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Sleep Disturbance And The Immunological Acute Phase Response In Hospitalized Post-Operative Adults.

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**SLEEP DISTURBANCE AND THE IMMUNOLOGICAL ACUTE PHASE RESPONSE
IN POSTOPERATIVE HOSPITALIZED ADULTS**

by

JEAN DOROTHY HUMPHRIES

DISSERTATION

Submitted to the Graduate School

of Wayne State University,

Detroit, Michigan

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

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MAJOR: NURSING

Approved By:

Advisor

Date

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DEDICATION

My dissertation is dedicated to the memory of my eldest brother, Robert R. Wolff, who was my inspiration to study sleep during acute care hospitalization. This dissertation is also dedicated to my husband Craig, my daughter Julie, my son Matthew and his wife Kristin who showered me with love and support during these past years to the finish of this scholarly work.

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CHAPTER 1 INTRODUCTION

Sleep is an innate physiological process which is essential to maintain good health; however, acutely ill hospitalized adults frequently experience disturbed sleep (Humphries, 2008; Redeker, 2000). According to the National Center for Health Statistics (2010), the most common reason for admission to a hospital acute care unit is a surgical procedure. In 1979 a landmark study reported that even a minor surgical procedure could cause major disruptions in night-time sleep (Kavey & Altshuler, 1979). This study examined the sleep patterns of 10 individuals undergoing elective hernia repair from the day of admission until discharge with polysomnography (sleep study). Their pre-operative sleep showed minor alterations, but sleep on the first postoperative two nights was characterized by restlessness, light sleep, and an absence of stage 3, 4 deep sleep followed by a gradual return toward normal sleep at day 4 and 5.

In the decades after this early study was conducted, many studies have reported sleep disturbance in post-operative adult patients hospitalized on surgical units. (Basse, et al., 2005; Büyükyılmaz, Şendir, & Acaroğlu, 2011; Chouchou, Khoury, Chauny, Denis, & Lavigne, 2014; Dolan, Huh, Sproat, & Camilleri-Brennan, 2016; Gögenur, Bisgaard, Burgdorf, van Someren, & Rosenberg, 2009; Gögenur, Rosenberg-Adamsen, Knill, Kehlet, & Rosenberg, 2001; Lane & East, 2008; Miller, Roth, Roehrs, & Yaremchuk, 2015; Lindseth & Denny, 2014). One recent review summarized the findings of 13 studies that examined the sleep of individuals undergoing a variety of general surgeries (Chouchou et al., 2014): many patients experienced reduced total sleep time and most experienced decreased duration of rapid eye movement (REM) sleep and non-rapid eye movement (NREM), and more frequent arousals after surgery. Another systematic review of 32 studies that examined sleep objectively with actigraphy reported that total sleep

time and sleep efficiency was reduced after surgery and number of awakenings was increased in patients undergoing major surgery (Madsen et al.,2013)

Studies have examined the patients' perception of sleep quality after surgery as well. Recent studies of post-operative hospitalized adults continue to report that 25 to 100% of subjects experience post-operative sleep disturbance with decreased night-time sleep and duration, fragmented sleep and frequent awakenings during the nighttime sleep period (Büyükyılmaz et al., 2011; Dolan et al., 2016; Lane & East, 2008).

Many factors may contribute to disrupted sleep patterns after surgery, including patient care activities, environmental factors and pain. After surgery, nurses monitor patients continuously during first few post-operative days. Night-time care activity includes assessments, medication administration, and early morning specimen collection for laboratory analysis. Inpatient unit noises and turning on room lights also will disturb night-time sleep (Büyükyılmaz et al., 2011; Klemann, Hansen, & Gögenur et al., 2015; Knill et.al., 1990; Lane & East, 2008). Pain occurs as a result of the surgical procedure and hospitalized post-operative surgical patients frequently report that pain disturbs their sleep (Basse, et al., 2005; Büyükyılmaz et. al., 2011, Chouchou et al., 2014; Closs, 1992; Dolan et.al., 2016; Lane & East, 2008; Lindseth & Denny, 2014; Miller et al., 2015).

Surgery-related sleep disturbing factors include the physiological response to the stress of the surgical procedure and pre-operative as well as post-operative anxiety about the surgery process and findings (Lanuza, 1995; DeVon & Saban, 2012). The physiological stress response to surgery activates the autonomic nervous system, neuroendocrine system and the immune system. The autonomic nervous system increases heart rate and rate variability, blood pressure, and myocardial oxygen demand. The neuroendocrine system triggers increased levels of cortisol,

epinephrine, and norepinephrine. Surgical trauma triggers inflammatory and immune responses in proportion to magnitude of the trauma (Winters, 2012). The intensity of these surgery – related stressors may influence the intensity of the sleep disturbance, sleep fragmentation, and awakenings, as well as pain perception and emotional distress.

Despite overwhelming evidence that sleep disturbance occurs in surgical patient, there is a paucity of research examining the relationship of the usual physiologic response to surgery (inflammatory, endocrine, autonomic) to the sleep disturbance. The inflammatory/immune system responds to surgical invasiveness and organ manipulation with activation of the acute phase response. This is a complex response of many cell types, including monocytes, macrophages, neutrophil, and endothelial cells. In response to tissue injury, these cells release cytokines: cytokines are chemical substance that activate and modulate the inflammatory acute phase response. Cytokine levels rise during the first 24-48 hours after surgery in proportion to the injury and begin to fall toward normal after 48 -96 hours (Weledji, 2014). The major cytokines released after surgery include interleukin (IL1), tumor necrosis factor (TNF- α ,) and IL-6. Two of these cytokines, IL1- β and TNF- α , are associated with sleep and directly or indirectly regulate/modulate NREM sleep to disturb sleep (Opp & Krueger, 2017).

An endocrine stress response occurs in the post-operative surgical patient and initiates the release of cortisol. Cortisol has a diurnal rhythm with peak plasma cortisol from 6:00 a.m. to 8:00 a.m. The lowest level is at midnight. Major surgery elevates plasma cortisol levels for up to 3 days after surgery (Else & Hammer, 2014). The stress response to surgery is also characterized by activation of the sympathetic nervous system (Desborough, 2000). Cortisol release and sympathetic nervous activity could disrupt sleep.

Sleep disturbance is primarily a physiological response related to the person, surgery and the hospital environment. The metaparadigm of nursing is four concepts: human beings, environment, health and nursing (Fawcett, 2005). Nursing theories support the study of the sleep disturbed patient who experiences surgical trauma during recovery in the hospital environment with nursing care. Theoretical structure guides the design of the nursing research, creates new understandings, and provides a structure to explore sleep disturbance research questions.

Neuman's Systems Model guides the design of this nursing research. Person (human beings), is a Physiological system. Sleep homeostasis, which establishes a sleep pattern, and the innate immune system homeostasis, which regulates body defense, continuously interacts with the person. The person continuously interacts with environment stressors. Stressors are positive, neutral or negative The Flexible Line of Defense, the Normal Line of Defense are barriers to environmental stressors. When a stressor penetrates Lines of Resistance, sleep disturbance, immune system response and physiological stress response will occur. Figure 1, Theoretical Framework, diagrams this structure.

Statement of the Problem

Disturbed sleep represents a major factor for individuals after surgery. While many factors that disturb sleep in surgical patients have been identified, the response to surgical trauma itself may be related to the sleep disturbance. The typical inflammatory/immune and neuroendocrine responses to surgery have been described and these responses are associated with the releases of factors known to disrupt sleep. To date, studies that examine the relationships among these variables were not found.

Statement of Purpose

The purpose of this study is to describe the sleep and the acute phase inflammatory and endocrine responses of adults undergoing major surgery. Neuman's Systems theory provides a structure that identifies the person, the environmental stressors and the varying status of the person's physiologic system during hospitalization.

Specific Aims

Specific Aim 1. To characterize the subjective sleep experience of hospitalized patients after major abdominal surgery.

Research question: What are the characteristics of the subjective sleep experience in hospitalized adults after major surgery?

Specific Aim 2. To objectively assess the sleep of hospitalized patients after major abdominal surgery.

Research question: What is the objective assessment of sleep in hospitalized patients after major abdominal surgery?

Specific Aim 3. To describe the immunologic acute phase response and the physiologic stress response of hospitalized patients after abdominal surgery.

Research question: What is the immunologic acute phase response, as measured by Interleukin 1- beta (IL1- β) and Tumor necrosis factor – alpha (TNF- α), in hospitalized patients after surgery? What is the physiological stress response, as measured by cortisol and systolic blood pressure, in hospitalized patients after major abdominal surgery?

Specific Aim 4. To examine the relationships among objective and subjective sleep, immune acute phase response, and stress responses in patients who have undergone major surgery.

Research question: What are the relationships among objective and subjective sleep, IL1- β and TNF- α levels, and cortisol levels in patients who have undergone major surgery?

Significance

This study will provide new information about sleep disturbance in surgical patients and potential correlations with the immune system and stressor responses during the recovery period. Nurses who provide care to surgical patients will benefit from the information in order to assess, plan, implement and evaluate strategies to improve the sleep periods of surgical patients. Recognition of sleep disturbing environmental factors may also be decreased or eliminated.

Significance to the Science of Nursing

Nursing theory provides a philosophy of how nurses view their practice. Research is guided by implementation of conceptual-theoretical empirical (C-T-E) models that provide a systems directed structure. This study utilizes Neuman's Systems nursing theory. This theory provides the structure to help nurses identify and evaluate the stressors affecting hospitalized patients in the hospital environment. The nurse will then be able to plan delivery of care that will support recovery and return to health. The findings of this study will support application in the use Neuman's nursing theory which contributes to the science of nursing.

Health Care and Society

The benefit to society is the focused delivery of nursing care during hospitalization that will maximize sleep periods to return the person to a stable health state. The ultimate outcome of this research trajectory is to diminish sleep disturbance during hospitalization and promote an active immune system response. Acute care nurses will be able to plan and protect sufficient undisturbed hours of sleep based upon the needs of the patient. Sufficient hours of sleep will maintain the active acute immune system response to support recovery. A length of stay is

determined for all adults admitted to an acute care hospital based upon the admitting diagnosis. Night-time sleep disruption, fragmented sleep periods and awakenings are associated may affect the recovery period in surgical patients, with potential for extending the period of hospitalization. As a result of this longer hospitalization, healthcare costs including hospitalization will continue to rise.

CHAPTER 2 REVIEW OF LITERATURE

The purpose of this study is to describe the sleep of patients undergoing major abdominal surgery and to determine whether the sleep disturbance is related to the immunological acute phase response and the physiological stress response during hospitalization. This literature review provides an overview of relevant research for the major study variables of sleep during hospitalization, sleep disturbing stressors, immune system, and physiological stress response.

Sleep During Hospitalization: Medical Surgical Units. Sleep disruption frequently occurs in acute care hospital units. The sleep of patients in critical care and acute care hospital units has been studied since the 1980's. In recent years studies, have found that 42 to 91% of the adult subjects hospitalized on medical-surgical units continue to report disturbed sleep. Inpatients have been studied on medical and/or surgical units, units surgical orthopedic units, and stem cell transplant units (Arora, et al., 2011; Boonstra et al., 2011; Büyükyilmaz, Şendir & Acaroğlu, 2011; Hacker, Patel, & Stainthorpe, 2013; Humphries, 2008; Lane & East, 2008; Lei, et al., 2009; Miller, Roth, Roehrs, & Yaremchuk, 2015; Missildine, 2008; Redeker, 2000; Rischer, Schwerwath, Zander, Koch & Schulz-Kindermann, 2009; Yilmaz, Sayin & Gurler, 2012; Yoder, Staisiunas, Meltzer, Knutson & Arora, 2012).

Subjective sleep measures were varied in 4 studies of hospitalized adults. Medical and surgical patients completed the Verran and Snyder-Halpern (VSH) Sleep Scale in a study by Humphries (2008). After the third night of hospitalization, subjects consistently reported high sleep disturbance, poor sleep effectiveness and supplemental daytime sleep. In a study by Rischer et al. (2009), subjects kept a sleep diary to record 'to bed' and 'wake' time. Sleep duration of less than 6 hours was reported. Büyükyilmaz et al. (2011) used the Pittsburgh Sleep Quality Index (PSQI), which is scored using a Likert Scale with 3 as the most extreme value. The mean score of 1.96 ± 1.22 was suggestive of shortened sleep duration. Yilmaz et al. (2012)

collect data using the PSQI for pre-admission surgical patients and their last week of hospitalization as a surgical inpatient. This study simply reported that “duration of sound sleep may be reduced” (p.187).

Actigraphy was used to measure sleep in 4 studies (Arora et al., 2011; Miller et al., 2015; Missildine, 2008, and Yoder et al., 2012). Actigraphy is an objective measure of sleep and wake that provides information about total sleep time, sleep efficiency, numbers of awakenings, and sleep fragmentation. Sleep time ranged from 215 to 337 minutes, which is 3.58 to 5.6 hours. The National Sleep Foundation recommends that an adult, age 26 to 64 years of age, sleep 7 to 8 hours (Hirshkowitz, et al., 2015).

Exogenous/Endogenous Stressors. Neuman’s Systems Model defines exogenous stressors as the external environment which consists of all factors that exist outside of the client. Conversely, endogenous stressors are defined as the internal environment which consists of all factors within the client system including intrapersonal factors. (Fawcett, 2013, p.144). Figure 1, Theoretical Framework depicts exogenous and endogenous stressors.

Stressors: Noise, Light, Delivery of Care.

Noise levels in acute patient care areas may affect sleep patterns (Lane & East, 2008; Lei et al. 2009, Missildine, 2008, Rischer et al. 2009, Yoder et al., 2012). Noise during sleep should be no more than 35 decibels (dB) (Farshidpanah, Pisani, Ely, & Watson, 2017). In four studies, inpatient room noise levels were found to have a relationship to patient sleep disturbance. Noise causing a disruption in sleep was reported by 446 adult subjects in three studies (Lane & East, 2008; Lei et al., 2009; Rischer et al., 2009). In 2012, Yoder and colleagues reported noise disrupting sleep was reported by 43% of the subjects. The peak noise level reached 80 dB (ringing telephone). Missildine (2008) studied the sleep of older adults during hospitalization.

Noise levels ranged from 78dB (flush toilet) -110 dB (power saw). Lei et al., (2009) found several sources of noise causing sleep disruption including nursing care to patients; telephones ringing; noise from air conditioners and treatment equipment; nurses talking to each other; and even nurse's shoes while walking. Lane and East (2008) reported that noise had the greatest association with sleep disturbance. Rischer et al., 2009 reported that 77% of stem cell transplant patients reported noise as the most frequent cause of sleep.

Light. Our circadian rhythm is influenced by the levels of light in our environment. During the usual night-time sleep period, room light may disrupt the person's normal circadian rhythm. Light inhibits the release of melatonin (Czeisler & Buxton, 2017). Peak light intensities occurred in the hospital inpatient room for 95 minutes during the night-time in the 2008 Missildine study. This study also reported a delay to return to sleep of up to 2 hours after the lights were again dimmed. In 2013, da Costa and Ceolim reported that in a study of 120 hospitalized adults, 65 of the inpatients indicated that disturbed sleep was caused by excessive lighting at least once a week. Of those 65, 40 indicated it occurred 5 or more time per week.

Delivery of Patient Care. The acuity of the patient determines the frequency of the nursing interaction and care. Patient interaction during a night shift ranges from hourly rounds to multiple visits when medication, patient care, positioning, and other interventions are necessary during the sleep period. In an early study by Redeker and colleagues (1998), there were 5 to 32 patient awakenings during the night. Two studies of stem cell transplant patients found that night time nursing care was associated with sleep disturbance. In 2009, Rischer and colleagues investigated the sleep patterns of patients prior to stem cell transplant and daily during the inpatient period. Over half (54%) of the 32 subjects reported in a sleep diary that nursing care disrupted night time sleep. This was a longitudinal study, with a loss of 36% of original subjects.

Boonstra and colleagues (2010) studied 89 subjects who identified factors causing sleep disturbance. Staff interruption was indicated by 80% of the subjects as a cause of sleep disturbance. Inpatients on 13 units in the da Costa and Ceolim (2013) study reported that disturbed sleep was caused by nursing care and-reported that their sleep was disturbed 1 to 5 or more times per week.

Sleep of Patients Undergoing Major Abdominal Surgery

According to the National Center for Health Statistics, the most common reason for admission to a hospital acute care unit is a surgical procedure (2010). There is a lack of research examining factors that may contribute to sleep disruption in post-surgical patients. Early studies examined investigated the sleep of surgical patients during hospitalization and how the surgical procedures affected sleep and the patients' subsequent recovery or deterioration (Kavey & Altshuler, 1979; Knill, Moote, Skinner, & Rose, 1990; Rosenberg-Adamson, Skarbye, Wildshiødtz, Kehlet, & Rosenberg, 1996). Many studies since then have found sleep disturbance in post-operative adult patients hospitalized on surgical units. (Basse, et al., 2005; Büyükyilmaz, Şendir, & Acaroğlu, 2011; Chouchou, Khoury, Chauny, Denis, & Lavigne, 2014; Dolan, Huh, Sproat, & Camilleri-Brennan, 2016; Gögenur, Bisgaard, Burgdorf, van Someren, & Rosenberg, 2009; Gögenur, Rosenberg-Adamsen, Kiil, Kehlet, & Rosenberg, 2001; Lane & East, 2008; Lindseth & Denny, 2014; Miller, Roth, Roehrs, & Yaremchuk, 2015).

The extent of the sleep disturbance found in studies prior to 2000 reported that after abdominal surgery, 68% of the subjects reported severe sleep disruption, with decreased hours of sleep and diminished slow wave sleep. Recent studies of post-operative hospitalized adults continue to report 25 to 100% of subjects' experience post-operative sleep disturbance. Decreased night-time sleep and duration, fragmented sleep and frequent awakenings during the

night-time sleep period were reported (Büyükyılmaz et al., 2011; Dolan et al., 2016; Gögenur et al., 2009; Gögenur et al., 2001; Lane & East, 2008; Miller et al., 2015). The sources of the sleep disturbance in surgical patients are patient care interactions, noise, light and postoperative pain.

Objectively measured sleep: Polysomnography and actigraphy. Polysomnography (PSG) is the ‘gold standard’ for measuring sleep (Hirshkowitz, 2017). PSG is commonly used as a sleep assessment to identify sleep stages and to diagnose sleep disorders. Actigraphy is used to measure sleep-wake rhythms with the advantage that it is easy to use, is a continuous measure for as long as two weeks, and is used in clinical settings (Stone & Ancoli-Israel, 2017). A review of 32 studies examined the use of actigraphy to measure the sleep-wake rhythms of hospitalized surgical patients (Madsen, Rosenberg, & Gögenur, 2013). Actigraphy was used to measure pre-and post-operative sleep in 6 general laparoscopic, major or both types of surgery. The total sleep time (TST) was increased in the first two post-operative days in one study of laparoscopic surgery patients. TST and number of awakenings (NAWS) were not changed in the two other laparoscopic studies. Post-operative major abdominal surgery patients increased daytime sleep, sleep efficiency (EFF) was reduced, and wake after sleep onset (WASO) and NAWS were increased.

Immune system and sleep. For centuries, it has been thought that sleep enhances recovery from an illness. During an illness, a person will extend their time in bed, rationalizing that sleep improved the response of the immune system. Research has found that sleep loss is known to have adverse effects on health. In a review by Imeri and Opp (2009), sleep loss was associated with reduced vaccine effectiveness, obesity, impaired glucose tolerance, and cardiovascular inflammatory processes. Sleep behavior is interactive with the immune system. There is bi-directional communication between these two systems. The central nervous system is linked with

innate immunity and antibody-mediated (humoral) immunity responses (Benca & Quintans, 1997; Krueger & Madje, 2003; Opp, 2005; Imeri & Opp, 2009).

Innate immunity inflammatory response. The immune system defends our body, the host, from microbial infection. Innate immune cell-mediated responses provide defense against non-specific infections (Widmaier, Raff & Strang, K.T., 2010). Skin, mucosal surfaces, and secretions are physiological barriers to microbial infections. A breach in these barriers provides an access for bacteria. The invading infectious bacteria will lodge in tissue beneath the site. The immune system initiates a complex response to the microbial invasion and/or tissue injury referred to as *acute phase response (APR)* (Opp & Krueger, 2017). This facilitated host defense by the immune system is driven by multiple mediators and systems.

Acute phase response. Initiation of an acute phase response is to orchestrate the disintegration of microbes at the invasion site. Prostaglandins, cytokines, leukotrienes, and histamines are pro-inflammatory chemical mediators. These mediators in the immune system network become the first responders to the injured and inflamed tissue. The resulting inflammation and edema attracts myeloid cell-descendent neutrophils, later myeloid cell-descendent monocytes. Monocytes are transformed into macrophages. Neutrophils, monocytes and macrophages damage the microbe cells by phagocytosis. Bacteria are enclosed by polymorphonuclear neutrophils (PMN's) and destroyed (Widmaier et al., 2010). Physiologic and behavioral responses include fever, excess sleep, anorexia, and secretion of stress hormones (Opp & Krueger, 2017).

Sleep Associated Cytokines, $IL-1\beta$, $TNF-\alpha$. Cytokines are small protein hormones that stimulate or inhibit normal cell functions. Cytokine cascades in the acute phase response activate the body's immune defense system to attack and destroy the invading bacterial organisms.

Interleukins, interferons, and chemokines are specific types of cytokines which are active in the immune response (Clinton, Davis, Zielinski, Jewett, & Krueger, 2011). Macrophages produce the pro-inflammatory cytokines of tumor necrosis factor (TNF), and interleukin-1 (IL-1). These two cytokines are primary triggers of the acute phase response (Opp & Krueger, 2017). Pro-inflammatory cytokines together with the prostaglandins, leukotrienes, and histamines, increase capillary permeability and vasodilation. These mediators continue in an acute phase response until the microbes are destroyed by the immune phagocytic cells (Harrisons Principles of Internal Medicine, 2012). Cytokines are classified as type I, pro-inflammatory, or type II, anti-inflammatory (Opp & Krueger, 2017). Specific pro-inflammatory cytokines active in the acute phase response promote non-rapid eye movement (NREM) sleep. Known type I, pro-inflammatory sleep associated cytokines are interleukin 1- beta (IL-1 β), and tumor necrosis factor-alpha (TNF- α) (Opp & Krueger, 2017). Anti-inflammatory cytokines active in the acute phase response are sleep inhibitors. Known type II, anti-inflammatory cytokines minimize acute phase response and inhibit spontaneous REM sleep (Clinton et al., 2011). IL-1 β and TNF- α influence sleep patterns, and are usually studied together. Cytokine secretion of IL-1 β and TNF- α occur as a pattern with peaks during sleep. TNF - α has a diurnal rhythm, with a peak at start of daylight (Krueger, 2006). IL-1 plasma concentrations peak at sleep onset (Imeri & Opp 2009).

Interleukin1 (IL-1). Interleukin 1(IL-1) is involved with many processes that occur in the human body. In a review by Dinarello (2011), IL-1 triggers responses in the metabolic, physiologic, hematologic, immunologic, and inflammatory processes. Fever, sleep changes, appetite suppression and sodium excretion are physiologic outcomes affected by IL-1 secretion. During an inflammatory response, IL-1 and TNF are increased, as well as elevation of other

inflammatory markers (Opp & Krueger, 2017) Increased levels of IL-1 β are related to an increase in non-REM sleep (NREM-S) (Krueger, Fang, Taishi, Chen, Kushikata & Gardi, 2006).

Tumor necrosis factor-alpha (TNF- α). TNF- α is considered one of the most important cytokines utilized by the innate immune system for the effective containment of infection (Williams Hematology, 2012). TNF- α is produced by macrophages and stimulates the macrophages to produce IL-1. TNF is “one of many substances . . . that constitutes the *sleep homeostat*” (Clinton et. al., 2014, p. 42). TNF- α is a fatigue-inducing cytokine, resulting in excessive N-REM sleep (Opp & Krueger, 2017).

Sleep pattern and immune studies: animal. Studies of animal sleep provided early landmark information about sleep and the response of the immune system. Four studies examined the effects of an immune system intervention and sleep. Male rabbits were inoculated with *staphylococcus aureus* and sleep was recorded. Findings were increased hours of sleep, elevated body temperature and an increase in blood cell counts (Toth & Krueger, 1988). In a similar study, rats underwent surgery for cecal ligation and puncture to study the effect of sepsis on sleep patterns (Baracchi, Ingiosi, Raymond, & Opp, 2011). The ligation surgical group experienced progressive disruption of their sleep-wake cycle during the four-day post-operative period. Sleep pattern changes were linked with postoperative sepsis. Evenson and Toth (2000) found that sleep deprivation ‘exhausted’ the host defense system. In this study, an abdominal incision was performed-paired rats. One rat experienced the sleep deprivation, and the other rat as control. Two weeks after surgery, rat pairings were examined in 5 day increments. Sleep deprived rats were found to have significantly increased bacterial infected body tissues prior to microbial presence in the blood stream. Restorative sleep, experienced by the paired rat controls, promoted immune function and limited bacterial presence in body tissues. Tang and colleagues

induced colitis in mice to study the effects of sleep deprivation and the severity of tissue damage. They found that acute sleep deprivation accelerated the colonic inflammation of colitis (2009).

Animal studies measured the levels of pro-inflammatory cytokines to further describe the relationship of sleep deprivation and immune response. Cearye, Churchill, and Krueger (2003) studied rats to identify if the brain exhibited a diurnal rhythm of IL-1 β and TNF- α . Rats, which are acclimated to 12-hour light/dark cycles, were sacrificed two hours after light or one hour after dark. Levels of IL-1 β messenger RNA (mRNA) and TNF- α mRNA were found in many regions of the brain. In a 2009 study, inflammatory markers were measured in paired rats who were subjected to 72 hours of sleep deprivation. One of the most significant increases after the sleep deprivation and 7 days later was the measure of IL-1 β as compared to the control rats. An increase was also found in the TNF- α level during both testing times. This study found that an inflammatory response continued after the period of sleep deprivation ended (Yehuda, Sredni, Carasso & Kenifsbuch-Sredni, 2009).

Sleep pattern and inflammatory response: healthy adults. Healthy adult volunteers were participants in seven studies of sleep pattern duration, sleep loss, sleep deprivation, and an associated inflammatory response (Born, Lange, Hansen, Mölle, & Fehm, 1997; Irwin, 2006 & 2010). A landmark study by Born and colleagues in 1997 investigated sleep deprivation and the immune function response of men in a sleep laboratory. During the 24 hours of wakefulness, elevated white blood cell counts, elevated IL-1 β , and elevated TNF- α were found as well as a circadian variation of cortisol. Irwin identified cellular and genomic mechanisms that occur during pro-inflammatory cytokine response to partial sleep deprivation (2006). After the period of sleep deprivation, IL-6 and TNF- α levels were significantly elevated in subjects the morning after sleep deprivation. Irwin's 2010 study was done to determine if gender affected the response

of the inflammatory system to sleep loss. After 4 hours of sleep deprivation, increased production of IL-6 and TNF- α morning levels were found in both sexes. The purpose of a study was to test the hypothesis that REM sleep deprivation would alter the immune response similar to total sleep deprivation. After 2 to 4 nights of total sleep deprivation, there were no significant differences in the percentage of sleep time spent in slow wave sleep and no significant effects on cytokine level of interest, IL-1 β (Ruiz, 2010).

Cortisol and sleep. The corticotropic axis is associated with a stress response. The hypothalamic-pituitary-adrenal (HPA) axis regulates the adrenocortical hormones. The hypothalamus releases corticotrophin-releasing hormone (CRH) that flows to the pituitary to produce adrenocorticotrophic hormone (ACTH) which then is circulated to the target adrenal gland for cortisol hormone production. Cortisol is a negative feedback regulator of cytokine production (Opp & Krueger, 2017). ACTH is also secreted as a negative feedback inhibition, and has a diurnal rhythm and episodic secretions. The peak level of plasma cortisol, outside of stress situations, is from 6:00 a.m. to 8:00 a.m. The lowest level is at midnight. Episodic secretions occur throughout the day. In sleep deprivation, lowest level of cortisol secretion occurs earlier than normal. Sleep onset and sleep offset is absent during sleep deprivation with elevated cortisol levels in the evening (Van Cauter & Tasiali, 2017). Cortisol maintains serum glucose levels, facilitates fat metabolism, supports vascular responsiveness, and immune function. Cortisol, as an inhibitory response, will prevent increased immune activity.

Physiological stress response. Endogenous environmental factors originate from body systems and processes. The physiological parameters of homeostatic stability are disrupted. Many physiological stressors are known to disrupt the sleep pattern of the hospitalized abdominal surgery patients. The physiological stress response to surgery activates the autonomic

nervous system, neuroendocrine and immune system. The autonomic nervous system increases heart rate and rate variability, blood pressure, and myocardial oxygen demand. The neuroendocrine system triggers increased levels of cortisol, epinephrine, and norepinephrine. Decreased resistance to infection occurs in the immune system (Winter, 2012). The intensity of these surgical related stressors influences the intensity of the sleep disturbance, sleep fragmentation, awakenings, pain perception and emotional distress. Cortisol is released as a response to physiological stress.

Surgery and acute phase response. Surgery results in tissue injury which leads to local inflammatory and immune responses to the surgical trauma. These local responses lead to systemic proinflammatory (cytokine) and immune responses known as the APR (Alazawi et al., 2016). Serum cytokine levels rise during the first 24-48 hours after surgery and fall back to normal after 48-96 hours; these levels could remain elevated if complications occur (Weledji, 2014). The magnitude of the rise in cytokine levels is proportional to the severity of tissue injury (Alazawi et al., 2016; Weledji, 2014) and can vary by the site and type of surgery (Alazawi et al., 2106). Overall, the cytokine response is intended to protect the host.

Studies in surgical patients support the idea that cytokines rise after surgery and peak before returning to normal. One study that tracked the systemic cytokine response in patients undergoing elective aortic surgery reported that plasma IL-1 β levels were very low before surgery, peaked at an average of 15 pcg/ml at 2 hours after the first incision, and approached baseline levels at 48 hours (Baigrie et al., 1992). Another study that examined perioperative cytokine responses reported that serum TNF- α levels averaged about 10 pcg/ml before surgery, still averaged about 10 pcg/ml at 12 hours after surgery, but on day 3 after surgery ranged from 15-20 pcg/ml. The 26 subjects in the study were divided into 2 groups based on whether surgery

was major or minor; those undergoing more minor surgeries had a smaller TNF- α response than those undergoing major surgeries (Scheingraber et al., 2005).

Another study of 34 patients undergoing elective surgery for colorectal cancer investigated peritoneal cytokine levels over 5 postoperative days to see if the cytokine levels would be predictive of complications (Ugrás et al., 2008). Patients without complications had cytokine levels decrease significantly over the 5 postoperative days, while those with complications showed increases over the 5 days. Among the cytokines measured, TNF- α levels were high (on average 35,000 pg/ml) in those without complications. This may be related to sample coming from very close to the area of injury in the peritoneum or perhaps due to the diagnosis of cancer. Unfortunately, the study did not report baseline cytokine levels.

Serum surgical stress markers were examined in laparoscopic and open abdominal surgery patients by Tabuchi and colleagues in 2011. Two of the inflammatory cytokines, IL1- β and TNF- α , were measured pre-operatively, and post-operatively on POD1, POD3, and POD7. This study found that IL-1 β and TNF- α were below standard measuring value. A similar study in 2012, major abdominal surgery patients were studied to examine inflammatory response, which included IL1- β and TNF- α , to different anesthesia induction techniques. Blood samples were collected pre-operatively, twice during surgery (T1, T2) and 60 minutes after surgery (T4). All IL1- β values were < 0.8 pg/ml except for T3 measure of 1.0 pg/ml using inhalation induction. The normal range of IL1- β is < 1.0 pg/ml (Kvarnström, A. L., Sarbinowski, R. T., Bengtson, J-P., Bengtsson, A. L., 2012).

A 2016 meta-analysis examined the peritoneal fluid levels of TNF- α , IL1- β and two other interleukins in 5 studies of patients undergoing colorectal surgery. On post-operative days (POD) 1, 2, and 3, those without complications had TNF- α levels that were flat around 0.3 ng/ml, with a

slight increase on POD 4 to about 0.5 ng/ml, and a slight decrease on POD 5. The normal level of TNF- α is < 8.8 picograms/ml, in nanograms (ng), the normal level is 0.088 ng/ml. IL1- β for POD 1, 2, and 3 in those without complications were slightly less than 0.2 ng/ml. Those experiencing complications showed a sharp increase on POD 3. Normal IL1- β level is > 1.0 pg/ml, in nanograms, the normal level is 0.001 ng/ml. (Sparreboom, et al., 2016). No baseline levels were reported and preoperative diagnoses included cancer and inflammatory bowel disease.

Surgery and stress: cortisol. There are few research studies describing how sleep pattern changes during hospitalization affect serum cortisol concentrations. Two studies measured cortisol levels in their study of inflammatory response. Adults undergoing major gastric surgery for gastric cancer also had cortisol levels drawn prior to surgery (Servis, Bisoc, Stipanivic, Patrlj & Gagro, 2008). Three hours after surgery, there was a significant elevation of serum cortisol concentration. A significant fall in serum concentration was found in the 24-hour postoperative sample. A study by Gögenur (2007) examined the relationship of circadian rhythm characteristics before and after major abdominal surgery. Melatonin, cortisol, and core body temperature were measured before surgery and every hour after surgery for 48 hours. Cortisol levels increased the day and night of the first and second postoperative day. No changes were found in melatonin or core body temperature. Ironically, the sleep pattern of the subjects was not studied. This study found that major surgery disturbs these circadian rhythm variables, suggestive of a correlation to sleep pattern changes.

Summary. Sleep patterns during hospitalization, the inflammatory response of the immune system, particularly the pro-inflammatory cytokines associated with sleep, and cortisol as a marker of stress response are the research variables that were reviewed in this chapter. Sleep

disruption during hospitalization has been well-established in the literature. The most frequently reported sources of sleep disruption are delivery of nursing care, noise and light, and pain. In the study of the inflammatory acute phase response, laboratory science animal studies were the subjects of the first studies. These studies of sleep deprivation found that bacterial infections change sleep patterns with elevation of the pro-inflammatory cytokines IL-1 β and TNF- α . In studies of healthy adults, the inflammatory response specific to IL-1 β and TNF- α reported mixed results.

Cortisol was found to be sensitive to sleep disruption in healthy adults. Major surgery initiates a stress response which includes the release of cortisol. The reviewed studies did not provide a definitive finding on serum cortisol levels during the post-operative period.

Conceptual Model

Neuman's Systems Model

Person. The Neuman's Systems Model (NSM) defines a human being as *client*. Client is depicted as concentric circles around a center circle. This center circle, termed *Basic Structure*, contain the core systems which support life. Examples of the core systems are thermo-regulatory, genetic structure, and ego structure. Three concentric circles with boundaries of dashed lines are identified as *Lines of Resistance*. The lines of resistance are dashed as tension-producing stimuli are capable of penetrating the boundaries to affect the basic structure circle. Gigliotti (1997) states that "the lines of resistance are mediators" which block the effect of a stressor reaction which has penetrated the lines of defense (p.138). Outside the lines of resistance, there is a circle with a solid line boundary defined as the *Normal Line of Defense*. The normal line of defense is our "usual wellness level, which has evolved over time" (Neuman, 2002, p.17). The normal line of defense is the health that is considered normal for a client. The outermost circle has dashed

lines. This is termed as the *Flexible Line of Defense*. It has an accordion-like structure in that it is capable of contracting or expanding depending on the stimuli. The flexible line of defense “acts as a protective buffer system for the client’s normal or stable state” (Neuman, 2002, p.17). Gigliotti (1997) clarifies that “variables in the flexible line of defense are situational”, and “are subject to rapid change”. . . “the flexible line of defense is conceptually a moderator (cushion)” (p. 138). Surgery, an external environmental stressor, penetrates both physiological external lines of defense, and lines of resistance. Surgical trauma occurs as a result of organ manipulation. The basic structure of the person is physiologically supported to maintain homeostasis during surgery and the recovery period. Anesthesia and narcotic pain management will influence sleep patterns for the next 48 or more hours. Surgery most likely disrupts the established sleep pattern.

The client system contains five variables that interact in all circles from the inner center basic structure core to the outer flexible line of defense. These variables are: physiological, psychological, sociocultural, developmental, and spiritual (Neuman, 2002, p. 16). Neuman states “the first four are commonly understood by nurses and members of other health professions”. The spiritual variable is considered as a spiritual energy force, or “seed” which has environmental “catalysts”; and is manifested in energy “for use first by the mind and then by the body” (Neuman, 2002, p. 16). Appendix A depicts the client system. Three physiological system variables will be studied. Sleep pattern, the innate immune system inflammatory response, and physiologic stress are the variables of this study.

Environment. The NSM identifies three conceptualizations of the environment. They are the external, internal, and created environment (Neuman, 2002, p. 18). The *external* environment consists of all factors that exist outside of the client. There are inter- and extra-personal external environmental stimuli that affect the client system. Conversely, the *internal* environment consists

of all factors within the client system. Intrapersonal stimuli originate in the internal environment. Unique to the NSM is the *created* environment. Neuman (2002) describes this as follows:

“The created environment is an open system exchanging energy with both the internal and external environment; . . . developed unconsciously by the client, is a symbolic expression of system wholeness. . . . represents the client’s unconscious mobilization of all system variables; its function is to offer a protective perceptive coping shield”. (p. 19-20).

The post-operative surgical inpatients’ created environment will exchange energy with their individual and unique, known and unknown, internal and external physiological and psychological stressors to begin reconstitution to wellness.

After surgery, a secondary prevention is treatment of symptoms. Tertiary prevention begins re-adaptation to a stable wellness sleep pattern. After the first 48 hours of the postoperative period, the effects of surgery lessen and the sleep pattern begins to normalize.

Stressors. The environment and client maintain a flow of energy. This interactive relationship between the client and the environment strives to maintain a balance. There are factors in the created, internal, and external environment that exert influences and/or stimuli on the client. These influences/stimuli are termed as *stressors*. The NSM defines stressors as “tension-producing stimuli or forces.” . . . Stressors are neutral; the client’s perception and encounter of the stressor will determine if there is a positive or negative effect” (Neuman, 2002, p. 21). *Intrapersonal stressors* are forces *within* a client that initiate tension-producing stimuli which have potential for causing client system instability resulting in a positive or negative reaction response. Intrapersonal stressors are found only in the internal environment of the client. *Interpersonal stressors* are forces *between* the internal and external environment of the client that

can initiate tension-producing stimuli which have the potential for causing client system instability with a positive or negative reaction response. *Extrapersonal stressors* are forces *outside* of the person that initiate tension - producing stimuli which have the potential for causing client system instability with a positive or negative reaction response (Neuman, 2002, p.18). Inter- and extrapersonal stressors are in the external environment. Surgery exerts an influence, as a stressor, within the person; between the internal and external environments; and extrapersonal stressors outside of the person. Sleep after major abdominal surgery may be a positive or negative experience.

Relational Statements. The primary focus in using this systems-based conceptual model is the human being (client)-environment interaction. This interaction is dynamic, ongoing, and reciprocal as the human being responds to “known, unknown, and universal environmental stressors” (Fawcett, 2005, p.177). NSM states that “a continuous relationship exists between the client and the environmental stress factors” (Neuman, 2002, p.3). The flexible line of defense functions as a protective buffer system for the client’s normal line of defense. The normal line of defense is the usual wellness of the system (Neuman, 2002, p. 17). The lines of resistance protect the human being’s basic core structure from damaging environmental stressor influence. Situational variables are found at the flexible line of defense. Within the normal line of defense and lines of resistance, learned variables provide client system stability.

Sleep as an innate physiological process can be characterized by using the NSM client system. Established, usual sleep patterns of the person represent the normal line of defense from harmful environmental stress factors. The flexible line of defense fluctuates to protect the client system from situational environmental variables. A stressor that has penetrated the normal line of

defense will affect the usual sleep pattern with changes in sleep length and/or continuity. Appendix A is construct/concept diagram.

Theoretical Framework

The NSM provides a theoretical framework to study sleep/wake patterns to identify the interactive energy exchange between the physiological systems of the human being and the environment. The person is linked by stressors to the environment. Client system stability is the balance between the person and the environment. This constant exchange “reflects the reciprocal interaction world view” (Fawcett, 2005, p. 169). This theoretical framework identifies the interactive energy exchange between the physiological systems of the human being and the environment.

Physiological systems of the sleep and immune response of the person will be in constant interaction within the hospital environment. The person is interactive to the exogenous sleep stressors of noise, light, delivery of care and pain in the hospital. The person is interactive to surgery associated endogenous stressors related to the abdominal surgical trauma, the acute phase response of the immune system and a stress response. Penetration of the normal line of defense will affect physiological sleep homeostasis and innate immune system homeostasis. Further penetration of the physiological lines of resistance will produce sleep disturbance, the acute phase response cytokine IL-1 β , TNF- α release and the stress response of cortisol. Appendix B Figure depicts the Theoretical Framework concepts of person, environment, lines of defense, and environmental stressors and physiological responses.

CHAPTER 3 METHOD

Design

The design for this study is descriptive and correlational. This nonexperimental study describes subjective and objective sleep, immunological acute phase responses, and stress responses in postoperative hospitalized adults. Correlations between sleep disturbance, acute phase response cytokines, and the physiological stress response were calculated.

Human Subjects Protection

Wayne State University (WSU) Human Investigation Committee approved the study protocol prior to the implementation of the study. Allina Health Systems, parent company of Abbott-Northwestern Hospital in Minneapolis, Minnesota reviewed and accepted study protocol. Quorum Review Board serves as the Institutional Review Board (IRB) for Allina Health. After review, Quorum IRB approved the study. Prior to the institutional reviews of the proposed study, the required Institutional Review Board (IRB) and HIPAA seminars were completed. Allina Health Systems granted access to the enrolled subjects' electronic medical records.

Confidentiality. The Health Insurance Portability Accountability Act (HIPAA) Privacy Rule is to protect the individual identifiable health information of subjects (OCR HIPAA Privacy, 2003). Potential subjects were informed of HIPAA regulations, and were given the written plan to maintain confidentiality. Informed consent was obtained prior to enrollment into the study. After enrollment, study participants were identified only by code number. Electronic Medical Record (EMR) documents that identified the participant's name and any other identifying information were cut off the printed record prior to leaving the nursing study unit. Only the participant's code number was on the document. Collected samples were identified,

tested, and results reported by the participant's code. All data collected during the study period were recorded, analyzed, and reported by the study participant's code number.

Record keeping. Written documents, including subject completion of study instruments and printed EMR records, have been kept by the researcher in a locked file box at a secure site, off-campus of Abbott-Northwestern Hospital.

Sample

A convenience sample of 22 adults, 21 to 65 years of age, undergoing abdominal surgery, was recruited; 2 participants did not meet study criteria and one declined stating data collection would be too early in the morning. Inclusion criteria for participation included: adults, male and female, 18 to 60 years of age; ability to read, write and understand English at sixth grade level; cognitive ability to consent to participate in the study; hospitalization of a 4-day minimum after invasive incision abdominal surgery; willingness to wear a wrist actigraph 24 hours a day during the study period; and willingness to provide saliva samples.

Exclusion criteria included: diagnosed sleep, seizure, or psychiatric disorder; routine use of anticonvulsants, antidepressants, antihistamines, barbiturates, opioids or selective serotonin reuptake inhibitors, one month prior to study; body mass index (BMI) of 40 or greater; reported symptoms of nocturia; women experiencing menopause symptoms; presence of co-morbid disease, including a known inflammatory disorder; routine use of medication, such as nonsteroidal anti-inflammatory drugs or corticosteroids, that affect inflammation one month prior to study; and employed nights as the primary work shift.

The above exclusion criteria are factors that may affect sleep or the inflammatory response. Sleep disorder treatment by medications or specialized equipment lowers the occurrence of disturbed sleep thus eliminating a natural sleep pattern. Medications prescribed for

seizures and psychiatric diagnoses are associated with somnolence and sedation. Corticosteroids and non-steroidal anti-inflammatory drugs suppress the immune system response. Obesity and increased neck size are significant risk factors for obstructive sleep apnea (Greenberg, Lakticova, & Scharf, 2017). Nighttime awakening occurs with nocturia and menopausal symptoms of disturbed sleep and trouble sleeping (Baker, Jaffe, & Lee, 2017). Exclusion of adults with comorbid diseases eliminates the potential for other factors causing changes in proinflammatory cytokines. Adults who work night-time shifts will experience circadian misalignment (Drake & Wright, 2011).

Recruitment. Surgeons who perform abdominal and/or colon-rectal surgery were contacted for referrals of potential subjects. The physicians provided verbal information about the study to the subject. The physician or the surgery scheduler in their respective offices provided contact information for the researcher to telephone the potential subject.

Adults referred to the Allina Health Virginia Piper Institute (VPI) meet with oncology physicians and nurses. A specialty Nurse Coordinator establishes a relationship with the patient upon intake, and then continues to serve as their primary contact as long as the person remains enrolled in VPI. The Colorectal Nurse Coordinator and the Cancer Care Nurse Coordinator also referred potential subjects to the researcher.

All potential subjects received a phone call from the researcher. Information about the study was provided. Enrollment into the study occurred during a face to face meeting either at a meeting prior to surgical date or on the morning of admission in Preoperative Unit.

Power analysis prior to study commencement suggested 92 participants should be recruited. However, recruitment of participants proved to be difficult. Many adults scheduled for abdominal surgery were over 60 years of age. Also, the advent of technologic improvements

resulted in fewer patients having open abdominal surgery and more individuals undergoing laparoscopic procedures. For these reasons, IRB approval was obtained to increase age to 65 years for study inclusion and to recruit individuals undergoing open or laparoscopic abdominal surgery.

Setting

Four inpatient care units in a 627-bed acute care hospital in Minneapolis, Minnesota were used for subject data collection.

Major Study Variables

The major variables were subjectively and objectively measured sleep, inflammatory response variables, and stress response variables. In Neumann's System Model, a nursing model which guided the conduct of this study, these major variables are interacting life processes of the person's physiological fluidity.

Measurements

Sleep. Conceptually sleep is an innate continuous cyclic, rhythmic pattern of fluctuation in depth of sleep, oscillation of regulatory body systems, and a decreased response to perceptive environmental stressors. Due to the influence of physiologic factors, sleep occurs predominantly at night. Sleep is a physiological process that is restorative and necessary to maintain life. Sleep, as a physiological process, is observable and measurable. Upon awakening from sleep, however, a person's perception of sleep may differ from objectively measured sleep. For that reason, subjective perception of sleep was measured, as well as objectively measured sleep.

Perception of sleep. The perception of sleep is defined as an outcome that occurs after an uninterrupted time period of disengagement from purposeful interaction with the environment and in which the physiological system energy returns to a state of balance. The individual's

perception of sleep was measured by the Verran and Snyder-Halpern (VSH) Sleep Scale (Snyder-Halpern & Verran, 1987). The VHS uses 3 scales to measure subjective sleep quality: sleep disturbance, sleep effectiveness, and sleep supplementation. The sleep disturbance scale assesses sleep fragmentation and latency as measured by 7 items. Fragmentation characteristics include mid-sleep awakening, wake after sleep onset, movement during sleep, soundness of sleep, and quality of disturbance. Latency characteristics include sleep latency and quality of latency. Sleep effectiveness, the individual's perception of sleep quality and length, is evaluated by 5 items: rest upon awakening, subjective sleep quality, sleep sufficiency evaluation, total sleep time, and total sleep period. Sleep supplementation, which is the degree to which the bulk sleep time is supplemented with additional sleep time, is measured by 4 items: daytime sleep, morning sleep, afternoon sleep, and wake after final arousal. Each characteristic is measured using a 100-mm visual analogue scale and the total score for the sum of the scores from each scale. The maximum score for sleep disturbance is 700. A lower total score on this scale indicates a lower degree of sleep disturbance. The maximum score for sleep effectiveness is 500 with a higher score representing greater sleep effectiveness. The maximum score for the sleep supplementation scale is 400 with higher scores indicating more supplemental sleep was needed. The VSH Sleep Scale also includes descriptive questions on current stress, present illness, and routine to achieve sleep. The VSH Sleep Scale has been used in a variety of research studies and has established reliability and validity (Redeker, Tamburri, & Howland, 1999). The questionnaire reliability coefficient, using theta, is 0.79 (Snyder-Halpern & Verran, 1987). Test-retest reliability coefficients ranged from 0.70 to 0.96. Construct validity was assessed by factor analysis and by correlations between this scale and two others (Snyder-Halpern & Verran, 1990).

Sleep quality is defined conceptually as the degree to which the sleep experience meets the individual's needs and expectations for sleep. Operationally sleep quality was indexed by the mean score on the Subjective Sleep Quality Questionnaire (Smith & Davis, 1987) (Appendix 3). This scale is a 14-item 6-point response Likert type scale with two subscales: quality of sleep (5 items) and effect of sleep (9 items). The scale responses range from 1 (strongly agree) to 6 (strongly disagree). The scale has been tested for reliability and validity with older adult populations. Item to item, item to subscale, and item to total scale correlations fell within the acceptable range of 0.70 as recommended by Nunnally (1978). Sleep Quality Questionnaire was used to measure sleep quality in the morning following each night in a sleep laboratory.

Sleep pattern. Sleep patterns will change with significant life-changing events, career changes, and physiologic influences in health and aging. For the purposes of this study, sleep pattern is defined as the repetitive behavior associated with the known physiological and psychological processes of sleep. Subjects were asked about their usual time before they get into bed for sleep as well as their usual awakening time. This information was collected with the Demographic & Additional Data Worksheet (Appendix D), an open-ended investigator-developed questionnaire. .

Objectively measured sleep. Wrist actigraphy was used to objectively measure sleep onset latency, sleep efficiency, sleep fragmentation, wake after sleep period, total sleep time, and daytime sleep supplementation periods. Recent sleep literature supports that actigraphy is an adequately reliable tool for producing objective measures of sleep (Rupp & Balkin, 2011). Actigraphy reliability is 0.89 to 0.98 for adults with normal sleep patterns (Stone & Ancoli-Israel, 2017).

The Actiwatch 2 (Phillips Respironics) was used for successive 24 hour periods of study. This wrist-watch type actigraph is a non-invasive, waterproof device that is worn on the wrist of the non-dominant hand. Data is recorded as digitally-integrated measures of gross motor activity that can be used to determine activity patterns or sleep. The actigraph recorded in 15 second intervals. These intervals are termed *epochs*. Epochs can be up to 1 minute in length. Actigraph 2 continuously recorded the sleep/wake history and physical activity with an event marker to record events of significance. The Actigraph 2 also recorded ambient light. When the actigraph was removed from the subject, the recorded information was downloaded into a personal computer that had the Actigraph 2 software program. The sleep/wake history download provided objective measures of sleep onset latency (time to fall asleep), sleep fragmentation (number of awakenings longer than 5 minutes), wake after sleep onset, total sleep time, total sleep period and daytime sleep supplementation. Sleep efficiency was calculated by dividing total sleep time by total sleep period.

Immunologic Acute Phase Response to Major Surgery. An incision with subsequent injury to tissue and body organs initiates the inflammatory response. Cellular level inflammation occurs as the result of the tissue injury and in proportion to the surgical trauma. The activated leukocytes and damaged endothelial cells at the site of injury produce cytokines that mediate the inflammatory response to injury and also initiate systemic inflammatory responses. The key cytokines released from activated leukocytes after surgery include interleukin-1 (IL-1), tumor necrosis factor- α (TNF- α), and IL-6 (Desborough, 2000). Two of these inflammatory cytokines, interleukin 1-beta (IL-1 β) and tumor necrosis factor – alpha (TNF- α), are associated with sleep and were measured as markers of the inflammatory response to surgery.

Test Site for Cytokine Analysis: Samples were tested by the Cytokine Reference Laboratory (CRL, University of Minnesota). This is a CLIA'88 licensed facility (license #24D0931212). The laboratory occupies 800 ft² and is located on the East Bank of the UMN campus in room 13-127 of the Phillips-Wangensteen Building, 516 Delaware St. SE., Minneapolis MN, 55455 (tel. 612-626-7057). This facility has extensive experience in the analysis of cytokines, chemokines and growth factors from a variety of biological sources. Dr. Mortari is also board-certified by the American Board of Medical Laboratory Immunology, the highest certification available to direct such a facility. The CRL has participated as a testing laboratory for many clinical trials over the past 20 years and is well experienced with immunoassays using ELISA (conventional as well as multiplex ELISA) and fluorescence bead-based antibody systems (Luminex platform) that allow multiple assays on a very small amount of material. Technical Personnel. Samples were analyzed by Mr. Michael Ehrhardt, BSc. Analysis Date. Samples were analyzed on 6-9-2016.

Materials. Samples were analyzed for IL-1beta, & TNF alpha using the Luminex platform and done as a high sensitivity multiplex. The magnetic bead set (cat. # LBHS000) were purchased from R&D Systems. The kit lot number was 339266. Samples were analyzed for Cortisol using the ELISA method and purchased from Alpco (cat. #11-CORHU-E01-SLV). The kit lot number was 160500.

Methods: Luminex. Samples were assayed according to manufacturer's instructions. Fluorescent color-coded beads coated with a specific capture antibody were added to each sample. After incubation, and washing, biotinylated detection antibody was added followed by phycoerythrin-conjugated streptavidin. The beads were read on a Luminex instrument (Bioplex 200) which is dual-laser fluidics based instrument. One laser determines the analyte being

detected via the color coding; the other measures the magnitude of the PE signal from the detection antibody which is proportional to the amount of analyte bound to the bead. Samples were run in duplicate and values were interpolated from 5-parameter fitted standard curves.

Methods: ELISA. Samples were assayed according to manufacturer's instructions. The assay follows the typical competitive binding scenario. Competition occurs between an unlabeled antigen (present in standards, controls and samples) and an enzyme-labeled antigen (conjugate) for limited number of antibody binding sites on the microwell plate. The washing and decanting procedures remove unbound materials. After the washing step, the enzyme substrate is added. The enzymatic reaction is terminated by addition of the stop solution. The absorbance is measured on the microtiter plate reader (Bio-Rad Model 550). The intensity of the color formed

Salivary IL-1 β , TNF- α . Submitted saliva samples were analyzed in the Cytokine Reference Laboratory at the University of Minnesota, Twin Cities. The laboratory is a CLIA-88 licensed Facility. Each SalivaBio Oral Swab (SOS) sample was tested using the following the procedure outlined by Salimetrics. A microtitre plate is coated with mouse antibodies to IL-1 β . IL-1 β in both the standards and the unknowns attach to the antibody binding sites. Plate is then incubated at room temperature for 1 hour, mixing constantly at 500 rpm. Plate is washed 4 times in a plate washer and blotted after last wash. Biotin conjugated to goat antibodies to human IL-1 β are added and attach to the bound IL-1 β . Plate is then incubated at room temperature for 2 hours, mixing constantly at 500 rpm. Plate is washed 4 times in a plate washer and blotted after last wash. Streptavidin conjugated to horseradish-peroxidase is then added and binds to the biotin conjugated to the goat antibodies. This is incubated for 20 minutes at room temperature, mixing constantly at 500 rpm. Tetramethylbenzidine solution is added to each well and the plate is incubated in the dark at room temperature for 20 minutes, mixing constantly at 500 rpm. Stop

solution is then added and mixed on a plate rotator for 3 minutes at 500 rpm until all wells have turned yellow. Results are read in a plate reader at 450nm within 10 minutes of adding stop solution.

Physiological stress response to surgery. Surgical intervention will initiate physiological stress, which includes the release of cortisol from the adrenal cortex. Diurnal variation occurs in cortisol levels with a peak in the early morning. After the 0600 to 0800 peak, levels begin to decline. Saliva was assessed for a cortisol level. The saliva samples that were collected at time of admission and after the third night of sleep in the hospital at 6 a.m. and 6 p.m. Another response to the stress of surgery is activation of the sympathetic nervous system (SNS). Anxiety, restlessness, and postoperative distress will elevate blood pressure (Winters, 2012). Cortisol can influence the cardiovascular system as evidenced by elevated heart rate, variability of heart rate, elevated blood pressure, and increased myocardial demand as evidenced by increased respiratory rate (Winters, 2012 p.98). SNS activation was assessed by review of vital signs in the EMR.

Salivary Cortisol Analysis. Submitted saliva samples were analyzed in the Cytokine Reference Laboratory at the University of Minnesota, Twin Cities. Each SalivaBio Oral Swab (SOS) sample was tested using the following the procedure outlined by Salimetrics. High Sensitivity Salivary Cortisol Enzyme Immunoassay Kit No. 1-3002 (Salimetrics, LLC, State College, PA) and following the procedure outlined by Salimetrics. A microtitre plate is coated with monoclonal antibodies to cortisol. Cortisol in standards and unknowns competes with cortisol linked to horseradish peroxidase for the antibody binding sites. The plate is mixed on rotator for 5 minutes at 500 rpm and incubated at room temperature for an additional 55 minutes. The plate is washed 4 times in a plate washer and blotted dry after last wash.

Tetramethylbenzidine solution is added to each well and plate is mixed on a plate rotator for 5 minutes at 500 rpm and incubated in the dark at room temperature for an additional 25 minutes. Stop solution is then added and plate is mixed on a plate rotator for 3 minutes at 500 rpm and read in a plate reader at 450nm within 10 minutes of adding stop solution.

Data Collection Procedure

The baseline saliva sample was collected from the subject after consent and admission into the research study prior to admission to the hospital. Most subjects were consented in the pre-operative admission unit. Two subjects were consented during a pre-operative visit to the hospital. The Demographic and Additional Information Forms were completed when the information was available after post-surgical admission to an inpatient unit.

The actigraphy unit was applied to the wrist of the subject's non-dominant hand within 3 hours of admission to the inpatient unit after surgery. The actigraph was set to record for 144 hours. The Actigraph 2 also recorded ambient light levels.

Subjects completed the VSH Sleep Scale in the morning within 90 minutes of awakening after the third night of sleep. The Sleep Quality scale was administered within 90 minutes of awakening after the fourth night of the study.

A sample of saliva was collected at 6 a.m. and 6 p.m. to measure the levels of TNF- α , IL-1 β , and cortisol. The samples were obtained beginning on post-operative day four after the third night of sleep on an inpatient surgical unit.

Procedure for Collecting Saliva. Saliva was collected within 30 minutes before or after 6 a.m. in the morning and 30 minutes before or after 6 p.m. in the evening. A SalivaBio Oral Swab (SOS) was used to collect saliva. Ten minutes prior to collecting the saliva sample, the subject rinsed their mouth thoroughly with water. The subject told the researcher when saliva

was pooling in under the tongue. The 3 mm swab was inserted for a minimum of 1 minute to saturate the swab. The saturated swab was collected from the subject and placed in a Swab Storage Tube. The tube was labeled with subject ID, date, and time of specimen collection. Samples were placed in a small plastic bag and then placed in an insulated bag with a blue ice-pack. Samples were placed into a freezer within 2 hours of collection time. Samples were delivered by the researcher to the Cytokine Reference Laboratory on the University of Minnesota campus. Samples were placed in laboratory freezer.

Additional demographic data were collected from the EMR, including age, sex, vital signs (pulse, respiratory rate, blood pressure, temperature) and the subject's pain levels. Documentation in the EMR was reviewed for surgical procedure, postoperative physician notes, medication administration, daily laboratory reports and any notations about sleep. The EMR at the research site is an interdisciplinary record and provided comprehensive progress notes. The researcher collected the data from this record.

Data Analysis

IBM SPSS version 23 was used to analyze the data. Demographic and surgery-related data were described with descriptive statistics.

Specific Aim 1. To characterize the subjective sleep experience of hospitalized patients after major abdominal surgery.

Research question 1. What are the characteristics of the subjective sleep experience in hospitalized patients after major abdominal surgery?

The VSH Sleep Scale, a subjective measure of perceptions about sleep characteristics, during the previous night yielded the following variables: sleep disturbance, sleep fragmentation, and sleep

supplementation. The SSQ measured overall perception of sleep quality. Statistical analyses included means, standard deviations and inclusive range.

Specific Aim 2. To objectively assess the sleep of hospitalized patients after major abdominal surgery using actigraphy.

Research question 2. What is the objective assessment of the sleep in hospitalized patients after major abdominal surgery using actigraphy?

Actigraphy. The use of actigraphy yielded the following sleep measures: time in bed, total sleep time, sleep latency, sleep efficiency, number of awakenings after sleep onset, and number of awakenings during night-time sleep after admission to their hospital room until discharge. Descriptive statistics including mean, standard deviation and inclusive range were applied.

Specific Aim 3. The cytokines, IL-1 β and TNF- α , were assessed before surgery and on day 3 postoperatively. Statistical analyses included means, standard deviations and inclusive range.

Research question 3. What is the immunological acute phase response, as measured by Interleukin 1- beta (IL1- β) and Tumor necrosis factor-alpha (TNF- α) in hospitalized patients after major abdominal surgery? What is the physiologic stress response, as measured by cortisol, in hospitalized patients after major abdominal surgery?

Specific Aim 4. To examine the relationships among objective and subjective sleep, immune acute phase responses, and stress responses in patients who have undergone major surgery. Correlations among the major study variables were determined.

Research question 4. What are the relationships among objective and subjective sleep, immune acute phase responses, and stress response in patients who have undergone major abdominal surgery?

CHAPTER 4 RESULTS

Subject Characteristics. The sample consisted of 19 subjects, with 9 women and 10 men. Age ranged from 25 to 60 years of age. Eleven of the subjects were married, 6 subjects were divorced, and 2 subjects were single. Recruitment began on April 2, 2015. The last day to enroll subjects was March 30, 2016. Table 1 describes characteristics of the sample.

Major abdominal surgery was performed on all study subjects. There were 10 laparoscopic surgeries and 9 incisional surgeries. Laparoscopic surgical procedures included sigmoid resections, anterior resections with an ileostomy or colostomy, and a hemicolectomy. Major surgeries with an abdominal incision were sigmoid resections, anterior resections, and exploratory laparotomies resulting in a colostomy or ileostomy. The hospitalization length of stay ranged from 4 to 11 days, with an average length of stay of 5.75 days. Table 2 lists surgical procedures and length of stay.

Research question 1. What are the characteristics of the subjective sleep experience in hospitalized patients after major abdominal surgery?

Sleep. The Verran & Snyder –Halpern (VSH) Sleep Scale, a subjective measure of perceptions about sleep characteristics during the previous night, examines the following scale sleep characteristics and variables: disturbance, effectiveness, and sleep supplementation. Individual VSH Sleep Scale characteristic scores ranged from 0 to 100. A scale score of 0 corresponds to the least and a score of 100 corresponds to greatest. Table 3 presents the VSH Disturbance Scale, a composite numerical score of fragmentation and latency characteristics. The Effectiveness Scale is a composite numerical score of quality and length characteristics. The Supplementation Scale is a composite numerical score of additional sleep time after the nighttime sleep period.

Disturbance scale measures five fragmentation characteristics and two latency characteristics. The maximum score for sleep disturbance is 700. A higher total score on this scale indicates a higher degree of sleep disturbance. The sample of 19 subjects reported sleep disturbance after the third night of sleep in the hospital with a minimum of 82 and maximum of 588, mean = 331.26 (SD = 126.46). All subjects reported fragmentation characteristics after the third night of sleep in the hospital with a minimum of 44 to maximum 392; mean= 254.95 (SD = 83.07). Sleep fragmentation was the measure of mid-sleep awakening (MSA) with a minimum of 11 to maximum 95; mean = 67.89 (SD = 24.91); wake after sleep onset (WASO) with a minimum of 13 to 82 maximum, mean = 45.53 (SD= 19.483); movement during sleep (MDS) with a minimum of 4 to maximum 85, mean = 36.63 (SD= 24.99); soundness of sleep (SS) with a minimum of 5 to maximum of 85, mean = 50.68 (SD = 22.83), and quality of disturbance (QOD) with a minimum of 11 to maximum 90, mean = 54.21 (SD = 23.19). The sleep latency (SL) characteristics of the 19 subjects were a minimum of 8 to maximum 196; mean 76.32 (SD = 61.93) and quality of the latency (QL) was a minimum of 55 to maximum 296; mean = 166.79 (SD = 61.93).

Effectiveness scale, which is the individual's perception of sleep quality and length, was assessed by quality and length characteristics. The maximum score for sleep effectiveness is 500 with a higher score representing greater sleep effectiveness. The sample of all 19 subjects were a cumulative minimum of 156 to a maximum of 583, mean = 333.11 (SD = 92.30). Sleep Quality characteristics of the 19 subjects were a minimum of 55 to maximum 296, mean = 166.79 (SD = 52.37). Subjects did report upon awakening, they felt rested and experienced quality sleep after the third night of sleep in the hospital. The sleep quality characteristics were rest upon awakening (RUA) with a minimum of 0 to maximum 100, mean = 54.79 (SD = 27.86),

subjective quality of sleep (SQS) with a minimum of 12 to maximum 100, mean = 53.21 (SD = 29.40), and sleep sufficiency (SSE) evaluation with a minimum of 2 to maximum 98, mean = 58.79 (SD =27.16). Two length characteristics were total sleep time (TST) with a minimum of 0 to a maximum 98, mean = 58.42, (SD=22.33) and total sleep period (TSP) with a minimum of 29 to a maximum 189, mean = 107.89 (SD = 33.71).

Supplementation scale measures 4 augmented sleep periods additional to the night-time sleep period. Individual supplemental sleep characteristic scores ranged from 0 to 100. The maximum score for the sleep supplementation scale is 400 with higher scores indicating more supplemental sleep was needed. Supplementation scores for the sample of 19 subjects ranged from a minimum of 7 to maximum of 315, mean = 185.68 (SD = 86.96). Supplementation sleep individual scores after the third night of sleep in the hospital ranged from a minimum score of 1 to maximum scores in the 90's, with a mean range of 38 to 49. The sample of 19 subjects reported supplementation characteristic variables of daytime sleep (DTS) which were a minimum of 1 to maximum 95, mean = 38.21, SD = 27.09), morning sleep (AMS) with a minimum of 0 to maximum of 94, mean = 53.16 (SD 31.75), afternoon sleep (PMS) with a minimum of 1 to maximum 90, mean =49.95 (SD=28.85). A sample of 18 subjects reported awake after final arousal (WAFA) with a minimum of 3 to maximum 95, mean = 46.83 (SD= 29.02). One subject did not make a mark for the WAFA scale.

Subjective sleep quality questionnaire (SSQQ) measures overall perception of the sleep experience that meets the individual needs and expectations for sleep. The results of the SSQQ were reported by a single value, with the highest possible score of 6, the better the perceived sleep quality. Eighteen subjects completed the SSQQ after the fourth night of sleep in the

hospital. The SQQS had a minimum of 1.78 to maximum 5.14, mean score of 3.28 (SD = 1.05). Table 3 displays the SQQS scores for the fourth night of hospitalization.

Research question 2. What is the objective assessment of the sleep in hospitalized patients after major abdominal surgery using actigraphy?

Actigraphy is an objective continuous measurement of the sleep variables (a) time in bed (TIB), (b) total sleep time (TST), (c) sleep latency (SL), (d) sleep efficiency (SE), (e) wake after sleep onset (WASO), and (f) night-time awakening (AWS). Continuous recording began upon admission to an inpatient room, day 1, to the morning of discharge.

Time in bed is a measure, expressed in hours, of the period of time to bed to out of bed during each 24-hour block of recording time. Hours and minutes were calculated to total minutes. Seventeen subjects on day 1 spent a minimum of 403 to a maximum of 1219 minutes, mean = 701.94 (SD = 230.73) Sixteen subjects on day 2 spent a minimum of 10 to a maximum of 1276 minutes, mean = 624.13 (SD = 278.423). Sixteen subjects on day 3 spent a minimum of 63 to a maximum of 899 minutes, mean = 561.81 (SD = 239.57). Fifteen subjects on day 4 spent a minimum of 270 to a maximum of 1388 minutes, mean = 601.67 (SD = 265.05). Table 4 presents descriptive statistics for the total sleep, time in bed, sleep latency, sleep efficiency, wake after sleep onset, and nighttime awakenings.

Total sleep time is a measure, expressed in hours, of the sleep time during the time in bed during each recording period. Hours and minutes were calculated to total minutes. Seventeen subjects on Day 1, were a sleep time, minimum of 245 to a maximum of 1019 minutes, mean = 535.59 (SD = 192.85). Data was collected for 16 subjects on day 2 and 3. The day 2 minutes were a minimum of 105 to a maximum of 804 minutes, mean = 447.56 (SD = 207.09). The day 3 minutes were a minimum of 11 to a maximum of 733 minutes, mean = 384.13 (SD = 218.25).

Fifteen subjects on day 4, the minutes were a minimum of 0 to a maximum of 1352, mean= 419.40 (SD =301.11) One subject, with 0 minutes of TST, signifies that there was an absence of sleep during the night-time hours. RM-ANOVA showed that total sleep time decreased significantly on the days after surgery, $F=2.93$; $df=3$, $p < 0.05$.

Sleep latency is a measure of the time starting after getting into bed until falling asleep. A score of 0 corresponds to falling asleep immediately after getting into bed. Fifteen subjects on day 1 experienced a latency time minimum of 0 to a maximum of 175.25 minutes. Sixteen subjects on day 2 experienced a latency time minimum of 0 to a maximum of 325.75 minutes, mean = 78.28 (SD = 43.80). Day 3 for 16 subjects experienced a latency time minimum of 1.50 to a maximum of 183.00 minutes, mean = 50.07 (SD = 56.79). Fourteen subjects on day 4 experienced latency a minimum of 0 to a maximum of 102.50 minutes, mean = 31.64 (SD = 33.63)

Sleep efficiency measures the percentage of sleep to time in bed. Seventeen subjects on Day 1 experienced an efficiency minimum of 37.05% to a maximum of 94.70%, mean = 78.01 (SD = 15.58). Day 2 with 16 subjects experienced a sleep efficiency minimum of 19.55% to a maximum 91.00%, mean = 66.59 (SD =20.85). Day 3 with 16 subjects experienced an efficiency minimum of 1% to a maximum 88.19%, mean = 67.00 (SD = 23.83). Fourteen subjects on day 4 experienced an efficiency minimum of 0 to a maximum 86.99%., mean = 54.91 (SD = 30.35). RM-ANOVA showed that sleep efficiency decreased significantly on the days after surgery, $F=6.29$; $df=3$, $p =.0001$.

Wake after sleep onset measures the minutes of wakening during the night-time sleep period. A score of 0 corresponds to no waking during the night-time sleep period. Seventeen subjects on day 1 experienced in minutes, a minimum time of 0 to maximum 388.50 minutes,

mean=106.35 (SD = 111.11) Sixteen subjects on day 2 experienced in minutes a minimum of 8.25 to a maximum of 161.00, mean = 94.03 (SD = 46.62). Day 3 results for 16 subjects experienced in minutes a minimum time of 0.50 to a maximum of 144.50, mean = 63.82 (SD = 37.90). Fourteen subjects on day 4 experienced in minutes, a minimum time of 0 to a maximum of 366.00, mean = 76.81 (SD = 90.66).

Night-time awakenings are the number of times an awakening occurs. Seventeen subjects on day 1 had a minimum of 0 to maximum of 210 awakenings, mean= 62.94 (SD = 49.61). There were 16 subjects on day 2, 3, and 14 subjects on day 4. Day 2 results were a minimum of 0 to a maximum of 210, mean = 62.94 (SD = 49.61). Day 3 results were a minimum of 1 to maximum 159, mean=48.81 (SD = 42.64). Day 4 results were a minimum of 0.00 to maximum 300, mean=50.81 (SD =73.18).

Table 5 lists the Sleep efficiency, Wake after sleep onset, and Nighttime awakenings statistical values.

Research question 3. What is the immunological acute phase response, as measured by Interleukin 1- beta (IL1- β) and Tumor necrosis factor-alpha (TNF- α) in hospitalized patients after major abdominal surgery? What is the physiologic stress response, as measured by cortisol, in hospitalized patients after major abdominal surgery?

Immune Acute Phase Response. Saliva was collected from each subject in the pre-operative admission unit for a baseline measure of cytokines IL-1 β and TNF- α . Table 5 describes IL1- β and TNF- α results.

IL1- β . The baseline line measure for the IL-1 β sample of 16 subjects was a minimum of 9.86 pg/ml to a maximum of 12264.66 pg/ml, mean = 1717.64 (SD = 3241.33). Normal IL1- β level is \leq 1.0 pg/ml according to the Cytokine Reference Laboratory at the University of

Minnesota. In 18 subjects after the third night of sleep in the hospital, the morning. IL-1 β measure was a minimum of 54.11 pg/ml to maximum of 13280.27 pg/ml., mean = 3248.19 (SD= 3932.60). In the evening sample of 16 subjects, the measure was a minimum of 64.45 pg/ml to a maximum of 12956.84 pg/ml, mean =1962.11, (SD = 3371.75). Sixteen subjects on Day 5, which is after the fourth night of sleep in the hospital, the morning. IL-1 β measure was a minimum of 0.10 pg/ml to maximum of 11494.23 pg/ml., mean = 3564.08 (SD=4608.29). RM ANOVA showed that IL 1 β levels changed significantly after surgery, $F=3.42;df=3, p < 0.05$.

TNF- α . Baseline TNF- α measures for 16 subjects were a minimum of 0.24 pg/ml to a maximum of 57.31pg/ml, mean = 8.33 (SD= 16.21). One subject had a result of < 0.24 pg/ml, which is the lower limit of quantification (LLOQ). The normal range of TNF- α is ≤ 8.8 pg/ml according to the Cytokine Reference Laboratory at the University of Minnesota. In 16 subjects on day 4, the morning TNF- α measure was a minimum of 0.24 pg/ml to a maximum of 276.36 pg/ml, mean = 20.31 (SD= 64.29). In 18 subjects on day 4, the evening. TNF- α measure was a minimum of 0.24 pg/ml to a maximum of 523.02 pg/ml, mean = 35.21 (SD= 15.67). In sixteen subjects on day 5, the morning TNF- α measure was a minimum of 0.24 pg/ml to a maximum of 49.35 pg/ml, mean = 10.18 (SD= 164.14).

Physiologic Stress Response. Cortisol levels were measured before surgery and twice daily beginning on day 4. until discharge. The first morning recorded systolic blood pressure measure was obtained daily for correlation to the daily 6 a.m. cortisol level. Statistical analyses included means, standard deviations, inclusive range and Pearson correlations. Table 6 displays cortisol and systolic blood pressure measures.

Cortisol. Baseline cortisol measure for 16 subjects was a minimum of 6.8 ng/ml to a maximum of 76 ng/ml, mean = 34.53 (SD= 18.22). The normal range of cortisol is 5 ng/ml to

21.6 ng/ml. Eighteen subjects on day 4, after the third night of sleep during hospitalization, the 6 a.m. cortisol measure was a minimum of 5.7 to a maximum of 93, mean = 35.09 (SD= 23.83). Sixteen subjects on day 4, the 6 p.m. cortisol measure was a minimum of 12.8 ng/ml to a maximum of 452.7 ng/ml, mean = 53.86 (SD= 107.05). In 16 subjects on Day 5, after the fourth night of sleep during hospitalization, the 6 a.m. cortisol measure was a minimum of 9.3 ng/ml to a maximum of 434.1 ng/ml, mean = 55.85 (SD= 102.41).

Systolic blood pressure. Baseline morning systolic blood pressure measures for 19 subjects were a minimum of 94 to a maximum of 149, mean = 122.53 (SD= 18.22). Nineteen subjects on day 4, after the third night of sleep during hospitalization, the 6 a.m. systolic blood pressure measure was a minimum of 97 to a maximum of 176, mean = 118.26 (SD= 17.87). Eighteen subjects on day 5, after the fourth night of sleep during hospitalization, the 6 a.m. systolic blood pressure measures were a minimum of 96 to a maximum of 170 mean = 122.33 (SD= 19.60). Table 8 displays Cortisol, a.m. and p.m. measures with 6 a.m. systolic blood pressure measures.

Research question 4. What are the relationships among objective and subjective sleep, immune acute phase responses, and stress response in patients who have undergone major abdominal surgery?

Correlations

Subjective and Objective Sleep. Pearson correlations with 2-tail significance were calculated for the VSH Sleep Scale scores and the SQQS score and cytokines. VSH Sleep Scale measures, on Day 4 after the third night of sleep in the hospital, were correlated to the cytokines IL1- β and TNF- α measure. The SSQQ score, on Day 5 after the fourth night of sleep in the

hospital, was correlated to the Day 5 cytokines IL1- β and TNF- α measure. Actigraph measures were correlated to the Day 4 and Day 5 IL1- β and TNF- α measures.

VSH and SSQS Sleep Scale. On Day 4 there are 2 significant correlations between sleep effectiveness and cortisol, $r = 0.62$ ($p < 0.01$) and between sleep effectiveness and morning systolic blood pressure, $r = 0.55$ ($p < 0.05$). There were no significant correlations among the SSQS score and IL1- β and TNF- α on Day 5.

VSH sleep scale and actigraphy. Pearson correlations with 2-tail significance were calculated for the VSH Sleep Scale scores and actigraphy measures. VSH sleep scale measures were correlated to actigraphy measures for the 24-hour post-operative period on day 3 of hospitalization. There were no significant correlations between the VSH Sleep Scale scores and actigraphy measures.

Immune acute phase response cytokines. The Pearson correlation was used to determine the relationship between the measure of cortisol, IL1- β and TNF- α for 16 subjects. There were no significant correlations among baseline cortisol, baseline IL1- β and baseline TNF- α for 16 subjects. The baseline correlation between IL1- β and TNF- α was $r = 0.55$ ($p < 0.02$). Eighteen subjects on day 4, after the third night of hospitalization, the correlation between IL1- β and TNF- α was $r = 0.70$ ($p < 0.01$). Sixteen subjects on day 5, after the fourth night of hospitalization, the correlation between IL1- β and TNF- α was $r = 0.87$ ($p < 0.0001$). The Pearson correlation was used to determine the relationship between IL1- β , and TNF- α measures. The 6 a.m. measure on day 4, the correlation between IL1- β and TNF- α was $r = 0.87$ ($p < .0001$). The 6 p.m. measure on day 4, the correlation between IL1- β and TNF- α was $r = 0.87$ ($p < .00001$).

Cytokines and objective sleep. The Pearson correlation was used to determine the relationship between the cytokines IL1- β , TNF- α and actigraphy measures of (a) time in bed (TIB), (b) total sleep time (TST), (c) sleep latency (SL), (d) sleep efficiency (SE), (e) wake after sleep onset (WASO), and (f) night-time awakening (AWS). Actigraphy measures the 24-hour total sleep time. Only one significant correlation was found. On day 4, with 14 subjects, the correlation between the 6 a.m. IL1- β and SE was $r = .550$ ($p < 0.04$). See Table 9.

Stress response cortisol and morning systolic blood pressure. The Pearson correlation was used to determine the relationship between these two variables. There were no significant correlations found between cortisol and systolic blood pressure. Table 9 displays the Cortisol and Systolic Blood Pressure correlations.

Cytokines and objective sleep. Because of the variability in the sample, Spearman's rank was used to examine relationships between objective sleep pattern variables and markers of inflammation and stress (Table 10). Significant positive correlations were found between median scores of TST and systolic blood pressure ($r_s = 0.56$, $p < 0.05$), between SE and IL1- β ($r_s = 0.76$, $p < 0.01$), between SE and TNF- α ($r_s = 0.56$, $p < 0.05$), and between NAWS and systolic blood pressure ($r_s = 0.52$, $p = 0.05$). There was a significant negative correlation between median scores of LAT and IL1- β ($r_s = -0.55$, $p < 0.05$).

CHAPTER 5 DISCUSSION

This site of this study was an Allina Health, 680 bed hospital in Minneapolis, Minnesota. Wayne State University Internal Review Board (IRB) reviewed and approved the study in October 2014. Allina Health Research reviewed and approved the study in December. Quorum, a for-profit IRB, reviews all Allina Health research studies. In March 2015, Quorum reviewed and approved the study. Enrollment of subjects began in April 2015. Few subjects were recruited in the following months as potential subjects were not referred from physician's offices. In August, hospital based nurses who work with the population of potential study subjects, began to refer potential subjects. Physicians responded to a request to increase referrals in February 2016. The last day of recruitment was March 31, 2016. The power analysis estimated a sample size for this study of 96 subjects. There were 19 subjects enrolled and who finished the study during the study period of one year. In addition, baseline saliva samples were not obtained for 3 subjects and actigraphy did not record any data for 3 subjects. Thus, because of small sample size and the missing data, it is difficult to adequately address the specific aims of this study.

Nevertheless, some interesting findings are described here. Sleep disturbance, both subjective and objective, occurred in the 19 subjects. The immunologic acute phase response of IL-1 β is a normal range level of < 1.0 pg/ml. There was considerable variability in the IL-1 β results at baseline. Of the 16 samples analyzed, 11 subjects had levels under 500 pcg/ml, while the other 5 samples yielded values over 1500 pcg/ml, with one as high as 12,000 pcg/ml. Since IL-1 β levels rise in response to inflammation, some subjects may have had inflammatory processes going on before surgery. IL-1 β levels displayed a lot of variability after surgery as well. On day 4, 12 subjects had IL-1 β levels under \leq 1070.00 and 2 subjects had levels over 10900.00 pg/ml. The extremely elevated IL-1 β results are an unexpected finding even in abdominal surgery patients.

The normal values for TNF- α are < 8.8 pg/ml. The mean value for TNF- α preoperatively was within normal limits. The mean TNF- α level was elevated to a mean level of 20.31 (SD 64.29) on day 4 in the am, continues to rise throughout day 4 pm to a mean level of 35.21 (SD 130.11), and is declining toward normal by day 5. There is variability in these results as well. One subject's TNF- α day 4 morning level was 276.36 pg/ml, and the evening measure was 523.02 pg/ml. This subject's measure greatly exceeded the second highest morning TNF- α level of 28.26 pg/ml and highest evening level of 10.95 pg/ml. All IL1- β measures were greater than the normal range for all subjects. TNF- α baseline measures were within normal limits for 15 subjects' measures. Increased levels of IL1- β and TNF- α will result in excessive NREM sleep. It could be speculated that the increase in cytokine measures may correspond to an attempt to increase NREM sleep (Opp & Krueger, 2017).

The stress response as measured by cortisol was elevated pre-operatively in 15 subjects. The level of one subject is within the range of 5 to 21.6 ng/ml. On day 4 morning, 11 subjects' cortisol measures were < 21.6 ng/ml, with a greatest value of 93 ng/ml. After the third night of sleep in the hospital, there were positive correlations between subjective and objective sleep, IL1- β , TNF- α , cortisol, and systolic blood pressure.

Research question 1. What are the characteristics of the subjective sleep experience in hospitalized patients after major abdominal surgery?

Sleep disturbance was reported in all 19 subjects after the third night of sleep during hospitalization. The VSH Sleep scale effectiveness was reported as a feeling of being rested, experiencing quality sleep. All subjects reported supplemental sleep outside of the usual nighttime sleep period. This result is in agreement with the findings in one study (Humphries, 2008). For the SSQQ, 18 subjects, after the fourth night of sleep during hospitalization, had a mean

score of 3.28, with a minimum of 1.78 to maximum of 5.14, 1.05 SD. This suggests that sleep quality ranges from poor to good. The maximum score for sleep quality is 6. This result is a new finding as no SSQQ scores were reported in the literature. SSQQ is an unpublished questionnaire.

Research question 2. What is the objective assessment of the sleep in hospitalized patients after major abdominal surgery using actigraphy?

Actigraph recordings provided information about objective sleep on 4 days after surgery for 16 of the 19 subjects, as two actigraph units did not record during the subject's hospitalization period. Each day of the 96-hour recording period, the condition of the subject differed. Day 1 and day 2 recordings reflect the two-day immediate post-operative period. Day 3 and 4 recordings of TIB minutes decrease on day 3, but on day 4, TIB the minutes are greater. Day 3 TST is the same as minutes' decrease, and on day 4, minutes are greater. LAT measures on day 1 reflect the immediate two-day post-operative period. LAT on day 3, and day 4 decrease. SE decrease daily. WASO was consistent as the range of minutes of awakenings range from 0 to over 300 each day. Number of awakenings decreased on day 2 and on day 3, day 4, the number of awakenings increased.

Day 1 sleep time possibly is influenced by the residual effects of anesthesia. The recommended adult sleep period is 7 to 9 hours of uninterrupted sleep. For 17 subjects: the TIB range is almost 7 to 21 hours; mean = 701.94 minutes, SD = 230.73, and the TST range is 5 to 17 hours, mean = 535.59 minutes, SD = 192.85. TIB is < 10 hours for 11 of the 17 subjects, with the TST < 10 hours for 6 of the 17 subjects. LAT is a range of 0 to 3.50 minutes; mean = 26.75 minutes, SD = 43.80. Lat is a range of 0 minutes to almost 3 hours, mean = 26.75 minutes, SD = 43.80. For 7 out of the 17 subjects, LAT is 0 minutes to < 17 minutes. The SE is a range of 37%

to 94%. WASO is range of 0 to 388.5 minutes, mean = 106.35, SD = 111.11 minutes. WASO is < 27 minutes for 3 subjects, to < 30 minutes for 14 subjects. The number of night-time awakenings range from 0 to 300, mean = 62.94, SD = 49.61). One subject had with 0 awakenings, and for 9 subjects, night-time awakenings < 50 times. There are 2 subjects with 146 and 210 awakenings. Upon admission to an inpatient room, immediate post-operative patients are checked frequently and receive frequent delivery of care. These sleep interruptions affect the minutes of waking after sleep onset and number of night-time awakenings.

Day 2 sleep time is typically influenced by continuous administration of generous analgesic medication. For 16 subjects TIB and TST hours are a small decrease, as evidenced with a TIB range of 334 to 1276 minutes, mean = 624.13 minutes, SD = 278.42, and TST < 2.5 hours for 2 of the 16 subjects, mean = 441.50 minutes, SD = 210.93. LAT is a range of 0 minutes to almost 6 hours, mean = 78.28 minutes, SD = 104.33. For 1 subject, LAT was 0 and for 7 subjects of the 16 subjects; the minutes are < 60 minutes. The SE is a range of 20 % to 91%, similar to day 1. WASO is a range of 8 and < 60 minutes for 11 subjects of 16 subjects. There are 14 to 130 night-time awakenings, mean = 51.44, SD =32.66. Two subjects experience 119 and 130 awakenings.

Day 3 sleep time is influenced by the increased activity of being up in a chair and hallway ambulation. For 16 subjects, TIB is and TST are decreased with a TIB range of 1 to almost 15 hours, mean = 561.81 minutes, SD = 239.57 minutes, and TST range is 11 minutes to < 12 hours, mean = 384.13 minutes, SD = 218.25. LAT is a range of 1.5 to 183 minutes, mean = 78.28 minutes, SD = 56.79. Three subjects, experience a LAT of < 60 minutes. The SE is a range of 1% to 88%., mean = 67 .00 minutes, SD= 23.83. WASO range is 30 to 144.5 minutes, mean = 63.82, SD = 37.90. WASO for 11 subjects is < 60 minutes of total sleep time. There are 1 to159

night-time awakenings, mean = 76.81 awakenings, SD = 90.66. There are 3 subjects who experience 100,103, and 159 awakenings.

Day 4 sleep time is influenced by the same activity levels. TIB range is 0 to < 23 hours, mean = 543 minutes, SD = 324.80 for 16 subjects on day 4. The TST range is 0 to < 22 hours, mean = 378.50 minutes, SD = 322.57. There are 0 hours of sleep time for 1 subject, and for 1 subject, 22 hours of sleep time. LAT is a range 0 to 102.50 minutes, mean = 31.64, SD = 33.63. LAT is 0 minutes for 4 subjects and for 7 subjects, minutes are < than 60 minutes The SE is 0 to 87%., mean = 54.91, SD = 30.35. WASO range is 0 to 366 minutes (6 hours); mean = 76.81, SD = 90.66. NAWS range is 0 to 300 awakenings, mean = 50.81, SD = 73.18. There are 0 to < 300 night-time awakenings.

Day 1 and 2 results agree with the increased TST in 2 other studies that measured sleep with actigraphy in patients undergoing major abdominal surgery. Gögenur et al. (2007, 2009) reported decreased sleep efficiency, and increase number of awakenings and increased wake after sleep onset, but no change in TST. These studies examined sleep with actigraphy for several days preoperatively. Perhaps in these studies TST was reduced before surgery; so in these patients if post-operative sleep is compared to pre-operative sleep, TST would not be reduced. Future studies in this population would benefit from an evaluation of the subjective perception and objective measurement of their sleep before surgery. These results report new findings as both TIB and TST are increased on day 1, with only a slight decrease on day 2. Reduced SE results conflict with results from two reviewed studies. WASO and NAWS disagree with the results of three reviewed studies, but conflicts with the results of a 2013 actigraphy review (Madsen, Rosenberg, & Gögenur, 2013).

Day 3 and 4 results extend the findings of total sleep time. In 3 reviewed studies, day 3 and day 4 TST range from 142 to 453 minutes in postoperative abdominal surgery patients (Bisgaard et al, 1999; Gögenur et al. 2007, 2009). Day 3 and 4 SE results extend findings of SE of 0 to 87% in this study. Both WASO and NAWS findings are extended results as the findings of 1 reviewed study, WASO is 239 as compared to 366 in this study and NAWS is 29 as compared to 300 awakenings on day 4.

Research question 3. What is the immunological acute phase response, as measured by Interleukin 1- beta (IL1- β) and Tumor necrosis factor-alpha (TNF- α) in hospitalized patients after major abdominal surgery? What is the physiologic stress response, as measured by cortisol, in hospitalized patients after major abdominal surgery?

IL1- β . The normal level for IL1- β is < 1.0 pg/ml. The pre-operative IL1- β levels of 16 subjects exceeded the norm as the range is 9 to 12,264 pg/ml. All subjects are elective surgical patients. There is no clear explanation for the IL1- β elevation results for the 8 subjects with a level ≤ 147 to 354, and the 5 subjects with a level $\leq 1,827$ to 12,264 pg/ml. Office visit records are not available for review. Perhaps, patients had preoperative conditions associated with inflammation. All IL1- β levels on Day 4, after the third night of hospital sleep, the morning level again exceed the norm as the range is 54 to 13,280 pg/ml. On day 4, the evening level again exceeds the norm, as the range is 64 to 12,956 pg/ml for 16 subjects. No clear explanation was found for the 6 subjects with levels ≤ 112 to 760, and the 6 subjects with levels $\leq 1,898$ to 12,956 pg/ml. There are 16 subjects on day 5, after the fourth night hospital sleep. The IL1- β morning levels decrease as the range is <0.10 to 11.49 pg /ml. Decreased levels in 6 subjects now are ≤ 56 to 797 pg/ml. Six subjects continue to exceed the normal level with $\leq 1,122$ to 11,494 pg/ml. In 2 studies, the IL1- β results extends the reviewed findings of IL1- β measures pre-operative, and day

3 and 4 in hospitalized abdominal surgical patients (Torres, et al., 2007, Yamamoto et al., 2011). In one study, IL1- β results disagree the reviewed findings of IL1- β measures pre-operative, and day 3 and 4 in hospitalized abdominal surgical patients (Kvarnström et al., 2012).

TNF- α . The measure of this cytokine differed when compared to the of IL1- β results. The TNF- α normal level is < 8.8 pg/ml. The pre-operative TNF- α measures for 14 of the 16 subjects are within the normal range < 8.8 pg/ml ng/ml. Two subjects were above normal range with measures of 40 and 57.3 pg/ml. After the third night of sleep in the hospital, Day 4, morning levels are a minimum of 0.24 to a maximum of 276.36 pg/ml, mean = 20.31 The second highest TNF- α level was 28.26 pg/ml for that same time. The Day 4 evening measures are a range of 0.24 to 523.02 pg/ml, mean = 35.21, SD = 130.11. Elevated levels continue in the same subject as the evening measure is 523.02 pg/ml, which again greatly exceeds the measures of the other subjects. The second highest measure was 10.95 pg/ml. Day 5 measures decrease, a range of 0.24 to 49.35 pg/ml. Three subjects' measures are a range ≤ 12.92 to 49.35. This TNF- α finding agrees with 2 reviewed research finding of TNF- α measures on post-operative day 3 and Day 4 in hospitalized abdominal surgical patients. In a study of post-operative colorectal inpatients, peritoneal samples were collected after the fifth post-operative day to measure TNF- α levels as a prospective indicator for anastomotic leakage. Studied patients without anastomotic leakage, the TNF- α levels were decreased each day (Uğras, et al., 2008). The TNF- α findings differ in 3 studies of post-operative abdominal surgery patients, as these findings conflict with the results. Systemic TNF- α levels in abdominal surgery patients were unchanged post-operatively for 45 hours after surgery (Jansson et al., 2004) and unchanged in 24 hours after surgery (Kvarnström et al. 2012). The results disagree with the results of two similar studies of post-operative colorectal surgery patients. Both studies reported TNF- α levels were significantly

decreased on all post-operative days (Tabuchi, et al., 2011; Yamamoto et al., 2011). In both studies serum was drawn pre-operatively, and up to 7 days after colorectal surgery. All levels of TNF- α were below measuring value in both studies.

Research Question 4. What are the relationships among objective and subjective sleep, immune acute phase responses, and stress responses in patients who have undergone major surgery?

Subjective sleep. There was one significant negative correlation between VSH sleep supplementation and TNF- α . $r = .465$, ($p = .05$). There are no significant correlations among the SSQQ score and IL1- β and TNF- α . measures.

Subjective sleep and actigraphy. There are no significant correlations among the measures of VSH characteristics and actigraphy. In 4 studies, a self-reporting activity visual analog scale was correlated to actigraphy. One study of hospitalized major abdominal surgery patients found that between subjective sleep and actigraphy, there was a mean agreement of 80%, SD = 12% (Bisgaard et al 1998). In 1 study, subjective sleep quality was worse in the first 2 days for laparoscopic surgical patients and for 4 days in the incisional abdominal surgical patients, and was correlated to decreased night-time sleep (Gögenur, et al, 2009). The result of this study agrees with 2 studies of surgical patients that found that there was no correlation between the subjective sleep ratings and actigraphy/polysomnography (Kavey & Altshuler, 1979; Gögenur et al 2007).

Actigraphy and IL1- β and TNF- α . There are two negative correlations between the Day 4 SE measures. On Day 4, there is a correlation between SE and morning measure IL1- β as $r = 0.45$ ($p < 0.08$). The next IL1- β measure is a correlation between SE and the evening measure of IL1- β as $r = 0.55$ ($p < 0.04$). In a study by Lee, et al. (2014), sleep duration and cytokines

were measured to determine the association between sleep duration and several cytokine levels in adults with HIV/AIDS. IL1- β results: Mean = 4.20, SD = 3.64. TNF- α results: Mean = 12.4, SD = 11.7. Only measures WASO and TST were used to estimate sleep durations. WASO values ranged from 15 to 25% of TST. The number of subjects is much smaller than the suggested power analysis for 96 subjects. With an increased number of subjects, it is likely that these correlation results would change.

Actigraphy and cortisol, systolic BP. There is a correlation between the measures of WASO and NAWS and cortisol. On day 4, the morning measure of between WASO and cortisol is $r = 0.86$, ($p < 0.00$). For day 5, the morning measure between NAWS and cortisol is $r = 0.89$ ($p < 0.00$). This is a new finding as no studies were found that correlated actigraphy and cortisol, systolic blood pressure. There are significant correlations between WASO and NAWS and systolic blood pressure. On day 4, the measure between WASO and evening systolic blood pressure is $r = 0.83$, ($p < 0.00$). For day 5, the morning measure between NAWS and systolic blood pressure is $r = 0.57$ ($p < 0.02$). This is a new finding as no reviewed studies correlated actigraphy and cortisol, systolic blood pressure. Cortisol measures on day 4 morning, for all but one subject, are above the normal range of $5 < 21.6$ ng/ml. The day 5 morning measure, all the subjects again are above the normal range. This result agrees with the literature findings of physiological stress response. The peak level of cortisol is from 6:00 to 8:00 a.m. Elevated cortisol levels were found on day 4 morning and day evening. The first days after major surgery and hospitalization disruptive sleep patterns. The elevated cortisol levels in the evening are associated with disrupted sleep offset and onset (Van Cauter, 2017). There is a correlation between cortisol and systolic blood pressure. The day 4 elevated cortisol levels to morning systolic BP measures were a range of 97 to 176, mean = 118.26, SD = 17.87. The elevated

evening cortisol levels to the systolic measures BP were a range of 99 to 175, mean = 121.06, SD = 16.80.

Conclusions. This small sample of subjects undergoing laparoscopic and major abdominal surgery reported average subjective perception of sleep quality on day 4 and 5 after surgery. Sleep that was objectively measured by actigraphy found Total sleep time (TST) varied during the 4 post-operative days. TST was on average 8.9 hours on day 1. This may be a result of the residual effects of anesthesia and analgesia. On day 2, total sleep time was on average 7.3 hours. This is within the range of 7-9 hours for a healthy adult; however, someone recovering from a surgical procedure may require more sleep for healing and repair. On days 3 and 4 total sleep time drops to 6.9 hours and 6.3 hours which might be considered inadequate. Actigraphy sleep latency for all days was $0 \leq 21$ minutes. Sleep latency is 10 minutes in healthy persons (Hirshkowitz, 2004). Day 1, LAT was <12 minutes, day 2, = 21 minutes; day 3, < 12 minutes, and day 4, 6 minutes. Sleep Efficiency (SE) decreased for all subjects during the recording period, with the least SE on day 4 of 87%. WASO minutes on day 1 and day 4 were 0 to almost 400 minutes, which is over 6 hours of waking during the night-time sleep period. The day 1 mean = 106.35, day 4 mean = 76.8 minutes. WASO minutes decreased on day 2 and day 3 with a range of 30 seconds to 161 minutes which is less than 3 hours of waking during the night-time sleep period. NAWS day 1 and day 4 were 0 to 300 awakenings. Day 2 and day 3 awakenings decreased to 14 to 159 awakenings.

Sleep disturbance. All subjects reported sleep disturbance and sleep fragmentation on day 4. Sleep supplementation, is reported as a few to several sleep periods outside of the usual night-time sleep. Sleep quality, as reported by both questionnaires, is scored as average. Actigraphy Total sleep time (TST) varied during the 4 post-operative days. TST was on average

8.9 hours on day 1. This may be a result of the residual effects of anesthesia and analgesia. On day 2, total sleep time was on average 7.3 hours. This is within the range of 7-9 hours for a healthy adult; however, someone recovering from a surgical procedure may require more sleep for healing and repair. On days 3 and 4 total sleep time drops to 6.9 hours and 6.3 hours which might be considered inadequate. Actigraphy sleep latency for all days was $0 \leq 21$ minutes. Day 1, LAT was < 12 minutes, day 2, = 21 minutes; day 3, < 12 minutes, and day 4, 6 minutes. Sleep efficiency (SE) decreased for all subjects during the recording period, with the least SE on day 4 of 87%. WASO for all days was $141 \leq 388$ minutes. Day 1 and Day 4, greatest number of minutes were respectively 388 and 366, which is over 6 hours during the night-time sleep period. Day 2 and day 3, with the lesser minutes respectively of 161 and 141, correspond to over 2 hours of awakening during the sleep period. Some individuals within the sample experienced extremely poor objective and subjective sleep; the factors contributing to their sleep quality merit further study.

Immunological acute phase response. One of the most important findings is the greatly elevated IL1- β levels in all four samples, pre-operatively and on post-operative day 4 and day 5 for 5 individuals. The immune system initiates a complex response to surgical trauma. The acute phase response includes pro-inflammatory chemical mediators including the IL1- β and TNF- α cytokines. Physiologic responses include excess sleep and secretion of stress hormones. Pre-operative measures of IL1- β and TNF- α would be expected to within the normal range, yet all baseline levels of IL-1 β , and in 3 subjects, TNF- α measures exceeded the normal range.

Elevated cytokines are a thought to reflect systemic immune system activation and the degree of the surgical stress after abdominal surgery (Sido et al., 2005). However, 5 individuals had very high IL 1- β levels before surgery, suggesting another event/condition was already

inducing an inflammatory response in them. This has interesting implications for future research in this area. Firstly, it would be interesting to examine sleep for several days before the surgery. This could shed light on sleep quality in the home before coming to the hospital environment. It could also possibly show whether those who had high IL 1- β levels were experiencing sleep quality that was different from those with normal levels before the stress of surgery. Secondly, cytokines are reported to be associated with several chronic conditions, including depression (Dahl et al., 2014), heart failure (Briasoulis et al., 2016), and the development of cancer (Fernandes et al., 2015). It would be important to examine the histories of patients before abdominal surgery to identify various factors associated with elevated cytokines. One study reported elevated TNF- α measures in 4 post-operative major abdominal surgery patients that developed anastomotic leakage. TNF- α levels decreased by 10,000 pg/ml per day in the post-operative patients who did not develop a leakage (Uğras et al. 2008).

Physiological stress response. The normal range for cortisol is 5 ng/ml to 21.6 ng/ml. All baseline pre-operative measures are above the baseline level, with one subject with a level of 76 ng/ml. The highest baseline systolic blood pressure is 149. The blood pressure measure and the collection of the saliva sample occurred in the pre-operative surgical for all but two subjects, which may reflect anticipation of impending surgery. day 4, after the third night of sleep during hospitalization, the 6 a.m. cortisol is a range of 5.7 ng/ml to 93 ng/ml, the mean = 35.09. This means that the levels of all but one subject were above normal maximum level of 21.6 ng/ml. The systolic blood pressure mean was 118. There is an insignificant correlation between cortisol and systolic blood pressure.

Implications

Sleep disturbance. Sleep disturbance continues to be reported by post-operative hospitalized adults. Actigraphy revealed that in the first two days after a major surgical procedure, patients experience as few as 2 hours of sleep time, yet also may experience up to 14 hours of sleep time.

Delivery of care, noise, light and post-operative pain are known to disturb sleep. It is unknown if the stressors disturbed the sleep of these subjects. Implications include sleep education of the physiological and circadian process; begin collaborative hospital provider efforts to promote sleep based upon knowledge of the sleep process; and minimize specific disturbing factors in each nursing unit.

Future studies in surgical patients would benefit from including a preoperative evaluation of subjective and objective sleep. The prospect of surgery is anxiety-producing and may be influencing sleep before admission to the hospital environment.

Neuman's Systems Model provides a theoretical framework for future study of sleep in surgical patients. The stressor relationship between the person and the environment corresponds to sleep homeostasis as well as major body system physiological homeostasis. Study of the pre-operative and the post-operative hospitalization period may lead to new understandings of the sleep disturbance stressors in surgical patients. External and internal stressors are able to penetrate of the lines of defense. Examination of multifactorial stressors such as impending surgery, surgical intervention, immune acute phase response, and physiological stress response may lead to new findings in understanding the experience of sleep disturbance, immunological acute phase response and physiological stress response as experienced by major surgery patients.

Immunological acute phase response. There is little correlation of sleep characteristics and cytokines/cortisol results in hospitalized adults in this study. Since power analysis suggested

96 subjects, a larger sample size may have resulted in different results. This study should be repeated to determine if these cytokine results (extreme variability) occur in other major abdominal surgical patients. IL1- β and TNF- α ‘directly/indirectly modulate/regulate NREM sleep’ (Opp & Kruger, 2017). It is not known if there is a relationship between IL1- β , TNF- α levels and a response effecting NREM sleep in post-operative hospitalized adults. There may be a relationship between the postsurgical cytokine response and the quality of sleep; however, a larger sample size is probably needed.

Table 1
Characteristics of Subjects

Characteristic	N	%
Gender		
Male	10	52.6
Female	9	47.4
Marital Status		
Single	6	31.
Married	11	57.9
Divorced	2	10.5
Age		
19 to 39 years of age	5	27.0
40 to 49 years of age	4	21.0
50 to 60 years of age	10	52.0

Table 2

Surgical Procedure and Length of Stay

Laparoscopic Surgery (10)	N	%
Anterior resection w/ ileostomy or colectomy	4	40.0
Sigmoid resection	4	40.0
Hemicolectomy	2	20.0
Incisional Surgery (9)		
Anterior resection w/ ileostomy	3	33.0
Exploratory Laparotomy w/ colostomy or ileostomy	4	45.0
Hemicolectomy	1	11.0
Ventral hernia repair	1	11.0
Length of Stay		
≤ 5 days	9	49.0
6 to 8 Days	9	49.0
9 < Days	1	2.0

Table 3

*Subjective Sleep Scores, Mean & Standard Deviation**Third and Fourth Night of Hospitalization*

Characteristic	N	Minimum	Maximum	Mean	Std Deviation
Third Night					
Sleep Disturbance	19	82	588	331.26	126.46
Sleep Effectiveness	19	156	583	333.11	92.30
Sleep Supplementation	19	7	315	185.68	86.96
Fourth Night					
SSQQ	18	1.78	5.14	3.28	1.05

Table 4

Descriptive statistics and RM-ANOVA for objective sleep patterns

Variables	Day of surgery n=17	Day 1 n=16	Day 2 n=16	Day 3 n=15	F	p
Time in bed (min)						
M (SD)	701.94 (230.73)	624.13 (278.42)	561.81 (239.57)	601.67 (265.05)	1.62	0.19
Range	(403-1219)	(10-1276)	(63-899)	(270-1388)		
Total sleep time (min)						
M (SD)	535.59 (192.85)	441.5 (210.93)	384.13 (218.25)	419.4 (301.11)	2.93	0.03
Range	(245-1019)	(105-804)	(11-733)	(0-1352)		
Sleep efficiency (%)						
M (SD)	78.01 (15.58)	66.59 (20.85)	67.00 (23.83)	54.91 (30.35)	6.29	0.001
Range	(37.05-94.7)	(19.55-91.00)	(1.00-88.17)	(0-86.99)		
Sleep onset latency (min)						
M (SD)	26.75 (43.8)	78.28 (104.33)	50.07 (56.79)	31.64(33.63)	1.98	0.14
Range	(0-175.25)	(0-325.75)	(1.5-183)	(0-102.5)		
Wake after sleep onset (min)						
M (SD)	106.35 (111.1)	94.03 (46.62)	63.82 (37.9)	76.81 (90.66)	0.934	0.43
Range	(0-388.5)	(8.25-161)	(0.50- 144.5)	(0-366)		
# of awakenings						
M (SD)	62.94 (49.61)	51.44 (32.66)	48.81 (42.64)	50.81 (73.18)	0.475	0.7
Range	(0-210)	(14-130)	(1-159)	(0-300)		

Table 5

Descriptive statistics and RM-ANOVA for cytokines

	Baseline	Day 4: 6 am	Day 4: 6 pm	Day 5: 6 am	F	p
	n=16	n=18	n=16	n=16		
IL1- β						
M (SD)	1717.64 (3241.33)	3248.19 (3932.6)	1962.11 (3371.75)	3564.08 (4608.29)	3.42	0.03
Range	9.86 12264.64	- 54.11- 13280.27	64.45- 12956.84	.01- 11494.23		
TNF- α						
M (SD)	8.33 (16.21)	20.31 (64.29)	35.21 (130.11)	10.18 (15.67)	0.68	0.57
Range	0.24-57.31	0.24-276.36	0.24-523.02	0.24-49.35		

Table 6

Cortisol and Systolic Blood Pressure Measures

Cortisol	N	Minimum	Maximum	Mean	Std Deviation
Baseline	16	6.8	76.0	34.53	18.22
Day 4 6 a.m.	18	5.7	93.0	35.09	23.83
Day 4 6 p.m.	16	12.8	452.7	53.86	107.05
Day 5 6 a.m.	16	9.3	434.1	55.85	102.41
Systolic BP	N	Minimum	Maximum	Mean	Std Deviation
Baseline	19	94	149	122.53	16.30
Day 4 6 a.m.	18	97	176	118.26	17.87
Day 4 6 p.m.	17	99	175	121.06	16.80
Day 5 6 a.m.	18	96	170	122.33	19.60

Table 7

Correlations among VHS subjective sleep variables, cytokines, cortisol and systolic blood pressure (n=18)

		SLDIS	SLEFF	SLSUP	IL1- β	TNF- α	CORT	SBP
SLDIS	Pearson Correlation Sig. (2-tailed)	1						
SLEFF	Pearson Correlation Sig. (2-tailed)	.088 .719	1					
SLSUP	Pearson Correlation Sig. (2-tailed)	.410 .081	.091 .712	1				
IL1- β	Pearson Correlation Sig. (2-tailed)	.127 .616	-.082 .745	-.146 .563	1			
TNF- α	Pearson Correlation Sig. (2-tailed)	-.045 .859	.008 .976	-.465 .052	.706** .001	1		
CORT	Pearson Correlation Sig. (2-tailed)	-.009 .971	.621** .006	.012 .963	-.371 .130	-.331 .180	1	
SBP	Pearson Correlation Sig. (2-tailed)	.339 .156	.554* .014	.222 .361	-.037 .884	.165 .514	.361 .141	1

** . Correlation is significant at the 0.01 level (2-tailed).

* . Correlation is significant at the 0.05 level (2-tailed).

Table 8

Correlations among subjective sleep as measured by SSQS, cytokines, cortisol and systolic blood pressure

		SSQS	IL1-β3	TNF-α	CORT	SBP
SSQS	Pearson Correlation Sig. (2-tailed)	1				
IL1-β	Pearson Correlation Sig. (2-tailed)	.119 .660	1			
TNF-α	Pearson Correlation Sig. (2-tailed)	.225 .402	.873** .000	1		
CORT	Pearson Correlation Sig. (2-tailed)	-.439 .089	-.272 .308	-.240 .370	1	
SBP	Pearson Correlation Sig. (2-tailed)	-.120 .634	-.328 .216	-.342 .195	.365 .164	1

** . Correlation is significant at the 0.01 level (2-tailed).

Table 9. Correlations among actigraphy variables, cytokines, cortisol and blood pressure

		TIB	TST	LAT	SE	WASO	AWS	IL1- β	TNF- α	CORT	SBP
TIB	Pearson Correlation Sig. (2-tailed)	1									
TST	Pearson Correlation Sig. (2-tailed)	.709**	1								
LAT	Pearson Correlation Sig. (2-tailed)	.415	-.026	1							
SE	Pearson Correlation Sig. (2-tailed)	.013	.655**	-.495	1						
WASO	Pearson Correlation Sig. (2-tailed)	.555*	.787**	-.029	.500*	1					
AWS	Pearson Correlation Sig. (2-tailed)	.574*	.698**	.023	.386	.907**	1				
IL1- β	Pearson Correlation Sig. (2-tailed)	-.177	.030	-.376	.457	.100	.280	1			
TNF- α	Pearson Correlation Sig. (2-tailed)	-.039	.089	-.269	.239	.164	.283	.706**	1		
CORT	Pearson Correlation Sig. (2-tailed)	.322	.145	.463	-.073	-.159	-.198	-.371	-.331	1	
SBP	Pearson Correlation Sig. (2-tailed)	.088	.085	.384	-.078	.244	.262	-.037	.165	.361	1
		.746	.754	.142	.773	.362	.327	.884	.514	.141	

** . Correlation is significant at the 0.01 level (2-tailed).

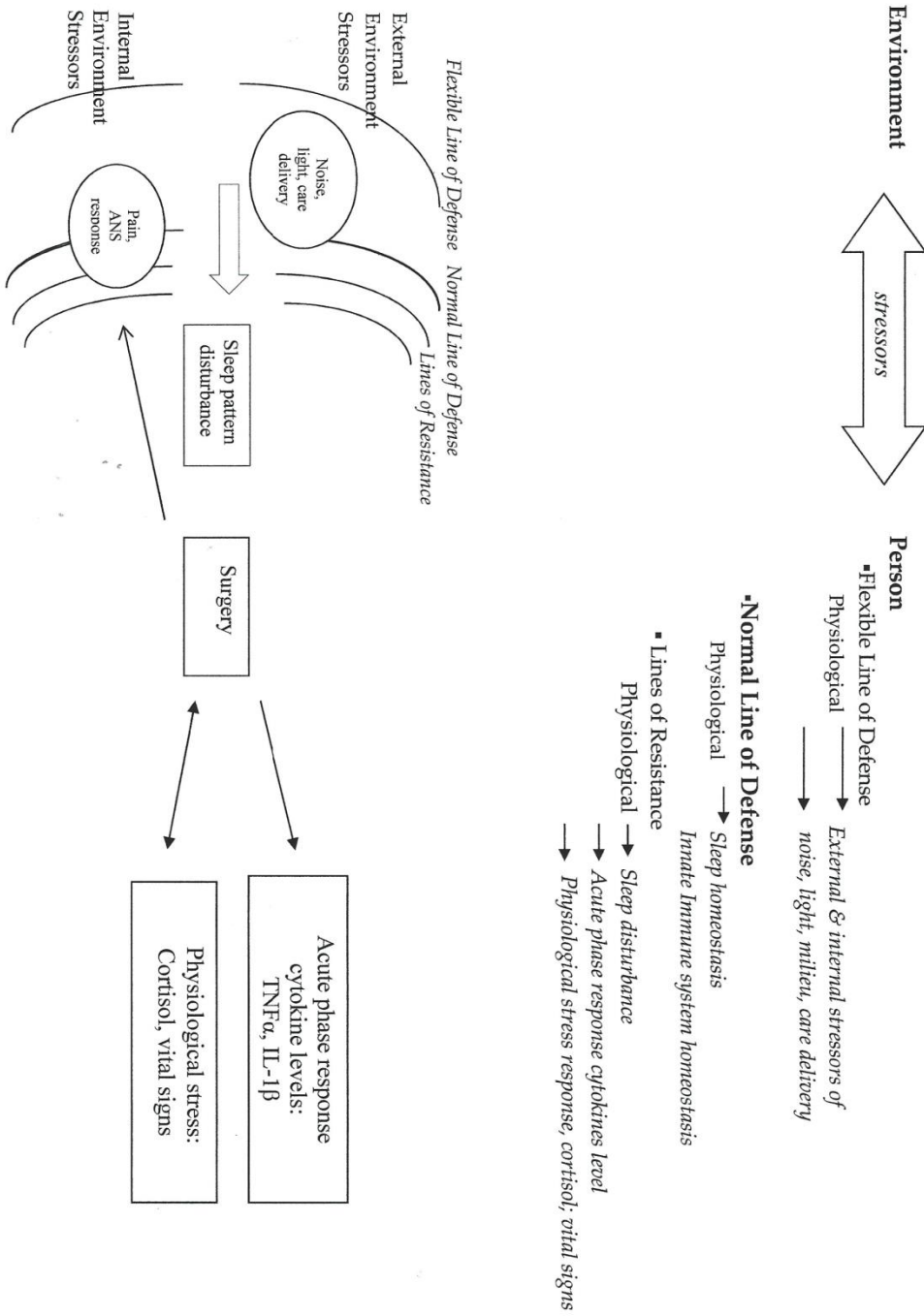
* . Correlation is significant at the 0.05 level (2-tailed).

Table 10. Relationships between objective sleep pattern and inflammatory response variables

	IL1- β		TNF- α		Cortisol		Blood Pressure	
	r_s	p	r_s	p	r_s	p	r_s	p
Total sleep time (min)	.23	.42	.13	.66	-.08	.79	.56*	.03
Sleep efficiency (%)	.76**	.002	.56*	.04	-.28	.34	-.21	.46
Sleep onset latency (min)	-.55*	.04	-.43	.13	.11	.72	.44	.10
Wake after sleep onset (min)	.26	.37	.36	.08	-.23	.43	.41	.13
Number of awakenings	.28	.34	.33	.25	-.25	.39	.52*	.05

Nonparametric correlations for day 3. Bold values are significant. ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

Appendix A, Figure 1
THEORETICAL FRAMEWORK



Appendix A Figure 1

Theoretical Framework

Environment

STRESSORS

Person

Flexible Line of Defense

Physiological → External & internal stressors of noise, light, milieu, care delivery

Normal Line of Defense

Physiological → Sleep homeostasis
 ↳ Innate Immune system homeostasis

Lines of Resistance

Physiological → Sleep disturbance
 ↳ Acute phase response cytokines level
 ↳ Physiological stress response, cortisol, vital signs

Flexible Line of Defense Normal Line of Defense

Lines of Resistance

External Environment Stressors

Noise, light, care delivery

Sleep pattern disturbance

Surgery

Acute phase response cytokine levels: TNF α , IL-1 β

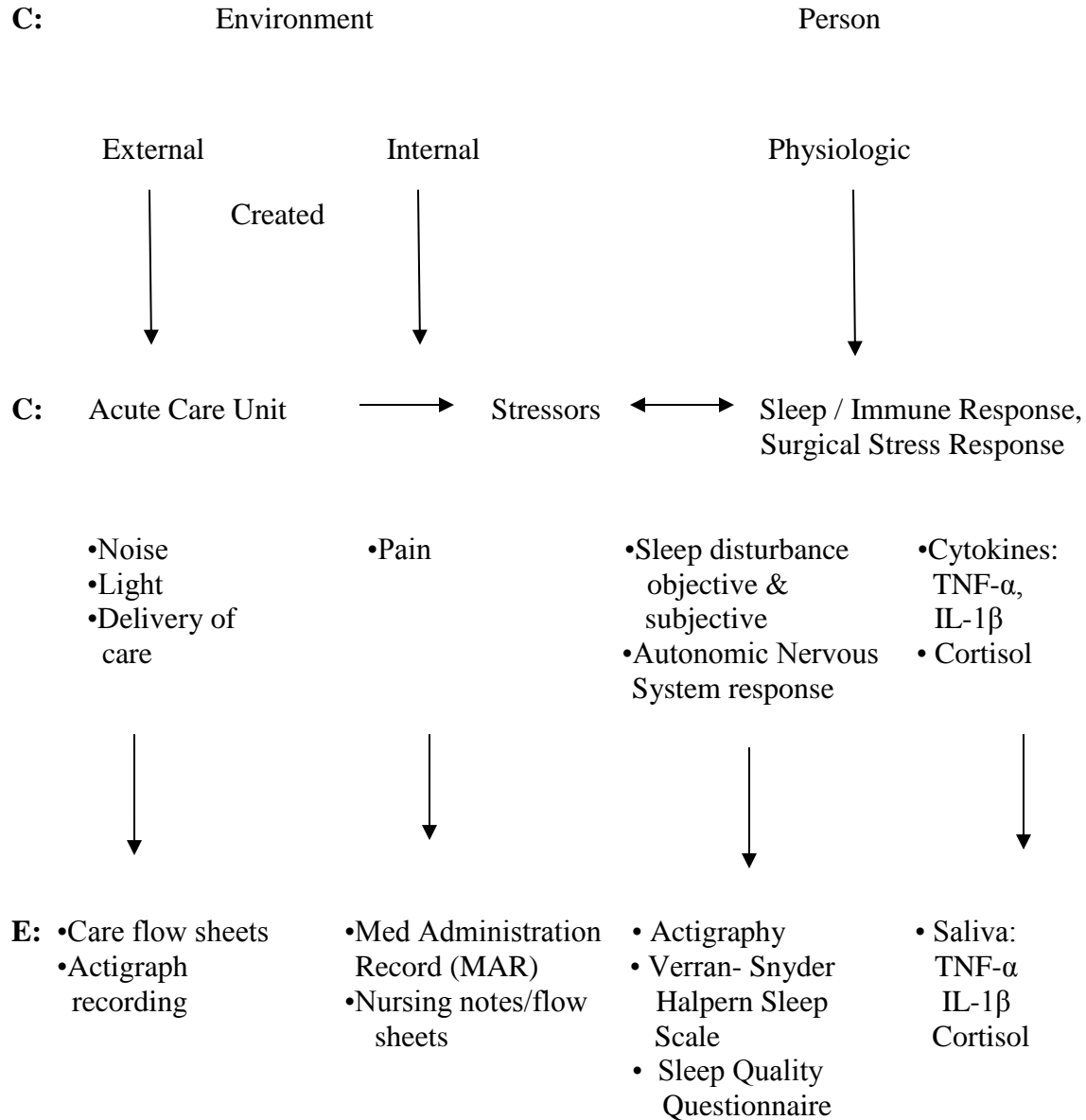
Physiological stress: Cortisol, vital signs

Internal Environment Stressors

Pain, ANS response

Appendix B, Figure 2

Appendix A

CONSTRUCT – CONCEPT -EMPIRICAL MODEL

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ABSTRACT**SLEEP DISTURBANCE AND THE IMMUNOLOGICAL ACUTE PHASE RESPONSE
IN POSTOPERATIVE HOSPITALIZED ADULTS**

by

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The purpose of this study was to examine the subjective and objective (actigraphy) sleep patterns, the immunological acute phase response of IL1- β and TNF- α , and the physiological stress response of cortisol and systolic blood pressure in post-operative abdominal surgical patients. Nineteen subjects, 10 men and 9 women, mean age 45.63 years (SD = 11.44) were enrolled between April 2015 and March 2016. All subjects were elective major invasive abdominal surgery patients. Laparoscopic surgery occurred in 10 patients and incisional surgery occurred in 9 patients. This descriptive correlational design included the sleep questionnaires Verran-Snyder-Halpern Sleep Scale and the Subjective Sleep Quality Questionnaire. Time in bed, total sleep time, sleep latency, sleep efficiency, wake after sleep onset, and night-time awakenings actigraph measures from day of surgery to morning of discharge, and 5 submitted saliva samples for baseline, 6 a.m. and 6 p.m. interleukin1- β , tumor necrosis factor- α , and cortisol. Sleep disturbance, both subjective and objective, occurred in all 19 subjects. Sleep disturbance with fragmentation, sleep latency and supplemental daytime sleep was reported by all subjects. Time in bed and total sleep decreased on day 2 and 3, with an increase on Day 4. Sleep latency range was 0 to over 300 minutes on all days. Wake after sleep onset ranged from 0

to over 300 minutes during the 4 days. Frequent night-time awakenings mean = 62.94 (SD= 49.61) for day 1 and 2. The immunological acute phase response of IL1- β measures greatly exceeded the normal range with pre- and post-operative measures ≤ 1070 pg/ml, and for 2 subjects, levels were <10900 pg/ml during the 4 post-operative days of hospitalization. TNF- α levels were also elevated, with highest level range of 57.31 to 523.02 pg/ml during the 4 days of hospitalization. Pre-operative cortisol levels were elevated; on day 4, 11 subjects' cortisol levels were within normal range. After the third night of sleep during hospitalization, there were positive correlations between VSH sleep effectiveness scale and cortisol was $r = 0.62$ ($p < 0.006$); sleep effectiveness and systolic blood pressure was $r = 0.55$ ($p < 0.014$). Actigraphy time in bed to total sleep time was $r = 0.70$ ($p < 0.002$); time in bed to wake after sleep time was $r = 0.55$ ($p < 0.026$); time in bed to night-time awakenings was $r = 0.57$ ($p < 0.020$); total sleep time to sleep efficiency was $r = 0.65$ ($p < 0.006$); total sleep time to wake after sleep onset was $r = 0.78$ ($p < 0.000$); time in bed to night-time awakenings was $r = 0.69$ ($p < 0.003$); sleep efficiency to wake after sleep onset was $r = 0.50$ ($p < 0.049$); wake after sleep onset to night-time awakenings was $r = 0.90$ ($p < 0.000$); and IL1- β to TNF- α was $r = 0.70$ ($p < 0.001$).

AUTOBIOGRAPHICAL STATEMENT

After a year's experience on a medical-surgical hospital unit, Jean Wolff Humphries began her nursing career in the Emergency department at Greater Southeast Hospital in the Washington, D.C. metropolitan area. In this busy inner-city ED, skills were developed in critical care as well as routine earaches and sore throats. After a move, back to Minnesota, practice continued as an emergency nurse, eventually earning certification (CEN). I completed a Bachelor's of Science in Nursing at Augsburg College in Minneapolis, MN. I accepted a position as nurse manager of a busy Emergency Department. I went back to school again to increase my knowledge as a nurse manager. I earned a Master's degree in Nursing Administration from the University of Minnesota. I started a new career as nursing faculty at a community college, then a 4-year college, then to a nursing faculty position at Minnesota State University, School of Nursing. I discovered the need to go back to school again . . .for the doctoral degree to teach at the university level. My brother's diagnosis of Multiple Myeloma created my passion to improve sleep in hospitalized adults. I have been active in professional associations including Emergency Department Nurses Association, American Organization of Nurse Executives, and Sigma Theta Tau International – Zeta chapter.