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Cancer impacts millions of people in the United States. Understanding the precursors to cancer is important for prevention efforts. The purpose of this study was to investigate potential relationships between sleep, allostatic load, and future cancer occurrence. A conceptual framework of responses to stress adapted from a model for allostatic load was used to guide this investigation. The framework depicts cognitive-behavioral responses to stress and physiologic responses to stress impacting future disease occurrence. Subjective sleep quality and sleep duration (cognitive-behavioral responses to stress) and allostatic load (physiologic response to stress) were suspected of having an impact on future cancer occurrence.

Secondary data analysis of longitudinal data from the Midlife in the United States study of middle aged and older adults in the United States was employed to explore a relationship between sleep and future cancer occurrence, a relationship between allostatic load and future cancer occurrence, a relationship between sleep and allostatic load, and lastly, a possible mediating role for allostatic load in the sleep – future cancer occurrence relationship A nationally representative sample of 806 persons with oversampling for men, older adults, and African Americans was used for analysis.

Sleep parameters were measured by the Pittsburgh Sleep Quality Index (PSQI), a scale with 21 items in seven domains. Overall subjective sleep quality and the seven sleep were analyzed in relation to future cancer occurrence and in relation to allostatic load. In addition to the variable for sleep duration found in the PSQI, continuous hours

of sleep, categorical sleep duration based on National Sleep Foundation recommendations, and categorical sleep duration derived from the actual data were analyzed in relation to future cancer occurrence and in relation to allostatic load. Allostatic load was comprised of 23 individual measures across seven physiologic domains compiled using a validated bifactor model. Overall allostatic load and the seven physiologic domains were analyzed in relation to future cancer occurrence. Statistical models included individual differences (age, race, gender, education, and income) and other cognitive-behavioral responses to stress (smoking, alcohol use, physical activity, and depression) thought to be related to the three main concepts of interest (sleep, allostatic load, and future cancer occurrence).

Of the permutations of sleep duration, categorical sleep derived from the data fit the best. Short sleep duration (<5.3 hours per night) was associated with a 4.5 times increase in the odds of future cancer and long sleep duration (>7.5 hours per night) was associated with a 2.2 times increase in the odds of future cancer when compared to the referent sleep duration category (5.3-7.5 hours per night). Age was the only other measure to show a relationship with future cancer; each increasing year of age was associated with a 3% increase in the odds of future cancer occurrence.

Poor subjective sleep quality was associated with increased allostatic load. Poor subjective sleep quality was associated with decreased hypothalamic-pituitary-adrenal axis domain scores. No relationship was found between subjective sleep quality or the seven sleep domains and future cancer occurrence. No relationship was found between allostatic load or the seven physiologic domains and future cancer occurrence. No

relationship was found between sleep duration and allostatic load. Finally, allostatic load did not play a mediating role in the sleep – future cancer occurrence relationship.

This analysis demonstrates that sleep is an important facet of health, and should be routinely assessed by Advanced Practice Registered Nurses as a part of health maintenance and guidance about sleep should be offered to adults. In nursing education, sleep problems should be emphasized as a risk factor for health problems.

EXPLORATION OF SLEEP AND ALLOSTATIC LOAD

AS PREDICTORS OF FUTURE CANCER

by

Angela Kabbe

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To my children, Serena and Jared, for being the best cheerleaders and for bravely tolerating all of the times mommy had to “work.”

To my parents, Robert and Connie Kabbe, whose unwavering support gave me the resources to succeed.

APPROVAL PAGE

This dissertation written by ANGELA KABBE has been approved by the following committee of the Faculty of the Graduate School at The University of North Carolina at Greensboro.

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CHAPTER I

INTRODUCTION

Prevention of cancer is an important role for health professionals due to the continued incidence, mortality, quality of life, and health care costs. Traditional prevention efforts have included health behavior change, reducing environmental exposure to toxins, and identifying high risk demographic groups and geographic areas. More recently, genetic marker tests for several cancer types indicate lifelong risk. However, existing research does not indicate how specific responses to stress are associated with future cancer occurrence. The need is for investigation of how responses to stress over time may result in cancer. Two important areas to explore are cognitive-behavioral responses to stress and physiologic responses to stress as precursors to cancer.

Sleep is known to be important for health, but why humans sleep and the cognitive and physiologic changes humans undergo during sleep and still being explored (Harvard Medical School, Division of Sleep Medicine, 2007). There is no accepted medical definition of sleep and sleep researchers define sleep by its characteristics (Harvard Medical School, Division of Sleep Medicine, 2007). Sleep is differentiated from wakefulness by changes in consciousness and physiologic functions (Harvard Medical School, Division of Sleep Medicine, 2007). Sleep is both an involuntary action, such as breathing, as well as a behavior able to impacted by individual experiences

(Perry, Patil, & Presley-Cantrell, 2013). This study considered sleep to be a cognitive-behavioral response to stress. Sleep as a precursor to cancer is understudied.

Allostasis is the mechanism by which the body adapts to internal and external stimuli and allows the body to continue healthy functioning. Allostasis is a mechanism for maintaining life. Allostatic load is defined as "the wear and tear on the body and brain resulting from chronic overactivity or inactivity of physiological systems that are normally involved in adaptation to environmental challenge" (McEwen, 1998b, p. 37). Conceptually, allostasis is the body's adaptation to challenges in the short term that maintain life. Allostatic load is the long-term consequence of allostasis. This study considered allostatic load to be a physiologic response to stress.

This study examined potential links between sleep, allostatic load, and future cancer occurrence. Existing evidence was used to build rationale for the study. When limited evidence was found amongst sleep, allostatic load, and future cancer, the review of the literature was expanded to include existing cancer.

Cancer

Cancer is a disease "characterized by uncontrolled growth and spread of abnormal cells" (National Cancer Institute, n.d.-d). Cancer is an ancient disease, with the first documentation of cancer estimated to be from around 2500 B.C. (National Cancer Institute, n.d.-a). Historically, cancer was considered a fatal disease, and over the last century, cancer deaths have increased substantially. In 1900 in the United States (US), the annual rate of cancer deaths was 64 per 100,000 people (Silverberg & Holleb, 1972). By 1968, the mortality rate for cancer was 159 deaths per 100,000 people (Silverberg &

Holleb, 1972). The mortality rate for cancer peaked in 1999 at 215.1 deaths per 100,000 people and by 2014, the mortality rate for cancer had declined to 166.1 (National Cancer Institute, n.d.-c). In 2017, NCI estimates there will be over 600,000 deaths from cancer (National Cancer Institute, n.d.-b).

Persons with cancer comprise a large segment of the population. In 2017, it was estimated that 1,688,780 persons in the United States were diagnosed with a new cancer (National Cancer Institute, n.d.-c). With improvements in screening for cancer and cancer treatment, there were an estimated 15.5 million cancer survivors in the United States in 2016, and this number is projected to increase to 26 million by 2040 (Bluethmann, Mariotto, & Rowland, 2016). By any metric, cancer has considerable impact on United States citizens. Advances in treatment modalities for cancer are an important area of study, but research examining cancer causes, with the goal of cancer prevention, needs significant attention. Although many factors believed to be associated with carcinogenesis have been identified, understanding the causal pathways leading to cancer formation requires further investigation. Two important areas needing investigation are cognitive-behavioral responses to stress and physiologic responses to stress as precursors to cancer.

Sleep

Sleep has been shown to be vital for good health (Buysse, 2014; Irwin, Witarama, Caudill, Olmstead, & Breen, 2015). Sleep is both an involuntary action, such as breathing, as well as a behavior able to impacted by individual experiences (Perry et al., 2013). The Centers for Disease Control and Prevention (CDC) reports that insufficient

sleep is associated with chronic diseases and injuries (Centers for Disease Control and Prevention, 2017a). Objective sleep measures can be useful in assessing sleep and in diagnosing sleep problems like sleep apnea, but subjective measures are important to consider. The diagnosis of insomnia is made from subjective sleep information alone (American Psychiatric Association, 2013; Irwin et al., 2015). There is no single definition of healthy sleep. However, there is some consensus on a few parameters of healthy sleep. For example, the National Sleep Foundation (NSF) established recommended sleep duration by age (Hirshkowitz et al., 2015a). NSF recommends most adults ages 18-64 get between 7 and 9 hours a sleep per day and adults 65 and older get between 7 to 8 hours of sleep per night (Hirshkowitz et al., 2015a). Some adults ages 18-64 may need as few as 6 hours or as many as 10 hours of sleep per night (Hirshkowitz et al., 2015a). Other indicators of healthy sleep include sleep efficiency (defined as the ratio of time asleep to time in bed), sleep latency (defined as the amount of time it takes to fall asleep), and awakenings or disturbances (defined as the number of occurrences of wakefulness lasting more than 5 minutes) (Ohayon et al., 2017). The ranges of each indicator vary by age and by sex. In addition, sleep requirements can vary at the individual level by season, geographic latitude, and by life schedule such as work or school (Ohayon et al., 2017). In short, sleep is an important, necessary component of health, but the parameters of healthy sleep can vary widely on the individual level.

Sleep problems are common in the United States, and sleep duration is a frequently studied sleep parameter. Too little sleep and too much sleep are both considered to be concerning (American Psychiatric Association, 2013). In 2014, the

prevalence of short sleep duration (defined as <7 hours per day) among adults ranged from 26-39% depending on age group (Centers for Disease Control and Prevention, 2017b). The prevalence of long sleep duration (defined as >9 hours per day) was 37% among all adults in 2007 (Bin, Marshall, & Glozier, 2013). Sleep duration has shown significant variation is different populations. People who are obese, those who are physically inactive, and those who smoke are more likely to report having a short sleep duration (Centers for Disease Control and Prevention, 2017b). By race and ethnicity, white Americans are less likely to report having a short sleep duration compared to any other group (Centers for Disease Control and Prevention, 2017b). Native Hawaiians/Pacific Islanders (46%) and black Americans (46%) are the groups with the greatest prevalence of short sleep duration is (Centers for Disease Control and Prevention, 2017b).

Sleep problems as precursors to poor health outcomes are increasingly being studied. Short sleep duration has been linked to obesity, diabetes, elevated blood pressure, and all-cause mortality risk (Cappuccio et al., 2008; Cappuccio, D'Elia, Strazzullo, & Miller, 2010; Cappucio, D'Elia, Strazzullo, & Miller, 2010; Ju & Choi, 2013; Knutson et al., 2009). Outside of sleep duration, other parameters of sleep have been less studied. There is limited evidence that self-reported sleep quality is associated with health outcomes. A large prospective study of over 50,000 men and women in Norway found that self-reported problems initiating sleep, maintaining sleep, and experiencing nonrestorative sleep are associated with an increase of risk of future myocardial infarction (Laugsand, Vatten, Platou, & Janszky, 2011). A study of adults in

the United Kingdom found self-reported good sleep quality was associated with better mental and physical health (Gadie, Shafto, Leng, Cam-CAN, & Kievit, 2017). In contrast, a large prospective study of over 14,000 men and women in Japan found no relationship between sleep quality and risk of mortality from cardiovascular disease (Suzuki et al., 2009).

Cancer and Sleep

Sleep is widely known to be a problem for patients with existing cancer diagnoses, but prevalence and causes are not firmly established (Otte et al., 2015). Subjective sleep quality is a commonly studied sleep parameter in individuals with cancer, and there is limited information on sleep duration for persons living with cancer. Sleep quality has been shown to be a problem for people diagnosed with cancer before, during and after treatment (Ancoli-Israel et al., 2006; Lauren Clevenger et al., 2012; L. Liu et al., 2012; Tian, Chen, & Zhang, 2015). In addition, there is some information on sleep in cancer survivors, with one-third of cancer survivors experiencing shorter sleep duration or sleep disturbance lasting four or more years after diagnosis (Bardwell et al., 2008; Klyushnenkova, Sorkin, & Gallicchio, 2015).

As with other research into sleep as a potential risk factor for disease processes, interest in sleep problems as risk factors for future cancer occurrence has increased. Sleep duration is the most studied parameter for this area although the evidence is scant. Studies of sleep duration have not found a link between sleep duration and incidence of breast cancer, however, there is evidence demonstrating that shorter sleep duration may be associated with more aggressive breast cancer type (Qin, Zhou, Zhang, Wei, & He,

2014; Soucise et al., 2017; Thompson & Li, 2012; Wong et al., 2017). The evidence for sleep problems as a risk factor for other cancers is mixed. Some studies of sleep duration have reported sleep duration is associated with an increased risk of future colon cancer occurrence, while other researchers have found no link between colon cancer risk and sleep duration (Devore et al., 2017; Jiao et al., 2013; Thompson et al., 2011). A prospective study of Finnish men found an increase in lung cancer incidence related to sleep duration (Luojus, Lehto, Tolmunen, Erkkilä, & Kauhanen, 2014). A study of rural Chinese citizens over the life course showed men over 41 years of age had an increased risk of lung cancer mortality associated with sleep duration, (Wong et al., 2017). Among Chinese women, short sleep duration was associated with an increased risk of lung cancer mortality for ages 51 and older; long sleep duration was associated with an increased risk of lung cancer in women 60 and younger (Wong et al., 2017).

Other sleep parameters, such as sleep quality, in relation to future cancer risk have been even less studied. Self-reported average or poor sleep quality has been found to be associated with more aggressive breast cancer among African-American women (Soucise et al., 2017). Self-reported sleep problems of difficulty falling asleep and difficulty staying asleep were associated with an increased risk of prostate cancer 3 to 7 years later (Sigurdardottir et al., 2013). In a retrospective study using Taiwan's National Health Insurance Research Database (which covers 98% of Taiwan's population), Fang et al (2015) found an increased risk of breast cancer, nasal cancer, liver cancer, cervical cancer, oral cancer colon cancer lymphatic cancer, thyroid cancer, myeloma, prostate

cancer, bladder cancer, kidney cancer and other cancers among those with a diagnosis of insomnia at least 2 years prior to cancer diagnosis.

The relationship between sleep problems and people with cancer is well known, even though the prevalence and causal pathways have yet to be specified. The role of sleep in carcinogenesis, however, has received little attention. Although the evidence is scant, there are indications that sleep parameters, such as sleep duration and subjective sleep quality, may play a role in carcinogenesis. Longitudinal studies are needed to establish a link between sleep and future cancer occurrence.

Allostatic Load

The term allostasis was coined by Sterling and Eyer in 1988 and is defined as "the operating range, and the ability of the body to increase or decrease vital functions to a new steady state on challenge" (McEwen & Stellar, 1993, p. 2094). Allostasis is the mechanism by which the body adapts to stressors and allows the body to continue functioning. Allostasis is distinct from homeostasis. The principle of homeostasis reflects the idea that the body, in response to some physiologic disruption, will work to return to a rigid, unchanging set point (McEwen & Wingfield, 2010). In contrast, allostasis specifies that in the face of changes in physiologic condition, the body will respond to challenges to return to flexible, adaptable set points (McEwen & Wingfield, 2010). For example, when a person undergoes the stress of rapidly change from a sitting to a standing position, the body alters the blood pressure and heart rate to prevent syncope. In this example, the principle of homeostasis requires blood pressure and heart rate to return to narrowly defined, unchanging "normal" set points. Allostasis, on the

other hand, allows for the body to adapt to new "normal" set points for blood pressure and heart rate based on internal and external environmental circumstances to prevent syncope. Allostasis is a mechanism for maintaining health. Several years after the concept of allostasis was developed, the term allostatic load was coined by McEwen and Stellar (1993) to describe the overuse or abnormal performance of the body's systems of allostasis that can accumulate over time and lead to disease. Conceptually, allostasis is the body's adaptation to challenges in the short term that maintain life. Allostatic load is the long-term consequence of allostasis. Allostatic load is defined as "the wear and tear on the body and brain resulting from chronic over-activity or inactivity of physiological systems that are normally involved in adaptation to environmental challenge" (McEwen, 1998b, p. 37). In other words, adapting to stressors to maintain the body "has a price, and we have come to define the cost of adaptation as allostatic load" (McEwen, 1998b, p. 37). Ten years after allostatic load was defined, the term allostatic overload began to appear in the literature, and is defined as the point at which allostatic load becomes critical and leads to serious pathology (McEwen & Wingfield, 2003). Allostatic load and allostatic overload differ in that allostatic load represents the accumulation of the effects of allostasis over time, and allostatic overload reflects the point at which this accumulation becomes pathological. As the point at which allostatic load becomes allostatic overload is not established for cancer, this study uses allostatic load as a concept.

Since the concept of allostatic load was conceived, it has been operationally defined and used in research in a variety of ways. In general, allostatic load has been studied by measuring a variety of biomarkers of various physiological processes in an

attempt to examine physiological dysfunction in multiple systems and the impact on health. One of the earliest studies using allostatic load was a study of aging (T. E. Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). This study measured systolic and diastolic blood pressure, waist-hip ratio, serum high-density lipoprotein (HDL), serum total cholesterol, serum glycosylated hemoglobin (HbA1c), serum dehydroepiandrosterone sulfate (DHEAS), 12-hour urinary cortisol, and 12-hour urinary norepinephrine and epinephrine. Each of these 10 biomarkers was then categorized into quartiles of risk based on the distribution of results from the healthiest participants (T. E. Seeman et al., 1997). A participant's allostatic load score was then calculated by summing those biomarkers that fell into the highest quartile of risk (T. E. Seeman et al., 1997).

In the twenty years since the publication of this study, operationalization of allostatic load has evolved and been adapted depending on the hypotheses about the outcomes of a particular study. New methods continue to emerge. Allostatic load measures can be comprised of neuroendocrine biomarkers (such as cortisol, DHEAS, epinephrine and dopamine), immune biomarkers (such as interleukin-6, C-reactive protein, and insulin-like growth factor-1), metabolic biomarkers (such as HDL, HbA1c, and creatinine), cardiovascular biomarkers (such as systolic blood pressure and heart rate), respiratory biomarkers (such as peak expiratory flow), and anthropomorphic biomarkers (such as waist-hip ratio) (Juster, McEwen, & Lupien, 2010). The biomarkers comprising allostatic load in a particular study vary based on the hypothesized mechanism of the relationships between concepts and outcomes of interest.

Traditionally, allostatic load was treated as a composite of biomarkers with high risk values (Juster et al., 2010). High risk values for biomarkers were identified either by analyzing the distribution of results from study subjects or by using a priori identified clinically meaningful values (Juster et al., 2010). Recent publications have used case-based computational modeling and structural equation modeling for analysis (Galen Buckwalter et al., 2016; Wiley, Gruenewald, Karlamangla, & Seeman, 2016). Regardless of the measure or calculation, higher levels of allostatic load indicate higher levels of physiologic dysfunction. Although research into allostatic load is emerging, there is evidence linking allostatic load to all-cause mortality, physical functioning, cognitive functioning, hypertension, diabetes, and cardiovascular disease (Judith E. Carroll, Irwin, Merkin, & Seeman, 2015; X. Chen, Redline, Shields, Williams, & Williams, 2014; Clark et al., 2014).

Cancer and Allostatic Load

The relationship between cancer and allostatic load is unclear from current evidence. In fact, only one study was identified that examined cancer issues in relation to allostatic load as an indicator of multisystem dysfunction. In this study of breast cancer disparities between black and white women, black women with breast cancer were found to have elevated allostatic load, but this was not true among white women (Parente, Hale, & Palermo, 2013). No research was identified that examined allostatic load in relationship to future cancer occurrence.

While the evidence linking allostatic load to cancer is rare, some studies have investigated the relationship between cancer and individual biomarkers thought to

comprise allostatic load. Research has demonstrated links between cortisol, insulin growth factor-1, intercellular adhesion molecule-1, and interleukin-6 and patients with cancer (Mazzoccoli et al., 2003; Mills et al., 2008; Schrepf et al., 2015; S. E. Sephton et al., 2013; S. Sephton, Sapolsky, Kraemer, & Spiegel, 2000; Wang et al., 2010). Only one study was identified that investigated biomarkers as predictors of future cancer occurrence, reporting that high blood glucose was associated with an increased risk in breast cancer up to 15 years later (Agnoli et al., 2015).

Sleep and Allostatic Load

There have been a small number of studies investigating the relationship between sleep and allostatic load. Sleep duration is the most commonly studied sleep parameter. Studies of sleep duration and allostatic load have shown mixed results. Some reports indicate sleep duration are associated with increased allostatic load; others studies have not identified this relationship (Judith E. Carroll et al., 2015; X. Chen et al., 2014; Clark et al., 2014). Allostatic load has been examined in relation to sleep disorders. The prevalence of increased average allostatic load was found to be high among adults with sleep apnea, snoring, snorting/stop breathing, insomnia and diagnosed sleep disorders compared with persons without these sleep disturbances (X. Chen et al., 2014). Very little research has been devoted to relationships between subjective sleep quality and allostatic load in cancer patients or in any population.

Overall, the concept of allostatic load is nascent, and consequently there is a need for future research into factors associated with allostatic load and into connections between allostatic load and health outcomes. Cancer in particular has been neglected by

researchers of allostatic load. Longitudinal studies of allostatic load and future cancer occurrence would illuminate whether a relationship exists between the two and provide areas for prevention. Additionally, there are no studies investigating all three concepts of allostatic load, sleep parameters, and future cancer occurrence.

Purpose of the Study

Understanding the factors that can lead to cancer occurrence will help guide cancer prevention efforts. Healthy sleep is required for good health (Centers for Disease Control and Prevention, 2017a; National Sleep Foundation, 2017). Although sleep problems have been implicated in morbidity and mortality outcomes, little study has been devoted to investigating the potential role poor sleep could play in carcinogenesis. This study investigated the potential relationship between sleep problems and future cancer occurrence. Allostatic load is an important concept that seeks to explain the processes by which daily life occurrences and major life events are manifested in the body physiologically. There is evidence that allostatic load is associated with morbidity and mortality, but no research has yet been devoted to investigating the role of allostatic load in future cancers. This study investigated the potential relationship between allostatic load and future cancer occurrences. Lastly, the potential mediating role allostatic load may play in the pathway between sleep problems and cancer incidence was explored.

Conceptual Framework

There is at present no theory connecting sleep, allostatic load, and cancer. However, the conceptual model of allostatic load can be adapted to encompass the aspects of this proposed study (McEwen, 1998a, p. 172). The revised model shows

individual differences influencing cognitive-behavioral responses to stress and physiologic responses to stress, and cognitive-behavioral responses to stress impacting physiologic responses to stress. The model then shows relationships between cognitive-behavioral responses and disease occurrence and between physiological responses and disease occurrence.

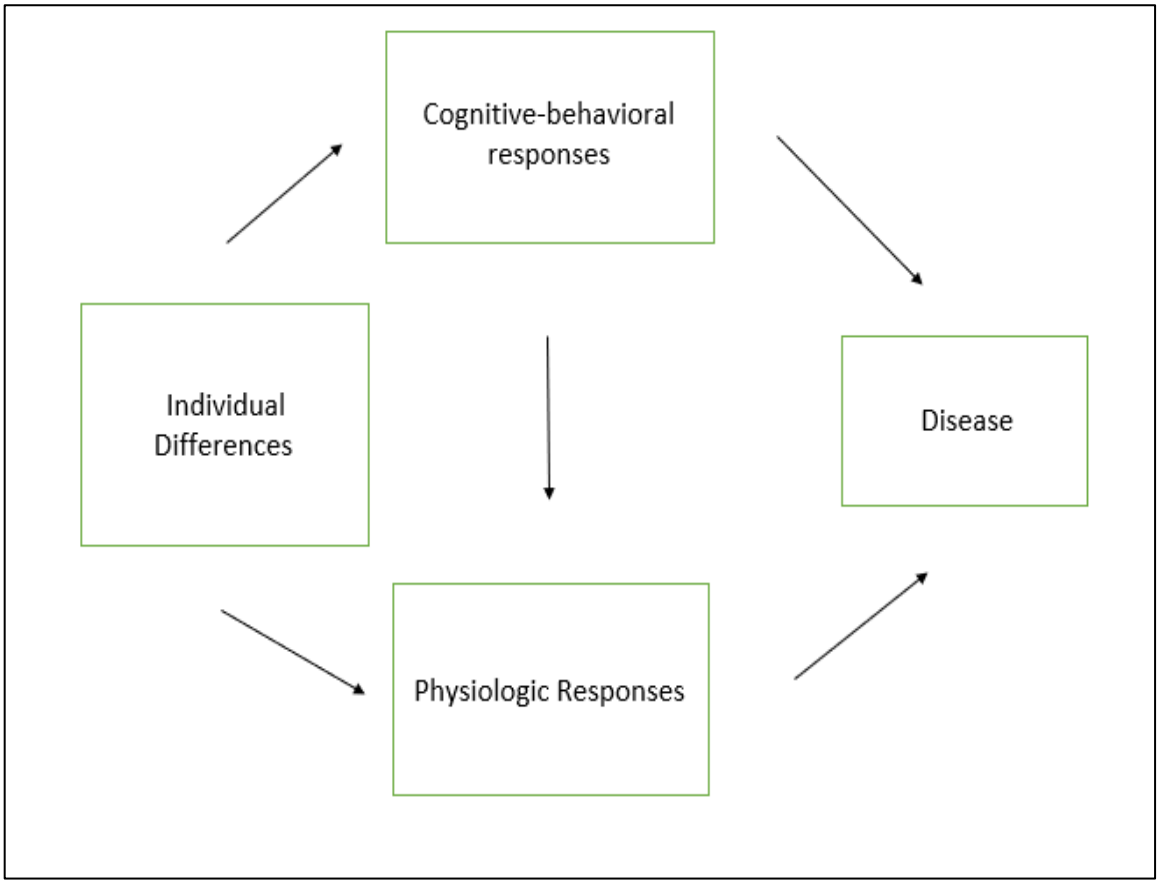
This study defines stress as the individual experience of everyday life stress and stressful life events. The American Psychological Association surveys Americans about stress annually. In 2017, American's average reported stress level was 5.1 on a 10 point scale (ranging from "very little stress" (1) to "a great deal of stress" (10)) (American Psychological Association, 2017, p. 1). Additionally, 80% of respondents reported experiencing at least one physical or emotional symptom of stress in the past month, while 20% of respondents rated their experience of stress as "extreme" (American Psychological Association, 2017). In short, it is a safe assumption that all humans experience stress in their lives. The focus of this study is not to measure stress, but response to stress and the impact on cancer occurrence.

The concepts in the model key to the purpose of this study were cognitive-behavioral responses to stress, physiologic responses to stress, individual differences, and disease. This study defined cognitive-behavioral responses to stress as thoughts, reasoning, feelings, and actions in response to stimuli. Sleep was the primary cognitive-behavioral response to stress in this proposed study. Additional cognitive-behavioral responses to stress included sleep, health behaviors (alcohol use, smoking, physical activity), and depressive symptoms. Physiologic responses to stress were defined as the

biologic embodiment of reaction to stimuli and the primary physiologic response to stress in this proposed study is allostatic load. Allostatic load encompasses biomarkers from specific physiologic domains. The conceptual framework shows both cognitive-behavioral and physiologic responses to stress as influencing disease occurrence. Disease was defined as a change from normal functioning that causes harm and in this study was considered cancer. Individual differences were defined as personal characteristics that may result in variations in disease. Examples of individual differences included in this study were age, race, gender, education and income. The model depicts individual differences as impacting physiologic responses to stress and impacting cognitive-behavioral responses to stress via stress.

Figure 1

Model of Responses to Stress



Adapted from Bruce S. McEwen (1998a, p. 172).

Definitions of Major Concepts

1. Cancer was defined as uncontrolled growth and spread of abnormal cells (National Cancer Institute, n.d.-c). Cancer is a disease and was operationalized as future cancer occurrence.

2. Sleep was defined as "the natural periodic suspension of consciousness during which the powers of the body are restored" (Merriam-Webster, 2017). Sleep is differentiated from wakefulness by changes in consciousness and physiologic functions (Harvard

Medical School, Division of Sleep Medicine, 2007). Sleep is both an involuntary action, such as breathing, as well as a behavior able to impacted by individual experiences (Perry et al., 2013). Sleep is a cognitive-behavioral response to stress. For this study, sleep was operationalized as sleep duration and subjective sleep quality.

3. Other cognitive-behavioral responses to stress

A. Health behaviors

i. Physical activity was defined as participation in active leisure-time activities that result in raised heart rate and sweating.

ii. Alcohol use was defined as the consumption of alcohol containing beverages

iii. Smoking history was defined as use of cigarettes at present or in the past

B. Depressive symptoms were self-reported complaints of symptoms commonly associated with depression including "depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite and sleep disturbance" (Radloff, 1977, p. 386)

4. Allostatic load was defined as "the wear and tear on the body and brain resulting from chronic overactivity or inactivity of physiological systems that are normally involved in adaptation to environmental challenge" (McEwen, 1998b, p. 37). Allostatic load was a physiologic response to stress. This was operationalized through biomarkers, physical measures, and psychophysiologic measures from specific physiologic domains. Physiologic domain biomarkers included sympathetic nervous system hormones,

hypothalamic-pituitary-adrenal axis hormones, serum endocrine system measures, inflammatory markers, and cholesterol measures. Physical measures included measures of the cardiovascular system and obesity. Psychophysiologic measures included parasympathetic nervous system indicators.

5. Individual differences were personal characteristics that may reflect variation in responses to stress. Several indicators were used to determine this variation in response.

A. Age is a demographic measure defined as the length of a person's life in years and was operationalized as years of age

B. Gender is a demographic measure defined as behavioral cultural or psychological traits typically associated with one particular sex. In this study, there were two self-reported genders, female and male.

C. Race is demographic measure defined as a categorization of humans based on select physical characteristics, typically skin color. In this study, race was operationalized at white or not white.

D. Education is a socioeconomic measure defined as the highest type of formal learning program completed

E. Income is a sociodemographic measure defined as amount of incoming financial resources (whether in dollars or some kind of government assistance) for respondent's household in the year of study.

Research Questions

The following questions were examined in this study:

1. Research Question 1. Is there a relationship between sleep and future cancer occurrence among middle-aged adults in the United States?

Hypothesis 1.1: Poor self-reported, subjective sleep quality will be associated with increased future cancer occurrence.

Hypothesis 1.2: Short sleep duration and long sleep duration as compared to normal/healthy sleep duration will be associated with increased future cancer occurrence.

2. Research Question 2. Is there a relationship between allostatic load and occurrence of future cancers among middle-aged adults in the United States.? If there is, are there physiologic domains that are associated with the occurrence of future cancers?

Hypothesis 2.1: Increased allostatic load will be associated with increased occurrence of future cancers.

Hypothesis 2.2: The inflammation domain, sympathetic nervous system domain, and hypothalamic-pituitary-adrenal axis domain will be associated with the occurrence of future cancers.

3. Research Question 3. Is there a relationship between sleep and allostatic load among middle-aged adults in the United States? If a relationship exists, are there physiologic domains that are associated with sleep?

Hypothesis 3.1: Poor self-reported, subjective sleep quality will be associated with increased allostatic load.

Hypothesis 3.2: Short sleep duration and long sleep duration as compared to normal/healthy sleep duration will be associated with increased allostatic load.

Hypothesis 3.3: Poor sleep will be associated with the inflammation domain, glucose domain, lipid domain, and cardiovascular domain.

4. Research Question 4. If a relationship exists between sleep and the occurrence of future cancers among middle-aged adults, does allostatic load mediate that relationship?

Hypothesis 4.1: Allostatic load will mediate the sleep-future cancer occurrence relationship.

Summary

Prevention of cancer and its consequences is an important role for health care professionals. Cancer impacts millions of Americans; there are an estimated 15.5 million people living with cancer in the US, and this number is expected to increase substantially over the next 20-25 years (Bluethmann et al., 2016). While prompt diagnosis and treatment are key to cancer survival, understanding the precursors of carcinogenesis is important for disease prevention efforts. Two underexplored areas of interest are cognitive-behavioral responses to stress and physiologic responses to stress. Prior scant research into sleep, a cognitive-behavioral response to stress, indicates sleep may have a relationship with cancer occurrence. There is very limited research examining the links between allostatic load, a physiologic response to stress, and cancer. This study examined potential associations between sleep, allostatic load, and future cancer occurrence to help address this gap.

CHAPTER II

LITERATURE REVIEW

Introduction

This examination of the literature reviewed the available evidence related to cancer occurrence and sleep, a cognitive-behavioral response to stress, and allostatic load, a physiologic response to stress. As depicted in the conceptual framework shown in Figure 1, it was suspected that sleep and allostatic load are related to future cancer. Further, it was suspected that allostatic load may mediate the sleep-future cancer relationship. The available knowledge regarding cancer and sleep, cancer and allostatic load, sleep and allostatic load, and individual differences related to these three main concepts are summarized here.

Cancer

Individual Differences in Cancer

Cancer does not impact all populations equally; the risk of cancer increases with age and there are disparities in cancer for sex, race, and socioeconomic status. A relationship between increasing age and the risk of cancer is well established. The median age at cancer diagnosis is 66 (National Cancer Institute, 2015b). Less than 10% of all new cancers occur in ages 44 and below, meaning 90% of new cancers occur in middle aged and older adults (National Cancer Institute, 2015b). In the US, men are more likely to be diagnosed with cancer and die from cancer than women. The age-adjusted

incidence rate of cancer among men in U.S. was 480 per 100,000 in 2014 but only 426 per 100,000 among women (National Cancer Institute, n.d.-c). In 2014, the mortality rate for men was 194 per 100,000, but only 138 per 100,000 for women (National Cancer Institute, n.d.-c). Similarly, there are racial disparities in cancer. The incidence rate of cancer in white Americans was 460 per 100,000 in 2014 (National Cancer Institute, n.d.-c). For black Americans, the incidence rate of cancer was 453 per 100,000 in 2014 (National Cancer Institute, n.d.-c). Interestingly, the mortality rate for white Americans at 446 per 100,000 is slightly higher than the rate for black Americans at 434 per 100,000. (National Cancer Institute, n.d.-c). Breaking down racial disparities in cancer incidence by gender/sex, white women have a higher cancer incidence (430 per 100,000) than black women (389 per 100,000) (National Cancer Institute, n.d.-c). The opposite is true of men. Black men have a higher incidence rate of cancer (503 per 100,000) than white men (474 per 100,000) (National Cancer Institute, n.d.-c). Lastly, there is evidence that socioeconomic factors, such as education and income, are linked with cancer mortality outcomes, but less is known about these relationships. One recent study of cancer outcomes and socioeconomic factors examined over 60 years of cancer data in relation to U.S. Census derived socioeconomic measures and found lower socioeconomic status (including variables for lower education and lower income) was associated with an increase in cancer incidence and cancer mortality (Singh & Jemal, 2017).

Cognitive-Behavioral Responses to Stress and Cancer

Alcohol, tobacco and physical activity have known links to cancer. The U.S. Department of Health and Human Services and the International Agency for Research on

Cancer both label alcohol as a carcinogen (International Agency for Research on Cancer & Weltgesundheitsorganisation, 2012; National Cancer Institute, 2013). It is estimated that 3.2-3.7% of cancer deaths annually are attributable to alcohol (Nelson et al., 2013). Smoking has long been known to be a carcinogen and is a risk factor for developing many types of cancer (National Cancer Institute, 2014). Of the 480,000 annual deaths in the US attributable to tobacco, 36% are due to cancer (U.S. Department of Health and Human Services, 2014). Lastly, increasing levels of physical activity have been shown to reduce the risk of cancer (National Cancer Institute, 2017a).

There is a possible relationship between cancer and depression. In the US, the prevalence of depression is 7.6%. (Pratt & Brody, 2014). There is an increased risk of depression among some patients with cancer, such as those in pain or those experiencing physical weakness (National Cancer Institute, 2017b). A systematic review of studies examining depression in adults with cancer found that the prevalence of depression among cancer patients to be up to 16% in outpatients, 14% in inpatients, and 49% in palliative care (J. Walker et al., 2013). A study of the prevalence of depression by specific cancer types found the prevalence of depression to be lowest among those with a genitourinary cancer (5.6%) and highest among those with lung cancer (13.1%) (Jane Walker et al., 2014). There is some limited evidence that depression may be linked to cancer incidence, but the evidence is not definitive. It appears that chronic depression may be linked with cancer incidence (Currier & Nemeroff, 2014). There is less study of a link between depressive symptoms and future cancer occurrence (Currier & Nemeroff, 2014).

NCI identifies additional risk factors for cancer, including chronic inflammation, diet, hormones, immunosuppression, infectious agents, obesity, radiation, and sunlight (National Cancer Institute, 2015a). Cancer-causing substances such as asbestos as well as other chemical exposures also are risk factors for cancer (National Cancer Institute, 2015a). Two areas that have received little attention in relation to cancer occurrence are responses to stress. Sleep, a cognitive-behavioral response to stress, and allostatic load, a physiological response to stress, are two concepts that need further study. Sleep problems are known to be an issue for cancer patients, but prevalence and causes are not firmly established (Otte et al., 2015). Even less is known about sleep and future cancer occurrence. Virtually no attention has been given to a potential relationship between allostatic load and future cancers.

Sleep

Sleep is a biological human requirement and essential for human functioning. During the sleep state, physiologic changes occur, such as reduced blood pressure and temperature, increased cellular repair, and changes in brain activity (Harvard Medical School, Division of Sleep Medicine, 2007). Sleep is also a health behavior (Perry et al., 2013). Timing, duration, and quality of sleep can be consciously affected, and research shows variations in these aspect of sleep based on personal choices and environmental influences such as work schedules and use of social media (Perry et al., 2013). There is no single definition of healthy sleep, and sleep is comprised of several distinct domains, including sleep quality, sleep latency (how long it takes to fall asleep), sleep duration, sleep efficiency (difference between time spent in bed trying to sleep and time spent

asleep), sleep disturbances, and daytime dysfunction (impairments in daily functioning due to sleep problems). Sleep problems are common in the United States, and sleep duration is the most commonly studied domain. The prevalence of short sleep duration (<7 hours per day) among adults ranged 26.3-39.0% depending on age group in 2014 (Centers for Disease Control and Prevention, 2017b). The prevalence of long sleep duration (>9 hours per day) was 37.2% among all adults in 2007 (Bin et al., 2013).

Sleep and Individual Differences

Sleep duration requirements are dependent on age. The National Sleep Foundation updated their recommended sleep time durations by age in 2015 (Hirshkowitz et al., 2015a). For young adults and adults up to age 64, 7 to 9 hours per night is considered healthy (Hirshkowitz et al., 2015a). For older adults 65 and older, 7 to 8 hours of sleep per night is needed (Hirshkowitz et al., 2015a). The prevalence of sleep disturbances also varies by age, with the highest prevalence being among those 18-24 (18.1% for men and 25.1% for women) and the lowest among older adults (M.A. Grandner, 2017). Lastly, risk for sleep disorders, such as insomnia and sleep apnea, increases with age (M.A. Grandner, 2017).

The relationship between sleep and gender is less well established. A study of a nationally representative sample found that men have a shorter sleep duration than women, but that this relationship became non-significant after controlling for other factors such as family structure and socioeconomic status variables (Krueger & Friedman, 2009). In contrast, another study of a nationally representative sample found a statistically significant difference in sleep duration between men and women (Burgard &

Ailshire, 2013). Women in the study were found to sleep 11 minutes more per night than men (Burgard & Ailshire, 2013). Women also were more likely to have interrupted sleep and were more likely to nap compared to men (Burgard & Ailshire, 2013). Women report more sleep disturbances compared with men and are more likely to report insomnia, while men are at higher risk for sleep apnea (M.A. Grandner, 2017).

There is evidence of racial and socioeconomic differences in sleep. Black Americans have an increased likelihood of short sleep duration and poor sleep quality compared to white Americans (X. Chen et al., 2015; Krueger & Friedman, 2009). Black Americans are also more likely to have a long sleep duration than white Americans (Krueger & Friedman, 2009). Studies of sleep and socioeconomic factors have shown that low education level was associated with poor sleep (Michael A. Grandner et al., 2013, 2015). Low income also has been found to be associated with poor sleep (Michael A. Grandner et al., 2015). Low income and low education are linked to both short and long sleep duration (Krueger & Friedman, 2009). Race and socioeconomic factors frequently confound each other in research on disparities in sleep (M.A. Grandner, 2017).

Sleep and Cognitive-Behavioral Responses to Stress

Cognitive-behavioral factors are also related to sleep. Researchers have found links between sleep problems and alcohol, tobacco, physical activity and depression. Alcohol dependence is associated with insomnia, short sleep duration, sleep apnea, and circadian disruptions (Chakravorty, Chaudhary, & Brower, 2016). Even a single night where 1-2 drinks are consumed in the evening before sleep has been shown to disrupt sleep (Ebrahim, Shapiro, Williams, & Fenwick, 2013). Similarly, smoking is associated

with poor sleep quality and shorter sleep duration (Cohrs et al., 2014; Michael A. Grandner et al., 2015; Zhang, Samet, Caffo, & Punjabi, 2006). Researchers report a link between sleep and physical activity level. In one study using a nationally representative sample, subjects with at least 150 minutes of moderate physical activity per week or 75 minutes of vigorous activity per week reported less daytime sleepiness than subjects who were more physically inactive (Loprinzi & Cardinal, 2011). In an experiment examining the impact of physical activity on sleep, young adults in the control group were sedentary for one week while the control group maintained their usual physical activity levels (Edwards & Loprinzi, 2017). The sedentary group experienced decreases in subjective sleep quality post-intervention (Edwards & Loprinzi, 2017). Lastly, sleep problems and depression are frequently co-morbid and share correlates (Herrick & Sateia, 2016; Poole & Jackowska, 2017). In fact, having insomnia or hypersomnia is one the diagnostic criteria for major depression (American Psychiatric Association, 2013). Specific sleep problems such as increased insomnia symptoms and increasing number of nighttime awakenings are associated with depression (Taylor, Lichstein, Durrence, Reidel, & Bush, 2005). Also, depression is associated with self-report of poor sleep satisfaction (Mayers, Grabau, Campbell, & Baldwin, 2009).

Sleep and Health Outcomes

Compromised sleep can have significant consequences, including cognitive impairment, morbidity and mortality. There is a substantial body of work on how sleep impacts cognition. Killgore (2010) provides a thorough summary of known sleep-cognition relationships. In sum, alertness, vigilance, attention, motor-tracking,

visuospatial perception, auditory perception, olfactory perception, memory formation, learning, and creativity are all impacted negatively by sleep deprivation (Killgore, 2010). Additionally, sleep deprivation is associated with increased negative mood, depression, anxiety, paranoia, decreased emotional intelligence, increased risk-taking, poorer judgement, reduced empathy, feelings of persecution and slower decision-making (Killgore, 2010). Lastly, sleep deprivation is associated with increased somatic complaints and hyperalgesia (Killgore, 2010).

Sleep and Morbidity

Sleep problems have been studied for their impact on physical health. For example, sleep has been studied in relation to diseases such as hypertension and diabetes as well as in relation to other health problems such as obesity. Shorter sleep duration has been found to have health consequences. Meta-analyses with large pooled sample sizes have concluded that shorter sleep is associated with an increased odds of obesity and an increased odds of metabolic syndrome (Cappuccio et al., 2008; Ju & Choi, 2013). Cross sectional and longitudinal data have demonstrated higher systolic and diastolic blood pressure and hypertension with short sleep duration (Knutson et al., 2009). A population-based, prospective study of Taiwanese adults reported an increased risk of coronary heart disease with short sleep duration (Lao et al., 2018). In contrast, a prospective study of adult women in the US found no significant relationship between short or long sleep duration and risk of cardiovascular disease, but did find an increase disease risk in women with long sleep duration and women with insomnia (Sands-Lincoln et al., 2013). A meta-analysis with a large pooled sample size found short sleep duration to be

associated with an increased relative risk of diabetes (Cappuccio et al., 2010). Less study has been devoted to long sleep duration and health outcomes, but meta-analyses have shown long sleep duration to be associated with an increased odds of metabolic syndrome and an increased relative risk of diabetes (Cappuccio et al., 2010; Ju & Choi, 2013).

Other sleep parameters beyond sleep duration have been examined in relation to health problems. Difficulty initiating sleep and difficulty maintaining sleep are associated with an increased relative risk of diabetes, and (Cappuccio et al., 2010). Difficulty falling asleep and use of sleep medications are associated with an increased risk of coronary heart disease (Lao et al., 2018). A large longitudinal study found that difficulty initiating sleep every night, difficulty maintaining sleep every night and feelings of nonrestorative sleep more than once a week were all associated with a moderate increase in risk of acute myocardial infarction (Laugsand et al., 2011). Chronic insomnia (defined as insomnia for more than one year) is associated with a higher odds of diabetes and with a higher odds of hypertension (Alexandros N. Vgontzas, Liao, Pejovic, et al., 2009; Alexandros N. Vgontzas, Liao, Bixler, Chrousos, & Vela-Bueno, 2009). In the studies of chronic insomnia, those at greatest risk for diabetes and hypertension were those that experienced both chronic insomnia and short sleep duration (Alexandros N. Vgontzas, Liao, Pejovic, et al., 2009; Alexandros N. Vgontzas, Liao, Bixler, et al., 2009).

Sleep and Mortality

Problems with sleep are associated with an increased all-cause mortality risk, although the evidence is not yet conclusive. A meta-analysis of almost 1.4 million adults found that both short and long sleep duration is associated with an increase in all-cause

mortality (Cappucio et al., 2010). A separate meta-analysis of just over 2.2 million adults showed similar results, however, analyses of men and women separately found that short sleep duration in females was associated with increased all-cause mortality risk but short sleep duration in males was not (T.-Z. Liu et al., 2017). A separate study of insomnia found the opposite effect; all-cause mortality risk was increased in men with insomnia with short sleep duration, but not for women with insomnia with short sleep duration (Alexandros N. Vgontzas et al., 2010).

There is limited evidence that sleep problems impact cause-specific mortality. One longitudinal study of men and women in the United Kingdom assessed sleep at baseline and then followed participants for 22 years (Rod et al., 2014). In men, neither short sleep duration nor self-reported disturbed sleep were associated with mortality from cardiovascular (CV) disease, however, men who experienced both short sleep duration and disturbed sleep at baseline had a higher risk of future CV mortality (Rod et al., 2014). In women, both short sleep duration and self-reported disturbed sleep at baseline were both independently associated with increased risk of CV mortality (Rod et al., 2014). Women with both short sleep duration and disturbed sleep had the highest risk of CV mortality (Rod et al., 2014). Researchers also examined the relationships between other causes of death (including cancer), and found no relationship (Rod et al., 2014). A meta-analysis synthesizing the results of 19 studies concluded both short and long sleep duration are associated with an increased risk for cardiovascular mortality (Krittanawong et al., 2017).

Sleep and Cancer

Sleep has long been established as a problem for people with cancer. There are studies examining sleep in cancer patients at various stages of the cancer experience, including before, during and after treatment, and during survivorship. The sleep issues studied include subjective sleep quality, disturbed sleep, and insomnia. The majority of the research on cancer and sleep has been done in patients with breast cancer.

Cancer and sleep prior to treatment. A number of studies were identified that investigated sleep in cancer patients prior to the initiation of a particular cancer treatment. In general, a substantial number of patients with cancer begin cancer treatment with sleep problems. Longitudinal and cross-sectional studies have documented that subjective sleep quality is poor in women with breast cancer after surgical intervention but prior to the initiation of chemotherapy (Ancoli-Israel et al., 2006; L. Liu et al., 2012). The longitudinal results show that not only is sleep quality poor prior to the start of chemotherapy, but poor sleep quality persists throughout treatment (L. Liu et al., 2012). A small number of studies examined the prevalence of sleep problems prior to undergoing a specific treatment (surgery, radiation therapy, chemotherapy, or hormone therapy). Poor self-reported sleep quality has been found in ovarian cancer patients undergoing surgical intervention and in cervical cancer patients prior to initiating chemotherapy or radiation therapy, (Lauren Clevenger et al., 2012; Tian et al., 2015). Similarly, a study of patients with a variety of types of cancers have found patients had disturbed sleep prior to undergoing radiation therapy (Hickok, Morrow, Roscoe, Mustian, & Okunieff, 2005). Lastly, a study of patients with a variety of cancers prior to the

initiation of any non-surgical therapy found that the majority met criteria for insomnia syndrome or reported insomnia symptoms (Savard, Villa, Ivers, Simard, & Morin, 2009). A significant problem with the studies reporting on sleep problems prior to cancer treatment initiation is that the majority of them do not specify if patients had already undergone other treatment modalities prior to the start of the study. Only two studies (Ancoli-Israel et al., 2006; Tian et al., 2015) document if patients had already undergone a treatment prior to initiation of the one under study; the remainder of the studies reviewed do not document whether or not patients had experienced prior therapies which limits the conclusions that can be drawn.

Cancer and sleep during and after treatment. Few studies of sleep problems in cancer patients during and after treatment were identified. In a very small study of lung cancer patients, most were found to be self-reported poor sleepers and poor sleepers had a short sleep duration while undergoing treatment with chemotherapy (Dean et al., 2013). A study of patients with a variety of cancers found 43% had insomnia syndrome after initiating chemotherapy (Palesh et al., 2010). One study examined sleep problems before and after initiating treatment and found an increased prevalence of sleep problems during treatment (Tian et al., 2015). One study was identified that examined sleep in breast cancer patients immediately post-treatment; researchers found 65% of them reported poor subjective sleep quality (Bower et al., 2011).

Cancer survivors and sleep. A few studies have examined sleep problems in cancer survivors at time points beyond diagnosis and treatment. Longitudinal studies, one of ovarian cancer survivors and one of survivors of a variety of cancers, have

demonstrated that some cancer patients report poor subjective sleep quality and insomnia up to 12 to 18 months after diagnosis (L. Clevenger et al., 2013; Savard, Ivers, Villa, Caplette-Gingras, & Morin, 2011). Sleep problems in long-term cancer survivors have also been studied. Two studies of breast cancer survivors with non-metastatic disease have shown over one-third of survivors had insomnia symptoms or short sleep duration four or more years after diagnosis (Bardwell et al., 2008; Klyushnenkova et al., 2015). Only one study was identified of cancer patients at the end of life. In 219 patients admitted to a palliative care unit with a variety cancers in advanced stages, 100% of them were found to have sleep disturbances (Mercadante et al., 2017).

Factors associated with sleep problems in cancer. Few studies have examined factors associated with sleep problems in cancer patients beyond tumor and treatment-related factors. Some of the other factors that have been studied include coping strategies, depression, anxiety, fatigue, gender, and cancer symptoms. Unfortunately, rarely was more than one study identified for each factor studied, limiting the conclusions that can be drawn. Avoidance coping has been shown to be associated with worse sleep in breast cancer and prostate cancer patients during treatment with radiation therapy (Thomas, Bower, Hoyt, & Sepah, 2010). Insomnia is associated with depression and anxiety; insomnia was significantly worse for those with increased levels of anxiety and depression among cancer patients in a palliative care unit (Bardwell et al., 2008; Mercadante et al., 2017; Palesh et al., 2010; Savard et al., 2011). Fatigue is worse in cancer patients receiving chemotherapy who have insomnia (Palesh et al., 2010). Dysfunctional beliefs about sleep and poor sleep behaviors are associated with an

increased risk of insomnia in cancer patients undergoing treatment (Savard et al., 2009). Women with cancer have an increased risk of insomnia compared with men (Savard et al., 2009).

Cancer outcomes and sleep. Only two studies were identified that investigated sleep in relation to cancer outcomes. In a small study of lung cancer patients undergoing treatment, those with insomnia had more reported symptoms related to cancer (Dean et al., 2013). In a much larger sample (>3000) of survivors of early-stage breast cancer, women who consistently had a short or long sleep duration over time did not have increased risks of disease recurrence or cause-specific or all-cause mortality (Marinac et al., 2017).

Future cancer occurrence and sleep. As sleep has been increasingly studied as a potential risk factor for disease, interest in sleep problems as risk factors for cancer has grown. However, there have been few studies examining this. Sleep duration is the most studied sleep parameter. Studies of sleep duration and risk of breast cancer have not found a link between sleep duration and incidence of breast cancer (Qin et al., 2014; White et al., 2017). However, there is evidence demonstrating that shorter sleep duration may be associated with more aggressive breast cancer type (Soucise et al., 2017; Thompson & Li, 2012). Two studies found short sleep duration has been shown to be associated with colon cancer (Jiao et al., 2013; Thompson et al., 2011). One study found long sleep duration was associated with an increased risk of colon cancer (Jiao et al., 2013). Other researchers found no link between colon cancer and sleep duration (Devore et al., 2017). Longitudinal studies from Finnish men and male and female rural residents

of China found an increased incidence of lung cancer with short sleep duration and long sleep duration among Finnish and Chinese men and among Chinese women (Luojus et al., 2014; Wong et al., 2017). A prospective cohort study of adult women reported an increased risk of liver cancer among women with long sleep duration, with the highest risk being among obese women (Royse et al., 2017).

One challenge in interpreting the findings from studies of sleep duration and cancer risk is the wide variation in operationalization of short sleep duration and long sleep duration. Studies of short sleep duration defined it as four, five, six, six and a half, or seven hours of sleep per night (Devore et al., 2017; Jiao et al., 2013; Luojus et al., 2014, 2014; Qin et al., 2014; Royse et al., 2017; Soucise et al., 2017; Thompson et al., 2011; Thompson & Li, 2012; Wong et al., 2017). Studies of long sleep duration defined it as greater than 8 hours, 9 hours or 10 hours of sleep per night (Devore et al., 2017; Jiao et al., 2013; Luojus et al., 2014; Qin et al., 2014; Royse et al., 2017; Soucise et al., 2017; Wong et al., 2017). All the studies reviewed used a priori definitions of short and long sleep duration, none explored the data for possible sleep duration cut points.

Other sleep parameters, such as sleep quality, have been studied less in relation to risk of future cancer. Difficulty sleeping has been shown to be associated with an increased risk of breast cancer and self-reported average or poor sleep quality was associated with more aggressive breast cancer among African-American women (Soucise et al., 2017; White et al., 2017). A study from Norway demonstrated an increased risk of breast cancer in women who reported having nonrestorative sleep, difficulty initiating sleep, and difficulty maintaining sleep; women with only one or two insomnia symptoms

did not show an increased risk of breast cancer (Sen et al., 2017). Self-reported difficulty falling asleep and difficulty staying asleep were associated with an increased risk of prostate cancer among Icelandic men (Sigurdardottir et al., 2013). A retrospective study using Taiwan's National Health Insurance Research Database (which covers 98% of Taiwan's population), found an increased risk of breast cancer, nasal cancer, liver cancer, cervical cancer, oral cancer colon cancer lymphatic cancer, thyroid cancer, myeloma, prostate cancer, bladder cancer, kidney cancer and other cancers among those with a diagnosis of insomnia at least 2 years prior to cancer diagnosis (Fang et al., 2015).

Allostatic Load

Allostatic load is a physiologic response to stress. Research has demonstrated allostatic load is impacted by a spectrum of life factors, including childhood experiences, social relationships, discrimination, caregiving, workplace issues, personal psychological characteristics, and neighborhood factors (Bird et al., 2010; Brooks et al., 2014; Judith E. Carroll et al., 2013; E. Chen, Miller, Lachman, Gruenewald, & Seeman, 2012; de Castro, Voss, Ruppin, Dominguez, & Seixas, 2010; Friedman, Karlamangla, Gruenewald, Koretz, & Seeman, 2015; Gallo, Jiménez, Shivpuri, Monteros, & Mills, 2011; Hasson, Von Thiele Schwarz, & Lindfors, 2009; Hawkley, Lavelle, Berntson, & Cacioppo, 2011; Mair, Cutchin, & Kristen Peek, 2011; Merkin et al., 2009; Ong, Williams, Nwizu, & Gruenewald, 2017; Robinette, Charles, Almeida, & Gruenewald, 2016; Roepke et al., 2011; Slopen, Chen, Priest, Albert, & Williams, 2016; Song et al., 2014; Sun, Wang, Zhang, & Li, 2007; Upchurch et al., 2015; Utumatwishima et al., 2017; Vadiveloo & Mattei, 2017; van Deurzen et al., 2016; Zilioli, Slatcher, Ong, & Gruenewald, 2015).

Allostatic load has been shown to vary by individual differences and cognitive-behavioral factors and it has been linked with health outcomes, including morbidity and mortality.

Allostatic Load and Individual Differences

Studies have shown age to have a significant relationship with AL (Crimmins, Kim, & Seeman, 2009; Hasson et al., 2009; Robinette et al., 2016; Schnorpfeil et al., 2003; T. Seeman et al., 2004; T. E. Seeman, Singer, Ryff, Love, & Levy-Storms, 2002; Sun et al., 2007). One study was identified that did not find a relationship between increasing age and increased allostatic load among Japanese elders (Kusano et al., 2016). While age is universally included as a covariate in studies of AL, only one study investigated the age-allostatic load relationship directly. Crimmins et al (2003) used nationally representative US data to demonstrate that allostatic load gradually increases over the early/mid decades of adulthood to essentially plateau after age 65 in the US. Allostatic load increases by 0.4-0.5 units every 5 years in the 20's and 30's, then allostatic load increases by 0.2-0.3 units every 5 years in the 40's and 50's before leveling off at around age 65 (Crimmins et al., 2003).

Similar to studies of age and allostatic load, gender is typically included in studies investigating allostatic load as a covariate, but few studies have studied the gender-AL relationship directly. A nationally representative sample of adults in the US demonstrated that women had higher AL scores compared with men (Geronimus, Hicken, Keene, & Bound, 2006). Conversely, a study of black, white, and Hispanic older adults in Chicago and a study of elderly Japanese both found men to have higher AL scores compared with women (Hawkley et al., 2011; Kusano et al., 2016).

Numerous studies have investigated the relationship between race and/or ethnicity and allostatic load. The majority of those reviewed focused on black/white differences. Most studies including black participants found that black race is associated with higher AL (Chyu & Upchurch, 2011; Geronimus et al., 2006; Kaestner, Pearson, Keene, & Geronimus, 2009; Mair et al., 2011; Merkin et al., 2009; Parente et al., 2013; Tomfohr, Pung, & Dimsdale, 2016; Wallace et al., 2013). The percent of the sample that was black in the studies finding black race associated with higher allostatic load ranged from 12-43% (Chyu & Upchurch, 2011; Geronimus et al., 2006; Kaestner et al., 2009; Merkin et al., 2009; Parente et al., 2013; Peek et al., 2010; Tomfohr et al., 2016; Wallace et al., 2013). Some studies adjusted for various covariates and some studies did not account for covariates. Two studies reviewed found no racial differences in AL (Hawkley et al., 2011; T. Seeman et al., 2010). Of these two studies, one was a study that used SEM methods to study allostatic load with 55% black participants (in contrast to the regression analyses using composite allostatic load typically used), and one was a study of older adults with equal percentages of black, white and Hispanic participants (Hawkley et al., 2011; T. Seeman et al., 2010). Using typical regression analyses with composite allostatic load, the evidence supports the idea that black race is associated with higher allostatic load. It is less obvious what to conclude if the two contrasting results studies are included given that their samples and/or methods are different from the majority of the studies reviewed.

A number of studies have investigated the possibility of a relationship between allostatic load and socioeconomic status (SES). SES has been operationalized in a

variety of ways, including poverty status, education, occupation, income, self-reported financial status as compared to others, self-assessed current financial status, difficulty paying bills, and/or a composite index of some of these variables (Crimmins et al., 2009; Geronimus et al., 2006; Glei, Goldman, Chuang, & Weinstein, 2007; Gruenewald et al., 2012; Hawkley et al., 2011; Kubzansky, Kawachi, & Sparrow, 1999; T. Seeman et al., 2008; T. E. Seeman et al., 2004; Upchurch et al., 2015; Weinstein, Goldman, Hedley, Yu-Hsuan, & Seeman, 2003). One study from Taiwan added sex to their composite SES measure (Weinstein et al., 2003). Regardless of how SES was measured, each study reviewed found that lower SES was associated with higher allostatic load (Crimmins et al., 2009; Geronimus et al., 2006; Glei et al., 2007; Gruenewald et al., 2012; Hawkley et al., 2011; Kubzansky et al., 1999; T. Seeman et al., 2008; T. E. Seeman et al., 2004; Upchurch et al., 2015; Weinstein et al., 2003). Two studies examined potential mediators for the SES-AL relationship (Hawkley et al., 2011; Upchurch et al., 2015). In a study of middle aged US women ages 42-52, perceived stress, discrimination and hostility mediated relationship between income and allostatic load while perceived stress and hostility mediated relationship between education and allostatic load (Upchurch et al., 2015). A separate study of older US adults ages 51-69 examined stress, personality, psychosocial factors, coping, social networks and health behaviors as potential mediators of the SES-allostatic load association; of the variables examined, only poor sleep quality and hostility mediated the SES-allostatic load relationship (Hawkley et al., 2011).

In addition to being used as a proxy for SES or as part of a composite of SES, education level and income have been treated as an independent item in studies of

allostatic load. Frequently studies will control for education level or income but do not examine them or report on their impact on allostatic load directly. As with the studies using education as a factor in composite SES, lower education levels alone have been found to be associated with increased levels of allostatic load after controlling for sociodemographic and lifestyle factors (Chyu & Upchurch, 2011; Hux, Roberts, & Okun, 2017; T. Seeman et al., 2008; T. E. Seeman et al., 2004; Sun et al., 2007; Upchurch et al., 2015; Weinstein et al., 2003). Fewer studies have looked at income alone, but the available evidence indicates higher income is associated with lower allostatic load (Chyu & Upchurch, 2011). One study directly examined the relationship between poverty status and allostatic load (Crimmins et al., 2009). People who were poor had higher allostatic load than those who are not poor in their 20's, 30's, 40's, 50's, 60's and 70's (Crimmins et al., 2009). The effect disappeared in later ages (Crimmins et al., 2009).

Allostatic Load and Cognitive-Behavioral Responses to Stress

There is significantly less evidence about the relationship between allostatic load and the cognitive-behavioral factors of alcohol, tobacco, physical activity and depression. Only two studies were identified that examined lifestyle factors, including alcohol, tobacco, and physical activity, and allostatic load. One study reported that alcohol use predicted higher allostatic load in men but not in women (Hampson, Goldberg, Vogt, Hillier, & Dubanoski, 2009), while the other found no relationship between alcohol and allostatic load after controlling for covariates (Gustafsson, Janlert, Theorell, Westerlund, & Hammarström, 2011). Both studies found that smoking predicted higher allostatic load

in men but not in women, and reported that low physical activity predicted higher allostatic load in men but not in women (Gustafsson et al., 2011; Hampson et al., 2009).

The relationship between depression and allostatic load is not well established, but there is some limited evidence linking depression and allostatic load. In a study using a nationally representative sample, higher allostatic load was associated with increased depressive symptoms (Kobrosly, Seplaki, Cory-Slechta, Moynihan, & van Wijngaarden, 2013). Similar results were found in a study of community-based older adults (average age 76) (Kobrosly, van Wijngaarden, Seplaki, Cory-Slechta, & Moynihan, 2014). In a longitudinal study of older adults followed for six years, increased AL was associated with increased depressive symptoms in the same year of measurement, but there was no relationship between baseline allostatic load and future depressive symptoms (Juster, Marin, et al., 2011). A cross-sectional study of healthy workers from various professions found no association between allostatic load and depression (Juster, Sindi, et al., 2011).

Allostatic Load and Sleep

Studies of sleep duration and allostatic load have shown mixed results. Some studies have found short sleep duration to be associated with increased allostatic load, others have shown conflicting results; the same is true for studies of long sleep duration and allostatic load (J.E. Carroll et al., 2015; X. Chen et al., 2014; Clark et al., 2014). As with studies of sleep and future cancer, operationalization of short and long sleep duration was variable. Allostatic load has also been examined in relation to sleep disorders. The prevalence of increased mean allostatic load was high among adults with

sleep apnea, snoring, snorting/stop breathing, insomnia and diagnosed sleep disorders compared with persons without any sleep disturbances (X. Chen et al., 2014).

Only one study was identified that examined subjective sleep quality and allostatic load. In this study, black race was associated with allostatic load and this relationship was mediated in part by subjective sleep quality (Tomfohr et al., 2016). In serial mediation analyses, Tomfohr et al (2016) showed that there was a relationship between black race and discrimination, which was then related to the experience of anger, which then impacted subjective sleep quality, which then resulted in an increased allostatic load. This validates the conceptual framework for stress response depicted in Figure 1.

Although few studies of sleep and overall allostatic load were identified for review, some studies of sleep and individual biomarkers thought to be associated with allostatic load were found. Experimental sleep deprivation has been shown to reduce insulin sensitivity, impair glucose tolerance, and reduce insulin secretion (Broussard, Ehrmann, Van Cauter, Tasali, & Brady, 2012; Gonnissen, Hursel, Rutters, Martens, & Westerterp-Plantenga, 2013; Nedeltcheva, Kessler, Imperial, & Penev, 2009; Spiegel, Leproult, & Van Cauter, 1999; Van & Spiegel, 1999). Experimental sleep fragmentation and sleep deprivation have been shown to be associated with an increase in blood pressure readings and an increased risk for hypertension (Carrington & Trinder, 2008; Mullington, Haack, Toth, Serrador, & Meier-Ewert, 2009; Palagini et al., 2013). Similarly, self-reported short sleep duration and long sleep duration were associated with increased odds of having hypertension compared with normal (Gottlieb et al., 2006).

Sleep restriction has also been shown to impact heart rate variability in the direction of sympathetic activation (Spiegel et al., 1999; Van & Spiegel, 1999).

Half of the identified studies of experimental sleep deprivation and cortisol show altered cortisol levels by reducing levels and flattening diurnal rhythms, and the other half found cortisol levels increased or unchanged with sleep deprivation (Nedeltcheva et al., 2009; Omisade, Buxton, & Rusak, 2010; Pejovic et al., 2013; Redwine, Hauger, Gillin, & Irwin, 2000; Spiegel et al., 1999; Van & Spiegel, 1999; A. N. Vgontzas et al., 2004; von Treuer, Norman, & Armstrong, 1996; Wright et al., 2015). A handful of experimental studies have shown sleep deprivation increases IL-6 production (Irwin, Wang, Campomayor, Collado-Hidalgo, & Cole, 2006; Irwin et al., 2015; Pejovic et al., 2013; Redwine et al., 2000; A. N. Vgontzas et al., 2004). A systematic review of 72 studies of inflammation and sleep found that short sleep duration was associated with higher CRP and that long sleep duration was associated with higher CRP and IL-6 (Irwin, Olmstead, & Carroll, 2016). A longitudinal study found that insomnia and short sleep duration at baseline was associated with higher CRP and IL-6 five years later (Cho, Seeman, Kiefe, Lauderdale, & Irwin, 2015). Experimental sleep deprivation has been shown to be associated with increased epinephrine and norepinephrine (Nedeltcheva et al., 2009).

There are two studies that have examined the effects of sleep problems in natural settings. Among undergraduate men, shorter cumulative sleep time was associated with decreased heart rate variability during stress tests and prolonged increases in heart rate and diastolic blood pressure after stress tests (Mezick, Matthews, Hall, Richard Jennings,

& Kamarck, 2014). Among middle-aged women, higher sleep latency (or the time it takes to go from a fully awakened state to sleep) was associated with increased CRP, IL-6 and insulin resistance (Kim et al., 2016).

Allostatic Load and Health Outcomes

Physical and cognitive functioning. A few studies have examined allostatic load in relation to physical functioning and cognitive functioning. In terms of physical functioning, high allostatic load at baseline has been shown to be associated with worse physical functioning over time among the elderly (Karlamangla, Singer, McEwen, Rowe, & Seeman, 2002; T. E. Seeman, McEwen, Rowe, & Singer, 2001; T. E. Seeman et al., 1997). Similarly, allostatic load has been shown to be associated with frailty among the elderly (Gruenewald, Seeman, Karlamangla, & Sarkisian, 2009; Szanton, Allen, Seplaki, Bandeen-Roche, & Fried, 2008). A few longitudinal and cross-sectional studies have found that higher allostatic load is associated with worse cognitive functioning among the elderly (Karlamangla et al., 2014, 2002, T. E. Seeman et al., 2001, 1997). One longitudinal study of cognitive functioning and allostatic load did not find a relationship between overall composite allostatic load and cognitive functioning, but instead identified an association between the higher secondary outcomes allostatic load subscore and worse cognitive functioning in an elderly sample (Goldman et al., 2006). In the lone study of non-elderly subjects, patients with chronic fatigue syndrome with higher allostatic load had worse physical functioning; this relationship was not found among healthy controls (Goertzel et al., 2006).

Allostatic load and morbidity and mortality. A few studies have examined relationships between allostatic load and various health outcomes. Bone strength, chronic fatigue, delirium in hospitalized patients, and depression have been studied in relation to allostatic load. Higher allostatic load was found to be associated with lower bone density among men and women (Mori et al., 2014). Higher allostatic load was associated with worse bodily pain symptoms and more frequent, more intense fatigue symptoms among patients with chronic fatigue syndrome; this relationship was not found among healthy, non-fatigued controls (Goertzel et al., 2006). Overall composite allostatic load was not associated with delirium in elderly hospitalized patients, however an increase in a subscore of allostatic load (that included cortisol, norepinephrine, epinephrine and DHEA-S) did predict the incidence of delirium (Rigney, 2010). A longitudinal study of older adults found increased allostatic load was associated with increased depressive symptoms in the same year of measurement, but there was no relationship between baseline allostatic load and future depressive symptoms (Juster, Marin, et al., 2011). A cross-sectional study of healthy workers from various professions reported no association between allostatic load and depression (Juster, Sindi, et al., 2011). Both studies had small sample sizes (58 and 30 participants respectively) (Juster, Marin, et al., 2011; Juster, Sindi, et al., 2011). Lastly, studies of allostatic load and prevalent disease have indicated that higher AL was associated with abdominal obesity, hypertension, diabetes, cardiovascular disease and arthritis (Mattei, Demissie, Falcon, Ordovas, & Tucker, 2010; T. E. Seeman et al., 1997). Authors in a longitudinal study of

elder adults reported that baseline allostatic load was associated with the incidence of future cardiovascular events (T. E. Seeman et al., 2001).

A few studies examined allostatic load and mortality, and despite differences in methods, all of them found that higher allostatic load was associated with an increased all-cause mortality risk (Borrell, Dallow, & Nguyen, 2010; Goldman et al., 2006; Karlamangla, Singer, & Seeman, 2006; Robertson, Beveridge, & Bromley, 2017; T. E. Seeman et al., 2004, 2001). One study treated allostatic load as a mediator of the SES-mortality relationship and found that allostatic load explained 35.4% of the difference in mortality risk between people who had high SES and people who had low SES (T. E. Seeman et al., 2004). Similar to the studies of mortality, one study examined relationships between life expectancy, poverty and allostatic load (Crimmins et al., 2009). Those persons with the highest allostatic load levels had a life expectancy six years shorter than those persons with low allostatic load levels with similar poverty status and sex (Crimmins et al., 2009).

Allostatic Load and Cancer

Minimal investigation has been devoted to examining a potential relationship between allostatic load and cancer. In a cross-sectional study of breast cancer disparities between black and white women, black women with breast cancer were found elevated allostatic load, but this was not found in white women (Parente et al., 2013). This study used nine biomarkers of allostatic load from the cardiovascular, glucose, lipids, and inflammation domains of allostatic load (Parente et al., 2013). In a study of Puerto Ricans living in Boston, prevalent cancer was not associated with AL in Puerto Ricans

living in Boston (Mattei et al., 2010). This study used 10 biomarkers to comprise allostatic load from the HPA, sympathetic, cardiovascular, glucose and lipids domains of allostatic load (Mattei et al., 2010).

The remaining studies reviewed below evaluated the relationship between cancer and individual biomarkers instead of overall AL. Cortisol was the most commonly studied; flat cortisol patterns were found in subjects with cancer and were associated with decreased survival (Abercrombie et al., 2004; Bower et al., 2005; Cohen et al., 2012; Schrepf et al., 2015; S. E. Sephton et al., 2013; S. Sephton et al., 2000).

Preliminary research has demonstrated thyrotropin releasing hormone and growth hormone were higher in cancer patients prior to treatment while melatonin, thyroid stimulating hormone and IGF-I levels were higher in healthy controls (Mazzoccoli et al., 2003). In cancer patients undergoing treatment vascular endothelial growth factor, soluble intercellular adhesion molecule-1 (sICAM-1), soluble P-selectin and von Willebrand factor were all found to be higher post-chemotherapy as compared to pre-treatment levels (Mills et al., 2008). Interleukin-6, interleukin-10, and sTNF-R1 all increased over the course of chemotherapy and radiation treatment (Wang et al., 2010). Additionally, IL-6 and sTNF-R1 were associated with increased severity of cancer-related symptoms of fatigue and disturbed sleep (Wang et al., 2010).

Only one study was identified that investigated biomarkers as predictors of future cancer occurrence. A large case-cohort study from Italy (n=22,494) found that high blood glucose was associated with an increased risk in breast cancer up to 15 years later;

other biomarkers (cholesterol, blood pressure, obesity) were not associated with breast cancer risk (Agnoli et al., 2015).

Summary

The conceptual framework guiding this inquiry depicts individual differences impacting cognitive-behavioral responses to stress via perceived stress and impacting physiologic responses to stress directly. Cognitive-behavioral responses to stress impact physiological responses to stress. Finally, both cognitive-behavioral responses to stress and physical responses to stress can lead to disease.

A review of the literature demonstrated that cancer occurrence (disease), sleep (main cognitive-behavioral response to stress of interest), and allostatic load (physiologic response to stress) each have been shown to be impacted by individual differences. Gender, race, age, income, and education are related to each of these main concepts of interest in this proposed study, and therefore need to be included.

There is evidence that some cognitive-behavioral responses to stress are related to cancer. Alcohol use and smoking are firmly established as cancer risks. The evidence linking physical activity and cancer is weaker, but indicates a relationship is likely. Depression and depressive symptoms are frequently comorbid with cancer, but depression and future cancer occurrence and depressive symptoms and future cancer occurrence are understudied.

There is evidence that sleep is impacted by other cognitive-behavioral responses to stress including alcohol use, smoking, physical activity, and depression. Relationships between allostatic load and cognitive-behavioral responses to stress is scant. Initial

research reports from investigations of allostatic load and alcohol use, smoking, physical activity, and depression are mixed. The findings from the literature review underscore the need to include these cognitive-behavioral responses in this investigation.

As with other cognitive-behavioral factors, a relationship between sleep and allostatic load is understudied and the existing evidence is mixed. Preliminary research into allostatic load and diagnoses for sleep disorders demonstrated an increased prevalence of elevated allostatic load among people with sleep disorders such as sleep apnea and snoring. Some studies of short sleep duration and allostatic load and long sleep duration and allostatic load have found relationships while other studies have not identified such links. Additionally, each of the articles reviewed used a priori definitions of short and long sleep duration; none explored the data to identify relevant sleep duration cut points. A single study of subjective sleep quality and allostatic load reported a black race-allostatic load relationship was mediated in part by sleep quality (Tomfohr et al., 2016). Further investigation exploring a possible relationship between sleep and allostatic load is needed.

Sleep problems, including subjective sleep quality, disturbed sleep, and insomnia, are frequently comorbid with cancer. Sleep problems are known to occur across the cancer care trajectory, from before treatment initiation to survivorship. There is initial evidence that sleep parameters may be related to future cancer occurrence, but this is understudied. Initial evidence links short sleep duration and long sleep duration (as compared to healthy sleep) with future cancer occurrence, but studies of sleep duration and future cancer varied widely in their operationalization of short and long sleep

duration. As with sleep and allostatic load research, each of the articles of sleep duration and future cancer identified used a priori definitions of short and long sleep duration; none explored the data to identify relevant sleep duration. Preliminary evidence shows subjective sleep quality may play a role in future cancer, but this remains a largely unexplored relationship.

There is scant evidence of an association between allostatic load and cancer. Only two relevant studies were identified in this review. One cross-sectional study found black women with breast cancer had elevated allostatic load using nine biomarkers from four allostatic load domains (Parente et al., 2013). One cross-sectional study of Puerto Ricans living in Boston did not find a link between allostatic load and prevalent cancer using 10 biomarkers from 5 allostatic load domains (Mattei et al., 2010). Both of the identified studies examining cancer and allostatic load created an allostatic load composite using the sum of a priori clinical definitions of normal/abnormal biomarker results, a commonly used method of investigating allostatic load (Mattei et al., 2010; Parente et al., 2013). The problem with this approach to analyzing allostatic load is it can mask the impact of a particularly relevant biomarker and it fails to account for potential interrelationships between each of the biomarkers. Newer strategies for handling allostatic load, such as using structural equation modeling, allow for interactions among the indicators and for the impact of subclinical levels of biomarkers to be examined.

There is initial evidence demonstrating values for some individual biomarkers may be worse for people living with cancer, but the available findings mostly do not address future occurrence or recurrence of cancer. A single study of biomarkers and

future cancer was identified; researchers reported glucose is related to future cancer occurrence (Agnoli et al., 2015). The available findings are limited by the number of relevant studies, by populations studied, and by methodology for allostatic load. For example, it is suspected that inflammation may play a role in cancer development and progression (Korneev et al., 2017). However, of the allostatic load research identified for this literature review, inflammatory biomarkers were rarely included, and if inflammatory markers were included, it was only a single marker. Current knowledge of a relationship between comprehensive allostatic load and future cancer occurrence is limited and needs further investigation.

Regarding possible associations between cancer, cognitive-behavioral responses to stress, and physiologic responses to stress, no studies were identified that directly examined the relationship between sleep, allostatic load, and future cancer occurrence. As noted above, there is some evidence of a relationship between sleep and future cancer, while there is scant knowledge about a link between allostatic load and sleep and allostatic load and future cancer.

The proposed study will help to address the identified gaps in knowledge. Longitudinal data from a national sample of middle ages adults will be used to identify associations between the concepts of interest and future occurrence of cancer. Sleep measures include sleep duration and several domains of sleep quality, including sleep latency, habitual sleep efficiency, sleep disturbance, use of sleep medication, daytime dysfunction, and overall sleep quality. Methods addressing sleep duration will include a priori categories of short, normal, and long sleep duration based on sleep duration

recommendations from the National Sleep Foundation as well as cut points for short, normal, and long sleep duration identified from exploration of the actual data. Allostatic load will be treated as a latent variable measured by observed indicators comprised of biomarkers, physical exam measures, and psychophysiological measures, and structural equation methods will be used to model the complexity of allostatic load and allow for interrelationships between indicators. The expected knowledge gained in this study will illuminate predictors of future cancer occurrence and evaluate the influence of cognitive-behavioral responses to stress (sleep) and physiologic responses to stress (allostatic load) on future cancer. Findings will provide areas for possible intervention in cancer prevention efforts.

CHAPTER III

METHODS

Purpose

The purpose of this study was to identify cognitive-behavioral responses to stress and physiological responses to stress that are related to future disease, specifically future cancer occurrence. The primary cognitive-behavioral response to stress studied was sleep. Other cognitive-behavioral factors of interest included depression, physical activity, smoking and alcohol use. The physiologic response to stress studied was allostatic load. Allostatic load is comprised of biomarkers, physical measures, and psychophysiologic measures. Relevant individual differences included in the analysis in the context of their relationship to stress responses were age, race, gender, education and income.

Research Questions and Hypotheses

1. Research Question 1. Is there a relationship between sleep and future cancer occurrence among middle-aged adults in the United States?

Hypothesis 1.1: Poor self-reported, subjective sleep quality will be associated with increased future cancer occurrence.

Hypothesis 1.2: Short sleep duration and long sleep duration as compared to normal/healthy sleep duration will be associated with increased future cancer occurrence.

2. Research Question 2. Is there a relationship between allostatic load and occurrence of future cancers among middle-aged adults in the United States.? If there is, are there physiologic domains that are associated with the occurrence of future cancers?

Hypothesis 2.1: Increased allostatic load will be associated with increased occurrence of future cancers.

Hypothesis 2.2: The inflammation domain, sympathetic nervous system domain, and hypothalamic-pituitary-adrenal axis domain will be associated with the occurrence of future cancers.

3. Research Question 3. Is there a relationship between sleep and allostatic load among middle-aged adults in the United States? If a relationship exists, are there physiologic domains that are associated with sleep?

Hypothesis 3.1: Poor self-reported, subjective sleep quality will be associated with increased allostatic load.

Hypothesis 3.2: Short sleep duration and long sleep duration as compared to normal/healthy sleep duration will be associated with increased allostatic load.

Hypothesis 3.3: Poor sleep will be associated with the inflammation domain, glucose domain, lipid domain, and cardiovascular domain.

4. Research Question 4. If a relationship exists between sleep and the occurrence of future cancers among middle-aged adults, does allostatic load mediate that relationship?

Hypothesis 4.1: Allostatic load will mediate the sleep-future cancer occurrence relationship.

Methods

This study was a secondary analysis of existing data from the Midlife in the United States (MIDUS) study. MIDUS is a longitudinal study of the health of middle-aged Americans ("Midlife in the United States, A National Longitudinal Study of Health and Well-being," 2011). Begun in 1995, there have been three rounds of data collection, and more are planned ("Midlife in the United States, A National Longitudinal Study of Health and Well-being," 2011). In the second wave of data collection (known as MIDUS II), a subset of the MIDUS subjects participated in the collection of samples of biological samples, underwent a physical exam, and answered detailed questions about their health history and habits; this was termed the Biomarker Project. Data for the Biomarker Project was collected from 2004 to 2009. In the third wave of data collection, updated health history was collected from participants, including questions about medical problems such as cancer, from 2013-2014; this project is termed MIDUS III. Details about the sampling plan for all MIDUS time points, methods for data collection, inclusion and exclusion criteria and other information related to MIDUS research procedures can be found on the MIDUS website at http://midus.wisc.edu/ and on the Inter-University Consortium for Political and Social Research website where the data is housed at https://www.icpsr.umich.edu/icpsrweb/index.jsp. The original MIDUS sample included four subsamples: a national random digit dialing sample, oversamples from five large metropolitan cities, siblings of the participants from the random digit dialing sample, and a national random digit dialing sample of twin pairs (Brim et al., 2016). Samples for subsequent MIDUS waves were derived from this original sample. MIDUS

II added new participants, an oversample of African Americans from Milwaukee (Brim et al., 2016).

Sample

The sample for this project came from the Biomarker Project of MIDUS II (data collection at time one for the current study) and MIDUS III (time two for the current study). A total of 1,255 people participated in the Biomarker Project (C. D. Ryff, Seeman, & Weinstein, 2013c). Subjects who reported having a cancer either on the MIDUS II telephone survey or in the MIDUS II Biomarker Project were excluded from participating in this study. Data were then merged with MIDUS III telephone survey results for the question "have you ever had cancer". Data missing on this question were excluded. A final sample size of 806 participants was used for further analysis. In this sample, there were 78 cases of cancer.

For analyses utilizing allostatic load, 7 cases missing significant numbers of allostatic load indicators were excluded. Another 5 cases missing significantly on the glucose system factor indicators and another 25 cases missing significantly on sympathetic system indicators were excluded. For all analyses involving allostatic load, this resulted in a final sample size of 769 that includes 77 cases of cancer.

Data Collection

At time one for the proposed study, the existing MIDUS II Biomarker Project data collection took place over the course of two days at a data collection center. Medical history, self-administered questionnaire, and the Pittsburgh Sleep Quality Questionnaire data were obtained the evening of day one (C. D. Ryff et al., 2013c). Twelve hour urine

collection was initiated the evening of day one (C. D. Ryff et al., 2013c). The morning of day two, 12 hour urine collection was completed, fasting bloodwork was obtained, the psychophysiology experiment was conducted, and the short physical exam (vital signs, waist and hip measures, functional measures) was conducted (C. D. Ryff et al., 2013c). At time two for the proposed study (MIDUS III), cancer diagnosis since time one was assessed during a telephone conversation with a trained interviewer.

Measurement

Multiple variables and indicators of the conceptual framework were used. Tables 1 and 2 provide a list of concepts and variables.

Table 1

Concepts of Interest, Conceptual Definitions, and Indicators

Concept of Interest	Conceptual Definition	Indicator	Indicator Definition	Variable Measured	Response Set
Disease	A change from normal functioning that causes harm	Cancer	"Uncontrolled growth and spread of abnormal cells" (National Cancer Institute, n.d.-c)	Self-reported history of cancer	Yes/No
Individual differences	Personal characteristics and experiences	Age	The length of a person's life in years	Self-reported number of years of life	Years
		Gender/ Sex	Gender as behavioral cultural or psychological traits typically associated with one particular sex, and sex is defined as biological characteristic determined by a person's sex organs	Self-reported gender	Male/Female

		Race	A categorization of humans based on select physical characteristics, typically skin color	Self-reported race	White/Not white
		Education	The highest type of formal learning program participated in	Self-reported highest education level achieved	- Less than a high school diploma - High school graduate/GED or equivalent - Some college or AA degree - College graduate or above
		Income	Amount of incoming financial resources (whether in dollars or some kind of government assistance) for respondent's household	Self-reported household income	- <$20,000 - $20,000-$39,999 - $40,000-$59,999 -$60,000-$74,999 - $75,000 or more
Cognitive-behavioral responses	Thoughts, reasoning, feelings, and actions in response to stimuli	Sleep	"The natural periodic suspension of consciousness during which the powers of the body are restored" (Merriam-Webster, 2017b).	Self-reported hours of sleep duration	Hours

Subjective sleep quality	Component score 0, 1, 2, or 3
Subjective sleep latency	Component score 0, 1, 2, or 3
Subjective sleep duration	Component score 0, 1, 2, or 3
Subjective habitual sleep efficiency	Component score 0, 1, 2, or 3
Self-reported sleep disturbances	Component score 0, 1, 2, or 3
Self-reported use of sleep medication	Component score 0, 1, 2, or 3
Self-reported daytime dysfunction	Component score 0, 1, 2, or 3
Subjective global sleep quality	Good sleep (5 or less)/Poor sleep (>5) derived from total score of 0 - 21

Alcohol Use	The consumption of alcohol containing beverages	Self-reported alcohol use in past month	Any/None
Smoking	Use of cigarettes at present or in the past	Self-reported cigarette use history	Ever/Never
Physical Activity	Participation in active leisure-time activities that result in raised heart rate and sweating	Self-reported exercise (at least 20 minutes 3 times per week)	Yes/No
Depressive Symptoms	Self-reported complaints of symptoms commonly associated with depression including "depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite and sleep disturbance" (Radloff, 1977, p. 386)	Self-reported depression symptom-ology	Score of 16 or more/score less than 16 derived from total score of 0 - 60

Physiologic responses	Biologic embodiment of reaction to stimuli	Allostatic Load	"The wear and tear on the body and brain resulting from chronic overactivity or inactivity of physiological systems that are normally involved in adaptation to environmental challenge" (Bruce S. McEwen, 1998b, p. 37).	Please see Table 2

Table 2

Allostatic Load Component Conceptual Definitions and Indicators

Physiologic domain	Conceptual Definition	Indicator	Indicator Definition	Variable Measured
Sympathetic nervous system	One branch of the autonomic nervous system that is responsible for the fight-or-flight stress response	Norepinephrine	A hormone involved in the body's response to stress. Its actions on the body include increasing blood pressure, increasing blood flow to the heart and relaxation of intestinal muscles ("Noradrenaline," 2014).	12 hour urinary norepinephrine (ng/mL)

		Epinephrine	A hormone involved in the body's acute response to stress. Its actions on the body include increasing heart rate, increasing respiratory rate, slowing blood flow to the digestive tract, and increasing metabolism ("Adrenaline," 2014).	12 hour urinary epinephrine (ng/mL)
Parasympathetic nervous system	One branch of the autonomic nervous system that is responsible for the body's unconscious functions that occur at rest, such as salivation and digestion	Standard deviation of beat to beat intervals (HRV)	The standard deviation of the distance between each heart beat recorded by an electrocardiograph (EKG) (Allen, Chambers, & Towers, 2007).	
		Root mean square of successive differences of beat to beat intervals (HRV)	The square root of the mean of squared successive differences of the distance between each heart beat recorded by an EKG (Allen et al., 2007).	
		Low frequency heart rate variability	The number of low frequency (0.04-0.15 Hz) bands in beat-to-beat intervals that have been transformed into frequency (Allen et al., 2007).	

		High frequency heart rate variability	The number of high frequency (0.15-0.50 Hz) bands in beat-to-beat intervals that have been transformed into frequency (Allen et al., 2007).	
		Heart rate	Heart rate is the number of beats per minute.	
Hypothalamic-pituitary-adrenal axis	A system of complex endocrine interactions involving the hormones from the hypothalamus, pituitary, and adrenal endocrine glands; is influenced by the experience of stress; is involved in regulating many other physiologic systems	Cortisol	A hormone used in metabolism and in response to stress.	12 hour urinary cortisol (ug/dL)
		DHEAS	A hormone produced by the adrenal glands thought to play a role in aging	serum DHEAS (ug/dL)
Inflammation	Cellular level reaction to injury	C reactive protein	A protein associated with infections and inflammation ("C-reactive protein," 2014).	serum CRP (ug/mL)

	Interleukin 6	A protein involved in immunity that has both pro-inflammatory and anti-inflammatory actions and is thought to play a role in cancer development and progression (Korneev et al., 2017).	serum IL6 (pg/mL)
	Fibrinogen	A coagulation factor that has pro-inflammatory actions and is associated with cancer (“Fibrinogen,” 2014; Davalos & Akassoglou, 2012).	serum fibrinogen (mg/dL)
	Soluble E-selectin	Acellular adhesive molecule associated with inflammation that also appears to play a role in cancer	serum E-selectin (ng/mL)
	Soluble intracellular adhesion molecule 1	A cellular adhesion molecule associated with inflammation.	serum ICAM-1 (ng/mL)
Cardiovascular	Systolic BP	The pressure exerted on artery walls during systole (“Blood pressure,” 2014).	systolic BP (mmHg)
	Pulse Pressure	Calculated difference between systolic blood pressure reading and diastolic blood pressure reading.	pulse pressure (mmHg)

Glucose	Glucose	A simple sugar whose blood levels are maintained by hormones such as insulin and glucagon (“Glucose,” 2014).	serum glucose (mg/dL)
	Glycated hemoglobin	A form of hemoglobin with a molecule of glucose attached; the percent of hemoglobin that is glycated depends on blood levels of glucose (“Glycated haemoglobin,” 2014).	serum HbA1c (%)
	Homeostatic model of insulin resistance	A calculated measure of insulin resistance based on fasting glucose and fasting insulin (Matthews et al., 1985).	calculated HOMA-IR
Lipid	Waist to hip ratio	A measure of obesity calculated from the circumference of the waist and the hips (“Waist to hip ratio,” 2016).	waist and hip circumference
	High-density lipoprotein	A protein that transports cholesterol in the body and helps to remove cholesterol from the bloodstream (“High-density lipoprotein,” 2016).	serum HDL (mg/dL)
	Low-density lipoprotein	The main protein involved in transporting cholesterol in the bloodstream (“Low-density lipoprotein,” 2016).	calculated LDL

	Triglycerides	Glycolipids made up of glycerol and three fatty acids and are the manner in which digested fat is transported in the bloodstream (“Triglyceride,” 2016).	serum triglycerides (mg/dL)

The discussion below explains details of measurement in the original data collection and differences in the present study.

Outcome of interest. Cancer diagnosis at time two was assessed with a single question "have you ever had cancer?" via telephone interview. Reponses were recorded as a dichotomous "yes" or "no".

Cognitive-behavioral responses to stress. Cognitive-behavioral responses to stress were obtained at time one. Information on sleep quality was measured by the Pittsburgh Sleep Quality Index (PSQI), a commonly used subjective measure of sleep quality (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). This was collected at time one. The PSQI has been shown to be a reliable and valid measure of sleep quality, with a Cronbach's alpha coefficient ranging from 0.70 to 0.83 (Mollayeva et al., 2016). The PSQI is a 19-item measure with content in seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction (Buysse et al., 1989). Respondents are asked to answer the PSQI questions in relation to their experience of sleep in the past month (Buysse et al., 1989). Results for each domain are calculatedly separately, and an overall global score of sleep quality is calculated from the sum of the seven domains (Buysse et al., 1989). Total PQSI scores can range from 0 to 21, and possible domain scores range from 0 to 3 (Buysse et al., 1989). Higher scores on the individual PQSI domains indicate poorer sleep quality (Buysse et al., 1989). Per PSQI scoring instructions, total global PSQI is a binary variable, and participants whose sum of the seven sleep domain scores is 5 or more are considered to have poor sleep quality, while participants' scores of 5 or less

are considered normal sleep quality. In the current study, each of the individual domains as well as the global score of sleep quality were examined in relation to future cancer and allostatic load. The sleep efficiency domain calculated the difference between total time spent in bed and time spent asleep in bed. Thirty-eight cases reported a time asleep in bed greater than 100% of the total time in bed, but this is not possible. The global score for PSQI for these 38 cases was not calculated and left as missing data. The PSQI domain of sleep duration defines normal sleep as 7 hours per night or more; the other categories of sleep are 6-7 hours per night, 5-6 hours per night, and <5 hours per night (Buysse et al., 1989).

In the current study, additional variables defining sleep duration were examined in relation to future cancer occurrence and allostatic load. Sleep duration was treated as a continuous variable in hours as well as transformed into a categorical variable (short, normal, or long sleep). Both short sleep duration and long sleep duration were compared to normal sleep as the reference group. As there is no clear consensus in the literature about what constitutes short sleep duration and long sleep duration in relation to future cancer, sleep recommendations for adults from the National Sleep Foundation (NSF) were used to determine a priori categorizes for sleep duration. The NSF recommends 7 to 9 hours of sleep per night for adults aged 18 to 64, and 7 to 8 hours of sleep per night for adults 65 and older (Hirshkowitz et al., 2015b). However, the distribution of the data showed few participants sleeping more than 9 hours per day. As 7 to 8 hours of sleep per night is also considered normal for all adults 18 years and older, the decision was made to stratify sleep hours based on 7 to 8 hours as normal sleep. NSF sleep duration categories

were dummy coded into short (<7 hours of sleep per night), normal or referent (7-8 hours of sleep per night), and long sleep duration (>8 hours of sleep per night). Finally, the data were explored for relevant sleep duration categories based on cancer diagnosis in the future. A Chi-squared Automatic Interaction Detector (CHAID) decision tree in SPSS was used to identify categories of sleep duration based on future cancer occurrence. The CHAID decision tree examined data inputs to identify categorical cut points that minimize p-values. Results were dummy coded into short, normal (or referent), and long sleep duration categories.

Physical activity level was assessed with a single item. Participants were asked "do you engage in regular exercise, or activity, of any type for 20 minutes or more at least 3 times/week?" (C. Ryff et al., 2012c). Responses were recorded dichotomously as "yes" or "no". Assessing physical activity via self-report is a commonly used measurement method (Sylvia, Bernstein, Hubbard, Keating, & Anderson, 2014). Smoking status was a binary variable that denoted which subjects have ever smoked versus those that have never smoked (C. Ryff et al., 2012c). This is a standard measurement of assessing smoking status prevalence (Global Adult Tobacco Survey Collaborative Group, 2011). Alcohol use was assessed in the MIDUS Biomarker Project by asking how often alcoholic beverages were consumed on an average basis over the past month (C. Ryff et al., 2012c). For the current study, ordinal level responses ranging from every day to never were collapsed into a binary variable: any alcohol consumption in the past month versus no alcohol use in the past month. Measures of

self-reported alcohol use have been commonly used and were generally accurate (Sobell & Sobell, 2004).

Depressive symptoms were assessed using the Center for Epidemiological Studies Depression Inventory (CESD). The CESD is a commonly used measure of depressive symptoms with established reliability and validity in numerous populations as well the general population (Devins et al., 1988; Radloff, 1977; Roberts & Vernon, 1983). The Cronbach's alpha of the CESD in the general population ranges from 0.84 to 0.90 (Radloff, 1977). The CESD depression scale is comprised of 20 items assessing the experience of depressive symptoms over the past week (Radloff, 1977). Four of the items are stated in such a way as to not reflect depressive symptoms and must be reverse coded (Radloff, 1977). Then the number of affirmative answers are summed to give a total score that can range from 0 to 20 (Radloff, 1977). Higher scores indicated a greater number of depressive symptoms (Radloff, 1977). For the current study, depressive symptoms were transformed into a binary variable based on a cutoff score of 16 on the CESD; scores of 16 or more indicate probable clinical depression (Beekman et al., 1997; Lewinsohn, Seeley, Roberts, & Allen, 1997).

Physiologic response to stress. Physiologic response to stress was assessed at time one. Allostatic load was comprised of biomarkers, physical measures, and psychophysiologic measures from multiple physiologic systems obtained at time one. These measures are divided amongst seven physiologic domains of allostatic load as specified in Wiley et al (2016). The physiologic domains used in this study were sympathetic nervous system, parasympathetic nervous system, hypothalamic-pituitary-

adrenal axis, inflammation, cardiovascular, glucose, and lipid domains. Please see Table 2 for a complete list of domains and their associated measures.

Biomarkers. Three measures of serum lipids were used, including high-density lipoprotein (HDL), triglycerides (TG), and low-density lipoprotein (LDL). Low density lipoprotein (LDL) was a calculated variable from total cholesterol, HDL and TG using the Fridewald formula (LDL = TC-HDL-TG/5) (C. D. Ryff, Seeman, & Weinstein, 2013a). The LDL calculation is unreliable if TG are greater than 400 mg/dL, therefore 400 mg/dL was the value used for TG in the calculation of LDL (C. D. Ryff et al., 2013a). Additionally, extreme results from cholesterol testing that were altered. If HDL was greater than 120 mg/dL, it was truncated to 121 mg/dL regardless of value (C. D. Ryff et al., 2013a). Subsequently, calculations for LDL were made used this altered value of HDL (C. D. Ryff et al., 2013a). For the three measures of serum lipids were used as continuous variables.

Measures of inflammation were serum C-reactive protein (CRP), interleukin 6 (IL6), fibrinogen (FG), soluble E-selectin (ES), and soluble intracellular adhesion molecule-1 (ICAM-1). CRP is a protein associated with infections and inflammation ("C-reactive protein," 2014). IL6 is a protein involved in immunity that has both pro-inflammatory and anti-inflammatory actions and is thought to play a role in cancer development and progression (Korneev et al., 2017). FG is a coagulation factor ("Fibrinogen," 2014). It also has pro-inflammatory actions and is associated with cancer (Davalos & Akassoglou, 2012). ES is a cellular adhesive molecule associated with inflammation that also appears to play a role in cancer (Natoni, Macauley, & O'Dwyer,

2016). ICAM-1 is a cellular adhesion molecule associated with inflammation (Dowd, Goldman, & Weinstein, 2011). Extreme results for inflammatory markers were altered. CRP results less than 0.15 ug/dL or less than 0.16 ug/dL were reported as 0.14 ug/dL (C. D. Ryff et al., 2013a). ES results less than 0.1 ng/mL were reported as 0.09 ng/mL (C. D. Ryff et al., 2013a). ICAM-1 results less than 45 ng/mL were reported as 44 ng/mL (C. D. Ryff et al., 2013a). For the current study, CRP, IL6, FG, ES, and ICAM-1 are continuous variables.

Glucose is a simple sugar whose blood levels are maintained by hormones such as insulin and glucagon; high levels are associated with diabetes ("Glucose," 2014). Glycated hemoglobin (HbA1c) is a form of hemoglobin with a molecule of glucose attached ("Glycated haemoglobin," 2014). The percent of hemoglobin that is glycated depends on blood levels of glucose ("Glycated haemoglobin," 2014). Percent HbA1c was calculated by dividing the concentration of HbA1c by the total concentration of hemoglobin (C. D. Ryff et al., 2013a). Homeostatic model of insulin resistance (HOMA-IR) is a calculated measure of insulin resistance based on fasting glucose and fasting insulin (Matthews et al., 1985). HOMA-IR was calculated by multiplying fasting glucose by insulin and then dividing the result by 405 (C. D. Ryff, Seeman, & Weinstein, 2013e). Glucose, HbA1c, and HOMA-IR are continuous variables.

Cortisol is a hormone used in metabolism and in response to stress ("Cortisol," 2014). There was variability in the minimum amount of cortisol detectable by the assay for 12-hour urinary cortisol over the duration of data collection (C. D. Ryff et al., 2013a). To handle this, all cortisol levels reported with a "<" sign were recorded as 0.019 ug/dL

(C. D. Ryff et al., 2013a). Dihydroepiandrosterone sulfate (DHEAS) is a hormone produced by the adrenal glands thought to play a role in aging (Allolio, Arlt, & Hahner, 2012). Extreme DHEAS results were altered. DHEA-S results less than 1 ug/dL were all reported as 0.9 ug/dL (C. D. Ryff et al., 2013a). For the current study, both the 12-hour urinary cortisol and serum DHEAS variables were continuous.

Epinephrine and norepinephrine are hormones involved in the body's acute response to stress. Extreme results from catecholamine testing were altered. Urinary epinephrine results less than 0.05 ng/mL were recorded as 0.09 ng/mL (C. D. Ryff et al., 2013a). Overnight 12-hour urinary norepinephrine and epinephrine were continuous variables and the latter was truncated.

Physical exam measures. Systolic blood pressure (SBP) was measured in accordance with standard practices three times consecutively with a maximum of 30 seconds between each measurement (Centers for Disease Control and Prevention, 2017d; C. D. Ryff, Seeman, & Weinstein, 2013b). An average of the three SBP measurements reported in mm Hg was used in this study. Pulse pressure was a calculated variable derived from the difference between average SBP from 3 measurements and average diastolic blood pressure from 3 measurements. Waist-hip ratio (WHR) was a calculated variable obtained from the measurement of the subject's waist divided by the measurement of the subject's hips (Harvard T.H. Chan School of Public Health, 2012; C. D. Ryff et al., 2013b, 2013e). For the current study, SBP, pulse pressure, and WHR were continuous variables.

Psychophysiology measures. Measures of heart rate variability were calculated from an EKG obtained while seated, at rest, over several minutes (C. D. Ryff, Seeman, & Weinstein, 2013d). Heart rate variability at rest is governed by the parasympathetic nervous system (Allen, Chambers, & Towers, 2007). Resting heart rate was calculated as an average of all RR intervals and was converted from RR intervals into beats per minute (C. D. Ryff et al., 2013d). Two time-domain measures of heart rate variability will be used, the standard deviation of RR intervals (the standard deviation of the distance between each heartbeat, (SDRR)), and the root mean squared successive differences (the square root of the mean of squared successive differences of the distance between each heartbeat (rMSSD)). Two frequency-domain measures of heart rate variability were used, heart rate variability in the low frequency (LFHRV) and high frequency (HFHRV). LFHRV is the number of low frequency bands (0.04-0.15 Hz) in beat-to-beat intervals that have been transformed into frequency (Allen et al., 2007; C. D. Ryff et al., 2013d). HFHRV is the number of high frequency bands (0.15-0.50 Hz) in beat-to-beat intervals that have been transformed into frequency (Allen et al., 2007; C. D. Ryff et al., 2013d). For the current study, resting heart rate, SDRR, rMSSD, LFHRV, and HFHRV were continuous variables.

Individual differences. Individual differences were assessed at time one. Age was treated as a continuous variable measured in years, and MIDUS defined age as a person's age in years as of his or her last birthday (C. Ryff et al., 2012a). Gender of respondent was coded dichotomously as male or female. Race was assessed during the telephone interview by giving subjects a list of choices after asking subjects "which best

describes your race?" (C. Ryff et al., 2012d). For the current study, due to limitations in the sample composition, race was dichotomized into white versus not white. Education level was assessed in the telephone interview by asking respondents "what's the highest grade of school or year of college you completed?" (C. Ryff et al., 2012d). MIDUS utilizes 12 categories of education level (C. Ryff et al., 2012d). For the current study, educational level categories were collapsed into the four ordinal categories based on the National Health and Nutrition Examination Survey (NHANES) categories: less than a high school diploma, high school graduate/GED or equivalent, some college or AA degree, and college graduate or above (Centers for Disease Control and Prevention, n.d.). Income reflected the total annual income in dollars for a subject's household including income from wages, pensions, social security and government assistance (C. Ryff et al., 2012d). For the current study, continuous income was collapsed into five ordinal categories based on the NHANES income categories: <$20,000, $20,000-$39,999, $40,000-$59,999, $60,000-$74,999, and $75,000 or more (Centers for Disease Control and Prevention, n.d.)

Time. Although the preferred time metric was the duration of time between assessment of sleep parameters and allostatic load at time one and time to cancer diagnosis (or time to assessment of cancer status at time two for those participants without cancer), limitations in the data did not allow for this. Therefore, the time variable in this study used for analysis was the number of years between time one and time two.

Statistical Analysis

Exploratory data analysis was conducted in SPSS version 25 to examine data for its distribution, missing values and outliers, and multicollinearity (IBM Corp, 2017). There were three biologically implausible values for waist-to-hip ratio; these were changed to missing. Many of the indicators for allostatic load had extreme outliers. These were biologically plausible, but strongly impacted the distribution of the data. To address this, the upper and lower 0.5% of values for each indicator of allostatic load were Winsorized.

All variables in the data were checked for multicollinearity and no multicollinearity was found that would indicate inflated test statistics. The highest variance inflation factor found was for the HPA system at 3.10 (O'Brien, 2007). Correlation with cancer status at time 2 was assessed for all the variables of interest and none were found to be strongly correlated with cancer. Next, correlation with overall allostatic load and each of the seven domain-specific factor scores was assessed for all the variables of interest. There were weak correlations between depressive symptoms and the global PSQI score (0.36), between depressive symptoms and the daytime dysfunction domain of the PSQI (0.32), and between the HPA system and age (-0.43). The only moderate strength correlation identified was between overall allostatic load and gender (alpha was -0.58). The data for gender were coded as 1 for male and 2 for female, therefore a negative correlation indicates a potential association between male gender and allostatic load. In addition to analyzing the entire sample for a relationship between cancer and allostatic load, the data were stratified by gender and analyzed separately.

Power was calculated for research question 1 using G*Power (Faul, Erdfelder, Buchner, & Lang, 2009). Based on a hypothesized odds ratio of 1.5, an α of 0.05, and power of 0.8, the needed sample size is 709. Research questions 2, 3, and 4 which examine relationships between sleep (cognitive-behavioral response to stress), allostatic load (physiologic response to stress), and future occurrence of cancer (disease) were addressed via confirmatory factor analysis (CFA) due to the complex nature of the allostatic load concept. Power was estimated for the CFA analysis using McCallum et al's (1996) tables for power and sample size estimation in structural equation modeling. The estimated power for a sample size of 500 in a model with poor fit is 0.982 (MacCallum et al., 1996). As the sample size including allostatic load is 769, there was acceptable power in this analysis.

Initial exploration of the data included bivariate logistic regressions performed for cancer on every variable under consideration. Among the indicators of individual differences and cognitive-behavioral responses to stress other than sleep, the only significant relationship was found between age and future cancer. The odds of a future cancer occurring increase by 4% for each increase in age of one year. Relationships between future cancer and variables for gender, race, education, income, depressive symptoms, smoking status, alcohol use in past month, and physical activity were not found. Despite these null findings, since the conceptual framework specifically includes a number of factors for individual differences and cognitive-behavioral responses to stress based on existing evidence about relationships among these concepts, the decision

was made to proceed with analysis using all variables of interest rather than pursuing more parsimonious models at this time.

Even beyond the sibling relationships in the sample, the sampling strategy for the original MIDUS data was not random. In addition to sampling via random digit telephone dialing, some twin pairs and sibling groups were included, and African Americans, older Americans, and men were oversampled. MIDUS had calculated post-stratification using the Current Population Study from the Census Bureau sample weights for approximately half of the sample for the present study (C. Ryff et al., 2012b). Based on the sample weight calculations available for part of the sample of the current study, and in consideration of the MIDUS sample methods, bias, and overrepresentation, age, race, and gender were determined to be impactful to the present study. To account for these sampling issues, age, race, and gender, plus an interaction term of age X race X gender were included in every multivariate model.

Research question 1 examining sleep (cognitive-behavioral response to stress) and future cancer occurrence (disease) was addressed via logistic regression using Stata version 15 (StataCorp, 2017). The data were complex in that some participants in the sample are siblings from the same family and some of these are twin pairs. A solution to handling clustered sampling is using robust standard error estimating in analysis and accounting for the relationship amongst siblings. Additionally, there were only approximately 10% cancer cases in the data, causing concern for small sample bias (systematic error) in logistic regression. A solution that accounts for small sample bias was to use penalized maximum likelihood estimation, also called the Firth method (Firth,

1993). Unfortunately, it was not possible to both account for sibling groups in the data and to account for small sample bias impact on the error terms. To determine the best analytic method, logistic regression, logistic regression using a cluster-robust standard error estimator, and logistic regression using penalized maximum likelihood estimation were performed for each model of cancer on a sleep parameter. Based on comparisons of the standard error terms, there were few substantial differences between the model using logistic regression and the model using logistic regression with a cluster-robust standard error estimator. However, there were some instances where the standard error using penalized maximum likelihood estimation differed greatly from the other two. Therefore, the decision was made to proceed with analysis using Firth's penalized maximum likelihood estimation method.

The first step in answering research questions 2-4 was calculating allostatic load. Numerous methods of handling allostatic load and its associated indicators have been used over the years. This project utilized a recent allostatic load computation using confirmatory factor analysis (CFA) to generate the bifactor model for allostatic load as was validated by Wiley et al (2016). With this method, indicators were first loaded onto their appropriate physiologic domain (Wiley et al., 2016). Physiologic domains identified by Wiley et al (2016) are sympathetic nervous system, parasympathetic nervous system, hypothalamic-pituitary-adrenal axis, inflammation, cardiovascular, glucose, and lipid. Physiologic domains were allowed to co-vary with each other (Wiley et al., 2016). Next, in addition to loading on the appropriate physiologic domain, biomarkers loaded onto a second factor, a common factor for allostatic load. This

method was chosen as Wiley et al (2016) demonstrated biomarkers are both physiologic domain-specific and also share a common underlying process of allostatic load.

Allostatic load indicator data were checked for normality in SPSS prior to performing CFA. Natural log transformations of urinary norepinephrine, urinary epinephrine, R-R interval standard deviation, root mean square of successive differences, low-frequency power, high-frequency power, urinary cortisol, DHEAS, CRP, IL-6, E-selectin, glucose, HOMA-IR, glycosylated hemoglobin, and triglycerides were performed. Despite transformations, some indicators remained not normally distributed. To account for this, maximum likelihood estimation using robust standard errors was used. CFA was conducted in MPlus version 8 (Muthén & Muthén, 1998). Example Mplus syntax used by Wiley et al (2016) was from the Score-project website and served as a template for this analysis (Wiley, 2015).

After the CFA for allostatic load was completed, standardized physiologic domain factor scores and overall allostatic load factor scores were exported and used to examine the relationships between sleep and allostatic load, and allostatic load and future occurrence of cancer (research questions 2 and 3). Allostatic load factors were examined for normality and found to have an approximately normal distribution.

Research question 2 was addressed using logistic regression in Stata to evaluate the relationship between allostatic load and future cancer (StataCorp, 2017). As with the analysis for research question 1 above, the data clustered within sibling groups or twin pairs and the potential for small sample bias given the small number of cancer cases were cause for concern. It was not possible to both account for sibling groups in the data and

to account for small sample bias impact on the error terms. As with research question 1, results for bivariate regressions using regular logistic regression, logistic regression using a robust standard error estimator, and logistic regression using penalized maximum likelihood estimation (the Firth method) were compared. Based on comparisons of the standard error terms, there were few substantial differences between the model using logistic regression and the model using logistic regression with a cluster-robust standard error estimator. However, there were some instances where the standard error using penalized maximum likelihood estimation differed greatly from the other two. Therefore, the decision was made to proceed with analysis using Firth's penalized maximum likelihood estimation.

Research question 3 was addressed in Stata (StataCorp, 2017). As the allostatic load factor scores were approximately normal, linear regression with robust standard error estimation was used to examine the data for relationships among sleep parameters and allostatic load and physiologic system scores.

Finally, the possibility of allostatic load functioning as a mediator in the sleep-future cancer relationship was explored. Mediation analyses were performed using PROCESS version 2.16 by Andrew Hayes, a macro developed to perform mediation and moderation analyses (Hayes, 2018). This analysis is somewhat limited in that the PROCESS macro is not able use logistic regression accounting for a clustered sample or the effects of small sample bias, two issues in the MIDUS data, therefore interpretation has limitations.

Assumptions

A number of assumptions were made in this study. As it was a secondary analysis, it was assumed that the original data were collected using accurate and appropriate measures and proper equipment, and that assays were done correctly on properly calibrated equipment. It was further assumed that calculated variables are computed correctly. With regard to allostatic load, this study assumed that variables comprising allostatic load are appropriate and reflect cumulative wear on the body in response to stress. This study assumed that measures of cognitive-behavioral responses to stress and physiologic responses to stress obtained at a single moment in time were reflective of usual patterns for subjects (i.e. high allostatic load at data collection likely to be associated with chronic high allostatic load and that poor sleep was likely to be associated with sleep problems of a long duration). Lastly, it was assumed that all humans experience stress.

Human Subjects Protection

After the dissertation committee approved this project, application to the UNC-Greensboro IRB was made. The UNC-Greensboro IRB made the determination that this study does not constitute human subjects research and IRB approval was not required. The original MIDUS data is available via the Inter-university Consortium for Political and Social Research (ICPSR) to member institutions, of which UNC-Greensboro is a member. ICPSR is a repository of more than 7000 data collections ("Inter-university Consortium for Political and Social Research," 2016). The data used for this project are publicly available on the ICPSR website and do not contain any identifying information

that might lead to the standard or deductive identification of individual subjects. As such, data were stored on a UNC-Greensboro cloud server and for access by the student investigator and committee members.

Summary

This study used secondary longitudinal data among middle-aged Americans to examine links between subjective sleep quality and self-reported sleep duration and future cancers, for links between allostatic load and future cancers, and for links between sleep quality and sleep duration, allostatic load, and future cancer occurrence. Multiple cognitive behavioral responses to stress, physiological responses to stress, individual difference and cancer occurrence were used. Multiple methods of analysis were used to include the original data collection measures, to truncate or categorize measures, and to attenuate the sample bias and oversampling impact on findings. In addition, a validated modeling method for allostatic load was used. The sample size provided ample power for the study.

CHAPTER IV

RESULTS

The following reports on the findings from analysis of sleep duration, subjective sleep quality, overall allostatic load and seven physiologic domains, and future cancer occurrence. A description of the sample and results by research question are provided.

Description of the Sample

In a sample of middle aged and older adults who reported being cancer-free at time one, approximately 10% reported cancer at time two. Slightly more of the subjects were female (54%) than male (46%). The average age was 56.2 years, and age ranged from 35 to 86 years. The sample was racially homogeneous, with fewer than 8% reporting a race other than white. Over half of the sample reported a household income of $60,000 or more. Only 11.4% reported a household income of less than $20,000. Similarly, participants were educated, with almost half of the sample reporting a college degree or higher. Slightly more than half of the sample had never smoked. In the past month, one-third of subjects reported they had not consumed any alcohol. Overall, participants in the sample were physically active. Close to 80% reported exercising for at least twenty minutes 3 times per week. Twelve percent of the sample reported significant depressive symptoms. Ninety percent of the sample had 5 to 9 years between data collection times one and two; the median time between data collection time points was 6 years. Please see Table 3 for sample characteristics. Descriptive statistics for the sample

of n=806 and the sample of N=769 (used in analyses involving allostatic load) were compared and no substantial differences in the two groups were identified.

Table 3

Sample Characteristics

	Mean (SD) or Percent	range	# missing
Age	56.2 (10.6)	35-86	0
Gender			0
% male	46%		
% female	54%		
Race			2
% white	92%		
% not white	7.7%		
Income			18
<$20,000	11.4%		
$20,000-39,999	14.9%		
$40,000-59,999	18.9%		
$60,000-74,999	12.3%		
$75,000 or more	42.5%		
Education			2
< High School	3%		
High School	21%		
Some College	29%		
>/= College Degree	47%		
Smoking status			1
Never Smoker	56.8%		
Ever Smoker	43.2%		

Alcohol in past month			0
Never	33%		
Ever	67%		
Physical Activity (20 minutes 3x/week)			0
% Yes	79%		
% No	21%		
CESD Depressive symptoms	7.51 (7.67)	0-49	
CESD Depression (% 16 or greater)	12%		3
Years between time 1 and time 2	6.29 (1.37)	3-9	0
Cancer reported at time 2			
% Yes	9.7%		
% No	90.3%		

Note. N=806. SD is standard deviation. CESD is Center for Epidemiologic Studies Depression Scale.

Sleep Parameters

The number of hours of sleep per day averaged 6.9 and ranged 3 to 11. Mean overall global PSQI score was 5.76 and ranged from 0 to 18. Forty-five percent of respondents were categorized as having poor sleep global sleep quality. The NSF recommends 7 to 9 hours of sleep per night for adults aged 18 to 64, and 7 to 8 hours of sleep per night for adults 65 and older (Hirshkowitz et al., 2015a). However, the distribution of the data showed few participants sleeping more than 9 hours per day. As 7 to 8 hours of sleep per night is also considered normal for all adults 18 years and older, the decision was made to stratify sleep hours into short, normal, and long sleep duration based on 7 to 8 hours as normal sleep for the a priori sleep duration categories. With this

stratification, half of participants reported a normal sleep duration, and around 9% had long sleep duration. Please see Table 4.

Table 4

Descriptive Statistics for Sleep Parameters

Variable	Mean (SD) or percent	range	# missing
Global PSQI	5.76 (3.35)	0-18	40
Global PSQI >5 (%)	45.3%		
Sleep quality	0.97 (0.71)	0-3	1
Sleep latency	0.83 (0.88)	0-3	9
Sleep duration	0.79 (0.74)	0-3	3
Sleep efficiency	0.66 (1.14)	0-4	3
Sleep disturbances	1.26 (0.55)	0-3	3
Sleep medication use	0.55 (1.04)	0-3	1
Daytime dysfunction	0.79 (0.66)	0-3	1
Hours of Sleep - continuous	6.9 (1.10)	3-11	3
NSF sleep duration categories			
<7 hours (short)	41.5%		
7-8 hours (normal)	49.3%		
>8 hours (long)	9.2%		
Sleep duration identified from data			
<5.3 hours (short)	8.5%		
5.3-7.5 hours (normal)	67.4%		
>7.5 hours (long)	24.1%		

Note. PSQI is Pittsburgh Sleep Quality Index. NSF is National Sleep Foundation. SD is standard deviation

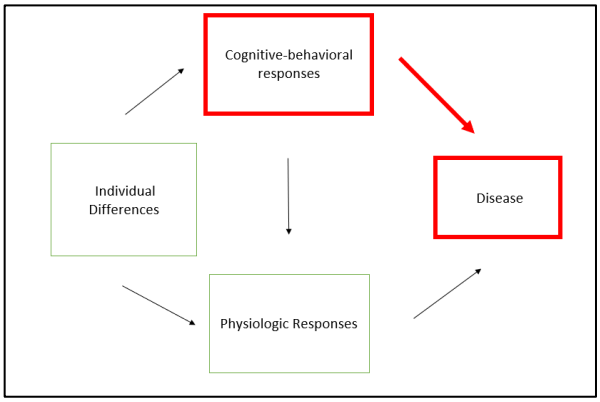
The data were explored for relevant sleep duration categories based on the variable for cancer diagnosis in the future. A Chi-squared Automatic Interaction

Detector (CHAID) decision tree in SPSS was used to identify categories of sleep duration based on the future cancer occurrence variable. A CHAID decision tree examines data inputs to identify categorical cut points that minimize p-values. This analysis yielded a short sleep duration category of less than 5.3 hours per night, a normal sleep duration of 5.3 to 7.5 hours per night, and a long sleep duration category of greater than 7.5 hours per night. In these sleep duration categories, 8.5% had short sleep duration, 67.4% had normal sleep duration, and 24.1% had long sleep duration. Please see Table 4.

Research Question 1 Results

Figure 2

Model of Sleep-Future Cancer Occurrence



Sleep and Future Cancer Occurrence

Research Question 1 pertained to investigating a relationship between sleep and future cancer occurrence. It was hypothesized that poor self-reported sleep quality would be associated with future cancers. To explore a possible relationship between subjective sleep quality and future cancer occurrence, cancer status at time two was analyzed with

the global PSQI and each PSQI domain subscore. Initially, bivariate logistic regressions were performed for cancer on sleep quality using logistic regression, logistic regression with a robust standard error estimator, and logistic regression using penalized maximum likelihood estimation (the Firth method). Please see Table 5 for results. As noted in Chapter III, the Firth method was chosen due to the impact of the small number of cancer cases on the data. No significant relationship was found between any sleep quality parameter from the PSQI and future cancer occurrence in bivariate logistic regression models.

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Table 5

Odds Ratio of Future Cancer Occurrence with Subjective Sleep Quality Parameters. Odds Ratios, Standard Errors and P-Values for Bivariate Logistic Regression, Logistic Regression with Clustered Robust Standard Error Estimation and Firth Logit Regression with Penalized Maximum Likelihood Estimation

	Logistic Regression			Logistic Regression with Clustered Robust SE Estimation			Firth Logit Regression with Penalized MLE		
Sleep parameter	OR [CI]	SE	p-value	OR [CI]	SE	p-value	OR [CI]	SE	p-value
Global PSQI	0.94 [0.87, 1.01]	0.037	0.115	0.94 [0.87, 1.02]	0.038	0.124	0.94 [0.87, 1.02]	0.039	0.128
Sleep quality	0.74 [0.52, 1.06]	0.137	0.106	0.74 [0.51, 1.07]	0.139	0.112	0.75 [0.52, 1.07]	0.184	0.118
Sleep latency	0.89 [0.68, 1.18]	0.126	0.419	0.89 [0.66, 1.21]	0.138	0.458	0.90 [0.68, 1.18]	0.140	0.446
Sleep duration	0.81 [0.58, 1.12]	0.136	0.203	0.81 [0.54, 1.19]	0.161	0.282	0.81 [0.58, 1.13]	0.168	0.218
Sleep efficiency	0.99 [0.81, 1.22]	0.104	0.944	0.99 [0.81, 1.22]	0.103	0.943	1.00 [0.82, 1.23]	0.104	0.995

Sleep disturbances	0.81 [0.53, 1.26]	0.181	0.355	0.81 [0.55, 1.21]	0.166	0.314	0.82 [0.53, 1.27]	0.221	0.373
Sleep medication use	0.88 [0.69, 1.13]	0.111	0.324	0.88 [0.69, 1.13]	0.111	0.326	0.89 [0.70, 1.14]	0.124	0.367
Daytime dysfunction	0.75 [0.52, 1.09]	0.141	0.131	0.75 [0.54, 1.05]	0.127	0.094	0.76 [0.53, 1.09]	0.186	0.138

Note. PSQI is Pittsburgh Sleep Quality Index. OR is odds ratio. CI is 95% confidence interval. SE is standard error. MLE is maximum likelihood estimation.

Similarly, a model of future cancer occurrence on global PSQI including all variables of interest yielded no significant results. Please see Table 6. Given the lack of significant findings between future cancer occurrence and global sleep quality, models of future cancer occurrence on PSQI subdomains that included all variables of interest were not pursued.

Table 6

Firth Logit Regression with Penalized MLE for Future Cancer Occurrence, Global PSQI, and Other Variables of Interest

Variable	OR [CI]	SE	p-value
Global PSQI	0.99 [0.91, 1.08]	0.043	0.586
Age/race/gender interaction term	0.97 [0.46, 1.02]	0.240	0.227
Gender	0.75 [0.45, 1.26]	0.261	0.281
Age	1.03 [1.01, 1.06]	0.012	0.008
Race	8.62 [0.34, 216.07]	1.640	0.190
Education	1.15 [0.85, 156]	0.155	0.361
Smoking status	1.39 [0.84, 2.28]	0.253	0.198
Depressive symptoms	0.40 [0.13, 1.26]	0.584	0.117
Alcohol use	0.85 [0.51, 1.43]	0.266	0.541
Income	0.96 [0.87, 1.26]	0.094	0.633
Physical activity	0.88 [0.47, 1.65]	0.322	0.683
Time	1.08 [0.90, 1.30]	0.094	0.424

Note. N=745; McFadden's $R^2 = 0.05$; $X^2(14df) = 21.6$, $p>0.05$. PSQI is Pittsburgh Sleep Quality Index. OR is odds ratio. CI is 95% confidence interval. SE is standard error. MLE is maximum likelihood estimation.

Hypothesis 1.2

The second hypothesis for Research Question 1 predicted that both short sleep duration and long sleep duration as compared to normal/healthy sleep duration would be associated with increased future cancer occurrence. To explore a possible relationship between sleep duration parameters and future cancer occurrence, cancer status at time two was analyzed with continuous hours of sleep, categorical sleep duration based on NSF sleep recommendations, and data-derived categories of sleep duration. Initially, bivariate logistic regressions were performed for cancer on each operationalization of sleep duration using logistic regression, logistic regression with a robust standard error estimator, and logistic regression using penalized maximum likelihood estimation (the Firth method). Please see Table 7 for results. Recall the Firth method was chosen due to the impact of the small number of cancer cases on the data.

Table 7

Odds Ratio of Future Cancer Occurrence with Sleep Duration Parameters. Odds Ratios, Standard Errors and P-Values for Bivariate Logistic Regression, Logistic Regression with Clustered Robust Standard Error Estimation and Firth Logit Regression with Penalized Maximum Likelihood Estimation

	Logistic Regression			Logistic Regression with Clustered Robust SE Estimation			Firth Logit Regression with Penalized MLE		
Sleep parameter	OR [CI]	SE	p-value	OR [CI]	SE	p-value	OR [CI]	SE	p-value
Continuous hours of sleep	1.27 [1.02, 1.57]	0.141	0.035	1.26 [0.98, 1.63]	0.165	0.071	1.26 [1.02, 1.57]	0.111	0.036
NSF Short sleep <7 hours	0.77 [0.46, 1.3]	0.205	0.336	0.77 [0.46, 1.30]	0.204	0.335	0.78 [0.47, 1.31]	0.263	0.344
Short sleep <5.3 hours	2.34 [1.11, 4.97]	.898	0.026	2.34 [1.10, 4.99]	0.903	0.026	2.41 [1.16, 5.04]	0.375	0.019
NSF Long sleep >8 hours	1.95 [0.98, 3.87]	0.681	0.055	1.95 [0.98, 3.88]	0.685	0.057	1.99 [1.01, 3.90]	0.344	0.046
Long sleep >7.5 hours	2.59 [1.55, 4.31]	0.673	0.000	2.59 [1.55, 4.33]	0.678	0.000	2.59 [1.56, 4.30]	0.258	0.000

Note. OR is odds ratio. CI is 95% confidence interval. SE is standard error. MLE is maximum likelihood estimation. NSF is National Sleep Foundation.

In bivariate analysis, hours of sleep treated as a continuous variable was significant at a <0.05 p-value. For each hour increase in sleep per day, the odds of having cancer occur in the future increase by 26%. When sleep duration was categorized using NSF recommendations, short sleep duration (<7 hours per night) was not related to future cancer, but long sleep duration (>8 hours per night) was weakly related (p=0.046). Compared with a normal sleep duration of 7-8 hours per night, the odds of cancer occurring in the future with >8 hours of sleep per night are 1.99 times higher, however the 95% confidence interval for this result comes very close to including the number one (95% CI 1.01-3.90). Finally, the sleep duration categories derived from the data proved to have a strong relationship with future cancer. Compared with a normal sleep duration (5.3-7.5 hours per night), the odds of a future cancer occurrence are 2.41 times higher for those with less than 5.3 hours of sleep per night. Compared with a normal sleep duration of 5.3-7.5 hours per night, the odds of a future cancer occurrence are 2.59 times higher for those with more than 7.5 hours of sleep per night.

When all other variables of interest are added to the model, continuous hours of sleep no longer had a significant relationship with future cancer (see Table 8).

Table 8

Firth Logit Regression with Penalized MLE for Future Cancer Occurrence, Continuous Hours of Sleep, and Other Variables of Interest

Variable	OR [CI]	SE	p-value
Continuous hours of sleep	1.20 [0.95, 1.52]	0.120	0.130
Age/race/gender interaction term	0.77 [0.93, 1.02]	0.024	0.272

Gender	0.74 [0.45, 1.22]	0.255	0.240
Age	1.37 [1.01, 1.06]	0.012	0.008
Race	6.68 [0.29, 155.42]	1.606	0.237
Education	1.11 [0.83, 1.50]	0.151	0.481
Smoking status	1.44 [0.88, 2.35]	0.251	0.148
Depressive symptoms	0.53 [0.85, 1.43]	0.507	0.209
Alcohol use	0.87 [0.52, 1.47]	0.264	0.610
Income	1.04 [0.87, 1.25]	0.093	0.664
Physical activity	1.23 [0.44, 1.52]	0.319	0.520
Time	1.09 [0.91, 1.31]	0.093	0.333

Note. N=777; McFadden's $R^2 = 0.054$; $X^2(14df) = 23.6$, $p>0.05$. OR is odds ratio. CI is 95% confidence interval. SE is standard error. MLE is maximum likelihood estimation.

A model of sleep duration categorized according to NSF recommendations that included variables for individual differences and other cognitive-behavioral responses to stress, the relationship between the long sleep category (>8 hours per night) and future cancer improved in strength (p=0.024). In this model, the odds of future cancer occurrence increase 122% for those sleeping more than 8 hours a night compared to those sleeping 7-8 hours per night (see Table 9).

Table 9

Firth Logit Regression with Penalized MLE for Future Cancer Occurrence, NSF Sleep Duration Categories, and Other Variables of Interest

Variable	OR [CI]	SE	p-value
NSF Short sleep (<7 hours)	0.93 [0.54, 1.58]	0.271	0.776

NSF Long sleep (>8 hours)	2.22 [1.11, 4.46]	0.355	0.024
Age/race/gender interaction term	0.97 [0.93, 1.02]	0.024	0.255
Gender	0.74 [0.45, 1.22]	0.256	0.234
Age	1.03 [1.01, 1.06]	0.012	0.008
Race	7.39 [0.32, 172.43]	1.607	0.213
Education	1.12 [0.83-1.51]	0.151	0.451
Smoking status	1.46 [0.89-2.40]	0.252	0.132
Depressive symptoms	0.50 [0.18-1.34]	0.506	0.169
Alcohol use	0.89 [0.53-1.49]	0.266	0.651
Income	1.05 [0.87-1.26]	0.093	0.627
Physical activity	0.81 [0.43-1.52]	0.320	0.518
Time	1.10 [0.92-1.32]	0.094	0.309

Note. N=777, McFadden $R^2 = 0.061$; $X^2(14df) = 26.9$, $p<0.05$. NSF is National Sleep Foundation. CI is 95% confidence interval. SE is standard error. MLE is maximum likelihood estimation.

Finally, when all other variables of interest at added the model, the relationships between sleeping less than 5.3 hours per night and future cancer and sleeping more than 7.5 hours per night and future cancer remained strong. The odds of future cancer were 4.5 times higher for those sleeping less than 5.3 hours per night compared with those sleeping 5.3-7.5 hours per night. However, the confidence interval for this odds ratio is large (95% CI ranged 2.03 to 9.99). The odds of future cancer were 2.88 times higher for those sleeping more than 7.5 hours per night compared with those sleeping 5.3 to 7.5 hours per night (see Table 10).

Table 10

Firth Logit Regression with Penalized MLE for Future Cancer Occurrence, Data-Derived Sleep Duration Categories, and Other Variables of Interest

Variable	OR [CI]	SE	p-value
Short sleep (<5.3 hours)	4.51 [2.03, 9.99]	0.406	0.000
Long sleep (>7.5 hours)	2.88 [1.70, 4.90]	0.271	0.000
Age/race/gender interaction term	0.97 [0.93, 1.02]	0.023	0.234
Gender	0.66 [0.39, 1.09]	0.261	0.106
Age	1.03 [1.01, 1.06]	0.012	0.006
Race	6.57 [0.30, 142.82]	1.571	0.231
Education	1.14 [0.84, 1.55]	0.156	0.410
Smoking status	1.48 [0.90, 2.44]	0.255	0.125
Depressive symptoms	0.40 [0.14, 1.12]	0.529	0.082
Alcohol use	0.89 [0.52, 1.50]	0.268	0.652
Income	1.08 [0.89, 1.30]	0.096	0.448
Physical activity	0.79 [0.42, 1.49]	0.326	0.460
Time	1.14 [0.95, 1.38]	0.095	0.157

Note. N=777, McFadden $R^2 = 0.098$; $X^2(14df) = 43.3$, $p<0.05$. OR is odds ratio. CI is 95 %confidence interval. SE is standard error. MLE is maximum likelihood estimation.

Individual Differences and Other Cognitive-Behavioral Responses to Stress

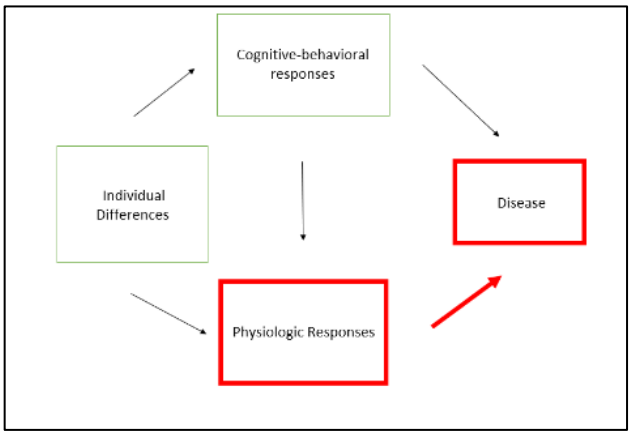
Contrary to expected based on the literature review, age was the only individual differences variable that was significantly related to future cancer in all models. Other individual differences (gender, race, income, and education) and other cognitive-

behavioral responses to stress (smoking, alcohol use, physical activity, and depressive symptoms) were not associated with future cancer occurrence.

Research Question 2 Results

Figure 3

Model of Allostatic Load-Future Cancer Occurrence



Allostatic Load and Future Cancer Occurrence

Research Question 2 pertained to exploring a possible relationship between allostatic load and the seven physiologic domains and future cancer occurrence. In order to be able to answer Research Question 2, values for allostatic load for each participant needed to be computed using confirmatory factor analysis for a previously validated bifactor model (Wiley et al., 2016). Descriptive statistics for the sample for each allostatic load indicator are listed in Table 11. Figure 2 shows a diagram of the CFA.

Table 11

Descriptive Statistics for Allostatic Load Indicators

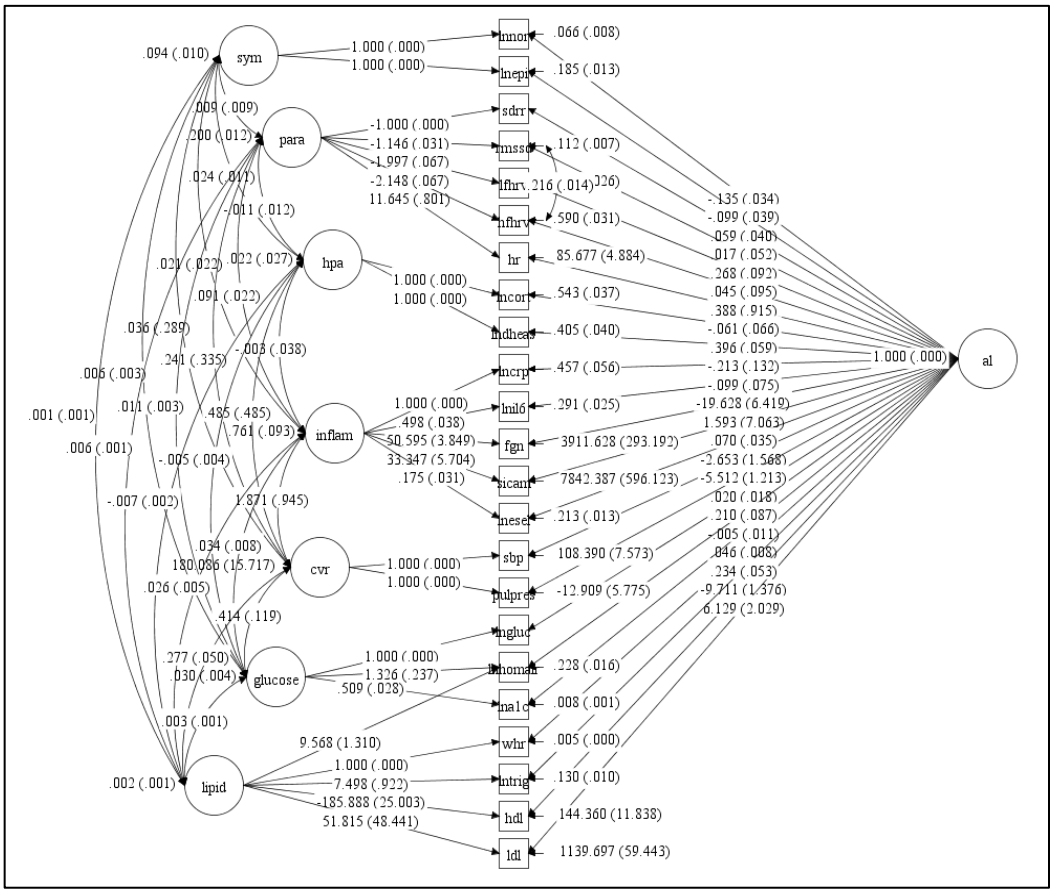
Indicator	Mean (SD)	# of cases missing data
Sympathetic nervous system		
Urinary epinephrine (ng/mL)	1.32 (0.78)	5
Urinary norepinephrine (ng/mL)	17.85 (8.77)	0
Parasympathetic nervous system		50
R-R interval standard deviation, ms	35.66 (17.30)	
Root mean square of successive differences, ms	21.78 (16.96)	
Low-frequency heart rate variability, ms^2	441.76 (627.80)	
High-frequency heart rate variability, ms^2	282.89 (733.07)	
Resting heart rate, beats/min	72.74 (10.64)	
Hypothalamic-pituitary-adrenal axis		
Urinary cortisol (ug/dL)		0
Dehydroepiandrosterone (ug/dL)	111.86 (76.96)	1
Inflammation		
C-reactive protein (ug/mL)	2.45 (3.43)	4
Interleukin-6 (pg/mL)	2.49 (2.13)	0
Fibrinogen (mg/dL)	333.63 (79.01)	4
Soluble E-selectin (ng/mL)	40.94 (20.11)	0
Soluble intracellular adhesion molecule 1 (ng/mL)	279.79 (93.29)	0
Cardiovascular		
Pulse pressure (mmHg)	54.78 (14.09)	0
Systolic blood pressure (mmHg)	130.15 (17.38)	0
Glucose		
Fasting blood glucose (mg/dL)	100.52 (22.62)	0
Glycosylated hemoglobin, %	5.96 (0.91)	4

Homeostasis model-assessed insulin resistance	3.21 (2.99)	0
Lipids		
Waist-to-hip circumference ratio	0.89 (0.91)	4
High-density lipoprotein cholesterol (mg/dL)	54.66 (17.16)	1
Low-density lipoprotein cholesterol	107.40 (34.39)	1
Triglycerides (mg/dL)	131.11 (82.22)	0

Note. N=769. SD is standard deviation.

Figure 4

Diagram of the Confirmatory Factor Analysis for Allostatic Load



The factor loadings for each indicator on both its domain-specific factor and the overall allostatic load factor are reported in Table 12. All factor loadings are significant at a <0.05 p-value with the exception of the loadings for WHR and HDL onto the lipid factor.

Table 12

Standardized Factor Loadings for Bifactor CFA

Domain Indicator	Domain loadings [CI]	p-value	AL loadings [CI]	p-value
Sympathetic nervous system				
Urinary epinephrine	0.620 [0.569, 0.670]	0.000	0.138 [0.009, 0.266]	0.036
Urinary norepinephrine	0.772 [0.713, 0.832]	0.000	0.347 [0.243, 0.451]	0.000
Parasympathetic nervous system				
R-R interval standard deviation	-0.993 [-1.006, -0.980]	0.000	-0.115 [-0.228, -0.002]	0.047
Root mean square of successive differences	-0.825 [-0.854, -0.795]	0.000	-0.125 [-0.231, -0.019]	0.021
Low-frequency power	-0.831 [-0.862, -0.800]	0.000	-0.052 [-0.169, 0.064]	0.377
High-frequency power	-0.768 [-0.804, -0.732]	0.000	-0.142 [-0.242, -0.043]	0.005
Resting heart rate	0.481 [0.422, 0.541]	0.000	0.033 [-0.089, 0.155]	0.598
Hypothalamic-pituitary-adrenal axis				

Urinary cortisol	0.372 [0.279, 0.464]	0.000	0.035 [-0.062, 0.132]	0.479
Dehydroepiandrosterone	0.450 [0.330, 0.569]	0.000	0.221 [0.126, 0.315]	0.000
Inflammation				
C-reactive protein	0.806 [0.730, 0.881]	0.000	0.225 [0.100, 0.350]	0.000
Interleukin-6	0.564 [0.488, 0.639]	0.000	0.252 [0.170, 0.334]	0.000
Fibrinogen	0.613 [0.542, 0.684]	0.000	0.062 [-0.036, 0.159]	0.218
Soluble E-selectin	0.169 [0.083, 0.255]	0.000	0.274 [0.188, 0.361]	0.000
Soluble intracellular adhesion molecule 1	0.214 [0.121, 0.307]	0.000	0.236 [0.140, 0.333]	0.000
Cardiovascular				
Pulse pressure	0.992 [0.966, 1.019]	0.000	0.100 [0.008, 0.193]	0.000
Systolic blood pressure	0.796 [0.767, 0.824]	0.000	0.254 [0.179, 0.330]	0.034
Glucose				
Fasting blood glucose	0.928 [0.890, 0.966]	0.000	0.372 [0.277, 0.467]	0.000
Glycosylated hemoglobin, %	0.640 [0.553, 0.727]	0.000	0.239 [0.128, 0.323]	0.000
Homeostasis model-assessed-IR	0.351 [0.265, 0.437]	0.000	0.621 [0.507, 0.708]	0.000
Lipids				
Waist-to-hip circumference	0.326 [-0.084, 0.737]	0.119	0.801 [0.666, 0.936]	0.000

HDL cholesterol	0.173 [-0.088, 0.433]	0.194	-0.649 [-0.731, -0.568]	0.000
LDL cholesterol	-0.230 [-0.328, -0.131]	0.000	0.128 [0.008, 0.247]	0.036
Triglycerides	-0.429 [-0.734, -0.124]	0.006	0.693 [0.523, 0.836]	0.000

Note. CI is 95% confidence interval. AL is allostatic load. IR is insulin resistance. HDL is high density lipoprotein. LDL is low density lipoprotein.

Goodness of fit test results for the CFA are reported in Table 13. Overall, adequate model fit was achieved given a RMSEA of 0.064 and a CFI of 0.913.

Table 13

Goodness of Fit Testing of Bifactor CFA

Fit test			
Chi square	776.454	189 degrees of freedom	p-value 0.000
RMSEA	0.064	90% CI 0.059-0.068	Probability RMSEA < 0.05= 0.000
CFI	0.913		
TLI	0.883		

Note. RMSEA is root mean square error of approximation. CFI is comparative fit index. TLI is Tucker Lewis index.

Standardized factor scores for allostatic load and for the 7 individual domains of allostatic load for each study participant were exported from MPlus into SPSS and Stata for analysis to answer research questions 2 through 4. Table 14 reports descriptive statistics for the standardized allostatic load factor scores.

Table 14

Descriptive Statistics for Standardized Factor Scores for Allostatic Load and for 7 Physiologic Domains of Allostatic Load

Variable	Mean (SD)	Range
Allostatic load	0 (0.92)	-2.213 to 2.696
Sympathetic Nervous System Domain	0 (0.30)	-0.996 to 0.998
Parasympathetic Nervous System Domain	0 (0.43)	-1.467 to 1.946
Lipid Domain	0 (0.02)	-0.070 to 0.069
Glucose Domain	0 (0.16)	-0.362 to 1.045
HPA Axis Domain	0 (0.22)	-0.902 to 0.53
Cardiovascular Domain	0 (13.93)	-29.024 to 52.107
Inflammation Domain	0 (0.79)	-2.019 to 2.585

Note. SD is standard deviation.

Hypothesis 2.1

It was hypothesized that increased allostatic load would be associated with increased future cancer occurrence. Bivariate analysis results for cancer on allostatic load factor scores were performed using logistic regression, logistic regression with a robust standard error estimator, and logistic regression using penalized maximum likelihood estimation (the Firth method). Please see Table 15.

Table 15

Odds Ratio of Future Cancer Occurrence with Allostatic Load. Odds Ratios, Standard Errors and P-Values for Bivariate Logistic Regression, Logistic Regression with Clustered Robust Standard Error Estimation and Firth Logit Regression with Penalized Maximum Likelihood Estimation

	Logistic Regression			Logistic Regression with Clustered Robust SE Estimation			Firth Logit Regression with Penalized MLE		
	OR [CI]	SE	p-value	OR [CI]	SE	p-value	OR [CI]	SE	p-value
Allostatic load	0.98 [0.76, 1.26]	0.127	0.864	0.98 [0.76, 1.26]	0.127	0.864	0.98 [0.76, 1.26]	0.127	0.864
Sympathetic	1.28 [0.58, 2.85]	0.522	0.539	1.28 [0.60, 2.75]	0.500	0.521	1.28 [0.58, 2.83]	0.406	0.547
Parasympathetic	1.81 [1.05, 3.13]	0.504	0.032	1.81 [1.01, 3.25]	0.540	0.045	1.81 [1.05, 3.12]	0.277	0.033
Lipid	287317 [10.52, $7.84x10^{9}$]	1497412	0.016	287317 [5.48, $1.51x10^{10}$]	1593008	0.023	268337 [10.2, $7.1x10^{9}$]	5.19	0.016
Glucose	1.50 [0.38, 6.01]	1.062	0.564	1.50 [0.38, 6.05]	1.068	0.567	1.62 [0.42, 6.32]	0.694	0.486
HPA	0.85 [0.29, 2.46]	0.461	0.761	0.85 [0.29, 2.46]	0.471	0.766	0.84 [0.29, 2.42]	0.542	0.744
Cardiovascular	0.99 [0.98, 1.01]	0.009	0.388	0.99 [0.97, 1.01]	0.009	0.411	0.99 [0.98, 1.01]	0.009	0.409

Inflammation	0.89 [0.66, 1.21]	0.137	0.463	0.89 [0.65, 1.22]	0.141	0.478	0.90 [0.66, 1.21]	0.153	0.474

Note. OR is odds ratio. CI is 95% confidence interval. SE is standard error. MLE is maximum likelihood estimation. HPA is hypothalamic-pituitary-adrenal axis.

As noted in Chapter III, the Firth method was chosen due to the impact of the small number of cancer cases on the data.

Bivariate analysis for future cancer occurrence on allostatic load showed overall allostatic load did not have a relationship with future cancer occurrence. To investigate the correlation identified between male gender and allostatic load, the sample was stratified by gender and analysis repeated. No relationship was found between future cancer occurrence and allostatic load and male gender or female gender (results not shown).

Consistent with the bivariate analysis, a model of future cancer occurrence on allostatic load including all variables of interest yielded no significant results. Please see Table 16.

Table 16

Firth Logit Regression with Penalized MLE for Future Cancer Occurrence, Allostatic Load, and Other Variables of Interest

Variable	OR [CI]	SE	p-value
Allostatic load	0.81 [0.58, 1.14]	0.172	0.233
Age/race/gender interaction term	0.97 [0.93, 1.02]	0.023	0.239
Gender	0.61 [0.33, 1.14]	0.317	0.124
Age	1.03 [1.01, 1.06]	0.012	0.005
Race	6.01 [0.27, 133.26]	1.581	0.257
Education	1.10 [0.82, 1.49]	0.152	0.513
Smoking status	1.45 [0.89, 2.38]	0.251	0.139
Depressive symptoms	0.48 [0.18, 1.30]	0.506	0.150

Alcohol use	0.87 [0.52, 1.46]	0.265	0.589
Income	1.04 [0.87, 1.25]	0.093	0.675
Physical activity	0.88 [0.47, 1.67]	0.325	0.704
Time	1.10 [0.92, 1.33]	0.094	0.288

Note. N=747; McFadden's $R^2 = 0.053$; $X^2(14df) = 23.1$, $p>0.05$. OR is odds ratio. CI is 95% confidence interval. SE is standard error. MLE is maximum likelihood estimation.)

Hypothesis 2.2

It was predicted that the inflammation domain, sympathetic nervous system domain, and hypothalamic-pituitary-adrenal axis domain would be associated with the occurrence of future cancers. Bivariate logistic regression results of future cancer occurrence on the seven physiologic domain factor scores are all non-significant except in the case of the parasympathetic domain factor and the lipid domain factor. None of the hypothesized domains proved to be related to future cancer. As the other physiologic domains did not demonstrate a relationship with future cancer occurrence, exploration of a full model containing all variables of interest was pursued only for the parasympathetic nervous system domain and the lipid domain. In the full model, the relationships between parasympathetic nervous system domain score and future cancer and between lipid domain score and future cancer were no longer significant. Please see Table 17 for parasympathetic nervous system domain full model results and Table 18 for lipid domain full model results.

Table 17

Firth Logit Regression with Penalized MLE for Future Cancer Occurrence, Parasympathetic Nervous System Domain, and Other Variables of Interest

Variable	OR [CI]	SE	p-value
Parasympathetic nervous system	1.66 [0.94, 2.94]	0.292	0.082
Age/race/gender interaction term	0.98 [0.93, 1.02]	0.024	0.294
Gender	0.70 [0.42, 1.18]	0.261	0.180
Age	1.03 [1.00, 1.05]	0.013	0.022
Race	5.72 [0.24, 136.26]	1.617	0.281
Education	1.12 [0.83, 1.15]	0.151	0.446
Smoking status	1.44 [0.88, 2.35]	0.252	0.151
Depressive symptoms	0.47 [0.17, 1.27]	0.506	0.137
Alcohol use	0.90 [0.53, 1.51]	0.265	0.679
Income	1.04 [0.87, 1.25]	0.094	0.658
Physical activity	0.82 [0.44, 1.53]	0.320	0.528
Time	1.09 [0.91, 1.31]	0.093	0.339

Note. N=747, McFadden $R^2 = 0.057$; $X^2(14df) = 24.8$, $p<0.05$. OR is odds ratio. CI is 95% confidence interval. SE is standard error. MLE is maximum likelihood estimation.)

Table 18

Firth Logit Regression with Penalized MLE for Future Cancer Occurrence, Lipid Domain, and Other Variables of Interest

Variable	OR [CI]	SE	p-value
Lipid domain	1479.51 [0.01, $17.6x10^7$]	5.962	0.221
Age/race/gender interaction term	0.97 [0.93, 1.02]	0.024	0.276

Gender	0.89 [0.51, 1.55]	0.282	0.678
Age	1.03 [1.01, 1.06]	0.012	0.008
Race	6.01 [0.26, 139.02]	1.602	0.263
Education	1.12 [0.83, 1.50]	0.151	0.468
Smoking status	1.40 [0.85, 2.30]	0.253	0.183
Depressive symptoms	0.49 [0.18, 1.33]	0.508	0.161
Alcohol use	0.88 [0.52, 1.48]	0.265	0.627
Income	1.05 [0.87, 1.26]	0.094	0.609
Physical activity	0.84 [0.45, 1.58]	0.320	0.595
Time	1.12 [0.93, 1.34]	0.094	0.241

Note. N = 747, McFadden $R^2 = 0.053$; $X^2(14df) = 23.2$, $p>0.05$. OR is odds ratio. CI is 95% confidence interval. SE is standard error. MLE is maximum likelihood estimation.

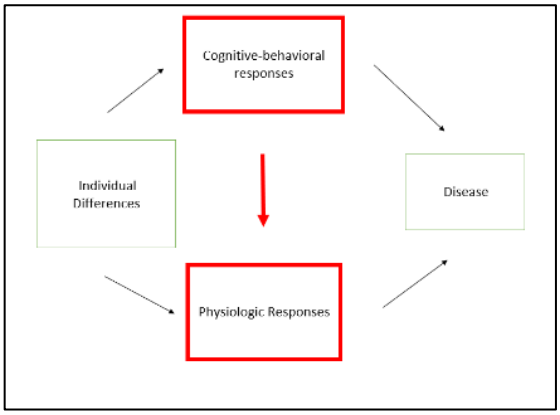
Individual Differences and Other Cognitive-Behavioral Responses to Stress

Consistent with results from analysis for Research Question 1, age is the only individual differences variable associated with future cancer occurrence. Other individual differences (gender, race, income, and education) and other cognitive-behavioral responses to stress (smoking, alcohol use, physical activity, and depressive symptoms) were not associated with future cancer occurrence.

Research Question 3 Results

Figure 5

Model of Sleep-Allostatic Load



Sleep and Allostatic Load

Research Question 3 investigated the relationship between subjective sleep quality, sleep duration and allostatic load and the seven physiologic domains. It was hypothesized that poor self-reported, subjective sleep quality would be associated with increased allostatic load. To answer this research question, a relationship between the subjective sleep quality parameters measured by the PSQI was investigated. Only full model linear regressions including all variables of interest were conducted. Results show poor global sleep quality was associated with increased allostatic load as hypothesized. Please see Table 19.

Table 19

Linear Regression Results for Allostatic Load, Global PSQI Sleep Quality, and Other Variables of Interest

Variable	Coefficient [CI]	SE	p-value
Global sleep quality	0.14 [0.03, 0.29]	0.009	0.014
Age/race/gender interaction term	0.00 [-0.01, 0.01]	0.004	0.964
Gender	-1.12 [-1.23, -1.01]	0.060	0.000
Age	0.00 [-0.01, 0.00]	0.003	0.832
Race	-0.09 [-0.76, 0.57]	0.341	0.780
Education	-0.10 [-0.17, -0.03]	0.036	0.006
Smoking status	0.02 [-0.10, 0.13]	0.060	0.752
Depressive symptoms	0.09 [-0.09, 0.28]	0.096	0.330
Alcohol use	-0.11 [-0.23, 0.01]	0.061	0.081
Income	-0.03 [-0.07, 0.01]	0.020	0.087
Physical activity	0.30 [0.17, 0.43]	0.064	0.000
Time	0.01 [-0.03, 0.05]	0.021	0.614

Note. N=747; R^2 = 0.38. PSQI is Pittsburgh Sleep Quality Index. CI is 95% confidence interval. SE is standard error.

Hypothesis 3.2

It was hypothesized that short sleep duration and long sleep duration as compared to normal/healthy sleep duration would be associated with increased allostatic load. Data were analyzed for relationships between the sleep duration variables and allostatic load. No relationship was identified between overall allostatic load and any measure for sleep duration. Please see Tables 20, 21, and 22.

Table 20

Linear Regression Results for Allostatic Load, Continuous Hours of Sleep, and Other Variables of Interest

Variable	Coefficient [CI]	SE	p-value
Continuous hours of sleep	-0.023 [-0.073, 0.026]	0.025	0.357
Age/race/gender interaction term	-0.001 [-0.008, 0.006]	0.003	0.791
Gender	-1.098 [-1.209, -0.987]	0.057	0.000
Age	-0.001 [-0.006, -0.005]	0.003	0.793
Race	-0.138 [-0.714, 0.437]	0.293	0.637
Education	-0.100 [-1.650, -0.035]	0.033	0.003
Smoking status	0.011 [-0.098, 0.121]	0.056	0.840
Depressive symptoms	0.129 [-0.400, 0.297]	0.086	0.135
Alcohol use	-0.109 [-0.224, 0.006]	0.590	0.064
Income	-0.360 [-0.076, 0.003]	0.020	0.071
Physical activity	0.311 [0.177, 0.444]	0.068	0.000
Time	0.010 [-0.029, 0.050]	0.020	0.608

Note. N=744; R^2= 0.378. CI is 95% confidence interval. SE is standard error.

Table 21

Linear Regression Results for Allostatic Load, NSF Sleep Duration Categories, and Other Variables of Interest

Variable	Coefficient [CI]	SE	p-value
Short sleep duration (<7 hours)	0.074 [-0.038, 0.187]	0.057	0.195
Long sleep duration (>8 hours)	0.125 [-0.650, 0.316]	0.097	0.198
Age/race/gender interaction term	-0.001 [-0.007, 0.006]	0.003	0.863
Gender	-1.101 [-1.212, -0.990]	0.056	0.000

Age	-0.001 [-0.006, 0.005]	0.003	0.794
Race	-0.159 [-0.733, 0.416]	0.293	0.588
Education	-0.099 [-0.164, -0.034]	0.033	0.003
Smoking status	0.009 [-0.100, 0.119]	0.056	0.871
Depressive symptoms	0.135 [-0.032, 0.303]	0.085	0.112
Alcohol use	-0.109 [-0.224, 0.006]	0.059	0.064
Income	-0.035 [-0.074, 0.005]	0.020	0.085
Physical activity	0.311 [0.178, 0.444]	0.068	0.000
Time	0.011 [-0.029, 0.051]	0.020	0.586

Note. N=744. NSF is National Sleep Foundation. CI is 95% confidence interval. SE is standard error.

Table 22

Linear Regression Results for Allostatic Load, Data-Derived Sleep Duration Categories, and Other Variables of Interest

Variable	Coefficient [CI]	SE	p-value
Short sleep duration (<7 hours)	0.128 [-0.072, 0.328]	0.102	0.209
Long sleep duration (>8 hours)	0.010 [-0.118, 0.138]	0.065	0.879
Age/race/gender interaction term	-0.001 [-0.008, 0.006]	0.003	0.770
Gender	-1.103 [-1.215, -0.992]	0.057	0.000
Age	-0.001 [-0.006, 0.005]	0.003	0.799
Race	-0.133 [-0.710, 0.445]	0.294	0.652
Education	-0.010 [-0.165, -0.035]	0.033	0.003
Smoking status	0.009 [-0.100, 0.119]	0.056	0.866
Depressive symptoms	0.125 [-0.044, 0.294]	0.086	0.149
Alcohol use	-0.107 [-0.223, 0.008]	0.059	0.068

Income	-0.035 [-0.075, 0.004]	0.020	0.082
Physical activity	0.312 [0.179, 0.445]	0.068	0.000
Time	0.012 [-0.028, 0.052]	0.020	0.556

Note. N=744. R^2=0.379. CI is 95% confidence interval. SE is standard error.

Female gender, increasing education level, and being physically active were all associated with lower allostatic load scores. Other individual differences and other cognitive-behavioral responses to stress were not found to have a relationship with allostatic load in the models of subjective sleep quality and allostatic load and models of sleep duration and allostatic load.

Hypothesis 3.3

It was hypothesized that poor sleep would be associated with the inflammation domain, glucose domain, lipid domain, and cardiovascular domain. Given that overall allostatic load was significantly related to global PSQI, relationships between the seven physiologic domain factors and subjective sleep quality were explored. The sympathetic nervous system domain, parasympathetic nervous system domain, glucose domain, lipid domain, inflammation domain, and cardiovascular domain were not associated with subjective sleep quality, contrary to what was anticipated. Only the HPA axis domain proved to be associated with subjective sleep quality. Subjects with poor global sleep quality had lower HPA factor scores (see Table 23). Recall that increasing scores for the HPA axis domain are indicative of worse physiologic dysfunction in the HPA axis domain. These results show the opposite finding from what was expected: poor sleep quality was associated with decreased, or better, HPA axis domain factor scores.

Table 23

Linear Regression Results for HPA Axis Domain, Global PSQI Sleep Quality, and Other Variables of Interest

Variable	Coefficient [CI]	SE	p-value
Global sleep quality	-0.04 [-0.07, -0.02]	0.014	0.002
Age/race/gender interaction term	0.00 [0.00, 0.00]	0.001	0.287
Gender	-0.17 [-0.20, -0.14]	0.014	0.000
Age	-0.01 [-0.01, -0.01]	0.001	0.000
Race	-0.06 [-0.20, 0.07]	0.071	0.354
Education	0.01 [0.00, 0.03]	0.008	0.086
Smoking status	0.01 [-0.02, 0.03]	0.014	0.666
Depressive symptoms	-0.02 [-0.07, 0.02]	0.023	0.359
Alcohol use	0.02 [-0.01, 0.05]	0.015	0.185
Income	-0.01 [-0.02, 0.00]	0.005	0.102
Physical activity	-0.02 [-0.05, 0.01]	0.015	0.166
Time	-0.01 [-0.02, 0.00]	0.005	0.260

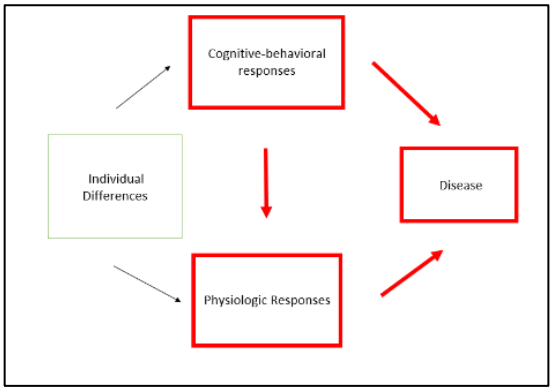
Note. N=747. R^2 = 0.362. HPA is hypothalamic-pituitary-adrenal axis. PSQI is Pittsburgh Sleep Quality Index. CI is 95% confidence interval. SE is standard error.

Female gender and older age were associated with lower HPA axis domain scores. Other individual differences (race, education, and income) and other cognitive-behavioral responses to stress (smoking status, alcohol use, depressive symptoms, and physical activity) were not associated with HPA axis domain scores.

Research Question 4 Results

Figure 6

Mediation Model



Allostatic Load as Mediator for Sleep-Future Cancer Occurrence

Research Question 4 pertained to investigating a potential mediating role for allostatic load in the sleep – future cancer occurrence relationship. The first step in answering this research question was to analyze future cancer occurrence, allostatic load, and sleep together. Results for models with future cancer occurrence, allostatic load, and each of the three sleep duration variables and sleep quality including all variables of interest are found in Tables 24-27. Analyzing all three main concepts together did not change results with one exception. Adding allostatic load to the model of future cancer occurrence and sleep duration categories derived from the data results in gender having a significant relationship with future cancer occurrence, with females having a 49% lower odds of cancer. Please see Table 24.

Table 24

Firth Logit Regression with Penalized MLE for Future Cancer Occurrence, Allostatic Load, Global PSQI Sleep Quality, and Other Variables of Interest

Variable	OR [CI]	SE	p-value
Allostatic load	0.79 [0.56, 1.12]	0.18	0.186
Short sleep duration (<5.3 hours)	4.74 [2.12, 10.63]	0.41	0.000
Long sleep duration (>7.5 hours)	2.97 [1.74, 5.07]	0.27	0.000
Age/race/gender interaction term	0.97 [0.93, 1.02]	0.02	0.254
Gender	0.51 [0.27, 0.96]	0.33	0.037
Age	1.03 [1.01, 1.06]	0.01	0.006
Race	5.80 [0.26, 128.29]	1.58	0.266
Education	1.10 [0.81, 1.49]	0.16	0.554
Smoking status	1.46 [0.88, 2.42]	0.26	0.138
Depressive symptoms	0.40 [0.14, 1.13]	0.53	0.082
Alcohol use	0.86 [0.51, 1.47]	0.27	0.588
Income	1.08 [0.90, 1.31]	0.10	0.407
Physical activity	0.87 [0.45, 1.67]	0.33	0.671
Time	1.16 [0.96, 1.40]	0.10	0.126

Note. N=747. McFadden's $R^2 = 0.054$; $X^2(14df) = 23.2$, $p>0.05$. MLE is maximum likelihood estimation. OR is odds ratio. CI is 95% confidence interval. SE is standard error.

Table 25

Firth Logit Regression with Penalized MLE for Future Cancer Occurrence, Allostatic Load, Continuous Hours of Sleep, and Other Variables of Interest

Variable	OR [CI]	SE	p-value
Allostatic load	0.82 [0.58, 1.14]	0.17	0.239

Global PSQI sleep quality	0.98 [0.59, 1.62]	0.26	0.932
Age/race/gender interaction term	0.97 [0.93, 1.02]	0.02	0.268
Gender	0.62 [0.33, 1.16]	0.32	0.132
Age	1.03 [1.01, 1.06]	0.01	0.005
Race	6.02 [0.27, 133.21]	1.58	0.256
Education	1.10 [0.82, 1.49]	0.15	0.514
Smoking status	1.45 [0.89, 2.37]	0.25	0.140
Depressive symptoms	0.49 [0.18, 1.34]	0.52	0.163
Alcohol use	0.87 [0.52, 1.46]	0.26	0.590
Income	1.04 [0.87, 1.25]	0.09	0.675
Physical activity	0.88 [0.47, 1.67]	0.32	0.706
Time	1.10 [0.92, 1.33]	0.09	0.290

Note. N=744. McFadden's $R^2 = 0.058$; $X^2(14df) = 25.1$, $p<0.05$. MLE is maximum likelihood estimation. PSQI is Pittsburgh Sleep Quality Index. OR is odds ratio. CI is 95% confidence interval. SE is standard error.

Table 26

Firth Logit Regression with Penalized MLE for Future Cancer Occurrence, Allostatic Load, NSF Sleep Duration Categories, and Other Variables of Interest

Variable	OR [CI]	SE	P-value
Allostatic load	0.80 [0.57, 1.12]	0.17	0.201
Short sleep duration (<7 hours)	0.96 [0.56, 1.63]	0.36	0.870
Long sleep duration (>8 hours)	2.35 [1.17, 4.75]	0.02	0.017
Age/race/gender interaction term	0.97 [0.93, 1.02]	0.32	0.285
Gender	0.59 [0.31, 1.09]	0.01	0.093
Age	1.03 [1.01, 1.06]	1.63	0.007
Race	6.28 [0.26, 152.38]	0.15	0.259

Education	1.10 [0.81, 1.48]	0.25	0.545
Smoking status	1.45 [0.88, 2.39]	0.37	0.141
Depressive symptoms	0.68 [0.19, 1.37]	0.51	0.181
Alcohol use	0.86 [0.51, 1.45]	0.27	0.573
Income	1.05 [0.87, 1.26]	0.09	0.606
Physical activity	0.89 [0.47, 1.68]	0.33	0.714
Time	1.11 [0.92, 1.34]	0.10	0.260

Note. N=744. McFadden's $R^2 = 0.067$; $X^2(14df) = 28.9$, $p<0.05$. MLE is maximum likelihood estimation. NSF is National Sleep Foundation. OR is odds ratio. CI is 95% confidence interval. SE is standard error.

Table 27

Firth Logit Regression with Penalized MLE for Future Cancer Occurrence, Allostatic Load, Data-Derived Sleep Duration Categories, and Other Variables of Interest

Variable	OR [CI]	SE	p-value
Allostatic load	0.82 [0.59, 1.15]	0.172	0.249
Continuous hours of sleep	1.20 [0.94, 0.52]	0.121	0.138
Age/race/gender interaction term	0.98 [0.93, 1.02]	0.024	0.302
Gender	0.61 [0.33, 1.13]	0.316	0.117
Age	1.03 [1.01, 1.06]	0.012	0.007
Race	5.77 [0.24, 138.19]	1.62	0.279
Education	1.09 [0.81, 1.47]	0.152	0.558
Smoking status	1.43 [0.87, 2.35]	0.252	0.153
Depressive symptoms	0.53 [0.20, 1.45]	0.508	0.218
Alcohol use	0.85 [0.51, 1.44]	0.265	0.552
Income	1.04 [0.87, 1.25]	0.09	0.665
Physical activity	0.87 [0.46, 1.65]	0.325	0.677

Time	1.10 [0.92, 1.33]	0.094	0.291

Note. N=744. McFadden's $R^2 = 0.106$; $X^2(14df) = 45.7$, $p<0.05$. MLE is maximum likelihood estimation. OR is odds ratio. CI is 95% confidence interval. SE is standard error.

Proceeding further with the analysis for Research Question 4 hinged on positive findings from Research Questions 1, 2, and 3. If no relationships were identified between sleep and future cancer, allostatic load and future cancer, or between sleep and allostatic load, then checking for mediation amongst these relationships is not possible. Although sleep duration was found to be related to future cancer in Research Question 1, subjective sleep quality was not related to future cancer. For Research Question 2, no relationship between allostatic load and future cancer was identified. In the bivariate logistic regression model, parasympathetic nervous system domain score and future cancer were related, but this relationship became non-significant in the full model. However, the parasympathetic nervous system domain was trending toward a relationship with cancer ($p = 0.082$). Lastly, for Research Question 3, overall allostatic load was found to be related to subjective sleep quality but not sleep duration. Given the lack of significant results for a relationship between the allostatic load and future cancer occurrence, and given that sleep duration was related to future cancer occurrence while subjective sleep quality was related to allostatic load, mediation analysis was not warranted.

Summary

With consideration given to individual differences (age, race, gender, education, and income) and other cognitive-behavioral differences (smoking, alcohol use in the last 30 days, physical activity, and depression), relationships between sleep, allostatic load,

and future cancer occurrence were explored. Of the permutations of sleep duration, categorical sleep derived from the data fit the best. Age was the only other measure to show a relationship with future cancer. Poor subjective sleep quality was associated with increased allostatic load. Female gender, increasing education level, and being physically active were all associated with lower allostatic load scores. Poor subjective sleep quality was associated with decreased hypothalamic-pituitary-adrenal axis domain scores. No relationship was found between subjective sleep quality or the seven sleep domains and future cancer occurrence. No relationship was found between allostatic load or the seven physiologic domains and future cancer occurrence. No relationship was found between sleep duration and allostatic load. Finally, allostatic load did not play a mediating role in the sleep – future cancer occurrence relationship.

CHAPTER V

DISCUSSION

The purpose of this study was to examine secondary data from US adults for potential relationships between sleep, allostatic load, and future cancer occurrence. The research questions were designed based on a conceptual framework of responses to stress. The model depicts sleep, a cognitive-behavioral response to stress, as influencing allostatic load, a physiologic response to stress, and cancer, a disease. Additionally, the model depicts allostatic load influencing cancer. Sleep was operationalized as subjective sleep quality and sleep duration and measured at time one. Information from the Pittsburgh Sleep Quality Index questionnaire was the source of all sleep variables. A priori cut points for categorical sleep duration based on National Sleep Foundation recommendations were used for analysis; data were also explored for pertinent sleep duration categories in relation to the future cancer occurrence outcome variable. Allostatic load was operationalized using a validated bifactor model and measured at time one. Cancer status was assessed at time two by self-report and was operationalized to include any cancer that occurred since time two. Results confirm aspects of the relationships predicted by the conceptual framework. Findings demonstrate a relationship between future cancer occurrence and categorical sleep duration, but no relationship between subjective sleep quality and future cancer occurrence. Allostatic load is not associated with future cancer occurrence. Subjective sleep quality is

associated with allostatic load but sleep duration is not. Finally, no interplay between all three main concepts was identified.

Sleep and Future Cancer Occurrence

Subjective Sleep Quality and Future Cancer Occurrence

This study sought to investigate a potential relationship between subjective sleep quality and future cancer occurrence. However, models of future cancer on self-reported, subjective sleep quality as measured by the Pittsburgh Sleep Quality Index (PSQI) did not show any relationship between sleep quality and future cancer. Very few studies of subjective sleep quality in relation to future cancer were identified for comparison purposes and none utilized the PSQI to measure sleep quality. One study found an increased risk of breast cancer in women with all three sleep quality complaints of nonrestorative sleep, difficulty initiating sleep, and difficulty maintaining sleep (Sen et al., 2017). Self-reported difficulty initiating and difficulty maintaining sleep were associated with an increased risk of prostate cancer (Sigurdardottir et al., 2013). An increased risk for multiple cancer types was found among those with a diagnosis of insomnia at least 2 years prior to cancer diagnosis (Fang et al., 2015). None of the comparison studies' samples included US adults, the population studied in the current sample. All the comparison studies used similar parameters of sleep quality to each that are different than those used by the present study. These studies used a diagnosis of insomnia or criteria for the diagnosis of insomnia to measure sleep quality. The present study utilizes self-reported sleep quality as measured by the PSQI which includes the

domains of sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, sleep medication use, and daytime dysfunction (Buysse et al., 1989).

Sleep Duration and Future Cancer Occurrence

Most of the studies of sleep and future cancer to date have examined sleep duration as the sleep parameter of interest, however operationalization of sleep duration varied widely. This study examined sleep duration in several ways to determine what the best measure of sleep duration in relation to future cancer might be. Sleep duration variables examined in this study included continuous hours of sleep per night, sleep duration categories based on sleep duration recommendations from the National Sleep Foundation (NSF), and sleep duration categories generated from the data based on the future cancer occurrence outcome. After controlling for individual differences (age, race, gender, income, and education) and other cognitive behavioral responses to stress (smoking, alcohol use, physical activity, and depressive symptoms), future cancer had no relationship with continuous hours of sleep, a weak relationship with sleep duration categories based on NSF recommendations, and a strong relationship with sleep duration categories derived from the future cancer occurrence variable. Recall normal sleep per NSF recommendations was 7 to 8 hours per while and normal sleep duration category derived from the data was 5.3 to 7.5 hours per night.

A review of the literature identified some evidence that concurs and some that disagrees with these findings. A few studies that categorized short sleep duration similarly to the present study (between <5-6 hours per night) found short sleep duration to be associated with an increased risk of cancer. A large prospective European study

found an increased risk of cancer (defined as any type of cancer) associated with <6 hours of sleep at night baseline (von Ruesten, Weikert, Fietze, & Boeing, 2012). Two studies of women and colon cancer found conflicting results. One (Jiao et al., 2013) found the risk for colon cancer increased for those sleeping =/<5 hours; in contrast, the other did not identify an increased risk of colon cancer for those sleeping <5 hours per day (Devore et al., 2017). Results from the Women's Health Initiative Study found no increased risk of liver cancer for short sleep duration of <5 hours (Royse et al., 2017). Of the 4 comparison studies identified here, 3 are of US women for specific cancer types. The remaining study of European men and women included all cancer except non-melanoma skin cancer as the outcome. In contrast, the present study is of middle-aged US adults and likely includes non-melanoma skin cancer in the future cancer occurrence outcome.

Less evidence was found that concurred with the finding of an increased odds of future cancer occurrence with long sleep duration (defined as >7.5 hours per night). Three studies operationalized long sleep duration similarly to the present study (between 7-8 hours per night). These comparison studies of cancer (of any kind), colon cancer, and lung cancer did not find an increased cancer risk with long sleep duration (Devore et al., 2017; Luojus et al., 2014; von Ruesten et al., 2012). Of these three comparison studies, two are from Europe, one is of men only, and one is of women only. Finally, one study of women that defined long sleep duration as 9 or more hours of sleep per night, different from the present study, showed an increased risk of liver cancer (Royse et al., 2017).

Allostatic Load and Future Cancer Occurrence

A relationship between allostatic load and future cancer had not been examined yet per the literature reviewed for the development of this study, and only a single article was identified that reported on an investigation of individual biomarkers as predictors of future cancer. Results of that study showed higher blood glucose values were associated with an increased risk of future breast cancer (Agnoli et al., 2015). Given the lack of evidence for or against an allostatic load- future cancer relationship, this study sought to determine if allostatic load was associated with future cancer occurrence. Although it was hypothesized that overall allostatic load would be associated with future cancer, analysis of the data did not support this.

Physiologic Domains of Allostatic Load and Future Cancer Occurrence

Despite the lack of relationship between allostatic load and future cancer, the 7 physiologic system factor scores were examined as predictors of future cancer. This analysis was pursued in the hopes of identifying systems or indicators that might be related to future cancer for inclusion in subsequent studies of allostatic load and cancer. In bivariate logistic regressions, the parasympathetic system domain factor and the lipid domain factor each showed a relationship with future cancer, while the sympathetic system, HPA axis, inflammation system, glucose system, and cardiovascular system domains were not related to future cancer. Higher, meaning worse, parasympathetic system domain scores were associated with increased future cancer. This relationship disappeared in the full model in which age is a significant predictor of future cancer, indicating that parasympathetic system function worsens with increasing age. However,

the relationship was trending toward significant (p-value = 0.08). A review of the literature did not identify any studies examining parasympathetic system indicators as a predictor of future cancer occurrence. However, one study was identified that demonstrated reduced heart rate variability (a component of the parasympathetic system domain) in cancer patients was associated with decreased survival (Guo et al., 2015).

The lipid factor was significantly related to future cancer in the bivariate logistic regression, but as with the parasympathetic system, this relationship was eliminated in the full model. However, the lipid factor produced unexpected results in relation to future cancer occurrence and needs further discussion. In the bivariate logistic regression, the odds of future cancer are 268,337 times higher for each standard deviation increase in lipid factor score with a 95% confidence interval of 10 to over 7 million. There are a number of possible explanations for this unusual result. First, the scale of the lipid factor differs from the other physiologic factors: for example, the standard deviation for overall allostatic load is close to 1, while the standard deviation of the lipid factor is 0.02. Another avenue that needs exploration is the derivation of the lipid factor. In the established CFA utilized by this study, the lipid factor contains 5 indicators: waist-to-hip ratio, HDL, LDL, triglycerides and HOMA-IR (Wiley et al., 2016). In the present study, LDL, triglycerides, and HOMA-IR load significantly both onto the lipid factor and onto the overall allostatic load factor. Waist-to-hip ratio and HDL, however, load significantly onto overall allostatic load but not onto the lipid factor (please refer to Table 10 in Chapter IV for details). It is possible the factor structure for the lipid factor does not fit as well for this study's sample as it did in the original CFA study upon which this study is

based. For example, the original CFA was produced with a larger sample size that included participants with cancer, and it is possible something about the physiologic function of the indicators for the lipid factor differs significantly for people with and without existing cancer.

Sleep and Allostatic Load

Subjective Sleep Quality and Allostatic Load

Like the exploration of allostatic load on future cancer, there was little solid evidence on which to base suspicions of a relationship between allostatic load and subjective sleep quality. Despite the limited evidence, conceptually it is reasonable to hypothesize that poor subjective sleep quality is related to higher allostatic load, and the results of the analysis support this supposition. Analysis of the data determined a relationship between allostatic load and subjective sleep quality was present. Overall allostatic load was increased by poor global sleep quality, meaning poor sleep quality was associated with worse physiologic dysfunction. Two studies were identified for comparison. One study was identified that analyzed sleep quality using the PSQI and allostatic load directly. Poor sleep quality was associated with higher allostatic load, but this relationship became non-significant after adjusting for self-reported health status (Judith E. Carroll et al., 2015). The present study did not take health status into consideration. Additionally, while Carroll et al (2015) used similar indicators for allostatic load as the present study, allostatic load scores were calculated using a different method. Each physiologic system was assigned a score between 0 and 1 based on the proportion of indicators for each system that fell into the highest quartile of risk, then

physiologic system scores were summed to compute overall allostatic load (Judith E. Carroll et al., 2015). The authors specify that this method allows for each physiologic system to be weighted equally in the total allostatic load score regardless of the number of indicators per system (Judith E. Carroll et al., 2015). The present study does not weight each physiologic domain equally and allows for the retention of substantial variability from the data. Another comparison study was identified that studied allostatic load in relation to sleep quality. In that study, serial mediation analyses showed a relationship between black race and discrimination, which was then related to the experience of anger, which then impacted subjective sleep quality, with then resulted in an increased allostatic load (Tomfohr et al., 2016). Tomfohr et al (2016) calculated allostatic load from 11 indicators using methods similar to those of Carroll et al (2015).

Sleep Duration and Allostatic Load

Contrary to expectations, there was no relationship between overall allostatic load and any operationalization of sleep duration. Three comparison studies of allostatic load and sleep duration were identified. In contrast to this study's results, Carroll et al (2015) did find a relationship between shorter sleep duration (<5 hours per night) and higher allostatic load as well as a relationship between longer sleep duration (>8.5 hours per night) and higher allostatic load when compared with normal sleep duration (6.5 to <8.5 hours of sleep per night). Chen et al (2014) found a relationship between increased allostatic load and short sleep duration (<6 hours per night) but no relationship between allostatic load and long sleep duration (9 or more hours per night). Clark et al (2014) found the opposite and showed that short sleep (<6 hours of sleep per night) was not

related to allostatic load, but long sleep duration (9 or more hours per night) was associated with increased allostatic load. As with the studies of allostatic load and sleep quality, the number of indicators for allostatic load and methods for calculating allostatic load differed between the present study and comparison studies. It is likely that scores for allostatic load in the present study differ greatly from the scores for allostatic load used by the three comparison studies, potentially explaining the differences in results.

Sleep Quality and Allostatic Load Physiologic Domains

Of the individual physiologic system factors, only the HPA factor was associated with global sleep quality. In this study, the direction of the results was unexpected. Poor sleep quality was associated with decreased HPA factor scores, when higher HPA scores were hypothesized. In the CFA model of allostatic load, increased allostatic load is indicative of worse physiologic dysfunction. However, the results of the subjective sleep quality and HPA factor analysis shows poor sleep quality to be associated with less physiologic dysfunction (better HPA scores). One possible explanation for these results is that the relationship between the HPA factor and sleep quality is nonlinear. The CFA assumes a linear relationship between urinary cortisol and serum DHEAS as they load onto the HPA factor and the overall allostatic load factor. It is possible that the relationship between cortisol and DHEAS and the HPA system factor are not linear and instead are curvilinear. In a curvilinear relationship, both low and high levels of cortisol and DHEAS would be problematic. A brief check of the literature supports the idea that low cortisol and DHEAS could be related to health concerns. For example, a study of adolescent rape survivors with PTSD and matched controls found the rape survivors had

significantly lower cortisol and DHEAS levels (Bicanic et al., 2013). Another study found adults reporting high perceived stress at work had a decreased DHEAS response to acute stress (Lennartsson, Theorell, Kushnir, Bergquist, & Jonsdottir, 2013). A study of adults with burnout, cortisol, and allostatic load (not including cortisol) found high allostatic load and high burnout to be associated with lower cortisol levels (Juster, Sindi, et al., 2011). In the CFA model of allostatic load used in the present study, it seems the linear aspect of the relationship between cortisol and DHEAS and the HPA and allostatic load factors is driving the factor loadings, while the analysis of the HPA factor on sleep quality is hinting at the potential curvilinear aspect of the relationship. Unfortunately, the methods used in this analysis do not allow this to be explored, and these unexpected results will need further investigation. Future investigations of allostatic load should investigate the indicators of the HPA system for a curvilinear relationship with allostatic load and outcomes of interest.

Relationship Among Sleep, Allostatic Load, and Future Cancer Occurrence

It was hypothesized allostatic load would mediate a relationship between future cancer occurrence and sleep. This proved not to be the case. In models that included all three main concepts, sleep, allostatic load, and future cancer, no relationships were found. Additionally, analysis results showed that sleep duration, but not subjective sleep quality, was associated with future cancer occurrence. The opposite relationship to sleep parameters was found for allostatic load: subjective sleep quality, but no sleep duration, was associated with allostatic load. Based on these results, some aspects of the conceptual model of perceived responses to stress were supported and some were not.

Nursing Implications

Sleep is an established important dimension of health. Sleep has long been known to be related to depression, and presence of hypersomnia or insomnia is a criteria for a diagnosis of depression (American Psychiatric Association, 2013; Herrick & Sateia, 2016; Poole & Jackowska, 2017). There is evidence that sleep is related to physical health problems as well (Cappuccio et al., 2008, 2010; Cappucio et al., 2010; Ju & Choi, 2013; Knutson et al., 2009; Lao et al., 2018). Sleep is both an involuntary activity required for human life, as well as a behavior that humans can consciously influence. The timing, location, and duration of sleep can be intentionally modified. Understanding of the purpose, function, and activities of sleep is still evolving, but that short and long sleep duration are known to be associated with health problems and risk for health problems, and this study's results adds to that body of evidence. This has implications for nursing practice. From the primary care perspective, it is important to ask about sleep as a part of routine health maintenance, and sleep health should be taught to primary care nurse practitioners. Typically, medicine is concerned about diagnoses of sleep disorders, such as sleep apnea or insomnia, and sleep is only addressed in patient-provider visits if a patient reports a sleep related complaint. Routine sleep guidance is not regularly given to adults. Based on the evidence identified by a review of the literature and the findings of this study, sleep, like other lifestyle-related behaviors such as diet, exercise, and smoking, should be included in the routine assessment of social history, and questioning patients about sleep should be a routine part of health maintenance. From the acute care perspective, sleep is already a component of training to become a registered nurse, but its

role as a risk factor for health problems should be emphasized. Further, in the acute care environment, it is important to minimize setting-based disruptions and reductions of sleep.

Limitations

One of the potentially limiting factors of this study is that due to limitations in the data, future cancer of any kind was considered for the outcome. In contrast, most other research studies of cancer and sleep focused on a single type of cancer. Given the mixed findings in the literature about the sleep duration-cancer relationship and the sleep quality-cancer relationship, it is possible that the relationship between sleep and future cancer occurrence is not the same for all cancers. Additionally, it is possible that the present study included a large proportion of non-melanoma skin cancers. The study sample of 78 cancer cases includes 31 cases that reported having skin cancer, and it is not possible to differentiate between melanoma and non-melanoma skin cancer in the data. Given that 90% of non-melanoma skin cancers are related to sun exposure, if enough of the cancer cases included in this study are due to factors such as sun exposure, it seems logical that there would not be a relationship between the future cancer outcome and physiologic dysfunction (Skin Cancer Foundation, 2018). One strategy for addressing this issue in the current dataset would be to repeat the analysis using a case-control sample using only non-skin cancer cases and matched controls. Future studies should consider using a larger sample of cancer cases and examining the sleep-cancer relationship with both any cancer and specific cancer types.

Another limitation of this study is the number of years between assessments. The years between time 1 (assessment of allostatic load and sleep) and time 2 (assessment of cancer status) in the study ranged 3-9 years. It is possible the induction and latent periods of cancer in relation to sleep quality and allostatic load are longer than 3 to 9 years, and longer-term follow up is required to identify relationships.

Future Research Directions

In future research endeavors exploring the relationships between cognitive-behavioral responses to stress, physiologic responses to stress, and disease, care should be taken to carefully conceptualize and operationalize the phenomena at work. For example, measures of future cancer, a disease, need to be carefully selected, and cases of non-melanoma skin cancer should perhaps be examined separately. In addition to cancer, other chronic diseases have become epidemic in the US (Centers for Disease Control and Prevention, 2017c). Although the results of this study do not support the full conceptual framework, it may prove to be an appropriate framework for studying other disease outcomes. It may worth repeating this project with a different outcome, such as heart disease or diabetes, to examine for relationships between sleep parameters, allostatic load, and disease.

Future research should examine the best measurement of sleep quality. While the PSQI is established as a reliable and valid measure of sleep quality, the results of the present study identify one flaw in the PSQI. The PSQI considers any sleep duration of 7 hours or more to be normal, and it does not consider the possibility that long sleep duration could be problematic. As demonstrated in the findings of this study, it is likely

that sleep duration is similar to caloric intake in that health problems can occur if it is either too small or too large.

Research investigating the purpose and function of sleep, the parameters of sleep related to health, and how sleep can impact health and disease is evolving and our understanding of the sleep-health relationship is emerging. The existing evidence of sleep duration and future cancer is mixed. No studies were identified by a review of the literature that examined their data for relevant categories of sleep duration. Future research should continue to explore populations for significant categories of sleep duration in relation to disease occurrence. As research progresses, parameters of sleep may be identified that are more meaningful to health and disease development than sleep duration. For example, research of circadian disruption and risk for cancer is showing some promise (Cordina-Duverger et al., 2018).

In future studies, indicators of allostatic load should be thoughtfully selected for inclusion, and relevant measures of selected indicators utilized. Conceptually, allostatic load is a measure of cumulative multi-system physiologic dysfunction. Typically in studies of allostatic load, baseline resting catecholamines and cortisol are measured and used to comprise allostatic load, and these measures were used in this study. However, perhaps these baseline values are not as relevant as measures of the acute stress response. The conceptual framework assumes a cumulative build-up of physiologic dysfunction in response to stress, and maybe baseline values do not capture that dysfunction as well as stress test measures. Perhaps physiologic response to stress, a main concept in this study, could be captured better if it was measured in acute stress situations.

The methods for capturing the HPA domain of allostatic load need further investigation. The CFA assumes a linear relationship between urinary cortisol and serum DHEAS as they load onto the HPA factor and the overall allostatic load factor. The results of the present study indicate the relationship between cortisol and DHEAS and the HPA axis domain are not linear and instead are curvilinear. In a curvilinear relationship, both low and high levels of cortisol and DHEAS would be problematic. Future studies of allostatic load should consider exploring the possibility of cortisol and DHEAS having a curvilinear relationship with allostatic load.

Conclusions

Cognitive-behavioral responses to stress, physical activity, smoking, and alcohol use, have become critical to the management and prevention of chronic disease (Centers for Disease Control and Prevention, 2017c). The results of this study indicate sleep may play a similar role for cancer. Although further research is needed, the results of this study's analysis of sleep duration and future cancer seem to indicate the National Sleep Foundation's recommendations for healthy sleep duration may not be appropriate in relation to developing a cancer in the future.

This study was developed based on a conceptual framework of responses to stress that connects sleep, allostatic load and future cancer. The results show that sleep parameters related to subjective sleep quality are not related to future cancer, but certain parameters of sleep duration are associated with future cancer. Next, the results show that allostatic load is not related to future cancer. Finally, the results show allostatic load and subjective sleep quality are related, but allostatic load and sleep duration are not.

Given these findings, it seems that sleep and cancer and, separately, sleep and allostatic load are likely operating on different pathways, but the results are not definitive. Potential relationships between sleep parameters, allostatic load, and future cancer need further exploration.

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