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Insufficient Sleep and Onset of Coronary Artery Disease

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Insufficient Sleep and Onset of Coronary Artery Disease

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Each person whose signature appears below certifies that this doctoral project in her opinion is adequate, in scope and quality, as a doctoral project for the degree Doctor of Psychology.

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ABBREVIATIONS

CAD	Coronary Artery Disease
CBT-I	Cognitive Behavioral Therapy-Insomnia
HDL	High Density Lipoprotein
HPA	Hypothalamic-Pituitary-Adrenal Axis
IL-6	Interleukin-6
LDL	Low Density Lipoprotein
MDD	Major Depressive Disorder
MET	Metabolic Equivalent
MI	Myocardial Infarction
SCD	Sudden Cardiac Death
SMI	Silent Myocardial Infarction
SNS	Sympathetic Nervous System
TNF	Tumor Necrosis Factor

ABSTRACT OF THE DOCTORAL PROJECT

Insufficient Sleep and Onset of Coronary Artery Disease:
An Integrated Model of Mediators and Moderators

by

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Dr. Janet L. Sonne, Chairperson

Coronary artery disease (CAD), a consequence of coronary atherosclerosis, is the most common form of cardiovascular disease. Recent research suggests that compared to individuals with normal sleep duration, those with insufficient sleep, defined as short sleep duration (i.e., less than 6 hours per 24-hour period) have a 79% higher risk of developing coronary artery disease. In this review, selected physiological factors (including vascular inflammation, sympathetic overactivity, and increases in blood pressure), behavioral factors (including sedentary behavior and dietary choices), psychological factors (including hostility, fatigue, and major depressive disorder/depressive affect), and sociocultural factors (including race/ethnicity, socioeconomic status, and health literacy) were examined as they result from insufficient sleep and, downstream, to the onset of CAD. Based on the empirical literature published to date, a comprehensive model of CAD risk factors and the role of insufficient sleep is offered to highlight potential areas for new research. This review also proposes clinical implications including the development of more targeted assessment factors related to insufficient sleep and CAD onset, as well as the development of multifactorial treatment recommendations for those patients demonstrating risk factors (including insufficient

sleep) to prevent CAD onset.

CHAPTER ONE

INTRODUCTION

Through a review of the empirical literature regarding the onset of coronary artery disease (CAD), this project aims to elucidate the mechanisms of the influence of insufficient sleep (specifically short sleep duration) on certain physiological, behavioral, psychological, and sociocultural CAD risk factors. An empirically-based model of the relationships among insufficient sleep and of each of these risk factors is proposed, and implications for further research and the development of assessment and intervention protocols for insufficient sleep among individuals at risk for the development of CAD are presented.

CHAPTER TWO

AN OVERVIEW OF CORONARY ARTERY DISEASE

Cardiovascular disease includes many types of diseases that affect the heart including CAD, stroke, congenital heart defects, and peripheral heart disease. CAD, a consequence of coronary atherosclerosis, is the most common form of cardiovascular disease (Willerson, & Holmes, 2015). Often also referred to as Coronary Heart Disease, CAD is defined as the pathologic process affecting coronary arteries. Historically, CAD was believed to be a process of artery narrowing due to the progressive growth of smooth muscle cells lining the artery wall, ultimately resulting in complete vessel blockage (and subsequently myocardial infarction). However, evidence is now pointing to the thickening of the innermost layer of the artery, the intima, resulting in atherosclerosis. An atherosclerotic plaque consists of foam cells (lipid-filled macrophages and smooth muscle cells) which are enclosed by a fibrous cap (a collagen and elastin-rich region of the intimal layer). Generally, the spectrum of coronary plaque can range from stable, corresponding to a plaque that is lipid-poor and having a thick fibrous cap, to unstable, which are lipid-rich and have a thin fibrous cap. As the plaque grows in size, it can eventually result in a restriction of blood flow. The more unstable the plaque is, the more likely it is to rupture. Once the plaque ruptures, prothrombotic and vasoconstrictive factors are released by the artery to repair the site of injury. These factors aggregate around the site to form a solid mass, or thrombus, around the wound, increasing the likelihood of complete occlusion of the artery (Ashley & Niebauer, 2004; Hansson, 2005).

Symptomatic Characteristics of CAD

Symptomatic characteristics of CAD typically include angina pectoris, myocardial infarction (MI), silent myocardial ischemia (SMI), and sudden cardiac death (SCD) (De Lemos & Omland, 2017). Angina pectoris occurs when myocardial oxygen demand is greater than the ability of coronary arteries to supply a sufficient amount of oxygenated blood, often due to the restriction of blood flow within the artery. Restriction of blood flow usually results from coronary artery atherosclerosis but may also occur as a result of coronary artery spasm, or rarely, coronary artery embolism. If the restriction is partial or transient, acute coronary thrombosis can cause angina. However, if the thrombosis is prolonged, the result is often MI. It is important to note that myocardial oxygen demand is largely determined by heart rate, systolic wall tension, and contractility. Thus, in chronic stable angina, the narrowing of a coronary artery that culminates in angina is usually initiated by exertion and relieved by cessation of activity (Sweis & Jivan, 2018). Contrarily, angina that occurs when the individual is at rest or spontaneously is regarded as unstable angina. Unstable angina is an intermediate condition between stable angina and MI. Accordingly, unstable angina commonly precedes MI; patients in some studies report experiencing "chest discomfort consistent with unstable angina" in the week before infarction (Ambrose & Dangas, 2000, pg. 25; Harper, Kennedy, DeSanctis, & Hutter, 1979; Stowers & Short, 1970).

During MI, the plaques formed within the interior walls of the coronary arteries result in reduced blood flow to the heart and, due to lack of oxygen supply, injure the heart muscles (Lu, Liu, Sun, Zheng, & Zhang, 2015). Without oxygenated blood delivery to the heart, the muscle cells served by the blocked artery begin to die, or infarct, with

irreversible damage beginning as early as within 30 minutes of the blockage (Johns Hopkins Medicine, n.d.). In 2000, the First Global MI Task Force, which was a collaborative joint committee of the European Society of Cardiology and the American College of Cardiology, articulated a new definition of MI that was founded on the principle that "any amount of myocardial necrosis caused by ischemia should be labeled as [myocardial] infarct" (Morrow, 2016, pg. 3).

MI symptom characteristics and severity can vary from individual to individual. Frequently noted symptoms include "chest pain, which travels from left arm to neck, shortness of breath, sweating, nausea, vomiting, abnormal heart beating, anxiety, fatigue, weakness, stress, [and] depression" (Lu, Liu, Sun, Zheng, & Zhang, 2015, pg. 865). MI can also be recognized by an initial rise and subsequent fall in serum and/or plasma biomarkers of myocardial necrosis (Morrow, 2016). Cardiac troponin I and T are the specific biomarkers of interest because they comprise the contractile apparatus of myocardial cells and they are found almost exclusively in the heart (Thygesen et al., 2012).

In contrast, the most common manifestation of CAD, silent myocardial ischemia (SMI) often goes undetected due to its asymptomatic presentation (Cheng Chang et al., 2016). SMI is of serious concern because it increases the risk for a potentially fatal cardiac event. Notably, many patients whose first clinical manifestation of CAD is sudden death or MI (Cohn, 1984). SMI may be identified through electrocardiogram during which abnormal changes in the electrical activity of the heart can be detected (Conti, Bavry, & Petersen, 2012). Some individuals are at higher risk for SMI, particularly individuals with comorbid diabetes. For these individuals, there may exist a

neuropathic basis for painless ischemia (Cohn, 1984). In other individuals without a diabetes diagnosis who have survived MI, the infarction may have destroyed cardiac nerve endings, reducing their ability to detect pain during ischemia (Cohn, 1984). Several small studies have suggested that asymptomatic coronary patients with SMI may have better prognosis than symptomatic patients as there is evidence from this group that painless episodes can be of shorter duration and cause less left ventricular dysfunction than symptomatic episodes (Chierchia, Lazzari, Freedman, Burnelli, & Maseri, 1983). However, other researchers suggest that alterations in pain tolerance may put these patients at added risk for MI or sudden death due to the consequent limitation in their anginal warning system, specifically during exertion as stable angina can be alleviated with rest (Cohn, 1980).

Sudden cardiac death (SCD) is an unforeseen failure of the heart due to cardiac "arrhythmias, initiated by transient ischemia… in the absence of previously [identified CAD]" (Myerburg & Junttila, 2012, pg. 1047). Symptoms of SCD include palpitations, vomiting and fatigue, followed by more life-threatening symptoms such as rapid syncope, loss of breathing, loss of pulse, collapse, and eventually death (Ajaipal, Dhadial, Adameova, Ashga, & Dhalla, 2016). SCD can occur upon the experience of extreme stress or as a consequence of acute neurologic disease during which the control by the autonomic nervous system of the cardiovascular system becomes imbalanced (Japundžić-Žigon et al., 2018). Specifically, overstimulation by the sympathetic nervous system can affect the electrical conduction system of the myocardium, leading to the failure of the heart muscle (Rabinstein, 2014).

Incidence

The original Framingham Study cohort, which contains data from 44 years of follow up, measured the incidence of coronary events including MI, angina pectoris, unstable angina, and sudden and non-sudden coronary deaths. Results indicated that for people aged 40 years, the lifetime risk, or likelihood of developing CAD, was 49% in men and 32% in women (Lerner & Kannel, 1986). While the incidence of CAD is declining in developed countries, it remains the number one cause of death in adults from low-, middle-, and high-income countries (Lopez, Mathers, Ezzati, Jaimson, & Murray, 2006). Although this report is 13 years old, more recent data from the World Health Organization identifies cardiovascular diseases as the number one cause of death globally (WHO, 2017); CAD is one disorder that falls under the umbrella of cardiovascular diseases.

Approximately 610,000 individuals die of CAD in the United States every year. CAD is the leading cause of death for both adult men and women in the United States, accounting for 1 in every 4 deaths, with a trend of CAD prevalence increasing with age beginning at 20 years (CDC, 2017; American Heart Association, 2015).

Physical Costs

In addition to death, CAD has also been associated with clinically significant declines in quality-of-life. The Global Burden of Disease study (2010) found that CAD was the leading cause of disability-adjusted life years, which are the total number of years of life lost due to premature mortality and years lived with disability (Murray et al., 2012).

Financial Costs

Medical cost of treatment in just the first year of CAD diagnosis in the US totaled $5.54 billion, with five- and ten-year cumulative costs in 1995 dollars for patients who were initially free of CAD estimated at $9.3 billion and $16.5 billion, respectively (Russell, Huse, Drowns, Hamel, & Hartz, 1998). In addition to substantial direct medical costs, CAD survivors' losses in individual earnings are also significant. These reductions range from 8% to 31% three years post-hospitalization (Garland et al., 2019).

CHAPTER THREE

INSUFFICIENT SLEEP

Sleep plays an integral role in good health and well-being throughout the lifespan by impacting brain function as well as other physical systems. Several brain functions are affected by sleep, including cognitive performance, safe motor vehicle operation, regulation emotions, memory consolidation, pain perception, and removal of metabolic waste from the brain. (Consensus Conference Panel of the American Academy of Sleep Medicine, 2015). Beyond brain function, sleep also plays a vital role in "systemic physiology, including metabolism, appetite regulation, immune and hormone function, and cardiovascular system [function]" (Consensus Conference Panel of the American Academy of Sleep Medicine, 2015, pg. 1161).

In research examining the role of sleep in physical health, sleep has been defined in various ways including sleep duration, sleep timing, self-reported sleep quality, day-to-day variability in sleep duration, napping, and sleep disorders. According to the Consensus Conference Panel of the American Academy of Sleep Medicine, sleep duration, is the "most widely-studied, best supported, and most straightforward sleep measure to address in relation to health" (Consensus Conference Panel of the American Academy of Sleep Medicine, 2015, pg. 1161). For example, numerous studies have found that mortality risk has been strongly associated with nightly sleep duration. Specifically, the relationship between sleep duration and mortality is a curvilinear one (a U-shaped curve), such that the lowest risk is found in individuals who sleep between 7-8 hours (Grandner, Hale, Moore, & Patel, 2010). Deviation from the 7-8 hour range, with either fewer or more hours, almost uniformly increases mortality risk. The focus of this review

is on sleep duration—more specifically on one side of the curve--insufficient sleep. Insufficient sleep is defined as short or inadequate sleep duration or insomnia.

Incidence

Unfortunately, insufficient sleep is a rather common problem in the U.S. According to a recent survey by the Centers for Disease Control and Prevention, many Americans have long-term sleep deprivation associated with inadequate sleep duration. One in three adults report getting less than the recommended amount of sleep (7-9 hours; CDC, 2018). Further, 37% of individuals aged 20-39 report short sleep duration (<6 hours), and this figure rises to 40% among individuals aged 40-59 years old (American Sleep Association, 2018). The cause for this appears to be multifactorial. Changes in modern society necessitating longer hours of work and 24/7 availability of goods have contributed to the reduction in average sleep duration, with increased reports of fatigue, tiredness, and excessive daytime sleepiness (Cappuccio, Cooper, D'elia, Strazzullo, & Miller, 2011). According to a 2001 poll by the National Sleep Foundation, approximately 45% of adults report that they sleep less to "get more work done," 43% "stay up watching television," and 22% "have difficulty falling asleep" (Ayas et al., 2003).

Role of Insufficient Sleep in Development of CAD

Recent research suggests that compared to individuals with normal sleep duration, those with insufficient sleep, defined as short sleep duration (i.e., less than 6 hours per 24-hour period; Consensus Conference Panel of the American Academy of Sleep Medicine, 2015) have a 79% higher risk of developing CAD (Hoevenaar-Blom,

Spijkerman, Kromhout, van den Berg, & Verschuren, 2011; Itani, Jike, Watanabe, & Kaneita, 2017). Research indicates that sleep has a variety of effects on several cardiovascular and autonomic nervous system functions including "blood pressure control, heart rate variability, and adjustment of sympathetic activity" (Wolff et al., 2008). Insufficient sleep even over the short term can cause adverse physiologic effects on those systems. Studies in which healthy participants were sleep-deprived for 6 nights (i.e. 4 hours per night) resulted in higher cortisol levels, lower glucose tolerance, and higher sympathetic nervous system activity (Spiegel, Leproult, & Van Cauter, 1999). Of note is that adverse physiologic effects were also observed in healthy individuals who were sleep deprived for only one night (i.e. 3.6 hours of sleep; Tochikubo, Ikeda, Miyajima, & Ishii, 1996). These subjects experienced increased blood pressure and sympathetic activity compared with individuals who received 8 hours of sleep.

Further, 5 or fewer hours of sleep per night has been shown to be associated with a 39% increase in CAD, and 6 hours per night with an increase of 18%, compared to 8 hours of sleep per night (Ayas et al., 2003). This association was persistent even after adjusting for age, smoking status, obesity, hypertension, diabetes mellitus, and other cardiovascular risk factors. In addition, shorter sleep duration has been associated with higher carotid intima-media thickness (IMT; i.e., the thickness of the inner two layers of the carotid artery—the intima and media; Sands et al., 2012).

Although the several factors (and resulting physiological mechanisms) contributing to the onset of CAD have been identified, the role of insufficient sleep in that process, whether as a trigger for, or a mediator or moderator has not been studied in the context of several domains. The remainder of this project will review multiple

contributing factors and mechanisms involved in CAD. Each is followed by a description of the possible role of insufficient sleep. Then, a theoretical model is proposed linking each of these factors from insufficient sleep to the onset of CAD. Finally, the research and clinical implications of these relationships are discussed.

CHAPTER FOUR

FACTORS ASSOCIATED WITH THE ONSET OF CORONARY ARTERY DISEASE AND THE ROLE OF INSUFFICIENT SLEEP

The relationship of insufficient sleep and the onset of CAD has been studied in the context of their physiological, behavioral, psychological, and sociocultural mechanisms (e.g. Barth et al, 2004; Bentzon, Otsuka, Virmani, & Falk, 2014; Brummett et al., 2005; Jean-Louis et al., 2001). However, previous studies have not examined the interrelationships among all of these factors. In this review, selected physiological factors (including vascular inflammation, sympathetic overactivity, and increases in blood pressure), behavioral factors (including sedentary behavior and dietary choices), psychological factors (including irritability, fatigue, and depressive affect), and sociocultural factors (including race/ethnicity, socioeconomic status, and access to health care) will be examined as they are stemming from insufficient sleep and, downstream, to the onset of CAD.

Physiological Factors

Inflammation and CAD

Increasing evidence suggests that inflammation has an important role in atherosclerosis and CAD. Although CAD was previously regarded as a lipid-storage disease, substantial evidence has illuminated the role of immune mechanisms in early atherosclerotic lesions. In fact, inflammation has been found to occur in conjunction with incipient lipid accumulation (Libby, Ridker, & Maseri, 2002). Studies have demonstrated

that “hypercholesterolemia causes focal activation of endothelium in large and medium-sized arteries” (Hansson, 2005, pg 1687). Particularly, the retention and subsequent infiltration of low-density lipoprotein (LDL) cholesterol in the arterial intima begin an inflammatory response in the artery wall (Skålén et al., 2002). LDL is modified through oxidation or enzymatic alteration in the intima, leading to the release of inflammatory lipids that prompt endothelial cells to express leukocyte adhesion molecules—a prerequisite to activating the immune response (Figure 1). As a result, monocytes traveling along the vascular surface adhere at the site of activation. Once the monocytes have attached, chemokines produced in the inflamed intima induces monocytes entering the lesion to differentiate into macrophages. This is a critical step in the development of atherosclerosis because it is associated with the up-regulation of scavenger and toll-like receptors (Smith et al., 1995). Scavenger receptors internalize a variety of molecules bearing similarity to pathogen-like molecular patterns, while toll-like receptors perform this function as well as initiate a signal cascade that leads to further inflammatory cytokine production (Peiser, Mukhopaghyay, & Gordon, 2002). Thus, scavenger and toll-like receptors bind to the activated macrophage, which holds the antigen, oxidized LDL. Once the patrolling immune cells in search of antigen, particularly T cells, bind to the antigen, an activation cascade is initiated, resulting in the expression of cytokines, including interleukin-6 (IL-6) and C-reactive protein. In this way, the activation of a limited number of immune cells can begin a strong inflammatory cascade in the forming lesion, and systemically throughout the body

The Role of Insufficient Sleep

Research suggests that sleep loss can lead to an inflammatory response that could support the CAD process. Short sleep duration simulated in experimental sleep deprivation studies has been associated with increased inflammatory response, marked by elevating circulating levels of inflammatory markers including IL-6, tumor necrosis factor (TNF) α, and C-reactive protein (Shearer et al., 2001; Meier-Ewert et la., 2004). Sleep loss was also found to induce a more than 3-fold increase in transcription of IL-6 mRNA and 2-fold increase in TNF- α mRNA (Irwin, Wang, Campomayor, Collado-Hidalgo, & Cole, 2006). IL-6 and TNF- α have been found to be significant predictors of the severity of CAD. More coronary vessel disease, marked by >70% stenosis, was correlated with increasing levels of serum IL-6 and TNF- α, indicating a chronic inflammatory burden and marker of atherosclerotic risk (Gotsman et al., 2008).

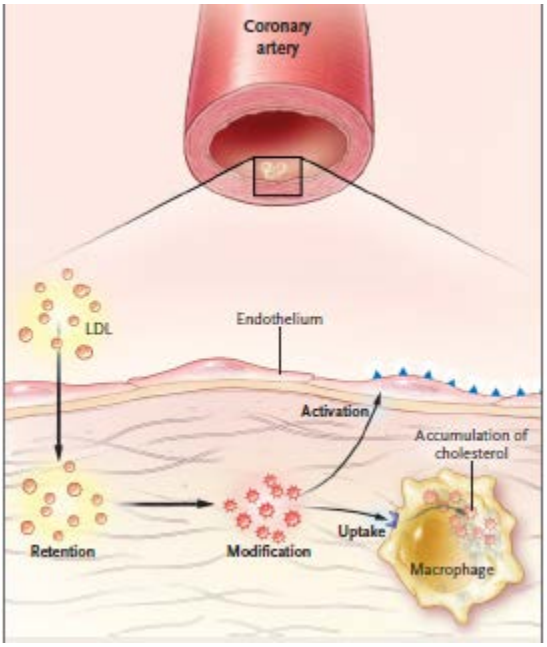

Figure 1. Endothelial activation resulting from LDL retention. (Hansson, 2005)

Sympathetic Overactivity and CAD

The sympathetic nervous system (SNS) is a significant controller of the cardiovascular system in a variety of ways. Specifically, it plays a key role in the control of arterial pressure, regulating the vasoconstriction in the blood vessels of many key organs in the body, including the heart. Increasing or decreasing blood flow through the heart affects the function of the organ. Unlike motor nerves, sympathetic nerves are persistently active. Thus, all innervated blood vessels remain under varying levels of sustained contraction (Malpas, 2010). In individuals with increased sympathetic tone, the term "hyperkinetic circulation" has been used to summarize the constellation of high plasma norepinephrine values and elevated cardiac output and heart rate (Julius, 1993). From a mechanistic perspective, continuous and prolonged activation of the SNS could lead to a gradual decline in cardiac contractile function (Kaye et al., 1995). Furthermore, elevated sympathetic tone has been shown to manifest as greater baseline heart rate and a modest increase in systolic blood pressure (Brum, Losek, Patterson, Bernstein, & Kobilka, 2002). Conditions that have been associated with increased cardiac sympathetic nerve activation include ventricular arrhythmias, which cause the heart to beat at an increased pace, preventing oxygen-rich blood from circulating to the brain and body (Brum, Kosek, Patterson, Bernstein, & Kobika, 2002). As a result, increased cardiac sympathetic nerve activation may result in MI. Because CAD is a chronic inflammatory process triggered by injury to the vascular endothelium, recurrent endothelial injury will further the manifestation of CAD. In particular, this can be accomplished through high levels of circulating catecholamines, such as norepinephrine, which promote procoagulant processes by potentiating platelet activation (Crawford, DiMarco, & Paulus,

2010).

The Role of Insufficient Sleep

Insufficient sleep has been shown to contribute to the increased risk of CAD through depriving the individual of the opportunity to decrease sympathetic stimulation of the cardiovascular system at night (Burgess, Trinder, Kum, & Luke, 1997). A study examining sleep arousals as a consequence of environmental noise found that repeated arousals (likely linked to insufficient sleep) led to chronic sympathetic activation (Chouchou et al., 2013), at least likely partially due to the fact that insufficient sleep leads to more exposure to waking physical and psychosocial stressors (Gangwisch, 2009).

Increased Blood Pressure and CAD

Blood pressure adjusts according to surrounding temperature, body posture, physical activity, and autonomic nervous system activity (Tochikubo, Ikeda, Miyajima, & Ishii, 1996). Epidemiological evidence suggests a strong and consistent association between hypertension and CAD. Pathophysiological mechanisms of arterial pressure as a risk factor for CAD include the influence of blood as a physical force on the development of atherosclerotic plaque (Weber et al., 2016). As systolic blood pressure increases, intramyocardial wall tension increases, leading to a higher myocardial oxygen demand (Rosendorff et al., 2015). In older individuals, systolic hypertension is often attributable to "high aortic impedance, which results from decreased aortic diameter or increased effective stiffness caused by aortic wall thickening and changes in wall composition" (Rosendorff et al., 2015, pg. e441). Hypertension as a mechanical force can also activate

oxidative stress, and specifically, oxidation of LDL cholesterol, which increases the expression of monocyte chemoattractant protein-1 and vascular cell adhesion molecule-1, thus activating the atherosclerotic process (Rosendorff et al., 2015).

The Role of Insufficient Sleep

Some studies have shown that sleep deprivation in healthy individuals leads to an acute increase in blood pressure. Further, in a study among hypertensive and normotensive participants increases in blood pressure were observed after sleep was restricted to 3.6 to 4.5 hours (Lusardi et al., 1996; Lusardi et al., 1999).In particular, prolonged insufficient sleep was shown to lead to hypertension through sustained "exposure to raised blood pressure and heart rate, elevated sympathetic nervous system activity, and increased salt retention" (Gangswisch et al., 2006, pg. 833). Insufficient sleep deprives the individual of the typical pattern of lowering blood pressure (and sympathetic nervous system activity) at night during rest.

These sustained activity forces could lead to both structural and mechanistic adaptations of the cardiovascular system in order to function at an overall higher pressure equilibrium. Specifically, over the long-term, increased hemodynamic load, as a result of higher blood pressure over the 24-hour day, could lead to left ventricular hypertrophic remodeling, which could progressively lead to an elevated cardiovascular pressure equilibrium (Mayet & Hughes, 2003).

Significant increases in blood pressure have been shown to be accompanied by increases in urinary excretion of norepinephrine, suggestive of increased sympathetic nervous system activity (Lusardi et al., 1999). Thus, it is hypothesized that a mechanism

by which sleep deprivation elevates blood pressure is through the production of catecholamines, such as norepinephrine. Another hypothesized mechanism for increased blood pressure as a result of chronic insufficient sleep is the disruption of circadian rhythmicity and autonomic balance. The central biological clock, or suprachiasmatic nucleus (SCN), is responsible for synchronizing activity and rest according to the rising and setting of the sun. In addition to light exposure, in order to organize autonomic rhythms, the SCN requires repeated metabolic cues from sleep, activity, and feeding. Thus, alterations in sleep are hypothesized to cause the brain to perceive an environmental disruption, resulting in a higher than normal blood pressure profile (Gangswisch et al., 2006).

Behavioral Factors

Physical Activity and CAD

There exist a variety of recommendations for the minimum requirement of physical activity for adults for health maintenance. The majority of these recommendations indicate 30 minutes of moderate-intensity activity for five days per week, or 20 minutes of vigorous-intensity physical activity for three days per week (Haskell et al, 2007; Knight, 2012). According to the World Health Organization, adults should accumulate at least 150 minutes of moderate-intensity physical activity throughout the week, or participate in at least 75 minutes of vigorous-intensity physical activity throughout the week. (World Health Organization, 2010). One method for estimating the intensity of physical activity is through the measure of metabolic equivalents (METs).

One MET is an individual's resting metabolic rate. Thus, an activity that is 4 METs requires the body to use approximately four times more oxygen than when at rest. Accordingly, intensity of physical activity may be classified as light (<3 METs), moderate (3-6 METs), and vigorous (>6 METs; Pate et al., 1995).

Previously published studies have indicated that physical activity both prevents and aids in the treatment of many established risk factors for atherosclerosis, including hypertension, insulin resistance and glucose tolerance, elevated triglyceride concentrations, low HDL cholesterol concentrations, and obesity (Thompson et al., 2003). Additionally, exercise coupled with weight reduction can decrease LDL cholesterol concentrations. In a meta-analysis of 52 exercise training trials of greater than a 12-week duration, a 4.6% average increase in HDL concentration levels, and a 3.7% and 5.0% decrease in triglyceride and LDL concentrations, respectively, were observed (Leon & Sanchez, 2001). In the HERITAGE (health, risk factors, exercise training, and genetics) study, 675 normolipidemic subjects (299 men and 376 women) participated in 5 months of exercise training. The men showed a 3.3% increase in HDL concentrations, and 2.7% and 0.8% decrease in triglycerides and LDL concentrations, respectively. Among the women, HDL concentrations increased by 3%, and triglycerdies and LDL concentrations decreased by 0.6% and 4.0%, respectively (Leon et al., 2000).

The mechanism by which physical activity is hypothesized to reduce the onset of CAD is through its reduction on resting blood pressure, as discussed in the Physiological Factors section above (Thompson et al., 2003). Physical activity has been further shown to delay atherosclerotic processes through reducing coronary vasospasm, enhancing myocardial electrical stability, and increasing fibrinolysis. Coronary vasospasm is

hypothesized to have a role in acute MI (Maseri et al., 1978). In a study with dogs, physical training reduced coronary vasospasm during adrenergic stimulation (Bove & Dewey, 1985). In humans, physical training has been shown to increase cardiac parasympathetic tone and reduce ventricular fibrillation, or erratic rhythmic disturbances, during cardiac ischemia (Kenney, 1985; Redwood, Rosing, & Epstein, 1972).

The Role of Insufficient Sleep

There are some important relationships between insufficient sleep, physical activity, and CAD. Some studies have shown that short sleep duration is associated with reduced participation in physical activity as a result of feeling fatigued (Garaulet et al., 2011). And, exhaustion from insufficient sleep has been purported to lead to reduced physical activity to sustain extended wakefulness (Markwald et al., 2013). For example, in a study among adults with a parental history of type 2 diabetes, when sleep was reduced by 2.3 hours per day, participants had 31% fewer daily activity counts and spent 24% less time in moderate-vigorous physical activity (Bromley, Booth, Kilkus, Imperial, & Penev, 2012). In those who were allowed to exercise during the study, 30 minutes of moderate-vigorous activity was reallocated to light and sedentary activity.

The mechanism through which exercise is purported to decrease cardiovascular risk is through decreasing resting blood pressure, known as postexercise hypotension, which resets the baroreflex to lower operating pressures (MacDonald, MacDougall, & Hogben, 2000). Accordingly, it is purported that decreased physical activity would not result in these favorable cardiovascular outcomes.

Sedentary Behavior and CAD

The Sedentary Behavior Research Network offers the following definition of sedentary behavior: "any waking behavior characterized by an energy expenditure ≤1.5 METs while in a sitting or reclining posture" (Sedentary B.R.N., 2012).

Sedentary time is ubiquitous. It is collected throughout day while commuting, at school, in the workplace, at home, and in leisure activities. Economic, social and technological changes in recent years have also led to increased use of screen-based entertainment and communication devices, more suburban development, and increased motorized transport, all of which have increased sitting time over the past decade (Sugiyama et al., 2012). These changes have improved the efficiency with which individuals extract energy from their environments, necessitating a lower level of energy expenditure to subsist. For adults, sedentary behaviors are even more of a health concern due to progressive age-related loss of muscle mass and increased fat mass, augmenting their risk of developing chronic diseases including cardiovascular disease, obesity, and diabetes (Zamboni et al, 2008).

New evidence regarding the effects of sedentary behavior on health suggests that its effects may be independent of levels of physical activity. More specifically, further research has supported the premise that sitting time has hazardous cardiovascular and metabolic effects that are independent of meeting physical activity guidelines (Hamilton, Healy, Dunstan, Zderic, & Owen, 2008).

In a 12-year mortality follow-up of the Canada Fitness Survey, a clear dose-response relationship between daily sitting time and all-cause and cardiovascular disease mortality was evident in both men and women (Katzmarzyk, Church, Craig, & Bouchard,

2009). Some recent studies observed that weekend sedentary behavior was positively associated with arterial stiffness in both men and women, even after adjustment for vigorous physical activity (Huynh et al., 2014). In another study of 614 healthy middle-aged adults, the proportion of time spent in sedentary activity was found to be directly associated with carotid artery wall thickness, implicated in the manifestation of cardiovascular disease (Kozàkovà et al., 2010). These data provide preliminary evidence that sedentary behavior is related to impaired cardiovascular function as an independent risk factor.

The Role of Insufficient Sleep

Sedentary behavior and sleep are both low energy-expending activities. Thus, it may be intuitive to expect shorter sleep duration to be associated with greater energy expenditure while awake. However, evidence from both clinical and population-based studies demonstrate that insufficient sleep is associated with overweight in both adults and children (Singh, Drake, Roehrs, Hudgel, & Roth, 2005), suggesting lower energy expenditure while awake following shortened sleep.

A mechanism that may connect sedentary behavior to insufficient sleep is the isotemporal substitution paradigm because it acknowledges the health impacts of sleep and sedentary behavior depend on the behaviors they displace (Buman et al., 2013). Because time in a day is finite, increasing time in one behavior consequently requires reducing the time in another behavior. While slow walking may be protective against weight gain if it displaces an equal duration of TV-watching, slow walking may not be as beneficial when it replaces brisk walking or jogging (Mekary, Willett, Hu, & Ding,

2009). In fact, research findings suggest that in response to experimental sleep reduction, adults spent more time in sedentary behavior than in moderate to vigorous physical activity (Bromley, Booth, Kilkus, Imperial, & Penev, 2012). And, more time spent in sedentary behavior that reduces time spent in physical activity appears to increase cardiovascular risk (Buman et al., 2013).

Diet and CAD

Research has shown that the normalization of abnormally elevated lipoprotein levels has been shown to delay the progression of coronary atherosclerotic lesions, and even the regression of plaques in some individuals. The atheroprotective effects of lipid modification are correlated with fewer clinical events and decreased mortality from CAD (Schuler et al., 1992). Thus, dietary modifications that reduce serum lipoprotein levels is associated with delayed onset of CAD.

While the primary cause(s) or initiator(s) of CAD are unknown, one hypothesis for the development of atherosclerosis is the free radical damage to cholesterol in circulating LDL (Ulbricht & Southgate, 1991). One study acknowledged seven dietary factors that are involved in these processes. Two of these factors promote CAD—namely, cholesterol-raising saturated fatty acids and thrombogenic saturated fatty acids, both found in animal products including pork, poultry with skin, butter, and dairy products made with whole or reduced-fat milk. Five of these factors are protective—polyunsaturated fatty acids of the n-6 (linoleic) and n-3 (linolenic) acid series, monounsaturated fatty acids, dietary fiber, and antioxidants. It is inconclusive about whether the effects of each of these factors are additive or integrative, though intuitively

it is expected that these factors affect the onset of CAD in an integrated manner. In a study examining isocaloric replacement of 5% energy from saturated fatty acids with polyunsaturated fatty acids, monounsaturated fatty acids, and whole grain carbohydrates, a 25%, 15% and 9% (respectively) lower risk of CAD was detected (Houston, 2018).

Data from epidemiological and cohort studies reinforce the potential protective effects of antioxidants in the diet. The findings show that increased consumption of antioxidant-rich foods such as fruits, vegetables and legumes, grains, and nuts may be associated with decreased risk of CAD, and deaths attributed to CAD (Singh et al., 2002). Conversely, a diet low in fruits and vegetables, and correspondingly deficient in antioxidants such as vitamin A and C, have been shown to allow overproduction of free radicals, increasing the risk of CAD.

The Indo-Mediterranean diet rich in α-linolenic acid, a type of omega-3 fatty acid, has been demonstrated to be associated with significant reductions in non-fatal MI and SCD (Singh et al., 2002). These dietary patterns involving omega-3 fatty acid and antioxidant status appear to have an effect on the mechanism of atherosclerotic plaque vulnerability and the progression of thrombosis (Robertson & Smaha, 2001). For example, platelet adhesion, important in thrombosis, has been shown to occur when antioxidant and omega-3 fatty acid status is low (Singh et al., 2002).

Epidemiological and experimental evidence suggests that a diet high in saturated fatty acids is associated with high levels of serum cholesterol, which contributes to high incidence of CAD (Ulbricht & Southgate, 1991). Thus, the presumed atherogenic saturated fatty acids are lauric (12-carbon atom chain; e.g. coconut milk), myristic (14-carbon atom chain; e.g. palm kernel oil), and palmitic (16-carbon atom chain; Keys,

1965; e.g. full fat cheese). Myristic acid is hypothesized to be the most atherogenic, which approximately four times the cholesterol-raising potential of palmitic acid (Dabadie, Peuchant, Bernard, LeRuyet, & Mendy, 2005).

The Role of Insufficient Sleep

Diets high in fat have been associated with lower sleep efficiency, which refers to the percentage of time asleep while in bed, and greater time spent awake after having fallen asleep (Crispim et al., 2011). Some studies show that short sleep is associated with greater desire for high fat foods and sweets (St-Onge et al., 2011; Spiegal, Tasali, Penev, & Cauter, 2004). One proposed neural mechanism is that foods high in fat and sugar stimulate the brain's dopaminergic system, suggesting that insufficient sleep promotes hedonic stimulus processing of food (St-Onge, Wolfe, Sy, Shechter, & Hirsch, 2014).

To reduce the CAD health risks associated with excess adiposity, many individuals consider a diet-induced weight loss strategy. However, because mammalian sleep is closely integrated with the regulation of energy balance, lack of sufficient sleep may compromise the efficacy of efforts such as calorie restriction (Spiegel, Tasali, Penev, & Van Cauter, 2004). Neuroendocrine changes associated with sleep deficiency including higher concentrations of ghrelin may facilitate the retention of fat (Tschöp, Smiley, & Heiman, 2000). As ghrelin is also a hormone that stimulates appetite, increased appetite as a result of insufficient sleep could also result in higher dietary intake of cholesterol, trans fats, and saturated fat. Furthermore, increased hunger could counter caloric-restriction efforts. In one study that examined experimental sleep and energy restriction among overweight adults, researchers found decreased loss of fat and increased loss of

fat-free body mass with sleep restriction (Nedeltcheva, Kilkus, Imperial, Schoeller, & Penev, 2010). These findings suggest the importance of sufficient sleep both for the efficacy of calorie restriction weight loss and for maintenance of fat-free body mass as strategies for CAD onset risk reduction.

Tobacco Smoking and CAD

Accounting for 10-15% of the risk of CAD onset, tobacco smoking plays a central role in inducing atherosclerosis and increasing the risk of MI and SCD (Steenaard et al., 2015). Studies have shown that the mechanism through which smoking increases the risk of developing CAD is DNA methylation, which refers to the attachment of a methyl group to a nucleotide (the basic structural unit of DNA). Among its many functions at different locations in the human genome, one influence of methylation is gene expression (Phillips, 2008). Heavy smokers have been found to have a higher incidence of infarction and mortality from CAD than light smokers (Aronow, 1974). Furthermore, experimental data suggest that carbon monoxide, inhaled from smoking tobacco, and nicotine-induced platelet aggregation may be a link between tobacco smoking and the pathogenesis of coronary atherosclerosis (Aronow, 1974).

Smoking cigarettes has also been shown to increase systolic and diastolic arterial pressure and heart rate (Aronow, 1974). The presence of nicotine in cigarettes has been shown to cause increases in catecholamine production from the adrenal medulla and chromaffin cells of the heart, suggesting sympathetic nervous system activation (Aronow, 1974). Moreover, tobacco smoking has been long known to cause elevated carboxyhemoglobin levels, decreasing the amount of oxygen available to the

myocardium. Hemoglobin has a 245 times greater affinity to carbon monoxide than to oxygen (Light, Grass, Pursley, & Krause, 2007). Additionally, the presence of carbon monoxide in the blood induces a tighter binding of hemoglobin to oxygen, reducing the availability of oxygen to the tissues. Therefore, stable angina is likely to onset after exercising, following smoking because (1) nicotine increases myocardial oxygen demand and (2) carboxyhemoglobin decreases oxygen delivery to the heart muscle. Increases in incidence of MI and SCD may be related to the carbon monoxide interference with myocardial oxygen demand.

The Role of Insufficient Sleep

Smoking tobacco has been shown to be associated with many sleep disorders, including insufficient sleep (Krueger & Friedman, 2009). In fact, one study found that individuals smoking tobacco have more than twice the odds of insufficient sleep compared to non-smokers (Sabanayagam & Shankar, 2011). The same study found second-hand smoke exposure also to be associated with higher odds of insufficient sleep among never and former smokers.

In addition, there is evidence to suggest that smoking tobacco may lead to insufficient sleep. Accordingly, the relation between smoking tobacco and insufficient sleep appears to be bidirectional. The mechanism through which smoking tobacco affects sleep has been established to be through nicotine, the active component of tobacco, which stimulates the release of sleep-regulating neurotransmitters, including dopamine and serotonin (Sabanayagam & Shankar, 2011). Particularly, nicotine, and acute withdrawal from it, is associated with disturbances in sleep architecture, including lighter sleep,

delayed sleep initiation, lower sleep efficiency, and greater daytime urges to sleep (Zhang, Samet, Caffo, & Punjabi, 2006).

Psychological Factors

Depressive Affect and CAD

The DSM-5 (APA, 2013) requires the presence of either (a) depressed mood or (b) loss of interest or pleasure, and four or more of the following criteria for diagnosis of major depressive disorder (MDD): (1) significant weight loss or weight gain, (2) insomnia or hypersomnia, (3) psychomotor agitation, (4) fatigue or loss of energy, (5) feelings of worthlessness, (6) diminished ability to think or concentrate, and (7) recurrent thoughts of death. Considering depression is characterized by a constellation of factors, this section will review studies that examine both depressive affect and MDD as defined by the DSM-5 as a risk factor to the onset of CAD.

Unlike, hostility, which can be regarded as a chronic risk factor, the effect of depression as a psychological risk factor for CAD onset has shown to be episodic in nature. By definition, depression typically spans several months to 2 years and tends to recur. For those individuals experiencing recurrent MDD, CAD onset is likely to be more injurious than for individuals who are experiencing MDD for the first time. One study found that among individuals with a history of MDD and experiencing a recurrent episode of MDD, 40% suffered from mortality relative to those experiencing MDD for the first time during their MI (Lesperance, Frasure-Smith, & Talajic, 1996). In another study of 526 patients, 26.7% of participants had a history of depression and also

experienced more frequent angina, physical limitation, and worse quality of life after 7 months (Rumsfeld et al., 2003). Evidence suggests that CAD patients with first time incident MDD and those with recurrent MDD represent different subtypes among individuals with CAD.

Mechanisms implicated in the contribution of depression to the onset of CAD include changes in the sympathetic nervous system, and more generally, in the autonomic nervous system. Specifically, research has shown that individuals with recurrent MDD demonstrate hyperactivity of the sympathetic nervous system, which, in turn, is linked to decreased heart rate variability (HRV; a measure of cardiac autonomic activations), decreased vagal tone, and reduced heart rate recovery (Goodman, Shimbo, Haas, Davidson, & Rieckmann, 2008). Further evidence suggests that more global dysregulation of the autonomic nervous system has been correlated with depressive symptom severity (as measured by the Beck Depression Inventory). This dysregulation is marked by decreased HRV and reduced baroreflex, the mechanism through which blood pressure changes are regulated (Curtis, & O'Keefe, 2002, Dakak, Quyyumi, Eisenhofer, Goldstein, & Cannon, 1995). Reduced baroreflex sensitivity reflects decreased activation of the parasympathetic nervous system and dominance of the sympathetic response, increasing blood pressure variability and thereby CAD onset (Virtanen et al., 2003).

The Role of Insufficient Sleep

Not only a symptom, insufficient sleep is also a possible predictor of MDD. Chronic sleep insufficiency has been found to sensitize individuals to MDD (Novati et al, 2008). One study found that individuals who have insomnia are twice more likely to

develop MDD, compared to individuals without sleep difficulties (Baglioni et al., 2011). Another study reported insomnia symptoms for greater than two weeks forecasted a higher risk for developing depression within the subsequent three years (Reimann & Voderholzer, 2003). And, some studies show that the improved sleep outcomes of cognitive behavioral treatment for insomnia (CBT-I) endures for up to 2 years after the course of CBT-I is complete. This is particularly of relevance in the treatment of MDD as individuals who remain insomnia free are likely to be free of depression for longer than for those in whom insomnia recurs (Manber et al., 2008).

One proposed mechanism through which insufficient sleep contributes to depression is through negative emotionality. Insufficient sleep has been shown to alter goal-directed behaviors by attenuating the influence of the prefrontal cortex over other brain regions. Accordingly, sleep loss affects cognitive-energy resources required for coping with goal-hindrances. Further, the availability of cognitive resources contributes to the perception of the progression towards a goal. In situations where sufficient cognitive resources are perceived, positive emotions are promoted. Conversely, when a lack of resources is perceived, negative emotions are enhanced (Kahn, Sheppes, & Sadeh, 2013).

Hostility and Anger and CAD

Hostility has been generally conceptualized as irritability, easy anger-arousal, argumentativeness, and antagonistic interpersonal attitude (Koskenvuo et al., 1988, Barefoot, 1992). Hostility has been identified as a stable psychological trait associated with physiological characteristics that increase the risk of CAD incidence (Barefoot,

Dahlstrom, & Willams, 1983), specifically through the apparent effects of hostility on HRV and associated impact on the sympathetic nervous system. Research findings indicate that HRV decreases with negative emotion such as hostility (Billman, 2013). Evidence also suggests an association between increased sympathetic nervous system activity and hostility, with direct effects on the vasculature, elevating blood clotting factors, lipids, and hemodynamic responses to acute stressors (Kop, 1999). And, investigators have shown that increased sympathetic nervous system activity is related to low HRV among patients with CAD (Kleiger, Miller, Bigger, & Moss, 1987).

A closely related aspect of hostility, anger, is generally considered the emotional aspect of hostility. Anger has been purported to have a greater effect on cardiac dysfunction than other psychological stressors (Ironson et la., 1992). In one study, anger was associated with CAD onset in a dose-response relation over the course of a 7-year follow up among initially healthy men (Kawachi, Sparrow, Spiro, Vonkonas, & Weiss, 1996). In another 4-year study among men and women, risk of CAD onset was twice among normotensive individuals reporting high levels of anger than with those reporting low levels (Williams et al., 2000). Thus, the risk of CAD onset increases monotonically with increasing levels of self-reported anger.

The Role of Insufficient Sleep

Studies suggest angry feelings can disrupt sleep, though there is also evidence to suggest that disrupted sleep may increase anger (Kamphuis et al., 2012). Accordingly, the relation between anger tendencies and insufficient sleep appears to be bidirectional.

Few studies have investigated the link through which insufficient sleep

contributes to the experience of hostility. However, sleep deprivation has been associated with significant impairment in emotional regulation, typically "manifesting as irritability and reduced tolerance for frustration as well as…hostility" (Hildenbrand, Daly, Nicholls, Brooks-Holliday, & Kloss, 2013, pg. 409).

In one study during which participants were sleep restricted for 4 hours for 3 nights, increased anger was observed following the 3 nights (Haack & Mullington, 2005). The results of a survey found that adults who reported becoming angry or suppressing angry feelings also reported greater sleep onset latency and unintentional awakenings during the night (Caska et al., 2009).

Proposed mechanisms through which insufficient sleep elicits anger include higher sensitivity to recognition of negative stimuli, biasing individuals' processing toward more negative stimuli (Walker, 2010). Alternatively, an indirect mechanism suggests that individuals may be frustrated by external demands that interfere with the pursuit of sleep (Krizan & Hisler, 2018).

Conversely, the mechanism through which anger undermines sleep duration have been proposed to be through cognitive activity including rumination or worry, interfering with sleep initiation and maintenance. (Pillai, Steenburg, Ciesla, Roth, & Drake, 2014;Thomsen, Mehlsen, Christensen, & Zachariae, 2003). Additionally, enacting anger can create concern for potential consequences and induce physiological arousal that disrupts sleep (Åkerstedt,Kecklund, & Axelsson, 2007; Caprara et al., 1992).

Fatigue and Exhaustion and CAD

Fatigue, described as feelings of extreme tiredness and lack of energy, has a

substantial negative effect on quality of life. Throughout the day, levels of cortisol normally show a specific variation, with its level being highest in the morning, and lowest in the night. Fatigue is one of the most common premonitory symptoms in the majority of CAD patients across all stages of the disease (Keltikangas-Järvinen, Räikkönen, Hautanen, & Adlercreutz, 1996). It has been associated with low cortisol concentrations and unvarying cortisol daytime secretion (Kumari et al., 2009). Unvarying cortisol levels are associated with increased risk for cardiovascular mortality and CAD (Kumari, Shipley, Stafford, & Kivimaki, 2011; Nijm, Kristenson, Olsson, & Jonasson, 2007). Furthermore, cortisol reactivity is considered to be an index of hypothalamic-pituitary-adrenal axis (HPA) functioning as it is an end product of the HPA (Witrtz et al., 2007). Attenuated function of the HPA was demonstrated to predict onset of fatigue, indicating the potential contribution of abnormalities of the adrenal axis (Kumari et al., 2009). Abnormalities in HPA have been described in several chronic inflammatory disorders, including the pathogenesis of CAD (Nijm & Jonasson, 2009).

Conceptually similar to fatigue, exhaustion is conceptualized by a constellation of characteristics including “lack of energy, increased irritability, and demoralization” (Appels, 1990, p. 22). Exhaustion has been hypothesized as a consequence of prolonged psychological distress. The Rotterdam Civil Servants Study demonstrated the predictive value of exhaustion for cardiac problems by following 3877 healthy subjects for an average period of 4.2 years. Individuals who self-identified as exhausted, reporting a “loss of vitality, listlessness, loss of libido, and increased irritability,” were more than two times as likely to experience MI before the 4.2-year follow-up than individuals who did not (Arnim & Maseri, 1989, pg. 52). Historical experience of exhaustion has also

been indicated as a predictor of current exhaustion and subsequent MI (Appels & Schouten, 1991). In such a way, exhaustion can be regarded as a transient and recurrent risk factor, instead of chronic indicator, for CAD.

The Role of Insufficient Sleep

Perhaps the most evident result of insufficient sleep is the experience of fatigue (Oginska & Pokorski, 2006). Mechanisms for the relationship of fatigue to CAD have been proposed. In a study of participants who underwent 4 hours of sleep for each of 11 days, increases in inflammatory markers, such as IL-6, have been associated with increased self-reported fatigue (Haack, Sanchez, & Mullington, 2007). Elevation in IL-6 has been shown to be related to increased risk of CAD onset. Further, exhaustion from insufficient sleep has been purported to lead to reduced physical activity and increased food intake to sustain extended wakefulness (Markwald et al., 2013). Physical inactivity and increased caloric intake may predispose to excess adiposity, contributing to the onset of CAD. And, it would seem that exhaustion and fatigue both would reduce an individual's resolve to sustain dietary changes or exercise regimens necessary for the prevention of CAD onset.

Sociocultural Factors

Ethnicity (Race) and CAD

Race has been used as a research variable in social and biological sciences for hundreds of years (Roberts, 2011). However, there is no clear, universally accepted

definition of race (Kaplan, 2014). Some researchers regard race as a biological category, relying on modern concepts of population genomics (Roberts, 2011). However, evidence suggests that there are no known combination of genetic markers that dependably differentiate members of large groups from one another, and there is more variability within groups identified as biological races than between them (Barbujani, Magagni, Minch, & Cavalli-Sforza, 1997). However, researchers agree that race, when treated as a social, instead of biological, category may capture variance in outcomes of interest (Grandner, Williams, Knutson, Roberts, & Jean-Louis, 2016). In this way, race may represent other social, environmental, and cultural factors that tend to occur in social groups, such as exposure to and/or perception of racial discrimination. Race may also be useful in categorizing health disparities.

Ethnicity generally encompasses race and offers much more fluidity of characteristics within and between groups. Ethnicity refers to a "group that shares a history, culture, and geographic ancestry" (Grandner, Williams, Knutson, Roberts, & Jean-Louis, 2016, p. 3). For the purpose of this review, ethnicity will be operationalized as one sociocultural category, including race.

Ethnic minority populations face a disproportionately greater number of barriers to the diagnosis and care of medical problems related to CAD, receive lower quality treatment, and experience worse health outcomes than their White counterparts (Bonow, Grant, & Jacobs, 2005). This review will focus on the following ethnic minorities: African American/Blacks, Asian-Americans, and Hispanic/Latino. The research findings cited below are presented relative to individuals who self-identify as non-Hispanic Whites.

Relative to non-Hispanic Whites, African Americans/Blacks are 40% more likely to develop hypertension and 10% less likely than Whites to have their blood pressure under control (Schiller, Lucas, & Peregoy, 2012). Furthermore, they experience MI at a higher rate, and are 30% more likely to die from CAD (U.S. Department of Health and Human Services Office of Minority Health, 2016).

Among Asians, CAD occurs earlier in life and in a higher percentage of the population of Asian Indians specifically than any other ethnic group (Steinberg, Balfe, & Küstner, 1988). One reason for their higher risk may be higher lipoprotein levels in this group relative to any other ethnic group. Further, some of the highest smoking rates have been observed in Southeast Asian groups including Korean Americans, Vietnamese Americans, and Filipino American males, which promotes atherosclerosis and triggers symptoms of CAD (Tang, Shimizu, & Chen, 2005; CDC, 2014). Studies surveying the likelihood of ethnic groups to undergo systematic screening for CAD found South Asian males among the least likely to seek this service compared to white males (Bartys, Baker, Lewis, & Middleton, 2005).

Hispanic/Latino individuals generally have higher rates of cardiovascular risk factors. Patterns of dyslipidemia, and particularly higher levels of triglycerides and lower levels of HDL, relative to Whites have been noted among Hispanic groups (Allison et al., 2008). Elevated body mass index, a cardiovascular risk factor affecting all ages, racial/ethnic groups, and sexes, was found in very high rates among Hispanic American subgroups (Kurian & Cardarelli, 2007). Interestingly, it appears Hispanic individuals demonstrate lower rates of CAD (Mitchell, Stern, Haffner, Hazuda, & Patterson, 1990). However, lower relative prevalence of CAD among Hispanics may be due to low

incidence of CAD or a high case of fatality in this ethnic group. One study reported a higher rate of mortality after MI among Mexican Americans than among non-Hispanic Whites (Goff et al., 1993). Alternatively, a term referred to as the "Hispanic Paradox" explains an epidemiological phenomenon in which Hispanics in the US often experience better overall health outcomes than non-Hispanic Whites. While lower SES is a robust predictor of worse health outcomes, research findings suggest that acculturation moderates the relationship between SES and disease risk among Hispanics such that it buffers the stress of economic and environmental disadvantages (Ruiz, Steffen, & Smith, 2013).

The Role of Insufficient Sleep

One study reported significantly shorter mean sleep duration (5.9 versus 6.3 hours) for ethnic minorities (African American/Black/Caribbean, Asian, and Hispanic/Latino) compared to Whites (Jean-Louis, Kripke, Ancoli-Israel, Kauber, & Sepulveda, 2000). Among adults aged 35-50, another study found that sleep duration was significantly lower in African Americans compared to Whites, even after adjusting for several sociodemographic and behavioral factors (Lauderdale et al., 2006). In a study comparing African/Caribbean immigrant and non-Hispanic White employees, researchers found the former group slept an hour less per night on average (Ertel, Berkman, & Buxton, 2011). In examining the 2007-2008 National Health and Nutrition Examination Survey, researchers found that relative to non-Hispanic Whites, Black/African American and Hispanic/Latino individuals were 3.5 times more likely to be very short sleepers (<5 hours), and Asians/others were 5 times more likely to be very short sleepers (Whinnery,

Jackson, Rattanaumpawan, & Grandner, 2014).

Socioeconomic Factors and CAD

Socioeconomic factors generally include occupational status, household income, and education level. In a study examining the relation between social mobility and CAD, the prevalence of CAD was found to be greatest in workmen and other non-management men, diminishing progressively as management level increased (Hinkle et al., 1968). It is hypothesized that high job strain, defined as the "combination of… low job decision latitudes and high psychological job demands," is a predictor of cardiovascular illness (Theorell & Karasek, 1996, p. 309) In another study investigating the relation between educational attainment and biologic and behavioral risk factors for CAD among middle-aged women, the less self-reported education, the more atherogenic was their risk factor profile (Matthews, Kelsey, Meilahn, Muller, & Wing, 1989).

Socioeconomic factors also appear to be related to some of the behavioral risk factors for CAD described above. Studies have shown that declines in smoking among high socioeconomic status individuals has been followed by more aggressive marketing of tobacco to individuals of lower socioeconomic status (Davis, 1987; Barry, 1991).

A similar trend can be found in the production and marketing of high-fat foods, which are often targeted in less developed areas (Wing, Barnett, Casper, & Tyroler, 1992). This trend extends to the distribution of free dairy products, including cheese, in government programs. In addition, poor access to healthy and affordable food among low-income individuals may contribute to diet-related negative health outcomes, such as CAD (Beaulac, Kristijansson, & Cummins, 2009; Cheadle et al., 1991). Americans living

in low-income areas tend to have poor access to healthy foods due to restricted access to supermarkets and chain stores that sell more affordable food, and higher presence of independent and convenience stores in low-income neighborhoods that charge higher prices for healthy foods (Alcaly & Klevorick, 1971).

Based on the known health risks associated with physical inactivity and CAD onset, a clear public health goal is to promote an active lifestyle. A national survey in the US also revealed that perceived environmental barriers to physical activity and income are strongly related. Compared to moderate-income respondents, low-income respondents were more likely to identify lack of sidewalks as an obstacle to physical activity (17% vs. 11%). Moreover, twice as many low-income respondents (31%), relative to moderate-income respondents (15%), reported feeling concerned for their the safety of their neighborhood as an obstacle to physical activity (Moore, Glick, Romanowski, & Quinley, 1996).

The Role of Insufficient Sleep

Numerous studies have shown that individuals of lower socioeconomic status are more likely to report shorter sleep (Stamatakis, Kaplan, & Roberts, 2007; Whinnery, Jackson, Rattanaumpawan, & Grandner, 2014). Specifically, very short sleep (<5 hours) was reported among those earning less than $20,000, as well as $65,000-$75,000 (relative to > $75,000; Whinnery, Jackson, Rattanaumpawan, & Grandner, 2014). In the same study, it was also found that short sleep was more likely to be reported among those who did not complete college, and those with public health insurance only (relative to no health insurance), and those who identified as having very low food security.

One mechanism through which SES leads to poor sleep is through occupation. An individual's occupation influences specific sleep conditions through power, prestige, and access to resources (Kogevinas, Pearce, Susser, & Boffetta, 1997). Occupational factors such as working later shifts, holding multiple jobs, and long work hours have profound implications for sleep opportunity and timing, which has important effects on sleep duration (Bannai & Tamakoshi, 2014). In a prospective study, working more than 55 hours per week, relative to working 35-40 hours per week, was related to shortened sleep and difficulty falling asleep (Cheng et al., 2014).

A study among Taiwanese male workers completing a 12-hour night shift sheds some light on the physiological links among occupation schedule, insufficient sleep, and CAD. The workers showed delayed recovery of blood pressure and reduced heart rate variability, which may indicate arterial stiffness, suggesting that shortened sleep in this group with long work hours was associated with increased risk of CAD onset (Su et al., 2008; Kontsas et al., 2013). Further, individuals working long hours are more likely to be exposed to psychological stress, which can lead to dysregulation of the hypothalamic-pituitary-adrenal and sympatho-adreno-medullary axes (Cheng et al., 2014).

Exposure to environmental stressors may be another way that socioeconomic status influences sleep. For example, those living in impoverished neighborhoods are more likely to be exposed to air pollution, inopportune light exposure, noise, and irritants (e.g. environmental tobacco; Kingsbury, Buxton, Emmons, & Redline, 2013). Some of these factors, such as particulate air pollution, may additionally lead to increased risk of developing CAD through its effect on upregulating proinflammatory biomarkers (Campbell et al., 2005).

Health Literacy and CAD

Health literacy is a constellation of skills, which include "basic reading and numerical tasks required to function in the healthcare environment" (Hoc, 1999, p. 20). Individuals with poor health literacy levels face challenges that can range from "reading labels on a pill bottle…or dosing schedules to comprehending appointment slips, education brochures, or informed-consent documents" (Schillinger et al., 2002, pg. 475). These challenges extend beyond reading health information; individuals with poor health literacy may also have difficulty processing oral communication and conceptualizing risk (Doak & Doak, 1996). In the context of the current healthcare system, in which there is greater emphasis on self-management of chronic diseases, poor health literacy can be a threat to positive health outcomes.

A lack of health literacy has a demonstrated impact on patient health including "less preventive care, poorer understanding of their conditions and care, higher use of emergency and inpatient services and higher rates of re-hospitalization, lower adherence to medication schedules, and lower participation in medical decision-making" (U.S. Department of Health and Human Services, 2010, p. 18).

Notably, poor health literacy is more common among patients who have low educational attainment and among immigrants, older patients, and racial and ethnic minorities (American Medical Association, 1999). In a study from 1993 when the majority of healthcare material was written at a 10th grade reading level, more than half of American adults read at a lower grade level, and one in five read at or below the 5th grade level (Kirsch, 1993). The outcome of a more recent survey from 2003 showed "the average quantitative literacy scores of adults increased…though average prose and

document literacy did not differ significantly from 1992" (Kutner, Greenberg, & Baer, 2006, pg. 1).

Patients with variances in the nature of their English language and those with a primary language other than English are more likely to have poor understanding of their condition and its management, and often hold health beliefs that interfere with adherence to medical care plans (Williams, Baker, Honig, Lee, & Nowlan, 1998). Social and cultural variances among the English-speaking population can create misunderstandings in healthcare. In a study of black women aged 45-70 diagnosed with essential hypertension, 54 described their condition as "pressure trouble" or simply "pressure." Other beliefs that were endorsed included the notion that there were two diseases: "high blood," a disease in which the blood was too "hot," "rich," or "thick", and "high-pertension," a condition that involves blood "[shooting] up" toward their heads when they were emotionally excited and "fall back" when they calmed (CDC, 1990). In the Hmong community in California, where 90% of individuals have health insurance, 86% do not speak English. This language barrier creates challenges in disseminating health information as only 33% know that hypertension is preventable, and 80% think that hypertension is caused by pesticides in food (Wong, Mouanoutoua, Chen, Gray, & Tseng, 2005). Despite their access to the medical system, 53% of individuals missed their doctor appointments for hypertension "all or most of the time" (Wong, Mouanoutoua, Chen, Gray, & Tseng, 2005).

The Role of Insufficient Sleep

While there is limited research on health literacy related to sleep in adults,

Bonuck and her colleagues' work with children in a Head Start program showed a clear relationship between health literacy and insufficient sleep. They concluded that deficient health literacy among parents may be a factor in the "disconnect" between actual and perceived sleep hygiene, leading to insufficient sleep in their children (Bonuck, Schwartz, & Schechter, 2016). While further study on the relationship between health literacy and sleep is needed, inaccurate perception of sleep hygiene may contribute to insufficient sleep in adults.

CHAPTER FIVE

INTERRELATIONSHIPS AMONG INSUFFICIENT SLEEP AND OTHER RISK FACTORS FOR ONSET OF CAD

Based on the review of literature of the relationships among insufficient sleep and various risk factors for CAD onset, the following models are proposed. Dark blue arrows represent causal relationships between physiology and CAD onset identified in the literature. Dashed arrows represent proposed correlational relationships between each set of psychological, behavioral, and sociocultural factors, and physiological factors. While several interconnections may exist, we acknowledge that not all possible relationships are depicted in the following figures. The first figure illustrates the overall relationship scheme, while the subsequent models explicate the elements in behavioral and psychological factors and their specific relationships with each element of the physiological factor.

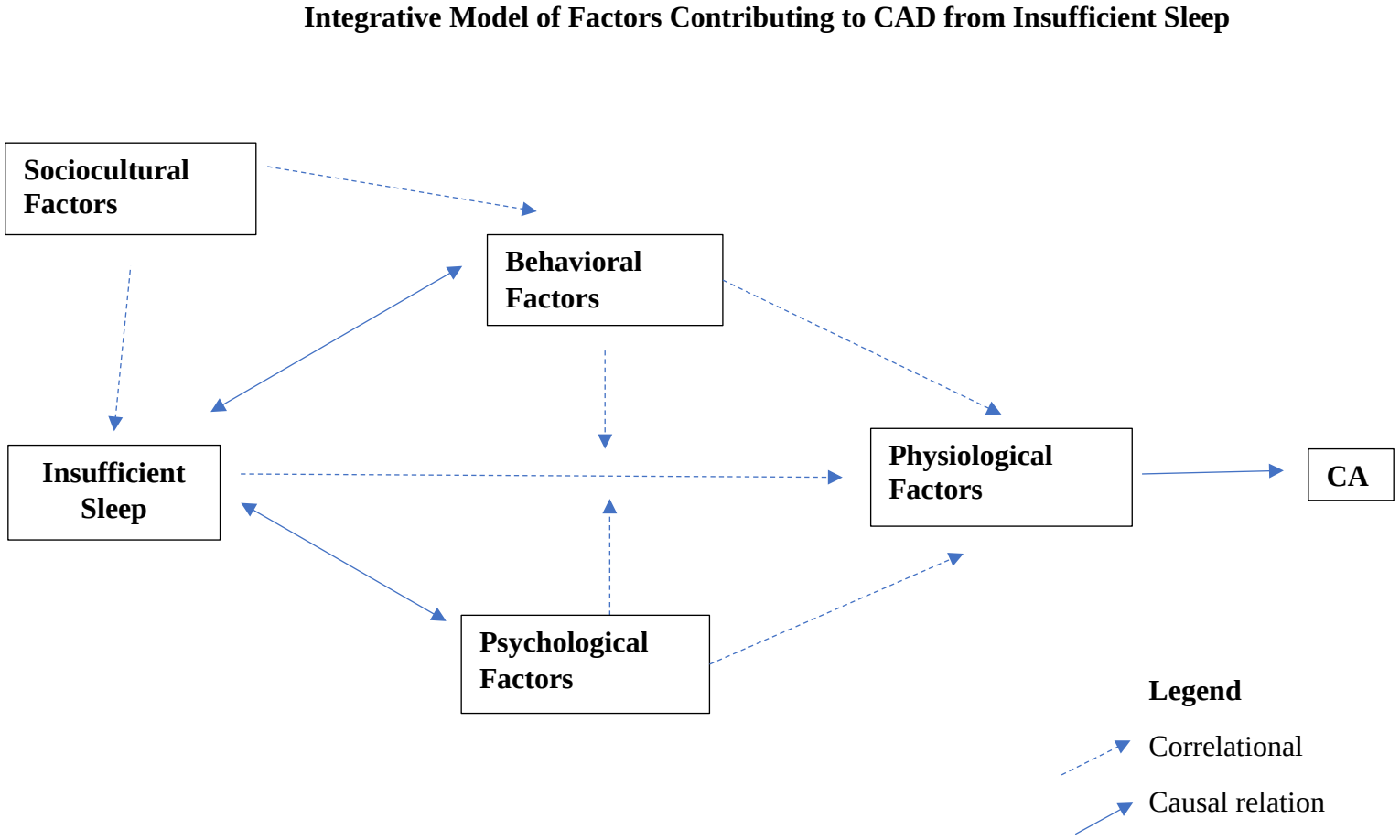

Figure 2. Conceptual models of interrelationships between insufficient sleep and onset of CAD.

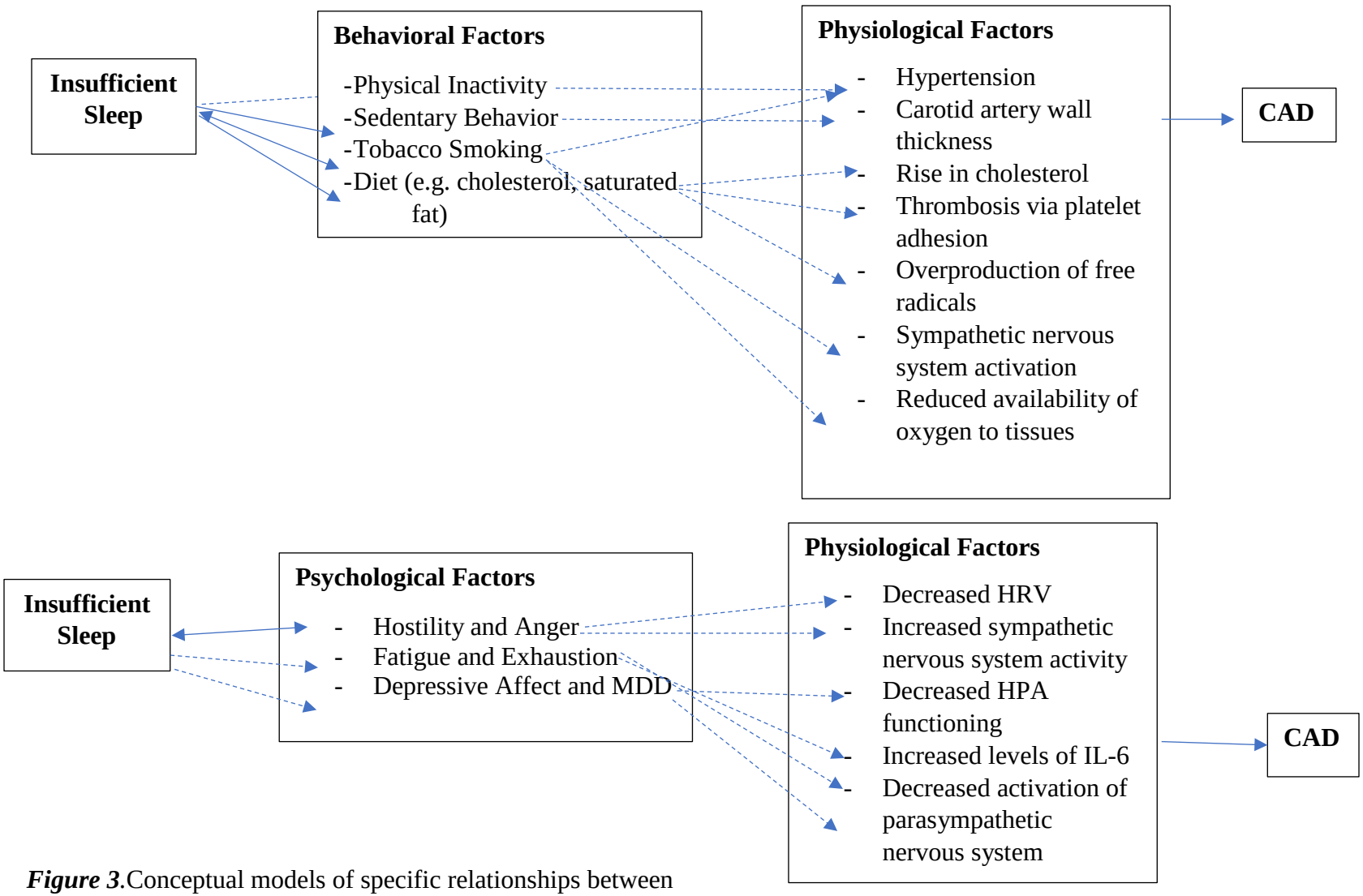

Figure 3.Conceptual models of specific relationships between insufficient sleep and elements of behavioral, psychological, and physiological factors.

CHAPTER SIX

RESEARCH AND CLINICAL IMPLICATIONS

Research Implications

Much research has examined sleep and its relationship to CAD, but many questions remain. Research is needed to investigate possible causal mechanisms by which insufficient sleep is related to CAD through the various other identified risk factors, whether unidirectional, bidirectional, moderating, or mediating. New research may benefit from several refinements in methodology. First, the definitions and operationalizations of the primary factors need clarification. Much of the available research cited in this review is limited to extreme sleep deprivation (~4 hours), without specifically assessing the more common experience of short sleep (6 hours per night). Further, future studies could consider the use of more objective measures of sleep, such as actigraphy and polysomnography. And, while this study focused on insufficient sleep, future research may consider the relationships between other types of sleep disorders and onset of CAD. Finally, clearer definitions of psychological factors are needed in studies investigating the role of transient emotional events and affective traits as they relate to sleep duration and CAD development.

Second, future research may focus on specific pathways of the Integrative Model of Factors Contributing to CAD from Insufficient Sleep proposed in this review. For example, the association of insufficient sleep with dietary cholesterol consumption and proinflammatory markers, and subsequent measures of CAD onset may be a fruitful investigation. Another stream of association for further study would be the relationship

between insufficient sleep and depressive affect, sympathetic nervous system activity, and CAD onset. The study of these pathways may clarify the specific mechanisms that link short sleep with CAD.

Clinical Implications

Adequate sleep duration is an integral part of health, particularly, as outlined in this review, cardiovascular health. While much research needs to be conducted to more fully define the relationship of insufficient sleep and CAD onset, and hopefully illuminate any specific causal relationships, we can begin with routine assessment of sleep duration using sleep diaries or polysomnography, in those patients for whom physiological risk factors for CAD (e.g., hypertension, heightened cholesterol, inflammation) are detected. Then, interventions may be offered to improve sleep for those who report short sleep duration. For example, individuals may be educated regarding sleep hygiene, including the importance of quiet, dark, relaxing space, the shutting off of screen-based devices when falling asleep, and avoidance of large meals, caffeine and alcohol before bedtime (CDC, 2016). To enhance the beneficial effects of education-based interventions a combination of problem-solving and cognitive-behavioral strategies may be required to improve sleep duration sustainably (Brown, Buboltz, Soper, 2006).

Focused assessment of the various psychological, behavioral, and sociocultural factors associated with poor sleep noted in this review may further inform the development of interventions to improve sleep and reduce CAD risk. For instance, instruments measuring sedentary behavior and/or health literacy may provide insight into

any potential trends towards risk. Sedentary behavior assessment measures such as the Rapid Assessment Disuse Index (Shuval et al., 2014) which measures time spent sitting, performing general movement, and stair climbing behaviors, and health literacy measures such as The Short Assessment of Health Literacy (AHRQ, 2016) which measures Spanish-speaking individuals' ability to process and understand health related information may be useful. As described in this review, however, several elements of each factor may interrelate in their associations with poor sleep, with important implications for clinical intervention. For example, due to the particular vulnerability of some groups, such as ethnic minority individuals, to insufficient sleep as well as to poor health literacy that may interfere with the efficacy of with traditional sleep hygiene didactic programs, such interventions should be culturally tailored to these groups. Interventions that are designed to increase access and reduce the complexity of health information (e.g. pictures to explain how the nervous system affects heart rate), engage individuals in activities that reinforce learned concepts (e.g. teach-back opportunities), use experiential teaching methods (e.g. sleep-promoting relaxation exercises led by a psychologist with participant involvement), and deliver health information in the individual's preferred language.

The context of these assessments and interventions is a crucial consideration. Among primary care providers, family medicine has often been touted as the champion of the biopsychosocial model of clinical care in which suffering, disease, and illness are affected by several layers of organization (Borrell-Carrio, Suchman, & Epstein, 2004). Evaluating proximal causes for physical illness, including CAD, has fostered important advances in healthcare but it has also been argued to be reductionistic and excessively

narrow among some groups. Critically examining the interrelationships of factors between insufficient sleep and the onset of CAD can illuminate a new paradigm in which modifiable factors (e.g. sleep, physical activity, diet, health literacy, depressed mood, and/or anger) can be viewed alongside objective biomedical data (e.g. hypertension, high cholesterol, inflammation). In such a way, personalized health plans can be developed, which can translate to more comprehensive care and more power to the patient in the clinical process. Furthermore, this model may be useful for behavioral health providers working in cardiology settings to implement tailored behavioral interventions. Nurses in these settings may be responsible for administering screening for insufficient sleep, psychological, behavioral, and sociocultural risk factors to identify vulnerable and patients at high-risk for CAD onset. These screenings may be administered during a lifestyle assessment visit or during an annual physical exam. By housing behavioral health within the cardiology clinic where patients can interact with each member of the multidisciplinary health services team alongside their physicians, potential stigma perceived about seeking behavioral health services may be reduced. Because this model proposes the use of additional behavioral health personnel, data demonstrating how integrating behavioral health services in medical settings can offset care costs may result in a higher prospect of administration funding the program (Blount et al., 2007).

CHAPTER SEVEN

CONCLUSION

The results of this review suggest interrelationships among insufficient sleep and potential mediating physiological, behavioral, psychological, and sociocultural factors associated with the onset of CAD. Exploring moderators and mediators is critical to identify the factors which may confer the greatest risk in CAD onset (moderators) and the mechanisms underlying specific risk factors (mediators). Understanding moderator variables could be useful in targeting interventions to appropriate factors, and exploring mediation could help to maximize therapeutic gains by enhancing intervention elements that impact key mechanisms. Improvements in treatment efficiency could result in fewer CAD diagnoses, reducing premature mortality and disability, and healthcare-related costs.

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APPENDIX A

GLOSSARY

Antigen A substance that elicits an immune response.

Antioxidants A substance that prevents cell damage via oxidation.

Arrhythmia A condition in which the heart muscle beats with an irregular pattern, too quickly, or too slowly.

Atherosclerosis The deposition of fat, cholesterol, calcium, and other substances that form plaque inside the artery.

Baroreflex A mechanism to regulate short-term blood pressure through controlling heart rate, contractility, and peripheral resistance.

Catecholamines Hormones made by the adrenal glands (e.g. norepinephrine and epinephrine).

Chemokines A substance secreted by a cell to signal the migration of other cells.

Cortisol A hormone that regulates several functions throughout the body including metabolism and immune response.

C-Reactive Protein A protein found in the bloodstream produced by the liver in response to inflammation.

Fibrinolysis The process by which fibrin, a protein formed during the clotting of blood, is broken down enzymatically.

Free Radicals Unstable atoms that damage cells, protein, and DNA.

Ghrelin A hormone that stimulates appetite, increases food intake, and promotes fat storage.

Hemodynamic The dynamic of blood flow.

Hypothalamic-Pituitary-Adrenal Axis A set of feedback interactions among the hypothalamus, pituitary gland, and adrenal glands, influencing the stress response and releasing cortisol.

Interleukin-6 A protein that serves as a pro-inflammatory cytokine, stimulating an immune reaction.

Ischemia A condition of reduced blood flow.

Isotemporal Substitution Paradigm A paradigm that assumes discretionary time in a day is finite and performing one activity involves substitution of another (Mekary, Willett, Hu, & Ding., 2009).

Macrophages A white blood cell that protects the body by ingesting cellular debris, foreign substances, microbes, and other harmful organisms.

Monocytes A type of white blood cell that can differentiate into macrophages.

Monounsaturated Fat A type of fat having one double carbon-carbon bond in its chemical structure.

mRNA Messenger ribonucleic acid conveys genetic information to specify the expression of protein to be produced.

Necrosis Premature cell death caused by injury, infection, infarction, toxin, or inflammation.

Polyunsaturated Fat A type of fat having more than one double carbon-carbon bond in its chemical structure.

Saturated Fat A type of fat having no double carbon-carbon bonds in its chemical structure.

Scavenger Receptor Receptors that are responsible for removing foreign substances and waste material.

Sympatho-Adreno-Medullary Axis A sympathetic nervous system response which causes the release of adrenaline from the medulla of the kidneys.

T Cells A type of white blood cell produced in the thymus gland, involved in the immune response.

Thrombus A blood clot in the circulatory system blocking blood flow.

Tumor Necrosis Factor Alpha (TNF-α) A cytokine produced by macrophages during acute inflammation.

Ventricular Fibrillation A condition in which the heart muscle beats with rapid, disorganized electrical activity causing the ventricles of the heart to quiver instead of pump blood.