (Knaus et al., 1991), length of mechanical ventilation, length of ICU stay, and documentation of delirium by provider were all collected by retrospective chart review, based on the subject's stay in ICU. Related clinical documentation of the subject's past medical history, including history of OSA, neurological disorder/injury or stroke, depression, and anxiety, were also collected via chart review.

The subject's demographic characteristics, such as age, sex, race and ethnicity, and level of education were collected at time of enrollment. The Pittsburgh Sleep Quality Index (PSQI), a subjective measure of sleep quality, assessed the subject's baseline sleep quality through self-report (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Subjects were asked to answer questions on the PSQI based on how they slept at home prior to hospital admission. In addition, the Stop-Bang Questionnaire (SBQ), a screening tool to determine risk of OSA, was administered (Chung et al., 2008). The Katz Index of Activities of Daily Living (Katz Index), a subjective measure of physical function, assessed the subject's baseline functional ability (i.e., prior to his/her hospital admission) to independently perform 6 ADLs: bathing, dressing, toileting, transferring, continence, and feeding. The patient was asked to comment on his/her baseline ability to perform each of these ADLs independently 2 weeks prior to hospital admission. This baseline data was entered for storage and analysis. The Katz Index was also utilized as a measure for study inclusion; subjects must have been functionally independent, community-dwelling older adults prior to hospital admission. Subjects' current functional status and expected discharge disposition were collected based on clinical documentation recorded by the rehabilitation therapy team.

Long-term patient outcomes were collected through prospective chart review after the subject had been discharged from the hospital. These data included the subject's disposition at time of hospital discharge and the time in days until hospital discharge. Follow-up telephone interviews were conducted at 1-month post-hospital discharge. During these voluntary interviews, the PSQI, the Katz Index, the NIH Toolbox Emotion Battery SS and FAS questionnaires, and the NIH Toolbox Sensation Battery PIT questionnaire were administered over the phone and recorded in data collection.

Procedures

Human Subjects Protection. The present study was determined to be a minimal-risk study. Prior to initiation of the study, approval was obtained from TGH and from the USF Institutional Review Board (IRB). The PI explained the risks and benefits to study participants, and emphasized that participation in the study is voluntary, and participation could be withdrawn at any time. The subject's assent and willingness to continue participation was assessed on an ongoing basis throughout administration of all measures. The PI thoroughly explained the nature of the study, the overall study objectives, procedures, risks and benefits, and study information in writing. The information included all elements required for informed consent, and included all pertinent contact information as well as information about withdrawal from the study. Subjects were given adequate time to consult with family members and/or friends to discuss participation in the study. Subjects and any present family members or friends were allowed to thoroughly review the consent form in private. The PI addressed the subjects' questions or concerns prior to signing the consent form. Written consent was obtained and copies were scanned into the TGH electronic medical record. Data were password-protected and uploaded to the USF Health Box, a secure web storage application. The PI accessed USF Health Box through a secure internet

connection with authentication and data logging. The PI assigned each subject a unique numerical identifier to conceal his/her identity. Data were stored and password-protected on the iPad. The PI regularly backed up all data files on a daily process during data entry and at least once a week overall. The USF Health server is additionally backed up every 24 hours.

Recruitment and Enrollment. The PI made daily rounds to the adult medical-surgical floors. During daily rounds, the PI spoke with the units' charge nurses and assigned bedside nurses regarding potential eligibility of older adult patients who were within 24-48 hours of ICU transfer to floor and previously mechanically ventilated while in ICU. The PI further verified patients' eligibility upon retrospective chart review of all study criteria prior to enrollment and before any data collection. The PI followed a study eligibility checklist when using the electronic medical record to screen for potential eligible subjects. If a patient met all study criteria, then the potential subject's capacity to consent was determined. The PI obtained written consent in accordance with the study's approval by the USF IRB (Pro00032017).

Data Collection Procedures. Data were collected within 24-48 hours of the subject's transfer out of ICU to a medical-surgical floor. Nighttime sleep quality data were collected over a 2-day, 2-night period of sleep observation, from 9:00 PM to 9:00 AM on both nights. After the first night of sleep observation, selected tests from the NIH Toolbox Batteries were conducted, between a time window of 9:00 AM to 12:00 PM.

Sleep quality data were obtained by actigraphy using the Actiwatch Spectrum. At the time of study enrollment, the Actiwatch Spectrum was placed on the subject's dominant wrist, and sleep data collection began immediately. However, only data that were collected between 9:00 PM until 9:00 AM on the two subsequent nights of sleep quality were used for further analyses. That is, if the subject was enrolled at 5:00 PM and the Actiwatch Spectrum was placed

on the subject's wrist at this time, the data from 5:00 PM to 8:59 PM were not analyzed. Similarly, data that were collected between 9:01 AM to 8:59 PM on the second day of observation were also not used in the analyses. The 9:00 PM to 9:00 AM time period coincided with the usual bedtimes and awakening times associated with patient care in the medical-surgical units; these timeframes were chosen to ensure data consistency between all subjects. The Actiwatch was removed after two full nights (9:00 PM to 9:00 AM) of sleep data collection. After the Actiwatch was placed on the subject's wrist, the PI administered the PSQI, SBQ, and Katz Index questionnaires.

Next, a 30-minute session of assessments was conducted the following morning after the first overnight sleep observation period, between a time window of 9:00 AM and 12:00 PM, to standardize the assessment times for all subjects. These assessments included motor, cognitive, psychological, and pain assessments from the NIH Toolbox. All NIH Toolbox assessments were delivered on an iPad electronic device platform. The selected Motor Battery assessments (GST, PDT, SBT) were administered first. The Motor assessments were administered first, in the event that subjects were unable to complete or opted out of the remainder of the assessments—the GST was the primary outcome measure and therefore was most crucial to the analysis. The selected Cognition Battery assessments (FICAT, DCCST) were administered second, the selected Emotion Battery questionnaires (SS, FAS) were administered third, and the selected Sensation Battery questionnaire (PIT) was administered last.

Chart Review. Following placement of the Actiwatch on the subject's wrist, the PI exited the subject's hospital room to obtain additional data from the subject's electronic medical record. Enrolled subjects' charts were reviewed for further data collection on demographic variables, clinical variables, and past medical history (refer to Table 5). The PI followed all

enrolled subjects remotely via the electronic medical record throughout their hospital stays and at discharge. Data were collected prospectively, regarding patient disposition at discharge and time in days to hospital discharge (refer to Table 5).

One-Month Follow-Up Interviews. The PI recorded hospital discharge dates for all enrolled subjects. After the subject's one month post-hospital discharge date, the PI called the subject at the telephone number that was voluntarily provided. During these follow-up telephone interviews, the PI administered the PSQI, Katz Index, NIH Toolbox Emotion SS and FAS, and the NIH Toolbox Sensation PIT questionnaires.

Data Analysis

Analysis of nighttime sleep quality data (TST, SE, WASO, SL, and NA) was descriptive and cross-sectional. Statistical analyses were conducted using the IBM SPSS Statistics Version 24 software program. First, for Aim 1, descriptive statistics were calculated to describe the characteristics of the sample on measures of sleep quality. Means and standard deviations were determined, as well as missing data. Descriptive statistics were analyzed according to demographic variables, such as age, sex, and race/ethnicity, as well as selected clinical variables (such as length of mechanical ventilation, length of ICU stay, or medical history). Shapes of the data distributions, missing data and outliers were examined by both graphs and statistical tests. The PI reviewed any data issues with her dissertation committee members and addressed each prior to formal data analysis.

Differences between groups on sleep quality were examined using a one-way ANOVA or the independent samples *t*-test, as well as the Tukey post-hoc test and Levene's Test for Equality of Variances when necessary. A one-way ANOVA was used to explore differences in SE between those with low, moderate, or high PSQI scores; the Tukey post-hoc test was conducted

to determine between-groups comparisons. The independent samples *t*-test and Levene's Test for Equality of Variances were utilized to compare length of hospital stay prior to study enrollment between those with TST less than 6 hours and those who with TST 6 hours or more. Among the subset of subjects with documented diagnoses of OSA, the independent samples *t*-test and Levene's Test for Equality of Variances were conducted to compare ICU length of stay between those who slept less than 6 hours and those who slept 6 hours or more. Data were further examined for differences in TST between subjects who received sleep-promoting medications and those who did not during the 2-day sleep observation period.

For Aims 2a and 2b, the analysis of data exploring the relationship between SE and grip strength first utilized the bivariate Pearson's correlation test; similarly, analysis of data exploring the relationship between WASO and grip strength also utilized Pearson's correlation test. The bivariate correlations and their respective significance values were analyzed for both predictor variables (SE and WASO) on the outcome variable (grip strength). Bivariate Pearson product-moment correlation coefficients were computed to assess the relationship between SE and grip strength, as well as the relationship between WASO and grip strength. Bivariate correlations of SE and WASO to grip strength were further explored by tertiles of low, moderate, and high SE, and by quartiles of low, low-moderate, moderate-high, and high WASO.

The independent samples *t*-test was utilized *a priori* to reveal differences in grip strength between male and female subjects. The independent samples *t*-test was also used *a priori* to consider differences in grip strength between study subjects with history of OSA and those who did not. Bivariate point-biserial correlation coefficients were also calculated to determine the relationship between sex and grip strength, as well as history of OSA and grip strength, based on the results of the aforementioned independent samples *t*-tests.

To address Specific Aims 2a and 2b, multiple regression analyses were conducted to explore the relationship between the selected sleep quality predictors (SE and WASO) and the outcome variable of motor function (grip strength). Preliminary analyses were conducted to ensure there were no violations of the assumptions of multiple regression: linear relationships between the independent variables and dependent variable, multivariate normality, no multi-collinearity, and homoscedasticity. Multivariate regression analysis was chosen to examine if SE and WASO will predict the subjects' grip strength. The regression *F* values, as well as the degrees of freedom for both the regression and residual error, were calculated. The *R*-square values, or how much of the variance is explained by the predictor variables, were presented. Finally, standardized beta coefficients for both predictor variables were calculated. Selected covariates and related clinical variables (such as age, sex, length of mechanical ventilation, length of ICU stay, history of OSA, ICU severity of illness, documentation of delirium, etc.) were explored as part of the regression analyses, based on the preliminary distribution of the data. Separate analyses were conducted to highlight the influence of sex and preexisting OSA on the relationship between sleep and grip strength.

Chapter 4: Results

The following chapter summarizes the results of this study. First, selected demographic and clinical variables are specified. Second, the preliminary results are presented. Finally, the results for each specific aim will be detailed.

Demographic and Clinical Characteristics

All 30 subjects' data were included in the final analysis. The mean age ± standard deviation (SD) was 71.37 ± 5.35 years (range 65-86 years). Eleven (36.7%) subjects were female, four (13.3%) identified as Black or African-American, and three (10%) identified as Hispanic or Latino. Eighteen (60%) subjects completed education beyond high school. A total of 17 (56.7%) subjects had a documented medical history of OSA. Twelve (40%) subjects were primarily admitted to the ICU for surgery or post-operatively. On average, study subjects spent 11.80 (SD 11.49) days in ICU and 5.18 (SD 7.40) days on mechanical ventilation. The mean APACHE score on ICU admission was 95.93 (SD 32.0). The majority of study subjects were transferred out of a medical ICU (46.67%) or a surgical ICU (33.33%), while others received intensive care for transplant (6.67%), trauma (6.67%), or neurology/neurosurgery (6.67%). Over half of the sample (53.33%) had documentation of delirium from at least one healthcare provider, and over one-third (36.7%) received at least one sleep-promoting medication during the study period. Seven (23.3%) subjects were evaluated and recommended for discharge to an inpatient rehabilitation facility, thirteen (43.3%) to a skilled nursing facility, and one (3.3%) to a long-term acute care facility. Table 6 provides further details regarding the demographic characteristics and clinical variables collected in this study.

Table 6. Summary of Demographic Characteristics and Clinical Variables

Variables	Mean ± SD or *n* (%)
Age, years	71.37 ± 5.35
Female sex, %	11 (36.7%)
Race/ethnicity, self-reported, %	
White/Caucasian	23 (76.67%)
Black/African-American	4 (13.33%)
Hispanic/Latino	3 (10%)
Level of education beyond high school diploma	18 (60%)
ICU length of stay, days	11.8 ± 11.49
Length of mechanical ventilation, days	5.18 ± 7.4
Length of inpatient stay prior to study enrollment, days	16.5 ± 13.86
Multiple ICU readmissions prior to study enrollment, %	
No ICU readmissions	25 (83.33%)
One ICU readmission	5 (16.67%)
Multiple intubations prior to study enrollment, %	
No re-intubations	21 (70%)
One re-intubation	5 (16.67%)
Two re-intubations	4 (13.33%)
Acute Physiology and Chronic Health Evaluation III severity of illness score, 0-299	95.93 ± 32.0
Pittsburgh Sleep Quality Index Global Score, 0-21	6.67 ± 2.68
Primary ICU admission diagnosis	
Medical	14 (46.67%)
Surgical, cardiovascular	10 (33.33%)
Surgical, transplant	2 (6.67%)
Trauma	2 (6.67%)
Neurological/neurosurgery	2 (6.67%)
History of obstructive sleep apnea, %	17 (56.7%)
History of neurological disorder or injury, %	6 (20%)
History of depression and/or anxiety, %	10 (33.33%)
Documentation of delirium by hospital provider, %	16 (53.33%)
At least one sleep-promoting medication administered during observation period, %	11 (36.7%)
Readmission to ICU after study completion, %	4 (13.33%)
Discharge recommendation, as evaluated by rehabilitation therapy team, %	
Home with assistance	1 (3.33%)
Home with home health	8 (26.67%)
Inpatient rehabilitation facility	7 (23.33%)
Skilled nursing facility	13 (43.33%)
Long term acute care hospital	1 (3.33%)
Disposition upon hospital discharge, %	
Home with assistance	1 (3.33%)
Home with home health	9 (30%)
Inpatient rehabilitation facility	5 (16.67%)
Skilled nursing facility	12 (40%)
Long term acute care hospital	1 (3.33%)
Transferred to another hospital/disposition unknown	2 (6.67%)
Total length of hospital stay, days	24.32 ± 17.1

Note. Values are mean ± standard deviation (SD) or *n* (%) of participants.

Outcome Variables

The mean grip strength of study subjects was 44.91 ± 23.63 lbs. The mean NIH Toolbox Motor PDT fully-corrected T-score was 30.04 ± 8.94. Only five (16.67%) of the 30 study

subjects were physically capable of completing the NIH Toolbox Motor SBT; of these five, the mean fully-corrected T-score was 34.4 ± 3.29. The mean NIH Toolbox Cognition DCCST fully-corrected T-score was 38.81 ± 9.2, and the mean NIH Toolbox Cognition FICAT fully-corrected T-score was 29.78 ± 7.22. The average summed score of the NIH Toolbox Emotion SS and FAS was 35.23 ± 12.42. The mean self-reported pain score on the NIH Toolbox Sensation PIT was 3.67 ± 2.81. A summary of study subjects' performance on these selected NIH Toolbox outcome variables is presented in Table 7.

Table 7. Summary of the NIH Toolbox Motor, Cognition, Emotion, and Sensation Outcome Variables

Outcome Variables	Mean ± SD or *n* (%)
NIH Toolbox Motor GST, raw grip strength, dominant hand, lbs	44.91 ± 23.63
NIH Toolbox Motor PDT, raw score, time in seconds	55.9 ± 36.96
NIH Toolbox Motor SBT, number of subjects physically able to complete assessment	5 (16.67%)
NIH Toolbox Cognition DCCST, fully-corrected T score, 0-100	38.81 ± 9.2
NIH Toolbox Cognition FICAT, fully-corrected T score, 0-100	29.78 ± 7.22
NIH Toolbox Emotion Sadness Survey and Fear-Affect Survey, total score, 0-75	35.23 ± 12.42
NIH Toolbox Sensation Pain Intensity Test, raw score, 0-10	3.67 ± 2.81

Note. Values are mean ± standard deviation (SD) or *n* (%) of participants.
GST, Grip Strength Test; PDT, 9-Hole Pegboard Dexterity Test; SBT, Standing Balance Test; DCCST, Dimensional Change Card Sort Test; FICAT, Flanker Inhibitory Control and Attention Test.

Results of Specific Aim 1

Aim 1 of the present study was to describe the post-ICU nighttime sleep quality of previously mechanically ventilated older adult patients within 24-48 hours of transfer out of the ICU. It was hypothesized that subjects' sleep quality, as defined by SE, WASO, TST, SL, and NA, will be abnormal and disturbed at 24-48 hours of transfer out of the ICU.

Of the 30 enrolled subjects, a total of 29 subjects completed the full sleep observation period from 9:00 PM to 9:00 AM on both nights. One patient emergently transferred back to ICU for surgical complications after completing one night of sleep observation; this subject's sleep data was still included in the overall analyses. On average, study subjects had a sleep efficiency (SE) of 63.24% ± 3.88%, and spent 135.39 ± 9.94 minutes awake after sleep onset (WASO). The

mean total sleep time (TST) among study subjects was 7.55 ± 2.52 hours, ranging from 2.02 to 10.84 hours of sleep, out of the 12 hours of total time in bed. A total of 6 (20%) subjects slept less than 5 hours each night, and a total of 6 (20%) subjects slept greater than 10 hours each night. The mean sleep latency (SL) among study subjects was 42.57 minutes, and ranged from 0.0 to 237.75 minutes. Sleep latencies were not equal between males and females. Sleep latencies among male subjects (19.95 ± 27.45 mins) were significantly lower than among female subjects (81.63 ± 80.66 mins), $t(11.36) = -2.46$, $p = 0.031$. Overall, study subjects' average number of awakenings or arousals (NA) was 78.28 ± 26.39, ranging from 35 to 136 awakenings. Table 8 further provides comparative descriptive statistics of sleep quality between sex groups and between subjects with and without history of OSA.

Table 8. Descriptive Statistics of Nighttime Sleep Quality

Sleep Characteristics	Mean ± SD	Range	Males (n = 19)	Females (n = 11)	P-value between sex groups	No history of OSA (n = 13)	History of OSA (n = 17)	P-value between OSA groups
Sleep efficiency (%)	63.24 ± 21.24	16.88-90.5	65.88 ± 21.04	58.66 ± 21.81	0.379	65.94 ± 18.56	61.17 ± 23.44	0.552
Wake after sleep onset (mins)	135.39 ± 54.43	54.88-264.0	131.13 ± 53.21	142.76 ± 58.3	0.582	148.48 ± 52.05	125.38 ± 55.6	0.256
Total sleep time (hrs)	7.55 ± 2.52	2.02-10.84	7.86 ± 2.49	7.03 ± 2.61	0.398	7.85 ± 2.18	7.33 ± 2.8	0.582
Sleep latency (mins)	42.57 ± 60.21	0.0-237.75	19.95 ± 27.45	81.63 ± 80.66	0.031[a]	26.7 ± 31.94	54.7 ± 73.79	0.174
Number of awakenings	78.28 ± 26.39	35.0-136.0	83.18 ± 28.43	69.82 ± 20.99	0.186	80.58 ± 28.79	76.53 ± 25.16	0.685

[a]Levene's Test for Equality of Variances revealed that the variances for sleep latency were not equal between males and females. Sleep latencies among male subjects (19.95 ± 27.45 mins) were significantly lower than among female subjects (81.63 ± 80.66 mins), $t(11.36) = -2.46$, $p = 0.031$.

The data were further examined for associations between sleep characteristics and related demographic and clinical variables. The correlations ranged from low to moderate in strength. There was a significant bivariate correlation between sleep latency and female sex. There was also a significant, positive bivariate correlation between increasing age and number of awakenings. Positive history of neurological disorder or injury was associated with lower SE and

TST. Further, administration of at least one sleep-promoting medication during the 2-night actigraphy observation period was also associated with lower SE and TST. Higher acuity of discharge disposition was negatively correlated with WASO. These bivariate correlations are summarized in Table 9.

Table 9. Correlations between Clinical Variables and Sleep Characteristics

Clinical Variables	Sleep Characteristics				
	SE	WASO	TST	SL	NA
Age, years	-.006	-.154	-.014	.088	.382*
Sex	-.167	.105	-.160	.502**	-.248
Race	.315	-.184	.319	-.216	.017
Hispanic/Latino	.089	-.051	.093	-.213	-.282
APACHE III score	.020	-.175	.029	-.136	-.215
Surgery as primary reason for ICU admission	-.009	.143	-.019	-.194	.413*
History of OSA	-.113	-.214	-.105	.234	-.077
History of neurological disorder or injury	-.389*	-.013	-.388*	-.022	-.181
ICU length of stay, days	.194	-.051	.203	-.144	-.223
Length of mechanical ventilation, days	.146	-.001	.154	-.196	-.255
Length of hospital stay prior to study enrollment, days	.269	-.142	.279	-.214	-.188
Pittsburgh Sleep Quality Index global score	-.316	-.147	-.316	.215	-.084
NIH Toolbox Motor PDT fully-corrected T-score	-.063	.347	-.057	-.150	.109
NIH Toolbox Cognition DCCS fully-corrected T-score	.069	.154	.068	-.169	.235
NIH Toolbox Cognition FICAT fully-corrected T-score	.261	-.014	.258	-.140	.128
NIH Toolbox Emotion SS and FAS total raw score	-.070	-.225	-.078	.024	-.001
NIH Toolbox Sensation Pain Intensity total raw score	.223	-.098	.219	-.236	.065
Administration of sleep-promoting medication	-.486**	.101	-.483**	.222	-.140
Administration of pain medication	.204	-.030	.196	.050	.181
Documentation of delirium by provider	-.030	-.093	-.022	.008	.032
Readmission to ICU after study completion	.135	-.278	.113	-.128	-.059
Discharge recommendation, as evaluated by rehabilitation	.198	-.429*	.185	-.005	-.018
Discharge disposition	.369	-.393*	.355	-.100	.079
Total length of hospital stay, days	.306	-.219	.318	-.201	-.185

Note. Bivariate correlations were calculated using Pearson product-moment correlation, point-biserial correlation, or Spearman's rank-order correlation.
*Correlation is significant at the $p < 0.05$ level.
**Correlation is significant at the $p < 0.01$ level.

Based on the aforementioned bivariate correlations, the data were further examined for observable trends. There was a slight trend between sleep duration and higher acuity of discharge disposition; however, a one-way ANOVA could not be calculated, secondary to limited sample size. There were noticeable trends between sleep duration and length of mechanical ventilation, ICU stay, and hospital stay prior to study enrollment. Graphic representations of these trends are pictured in Figures 4 and 5.

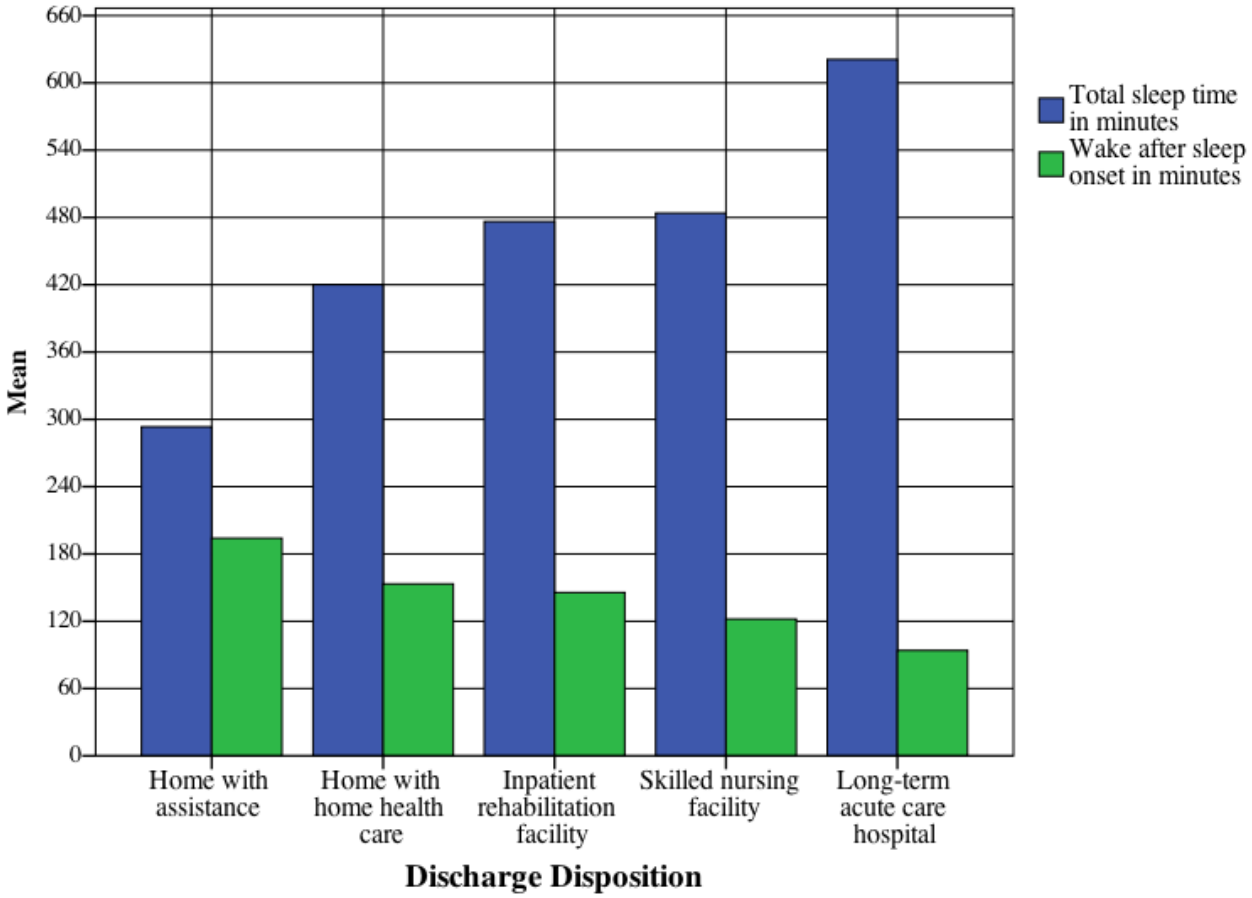

Figure 4. Sleep Duration and Sleep Fragmentation by Discharge Disposition

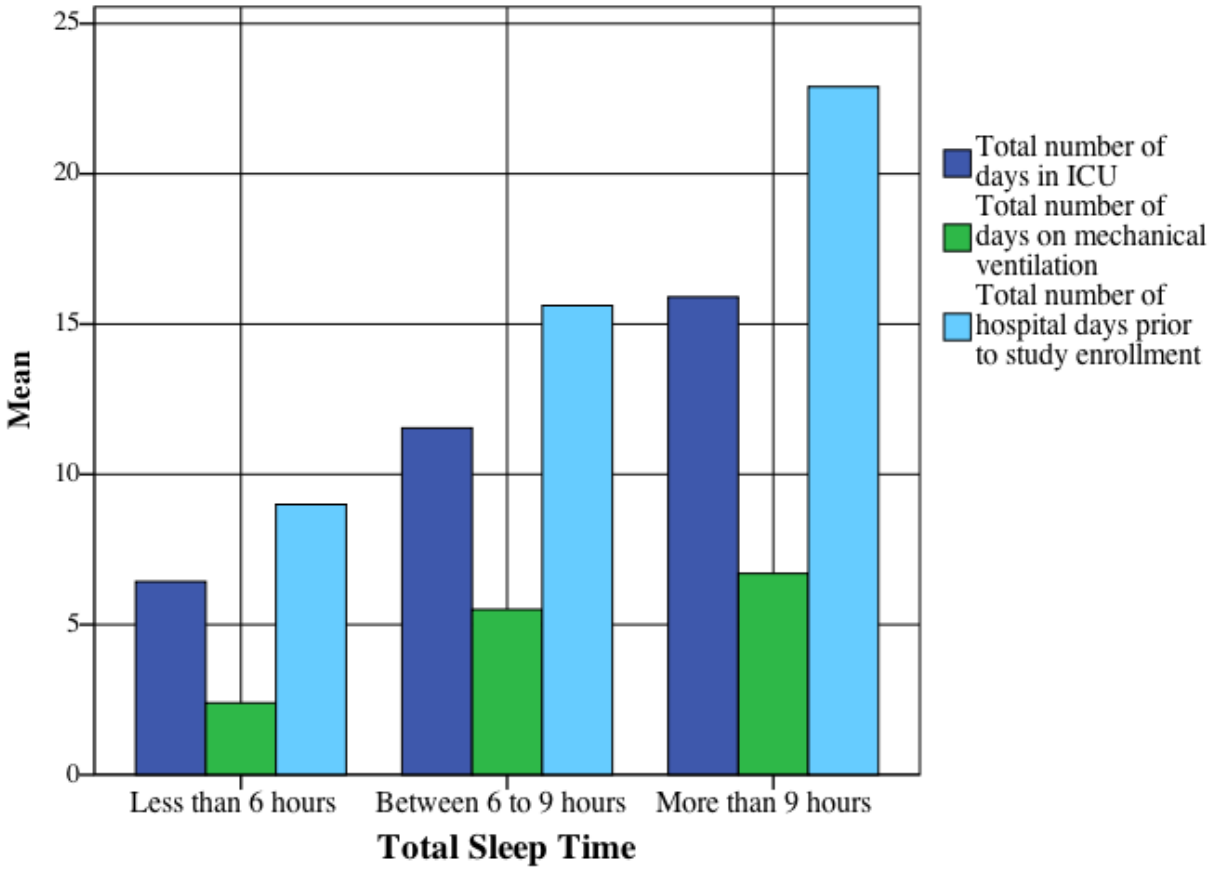

Figure 5. Sleep Duration by Length of Mechanical Ventilation, Length of ICU Stay, and Length of Hospital Stay Prior to Study Enrollment

A one-way ANOVA determined that there were significant differences between subjects with low, moderate, and high PSQI scores on average SE [$F(2, 27) = 4.647$, $p = .018$]. A Tukey post-hoc analysis revealed that subjects who had high self-reported PSQI global scores had significantly lower SE (48.62 ± 23.15%), when compared to the average SE of subjects with moderate PSQI scores (74.62 ± 15.4%) ($p = .014$). The difference in SE between the low and high PSQI groups did not reach statistical significance ($p = .207$). Further, subjects who slept 6 hours or more ($n = 23$) had significantly longer hospital stays (18.78 ± 15.02 days) compared to subjects who slept less than 6 hours (9.0 ± 3.87 days), $t(27.8) = -2.83$, $p = .009$. It was also found that the subjects with OSA who slept 6 hours or more ($n = 12$) also had significantly longer ICU lengths of stay (18.5 ± 15.31 days) compared to subjects with OSA who slept less than 6 hours

(7.6 ± 3.97 days), $t(13.85) = -2.29$, $p = .038$, $n = 17$. Additionally, subjects who received at least one sleep-promoting medication ($n = 11$) had significantly lower TST (358.84 ± 181.46 minutes) compared to subjects who did not receive any sleep-promoting medications (507.93 ± 100.19 minutes), $t(13.61) = 2.512$, $p = .025$, $n = 30$. Differences in WASO and SL between groups did not reach statistical significance; however, the visual trends in WASO and SL can be observed in Figure 6.

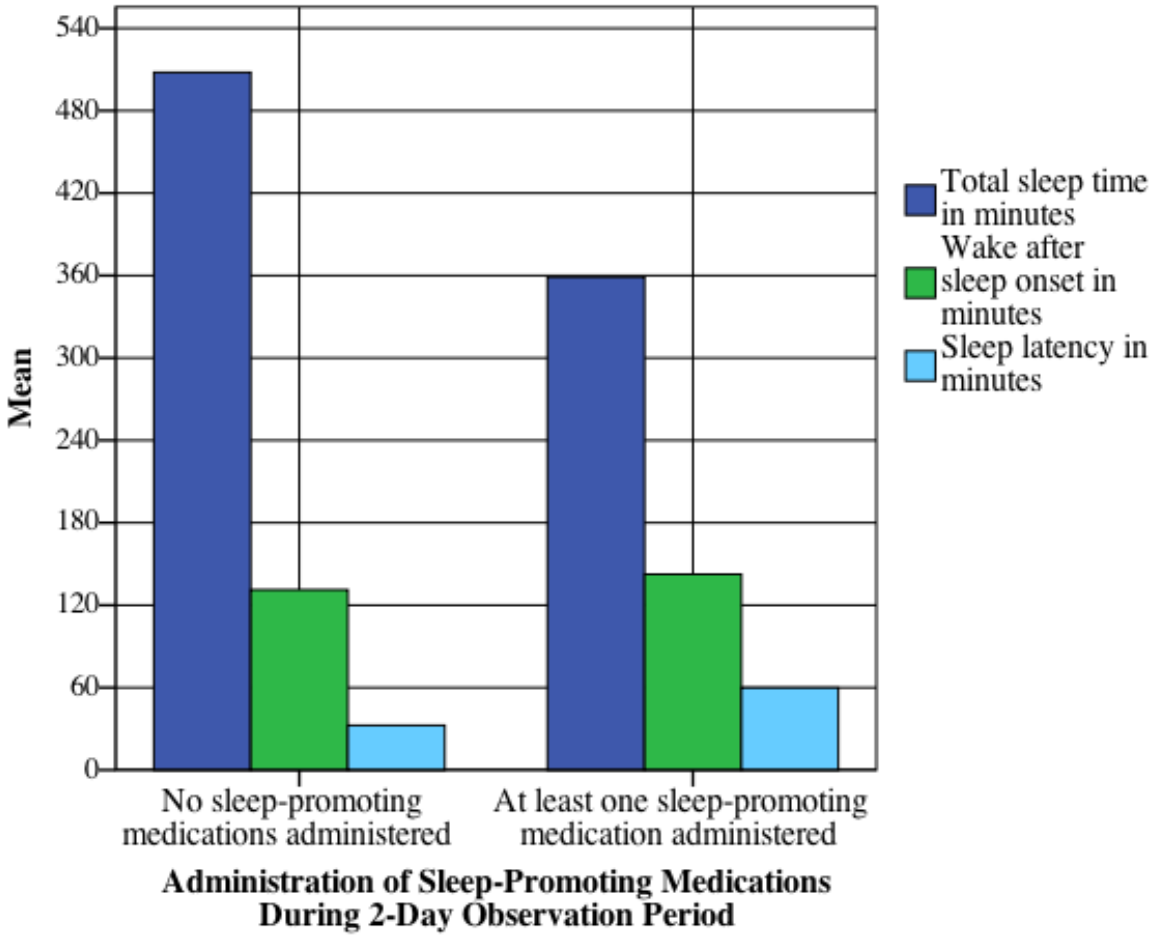

Figure 6. Administration of Sleep-Promoting Medications by Sleep Duration, Sleep Fragmentation, and Sleep Latency

Results of Specific Aims 2a and 2b

Specific Aims 2a and 2b explored the individual relationships between post-ICU SE (2a) and WASO (2b) with grip strength in previously mechanically ventilated older adult patients

within 24-48 hours of transfer out of the ICU. It was hypothesized that there was a direct, significant, positive relationship between post-ICU SE and grip strength among these older adult subjects. It was also hypothesized there was a direct, significant, negative relationship between post-ICU WASO and grip strength.

First, the data were examined for missing data and for outliers. There were no missing data for SE, WASO, or grip strength. Additionally, it was also determined that there were no outliers for SE, WASO, or grip strength. The mean grip strength of study subjects was 44.91 ± 23.63 lbs. (Descriptive analyses of SE and WASO were reported within the results of Specific Aim 1.)

Next, the associations between grip strength and other demographic and clinical variables of interest were examined. There was a significant, moderate, positive correlation between sex and grip strength, indicating that male subjects overall tended to have higher grip strength (r_{pb} = 0.53, n = 30, p = 0.003). There was also a significant, moderate, negative correlation between history of OSA and grip strength, indicating that subjects with OSA overall tended to have lower grip strength (r_{pb} = -0.528, n = 30, p = 0.003). It was found that male subjects had significantly higher grip strength (54.24 ± 23.07 lbs) compared to female subjects (28.79 ± 14.5 lbs), $t(28)$ = 3.289, p = .003. Further, subjects with OSA had significantly lower grip strength (58.95 ± 25.8 lbs) compared to subjects without OSA (34.18 ± 15.18 lbs), $t(28)$ = 3.292, p = .003.

Bivariate analyses. Bivariate Pearson product-moment correlation coefficients were first computed to assess the relationship between SE and grip strength, as well as the relationship between WASO and grip strength. The bivariate correlation between SE and grip strength was nonsignificant, r = -.131, p = .490, n = 30. The bivariate correlation between WASO and grip strength was also nonsignificant, r = .301, p = .106, n = 30. Bivariate correlations of SE and

WASO to grip strength were further explored by categorizing SE into tertiles of low, moderate, and high SE, and by categorizing WASO into quartiles of low, low-moderate, moderate-high, and high WASO. These exploratory correlations revealed a change in direction between the low SE tertile and the moderate-high SE tertiles. The correlation between SE and grip strength among the low SE group was positive; however, the correlations among the moderate and high SE tertiles were negative. Similarly, the bivariate correlations between WASO and grip strength among the low-to-moderate WASO quartiles were positive, while the correlations among the moderate-to-high WASO quartiles were negative. These are reported in Table 10.

Table 10. Bivariate Correlations between Selected Sleep Parameters and Grip Strength

Sleep Parameters	Grip Strength	Correlations
SE < 50% (TST < 6 hours)	48.84 ± 24.32 lbs	0.321 (n = 7)
SE 50 – 75% (TST 6-9 hours)	45.32 ± 20.02 lbs	-0.080 (n = 13)
SE > 75% (TST > 9 hours)	41.63 ± 29.10 lbs	-0.633* (n = 10)
WASO < 90 min (low WASO)	33.35 ± 20.49 lbs	0.044 (n = 8)
WASO 90-120 min (low-moderate WASO)	34.57 ± 21.05 lbs	0.548 (n = 7)
WASO 120-180 min (moderate-high WASO)	57.91 ± 22.97 lbs	-0.341 (n = 7)
WASO > 180 min (high WASO)	54.13 ± 23.16 lbs	-0.470 (n = 8)

Note. Bivariate correlations were calculated using Pearson product-moment correlations.
*Significant at the $p < 0.05$ level.

Regression analyses. In multiple regression analysis, SE was significantly and negatively associated with grip strength (β = -0.326, p = .036), after adjusting for potential confounding factors, including age, sex, race/ethnicity, history of OSA, history of neurological disorder or injury, APACHE III ICU severity of illness score, NIH Toolbox Cognition DCCST score, and documentation of delirium by provider (refer to Table 11). The results of the regression indicated that these model predictors explained 80.8% of the variance in grip strength, [R^2 = .808, $F(10, 15) = 6.324$, p = .001]. It was found that SE independently and negatively predicted grip strength. Higher SE was associated with poorer grip strength. Further, among the subset of subjects with moderate or high TST (sleep duration ≥ 6 hours, n = 23), there remained a significant, negative association between SE and grip strength (β = -0.296, p = .046, see Table

12). After adjusting for sex, history of OSA, APACHE III ICU severity of illness score, and cognitive performance, SE was independently and negatively associated with grip strength. The results of this model indicated that these model predictors explained 73.7% of the variance in grip strength, [R^2 = .737, F(5, 15) = 8.416, p = .001]. It was revealed that SE independently and negatively predicted grip strength among this subset of subjects with moderate or long sleep duration. The relationship between SE and grip strength among the subset of subjects with short duration of sleep (less than 6 hours' sleep duration, n = 7) did not reach statistical significance.

The association between WASO and grip strength was not significant among the full sample after adjusting for these potential confounding factors (refer to Table 11) , although the regression model did reach statistical significance [R^2 = .761, F(10, 15) = 4.776, p = .003]. However, among the subset of subjects with moderate-high or high WASO (≥120 minutes spent awake after sleep onset, n = 16), there was a significant association between WASO and grip strength (refer to Table 13). After adjusting for sex, history of OSA, cognitive performance, administration of sleep medication, and administration of pain medication, moderate-high and high WASO were independently and negatively associated with grip strength. The results of this model indicated that these predictors explained 91.4% of the variance in grip strength [R^2 = .914, F(6, 8) = 14.134, p = .001]. Greater WASO independently predicted worse grip strength (β = -0.276, p = .04).

Table 11 summarizes the relationships between SE, WASO, and grip strength among the entire study sample. Table 12 further examines the relationship between SE and grip strength among those with nighttime sleep duration of at least 6 hours or more. Table 13 specifically explores the relationship between WASO and grip strength among the quartiles of subjects with moderate-high and high WASO.

Table 11. Associations of Sleep Efficiency and Wake After Sleep Onset with Grip Strength (n = 30)

Dependent variable	Independent variable	Multivariate Model 1[a] R^2 β (95% CI)	p-value	Multivariate Model 2[b] R^2 β (95% CI)	p-value
Grip strength	SE (%)	0.764* -0.261 (-0.558, -0.023)	0.035*	0.808* -0.326 (-0.697, -0.027)	0.036*
Grip strength	WASO (mins)	0.730* 0.187 (-0.034, 0.196)	0.155	0.761* 0.165 (-0.062, 0.206)	0.273

SE, sleep efficiency; WASO, wake after sleep onset.
[a]Adjusted for age, sex, history of obstructive sleep apnea, APACHE III ICU severity of illness score, and NIH Toolbox Cognition Dimensional Change Card Sort Test fully-corrected T score.
[b]Adjusted for age, sex, race/ethnicity, history of obstructive sleep apnea, history of neurological disorder or injury, APACHE ICU severity of illness score, ICU readmissions, NIH Toolbox Cognition Dimensional Change Card Sort Test fully-corrected T-score, and documentation of delirium by provider.
β, standardized coefficients; CI, confidence intervals.
*Significant at the $p < 0.05$ level.

Table 12. Association of Sleep Efficiency with Grip Strength among Subjects with Total Sleep Time of at Least 6 Hours (n = 23)

Dependent variable	Independent variable	Multivariate Model 1[a] R^2 β (95% CI)	p-value	Multivariate Model 2[b] R^2 β (95% CI)	p-value
Grip strength	SE ≥ 50%	0.706* -0.302 (-1.167, -0.071)	0.029*	0.737* -0.296 (-1.202, -0.013)	0.046*

SE, sleep efficiency; WASO, wake after sleep onset.
[a]Adjusted for sex and history of obstructive sleep apnea.
[b]Adjusted for sex, history of obstructive sleep apnea, APACHE III ICU severity of illness score, and NIH Toolbox Cognition Flanker Inhibitory Control and Attention Test fully-corrected T-score.
β, standardized coefficients; CI, confidence intervals.
*Significant at the $p < 0.05$ level.

Table 13. Association of Wake After Sleep Onset with Grip Strength among Subjects with Moderate-High and High Wake After Sleep Onset (n = 16)

Dependent variable	Independent variable	Multivariate Model 1[a] R^2 β (95% CI)	p-value	Multivariate Model 2[b] R^2 β (95% CI)	p-value
Grip strength	WASO (mins) ≥ 120 min	0.854* -0.223 (-0.262, 0.032)	0.112	0.914* -0.276 (-0.276, -0.009)	0.040*

WASO, wake after sleep onset.
[a]Adjusted for sex, history of obstructive sleep apnea, and NIH Toolbox Cognition Dimensional Change Card Sort Test fully-corrected T score.
[b]Adjusted for sex, history of obstructive sleep apnea, NIH Toolbox Cognition Dimensional Change Card Sort Test fully-corrected T score, administration of sleep medications, and administration of pain medications.
β, standardized coefficients; CI, confidence intervals.
*Significant at the $p < 0.05$ level.

Relationships between sleep and grip strength among males. As previously mentioned, there were significant differences *a priori* between male subjects and female subjects with respect to grip strength, and sex was a significant covariate in the regression models.

Therefore, a separate regression analysis including only male subjects (n = 19) was conducted. In this regression analysis, SE remained significantly and negatively associated with grip strength (β = -0.353, p = .039; see Table 14), after adjusting for potential confounding factors, including age, history of OSA, APACHE III ICU severity of illness score, NIH Toolbox Cognition DCCST fully-corrected T-score, and surgery as the primary reason for ICU admission. Higher SE was associated with poorer grip strength among the male subjects in this study. The results of the regression for male subjects indicated that the model predictors explained 86.3% of the variance in grip strength, [R^2 = .863, F(7, 8) = 7.225, p = .006]. It was found that SE significantly predicted grip strength among male subjects. Comparatively, after adjusting for these potential confounding factors, the relationship between WASO and grip strength was not significant among these male subjects. Separate regression analyses were additionally conducted for female subjects; however, these regression models did not reach statistical significance. Table 14 shows the associations between SE, WASO, and grip strength among the 19 male study subjects.

Table 14. Associations of Sleep Efficiency and Wake After Sleep Onset with Grip Strength among Male Subjects (n = 19)

Dependent variable	Independent variable	Multivariate Model 1[a] R^2 Standardized β (95% CI)	p-value	Multivariate Model 2[b] R^2 Standardized β (95% CI)	p-value
Grip strength	SE (%)	0.820* -0.310 (-0.671, -0.008)	0.045*	0.863* -0.353 (-0.749, -0.024)	0.039*
Grip strength	WASO (mins)	0.737* 0.121 (-0.129, 0.234)	0.534	0.766* 0.087 (-0.164, 0.239)	0.677

SE, sleep efficiency; WASO, wake after sleep onset.
[a]Adjusted for age, history of obstructive sleep apnea, APACHE III ICU severity of illness score, NIH Toolbox Cognition Dimensional Change Card Sort Test fully-corrected T score.
[b]Adjusted for age, race/ethnicity, history of obstructive sleep apnea, APACHE III ICU severity of illness score, NIH Toolbox Cognition Dimensional Change Card Sort Test fully-corrected T score, and surgery as the primary reason for ICU admission.
β, standardized coefficients; CI, confidence intervals.
*Significant at the $p < 0.05$ level.

Relationships between sleep and grip strength among subjects with OSA. Grip strength varied greatly between subjects with and without documented history of OSA, as shown by the results of the *a priori* independent samples t-test mentioned previously. History of OSA

was also a significant covariate in the regression models. Therefore, another regression analysis including only subjects with documented diagnoses of OSA (n = 17) was conducted. In this regression analysis, SE was significantly associated with grip strength (β = -0.493, p = .033; see Table 15), after adjusting for potential confounding factors, including age, sex, APACHE III ICU severity of illness score, NIH Toolbox Cognition DCCST fully-corrected T-score, and ICU length of stay. Higher SE was significantly related to poorer grip strength among subjects with OSA. The results of the regression for subjects with preexisting OSA indicated that the model predictors explained 74.2% of the variance in grip strength, [R^2 = .742, F(6, 8) = 3.842, p = .042]. It was found that SE significantly predicted grip strength among subjects with OSA. Higher SE was significantly related to poorer grip strength among subjects with OSA. However, after adjusting for these potential confounding factors, the relationship between WASO and grip strength was not significant among these 17 subjects with OSA. Table 15 shows the associations between SE, WASO, and grip strength among the study subjects with preexisting OSA.

Table 15. Associations of Sleep Efficiency and Wake After Sleep Onset with Grip Strength among Subjects with Obstructive Sleep Apnea (n = 17)

Dependent variable	Independent variable	Multivariate Model 1[a] R^2 β (95% CI)	p-value	Multivariate Model 2[b] R^2 β (95% CI)	p-value
Grip strength	SE (%)	0.720* -0.453 (-0.544, -0.043)	0.026*	0.742* -0.493 (-0.607, -0.032)	0.033*
Grip strength	WASO (mins)	0.650* 0.362 (-0.020, 0.218)	0.093	0.655 0.378 (-0.037, 0.244)	0.128

SE, sleep efficiency; WASO, wake after sleep onset.
[a]Adjusted for sex, APACHE III ICU severity of illness score, NIH Toolbox Cognition Dimensional Change Card Sort Test fully-corrected T score.
[b]Adjusted for age, sex, APACHE III ICU severity of illness score, NIH Toolbox Cognition Dimensional Change Card Sort Test fully-corrected T score, and ICU length of stay.
β, standardized coefficients; CI, confidence intervals.
*Significant at the $p < 0.05$ level.

Chapter Five: Discussion and Conclusions

This final chapter synthesizes the study results, providing a discussion of the study findings, conclusions, and implications for future research. The present study was guided by the following specific aims: 1. to describe the post-ICU nighttime sleep quality (TST, SE, WASO, SL, and NA) of previously mechanically ventilated older adult patients within 24-48 hours of transfer out of the ICU; and 2. to explore the relationships between post-ICU SE and WASO with grip strength in these older adult survivors of critical illness.

Discussion of Findings

To the author's knowledge, no prior study has described the nighttime sleep quality of previously mechanically ventilated older adults within 24-48 hours of transfer out of ICU to a medical-surgical floor. The average TST among healthy 70-year-old adults is about 6 hours, according to a large meta-analysis of quantitative sleep parameters (Ohayon et al., 2004). The average TST among this study sample between 9:00 PM to 9:00 AM on both nights was unexpectedly higher, at about 7.55 hours. Further, the average WASO among healthy 70-year-old adults is slightly below 60 minutes (Ohayon et al., 2004). The average WASO among this sample was also much higher, at about 135 minutes. These descriptive results indicate that, although these older adult ICU survivors spent more time asleep at night when compared to their healthy counterparts, their sleep was also much more fragmented.

Interestingly, at the time of study enrollment, subjects who slept 6 hours or more had also been hospitalized for much longer than those who slept less than 6 hours. Specifically, among the subset of subjects with OSA, those who slept 6 hours or more had been in the ICU much

longer than those who slept less than 6 hours. In addition, among the subset of subjects who were administered at least one sleep-promoting medication during the 2-day study period, TST was significantly shorter, while WASO was slightly higher and SL latency was slightly longer. These comparative results provide insight into the sleep quality of post-ICU older adults who required mechanical ventilation.

No prior study has explored the association between nighttime sleep quality and motor function in this population of post-ICU older adults who required mechanical ventilation. Surprisingly, higher nighttime SE was independently associated with weaker grip strength. This negative association remained significant after controlling for potential confounding variables, including age, sex, race/ethnicity, history of OSA, history of neurological disorder or injury, severity of illness on ICU admission, number of ICU readmissions, cognitive performance, and delirium. Moreover, there was a significant, negative relationship between SE and grip strength among the subset of subjects with nighttime sleep duration of 6 hours or longer. No significant association was identified among the subjects with nighttime sleep durations of less than 6 hours, likely due to the small sample size in this subgroup. These findings suggest that among older adult survivors of critical illness, longer nighttime sleep duration while hospitalized may be independently associated with ICU-acquired weakness. Yet, as expected, among the two quartiles of subjects with more severe sleep fragmentation, greater nighttime WASO was independently associated with weaker grip strength, after adjusting for sex, history of OSA, cognitive performance, administration of sleep medications, and administration of pain medications. This implies that sleep fragmentation may be an independent predictor of ICU-acquired weakness and poor motor function among older adult ICU survivors.

In addition, the present study explored the association between sleep efficiency and grip strength among male subjects and among subjects with preexisting OSA. In the exploratory analysis of only male subjects, higher SE was associated with poorer grip strength after adjusting for confounding factors, including age, race/ethnicity, history of OSA, severity of illness on ICU admission, surgery as the primary reason for ICU admission, and cognitive performance. In the exploratory analysis of only subjects with OSA, similar results were yet again found: higher sleep efficiency was associated with worse grip strength after controlling for age, sex, severity of illness on ICU admission, ICU length of stay, and cognitive performance. These results suggest possible influences of sex and sleep-disordered breathing (such as OSA) on ICU-acquired weakness.

Poor sleep can reduce levels of circulating testosterone, a hormone involved in protein synthesis and muscle anabolism (Andersen & Tufik, 2008). Also, sleep-disordered breathing, such as that seen in OSA, has been previously associated with lower free testosterone levels and lower grip strength (Andersen & Tufik, 2008; Hammoud et al., 2011). However, a recent, large cross-sectional study of community-dwelling older men indicated that testosterone levels tend to increase with longer sleep duration up to 9.9 hours—but then decrease with 10 or more hours of sleep. This suggests an inverted U-shaped relationship between sleep and testosterone (Auyeung et al., 2015). Such a decrease in testosterone with 10 or more hours of sleep may partially explain the weaker grip strength among the older adult males in the present study.

The findings of Specific Aim 2a differed from the reported results of a few large studies of healthy older adults, which concluded that lower nighttime SE may result in worse motor function among community-dwelling adults ages 65 years or older. For example, the Osteoporotic Fractures in Men Study of 2862 community-dwelling white males ages 67 years or

older showed that lower SE and increased nocturnal awakenings were significantly associated with worse grip strength (Dam et al., 2008). It is thus still possible that less nighttime sleep could be associated with worse motor function in community-dwelling elderly women. Moreover, the Study of Osteoporotic Fractures of community-dwelling older women also found longitudinal evidence of a decline in motor function with poorer nighttime sleep. Older women in the Study of Osteoporotic Fractures with lower SE had 65% greater odds of motor impairment than those with the highest (Spira et al., 2012). The present study, however, found a significant, negative correlation between SE and grip strength among a sample of 30 hospitalized elders, as well as among the males-only subset of subjects and the subset of subjects with history of OSA. It is thus important to emphasize that the population of the present study included only older adults who recently transferred out of an ICU and required mechanical ventilation for life-threatening critical illness, injury, or post-operatively.

Yet, similar to the results of Specific Aim 2a, some large studies of community-dwelling older adults did find significant relationships between longer sleep duration and worse grip strength. For example, among community-dwelling older men in the Yilan Study, there was a noted association between longer sleep duration ($\geq$ 9 hours) and weaker grip strength (Chen, Hsu, & Chou, 2017). In addition, another study of community-dwelling elders corroborated weaker grip strength among men who slept longer than 9 hours (Fu et al., 2017). Further, the InCHIANTI study of community-dwelling older adults reported that extended time spent in bed, coupled with longer TST, were associated with greater decline in motor strength, than was observed among those with short or moderate durations of sleep (Stenholm, Kronholm, Bandinelli, Guralnik, & Ferrucci, 2011).

It has been proposed that there is an inverted U-shaped relationship between sleep duration and sarcopenia or physical performance in community-dwelling older adults (Auyeung et al., 2015; Chien, Wang, & Chen, 2015; Fu et al., 2017; T. Y. Wang, Wu, Wang, Li, & Zhang, 2018). Most of these studies had also found differences in these associations between the sexes. In the present study, 20% of subjects slept more than 10 hours on average between 9:00 PM to 9:00 AM, and another 20% of subjects slept less than 5 hours on average each night. Separate exploratory analyses of the relationships between short, moderate, and long sleep durations (< 6 hours, 6-9 hours, and > 9 hours, respectively) and grip strength did not reach statistical significance, likely due to the small sample size of this study. This limited the exploration of an inverted U-shaped relationship. However, among the subset of subjects with moderate or high TST (nighttime sleep duration ≥ 6 hours), SE was independently and negatively associated with grip strength, after adjusting for sex, history of OSA, severity of illness, and cognitive performance.

At the same time, the results of Specific Aim 2b did find a significant, negative relationship between WASO and handgrip strength among the subset of subjects with moderate-high WASO and high WASO. The hypothesis was thus partially supported. These findings were consistent with the findings of the Study of Osteoporotic Fractures of community-dwelling older women, which concluded that women who spent 1.6 hours awake after sleep onset had worse grip strength than the women who spent less than 45 minutes awake after sleep onset (Goldman et al., 2007). Further, the community-dwelling women in the Study of Osteoporotic Fractures with the highest WASO and the lowest SE had almost 90% greater odds of decline in grip strength than those with the least WASO and highest SE (Spira et al., 2012).

In this study, SE almost perfectly correlated with TST ($r = .999$, $p < .001$), which also reflects that almost all of the subjects had likely spent all 12 nighttime hours (9:00 PM to 9:00 AM) in bed. Considering the frailty of this population, these subjects were, by majority, inactive and/or bedridden upon transfer out of ICU, despite their community dwelling status and functional independence prior to ICU admission. It is quite possible that many subjects slept additionally during the daytime hours between 9:00 AM to 9:00 PM; these data will be analyzed in a future study. Although clinical neurological status was not directly assessed in this study, the mean fully-corrected T-score on the NIH Toolbox Cognition DCCST was 38.81, and the mean fully-corrected T-score on the NIH Toolbox Cognition FICAT was 29.78 – far below the national averages for healthy community-dwelling older adults (Weintraub et al., 2013). It is possible that the overall poor performance on these assessments of attention and cognitive flexibility could be attributed to the excessive somnolence and worse level of consciousness, commonly observed in ICU and post-ICU patients, especially among those with hypoactive delirium. The relationship between ICU delirium and poor physical function has been previously established in the literature (Brummel et al., 2014).

The relationship between sleep quality and motor function among hospitalized older adults recovering from critical illness is likely multifactorial and complex. Though studies have examined associations between sleep quality and motor function in healthy, community-dwelling older adults, the exact physiologic impact of poor sleep on motor function among critically ill older adults remains unknown. A possible explanation of the present study's findings might be related to disturbances in slow-wave sleep and REM sleep with greater sleep fragmentation. Greater sleep fragmentation, and subsequent reductions in protein synthesis and increases in protein degradation, may explain the relationship between nighttime sleep quality and motor

function. Additionally, it is important to consider that while these subjects slept longer in duration overall, this does not necessarily mean that they also experienced more slow-wave or REM sleep. In fact, it is probable that, given such severe sleep fragmentation, they experienced little to no slow-wave sleep or REM sleep—it has been established in the literature that ICU patients experience almost a virtual absence of slow-wave or REM sleep (Cooper et al.; Krachman et al., 1995). Decreased sleep fragmentation and improved sleep quality, as opposed to quantity or duration of sleep, may ameliorate motor strength. This, in turn, may optimize functional outcomes among older adult survivors of life-threatening critical illness, who are at high risk for new institutionalization and ICU-acquired weakness.

Maintaining strength, physical performance, and mobility are crucial to living independently in older age. On average, adults ages 65 and older experience a loss in grip strength of about 2.4% per year, and a further loss of 2.9% per year after reaching age 80 (Forrest, Zmuda, & Cauley, 2006). Grip strength may identify older adults who are at increased risk of functional and overall health decline (Rantanen et al., 2003). Notably, with respect to the post-ICU patient population, grip strength has been identified as a simple test for ICU-acquired weakness (Ali et al., 2008). In this sample of post-ICU older adults who required mechanical ventilation, the average dominant hand grip strength for males was about 54 lbs, and for females the average was about 29 lbs. These values are far below the normative values for grip strength: approximately 86 lbs for 70-year-old males and 52 lbs for 70-year-old females (Dodds et al., 2014). Older adults with poor grip strength may be at higher risk for frailty and new institutionalization at a skilled nursing facility or long-term care facility. Moreover, grip strength is consistently predictive of all-cause mortality in elderly individuals (Sasaki, Kasagi, Yamada, & Fujita, 2007). Optimal sleep quality while hospitalized may indirectly promote better

discharge outcomes, as grip strength is linked to length of hospital stay, discharge disposition, and worsened functional decline (Bohannon, 2001). Findings from the present study are in concordance with the literature: lower grip strength was significantly correlated with higher acuity of discharge disposition (r_s = -0.446, p = 0.017). It is thus important to identify risk factors for poor grip strength and ICU-acquired weakness, especially among frail hospitalized elders; the findings of this study suggest disturbed nighttime sleep may be one influential factor.

Study strengths and limitations. The cross-sectional design of the present study may not allow for the determination of temporality in the relationship between sleep quality and motor function. Future studies should include longitudinal follow-up of objective measures of sleep quality and of motor function. In addition, polysomnography is considered the gold standard of objective measurements of sleep; the present study utilized wrist actigraphy to objectively measure sleep quality. Use of polysomnography would help elucidate how much slow-wave and REM sleep hospitalized older adult ICU survivors experience. Although polysomnography provides the highest level of reliability and accuracy, the participant-specific accuracy of actigraphy as an objective tool to measure sleep is relatively high, at about 86% (Marino et al., 2013). Actigraphy has thus been determined to be a valid means of objectively estimating sleep parameters in clinical studies, as a more feasible and much less burdensome substitute for polysomnography. Patient enrollment in this study was based on convenience sampling; minorities were enrolled, but in a proportionally lower percentage than was anticipated, in comparison to the overall demographics of Hillsborough County, Florida. Despite this sampling method, there was no known bias in enrollment—subjects were approached, recruited, and enrolled as soon as possible after transfer out of ICU and if all eligibility criteria were met. The imbalance may have been a consequence of the small sample size. Subjects

included in this study also had a wide variety of admitting diagnoses and were recruited from all 12 divisions of medical-surgical units at Tampa General Hospital, a Level 1 trauma hospital. Finally, enrolled subjects must have been functionally independent and living at home prior to hospital admission for study eligibility, so the results of the present study may not translate to hospitalized older adult ICU survivors with worse physical function at baseline. However, this also attests to a powerful clinical implication of this study's findings. While all of these older adults were fully independent prior to hospital admission, those who experienced longer nighttime sleep duration and higher sleep fragmentation tended to have significantly weaker grip strength, and are presumably at higher risk for delayed recovery or additional functional decline.

Conclusions

The present study included hospitalized older adult survivors of critical illness who were functionally independent at baseline, and required mechanical ventilation in the ICU for life-threatening illness, injury, or postoperatively. In this study of 30 older adults recently transferred out of ICU to a medical-surgical unit, nighttime sleep quality was severely abnormal: TST was markedly higher and WASO was much greater than the normative sleep parameters for healthy older adults. Subjects who slept 6 hours or more had been hospitalized for much longer than those who slept less than 6 hours; among the subset of subjects with OSA, those with moderate or long sleep durations had been in the ICU much longer than those with short sleep durations. Yet, surprisingly, TST was shorter, WASO was slightly higher, and SL was slightly longer among the group of subjects who were administered at least one sleep-promoting medication. Greater SE and longer TST were negatively associated with weaker grip strength. Among the subset of subjects with TST of 6 hours or more, there remained a significant, negative association between SE and grip strength. Among the subset of male subjects, there remained a

significant, negative relationship between SE and grip strength. Among the subset of subjects with documented diagnoses of OSA, there also remained a significant, negative association between SE and grip strength. Finally, greater WASO was associated with weaker grip strength, among the subset of subjects with moderate or high WASO. While these frail older adults may have slept longer than the average healthy older adult, quantity of sleep does not necessarily translate to quality of sleep—their sleep was still severely fragmented, which likely limited adequate slow-wave sleep and REM sleep. Such poor sleep quality may contribute to ICU-acquired weakness and new institutionalization.

Implications for Future Research

This cohort of previously mechanically ventilated, hospitalized older adults demonstrated abnormal actigraphy patterns, suggesting poor sleep consolidation following transition of care out of ICU. Longer nighttime sleep duration and greater sleep fragmentation may independently predict ICU-acquired weakness among hospitalized older adult survivors of critical illness who required mechanical ventilation. Greater sample size, with adequate representation of both sexes and of minority racial and ethnic groups, is warranted to further evaluate the association between post-ICU nighttime sleep quality and motor function. Further research is needed to identify the biological mechanisms involved. A longitudinal study design may be beneficial to assess the temporality of this relationship and the potential risk for decline in motor function among older adult ICU survivors who were functionally independent at baseline. Future cohort studies should explore associations between prolonged sleep, sleep fragmentation, and actigraphy-observed inactivity periods with post-ICU outcomes among older adult survivors of critical illness. Experimental studies targeting improvements in functional outcomes among older ICU survivors should promote an optimal window of sleep duration and decreases in sleep fragmentation.

Prevention trials are necessary to evaluate whether improvement in sleep quality preserves motor function among hospitalized older adult survivors of critical illness.

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