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POST TRAUMATIC STRESS DISORDER AND SLEEP DISORDERS: EFFECTS ON CARDIOVASCULAR DISEASE RISK IN ACTIVE DUTY ENLISTED SOLDIERS

by

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Dissertation submitted to the Faculty of the
Medical and Clinical Psychology Graduate Program
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In partial fulfillment of the requirements for the degree of
Doctor of Philosophy 2021

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
SCHOOL OF MEDICINE GRADUATE PROGRAMS
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September 24, 2020

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SUBJECT: Appointment to the Final Doctoral Examination Committee for Elizabeth Belleau

In accordance with the School of Medicine Graduate Program Guidelines, you are formally appointed to the Final Examination Committee of Elizabeth Belleau, doctoral student in the Department of Medical and Clinical Psychology.

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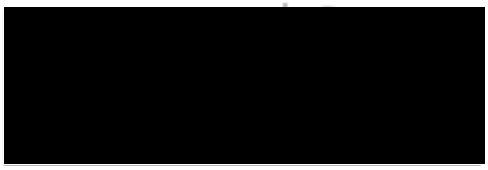
The Private Defense for Elizabeth Belleau will take place on Thursday, September 17, 2020 via Zoom meeting.

Dr. David S. Krantz is appointed Chair of the Examination Committee. Dr. Krantz will oversee the examination. Passage of the Private Defense will be by majority vote. If corrections to the Dissertation are needed, the Chair may oversee this process and sign-off after the corrections are made.

The Committee Chair should return the signed and dated Final Examination/Private Defense Form and the Dissertation Approval Form to the Graduate Education Office.

GEO thanks you in advance for your participation in the SOM Graduate Program process.



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FINAL EXAMINATION/PRIVATE DEFENSE FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN THE DEPARTMENT OF MEDICAL AND CLINICAL PSYCHOLOGY

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Name of Candidate: Elizabeth Belleau
Doctor of Philosophy Degree
September 17, 2020

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I truly could not have accomplished this without each of you!

DEDICATION

My work is dedicated to my grandfather, Richard, who showed me the impact of hard work and who was the greatest supporter of my military service. I will always strive to emulate your limitless drive to achieve your dreams and your ability to connect and care for others. I salute you.

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ABSTRACT

Post Traumatic Stress Disorder And Sleep Disorders: Effects on Cardiovascular Disease Risk in Active Duty soldiers

Elizabeth Belleau, Doctor of Philosophy, 2021

Thesis directed by: David Krantz, Professor, Department of Medical and Clinical Psychology

Background:

Although military service members are typically viewed as a healthy population, significant numbers have cardiovascular disease (CVD) risk factors and later develop CVD. Risk factors for CVD include a range of physiological, psychosocial, and behavioral variables, and there is evidence that posttraumatic stress disorder (PTSD) also may be a risk factor. Several CVD risk factors are commonly seen in individuals with a diagnosis of PTSD, and these risk factors may partially explain why individuals with PTSD have an increased risk of CVD. In particular, sleep disruption is one of the diagnostic criteria for PTSD. It is presently unknown whether individuals with a diagnosis of comorbid PTSD and a sleep disorder diagnosis are at increased risk of adverse cardiovascular outcomes compared to individuals with PTSD or a sleep disorder alone. The present study investigated CVD risk associated with PTSD, sleep disorders, and comorbid PTSD and sleep disorders.

Methods:

This study utilized data from the 2004-2009 Army STARRS Historical Administrative Database (HADS). Units of analyses were person-month records (average 28 per individual). In

order to capture all CVD cases, individuals with the following ICD-9 diagnoses were identified based on CVD severity: hypertension, coronary artery disease (CAD)/CVD, stroke, myocardial infarction, and congestive heart failure. To form a non-CVD group and assure that the overall study sample remained representative of the STARRS Army population, a representative sample of person-months without a cardiovascular diagnosis were identified based on deployment status, gender, rank, race, and time in service. Medical diagnoses and risk factor categories available in the database were identified based on ICD-9-CM codes. ICD-9 codes for CVD risk factors included in the study were divided into medical risk factors (MRF; obesity and type 2 diabetes mellitus) and behavioral risk factors (BRF; tobacco use disorder and alcohol use disorder). Psychological risk factors for CVD were ICD-9-CM codes for PTSD and depression. Diagnoses of sleep disorders, such as insomnia, hypersomnia, obstructive sleep apnea, also were identified based on ICD-9 codes.

Data Analysis:

Initial analyses included phi-correlations (φ) to examine the relationship between each binary independent and covariate variable in this study. Primary analyses for the study were logistic regression analyses with presence/absence of PTSD and/or presence/absence of sleep disorders as the independent variables and occurrence of CVD (All CVD diagnoses, Hypertension Only, or Other CVD diagnoses) as dependent variables. Covariates for this study were presence/absence of MRF, BRF, and depression. All analyses adjusted for demographic variables.

Results:

The final sample was 86.6% male, and included 50,804 active duty enlisted soldiers' person-months with CVD (48,363 hypertension; 2,441 other CVD diagnoses) and 242,844 person-months without CVD. There were 8,060 person-months with PTSD.

In analyses adjusting for covariates known to be associated with both PTSD and CVD (demographic variables, obesity and/or diabetes, nicotine use and/or alcohol abuse, and depression diagnosis), PTSD was positively associated with All CVD diagnoses, OR = 2.01 (95% CI: 1.92, 2.10), $p < 0.001$). Similarly, after adjusting for covariates, sleep disorders were positively associated with All CVD diagnoses, OR = 1.69 (95% CI: 1.62, 1.74), $p < 0.001$). When both PTSD and sleep disorders were entered into the logistic regression and after adjusting for all covariates from previous analyses, PTSD remained positively associated with All CVD diagnoses OR = 1.79 (95% CI: 1.71, 1.87; $p < 0.001$), and sleep disorders remained positively associated with All CVD diagnoses (OR = 1.58, 95% CI: 1.53,1.63; $p < 0.001$).

Lastly, a variable was created to determine if comorbid diagnoses of PTSD and a sleep disorder were more strongly associated with CVD than a diagnosis of PTSD or a sleep disorder alone. With all covariates included in these analyses, the group with comorbid PTSD and sleep disorders had the strongest association with the CVD dependent variables. For All CVD, comorbid PTSD and sleep disorders had an OR=2.554 (CI:2.388, 2.732; p<0.001). Individual comparisons among groups formed by the various PTSD (yes/no) and sleep disorder (yes/no) combinations indicated that, compared to individuals with no PTSD and no sleep disorders, the comorbid group with had a significantly stronger association with CVD compared to all other groups.

Conclusion:

PTSD in active Army enlisted service members was associated with a greater than 2-fold increase in incidence of both overall CVD overall and hypertension. Results were independent of depression and medical and behavioral risk factors associated with PTSD. In addition, sleep disorders were also independently associated with CVD, and co-morbid sleep disorders and PTSD were more strongly associated with CVD than either PTSD alone or sleep disorders alone. These

results suggest that attention to both the medical and the psychological consequences of PTSD and sleep disorders is warranted in active duty service members.

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CHAPTER 1: Introduction

OVERVIEW

Cardiovascular disease (CVD) is a broad term that encompasses multiple diseases of the heart and blood vessels, including coronary artery disease, hypertension, and other disorders of the heart and arteries (75). It is estimated that approximately 40% of all deaths and 10% of the total disease burden worldwide can be attributed to CVD (507). A risk factor is a characteristic of an individual or population that increases the likelihood of developing a disease. Risk factors for CVD span the range of biopsychosocial variables and include type 2 diabetes mellitus (DM2), elevated body mass index (kg/m^2; BMI), nicotine use, alcohol use, low physical activity levels, depression, anxiety, hostility, low levels of social support, as well as sleep disruptions and disorders (34; 120; 164; 253; 335). Many of these risk factors for CVD also are found in individuals with a diagnosis of post traumatic stress disorder (PTSD) (79). This overlap in risk factor presentation may in some part explain why individuals with diagnoses of PTSD have an increased risk of CVD (391). Due to the high prevalence of PTSD in the military population (44; 138; 178; 244; 261; 326), military service members may be a particularly important high-risk subgroup to target for the prevention of cardiovascular health issues. Thus, better understanding cardiovascular risk factors in military service members with PTSD is warranted.

Sleep disruptions and sleep disorder diagnoses also are known to be an independent risk factor for CVD and directly impact the previously identified biopsychosocial risk factors for CVD (126; 142; 143; 347; 367; 487) (346; 413).

Additionally, disruptions to quality of sleep are found in two of the diagnostic criteria for PTSD, specifically sleep difficulties and nightmares (9; 209). However, individuals may also have a comorbid sleep disruption or sleep disorders with a PTSD diagnosis as a result of sleep issue above and beyond what is attributed to PTSD. These comorbid sleep disorders and PTSD diagnoses may be particularly relevant for military populations, given that active duty military frequently report work-related sleep disruptions due to deployments, workload, and shift work (31; 140; 246; 317).

However, the contribution of sleep disruption to cardiovascular risk among individuals with PTSD is poorly understood, because of the inclusion of sleep disturbances as part of the PTSD diagnostic criteria. It is unknown if individuals with a comorbid diagnosis of PTSD with sleep disorders are at increased risk of adverse cardiovascular outcomes compared to individuals with a diagnosis of PTSD without sleep disorders.

Therefore, is the present project aims to examine the relationships between CVD and two of the psychosocial risk factors for CVD (PTSD, sleep disorders) while accounting for other biopsychosocial risk factors for CVD. Due to the nature of the dataset, the biopsychosocial risk factors included in the present project only include medical and mental health diagnoses, thus precluding consideration of known risk factors (diet, physical activity, etc.) that do not have an associated medical or mental health diagnosis. The proposed study seeks to determine if individuals with PTSD have higher rates of biopsychosocial CVD risk factors and CVD diagnoses compared to those without PTSD as well as the individual and additive effect of a comorbid diagnosis of a sleep disorder on CVD risk. By elucidating the relationships among PTSD, sleep disorders, and

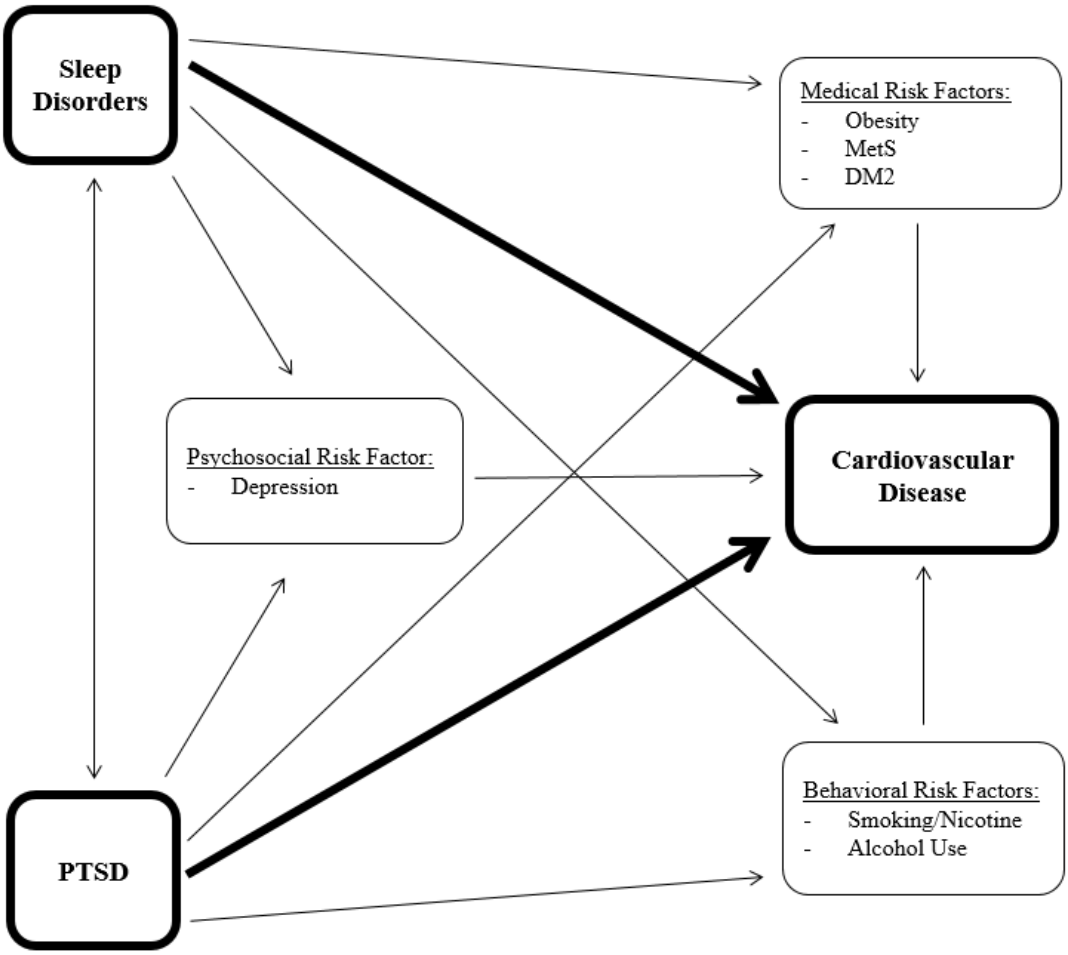
other biopsychosocial risk factors for CVD, the proposed study may identify specific biopsychosocial risk factors to target during treatment of PTSD and sleep disorders in active duty military members in order to reduce CVD risk and improve cardiovascular health.

The organization of this Introduction will begin with a review of CVD followed by a review of PTSD and sleep disorders, and their associations with CVD. Within each section on the biopsychosocial CVD risk factors, a brief overview of the CVD risk factor will be provided, along with information about how the factor may related to CVD, PTSD and sleep disorders.

CONCEPTUAL MODEL

Below is the conceptual model that guided the present research. The bold lines portray the association of PTSD and sleep disorders with CVD. The thin lines portray the association of PTSD and sleep disorders with CVD biopsychosocial risk factors. In this model, PTSD and sleep disorders directly influence the development of CVD. Additionally, in this model, PTSD and sleep disorders indirectly influence the development of CVD through the physiological (obesity, metabolic syndrome (MetS), DM2), behavioral (smoking and alcohol use), and psychological (depression) risk factors for CVD.

Figure 1. Conceptual Model: PTSD and Sleep Disorders Association with CVD and CVD Biopsychosocial Risk Factors



CARDIOVASCULAR DISEASE (CVD)

In 2018, CVD was the leading cause of death in the United States (34). Between 2011 and 2014, an estimated 92 million people (36.6% of the United States population) experienced a cardiovascular event and almost 840,000 people died as a result of a cardiovascular event (34). It is estimated that approximately 40-50% of healthy adult men and 25-35% of healthy adult women will develop CVD later in their lives (264). As a result of CVD's extensive impact on health in the United States, it is estimated that over

$329 billion is spent on CVD each year in medical costs, disability, and lost productivity (34).

CVD encompasses a variety of heart and vascular conditions involving narrowed or blocked blood vessels, such as coronary heart disease (CHD) or ischemic stroke. (75). In addition to CHD, hypertension is another important cardiovascular disorder included in CVD. Hypertension is defined as chronically elevated blood pressure. There are two types of hypertension, primary and secondary. Primary or essential hypertension has no identifiable cause, but risk factors include age (over 64 years old), race (higher rates found in African Americans), family history, obesity, physical inactivity, and heavy alcohol use (76). In contrast, secondary hypertension is caused by an underlying medical condition and hypertension is a secondary symptom of the primary disorder including obstructive sleep apnea, kidney disease, adrenal gland tumors, and thyroid problems (76). In addition, medications including birth control, pain relievers, cold and flu medications and decongestants, and amphetamines also can result in blood pressure elevations (75).

Another important cardiovascular disorder included in CVD is atherosclerosis which is the accumulation of plaque that results in narrowing of the arteries, resulting in increased resistance within the arteries. When this accumulation restricts or blocks blood flow to areas of the heart, this can result in angina (i.e., chest pain). Coronary heart disease (CHD) also referred to as coronary artery disease (CAD), refers to a cluster of disorders that involve coronary atherosclerosis, the accumulation of plaque in coronary arteries (34). CHD also puts individuals at increased risk of myocardial infarction, also known as a heart attack, the death of cardiac tissue that may be caused by prolonged or severe reductions in blood flow to areas of the heart. The disease process of

atherosclerosis and CAD typically occurs over several years. Initially, lipids accumulate in microscopic amounts in artery walls often caused by an unhealthy diet, lack of physical activity, overweight or obesity, and smoking. Extracellular accumulation of lipid deposits and plaque causes a thickening of the artery wall, extending outward. Eventually, the lipid deposits encroach into the artery opening in a progressive manner (430), causing narrowing of the artery, or complete blockage.

The American Heart Association (AHA) has identified several physiological factors that predict an individual's higher risk for developing these CVD processes: elevated levels of blood glucose levels, elevated blood cholesterol, and increased BMI, as well as smoking nicotine and low levels of physical activity (34; 335). In addition to the physiological risk factors identified by the AHA, research has identified additional behavioral and psychosocial risk factors for CVD. Behavioral factors include excessive alcohol intake (335) and disturbed sleep (164). Psychosocial risk factors for CVD include depression (253), anxiety (120), and PTSD, a trauma and stress-related disorder (9).

As mentioned previously, military service members are one particular group that may be at an increased risk for CVD. The Defense Health Agency found that during the years 2007-2016, 18% of all active duty service members were diagnosed with at least one of the five assessed medical risk factors for CVD (310). These five medical risk factors included obesity, hyperlipidemia, essential hypertension, abnormal blood glucose levels, and DM2 (310). Comparing military men and women, men had higher rates of hypertension, hyperlipidemia, and DM2, while women had higher rates of obesity and abnormal glucose levels. Additionally, the Defense Health Agency found that approximately 700 medical evacuations from deployed locations between 2007-2016,

were related to CVD (310). Specifically, the primary CVD diagnoses for these medical evacuations were coronary atherosclerosis, acute myocardial infarction, and cerebral artery occlusion. Of these cardiac medical evacuations, 33.9% of these individuals were diagnosed with hypertension prior to deployment, and 34.6% were diagnosed with hyperlipidemia prior to deployment (310).

POST TRAUMATIC STRESS DISORDER (PTSD)

PTSD is a trauma and stress disorder resulting from experiencing, witnessing, or knowing someone who has experienced a traumatic event that involved death, serious threat to life (9). Examples of these traumatic events include violence such as combat, motor vehicle accidents, terrorist events, natural disasters, physical assault, or sexual assault (9). The diagnostic criteria for PTSD encompass biopsychosocial symptoms such as nightmares, flashbacks, avoidant measures of memories or reminders of the event, hypervigilance, overactive physiological reactive responses, and the diminished ability to experience positive emotions (9). It is also important to note that PTSD has been recognized as a psychological disorder that causes significant daily distress and affects an individuals' emotional, social, and occupational health (9).

Looking across the United States population, fifty to sixty percent will experience a traumatic event during their lives; however, only 7-8% of the population will develop PTSD during their lifetime (209; 344). Nevertheless, rates of PTSD are higher in active duty military and veteran populations. A meta-analysis in 2010 found that across studies, the prevalence of PTSD (at any time during their service) in active duty military personnel ranges from 2-17% and the lifetime prevalence ranges from 6-31% (361). These estimates are significantly higher than in the general population (209; 212).

Elevated rates of PTSD in the military may be at least partially explained by combat exposure. It is estimated that approximately 90% of active duty military service members with combat experience, have experienced a traumatic event, such as direct gunfire, direct attacks from the enemy, and/or observing human remains (44). Out of the high number of military service members experiencing a traumatic event (to include combat and non-combat related traumatic experiences), many Vietnam veterans (244) and approximately 12-23% of military service members from Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) met criteria for a diagnosis of PTSD (138; 178; 261). Furthermore, PTSD in veterans is long-lasting and can persist for many years. For example, one study found that the approximately 10% of Vietnam veterans continue to suffer from PTSD even after 40 years have passed since their combat exposure (326). In summary, service members and military veterans with combat or trauma exposure are at an increased risk for developing PTSD (179) and the estimated annual cost of treating PTSD within the Veterans Administration has risen to over $250 million (176).

These individuals, both military and civilian populations, with PTSD also may be at increased risk for adverse physical health outcomes. PTSD has been associated with more medical conditions, lower health-related quality of life, and increased mortality (327; 397). Additionally, veterans with PTSD, have been found to have higher rates of cardiovascular, gastrointestinal, autoimmune, and musculoskeletal system diseases than veterans without PTSD (44). In a study assessing the cumulative illness burden derived from PTSD, individuals with current PTSD were more likely to seek treatment for a medical illness (426) and utilize medical care services more than individuals without

PTSD (60; 68; 80; 118; 119; 273; 396). Studies estimate that individuals with PTSD have up to a 91% higher utilization of medical care services to include emergency, inpatient and outpatient services (80). This is a rate higher than has been seen with any other mental health disorder (80).

Not only does a diagnosis of PTSD increase risk for poor health outcomes, but also has been found to elevate an individual's risk for comorbid mental health disorders. Epidemiological studies have documented elevated risk for a broad spectrum of disorders, including depression, anxiety disorder, panic disorder, conduction disorder, personality disorders, and multiple types of substance abuse (15; 393; 491). Of particular relevance for this dissertation are associations between PTSD and CVD and their overlap in biopsychosocial risk factors. These associations will be reviewed in the next sections.

PTSD and CVD

The association between PTSD and CVD has been established in a variety of populations, including community samples of women, medical professionals, police, and terrorist survivors (46; 96; 198; 241; 242; 437; 506). The literature on associations between PTSD and CVD risk is extensive and has been consolidated in several review articles (92; 103; 115; 116). Of note, although multiple subgroups of the population have been studied, the largest body of research has focused on active duty military and veteran populations.

Prospective studies with military members and veterans have found an increased risk of CVD and CVD mortality in those suffering with PTSD (43; 45; 47; 203; 241; 242; 414). Specifically, a recent review of multiple prospective cohort studies, estimated that PTSD was associated with a 1.46 to 3.28 times increase in CVD events and/or CVD-

related deaths (45; 198; 242; 390; 457). One of the most extensive longitudinal studies that assessed the association between CVD and PTSD was the Vietnam Era Twin Study. This study followed approximately 4,000 twin pairs, in which both twins served in the military but only one twin was deployed to Vietnam. Twins were followed for 30 years to examine associations between a diagnosis of PTSD and the development of co-occurring physical illnesses including CVD (43; 45; 46). After adjusting for relevant demographics, military factors, psychological variables, substance use, comorbid mental health disorders, and other diseases, PTSD remained significantly associated with CVD outcomes (43; 45). In these analyses, individuals with PTSD had over two times the increased risk of cardiovascular-related deaths compared to their twins without PTSD (46).

In another prospective study that followed veterans for 7-years, veterans who were diagnosed with PTSD had a 39% increased risk for CVD over the course of the study compared to veterans without a diagnosis of PTSD (390). Kubzansky and colleagues (242) found that the more PTSD symptoms an individual endorsed, the higher their risk was of developing CHD. This positive association remained after controlling for traditional CVD risk factors (242). A recent meta-analysis of six studies, encompassing over 400,000 military and non-military participants with follow-ups ranging from 1 to 30 years after PTSD diagnosis, found that individuals with a new diagnosis of PTSD were at 1.5 to 3 times higher risk of CVD or mortality due to a cardiac event compared to individuals who did not have a diagnosis of PTSD (115).

Many studies have attempted to identify the underlying biopsychosocial mechanisms accounting for the relationship between PTSD and the development of CVD

(79). PTSD has been significantly associated with biological processes that increase CVD risk such as endothelial dysfunction (242), hypothalamic-pituitary-adrenal (HPA) axis dysfunction, autonomic nervous system reactivity, and inflammatory responses (79). However, determination of mechanisms is complicated because most, but not all, studies have found PTSD to remain independently associated with CVD events after controlling for traditional and psychosocial CVD risk factors such as obesity, diabetes, increased cholesterol, and smoking (79). In contrast to these findings, a recent study by Scherrer et al (391) reported that there was not an independent association of PTSD after controlling for known biopsychosocial CVD risk factors (391). This recent finding raises the possibility that at least some of the CVD risk associated with PTSD is due to other known risk factors.

Several CVD risk factors are known to overlap with PTSD symptom criteria. For example, sleep disruptions, stress reactivity, anger, and depressive symptoms are diagnostic criteria for PTSD (9). PTSD is also associated with biological mechanisms and risk markers for the development of CVD, such as increased sympathetic activation as well as neuroendocrine, vascular, metabolic, and immune changes (79).

Physiological Mechanisms of PTSD Associated with CVD Risk

PTSD involves trauma-induced alterations in activity of the sympathetic nervous system (SNS) and the hypothalamic pituitary adrenal (HPA) axis activity (102; 117). These disruptions of the SNS and HPA axis are possible physiologic mechanism that may account for the adverse medical conditions associated with PTSD. This SNS activation is consistent with the PTSD symptomology of hyperarousal and is positively correlated with PTSD symptom severity (502). PTSD is directly linked to elevated levels of

norepinephrine and epinephrine over a 24-hour period (232; 502). Consistently high levels of catecholamines, such as norepinephrine and epinephrine, impact the cardiovascular system by causing increased heart rate and blood pressure (295). Because of the effects of catecholamines on the cardiovascular system, individuals with PTSD have higher heart rate and blood pressure at baseline and in response to stress (61; 326).

PTSD also is associated with dysregulation in functions related to the hypothalamic-pituitary-adrenal (HPA) axis. HPA dysregulation resulting from PTSD is typically an overproduction and sustained production of cortisol, ultimately leading to diminished responsiveness to cortisol (254). HPA dysregulation can negatively affect immune system functioning, glucose metabolism, and psychological health (358).

The physiological dysregulation associated with PTSD can have a direct impact on the cardiovascular system and result in elevated resting heart rate, increased blood pressure, decreased vagal tone, and metabolic changes that increase an individual's risk for CVD (208; 276; 501). Additionally, increased cardiovascular responses to psychological stress are associated with dysfunction of the endothelium, the inner layer of arteries, which is thought to be an initial step in the development of coronary heart disease. (103; 208; 350; 401).

SLEEP DISRUPTION & SLEEP DISORDERS

Sleep is a biological requirement and is responsible for many of the body's restorative functions to include memory consolidation, emotion regulation, muscle repair, and hormone regulation (104). Multiple terms are used throughout the literature to describe problematic sleep. The National Heart, Lung, and Blood Institute defined "sleep deficiency" as insufficient sleep, irregular sleep-wake patterns, inefficient sleep, or a

diagnosed sleep disorder (305). Research reviews tend to use the term "sleep disturbances" to describe insufficient or excessive sleep duration, poor sleep quality, or a diagnosed sleep disorder including medically induced sleep disorders such as OSA (189; 231; 359).

Sleep disorders include medically based issues that cause sleep disturbances and deficiencies, and behavioral sleep disorders that are characterized by problems in specific or general sleep domains. For example, obstructive sleep apnea (OSA) is considered a medically-based sleep disorder in which an individual has episodes of upper airway closures during sleep. This can result in intermittent hypoxia, fragmented or disrupted sleep, and decreased total sleep time. Insomnia, as defined by the American Psychiatric Association's *Diagnostic and Statistical Manual for Mental Health Disorders 5th Edition* (DSM-5), is characterized by one or more of four sleep domains: difficulty initiating sleep, difficulty maintaining sleep, waking up earlier than desired, or nonrestorative sleep. For a diagnosis of sleep disorders within the DSM, sleep issues must be associated with impairments in daytime functioning (9).

Health Effects of Sleep Disturbances and Sleep Disorders

The National Sleep Foundation in the United States identified normal sleep duration as 7-9 hours for health adults (175). In their 2015 joint consensus statement, the Sleep Research Society and American Academy of Sleep Medicine recommended that adults regularly obtain 7 hours or more of sleep to promote optimal health and functioning (331). Yet only 65.2% of adult respondents in the 2014 Behavioral Risk Factors Surveillance System survey reported achieving 7 or more hours of sleep per night, resulting in almost 35% of the population not getting adequate sleep duration

(263). At the other end of the sleep duration spectrum, there is conflicting evidence linking long sleep duration to adverse health outcomes, and thus the health risks associated with sleeping 9 or more hours is not a settled issue (331).

The global functional impairments associated with a sleep disorder include impaired performance in cognitive, emotional, social, and physical domains (216; 347). Poor sleep quality has been associated with a number of physical problems (140; 268; 346; 413), such as obesity, diabetes, and cardiovascular disease (142; 143; 347; 367; 487), and psychological problems (126), such as increased negative affect, anxiety, depression and anger (346; 413).

Sleep problems, including sleep disturbances, deficiencies, and disorders also have been linked to dysregulation in many areas of physiological functioning to include metabolic (2) and endocrine health (395), as well as immune pathways (287). Insufficient sleep has been associated with elevated body mass index (167; 226), weight gain (332; 333), obesity (73; 144; 442; 467), metabolic syndrome (204), and DM2 (16; 156; 168; 499). In addition, the United States National Health and Nutrition Examination Survey (NHANES) identified an association between irregular sleep duration and stroke and CHD (353). Physical health impacts have revealed associations between these health conditions and dysregulated or insufficient sleep and with more severe sleep issues that warrant a sleep disorder diagnosis. For example, a population of firefighters who screened positive for a sleep disorder (37.2%; 28.4% OSA, 6% insomnia) were around two times more likely to have diabetes or CVD (20) compared to those who did not have a sleep disorder. OSA also has been associated with a large number of direct and indirect physical and psychological complications, including hypertension, heart disease and heart

failure, stroke, insulin resistance, impairments in neurocognitive functioning, workplace and driving accidents, and elevated psychological symptoms (31; 230; 233; 348; 503).

As noted previously, sleep disturbances, deficiencies, and disorders also are associated with mental health issues. Part of this association could be due to the overlap among diagnostic criteria of mental disorders and sleep disorders and the impact of sleep disorders on an individual's coping capabilities. Most relevant to the present study, mental health diagnoses, including PTSD and depression include sleep problems within their diagnostic criteria (9). It has been found that approximately 44-90% of individuals with a diagnosis of PTSD also meet criteria for insomnia (166; 223). Similarly, 50-90% of individuals diagnosed with depression also reported sleep problems (451). Disrupted sleep is associated with a number of deleterious effects such as low quality of life (509), poor emotional coping and decreased ability to handle life stressors (425), and risky drinking (441). Moreover, there is evidence that good and poor sleepers report experiencing similar numbers and types of stressful life events, but poor sleepers appraised the events as more stressful and perceived themselves as lacking control and unable to cope (294).

Sleep Disorders in Military Populations

Sleep disorders, such as insomnia, and sleep disorder symptoms are found in high rates within military populations, specifically ranging from 27–54% of military personnel and veterans (177; 302). These rates are two to three times higher than the general United States adult population (133; 380). Poor sleep quality is especially prominent among veterans, with 6–13% experiencing difficulty with sleep onset and 18–63% experiencing difficulty with sleep maintenance (307; 319). In one study, more than three-quarters of

veterans reported difficulty falling or staying asleep and, and more than half reported being at least moderately distressed about sleep that was restless or disturbed (455). Additionally, a 2009 report of the average sleep duration in the USA reported that 41.8% of military personnel obtained less than 5 hours of sleep per night compared with only 7.8% in the general population (238). Across all military branches from 2001 to 2009, rates of insomnia increased by 19 times and rates of OSA increased by almost 6 times (78; 148).

There are multiple contributing factors specific to the military lifestyle and environment that impact sleep for military personnel. Sleep disturbances in military personnel have been attributed to deployments, travel across multiple time zones, mission requirements, and emotional and/or physical stressors of the job. These lifestyle and environmental factors can result in circadian misalignment (31), chronic sleep deprivation (246), sleep fragmentation and insomnia (317), and maladaptive sleep practices such as excess caffeine intake and the use of sedative medication (140). Among 886 veterans screened in primary care, 88% met risk criteria for at least one sleep disorder, 49% met criteria for more than one sleep disorder, and 24% reported use of sleeping pills or alcohol at bedtime to help with sleep (301).

With regard to military deployments, sleep problems are particularly common among United States military veterans who have been deployed, with 600,000 to 1 million military personnel who served in Afghanistan (OEF) and Iraq (OIF) reporting difficulties with sleep upon returning home (10; 405). Sleep disturbance is also the second most common post-deployment concern for military personnel (37) and one of the most common reasons for a mental health referral in active-duty military member (93)

and veterans (196). Sleep complaints are also prevalent among veterans of earlier wars, including the Vietnam and Korea conflicts. Many of these military veterans reported that their sleep difficulties initially began during or immediately following their military service and persisted for decades following their separation from the military (185; 384). A study assessing sleep disturbances in a deployed environment (339) found that approximately 75% of study participants rated their quality of sleep significantly worse than before deployment. In this study, sleep efficiency and sleep onset latency were indicative of an insomnia diagnosis. During deployment, the military environment also seems to add additional factors that impact the quality and quantity of sleep that are not found during non-deployment related assignments. Deployed military personnel reported the following environmental factors impacting their sleep: poor sleep environment (33%), night-time duties (30%), personal stressors (11%), and combat-related disturbed sleep (10%; (286).

Insomnia symptoms are common among veterans with mental health disorders. For example, a large study of OEF/OIF service members, researchers found that military personnel with pre-deployment insomnia symptoms had greater odds of developing depression, anxiety, and PTSD at follow-up (146). Another longitudinal study found that insomnia measured at four-months post-deployment was a significant predictor of depression and PTSD at 12-months post-deployment (493). In addition to subjective sleep complaints, more than half of recently deployed soldiers with PTSD were diagnosed with both insomnia and OSA (486).

Sleep Disruptions/Disorders and CVD

The connection between sleep disruption and CVD was originally observed in

1982, when the Alameda County study identified that men and women who reported obtaining 7-8 hours of sleep consistently had the lowest mortality rates from ischemic heart disease (488; 489). Since this original study, epidemiological studies have found a U-shaped relationship between sleep duration and CVD, with sleep durations of less than 6 hours and greater than 9 hours at a higher risk of CVD (164). The most recent data from the 2017 United States Center for Disease Control and Prevention reported that 39% of patients with CVD slept less than 6.5 hours and 35% slept longer than 7.5 hours (243). Additionally, between 1982 and 2017, an association between sleep disruption (including sleep duration, insomnia symptoms, insomnia diagnoses, and OSA) and CVD was identified in numerous cross-sectional studies and meta-analyses. Of these studies, the National Health Interview Survey with approximately 30,000 participants, found that both short and long sleepers had increased odds of cardiovascular events (386). The participants from the same study who reported less than 5 hours of sleep per night were over twice as likely to report a cardiovascular event compared to participants reporting 7 hours of sleep. Those reporting greater than 9 hours of sleep were over 50% more likely than those reporting 7 hours of sleep to report cardiovascular events. These associations remained after adjustments for known sociodemographic, behavioral, and psychiatric risk factors (386).

CVD risk also has been identified with specific sleep disruptions and disorders. Disturbed sleep (74) as well as both short and long sleep duration were found to predict increased rates of hypertension (2.4% and 1.1%, respectively) compared to those getting 6-9 hours of sleep. (67; 157; 265; 283). Similarly, a 2013 meta-analysis of 7 studies with over 400,000 participants reported significant associations between insomnia symptoms

and hypertension in studies with follow-ups periods of greater than 1 year (284). In addition to earlier CVD risk markers such as hypertension, a 2014 meta-analysis of 17 cohort studies (including over 300,000 participants) of individuals free of CVD at baseline reported significant associations between insomnia and CVD outcomes including myocardial infarction, CHD, stroke, and CVD mortality (256). Overall, analyses found that presence of insomnia symptoms or disorder were associated with a 28-55% increase in risk for incident disease and a 33% increase in risk of CVD mortality compared with individuals without insomnia.

Mechanisms of CVD Risk Associated with Sleep Disorders

Sleep disruptions and disorders operate through multiple biological mechanisms that impact an individual's cardiovascular health. These mechanisms include inflammation, autonomic nervous system activity, and metabolic changes (164). A recent systematic review of 72 studies with more than 50,000 participants demonstrated that short sleep duration was significantly associated with increases in inflammatory markers, such as interleukin-6 (IL-6), and long sleep duration was correlated with increased levels of both IL-6 and C-reactive protein (CRP) (188). Another study found that those with chronic insomnia had increased levels of IL-6 compared to "good sleepers" (63).

Sleep deprivation also has been shown to decrease parasympathetic activity and increase sympathetic activity (511), which is known to increase the risk of CVD (172). Chronic metabolic dysfunction in the form of insulin resistance and impaired glucose tolerance is a risk factor for CVD morbidity and mortality (182), and is increased in individuals experiencing sleep disruptions and disorders. One study further demonstrated that restricting sleep to 4 hours per night for 6 consecutive nights in young, healthy

adults, significantly reduced blood glucose clearance and insulin response to glucose to abnormal levels typically observed in clinical populations (424). More recent studies have found that the risk for diabetes is almost 3 times higher in individuals with insomnia, even after adjusting for standard diabetes risk factors, depression, and sleep apnea (464). Additionally, a meta-analysis of 6 prospective studies including over 15,000 adults found that DM2 incidence was elevated among individuals' self-reported symptoms of insomnia (72).

Sleep Disruptions/Disorders and PTSD

Sleep disturbance is often considered to be an important element of PTSD, (148; 377) and formal DSM-5 criteria for PTSD includes sleep-related complaints of recurrent distressing dreams and sleep disturbances. Sleep disturbance has been recognized as both an early predictor of development of PTSD, and a marker of disease severity (31; 230; 377). Sleep disturbances are highly prevalent in PTSD and are among the most distressing and chronic symptoms (279).

It is estimated that 70-93% of individuals with PTSD experience sleep disturbances, some specifically related to their trauma experience (149; 288; 319; 416). Of the sleep disturbances experienced in individuals with a diagnosis of PTSD, 44% reported difficulty with sleep initiation, 52% reported nightmares, and 91% reported difficulty with sleep maintenance (307). These rates of sleep disturbances are 2-5 times higher than the rates found in healthy, populations without a mental health diagnosis (319). Furthermore, poor sleep quality has been identified as one of the most frequently reported symptoms of PTSD (288; 374; 377), with 60-90% of individual's meeting diagnostic criteria for insomnia (307; 319). Sleep problems are also highly correlated

with PTSD symptom severity (150) and associated with other negative health consequences related to PTSD, including physical health problems (78). In the National Comorbidity Survey Replication (NCS-R), individuals diagnosed with PTSD were 3.8 to 5 times more likely to have one of four sleep disturbance criteria associated with diagnosis of insomnia (380). Specifically, the NCS-R identified difficulty with sleep maintenance and nonrestorative sleep as the top sleep disturbances in individuals diagnosed with PTSD.

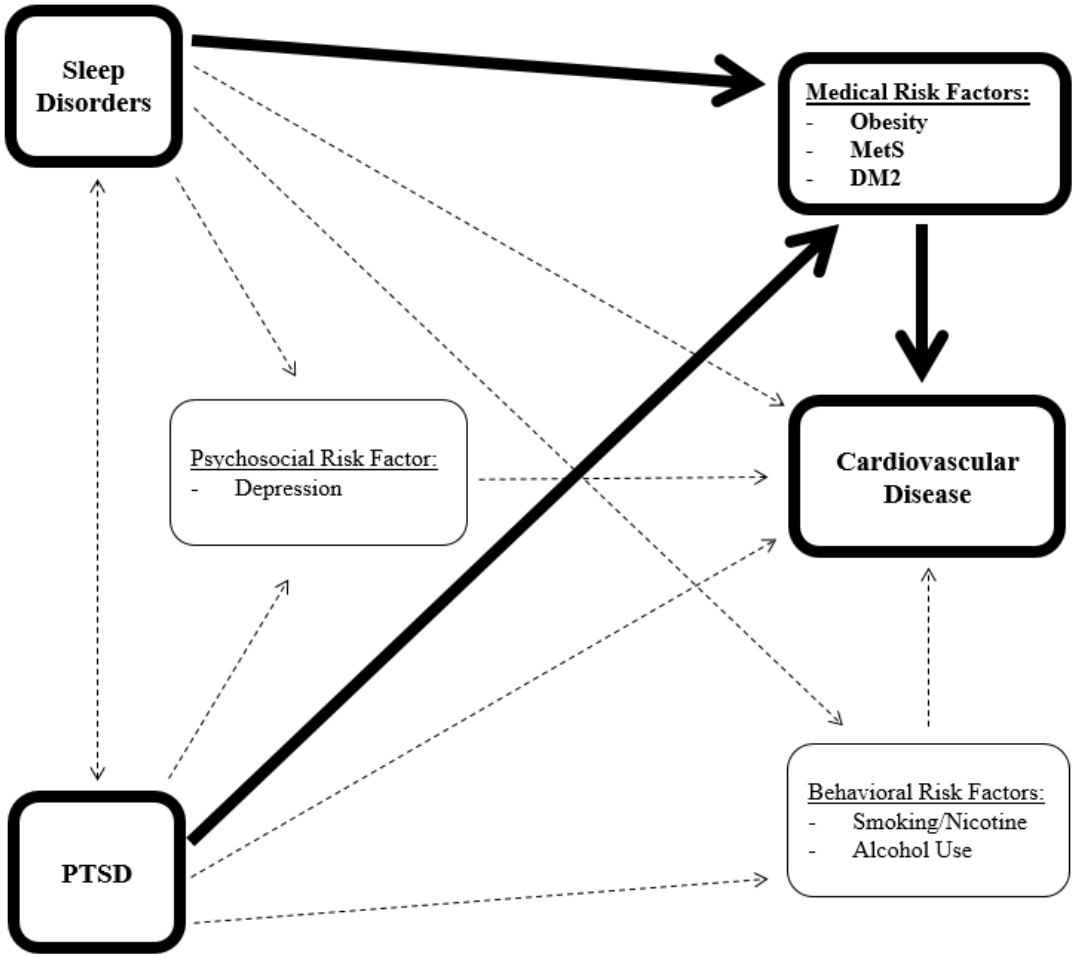
Among military populations, one of the most commonly reported symptoms of PTSD in OIF/OEF veterans is sleep disruption (279). Sleep disturbances occur in 90-100% of veterans with PTSD and this association has been established across multiple eras, from Vietnam to present-day military members (255; 307; 405). Among Vietnam veterans with a diagnosis of PTSD, sleep difficulties were the most prominent complaint (252; 378), specifically longer sleep latencies, longer time awake after sleep onset, and shorter total sleep time (319). In another veteran study, those veterans with PTSD, 41-44% reported experiencing difficulty falling asleep (sleep onset) and 47-91% reported experiencing difficulty staying asleep (sleep maintenance) (307; 319). Additionally, Miller et al. (288) found that 81% of veterans with PTSD reported trauma-related insomnia. Notably, trauma-related nightmares can cause or exacerbate insomnia symptoms (106; 147; 234).

PTSD's diagnostic criteria includes sleep disturbances (9) and a diagnosis of PTSD can lead to sleep disorders above and beyond the PTSD diagnostic criteria. However, sleep disorders have also been shown to increase an individual's risk of developing PTSD. In a longitudinal cohort study of combat veterans, pre-deployment

nightmares significantly predicted post-deployment PTSD symptomology, but insomnia was not predictive of post-deployment PTSD symptomology (460). However, an evaluation of the Millennium Cohort Study (18,175 participants) found that insomnia diagnoses, as well as those who slept less than 6 hours or greater than 8 hours pre-deployment were at greater odds of developing PTSD following deployment (146). Sleep disorders post-deployment have also been found to be an antecedent of PTSD post-deployment; however, PTSD post-deployment was not a significant predictor of insomnia (493).

OSA also has been identified as a sleep disorder that is associated with PTSD. In a recent study of deployed military members, 59.5% with comorbid OSA and insomnia also had a diagnosis of PTSD (302). Prevalence rates for comorbid OSA and PTSD range from 52-95% (194; 233; 503), and approximately 13% of veterans have comorbid OSA and PTSD. Overall, the odds of an individual having PTSD is 2.7 times higher in individuals with OSA compared to individuals without OSA (410).

Figure 2. Conceptual Model: PTSD and Sleep Disorders Association with CVD and CVD Physiological and Medical Risk Factors



Physiological Risk Factors for CVD

PTSD and sleep disorders are associated with neuronal, hormonal, and immunologic physiological responses that damage the body when activated over sustained periods of time (277; 282). In this regard, evidence indicates that individuals with PTSD and/or sleep disorders may have increased physiological risk factors for CVD, and they are also at risk for various non-cardiovascular disorders as well.

In this dissertation, emphasis was placed on the following physiological CVD risk factors and their association with PTSD and sleep disorders: obesity, DM2, and metabolic syndrome. Therefore, the focus will be on these risk factors. For each of these risk factors, this section will first present a discussion of its relationship to CVD, followed by a discussion of the risk factors relationships to PTSD and sleep disorders separately. For this dissertation, a risk factor was defined a characteristic of an individual or population that increases the likelihood of developing a disease.

Research has demonstrated multiple negative health consequences of PTSD and sleep disorders, including digestive, metabolic, nervous, endocrine, respiratory and circulatory diseases (140; 213; 216; 268; 287; 329; 347; 353; 395; 413; 477). The relationship between PTSD and negative health outcomes have primarily been researched in military veteran populations. Specifically, United States veterans from World War II, Korea, and Vietnam diagnosed with PTSD experience more medical conditions than veterans without PTSD (28; 399; 492). These medical conditions include cardiovascular, gastrointestinal, musculoskeletal (399), metabolic, digestive, endocrine, nervous, respiratory (43), and for women specifically, gynecological (492).

Sleep disorders are prominent in military populations (177; 302); however, the negative health outcomes of sleep disorders have been researched throughout many different populations in addition to military populations. Similarly to PTSD, individuals with diagnoses of sleep disorders experience more metabolic dysfunction (182; 464), cardiovascular disorders (74; 386; 488), and increases in inflammatory markers (63; 188), and SNS activity (511), than individuals without a sleep disorder diagnosis.

Overweight and Obesity

Body mass index (BMI) is calculated by dividing an individual's weight in kilograms by the square of their height in meters (1). A BMI between 25 and 30 is considered overweight, and 30 and above represents obesity. Obesity typically develops when energy intake is greater than energy expenditure. Diet, physical activity, and sleep each play an important role in the risk of weight gain and obesity. In 2016, over 39% of adults were overweight, and 13% were obese, worldwide (325); however, the prevalence of obesity for adults over the age of 20 in the United States was 37.3% (131). Overall, these numbers are continuing to rise. The number of people overweight worldwide has doubled since 1980 and is projected to increase to 1.1 billion by 2030 (206).

Obesity has been identified as a disease related to civilization and is recognized by the World Obesity Federation as the most serious chronic disease because of its direct link to the development of CVD, DM2, MetS (50). Of note, discharged veterans have been found to have higher rates of overweight and obesity compared to age-matched non-veterans (421). High rates of overweight and obesity are problematic because increased BMI and obesity have been associated with increased rates of adverse cardiometabolic outcomes (66; 114). Obesity predicts a broad range of health risks, including diabetes, hypertension, CVD, early mortality, and lower quality of life (314; 315). The next sections will examine the relationship between obesity and CVD, PTSD, and sleep disorders.

Obesity as a CVD Risk Factor

Obesity has been identified as an independent risk factor for CVD (64; 184) for both women (272) and men (365) throughout the world (447). Obesity has been found to increase an individual's risk for CVD by two to three times (272; 365). Obesity is also strongly associated with CVD risk factors to include increased abdominal obesity (64), dyslipidemia, hypertension (105; 110) DM2, and high total cholesterol (64), each of which are risk factors for developing CVD (110; 247; 360). However, after adjusting for blood pressure and lipid levels, obesity has been found to be an independent risk factor for CVD (110; 184; 409).

Obesity Related to PTSD

Obesity also has been associated with trauma exposure and PTSD. Current and lifetime PTSD have been linked with increased odds of overweight and obesity (420). Further support for the relationship between PTSD and excess weight has been found in women (103), veterans (152; 465), medical patients (327), and a nationally representative sample of adults in the United States (330). These samples showed a 10% increase in overweight and obesity in individuals with PTSD compared to individuals with no history of PTSD. Additionally, PTSD has a stronger association with obesity than other mood and anxiety disorders (22; 402).

The mechanisms linking trauma exposure with obesity are not well understood. One possible mechanism that has been proposed is stress-motivated high-caloric eating (450) as a coping mechanism to reduce stress reactivity and anxiety (290). It also is theorized that disordered eating may be used as emotion regulation for individuals with

PTSD (90; 439; 440). Individuals who have experienced trauma report higher rates of disordered eating, primarily bingeing and purging (289). Specifically, individuals may use disordered eating to cope with low mood and reminders of their trauma (55; 169).

Obesity Related to Sleep Disorders

In the 2005 National Health Interview Survey with over 50,000 participants, both short and long sleep duration were significantly associated with obesity, relative to sleeping 7-8 hours of sleep (67). In a meta-analysis incorporating 14 studies with approximately 198,000 participants, short sleep duration of less than 6 hours of sleep was associated with 1.45 times the risk of future obesity (494). This association was found to be statistically significant in both men and women.

One sleep disorder with a direct link to obesity is OSA. Obesity is one of the leading risk-factors for OSA (505), and research has found that for every one standard deviation increase in an individual's BMI there is a 4-fold increase in the prevalence of OSA (504). Specifically, 40-90% of individuals who are classified with severe obesity (BMI greater than 40) also had a diagnosis of OSA (136). A cross-sectional retrospective database review of outpatient medical records conducted across all 140 VHA facilities including approximately 2.5 million veterans' records, found that among obese veterans, OSA was also associated with increased risk of PTSD (17), however, this relationship was not observed in non-obese veterans.

These studies demonstrate bi-directionality between sleep disorders and obesity. Despite the prevalence of OSA and the prevalence of OSA with both obesity and PTSD, this study hypothesizes that sleep disorders directly impact CVD risk factors to include

obesity. This is counter to the OSA and obesity research presented, but does not discount this known relationship.

Metabolic Syndrome (MetS)

MetS is defined as a cluster of physiologic symptoms that when occurring together increase an individual's risk of DM2 and CVD (77). To meet criteria for MetS, two or more of metabolic abnormalities including dyslipidemia, obesity, elevated blood glucose levels and hypertension will be present (323) (3). Overall, in the United States, MetS has decreased over the last 20 years however, it still remains prevalent in over 20% of the adult population (5; 32).

Compared to the United States general population, the prevalence of MetS in active duty Air Force members was significantly lower. Specifically, in 2010, 24% of United States adult men had a diagnosis of MetS compared to 6.5% of active duty Air Force men, and 19.7% of United States adult women had a diagnosis of MetS compared to 4.2% of active duty Air Force women (171). In an analysis of active duty service members between 2002 and 2017, the incidence and prevalence of MetS in military service members over the last 15 years has declined similarly to the United States population. In 2012, 38.9 out of every 100,000 service members were diagnosed with MetS, and in 2017, 31.6 out of 100,000 service members had MetS (171). The next sections will examine the relationship between MetS and CVD, PTSD, and sleep disorders.

Metabolic Syndrome as a CVD Risk Factor

The risk of developing CVD is increased by 3-fold for individuals with MetS compared to individuals without MetS (141; 285; 296; 495), with a stronger risk association found in women (71; 141). The more components of MetS an individual has, the greater their risk for CVD (473), particularly if they have the presence of hyperlipidemia and hypertension (77). MetS is not only a known risk factor for CVD, but also type 2 diabetes, another known risk factor for CVD (34). Additionally, individuals with MetS often report other CVD behavioral risk factors, particularly decreased physical activity (18) and decreased sleep duration (496).

Metabolic Syndrome Related to PTSD

Overall, individuals with PTSD have a higher risk for MetS (92; 215) than the United States national average (24% of men, 20% of women; (171; 293), with estimates of approximately 40% of those with PTSD also have MetS (376; 490). PTSD has been associated with MetS in New York City police officers (466) and United States veterans (47; 170; 490). PTSD also has been associated with specific MetS symptoms. For example, compared to those without a PTSD diagnosis, OEF/OIF veterans with PTSD were at an elevated risk of having dyslipidemia (81), Brazilian police officers with PTSD had elevated cholesterol levels (269), and Bosnian war veterans with PTSD had more prevalent hyperglycemia and abdominal obesity (215).

Within the veteran population, veterans with more PTSD symptoms and higher PTSD symptom severity have been found to have increased rates of MetS (170; 490). Similarly, research in civilian populations also has demonstrated that individuals with

more severe PTSD are up to three times more likely to meet criteria for three or more of the MetS symptoms (see above) associated with CVD (215; 466). Interestingly, the association between PTSD and MetS remained after adjusting for traditional MetS risk factors, as well as age, race, BMI, smoking, and alcohol use (47).

Metabolic Syndrome Related to Sleep Disorders

A recent meta-analysis found a U-shaped relationship between duration of sleep and MetS (186). This U-shaped relationship also has been identified with sleep and CVD, in which short (<7 hours) and long (>9 hours) sleep durations are associated with increased negative health outcomes (142; 143; 347; 367; 487). In addition to sleep duration, poor sleep quality and sleep fragmentation also are associated with impaired glucose metabolism (427), one of the identifying mechanisms of MetS. Overall, poor sleep quality has been shown to increase an individual's risk of MetS by 30% (257). Additionally, individual aspects of sleep quality have been found to increase and individual's risk of MetS, specifically difficulty in falling sleep (18%), difficulty in maintaining sleep (15%) and sleep inefficiency (40%) (257).

Type 2 Diabetes Mellitus (DM2)

DM2 is a chronic medical condition in which the body is unable to adequately regulate blood glucose levels (13). DM2 has been identified as the 7th leading cause of death in the United States in 2013 and costing over 245 billion dollars in 2012 (87). Approximately 21 million adults in the United States have been estimated to have DM2 (34; 349). Within the DM2 disease process, cells throughout the body do not respond effectively to insulin and, therefore, blood glucose is not transferred to the cells for

energy, resulting in hyperglycemia, a condition in which high levels of glucose circulate within the blood stream (13). With increased blood glucose levels, the body produces more insulin resulting in a downregulation of insulin receptors and ultimately insulin resistance, in which the cellular structures of the body are less sensitive to insulin (483). Individuals who have low physical activity levels, have excess weight, or consume a low-quality diet are at an increased risk of developing DM2 (13; 14). DM2 was a disease historically diagnosed in adults over the age of 40, but has been increasingly diagnosed in youths and young adults (98). The next sections will examine the relationship between DM2 and CVD, PTSD, and sleep disorders.

DM2 as a CVD Risk Factor

Research has found that individuals with DM2 have a 2- to 4-fold higher risk of death from CVD compared to people without diabetes (34; 445). One study showed that individuals with DM2 have the same risk for myocardial infarction as individuals without DM2 but a history of previous myocardial infarctions (163). The underlying relationship between obesity, CVD, and diabetes has been reviewed extensively and is thought to be mediated through the adipokines released from abdominal fat (105; 200; 249; 375), which ultimately damage, harden and narrow blood vessels. Overweight and obesity are the most important predictors of DM2 (181; 304) and recent data suggest that the risk is specifically associated with abdominal fat accumulation (306). As discussed previously, although obesity may contribute to the DM2 as a risk factor for CVD, obesity is also an independent predictor of clinical CVD (183; 487).

DM2 Related to PTSD

PTSD has been associated with increased prevalence of DM2 throughout many populations to include primary care patients (475), Vietnam veterans (152; 392; 458), United States military service members (419), and female nurses (368). Vietnam veterans with PTSD were found to have a 40% higher risk of developing DM2 compared to their twins without combat experience and without diagnosis of PTSD (458). Much of the current research has identified a connection between PTSD and DM2; however, the direct impact of PTSD on the body's neuroendocrine and metabolic systems has not been identified.

DM2 Related to Sleep Disorders

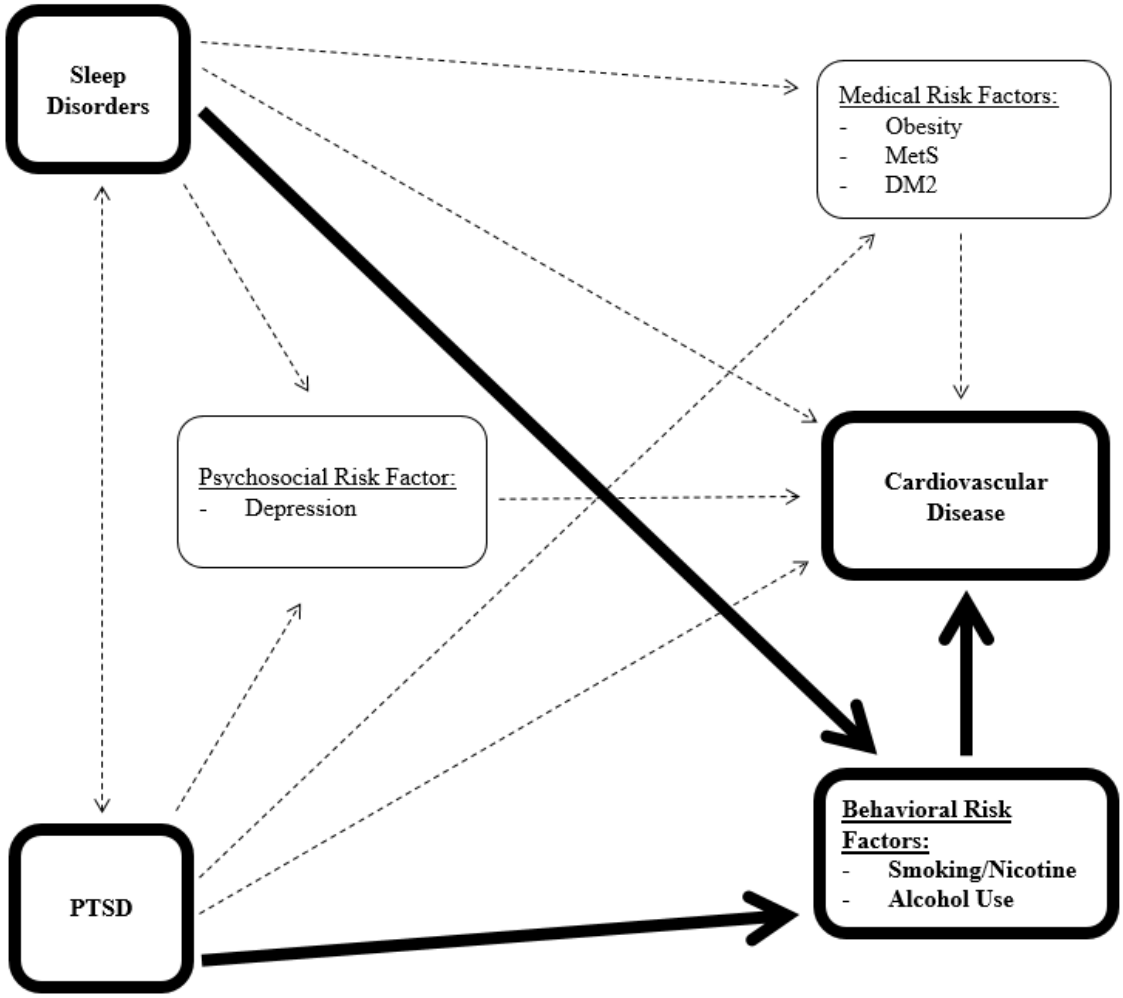
Sleep duration has been identified as an independent risk factor for DM2, specifically higher rates of DM2 have been found in individuals with sleep durations shorter or longer than 7 hours per night (195; 235). These results have been found in the epidemiological research of the Nurses' Health Study, Quebec Family Study, Sleep Heart Health, and National Health and Nutrition Examination Survey (143; 156; 443). Specifically, the National Health Interview found that individuals who reported less than 6 hours of sleep and greater than 8 hours of sleep were 1.6 times more likely to have DM2 (513). These results were consistent across race and ethnicities of the 29,818 Americans surveyed. Additional prospective cohort studies showed an increased risk for DM2 in individuals who received less than 6 hours of sleep per day and for individuals reporting poor sleep quality (49; 168; 180; 321; 497). However, not only does decreased sleep duration have negative metabolic health impacts, but increased sleep duration (more

than 8-9 hours of sleep per night) also has been found to increase an individual's risk of developing DM2 (72).

In addition to sleep duration, poor sleep quality also has been shown to increase an individual's risk of DM2 (72; 222). Furthermore, decreased sleep duration and poor quality of sleep have been associated with decreased insulin sensitivity and decreased glucose tolerance in laboratory studies where sleep was disrupted for only a few days (222). Sleep insufficiency also has been shown to cause risk factors and symptoms of DM2 to include dyslipidemia (202), adipocyte insulin resistance (57), hyperglycemia (72; 222), and weight gain (72; 222; 498). Short and long-term sleep disruptions and poor sleep quality also were associated with higher blood glucose levels in individuals with DM2 (250). In a recent meta-analysis of 36 studies with over 1 million participants, sleep duration, sleep quality, and OSA were found to be comparable to traditional risk factors for DM2 (overweight, family history of diabetes and physical inactivity) (11). Longitudinal studies indicated that the presence of OSA is associated with an increased risk of developing diabetes even after adjusting for adiposity (299; 356).

Behavioral Risk Factors for CVD

Figure 3. Conceptual Model: PTSD and Sleep Disorders Association with CVD and CVD Behavioral Risk Factors



As defined above, risk factors are characteristics of an individual or population that increases the likelihood of developing a disease. For the purposes of this dissertation, we will define a behavioral risk factor as a behavioral characteristic associated with increased development of CVD. Behavioral risk factors for CVD include a range of variables, including smoking, lack of exercise, poor diet, alcohol abuse, etc. However, for this dissertation, we have limited the behavioral risk factors to diagnoses of alcohol use and nicotine use because of limitations of the dataset used for the analyses. This section

will present a discussion of alcohol and nicotine use and their relationships to CVD, PTSD, and sleep disorders.

Alcohol Use

The National Institute on Alcohol Abuse and Alcoholism estimates that 16 million individuals in the United States have a diagnosis of alcohol use disorder (AUD)(6). Alcohol use disorder is characterized by loss of control over alcohol consumption, uncontrollable alcohol use, and negative effects when not drinking alcohol (9). In 2010, alcohol use was the third leading risk factor for global disease burden (5.5% of global disability) after high blood pressure (7%) and tobacco smoking (6.3%) (259). In one primary care-based study of 19,372 adults, less severe alcohol problems such as at-risk drinking were identified in 19.7% (132). In population-based studies hazardous drinking (pattern of alcohol consumption that places individuals at risk for adverse health events) ranged from 18% to 24% (12; 100) and harmful drinking (alcohol consumption that results in adverse physical or psychological events) from 0.3% to 14% (159; 173). Approximately 10% of OEF/OIF veterans have a diagnosis of AUD (403).

Approximately 33% of military service members endorse binge drinking within the past month compared to 27% of civilians (281). This rate is slightly higher in military members returning from deployment, with approximately 36% meeting criteria for alcohol misuse (65). Additionally, studies report that 22–40% of United States military veterans recently discharged after service during operations in Iraq and Afghanistan screen positive for potentially hazardous alcohol and/or alcohol use disorder (69). The next sections will examine the relationship between alcohol use and CVD, PTSD, and sleep disorders.

Alcohol Use as a CVD Risk Factor

Heavy alcohol consumption has long been associated with toxic effects on the cardiovascular system leading to cardiomyopathy, arrhythmias, hypertension, coronary artery disease, and stroke (127; 220; 312). However, previous studies have shown that light-to-moderate alcohol consumption is associated with a lower risk of CVD (91; 220; 372; 373; 510) and may be protective against CVD (109; 221; 366). This is in contrast to heavy and binge drinking, which is associated with adverse cardiovascular health (127). In different populations, a J- or U-shaped curve has been proposed to illustrate this relationship. The lowest point on the curve (light-to-moderate drinking) demonstrates the alcohol consumption is least likely to correspond with CVD, and increased risk of CVD in non-alcohol drinkers and the highest risk of CVD in heavy and/or binge drinking (101; 107).

In studies of United States veterans, a U-shaped relationship between alcohol consumption and CVD also was found and suggests that heavy drinking or an AUD is associated with a higher risk of CVD compared with light drinking (423). Beverage preference did not influence the alcohol-CVD relationship. The findings among United States Veterans were consistent with other large cohort studies that found a reduction in CVD risk with light-to-moderate alcohol consumption (30; 70; 137; 298). Studies also have shown that the benefit of light-to-moderate alcohol consumption can be reversed if an individual consumes alcohol in heavy episodic amounts (351). Binge drinking appears to be particularly harmful, as it is associated with a heightened risk of hypertension, MI, and stroke in a wide range of ages (340).

Possible mechanisms of the relationship between alcohol consumption and CVD include oxidative damage, mitochondrial dysfunction, deposition of triglycerides, altered fatty acid extraction, and impaired protein synthesis (357). One highly studied mechanism is the association of heavy alcohol consumption with increased prevalence of MetS (438). Heavy alcohol drinkers tend to have the highest mean waist circumference, systolic and diastolic blood pressure, blood glucose levels, and triglyceride levels compared to low and moderate drinkers (219), which are each risk factors for MetS. Furthermore, compared to non-drinkers, non-obese and obese males who were heavy and binge alcohol drinkers had an increased risk of MetS (316). Based on the research, heavy alcohol use is detrimental to cardiovascular health directly and through metabolic dysfunction leading to MetS, a physiological risk factor for CVD.

Alcohol Use Related to PTSD

PTSD has been associated with over double the risk of alcohol use and/or dependence (212) compared to those individuals without PTSD. Comorbid PTSD and substance use disorders are reported in both civilian and military populations with approximately 46% of civilians and 63-74% of veterans with PTSD also having a diagnosis of a substance use disorder (244; 343; 403). AUD has been reported as one of the most common co-occurring mental health disorders in individuals diagnosed with PTSD (343). Both men and women with PTSD are more than two times as likely to meet diagnostic criteria for alcohol abuse or dependence (212). The Normative Aging Study also found that the greater number of PTSD symptoms in male military veterans predicted increased likelihood of current alcohol problems (51; 398). Veterans with a

dual diagnosis of PTSD and AUD are at a higher risk of mortality due to physical illness and injury (38).

A recent meta-analysis explored four functional association models hypothesizing why PTSD and AUD commonly co-occur (435). These association models include the self-medication model, the high-risk model, the susceptibility model, and the shared vulnerability model. The self-medication model hypothesizes that individuals use alcohol to cope with symptoms of PTSD such as sleep, irritability, and hypervigilance (165; 251; 328; 415; 454) or "self-medicate" PTSD arousal and anxiety symptoms (53). The high-risk and susceptibility models hypothesize that individuals with AUD are at an increased risk of developing PTSD (4; 56; 217). The high-risk model posits that AUD impairs the ability to detect danger cues and ultimately increases the likelihood of trauma exposure. The susceptibility model increases risk of PTSD by interfering with an individual's ability to process emotions following trauma exposure. The high-risk and susceptibility models suggest causal relationships between AUD and PTSD due to the direct link between AUD and the instance of the traumatic event and an individual's ability to cope with a traumatic event. In other words, if the individual did not have an AUD, their risk for exposure would be decreased and they would most likely have improved coping skills should they experience a traumatic event (435). The final model, shared vulnerability, hypothesizes that PTSD and AUD have common risk factors such as genetics and environmental exposure (435). The different associational models above suggest that PTSD and AUD mutually maintain and exacerbate each other.

Also relevant to the shared vulnerability model, altered HPA-axis activity associated with PTSD has been found to have a direct impact on alcohol intake in rat

models. For example, when rats experienced an increase in glucocorticoids, their voluntary alcohol consumption increased (122; 123). It has also been hypothesized that due to the dopamine release and increase in glucocorticoids as a result of alcohol consumption, voluntary alcohol consumption may be a direct result of the reward system (39; 108).

Alcohol Use Related to Sleep Disorders

Sleep disruption can occur with acute or chronic alcohol consumption, but the pattern and severity of symptoms depends on the amount and timing of alcohol use (468). With consistent alcohol use around bedtime, individuals experience decreased sleep latency but an increase in later sleep disruptions (95; 134; 369). As a central nervous system depressant, alcohol can reduce sleep latency through its sedative effects. However, alcohol consumption tends to decrease REM sleep during the first half of sleep, and increase REM sleep during the second half of sleep (113; 370). In addition to the changes in REM sleep phases, alcohol has also been associated with more frequent episodes of wakefulness throughout sleep (434). A cycle of alcohol use and sleep disruption can develop when individuals use alcohol in an attempt to relieve insomnia symptoms (369). Individuals with PTSD also have reported utilizing alcohol as a strategy to assist with sleep disruptions (309). One study found that 100% of individuals with comorbid PTSD and alcohol dependence reported sleep problems (387).

In 2005, the National Sleep Foundation found that 11% of the general population used alcohol to help them sleep and was identified as one of the most commonly used non-prescription sleep aids (197; 370; 371). It is estimated that the cost of alcohol related problems exceeds $180 billion, out of which more than $18 billion is associated with

alcohol-related sleep disorders (446). Alcohol use and sleep disruptions are highly correlated (31) and have bidirectional components (i.e., they causally affect one another). Studies have found that individuals with insomnia reported higher levels of alcohol use (345). In addition, there is increasing evidence that sleep disruptions often precedes the development of alcohol use disorder (493).

In patients with alcohol use disorders, insomnia is often part of the withdrawal syndrome and increases risk for relapse (95; 468; 470). People with alcohol use disorders also suffer from severe and protracted sleep disruptions manifested by profound insomnia, excessive daytime sleepiness, and altered sleep architecture (58; 85; 446).

Nicotine Use

Nicotine use, specifically smoking tobacco or cigarettes, is a leading preventable cause of death (48). It is estimated that 15.1% of the United States population are current smokers (474). The estimated global prevalence of tobacco smoking in 2010 was 36.6% for men and 7.5% for women (324). The next sections will examine the relationship between nicotine use and CVD, PTSD, and sleep disorders.

Nicotine Use as a CVD Risk Factor

Tobacco use is also a leading cause in CVD morbidity and mortality (2). In a meta-analysis of CVD risk factors, smokers were at two times the risk of cardiovascular mortality compared to nonsmokers and former smokers (292). Among smoking related deaths, CVD accounts for approximately one-third of cases worldwide (266). Cigarette smoking is also a significant risk factor for stroke in both men and women (227; 453). People who smoke just 1 cigarette daily have been found to have 40-50% of the increased

CVD risk of those who smoke 20 cigarettes daily (162). Cigarette smoking accelerates atherosclerosis, resulting in premature coronary heart disease, peripheral vascular disease including stroke (36). Smoking accelerates the CVD process by increases the incidence of all phases from endothelial dysfunction to congestive heart failure (8; 227).

Nicotine activates the SNS, which could be a contributing factor for CVD (36). Nicotine is known to increase heart rate, constrict blood vessels, and increase myocardial contractility (35) each of which contributes to CVD disease processes (23; 508). Smoking a cigarette typically increases blood pressure for 15-30 minutes after smoking and increases heart rate for up to an hour. The result of these short blood pressure increases could be that blood flow is more turbulent among smokers, which could contribute to injury to the blood vessels (36). When the endothelium in blood vessels is injured, dilation and constriction of the blood vessels becomes impaired (472). Lastly, carbon monoxide, a product of cigarette smoking, is detrimental to cardiovascular health as it reduces the availability of oxygen to the myocardium and results in an increase in resting cardiac output (36).

Although smoking is an independent CVD risk factor, smoking also has been found to negatively impact other CVD risk factors such as hyperlipidemia, hypertension, and DM2 (406). Relevant to the physiological components of MetS and risk factors for DM2, nicotine also causes short-term increases in energy expenditure; therefore, smokers tend to weigh less than nonsmokers initially. However, overtime, smoking increases insulin resistance and abdominal fat accumulation (228; 303; 500), which can lead to the development of MetS and DM2. Smokers on average have a more atherogenic lipid profile than do non-smokers (94). Based on this research, cigarette smoking and nicotine

use is detrimental to cardiovascular health directly and through metabolic dysfunction leading to MetS and DM2, both physiological risk factors for CVD.

Nicotine Use Related to PTSD

Individuals diagnosed with PTSD have been found to be more likely to smoke tobacco than individuals without PTSD (130). Approximately 45% of individuals with PTSD are current smokers and 63% had a history of smoking, both rates are higher than individuals without a mental health diagnosis (248). Within the military and veteran populations, individuals with PTSD are more likely to be current smokers than military members and veterans without PTSD (152; 327). Additionally, combat exposure and higher PTSD scores among veterans predicted an increased likelihood of current smoking (398). Not only are individuals with a diagnosis of PTSD more likely to smoke compared to those without PTSD, but they also have been found to have some of the lowest quit rates compared to those with other psychological diagnosis (26; 124). Relevant to the self-medication model described previously, higher rates of smoking behaviors in individuals with PTSD have been examined as a mechanism to decrease an individual's anxiety (274) and negative affect (26; 27; 29; 88; 125).

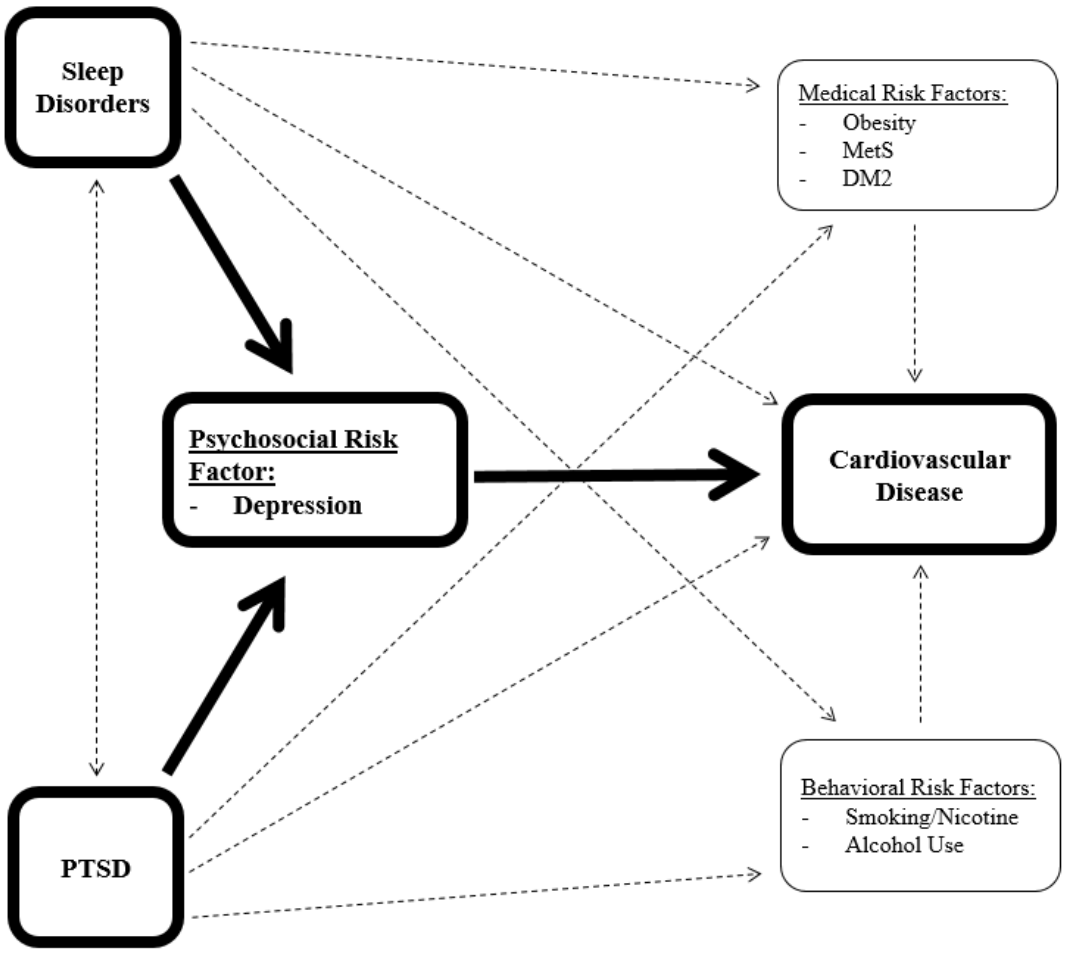
Nicotine Use Related to Sleep Disorders

Compared to individuals who do not smoke cigarettes, those who do smoke cigarettes are more likely to experience sleep problems such as sleep disordered breathing, sleep apnea, insomnia, and poor sleep quality as marked by sleep disturbances such as shorter sleep durations, increased sleep latency, daytime sleepiness, and increased difficulty maintaining sleep (84; 191; 193; 262; 280; 479). Several studies report that this

negative association between cigarette smoking and sleep quality (112) may be associated with increased withdrawal, cravings, and urges to smoke (352). Smokers may experience nocturnal cravings and withdrawal symptoms when blood nicotine levels decrease during sleep (478). Sleep-disturbing nicotine cravings (363) have been reported by 20-51% of smokers (112). Additionally, individuals attempting to quit smoking who reported more sleep-disrupting nicotine cravings were more likely to relapse to smoking within 6 weeks (338).

Psychosocial Risk Factors for CVD

Figure 4. Conceptual Model: PTSD and Sleep Disorders Association with CVD and CVD Psychosocial Risk Factor



Depression

Depression is a global public-health issue and the most common psychiatric condition in the general population (211; 417). Depression is characterized by feelings of sadness, loss of interest in pleasurable activities, feelings of guilt, low self-worth, disrupted sleep, changes in appetite, and poor concentration (9). A review of over 90 studies conducted between 1994 and 2004, including more than 1 million individuals,

estimated a 12.9% lifetime prevalence of depression and a 7.2% prevalence of depression in the past year (259). Additionally, in 2000 depression was rated as a leading cause of disease burden. Furthermore, the World Health Organization's 2019 survey of 60 countries found that 9.3% to 23% of participants with one or more chronic diseases had comorbid depression (322). Out of the comorbid psychiatric and physical diseases, comorbid depression worsened overall health scores more than any other comorbid chronic diseases (297).

Depression as a CVD Risk

As previously noted, depression and CVD are each ranked among the leading causes of disability worldwide (300). Moreover, the association between CVD and depression has long been recognized (271). However, in the past 20 years, numerous studies suggest that depression, and even depressive symptoms that do not meet criteria for a diagnosis for depression (9), are risk factors for: the development of CHD events in previously healthy patients (253), recurrent cardiovascular events in patients with established CHD (21; 121; 433; 461), and for adverse cardiovascular outcomes after coronary artery bypass grafting (CABG) surgery (42). In the INTERHEART study of more than 25,000 patients from 52 countries, psychosocial factors (depression, locus of control, perceived stress and life events) were stronger risk factors for cardiac events than diabetes, smoking, and obesity (506). This extensive body of research suggests that depression is likely an independent risk factor for CVD. For example, Ladwig et al. (245) showed that experiencing a depressed mood as an independent predictor of the risk to all-cause, cardiovascular, and CHD mortality. In this study, severity of depression was found

to be more strongly associated with CHD mortality than hypercholesterolemia and obesity (245).

In 2014, The American Heart Association released a Scientific Statement adding depression as a risk factor for future cardiovascular events for individuals who have previously experienced acute coronary syndromes (258). Longitudinal studies have shown that depressive symptoms in both healthy individuals and patients with coronary disease predict future coronary events, even after adjusting for associated health behaviors such as smoking and exercise (422). However, majority of the research examining the relationship between depression and/or depressive symptoms and CVD have been on patients with pre-existing cardiac symptoms, not with initially healthy populations. These studies have found that individuals with CHD and/or heart failure who also are depressed are more likely to report poor quality of life, greater physical limitations (158; 382), and are twice as likely to experience future cardiac events (308). Out of comorbid psychiatric and physical diseases, comorbid depression worsened overall health scores more than any other comorbid chronic physical diseases (297). Several studies suggest that clinical characteristics of depression, such as severity of depression and/or depressive symptoms, number of episodes and duration of depression, may moderate the relationship between depression and CVD (24).

Current literature suggests that the relationship between CVD and depressive symptoms may be bidirectional. For example, clinical and epidemiological studies have suggested that depression increases the risk of subsequent cardiovascular events by an average of about 50 percent (161; 260; 308; 448), In addition, CAD patients with depression, compared to those without depression, have a 2- to 3- fold increased risk of

future non-fatal and fatal cardiovascular events (135; 154; 381; 459) independent of age, diabetes, smoking, lipid levels, obesity, physical activity, and baseline severity of heart disease (480).

Possible Mechanisms Linking Depression to CVD

There are several behavioral and biological pathways and mechanisms that may link depression and CVD. Regarding behavioral mechanisms, depression has been associated with poor diet (512), lack of physical exercise (382), nonadherence to medications (145), low social support (19) and smoking (25; 237). Several studies also suggest that these behavioral factors mediate, at least in part, the association between depression and a poor prognosis (481; 494).

Biologically, depression has been linked to increased inflammation (418) and inflammatory markers (C-reactive protein, interleukin-1 and interleukin-6) (99; 199), autonomic nervous system dysregulation (388), impaired coronary artery flow (362), increased SNS activity, platelet dysfunction, and endothelial dysfunction (59; 99; 154; 161; 199; 229; 236; 260; 267; 354; 381).

The SNS hyperactivity associated with depression (199; 207; 388; 431) has been linked to arterial hypertension, decreased vagal tone, and increased recovery time after stress; all of which are related to increased cardiovascular mortality (270). The effects of this increase in sympathetic tone can result in vasoconstriction, heart rate elevation with reduced heart rate variability, and platelet activation contributing to accelerated atherosclerosis, arrhythmia, and thrombosis (199; 207; 431).

All these factors are related to the involvement of endothelial dysfunction in arteries associated with atherosclerosis. Specifically, depression and depressive

symptoms have been associated with impaired endothelial function in both healthy subjects and in patients with ischemic heart disease (41). Endothelial dysfunction may contribute to atherosclerosis, thrombosis, and vasospasm (41; 89; 355; 383; 411; 412).

Depression Related to PTSD

PTSD and depression are commonly co-occurring mental health disorders. It is estimated that 37-48% of individuals with PTSD report a lifetime history of depression (54; 212). A meta-analysis of 57 studies with over 6,600 participants found that depression had a 52% comorbidity rate with PTSD (385). However, other studies have found the lifetime prevalence rates of comorbid depression and PTSD to be as high as 65% (244; 278). This high overlap between PTSD and depression is consistent with that found in the general population in the United States National Comorbidity Survey, which reported lifetime comorbidity between PTSD and depressive disorders to be higher than 50% (212).

Among military veterans, PTSD and depression are the two most commonly diagnosed mental health disorders (342). PTSD has been commonly associated with depression among veterans from the United States, Britain and the Netherlands (40; 155; 160; 190; 205; 404; 462; 463). Between 50-75% of United States Vietnam, Korean, OEF, and OIF veterans with PTSD had comorbid PTSD and depression (40; 160; 187; 404). One study found that individuals diagnosed with PTSD were almost three times as likely to also have a diagnosis of depression compared to those without PTSD (343).

Compared to veterans with PTSD alone, those with comorbid PTSD and depression experienced greater symptom severity (187; 291; 407), decreased quality of life, reduced life satisfaction (187) and poor social and occupational functioning (291;

320). Research has demonstrated multiple negative health consequences of both PTSD and depression, including digestive, metabolic, nervous, endocrine, respiratory and circulatory diseases (213; 329; 353; 477).

Theoretical Explanations of Overlap Between PTSD, Depression, and CVD

The reasons for the high comorbidity of PTSD and depression, and the mechanisms that may account for the high co-occurrence of these two mental health diagnoses are still being explored. (428). Theories suggest the comorbidity between PTSD and depression may be explained in part by the many overlapping symptoms across the two diagnoses (128) and existence of common underlying dimensions of psychopathology (239; 469). Consistent with identifying dimensions that cut across descriptive diagnostic criteria, there are similar etiologic factors for depression and PTSD. For example, one common psychological/environmental factor for both PTSD and depression is having a traumatic exposure as a precipitating event (311). Another explanation of the comorbidity of PTSD and depression may be a causal relationship between the two diagnoses. Suffering from prior depression was found to increase the risk of developing PTSD (54), while other studies linked PTSD to the onset of depression (52; 151; 212). In terms of biological models, there also may be shared vulnerability for both disorders—e.g., PTSD and depression may share or have similar dysfunction in stress response pathways such as activation of the HPA axis (59). Specifically, PTSD and depression are both associated with neuronal, hormonal, and immunologic physiological responses that damage the body when activated over sustained periods of time (277). Relevant to risk of CVD, evidence further indicates that individuals with PTSD and/or

depression may share increased physiological risk factors for CVD and are also at risk for various non-cardiovascular disorders as well.

Despite the common comorbidity of PTSD and depression as well as the overlap in diagnostic criteria, multiple studies have found an association between PTSD and CVD persists after adjusting for depressive symptoms (46; 192; 242). A meta-analysis with a combined sample of over 400,000 found that individuals with PTSD were 55% more likely to develop CVD; however' after controlling for depression, they were 27% more likely to develop CVD (115). Data from the Millennium Cohort Study showed that service members deployed between 2001 and 2008 had higher rates of self-reported CVD, and those with a diagnosis of PTSD were more likely to have newly reported CVD compared to those without a diagnosis of PTSD (96). In contrast to the other study, however, findings were no longer significant after adjusting for depression.

Depression Related to Sleep Disorders

There is increasing evidence that sleep disturbance plays a key role in mental health and that insomnia often precedes the development of conditions such as depression, anxiety, and alcohol abuse (54; 341; 444; 476). Specifically, in depressive patients, sleep complaints are reported in approximately 90% of patients (451). Individuals in the National Comorbidity Survey Replication with depression were 3 to 6 times more likely to have one of the four sleep disturbance criteria of insomnia (379). Epidemiological studies identified an associations with insomnia symptoms in patients with depression (129; 224), with 41% of depressed patients reporting sufficient symptoms to warrant an additional DSM-IV diagnosis of insomnia (429). A civilian population survey based on health claims found that depression was significantly

associated with nonrestorative sleep, low sleep hours and poor sleep quality (389). Patients with depression experience abnormalities in sleep parameters across all phases of sleep architecture. Alterations in REM sleep have been identified as the most evident sleep characteristic in patients with depression, and those changes have been regarded as a distinctive biological marker of depression (482). There is also a strong relation between OSA and depression (7; 337). Individuals with depression are at a 5-fold greater risk for having OSA than healthy controls (318). With between 44.6% and 56% of patients with OSA meeting criteria for depression (201; 275).

Depressed patients who also experience sleep disturbances are more likely to present with more severe depressive symptoms and difficulties in treatment (174; 345). In a review of clinical trials of psychotherapy or pharmacotherapy for depression, insomnia was one of the most common residual symptoms in partial remission, and the most common residual symptom in full remission (449). Riemann and Voderholzer's 2003 (364) review of longitudinal, epidemiological studies found that insomnia at baseline increased risk for depression at follow-up 1-3 years later. Insomnia is the most common residual symptoms in depressed patients and is considered a vital predictor of depression relapse and may contribute to poor clinical outcomes (33; 174).

Similar results identifying the associations between depression and sleep disturbances also have been identified within military populations. In a study of 110 military personnel who had deployed recently, 71.4% of those who met criteria for comorbid OSA and insomnia also met criteria for depression (302). At 4-months post-deployment, insomnia was identified as a significant predictor of depression and was more severe than depressive symptoms at 12-months post-deployment (493).

SUMMARY AND OVERVIEW

The progression of CVD is influenced by a number of biopsychosocial risk factors. This review focused on PTSD and sleep disorders as primary CVD risk factors that also impact other known, diagnosable biopsychosocial CVD risk factors (obesity, MetS, DM2, smoking and alcohol use, and depression). By looking at the various biopsychosocial CVD risk factors, it is apparent that the development of CVD is complex and impacted both by independent and comorbid risk factors. This Introduction has reviewed data indicating that PTSD and sleep disorders predict increased risk of CVD but also are associated with increased prevalence or severity independent of each other. Additionally, this review has identified that each of the physiological and behavioral risk factors (i.e., obesity, MetS, DM2, smoking and alcohol use, and depression) were not only associated with the development of CVD but also with PTSD and sleep disorders.

The broad aim of this dissertation is to better understand the relationships, and possible mechanisms (via risk factors) of the relationships, between PTSD and sleep disorders and CVD. Since most research on PTSD and CVD has been conducted in older and veteran populations, the present study examined PTSD and sleep disorders, with the biopsychosocial risk factors for CVD, in younger, active duty military members. A second focus of this dissertation was to determine the involvement of biopsychosocial risk factors in the development of CVD among individuals diagnosed with PTSD and/or sleep disorders. By elucidating the relationships among PTSD, sleep disorders, and other biopsychosocial risk factors for CVD, the proposed study may identify specific aspects of PTSD, sleep disorders, or biopsychosocial risk factors to target for treatment in active duty military members in order to reduce CVD risk and improve cardiovascular health.

To examine these relationships, this dissertation used is the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS) Historical Administrative Data Study (HADS; see below). The data from HADS used in this dissertation, focused on soldier's medical records, specifically mental and physical health care utilization within the Medical Data Repository (MDR) and soldier's demographics from administrative data systems. The MDR data is comprised of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes.

SPECIFIC AIMS & HYPOTHESES

Specific Aim 1

To determine the relationships among behavioral, psychosocial, and medical risk factors for CVD. Psychosocial risk factors include PTSD, depression, and sleep disorders; medical risk factors include obesity and type 2 diabetes mellitus; and behavioral risk factors were defined as nicotine use, and alcohol use. Evidence of cardiovascular disease was defined as any of the following: hypertension, coronary artery disease, myocardial infarction, stroke and/or congestive heart failure.

Hypothesis 1a. PTSD will demonstrate a positive relationship with medical risk factors, behavioral risk factors, evidence of cardiovascular disease, and other psychosocial risk factors.

Hypothesis 1c. Sleep disorders will demonstrate a positive relationship with medical risk factors, behavioral risk factors, evidence of cardiovascular disease, and other psychosocial risk factors

Figure 5. Conceptual Model for Aim 1 Hypothesis 1: Correlations of PTSD with CVD and CVD Biopsychosocial Risk Factors

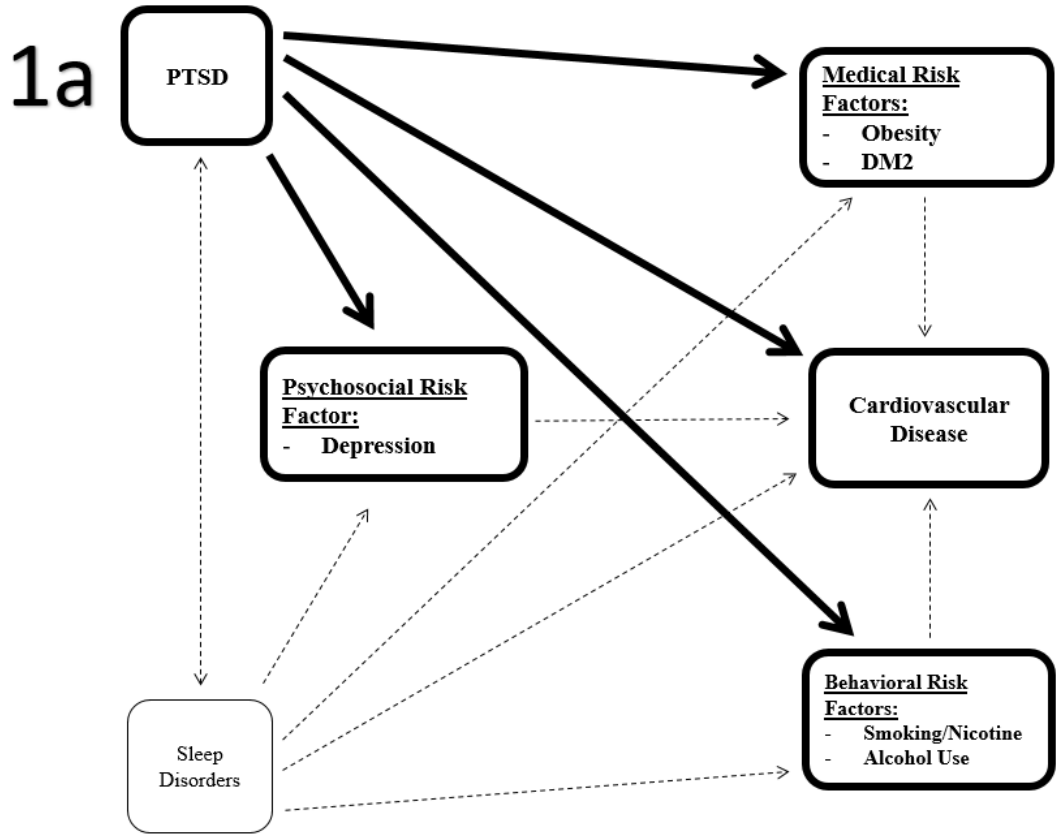
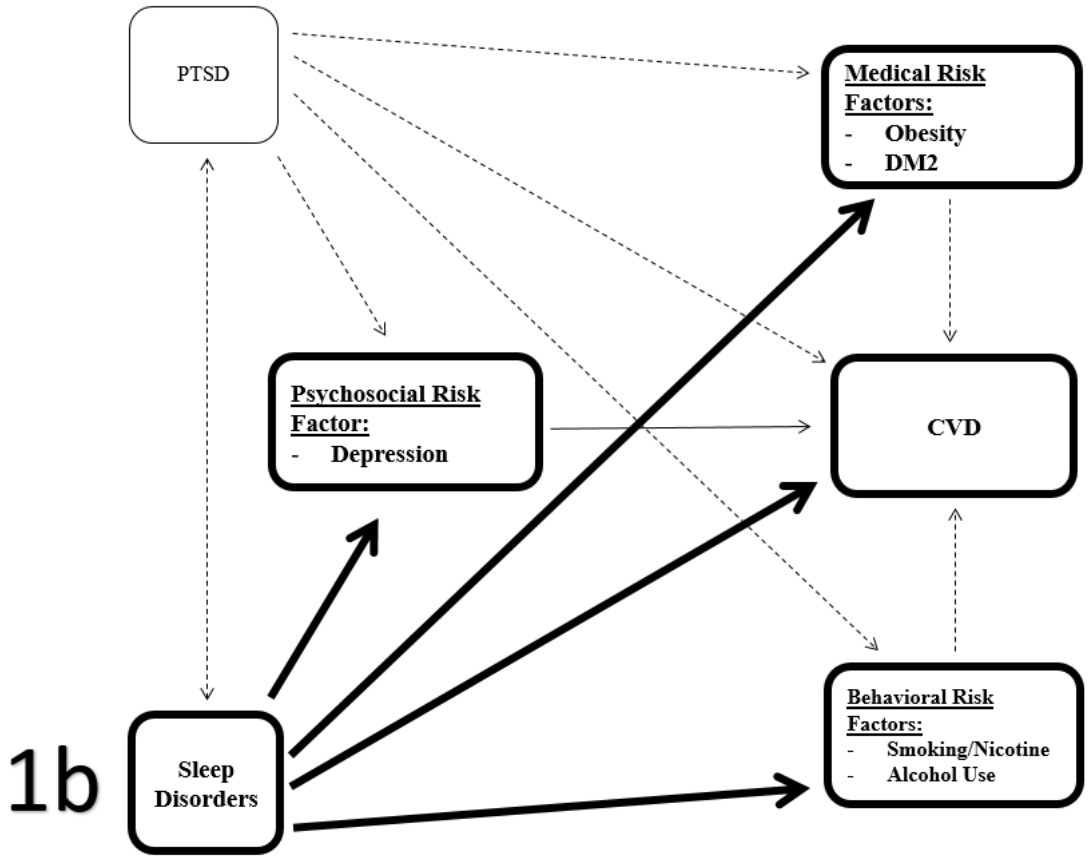


Figure 6. Conceptual Model for Aim 1 Hypothesis 2: Correlations of Sleep Disorders with CVD and CVD Biopsychosocial Risk Factors



Specific Aim 2

To determine the relationships between **PTSD** and **CVD** after accounting for medical risk factors for cardiovascular disease, behavioral risk factors for cardiovascular disease, and depression.

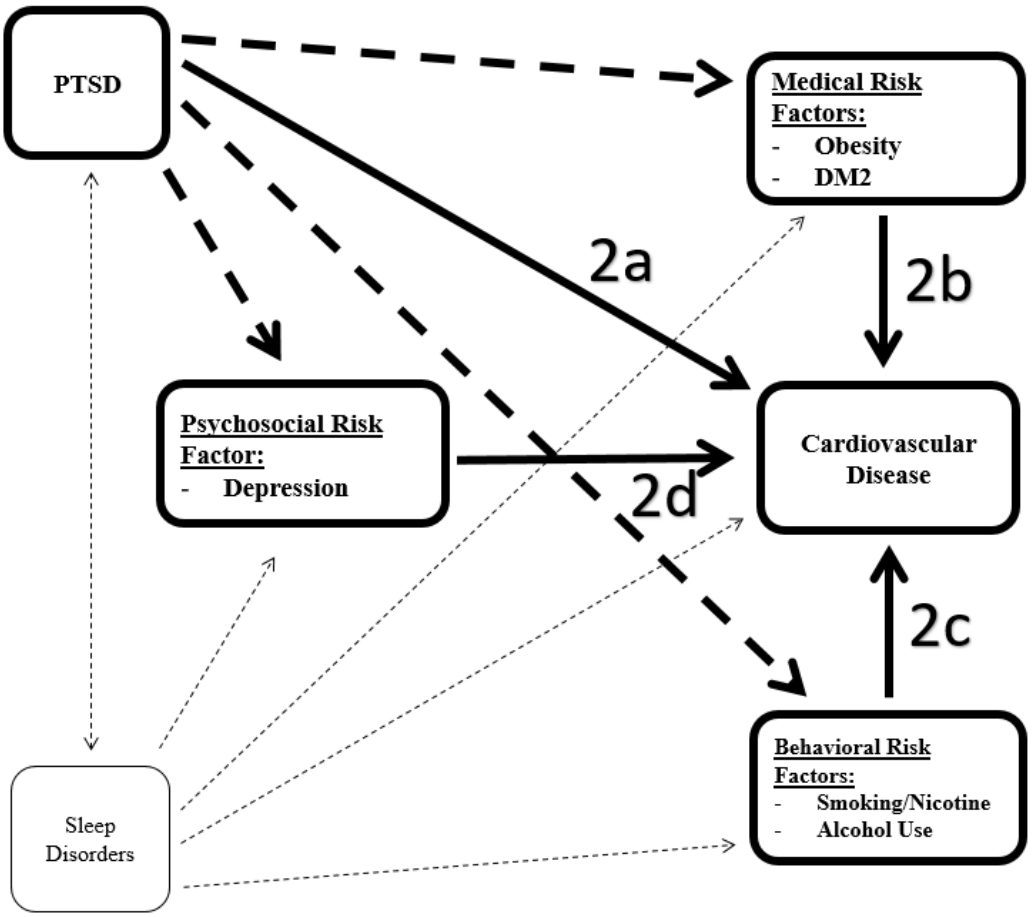
Hypothesis 2a. PTSD will be a significant predictor of CVD.

Hypothesis 2b. PTSD will continue to be an independent/significant predictor of CVD after accounting for medical risk factors for CVD (obesity and type 2 diabetes mellitus).

Hypothesis 2c. PTSD will continue to be an independent/significant predictor of CVD after accounting for medical risk factors and behavioral risk factors for CVD (smoking and nicotine use, and alcohol use).

Hypothesis 2d. PTSD will continue to be an independent/significant predictor of CVD after accounting for medical risk factors, behavioral risk factors, and depression.

Figure 7. Conceptual Model of Aim 2: PTSD and Association with CVD Accounting for CVD Biopsychosocial Risk Factors



Specific Aim 3

To determine the relationships between **a sleep disorder** and **CVD** after accounting for medical risk factors for cardiovascular disease, behavioral risk factors for cardiovascular disease, and depression.

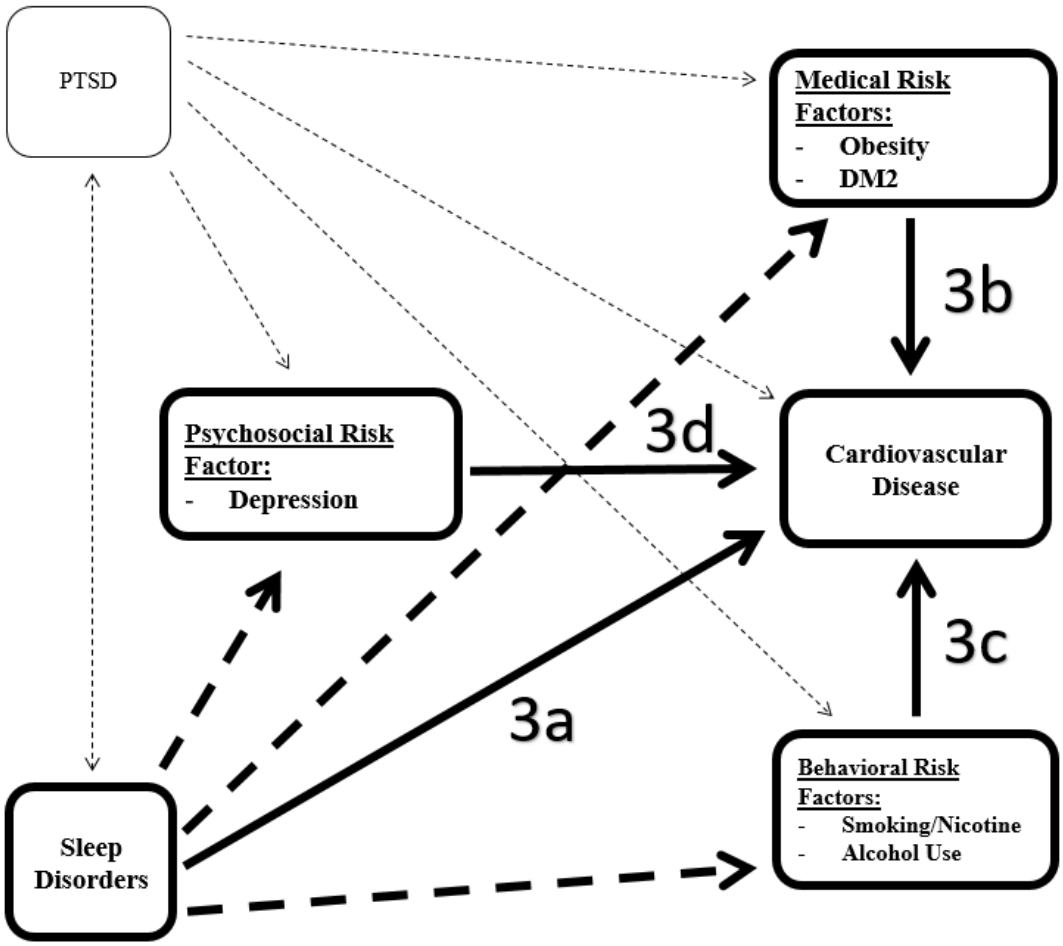
Hypothesis 3a. Sleep disorders will be a significant predictor of CVD.

Hypothesis 3b. Sleep disorders will continue to be an independent/significant predictor of CVD after accounting for medical risk factors for CVD (obesity and type 2 diabetes mellitus).

Hypothesis 3c. Sleep disorders will continue to be an independent/significant predictor of CVD after accounting for medical risk factors and behavioral risk factors for CVD (smoking and nicotine use, and alcohol use).

Hypothesis 3d. Sleep disorders will continue to be an independent/significant predictor of CVD after accounting for medical risk factors, behavioral risk factors, and depression.

Figure 8. Conceptual Model of Aim 3: Sleep Disorders and Association with CVD Accounting for CVD Biopsychosocial Risk Factors



Specific Aim 4:

To determine whether there is an additive relationship of **PTSD** and **sleep disorders** on the likelihood of CVD, and to determine if this additive effect remains after controlling for medical risk factors, behavioral risk factors, and depression.

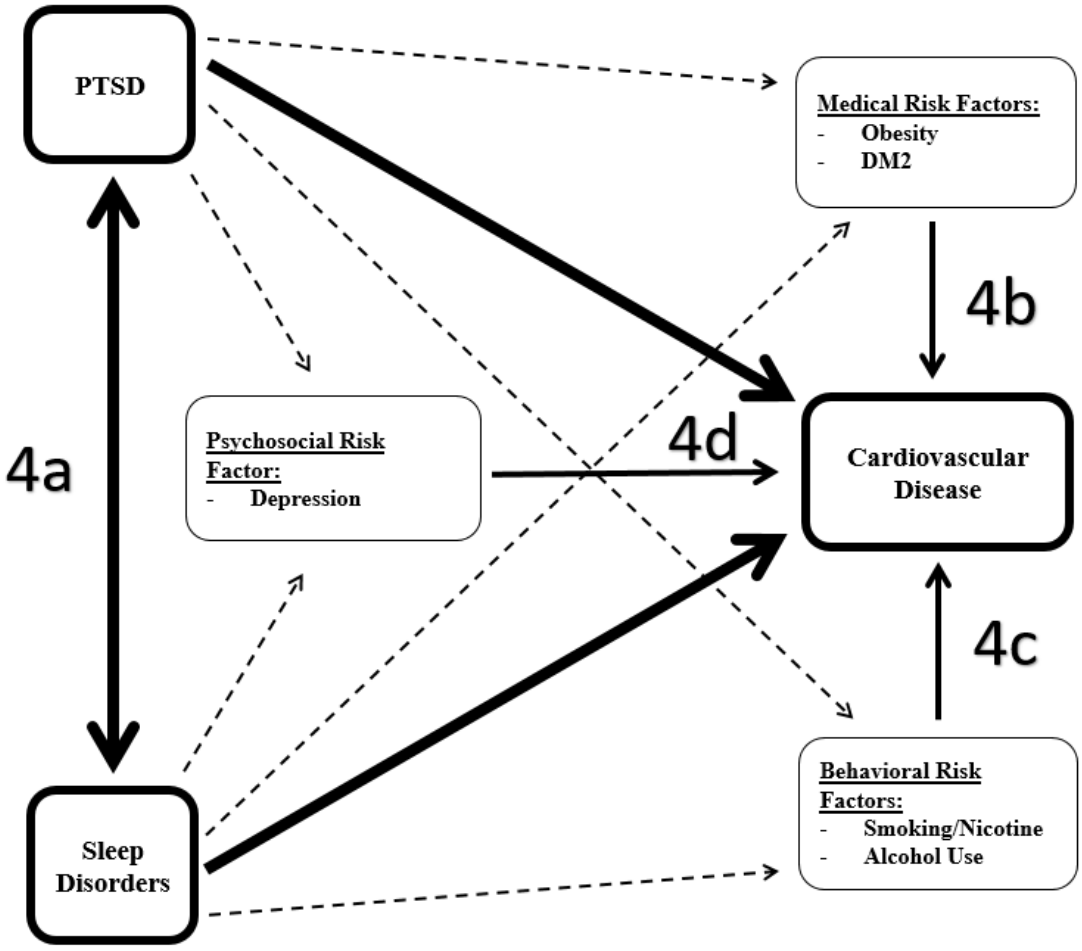
Hypothesis 4a. PTSD and **sleep disorders** together will be a stronger predictor of CVD compared to only a diagnosis of PTSD, only a diagnosis of a sleep disorder, and neither a diagnosis of PTSD or a sleep disorder.

Hypothesis 4b. PTSD and a **sleep disorders** together will continue to be a significant predictor of CVD after accounting for medical risk factors for CVD (obesity and type 2 diabetes mellitus).

Hypothesis 4c. PTSD and a **sleep disorder** will continue to be a significant predictor of CVD after accounting for medical risk factors and behavioral risk factors for CVD (smoking and nicotine use, and alcohol use).

Hypothesis 4d. PTSD and a **sleep disorder** will continue to be an independent/significant predictor of CVD after accounting for medical risk factors, behavioral risk factors, and depression.

Figure 9. Conceptual Model of Aim 4: PTSD and Sleep Disorders: Additive Association with CVD Accounting for CVD Biopsychosocial Risk Factors



CHAPTER 2: Methods

THE ARMY STARRS STUDY

The Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS) is a multi-component epidemiological and neurobiological study designed to examine antecedents of suicide and suicide-related behavior in all Active Duty, Active Reserve, and Active Guard Army soldiers at any point between 2004-2009 (456). There are multiple participating universities in the Army STARRS study, including the Uniformed Services University of the Health Sciences; University of Michigan Institute of Social Research; University of California, San Diego; and Harvard Medical School. Army STARRS involved multiple data collection methods and created several databases, which represented demographic, psychological, biological, neurological, behavioral, and social domains to help identify risk and resilience factors associated with suicide. One of the Army STARRS components, the Historical Administrative Data Study (HADS), was used in the present dissertation.

Historical Administrative Data Study (HADS)

Army STARRS HADS is an integrated administrative database containing key elements from 38 unclassified and de-identified Army and DoD data systems for over 1.6 million soldiers (Regular Army, Army Reserve, and National Guard) on active duty at some time during the calendar years of 2004-2009 (210). The HADS includes individual-level person-month records for all soldiers on active duty between January 1, 2004 and December 31, 2009 (N=1.66 million). There are approximately 55 million person-month records for the sample of 1.66 million soldiers. For all soldiers on active duty from 2004

through 2009, the HADS contains records going back to 1 January 2000.

These administrative data systems include databases such as training certifications (Army Training and Requirements Resource System: ATRRS), medical records (Medical Data Repository' MDR), and casualty reporting (Defense Manpower Data Center' DMDC). This dissertation study focused on soldier's medical records, specifically any mental and physical health care utilization within the MDR. DoD DMDC Master Personnel and Transaction Files as well as the Defense Enrollment Eligibility Reporting System, provided sociodemographic and Army service data; the Defense Manpower Data Center Contingency Tracking System provided data on deployments in support of OEF in Afghanistan and OIF. The MDR data comprises International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes. ICD-9-CM diagnostic codes, rather than the current ICD-10 diagnostic codes, were reported in HADS database due to the years of data collection (2004-2009).

This component of Army STARRS was approved by the Institutional Review Boards (IRB) of the Uniformed Services University of the Health Sciences, University of Michigan Institute for Social Research, University of California, San Diego, and Harvard Medical School. The IRB review determined that the present study did not constitute human research because it relies entirely on de-identified secondary data. The Army STARRS HADS data is stored on secure servers at the University of Michigan. Data is accessed remotely via secure computers.

Study Population

The initial sample for the present dissertation included approximately 975,000 active duty soldiers (approximately 37 million person-month records) who were on active

duty at some time point from 1 January 2004 and 31 December 2009. The 975,000 active duty soldiers included in this dissertation represent every soldier who served during this time period. The number of subjects for this dissertation was less than the total STARRS HADS (1.6 million soldiers) because this study did not include data from National Guard or Reserve soldiers or officers, warrant or commissioned. By limiting the study population to Active Duty US Army enlisted soldiers, the variance attributed to the differences between enlisted soldiers and officers on medical and mental health will be excluded. Previous Army STARRS studies have utilized this same procedure due to significant differences found between enlisted and officer service members. The demographics of the overall STARRS population are based on the averages over the six years of the study and the distribution of demographics were assumed to remain consistent over this period (see Table 1 below).

Table 1: Percentage Demographics in the Entire STARRS HADS Database (N=1.6 million soldiers) (400)

	Categories	Percentages (%)
Gender		
	Male	86
	Female	14
Age		
	17 – 20	12.5
	21 – 24	22.6
	25 – 29	22.9
	30 – 44	24.5
	> 45	3.5
Race		
	White	69.9
	Black	21.7
	Hispanic	10.6
	Asian	4.4
	Native American	1.0
Marital Status		
	Married	57.1
	Unmarried (no dependents)	23.1
	Unmarried (with dependents)	19.8
Rank		
	E1 – E2	10.4
	E3	11.9
	E4	23.2
	E5 – E9	38.2
	Warrant Officer	2.6
	Commissioned Officer	13.8
Time in Service		
	< 1 year	6.7
	1 – 2 years	6.4
	3 years	12
	4 year	11.1
	5 years	16.1
	6 – 10 years	19.9
	11 – 19 years	22.1
	> 20 years	5.7

In the entire HADS database, the woman-to-man ratio remained relatively stable from 2004 through 2009, and although the age of individuals changes over the course of the study due to the accession and separation, the average age remained relatively stable. The mean active duty service duration during the STARRS data collection period was 38

months. Please note also that since this dissertation used a selected sample from the HADS database (see next section), demographics for the study sample used in the present study can be found in Table 6 in the Results section under Sample Characteristics.

Strategy for Identification of the Present Study Sample and Initial Selection of the Study Population

In order to ensure all individuals with cardiovascular events were identified, the present study first sought to capture those individuals who had a cardiovascular diagnosis (defined in the next section: Selection and Categorization of Cardiovascular Cases) at some point during the study period. This sampling approach ensured a complete picture of CVD in the study population and allowed us to compare all CVD cases to controls (non-CVD data) on variables within the study. After the cardiovascular cases were identified, we adopted a strategy to reduce the size of the non-CVD control sample due to technical computing limitations. To form the non-CVD group and assure that the overall study sample remained representative of the HADS database, we selected a representative sample of Army soldiers without a cardiovascular diagnosis at a ratio of 122.73 non-CVD controls for each 1 CVD person-month. It is important to note that this method was not used to identify matched controls, but rather to identify a control sample that was representative of the overall STARRS Army population. This sampling method has been used in previous Army STARRS studies (436).

Selection and Categorization of Cardiovascular Cases

As noted above, we first identified all individuals with cardiovascular diagnoses. In order to capture all diagnoses while minimizing the number of cardiovascular variables

and including the most commonly used diagnoses, multiple cardiovascular diagnostic codes were grouped together into a smaller number of categories within the CVD cases. Specifically, various CVD ICD-9 diagnoses were grouped into five categories representing more specific cardiovascular outcomes. After these groups were identified (see Measures section below for more detail on identification of groups), the diagnostic groups were placed in approximate order of the progression of cardiovascular disease from least to least to most severe in terms of their manifestation. For purposes of this study, a diagnosis of hypertension was considered to be the least severe diagnostic category and congestive heart failure the most severe diagnosis.

The number of cardiovascular cases for each diagnostic group is tabulated in Table 3. As noted above, these numbers represent only an individual's most severe cardiovascular diagnosis. For example, if an individual had a diagnosis of both hypertension and coronary artery disease, they would only be counted in the CAD/CVD group and would not be represented in the hypertension sample. That is, each individual can only be represented in one of the cardiovascular groups. For subgroup analyses comparing hypertension diagnoses and the remaining disease categories, an individual's most severe diagnosis was also used.

The focus of this dissertation is on the psychological, medical, and behavioral diagnoses, as described in the Aims and Hypotheses, which occur prior to an individual's most severe cardiovascular diagnosis. Therefore, after an individual's most severe cardiovascular diagnosis was identified, their medical outcome data was right censored. This means that none of the medical records or medical diagnoses documented after the

month of their most severe cardiac event was taken into consideration for this dissertation.

Selection of Controls (Non-Cardiovascular Disease Cases)

After using individuals' most severe cardiovascular diagnosis to identify the CVD study sample, the individuals not included in the study sample were considered non-cardiovascular controls. Non-CVD subjects used in the present study could not include all the non-CVD individuals in the study sample due to limitations in computing power, and given that discrete-time survival coefficients can be estimated without bias when control person-months are randomly subsampled and weighted using the logic of a case-control analysis (394). We identified a representative sample from the total population of potential controls after subtracting the cases (n_{cases}= 50,804) from the overall population, and then weighted non-CVD sample to be comparable to the overall study sample for further analysis. For this study, our ratio of stratified sample to total population was 1 stratified data point representing 122.73 data points (person-months) in the total population. Therefore, within the analyses in this study, controls were weighted by 122.73.

Specifically, to identify this representative sample, the Controls were proportionately stratified based on five demographic variables: deployment status, gender, rank, race, and time in service. Table 1 presents the values for these variables used in the proportional stratification. Proportional stratification means that for each category, the sample was of the same proportion that is found in the population. The unit of analysis used for matching was person-months in the sample. For example, to identify

the stratified sample: if there were 100,000 men (gender), 30-44-years-old (age), Black (race) Soldiers, in service for 3 years (time in service), who had never deployed (deployment status), our Controls would have included a random sample of 814.8 of those 100,000, a 1 to 122.73 ratio, 1 stratified person-month representing 122.73 control person-months or 814.8 stratified person-months representing 100,000 control person-months. A ratio of 1:122.73 was determined by dividing the control sample of person-months (242,844), by the total sample of person-months (29,804,197 person-months). Thus, in the statistical analyses, data for each Control was weighted by 122.73 in order to account for the total population. Based on the population size, none of the stratified categories have less than 123 subjects; therefore, no sample of Controls was less than 1. For example, 1 weighted control represents 122.73 actual Controls.

Table 2. Stratification Demographics for Control Sample

Deployment Status	**Gender**	**Rank**	**Race**	**Time in Service**
Never	Male	E1 – E2	White	1 – 2 years
Current	Female	E3	Black	3 – 4 years
Previously	-	E4	Hispanic	5 – 10 years
-	-	E5 – E9	Asian	> 11 years
-	-	Warrant	Other	-
-	-	Commissioned	-	-

Data were analyzed using a discrete-time survival framework with person-month as the unit of analysis (485), such that each month in the career of a soldier was treated as a separate observational record. To ensure statistical power, a 1 to 586.65 ratio of cardiovascular cases to controls was implemented. Based on the initial number of cardiovascular cases (50,804), which are one person-month time-point, a total of over

29.8 million person-months, out of a total of 37 million person-months in the population, was selected for the control sample.

If an individual had a mental health diagnosis (i.e., PTSD, depression) or a sleep disorder within their first person-month record, they were included in the study sample since the medical data repository (MDR) includes historical data dating back to 1 January 2000 or their start of service date if after 1 January 2000. Additionally, soldiers are medically screened and excluded from military service for chronic medical and mental health diagnoses prior to service, and, therefore, should not have any chronic cardiac conditions upon entering the service. If a soldier left active duty service during the years of 2004-2009, they were not excluded from analyses because no data were available for these individuals after they left the service. The net result was similar to that for individuals with cardiac events (i.e., in those cases, no data after the cardiac event were evaluated due to right censoring).

STUDY MEASURES & SAMPLE SIZES

ICD-9 Codes and Diagnostic Groupings

This study utilized the MDR from HADS to analyze soldiers' medical diagnoses, all recorded as ICD-9-CM codes. Due to the use of ICD-9-CM codes, biopsychosocial risk factors for CVD were limited to risk factors that can be diagnosed (medical or mental health), and excluded biopsychosocial risk factors that cannot be diagnosed, such as diet and physical activity level. As noted above, in order to capture all diagnoses while minimizing the number of variables and including the most diagnoses used, similar diagnostic codes have been grouped.

Definition of Cardiovascular Diagnoses

For the purpose of this study, a cardiovascular disorder was defined as a diagnosis of hypertension, atherosclerosis, angina pectoris, coronary artery disease, cardiomyopathy, peripheral vascular disease, stroke, myocardial infarction, and/or congestive heart failure. These diagnoses were selected based on previous research of cardiovascular disease markers and input from experts in cardiovascular disease pathology and progression. Based on this information and on similarity of diagnosis, individual diagnoses were grouped into five categories of cardiovascular disease progression: hypertension, CAD/CVD, stroke, myocardial infarction, and congestive heart failure. The hypertension category included all types of hypertension in ICD-9-CM. The CAD/CVD category included arteriosclerotic cardiovascular disease markers that are found in both heart and peripheral arteries. The categories of stroke (153), myocardial infarction and congestive heart failure were comprised of ICD-9-CM codes with those labels.

Preliminary analysis of the HADS database indicated that of the 1.6 million soldiers in the HADS dataset, 50,804 had an ICD-9-CM code for any cardiovascular diagnosis (included in the five cardiovascular groups described above). Specifically, at some time point between 1 January 2004 and 31 December 2009, the most severe cardiac event in this time period for each soldier were hypertension (n = 48,363); CAD/CVD (n = 1,269); stroke (n = 520); myocardial infarction (n = 87); and congestive heart failure (n = 565; see Table 3 for a listing of category groupings by specific cardiac diagnosis).

Table 3: Categories of Cardiovascular Disease Progression with ICD-9-CM codes

Severity Hierarchy (least to most severe)	ICD-9 Code	Diagnosis	Cardiac Grouping	# of People in HADS as most severe
5	410	Essential Hypertension	Hypertension	48,363
	401.00	Malignant Hypertension		
	401.10	Benign Hypertension		
	401.90	Hypertension, Unspecified		
	402	Hypertensive Heart Disease		
4	440.00	Atherosclerosis	CAD	1,269
	414.40	Coronary Atherosclerosis		
	413	Angina Pectoris		
	414.00	Coronary Artery Disease		
	425	Cardiomyopathy		
	433.90	Peripheral Vascular Disease		
	429.20	Cardiovascular Disease, Unspecified		
3	433.01	Occlusion and Stenosis of Basilar Artery with Cerebral Infarction	Stroke	520
	433.11	Occlusion and Stenosis of Carotid Artery with Cerebral Infarction		
	433.21	Occlusion and Stenosis of Vertebral Artery with Cerebral Infarction		
	433.31	Occlusion and Stenosis of Multiple/Bilateral Precerebral Arteries with Cerebral Infarction		
	433.81	Occlusion and Stenosis of Other Precerebral Artery with Cerebral Infarction		
	433.91	Occlusion and Stenosis of Unspecified Precerebral Artery with Cerebral Infarction		
	434.01	Cerebral Thrombosis with Cerebral Infarction		
	434.11	Cerebral Embolism with Cerebral Infarction		
	434.91	Cerebral Artery Occlusion with Cerebral Infarction		
2	410.00	Myocardial Infarction, Acute, Anterolateral	Myocardial Infarction	87
	410.10	Myocardial Infarction, Acute, Anterior		
1	428.00	Congestive Heart Failure	CHF	565

Definition of Cardiovascular Medical Risk Factors

The medical risk factors for cardiovascular disease available in the database and examined in this study, which also are associated with PTSD, were: (1) obesity, (2) MetS, and (3) DM2. However, only obesity and DM2 were used in the present analyses because the specific MetS ICD-9 code was not found in the database. As noted above, for the present analyses, hypertension was coded as a cardiovascular disorder and therefore was not treated as a medical risk factor. As for the cardiovascular diagnoses, medical risk factors were defined using ICD-9 codes. For the diagnosis of DM2, both controlled and uncontrolled were included under the DM2 category.

Definition of Cardiovascular Behavioral Risk Factors

The behavioral risk factors for cardiovascular disease examined in this study, which also are associated with PTSD, were (1) tobacco use disorder, and (2) alcohol use disorder. As for cardiovascular disease and medical risk factors, behavioral risk factors were defined using ICD-9-CM codes. For tobacco use disorder, all ICD-9-CM diagnoses under tobacco use disorder were included. For alcohol use, ICD-9-CM diagnoses of alcohol withdrawal, alcohol-induced conditions, alcohol intoxication, alcohol dependence, and alcohol abuse were included. For purposes of this study, sleep disorders were defined by the ICD-9-CM codes under the "specific disorder of sleep of nonorganic origin" and "sleep disturbances" categories. This set of codes for sleep disorders has been utilized in previous STARRS studies utilizing the HADS database.

Table 4: Categories of Medical and Behavioral CVD Risk Factors with ICD-9-CM codes

CARDIOVASCULAR MEDICAL RISK FACTORS		
250.00 250.02	Diabetes Mellitus, II Controlled Diabetes Mellitus, II Uncontrolled	DM2
277.70	Metabolic Syndrome	MetS
278.00	Overweight & Obesity	Obesity
CARDIOVASCULAR BEHAVIORAL RISK FACTORS		
305.1 - 305.13	Tobacco Use Disorder	Tobacco
291.00	Alcohol Withdrawal Delirium	Alcohol
291.10	Alcohol-Induced Persistent Amnestic Disorder	
291.20	Alcohol-Induced Persisting Dementia	
291.30	Alcohol-Induced Psych Disorder with Hallucinations	
291.40	Idiosyncratic Alcohol Intoxication	
291.50	Alcohol-Induced Psych Disorder with Delusions	
291.80	Alcoholic Psychosis Nec	
291.81	Alcohol Withdrawal	
291.82	Alcohol Induced Sleep Disorder	
291.89	Other Specified Alcohol-Induced Mental Disorder	
291.90	Unspecified Alcohol-Induced Mental Disorder	
303.00	Alcohol Intoxication - Unspecified	
303.01	Alcohol Intoxication - Continued	
303.02	Alcohol Intoxication - Episodic	
303.03	Alcohol Intoxication - In Remission	
303.90	Alcohol Dependence Nec/Nos	
303.91	Alcohol Dependence Nec/Nos - Continuous	
303.92	Alcohol Dependence Nec/Nos - Episodic	
303.93	Alcohol Dependence Nec/Nos - In Remission	
305.00	Alcohol Abuse	
305.00	Alcohol Abuse – Unspecified	
305.01	Alcohol Abuse – Continuous	
305.02	Alcohol Abuse – Episodic	
305.03	Alcohol Abuse - In Remission	
307.40	Nonorganic Sleep Disorder, NOS	Sleep Disorders
307.41	Transient Insomnia	
307.42	Persistent Insomnia	
307.43	Transient Hypersomnia	
307.44	Persistent Hypersomnia	
307.45	Circadian Rhythm Sleep Disorder, Nonorganic	
307.46	Sleep Arousal Disorder	
307.47	Sleep Stage Dysfunction, NOS	
307.48	Repetitive Intrusions of Sleep	
307.49	Nonorganic Sleep Disorder, Other	
780.50	Sleep Disorder/Disturbance	
780.51	**Insomnia with Sleep Apnea**	
780.52	Insomnia, Unspecified	
780.53	**Hypersomnia with Sleep Apnea**	
780.54	Hypersomnia, Unspecified	
780.55	Disruptions of 24-Hour Sleep-Wake Cycle	
780.56	Dysfunctions soldier/ Sleep Stages or Arousal	

780.57	**Unspecified Sleep Apnea**	
780.58	Sleep Related Movement Disorder, NOS	
780.59	Insomnia, Other	

Definition of Psychological Risk Factors for Cardiovascular Disease

For the purpose of this study, psychological risk factors for cardiovascular disease were identified as PTSD and depression. PTSD was defined by the ICD-9-CM code for PTSD. Depression was defined by the ICD-9-CM codes for Dysthymic Disorders, Adjustment Disorders with depressed mood, and Depressive Disorders. This set of codes for depression has been utilized in previous STARRS studies utilizing the HADS database.

Table 5: Categories of Psychological CVD Risk Factors with ICD-9-CM codes

INDEPENDENT VARIABLES		
309.81	Post Traumatic Stress Disorder	PTSD
296.20 – 296.29	Major Depressive Disorder, Single Episode	Depression
296.30 – 296.39	Major Depressive Disorder, Recurrent Episode	
296.82	Atypical Depressive Disorder	
296.90	Unspecified Episodic Mood Disorder	
296.99	Other Specified Episodic Mood Disorder	
300.40	Dysthymic Disorder	
300.50	Neurasthenia	
309.00	Adjustment Disorder with Depressed Mood	
309.10	Prolonged Depressive Reaction	
311.00	Depressive Disorder NOS	
313.10	Misery and Unhappiness Disorder	

DATA ANALYSIS

The data were analyzed using a discrete-time survival framework (Willett & Singer, 1993). The unit of analysis is person-months – that is, each month between 1 January 2004 and 31 December 2009 for each soldier is treated as a separate observational record. In this study, 293,648 person-months were selected using five

stratified variables and weighted by 122.73. A total of 29.8 million person-months were used in the analyses. Using the severity hierarchy based on the severity of cardiac events previously described, the person-month in which the most severe cardiac event occurred for each soldier was identified. For each identified CVD case (n_{cases} = 50,804), the cases' previous medical history was evaluated from the cardiac event back in time to either their start of active duty service, if after 1 January 2000, or to 1 January 2000, whichever occurred earlier.

Power Analyses

The sample of cases (i.e., with a CVD diagnosis) comprised 50,804 person-months (using the most severe CVD diagnosis for each soldier), and the sample of controls (i.e., without a CVD diagnosis) comprised 293,648 unweighted (29,855,001 weighted) person-months. Power analyses using G*Power were conducted for PTSD and sleep hypotheses using the *a priori* logistic regression function. A moderate effect size of $p = 0.3$ was assumed for each of the power analysis calculations.

Based on previous research, the prevalence of PTSD for similar military/veteran populations serving in Operation Enduring Freedom and Operation Iraqi Freedom ranged from 12-23% of the population (123; 163; 242). To be conservative, the lower end of this prevalence range was utilized in the power analysis calculations. Previous research has estimated that PTSD is associated with a 1.3- to 8-fold increase in CVD (odds ratio = 1.30; (240). Using these parameters, a sample size of 1,477 was needed to detect the association between PTSD and CVD.

For the sleep analyses, the prevalence rates from previous research for similar populations ranged from 27-55% of the population (177; 302). For the power analysis

calculation, the lower end of the prevalence range for was utilized to be cautious in the power analysis calculations. Previous research also estimated sleep disorders were associated with a 1.57 to 2 times increase in CVD (386). Based on these factors, to assess the association between sleep disorders and CVD a total sample size of 318 (Odds ratio = 1.57) is needed.

Analysis Plan for Each Aim & Hypotheses

The analytic strategy for testing each study aim (1-4) and respective hypotheses is presented in the Results section.

CHAPTER 3: Results

ANALYTIC STRATEGY

In the following Results sections, we will first present the characteristics of the study sample. This includes the demographic characteristics (i.e., sex, race, education, marital status, and age) of (1) the full sample, and subsamples (2) with any CVD diagnoses, (3) only hypertension, and (4) CVD diagnoses other than hypertension (i.e., CAD, myocardial infarction, stroke, and CHF). Additionally, the rates of risk factor variables are presented for the same four study samples.

For the logistic regression analyses, the three CVD categories (All CVD diagnoses, Hypertension Only, and Other CVD diagnoses) were treated as binary dependent variables indicating presence or absence of that diagnosis. For the All CVD diagnosis variable, if an individual had one or more of the listed CVD diagnoses (Table 3), they were coded as 1 ("Yes"), and if they had none of the CVD diagnoses, they were coded as 0 ("No"). In each case, the most severe CVD diagnosis was coded, consistent with the criteria described in the Methods (Table 3).

In the case of the analyses of the diagnosis of Only Hypertension, the variable indicated presence = 1 or absence = 0 of hypertension as the most severe CVD diagnosis. In the case of Other CVD diagnoses, coding represented the presence/absence of a CVD diagnosis other than hypertension (CAD, myocardial infarction, stroke, or CHF) as the most severe CVD diagnosis.

After presenting the sample sizes of each demographic and biopsychosocial risk variable within the CVD categories, this section is organized around the aims and the

associated hypotheses, as defined earlier in the Methods section. For, Aim 1, phi-correlations (φ) were utilized to examine the relationship between each binary independent and covariate variable in this study. For Aims 2, 3, and 4, two additional sets of analyses were conducted to address each of the major hypotheses within each aim. For each major hypothesis (logistic regression including the covariates), we repeated the analyses to examine the effects of our predictors on Hypertension Only and Other CVD diagnoses.

Below is a breakdown of the logistic regression analyses for the CVD vs. Control analyses conducted (excluding the exploratory hypertension vs. other CVD analyses). For each of the logistic regression analyses, the variables were entered simultaneously.

Table 6: Dissertation Analyses for Aims 2, 3, and 4 and their Variables

		IV (s)	DV	Covariates
Aim 2				
	Hypothesis 2a	PTSD	CVD all	Demographics
	Hypothesis 2b	PTSD	CVD all	Demographics, Medical Risk Factors
	Hypothesis 2c	PTSD	CVD all	Demographics, Medical Risk Factors, Behavioral Risk Factors
	Hypothesis 2d	PTSD	CVD all	Demographics, Medical Risk Factors, Behavioral Risk Factors, Depression
Aim 3				
	Hypothesis 3a	Sleep Disorder	CVD all	Demographics
	Hypothesis 3b	Sleep Disorder	CVD all	Demographics, Medical Risk Factors
	Hypothesis 3c	Sleep Disorder	CVD all	Demographics, Medical Risk Factors, Behavioral Risk Factors
	Hypothesis 3d	Sleep Disorder	CVD all	Demographics, Medical Risk Factors, Behavioral Risk Factors, Depression
Aim 4				
	Hypothesis 4a	PTSD, Sleep Disorder	CVD all	Demographics
	Hypothesis 4b	PTSD, Sleep Disorder	CVD all	Demographics, Medical Risk Factors
	Hypothesis 4c	PTSD, Sleep Disorder	CVD all	Demographics, Medical Risk Factors, Behavioral Risk Factors
	Hypothesis 4d	PTSD, Sleep Disorder	CVD all	Demographics, Medical Risk Factors, Behavioral Risk Factors, Depression

For all primary analyses, the medical risk factors (obesity and DM2) were constructed into a binary variable. Medical risk variables are defined by the selected ICD-9 codes listed in Table 4. If an individual had one or both (obesity, DM2) medical risk factors, that variable was coded as 1 (“Yes”), and if the individual had neither medical risk factor, it was coded as 0 (“No”).

The behavioral risk factor variables (tobacco use and alcohol abuse) also were constructed into a binary variable. Each behavioral risk variable was defined by the selected ICD-9 codes listed in Table 4. If an individual had one or both (smoking, alcohol

abuse) behavioral risk factors, the variable was coded as 1 (“Yes”) and if the individual had neither behavioral risk factor, it was coded as 0 (“No”).

The psychological risk factors (PTSD, depression, and sleep disorders) were each constructed into binary variables (presence/absence). Each psychological risk variable was defined by the selected ICD-9 codes listed in Table 5 in the Methods section.

Individuals with a CVD diagnosis were coded as 1 (“Yes”) for medical, behavioral and/or psychological risk factors if they had the risk factor diagnosis in any person-month record prior to their CVD diagnosis. For individuals without a CVD diagnosis, they also were coded as 1 (“Yes”) if they had the risk factor(s) within any person-month record. In both groups, if an individual did not have any of the risk factor (medical, behavioral, psychological) diagnoses in any of their person-month records, these variables were coded as 0 (“No”).

Sample Characteristics.

The total sample consisted of 50,804 person-months that included the individual’s most severe CVD diagnosis and 293,648 unweighted, 29,855,001 weighted person-months without a CVD diagnosis. Individuals included in the study population had an average of 38 person-month records. The CVD cases (n_{cases}=50,804) were right censored after the most severe CVD diagnosis. The number of CVD cases (50,804 person-months) is small compared to the weighted person-month controls, only 0.17% of the total person-months included in the study. Therefore, for the 50,804 CVD cases that were right censored, the loss of person-month data after the most severe diagnosis, had a low risk of altering the analyses and results of this study. The number of CVD cases and weighted controls per year within the HADS database are listed in Table 7 below.

Table 7: Person-Month Rates of most severe CVD cases and weighted controls per year in the HADS database

Year	# of CVD (most severe) Cases	# of Weighted Controls	Total Sample (*n*)
2004	7,223	4,954,848	4,962,071
2005	7,854	4,826,472	4,834,326
2006	8,008	4,833,100	4,841,108
2007	8,265	4,943,311	4,951,576
2008	9,519	5,074,387	5,083,906
2009	9,935	5,172,079	5,182,014
Total	**50,804**	**29,804,197**	**29,855,001**

In the final sample, 86.6% were male, and the majority were white (58.7%), had a high school education (75.9%), and were currently married (56.6%). The complete breakdown of sex, race, education, marital status, and age is found in Table 8. The numbers for each demographic level are listed for the full unweighted sample, and subsamples of the CVD dependent variable (All CVD diagnoses, Hypertension Only, Other CVD diagnoses), and for the unweighted controls (non-CVD diagnoses).

Table 8: Demographics of the Full Sample, All CVD cases, Hypertension Only cases, and Other CVD cases

Characteristic	Characteristic Categories	Total # in Unweighted Full Sample (percent)	# with a CVD Diagnosis	# with Hypertension as their most Severe CVD Diagnosis	# with Other CVD as their most Severe CVD Diagnosis	# Unweighted Controls (without a CVD Diagnosis)
Sex	Female	39,430 (13.4)	5,854	5519	335	33,576
	Male	254,218 (86.6)	44,950	42,844	2,106	209,268
Race	White	172,340 (58.7)	25,722	24,484	1,238	146,618
	Black	70,969 (24.2)	17, 632	16,816	816	53,337
	Asian	11,650 (4.0)	1,749	1,667	82	9,901
	Hispanic	6,093 (2.1)	1,256	4,213	73	4,837
	Other	32,596 (11.1)	4,445	1,183	232	28,151
Education	< High School	35,807 (12.2)	4,674	4,480	194	31,133
	High School	223,007 (75.9)	37,114	35,442	1,672	185,893
	Some College	17,765 (6.0)	4,757	4,450	307	13,008
	College +	17,069 (5.8)	4,359	3,991	268	12,710
Marital Status	Never Married	114,321 (38.9)	12,837	12,330	507	101,484
	Previously Married	13,179 (4.5)	3,046	2,881	165	10,133
	Currently Married	166,148 (56.6)	34,921	33,152	1,769	131,227
Age	>20	39,952 (13.6)	2,336	2,225	111	37,616
	21-24	83,745 (28.5)	8,872	8,620	252	74,873
	25-29	66,975 (22.8)	10,151	9,887	264	56,824
	30-34	41,721 (14.2)	8,758	8,455	303	32,963
	35-39	35,682 (12.2)	10,469	9,952	517	25,213
	40<	25,573 (8.7)	10,218	9,224	994	15,355

For each of the medical, behavioral, and psychological risk factor variables, prevalence was examined in unweighted and weighted control samples, as well as in the total weighted sample, which includes the CVD cases with that risk factor (Table 9). In this study, 293,648 unweighted person-months were selected using five stratified variables and weighted by 122.73 (see Methods Section). A total of 29.8 million person-months (weighted) were used in the analyses. The total weighted sample includes the 29.8 million person-months plus the 50,804 CVD cases, for a total n of 29,804,197 person-months.

Table 9: Unweighted and Weighted* Control Sample (no-CVD) with Risk Factor Variables

CVD Risk Factor Variables	Unweighted: # of Risk Factor Diagnoses in the Control Sample	Weighted: # of Risk Factor Diagnoses, in the Control Sample	Weighted: Total # of Risk Factor Diagnoses in Full Sample** (percentage***)
Obesity	9,614	1,179,924	1,184,533 (3.97)
DM2	509	62,469	63,185.47 (0.21)
MetS	0	0	0
MRF	28,690	1,225,703	3,530,467 (11.83)
Nicotine	20,782	2,550,571	2,557,928 (8.57)
Alcohol	10,333	1,268,167	1,271,173 (4.26)
BRF	28,690	3,521,118	3,530,467 (11.83)
PTSD	3,540	434,463.5	436,723.5 (1.47)
Depression	15,033	1,844,997	1,850,611 (6.2)
Sleep Dx	7,938	974,229.2	978,944.2 (3.28)

*Note: Controls are weighted by 122.73
**Note: Full Sample = Weighted Control with Risk Factor diagnoses + CVD Cases with Risk Factor Diagnoses
***Note: Percent are calculated by dividing the weighted total # of risk factor diagnoses in the full sample** by total number of weighted controls (n = 29,804,197)
Note 1: MRF = number of individuals with presence of either or both medical risk factors (obesity, DM2).
Note 2: BRF = number of individuals with presence of either or both behavioral risk factors (nicotine use, alcohol abuse).

For each of the medical, behavioral, and psychological risk factor variables included in this study, the prevalence was examined for the CVD case groups (All CVD, hypertension Only, and Other CVD diagnoses) (Table 10). Within the All CVD group, a percentage of the risk factor was calculated by dividing by the total number of CVD cases (n_{cases}=50,804).

Table 10: Frequencies of Risk Factor Variables in CVD Case Samples

CVD Risk Factor Variables	# CVD Diagnosis with a Risk Factor Diagnosis (percent*)	# Hypertension as their most Severe CVD Diagnosis with a Risk Factor Diagnosis	# of Other CVD as their most Severe CVD Diagnosis with a Risk Factor Diagnosis
Obesity	4,609 (9.1)	4,362	247
DM2	716 (1.4)	635	81
MRF	5,151 (10.1)	4,850	301
Nicotine	7,357 (14.5)	6,842	515
Alcohol	3,006 (5.9)	2,899	107
BRF	9,349 (18.5)	8,769	580
PTSD	2,260 (4.4)	2,152	108
Depression	5,614 (11)	5,301	313
Sleep Dx	4,715 (9.3)	4,393	322

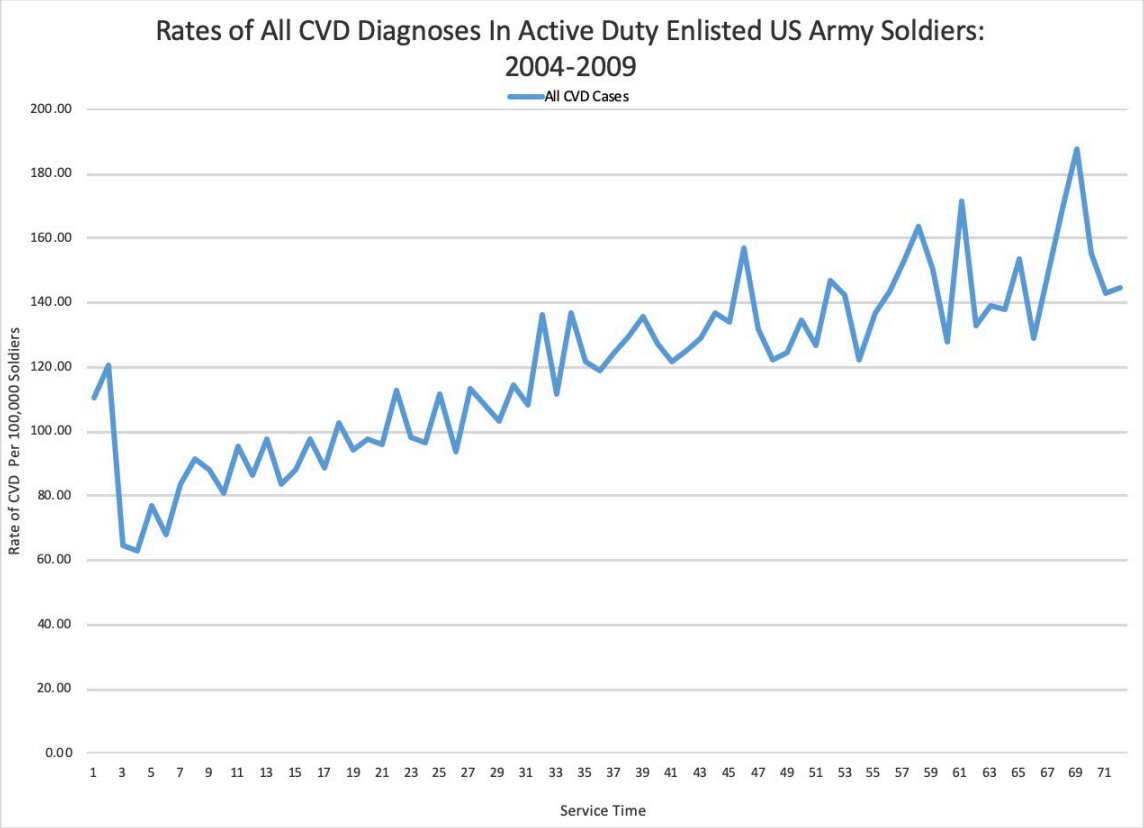
*Note: Percent is divided by total number of individuals with a CVD Diagnosis (n_{cases} = 50,804).
Note 1: MRF = number of individuals with presence of either or both medical risk factors (obesity, DM2).
Note 2: BRF = number of individuals with presence of either or both behavioral risk factors (nicotine use, alcohol abuse).

Initial Analyses

A hazard function graph in Figure 2, plots the rate of CVD per 100 soldiers over time as a function of soldiers' time in service. Since our analyses considered the most severe cardiovascular event that occurred during each soldier's time in service (ranging from diagnosis of hypertension to congestive heart failure), the graph plots that event and the month of service in which they received that diagnosis.

The hazard function plot revealed a positive linear relationship between the rate of CVD diagnoses in the sample and a soldier's time in service. This demonstrates that the longer soldiers are in service, the greater the risk of a CVD diagnosis. There is an increase in rate of CVD between the first and third month in the service, which immediately decreases at month 3 in the service. The rate of CVD then increases gradually. Finally, there is a 3-fold increase in rate of soldiers with CVD diagnoses between the 3rd and 72nd month (6 years) in the service.

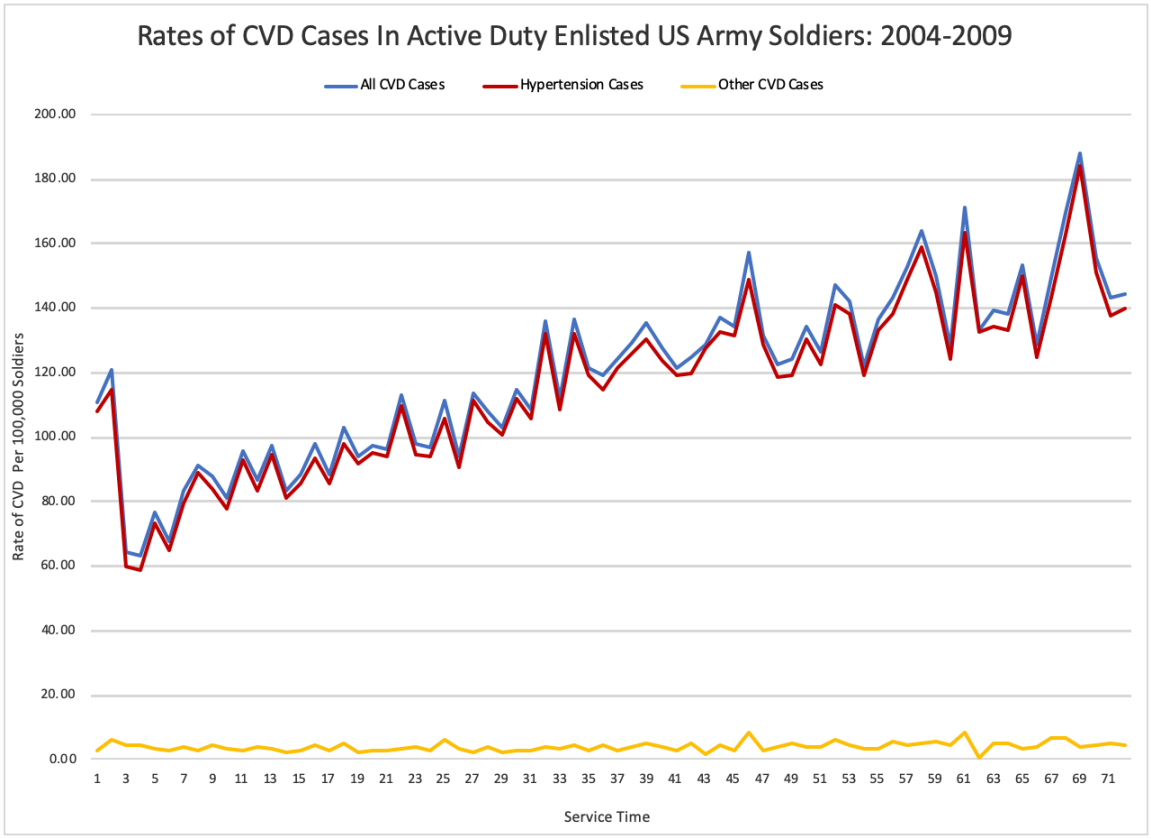
Figure 10: Rate of Most Severe CVD Diagnosis per 100 Soldiers as a Function of Time in Service.



To examine whether the hazard function was the same for rates of Hypertension Only versus Other CVD diagnoses (CAD, MI, Stroke, and CHF), we plotted two hazard

functions in relation to time in service: one for rate of hypertension and one for rate of Other CVD diagnoses. These graphs revealed a similar pattern for Only Hypertension but not for Other CVD diagnoses (see Figure 3). The hazard plots for Only Hypertension and All CVD were similarly positive and linear. However, the hazard plot for Other CVD diagnoses showed a linear plot line with the y-intercept much lower and the slope not nearly as steep. This figure suggests that Other CVD was much less prevalent and that most of the relationship of time in service to All CVD is driven by hypertension rates, which parallel the All CVD rates.

Figure 11: Rate of Most Severe All CVD Diagnosis, Rate of Only Hypertension, and Rate of Other CVD Diagnoses per 100 Soldiers as a Function of Time in Service.



ANALYSES BY STUDY AIM

Aim 1 Analyses

In order to determine the relationships among CVD and medical, behavioral, and psychological risk factors, we examined the relationship between each of pair of variables using Phi-correlations (φ). The results of these analyses are shown in Table 11. Correlations ranged from (0.008 to 0.231), and all were significant ($p < 0.001$) in this large sample.

Table 11: Unweighted Phi Correlations (φ) Among Diagnostic Categories and Risk Factors (n = 293,648)

Variable	1	2	3	4	5	6
1. CVD	1.00	0.01*	0.01*	0.01*	0.01*	0.01*
2. PTSD		1.00	0.23*	0.19*	0.04*	0.12*
3. Depression			1.00	0.09*	0.07*	0.17*
4. Sleep Dx				1.00	0.08*	0.12*
5. MRF					1.00	0.07*
6. BRF						1.00

Note: Phi Correlation (φ) effect sizes = 0.10 small, 0.30 medium, 0.50 large
Note 1: * = $p < 0.001$
Note 2: All variables were binary, coded 0 ("No") or 1 ("Yes")
Note 3: MRF = number of individuals with presence of either or both medical risk factors (obesity, DM2).
Note 4: BRF = number of individuals with presence of either or both behavioral risk factors (nicotine use, alcohol abuse).

Although all of the relationships were significant, most of the relationships had effect sizes smaller in magnitude than Cohen's small effect size (83). For a Phi correlation, Cohen's effect sizes are equal to the value of the Phi correlation. Of note, a few of the relationships between variables had effect sizes in the small to medium range. PTSD was significantly related to, and had a small to medium effect size relationship with depression (φ = 0.23), sleep diagnosis (φ = 0.19), and behavioral risk factors (φ =

0.12). Depression was significantly related to, and had a small to medium effect size relationship with behavioral risk factors (φ = 0.17). Lastly, sleep diagnoses were significantly related to behavioral risk factors (φ = 0.12). It is of particular interest that PTSD, depression, and sleep diagnoses showed a small relationship with behavioral risk factors for CVD (smoking nicotine and alcohol use). In summary, the relationship between each of these study variables demonstrates that each of the variables in the model are all related to varying extents. Relationships among the behavioral and psychological variables were the largest, while others, even though they were significantly related, did not reach the threshold for a small effect size (Cohen's φ = 0.10).

Aim 2 Analyses

For the Aim 2 hypotheses, a series of logistic regression analyses were conducted in which the model for each hypothesis adds an additional covariate to the logistic regression model. All models include the demographic covariates. For example, the model for hypothesis 2a includes PTSD as the independent variable, All CVD as the dependent variable, and the demographic variables as the only covariates. The hypothesis 2b model includes PTSD as the independent variable, All CVD as the dependent variable, and demographic variables and medical risk factors as the covariates. The hypothesis 2c model adds the behavioral risk factors as covariates, and the hypothesis 2d model adds depression as a covariate. Table 12 contains the odds ratios for all of the Aim 2 logistic regression models.

Hypothesis 2a Analyses

Hypothesis 2a. PTSD will be a significant predictor of CVD.

To assess the relationship between PTSD and CVD, a logistic regression was conducted with PTSD diagnosis as the independent variable and CVD diagnosis as the dependent variable. Both variables were binary (1 = "Yes"/ 0 = "No"). Demographic variables (sex, race, marital status, education, and age) were included as covariates in all of the logistic regression models for all of the analyses.

The first logistic regression examined incidence of CVD as a function of PTSD diagnosis. Soldiers with a diagnosis of PTSD were more likely to have a CVD diagnosis, OR = 2.70 (95% CI: 2.59, 2.82; $p < 0.001$), compared to soldiers without a diagnosis of PTSD (see Table 12 below). Thus, if a soldier has a diagnosis of PTSD, they are approximately 2.7 times (medium to large effect size) more likely to develop CVD compared to soldiers without PTSD, after controlling for demographic variables.

Hypothesis 2b Analyses

Hypothesis 2b. PTSD will continue to be an independent/significant predictor of CVD after accounting for medical risk factors for CVD (obesity and type 2 diabetes mellitus).

Next, the logistic regression described in Hypothesis 2a was repeated with the inclusion of the binary medical risk factor variable as a covariate in addition to the demographic variables. As noted in the Methods, obesity and DM2 were included in the medical risk factor variable because of their previous association with PTSD.

The medical risk factor variable was significantly associated with CVD in this logistic regression model at a medium effect size, OR = 1.99 (95% CI: 1.93, 2.05; $p <$

0.001). After controlling for medical risk factors for CVD and demographic variables, PTSD remained significantly related to a diagnosis of CVD at a medium to large effect size, OR = 2.57 (CI: 2.46, 2.68, $p < 0.001$), compared to soldiers without a diagnosis of PTSD. Thus, if a soldier has a diagnosis of PTSD, they are approximately 2.5 times as likely to develop CVD compared to soldiers without PTSD, after controlling for medical risk factors (obesity and DM2).

Hypothesis 2c Analyses

Hypothesis 2c. PTSD will continue to be an independent/significant predictor of CVD after accounting for medical risk factors and behavioral risk factors for CVD (smoking and nicotine use, and alcohol use).

Next, the logistic regression described in Hypothesis 2b was repeated with the inclusion of the binary behavioral risk factor variable as a covariate in addition to the medical risk factor variable and demographic variables. As noted in the Methods, nicotine use and alcohol abuse were included in the behavioral risk factor variable because of their previous association with PTSD.

After controlling for medical and behavioral risk factors, a diagnosis of PTSD was significantly associated with CVD above a medium effect size, OR = 2.31 (95% CI: 2.22, 2.42; $p < 0.001$), compared to not having a diagnosis of PTSD. Additionally, behavioral risk factors were also significant in the logistic regression model at a small effect size, OR = 1.44 (95% CI: 1.41, 1.48; $p < 0.001$). The medical risk factor variable also remained significantly associated with CVD in this logistic regression model at a medium effect size, OR = 1.92 (95% CI: 1.87, 1.98; $p < 0.001$) after behavioral risk factors were added as a covariate to the model.

Hypothesis 2d Analyses

Hypothesis 2d. PTSD will continue to be an independent/significant predictor of CVD after accounting for medical risk factors, behavioral risk factors, and depression.

In addition to medical and behavioral risk factors, depression, which is often co-occurs with PTSD, increases risk for CVD. Therefore, depression also was examined as a variable that may account for part of the relationship between PTSD and CVD. For this purpose, the logistic regression described in Hypothesis 2c was repeated with the inclusion of the binary depression variable as a covariate.

Depression was independently associated with increased the likelihood of CVD at less than a small effect size, OR = 1.39 (95% CI: 1.34, 1.43; $p < 0.001$). Both the medical risk factor variable, OR = 1.89 (95% CI: 1.84, 1.95; $p < 0.001$), and the behavioral risk factor variable, OR = 1.40 (95% CI: 1.37, 1.43; $p < 0.001$) also remained significantly associated with CVD. After entering depression, medical risk factors (obesity and DM2), and behavioral risk factors (nicotine use and alcohol abuse) a diagnosis of PTSD remained positively associated with CVD at a medium effect size, OR = 2.01 (CI: 1.92, 2.10; $p < 0.001$). Thus, if a soldier has a diagnosis of PTSD, they are approximately 2 times more likely to develop CVD compared to soldiers without PTSD, independent of medical risk factors, behavioral risk factors, and depression.

Table 12: Aim 2 Hypotheses Models: IV-PTSD, DV- All CVD (hypertension, CAD, MI, stroke, CHF) (*n*=29,804,197)

	Odds Ratio	95% Wald Confidence Limits	Chi-Sq test – Type 3 analysis	*p* value
2a Model				
- PTSD	2.70	2.59 – 2.82	2100.15	< 0.0001
2b Model				
- PTSD	2.57	2.46 – 2.68	1875.27	< 0.0001
- MRF	1.99	1.93 – 2.05	2102.58	< 0.0001
2c Model				
- PTSD	2.31	2.22 – 2.42	1450.80	< 0.0001
- MRF	1.92	1.87 – 1.98	1903.52	< 0.0001
- BRF	1.44	1.41 – 1.48	955.86	< 0.0001
2d Model				
- PTSD	2.01	1.92 – 2.10	909.66	< 0.0001
- MRF	1.89	1.84 – 1.95	1799.15	< 0.0001
- BRF	1.40	1.37 – 1.43	781.35	< 0.0001
- Depression	1.39	1.34 – 1.43	444.30	< 0.0001

Note: Demographics were included as covariates in all Aim 4 Models.
Note1: For each regression analysis (model), all variables were entered into the model at one time.
Note 2: The Chi-square type 3 analysis tests the null hypothesis for each of the variables individually. The chi-square test indicates if the variable(s) significantly improve the model fit.
Note 3: MRF = number of individuals with presence of either or both medical risk factors (obesity, DM2).
Note 4: BRF = number of individuals with presence of either or both behavioral risk factors (nicotine use, alcohol abuse).

Hypothesis 2d Additional Analyses

Hypertension accounted for 48,363 of the 50,804 CVD cases in this study. Therefore, we determined it was important to identify whether the association of PTSD with CVD was true for hypertension alone or if it was also found in the other, more severe CVD diagnoses (CAD, MI, stroke, CHF) as well.

PTSD & Hypertension Only

For this purpose, the logistic regression described in Hypothesis 2d was repeated with the dependent variable as hypertension (0 "No" / 1 "Yes"). After entering medical risk factors, behavioral risk factors, and depression in the model, PTSD was positively associated with hypertension at a medium effect size, OR = 2.03 (95% CI: 1.94, 2.13; $p <$ 0.001).

Depression was also significant within the logistic regression model for hypertension at a less than small effect size, OR = 1.38 (95% CI: 1.34, 1.42; $p < 0.001$). Both the medical risk factor (OR = 1.89, 95% CI: 1.83, 1.94; $p < 0.001$) and the behavioral risk factor variables (OR = 1.37, 95% CI: 1.34, 1.41; $p < 0.001$) remained significantly associated with CVD in this logistic regression model at a small to medium and less than small effect size respectively.

PTSD & Other CVD Diagnoses

Next, the logistic regression described in Hypothesis 2d was repeated for Other CVD diagnoses (0 "No" / 1 "Yes"). After entering the medical risk factor variable, the behavioral risk factor variable, and depression into the model, PTSD was still positively associated with Other CVD diagnoses at a small effect size, OR = 1.68 (95% CI: 1.37, 2.06; $p < 0.001$).

Depression was also significant in this logistic regression model at a small effect size, OR = 1.46 (95% CI: 1.28, 1.66; $p < 0.001$). Both the medical risk factor (OR = 2.00, 95% CI: 1.76, 2.26; $p < 0.001$) and behavioral risk factor variables (OR = 1.93, 95% CI:

1.75, 2.13; $p < 0.001$) remained significantly associated with CVD in this logistic regression model at medium effect sizes.

Table 13: Hypothesis 2d Models: PTSD Associations with the 3 different CVD dependent variables (All CVD, Hypertension Only, Other CVD) (n=29,804,197)

	Odds Ratio	95% Wald Confidence Limits	Chi-Sq test – Type 3 analysis	*p* value
2d Model (CVD all)				
- PTSD	2.01	1.92 – 2.10	909.66	< 0.0001
- MRF	1.89	1.84 – 1.95	1799.15	< 0.0001
- BRF	1.40	1.37 – 1.43	781.35	< 0.0001
- Depression	1.39	1.34 – 1.43	444.30	< 0.0001
2d Model (Hypertension)				
- PTSD	2.03	1.94 – 2.13	891.98	< 0.0001
- MRF	1.89	1.83 – 1.94	1681.30	< 0.0001
- BRF	1.37	1.34 – 1.41	685.35	< 0.0001
- Depression	1.38	1.34 – 1.42	411.74	< 0.0001
2d Model (Other CVD)				
- PTSD	1.68	1.37 – 2.06	24.60	< 0.0001
- MRF	2.00	1.76 – 2.26	120.62	< 0.0001
- BRF	1.93	1.75 – 2.13	175.17	< 0.0001
- Depression	1.46	1.28 – 1.66	32.94	< 0.0001

Note: All CVD = hypertension, CAD, MI, stroke, and CHF; Hypertension Only = hypertension; Other CVD = CAD, MI, stroke, and CHF
Note 1: Demographics were included as covariates in all Aim 2 Models.
Note 2: For each regression analysis (model), all variables were entered into the model at one time.
Note 3: The Chi-square type 3 analysis tests the null hypothesis for each of the variables individually. The chi-square test indicates if the variable(s) significantly improve the model fit.
Note 4: MRF = presence of either or both medical risk factors (obesity, DM2).
Note 5: BRF = presence of either or both behavioral risk factors (nicotine use, alcohol abuse).

Summary of Aim 2 Analyses

PTSD was a significant predictor of CVD in each of the logistic regression analyses presented in Aim 2. Specifically, in the series of logistic regression models with CVD All as the dependent variable, PTSD remained a significant predictor of all

diagnoses of CVD when covariates were added to the model. While PTSD remained significant in all the models, the odds ratio decreased from a medium-large to small effect size as more covariates were entered into the logistic regression model (Table 12). The range of odds ratios of PTSD in the model was from 2.70 (2a model) to 2.01 (2d model). In the series of logistic regression models, each term entered into the model as a covariate added significantly to the models' fit. Overall, PTSD remained a significant predictor of all CVD diagnoses, as well as medical risk factors, behavioral risk factors, and depression with small to medium effect sizes.

In the additional 2d models, Hypertension Only and Other CVD diagnoses were examined separately. Results indicated that the odds ratio for PTSD remained approximately the same for Hypertension Only (OR = 2.03, 95% CI: 1.92, 2.10; $p <$ 0.001 and for All CVD (OR = 2.01, 95% CI: 1.92, 2.10; $p < 0.001$). However, odds ratios decreased to a medium effect size for the Other CVD diagnoses (OR = 1.67, 95% CI: 1.37, 2.06; $p < 0.001$), as compared to the models in which all CVD diagnoses were examined together. Additionally, the odds ratios for the covariates (medical risk factors, behavioral risk factors, and depression) remained approximately the same when hypertension was examined separately. For the Other CVD diagnoses (CAD, MI, stroke, CHF), behavioral risk factors had larger odds ratios (medium effect sizes) as compared to the model in which all CVD diagnoses were examined together (less than small effect sizes). These results indicate that for hypertension, PTSD remains the predictor with the largest effect size.

Aim 3 Analyses

Similar to the Aim 2 analytic strategy, for the Aim 3 hypotheses examining effects of sleep disorders, a series of logistic regression analyses were conducted, with each hypothesis adding a covariate to the logistic regression model. Specifically, hypothesis 3a only included sleep diagnoses as the independent variable, All CVD as the dependent variable, and the demographics as the only covariate. The hypothesis 3b model includes sleep diagnoses as the independent variable, All CVD as the dependent variable, and demographics and medical risk factors as the covariates. The hypothesis 3c model adds the behavioral risk factors to the covariates, and the hypothesis 3d model adds depression to the covariates in the 3c model. Following the written analyses for hypotheses 3a through 3d, Table 14 contains the odds ratios for each of the variables within the Aim 3 logistic regression models.

Hypothesis 3a Analyses

Hypothesis 3a. Sleep disorders will be a significant predictor of CVD.

To assess the relationship between a sleep disorder diagnosis and CVD diagnoses, a logistic regression was conducted with sleep disorders as the independent variable and CVD as the dependent variable. Both variables were binary (1 = "Yes"/ 0 = "No"). Demographic variables (sex, race, marriage status, education, and age) were included as covariates in the logistic regression models for all of the analyses.

The first logistic regression examined incidence of CVD as a function of a sleep disorder diagnosis. This analysis revealed that diagnosis of a sleep disorder was

significantly and positively associated with all CVD diagnoses at a medium effect size, OR = 2.08 (95% CI: 2.01, 2.14; $p < 0.001$).

Hypothesis 3b Analyses

Hypothesis 3b. Sleep disorders will continue to be an independent/significant predictor of CVD after accounting for medical risk factors for CVD (obesity and DM2).

Next, the binary medical risk factor variable was added to the logistic regression as a covariate. The medical risk factor variable was significantly associated with CVD at a medium effect size, OR = 1.92 (95% CI: 1.86, 1.97; $p < 0.001$). Controlling for medical risk factors for CVD and demographic variables, sleep disorder diagnosis remained significantly related to CVD at a medium effect size, OR = 1.93 (95% CI: 1.87, 1.99; $p < 0.001$).

Hypothesis 3c Analyses

Hypothesis 3c. Sleep disorders will continue to be an independent/significant predictor of CVD after accounting for medical risk factors and behavioral risk factors for CVD (smoking and nicotine use, and alcohol use).

Next, behavioral risk factors were added into the model as additional covariates. After controlling for medical and behavioral risk factors, a diagnosis of a sleep disorder was significantly associated with CVD at a small to medium effect size, OR = 1.81 (95% CI: 1.76, 1.87; $p < 0.001$), compared to soldiers without a sleep disorder diagnosis.

The medical risk factor variable remained significantly associated with CVD at a small to medium effect size, OR = 1.86 (95% CI: 1.81, 1.92; $p < 0.001$). This relationship remained significant after behavioral risk factors were added as covariates to the model.

Additionally, behavioral risk factors were also significant within the logistic regression model at a small effect size, OR = 1.45 (95% CI: 1.41, 1.48; $p < 0.001$).

Hypothesis 3d Analyses

Hypothesis 3d. Sleep disorders will continue to be a significant independent predictor of CVD after accounting for medical risk factors, behavioral risk factors, and depression.

The logistic regression described in Hypothesis 3c was repeated with the inclusion of the binary depression variable as a covariate. After controlling for medical risk factors, behavioral risk factors and depression, a sleep disorder diagnosis remained positively associated with CVD diagnosis at a small effect size, OR = 1.69 (95% CI: 1.63, 1.74; $p < 0.001$), compared to soldiers without a sleep disorder diagnosis.

Depression was significant in the logistic regression model at a small effect size, OR = 1.42 (95% CI: 1.37, 1.46; $p < 0.001$). Both the medical risk factor variable (OR = 1.83, 95% CI: 1.78, 1.89; $p < 0.001$) and behavioral risk factor variable (OR = 1.39, 95% CI: 1.36, 1.43; $p < 0.001$) remained significantly associated with CVD with a small to medium and less than small effect size respectively.

Table 14: Aim 3 Hypotheses Models: IV-PTSD, DV- All CVD (hypertension, CAD, MI, stroke, CHF) (*n*=29,804,197)

	Odds Ratio	95% Wald Confidence Limits	Chi-Sq test – Type 3 analysis	p value
3a Model				
- Sleep Disorder	2.08	2.01 – 2.14	2189.18	< 0.0001
3b Model				
- Sleep Disorder	1.93	1.87 – 1.99	1750.29	< 0.0001
- MRF	1.92	1.86 – 1.97	1859.97	< 0.0001
3c Model				
- Sleep Disorder	1.81	1.76 – 1.87	1408.17	< 0.0001
- MRF	1.86	1.81 – 1.92	1686.79	< 0.0001
- BRF	1.45	1.41 – 1.48	974.29	< 0.0001
3d Model				
- Sleep Disorder	1.69	1.62 – 1.74	1029.90	< 0.0001
- MRF	1.83	1.78 – 1.89	1606.99	< 0.0001
- BRF	1.39	1.36 – 1.43	769.69	< 0.0001
- Depression	1.42	1.37 – 1.46	531.13	< 0.0001

Note: Demographics were included as covariates in all Aim 4 Models.
Note 1: For each regression analysis (model), all variables were entered into the model at one time.
Note 2: The Chi-square type 3 analysis tests the null hypothesis for each of the variables individually. The chi-square test indicates if the variable(s) significantly improve the model fit.
Note 3: MRF = presence of either or both medical risk factors (obesity, DM2).
Note 4: BRF = presence of either or both behavioral risk factors (nicotine use, alcohol abuse).

Hypothesis 3d Additional Analyses

Similar to hypothesis 2d, due to the majority of CVD cases identified as hypertension as the most severe CVD diagnosis (48,363 (95%) out of 50,804), we determined it was important to examine if the association of sleep disorder diagnoses with CVD was present for hypertension alone and/or if the association was evident for the other, more severe CVD diagnoses (CAD, MI, stroke, CHF) as well.

Sleep Disorder & Hypertension Only

For this purpose, the logistic regression described in Hypothesis 3d was repeated with the binary dependent variable of Hypertension Only (0 = "No" / 1 = "Yes"). After controlling for medical risk factors, behavioral risk factors, and depression, a sleep disorder diagnosis was positively associated with CVD diagnosis with a medium effect size, OR = 1.68 (95% CI: 1.62, 1.73; $p < 0.001$).

Depression was significant in the logistic regression model at a less than small effect size, OR = 1.42 (95% CI: 1.37, 1.46; $p < 0.001$). Both medical risk factor variable (OR = 1.83, 95% CI: 1.77, 1.89; $p < 0.001$) and behavioral risk factor variables (OR = 1.37, 95% CI: 1.34, 1.40; $p < 0.001$) remained significantly associated with CVD in this logistic regression model at a small-medium and less than small effect size respectively.

Sleep Disorders & Other CVD Diagnoses

Finally, the logistic regression described in Hypothesis 3d was repeated with the dependent variable as Other CVD diagnoses (0 = "No" / 1 = "Yes"). After controlling for medical risk factors, behavioral risk factors, and depression, a sleep disorder diagnosis was positively associated with Other CVD diagnoses at a medium to large effect size, OR = 1.82 (95% CI: 1.606, 2.062; $p < 0.001$), compared to soldiers without a diagnosis of PTSD.

Depression was significant within the logistic regression model at a small effect size, OR = 1.40 (95% CI: 1.24, 1.59; $p < 0.001$). Both the medical risk factor variable (OR = 1.89, 95% CI: 1.61, 2.14; $p < 0.001$) and the behavioral risk factor variables (OR =

1.89, 95% CI: 1.71, 2.08; $p < 0.001$) remained significantly associated with CVD in this logistic regression model at medium effect sizes.

Table 15: Hypothesis 3d Models: Sleep Disorder Associations with the 3 different CVD dependent variables (All CVD, Hypertension Only, Other CVD) (n=29,804,197)

	Odds Ratio	95% Wald Confidence Limits	Chi-Sq test – Type 3 analysis	p value
3d Model (All CVD)				
- Sleep Disorder	1.69	1.62 – 1.74	1029.90	< 0.0001
- MRF	1.83	1.78 – 1.89	1606.99	< 0.0001
- BRF	1.39	1.36 – 1.43	769.69	< 0.0001
- Depression	1.42	1.37 – 1.46	531.13	< 0.0001
3d Model (Hypertension)				
- Sleep Disorder	1.68	1.62 – 1.73	88.22	< 0.0001
- MRF	1.83	1.77 – 1.89	101.67	< 0.0001
- BRF	1.37	1.34 – 1.40	162.75	< 0.0001
- Depression	1.42	1.37 – 1.46	27.40	< 0.0001
3d Model (Other CVD)				
- Sleep Disorder	1.82	1.61 – 2.06	943.11	< 0.0001
- MRF	1.90	1.67 – 2.14	1507.19	< 0.0001
- BRF	1.89	1.71 – 2.08	653.20	< 0.0001
- Depression	1.40	1.24 – 1.59	503.87	< 0.0001

Note: All CVD = hypertension, CAD, MI, stroke, and CHF; Hypertension Only = hypertension; Other CVD = CAD, MI, stroke, and CHF
Note 1: Demographics were included as covariates in all Aim 4 Models.
Note 2: For regression analyses, all variables were entered into the model at the same time.
Note 3: The Chi-square type 3 analysis tests the null hypothesis for each of the variables individually. The chi-square test indicates if the variable(s) significantly improve the model fit.
Note 4: MRF = presence of either or both medical risk factors (obesity, DM2).
Note 5: BRF = presence of either or both behavioral risk factors (nicotine use, alcohol abuse).

Summary of Aim 3 Analyses

Sleep disorders were a significant predictor of CVD in each of the logistic regression analyses presented in Aim 3. Specifically, in the series of logistic regression

models with All CVD as the dependent variable, when covariates were added to the model, a PTSD diagnosis remained a significant predictor of all CVD diagnoses. It is important to note that although sleep disorders remained significant, for the All CVD outcome, the odds ratio for sleep disorders decreased from a medium to a small effect size as covariates were entered into the logistic regression model (Table 13). The range of odds ratios of sleep disorders in the regression models was 2.03 (3a model) to 1.69 (3d model). At each level of the regression model, covariates added had an odds ratio above 1 and based on the Chi-square type 3 analyses, each covariate significantly added to the model fit.

In the 3d models examining hypertension separately from the other CVD diagnoses, the odds ratio for sleep disorders remained approximately the same for Hypertension Only at a small effect size (OR = 1.69, 95% CI: 1.62, 1.73; $p < 0.001$) compared to All CVD (OR = 1.68, 95% CI: 1.62, 1.74; $p < 0.001$). However, the sleep disorder diagnoses association with Other CVD diagnoses had a small to medium effect size (OR = 1.82, 95% CI: 1.61, 2.06; $p < 0.001$) in these models. Additionally, the odds ratios for the covariates (medical risk factors, behavioral risk factors, and depression) remained approximately the same as in the models that examined All CVD diagnoses. For the Other CVD diagnoses (CAD, MI, stroke, CHF), medical and behavioral risk factors, and sleep disorders had medium effect sizes, while depression had a small effect size.

Aim 4 Analyses

As with Aims 2 and 3, Aim 4 hypotheses were tested with a series of logistic regression analyses in which other covariates were added to the logistic regression model

for each hypothesis. Hypothesis 4a analyses included PTSD and Sleep Diagnoses as the two independent variables, CVD All as the dependent variable, and the demographic variables as the covariates. The hypothesis 4b model includes PTSD and Sleep Diagnoses as the independent variables, CVD All as the dependent variable, and demographic variables and medical risk factor variables as the covariates. The hypothesis 4c model added the behavioral risk factors as a covariate, and the hypothesis 4d model added depression to the covariates. Table 16 contains the odds ratios for each of the variables in the Aim 4 logistic regression models.

Hypothesis 4a Analyses

Hypothesis 4a. PTSD and sleep disorders together will be a stronger predictor of CVD compared to only a diagnosis of PTSD, only a diagnosis of a sleep disorder, and neither a diagnosis of PTSD nor a sleep disorder.

To assess the relationships between presence of a PTSD diagnosis and a sleep disorder diagnosis with CVD, a logistic regression was conducted with both PTSD and sleep disorders as the independent variables and CVD as the dependent variable. All variables were binary (1 = "Yes"/ 0 = "No"). Demographic variables (sex, race, marriage status, education, and age) were included as covariates in the logistic regression models for all of the analyses.

The first logistic regression examined CVD with both PTSD and sleep disorder diagnoses in the model, with each diagnosis entered separately. This analysis again revealed that a PTSD diagnosis was associated with all CVD diagnoses at a medium effect size, OR = 2.18 (95% CI: 2.09, 2.28; $p < 0.001$), and that sleep disorder diagnoses

were significantly related to all CVD diagnoses at a small to medium effect size, OR = 1.84 (95% CI: 1.78, 1.89; $p < 0.001$).

Hypothesis 4b Analyses

Hypothesis 4b. Comorbid PTSD and sleep disorders will continue to be a significant predictor of CVD after accounting for medical risk factors for CVD (obesity and type 2 diabetes mellitus).

Next, the logistic regression described in Hypothesis 4a (relationship of sleep disorder and PTSD diagnoses to CVD diagnoses) was repeated with the inclusion of the binary medical risk factor variable entered into the model in addition to the demographic variables.

The medical risk factor variable was again significantly associated with CVD at a small to medium effect size, OR = 1.90 (95% CI: 1.84, 1.95; $p < 0.001$). After controlling for medical risk factors for CVD and demographics, a PTSD diagnosis also remained significantly related to a diagnosis of CVD at a medium effect size, OR = 2.14 (95% CI: 2.04, 2.23; $p < 0.001$), and a sleep disorder diagnosis remained significantly related to a diagnosis of CVD at a small to medium effect size, OR = 1.72 (95% CI: 1.67, 1.778; $p < 0.001$).

Hypothesis 4c Analyses

Hypothesis 4c. Comorbid PTSD and sleep disorder will continue to be a significant predictor of CVD after accounting for medical risk factors and behavioral risk factors for CVD (smoking and nicotine use, and alcohol use).

Similar to hypothesis 4b, the behavioral risk factor variables were added to the logistic regression model in addition to the previously described variables in Hypothesis 4b. Specifically, the relationship between PTSD and sleep disorder diagnoses were examined with both medical risk factors for CVD and behavioral risk factors in the model together with sleep disorders and PTSD.

With both medical and behavioral risk factors entered into the model, a PTSD diagnosis remained significantly related to a diagnosis of CVD at a medium effect size, with an OR = 1.98 (95% CI: 1.89, 2.07; $p < 0.001$), after controlling for a sleep disorder diagnosis, medical risk factors, and behavioral risk factors. Additionally, a diagnosis of a sleep disorder was significantly associated with CVD at a small effect size, OR = 1.65 (95% CI: 1.59, 1.69; $p < 0.001$).

The medical risk factor variable remained significantly associated with CVD in this logistic regression model at a small to medium effect size, OR = 1.85 (95% CI: 1.80, 1.90; $p < 0.001$). This relationship remained significant after behavioral risk factors were added as covariates to the model. Additionally, behavioral risk factors were also significant within the logistic regression model at a less than small effect size, OR = 1.40 (95% CI: 1.36, 1.43; $p < 0.001$).

Hypothesis 4d Analyses

Hypothesis 4d. Comorbid PTSD and sleep disorders will continue to be a significant predictor of CVD after accounting for medical risk factors, behavioral risk factors, and depression.

The logistic regression described in Hypothesis 4c was repeated with the inclusion of the binary depression variable added as a covariate. After controlling for

medical risk factors, behavioral risk factors and depression, a PTSD diagnosis remained significantly related to a diagnosis of CVD at a small to medium effect size, OR = 1.79 (95% CI: 1.71, 1.87; $p < 0.001$). Additionally, with these same covariates, a sleep disorder diagnosis was significantly associated with CVD diagnosis at a small effect size, OR = 1.58 (95% CI: 1.53, 1.63; $p < 0.001$).

Depression was significant within the logistic regression model at a less than a small effect size, OR = 1.30 (95% CI: 1.26, 1.34; $p < 0.001$). Both the medical risk factor variable (OR = 1.83, 95% CI: 1.78, 1.89; $p < 0.001$) and behavioral risk factor variables (OR = 1.36, CI: 1.33, 1.40; $p < 0.001$) remained significantly associated with CVD in this logistic regression model at a small-medium and less than small effect sizes respectively.

Table 16: Aim 4 Hypotheses Models: IV-PTSD, DV- All CVD (hypertension, CAD, MI, stroke, CHF) (*n*=29,804,197)

	Odds Ratio	95% Wald Confidence Limits	Chi-Sq test – Type 3 analysis	p value
4a Model				
- PTSD	2.18	2.09 – 2.28	1183.71	< 0.0001
- Sleep Disorder	1.84	1.78 – 1.89	1388.47	< 0.0001
4b Model				
- PTSD	2.14	2.04 – 2.23	1125.19	< 0.0001
- Sleep Disorder	1.72	1.69 – 1.78	1106.11	< 0.0001
- MRF	1.90	1.84 – 1.95	1803.18	< 0.0001
4c Model				
- PTSD	1.98	1.89 – 2.07	895.08	< 0.0001
- Sleep Disorder	1.65	1.59 – 1.70	918.33	< 0.0001
- MRF	1.89	1.80 – 1.90	1675.37	< 0.0001
- BRF	1.40	1.36 – 1.43	781.73	< 0.0001
4d Model				
- PTSD	1.79	1.71 – 1.87	609.34	< 0.0001
- Sleep Disorder	1.58	1.53 – 1.63	749.12	< 0.0001
- MRF	1.83	1.78 – 1.89	1598.81	< 0.0001
- BRF	1.36	1.33 – 1.40	665.07	< 0.0001
- Depression	1.30	1.26 – 1.34	287.41	< 0.0001

Note: Demographics were included as covariates in all Aim 4 Models.
Note 1: For each regression analysis (model), all variables were entered into the model at one time.
Note 2: The Chi-square type 3 analysis tests the null hypothesis for each of the variables individually. The chi-square test indicates if the variable(s) significantly improve the model fit.
Note 3: MRF = number of individuals with presence of either or both medical risk factors (obesity, DM2).
Note 4: BRF = number of individuals with presence of either or both behavioral risk factors (nicotine use, alcohol abuse).

In sum, PTSD and sleep disorder diagnoses were significant predictors of CVD diagnoses in each of the logistic regression analyses conducted for Aim 4. Specifically, in the series of logistic regression models with CVD All as the dependent variable, when covariates were added to the model PTSD and sleep disorder diagnoses both remained significant predictors of all CVD diagnoses studied in this dissertation. It is important to

note that although PTSD remained significant, the odds ratio decreased from a medium to a small to medium effect size as more covariates were entered into the logistic regression model (Table 16). The range of odds ratios of PTSD in the regression models was 2.18 (4a model) to 1.79 (4d model).

Additionally, sleep disorders also remained significant with the odds ratio remaining fairly consistent (with a decrease from a small to medium effect size to a small effect size) as more covariates were entered into the logistic regression model (Table 16). The range of odds ratios of sleep disorders in the regression models was 1.84 (4a model) to 1.58 (4d model). At each level of the regression model, covariates added had an odds ratio above 1 and based on the Chi-square type 3 analyses, each covariate significantly added to the models' fit.

In the final model with all of the covariates, medical risk factor diagnoses (OR = 1.83) and PTSD diagnoses (1.79) had small to medium effect sizes, whereas sleep disorder diagnoses (1.58), behavioral risk factor diagnoses (1.36), and depression diagnoses (1.30) had less than small to small effect sizes. It is important to note that the odds ratios for medical risk factors remained consistent with a range of 1.83 (4d) to 1.90 (4b).

Hypothesis 4d - Additive PTSD/Sleep Disorder Analyses

Upon conducting the Aim 4 analyses that included both PTSD & sleep disorder diagnoses as independent variables, it became apparent that these analyses did not assess for individuals with both PTSD and sleep disorder diagnoses. Although regression analyses for Aim 4 included PTSD and sleep disorder diagnoses as independent variables, they did not delineate between those who had only a PTSD diagnosis, only a

sleep disorder diagnosis, both PTSD and a sleep disorder diagnoses, and neither PTSD or sleep disorder diagnoses. In addition, they do not indicate whether the presence of both diagnoses is associated with greater risk than presence of each diagnosis alone. Therefore, we created a PTSD-Sleep variable using dummy coding to compare each of the first three groups (PTSD Only, Sleep Disorder Only, Both PTSD and Sleep) to the reference group (neither PTSD nor a sleep disorder). We then included this variable as the independent variable in the model used in hypothesis 4d, replacing PTSD and Sleep Disorder.

In this new additive model, the comparisons of each of the 3 PTSD-Sleep groups with the reference group were entered instead of the PTSD and sleep disorder binary independent variables. Additionally, as in all previous models, demographic variables, medical risk factors, behavioral risk factors, and depression were entered as covariates simultaneously with the 4-category PTSD-Sleep variable. Results indicated that a diagnosis of PTSD Only was positively associated with All CVD diagnoses at a medium effect size (OR = 1.95, 95% CI: 1.84, 2.07; $p < 0.001$ (see Table 17 below). Sleep Disorder Only was positively associated with a CVD diagnosis at a small effect size (OR = 1.63, 95% CI: 1.57, 1.69; $p < 0.001$). Finally, Both PTSD and Sleep Disorder was positively associated with a CVD diagnosis at a medium to large effect size (OR = 2.55, 95% CI: 2.39, 2.73; $p < 0.001$).

Depression remained significant within the logistic regression model at a less than small effect size, OR = 1.30 (95% CI: 1.26, 1.34; $p < 0.001$). The medical risk factor variable (OR = 1.83, 95% CI: 1.77, 1.88; $p < 0.001$) and behavioral risk factor variables (OR = 1.36, 95% CI: 1.33, 1.39; $p < 0.001$) also remained significantly associated with

all CVD diagnoses in this logistic regression model at small to medium and less than small effect sizes respectively.

Hypothesis 4d – Additive PTSD/Sleep Disorders & Hypertension Only

For this purpose, the logistic regression described in the previous section was repeated with the dependent variable as hypertension (yes/no). Results indicated that after controlling for medical risk factors, behavioral risk factors, and depression, diagnosis of PTSD Only was positively associated with Hypertension Only at a medium effect size (OR = 1.97, 95% CI: 1.86, 2.09; $p < 0.001$), compared to soldiers without either PTSD or sleep disorder diagnoses. A diagnosis of Sleep Disorder Only was positively associated with Hypertension Only at a small effect size (OR = 1.62, 95% CI: 1.56, 1.67; $p < 0.001$), compared to soldiers without either PTSD or sleep disorder diagnoses. Finally, Both PTSD and Sleep Disorder was positively associated with Hypertension Only at a medium to large effect size (OR = 2.57, 95% CI: 2.40, 2.75; $p < 0.001$), compared to soldiers without either PTSD or sleep disorder diagnoses.

Depression was also significant within the logistic regression model at a less than small effect size, OR = 1.30 (95% CI: 1.26, 1.34; $p < 0.001$). Both the medical risk factor variable (OR = 1.82, 95% CI: 1.77, 1.88; $p < 0.001$) and behavioral risk factor variables (OR = 1.34, 95% CI: 1.31, 1.37; $p < 0.001$) remained significantly associated with Hypertension Only in this logistic regression model at a small to medium and less than small effect sizes respectively.

Hypothesis 4d – PTSD & Other CVD Diagnoses

For this purpose, the logistic regressions described in the previous section were repeated with the dependent variable as Other CVD diagnoses (yes/no). Results indicated that after controlling for medical risk factors, behavioral risk factors, and depression, PTSD Only was positively associated with Other CVD diagnoses at a small effect size, OR = 1.59 (95% CI: 1.21, 2.10; $p < 0.001$). Sleep Disorder Only was positively associated with Other CVD diagnoses at a small to medium effect size, OR=1.80 (95% CI: 1.57, 2.05; $p < 0.001$). Lastly, Both PTSD and Sleep Disorder was positively associated with Other CVD diagnoses at a medium effect size, OR = 2.33 (95% CI: 1.75, 3.10; $p < 0.001$).

Depression was significant within the logistic regression model at a less than small effect size, OR = 1.33 (95% CI: 1.17, 1.52; $p < 0.001$). Both medical risk factor variable (OR = 1.88, 95% CI: 1.67, 2.14; $p < 0.001$) and behavioral risk factor variables (OR = 1.86, 95% CI: 1.69, 2.06; $p < 0.001$) remained significantly associated with Other CVD diagnoses in this logistic regression model at small to medium effect sizes.

Table 17: Comparisons of 4d Full Model (all covariates included) for the 3 different CVD dependent variables (All CVD, Hypertension Only, Other CVD)

	Odds Ratio	95% Wald Confidence Limits	Chi-Sq test – Type 3 analysis	*p* value
A-4d Model (All CVD)				
- *Only PTSD*	*1.95*	1.83 – 2.07	523.77	< 0.0001
- *Only Sleep Disorder*	*1.63*	1.57 – 1.69	751.72	< 0.0001
- ***Both PTSD & Sleep Dx***	***2.55***	2.39 – 2.73	747.26	< 0.0001
- MRF	1.83	1.77 – 1.88	1583.63	< 0.0001
- BRF	1.36	1.33 – 1.39	669.59	< 0.0001
- Depression	1.30	1.26 – 1.34	281.93	< 0.0001
A-4d Model (Hypertension)				
- *Only PTSD*	*1.97*	1.86 – 2.09	517.46	< 0.0001
- *Only Sleep Disorder*	*1.62*	1.56 – 1.67	679.11	< 0.0001
- ***Both PTSD & Sleep Dx***	***2.57***	2.40 – 2.75	715.51	< 0.0001
- MRF	1.82	1.77 – 1.88	1484.86	< 0.0001
- BRF	1.34	1.31 – 1.37	553.61	< 0.0001
- Depression	1.30	1.26 – 1.34	263.18	< 0.0001
A-4d Model (Other CVD)				
- *Only PTSD*	*1.59*	1.21 – 2.10	11.15	0.0008
- *Only Sleep Disorder*	*1.80*	1.57 – 2.05	74.08	< 0.0001
- ***Both PTSD & Sleep Dx***	***2.33***	1.75 – 3.10	33.58	
- MRF	1.88	1.69 – 2.14	100.57	< 0.0001
- BRF	1.86	1.69 – 2.06	155.17	< 0.0001
- Depression	1.33	1.17 – 1.52	18.66	< 0.0001

Note: Demographics were included as covariates in all Aim 4 Models.
Note 1: For each regression analysis (model), all variables were entered into the model at one time.
Note 2: The Chi-square type 3 analysis tests the null hypothesis for each of the variables individually. The chi-square test indicates if the variable(s) significantly improve the model fit.
Note 3: All CVD = hypertension, CAD, MI, stroke, and CHF; Hypertension Only = hypertension; Other CVD = CAD, MI, stroke, and CHF
Note 4: MRF = number of individuals with presence of either or both medical risk factors (obesity, DM2).
Note 5: BRF = number of individuals with presence of either or both behavioral risk factors (nicotine use, alcohol abuse).

Table 18. Pairwise Comparisons of 4 level PTSD-Sleep Disorder Variable with CVD all as the Dependent Variable

	Comparison Group	Odds Ratio	95% Confidence Intervals	*p* value
PTSD, Sleep	**PTSD**, No Sleep	1.32	1.43 – 1.21	< 0.0001
PTSD, Sleep	No PTSD, **Sleep**	1.56	1.69 – 1.45	< 0.0001
PTSD, No Sleep	No PTSD, No Sleep	1.95	1.84 – 2.07	< 0.0001
No PTSD, **Sleep**	No PTSD, No Sleep	1.63	1.57 – 1.69	< 0.0001
PTSD, No Sleep	No PTSD, **Sleep**	1.20	1.13 – 1.28	< 0.0001
PTSD, **Sleep**	No PTSD, No Sleep	2.55	2.39 – 2.73	< 0.0001

Note* = PTSD-Sleep Disorder Variable Levels: 1-PTSD only, 2 – Sleep disorder only, 3 PTSD & Sleep Disorder, 4-Neither PTSD or Sleep Disorder

A second approach was conducted to compare the effects of each diagnosis alone vs. both diagnoses. A pairwise statistical comparison was conducted between each of the 4 groups of the 4-category PTSD-Sleep variable (PTSD Only, Sleep Disorder Only, comorbid PTSD-Sleep Disorders, and neither PTSD or Sleep Disorders) to determine if there were any significant difference between the groups. For the pairwise comparisons, demographic variables, medical risk factors, behavioral risk factors, and depression which were entered as covariates. The pairwise comparisons show significant differences between each of the groups at the $p < 0.0001$ level.

The pairwise comparison odds ratio results for PTSD only, Sleep disorders only, and comorbid PTSD-Sleep disorders groups compared to the group with neither PTSD nor Sleep disorders group was consistent with the A-4d (All CVD) logistic regression results listed in Table 17. Results indicated that a diagnosis of PTSD Only was at a significantly higher risk of All CVD diagnoses compared to the neither PTSD or Sleep Disorder group at a medium effect size (OR = 1.95, 95% CI: 1.84, 2.07; $p < 0.001$). The Sleep Disorder Only group was at a significantly higher risk of All CVD diagnoses compared to the neither PTSD or Sleep Disorder group at a small effect size (OR = 1.63,

95% CI: 1.57, 1.69; $p < 0.001$). Finally, the Both PTSD and Sleep Disorder group was at a significantly higher risk of All CVD diagnoses compared to the neither PTSD or Sleep Disorder group at a medium to large effect size (OR = 2.55, 95% CI: 2.38, 2.73; $p < 0.001$).

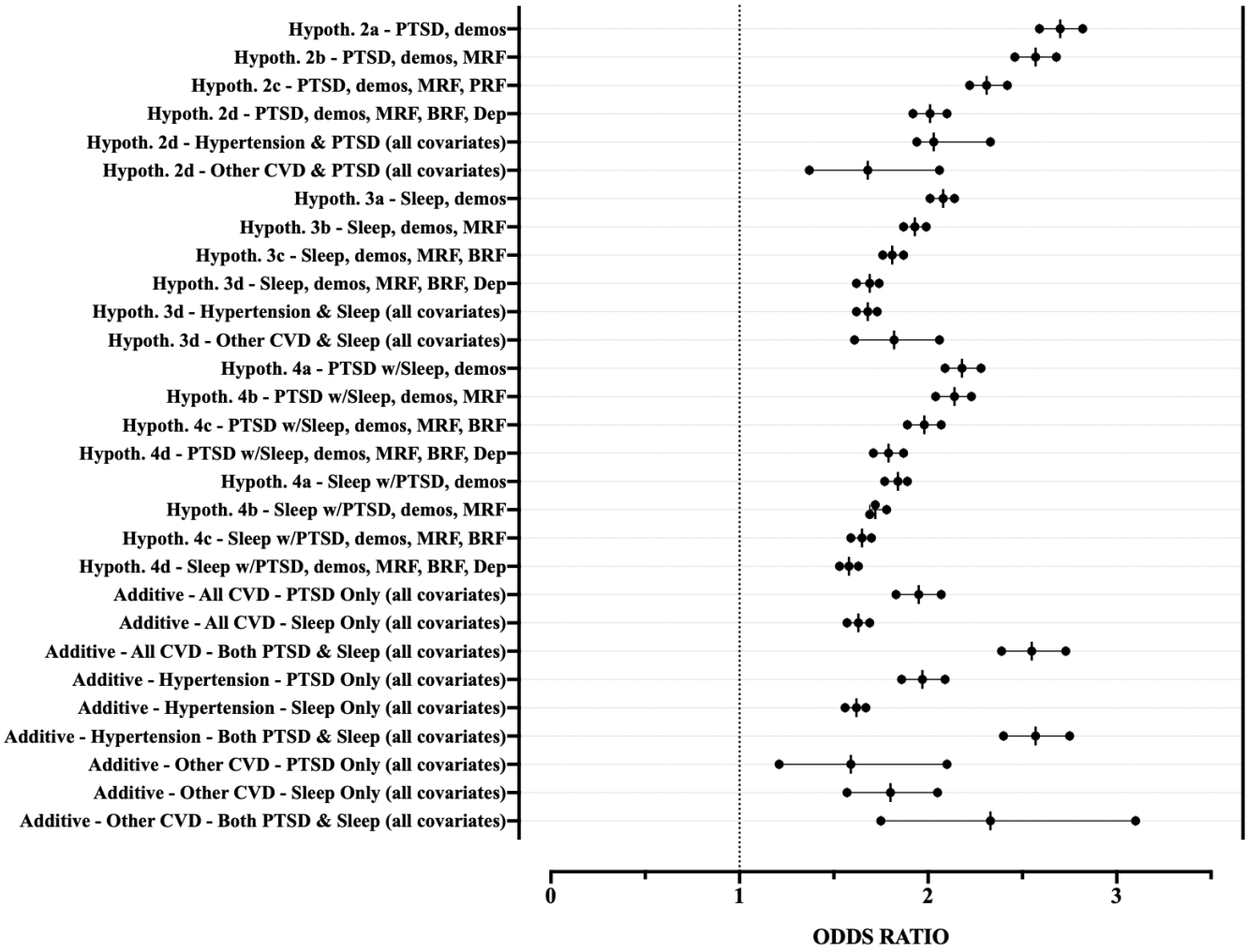
The group with Both PTSD and Sleep Disorder was at significantly higher risk of CVD compared to the group with PTSD only at a small effect size (OR = 1.32, 95% CI: 1.43, 1.21; $p < 0.001$) and Sleep Disorder Only group at a small effect size (OR = 1.56, 95% CI: 1.69, 1.45; $p < 0.001$). Similarly, the group with Sleep Disorder Only also differed from the group with PTSD only group (OR = 1.20, 95% CI: 1.13, 1.28; $p < 0.001$) (see Table 18 above).

SUMMARY OF RESULTS

The summary of results will begin with a forest plot with odds ratios plotted from each analysis. Following the forest plot, the summary will be organized by Aim.

Figure 4 is a forest plot depicting the odds ratios and confidence intervals of various combinations of predictor and outcome variables examined in this study. These results are summarized below.

Figure 12: Forest Plot of Odds Ratios from Aims 2, 3, and 4



Aim 1

The correlation matrix demonstrates that each of the variables in the model are related. Relationships among the behavioral and psychological variables were the largest, while others, even though they were significantly related in this large sample, did not reach the threshold for a small effect size (Cohen's $\varphi = 0.1$).

Aim 2

Aim 2 explored the relationship between a PTSD diagnosis and CVD diagnoses after controlling for a series of covariates. As demonstrated by the forest plot above (Figure 4), a PTSD diagnosis remained a significant predictor of all CVD diagnoses with an odds ratio above 2.0 (medium effect size) for each of the hypotheses and after all the covariates had been added to the logistic regression model. When the All CVD outcome was separated into two categories (hypertension and other CVD diagnoses), a PTSD diagnosis remained a significant predictor for each CVD outcome. The odds ratio remained above 2.0 (medium effect size) for Hypertension Only as the dependent variable, similar to the All CVD dependent variable. However, with Other CVD diagnoses as the dependent variable, the odds ratio was 1.68 (small effect size) and the confidence interval was substantially wider.

Overall, PTSD remained a significant predictor of All CVD in each of the logistic regression analyses presented in Aim 2, although the odds ratio decreased from a medium-large to medium effect size as more covariates were entered into the logistic regression model (Table 12).

Aim 3

Aim 3 explored the relationship between sleep disorder diagnoses and CVD diagnoses while controlling for a series of covariates. As demonstrated by the forest plot above (Figure 3), sleep disorders remained a significant predictor of all CVD diagnoses as more covariates were added to the logistic regression model, with odds ratios ranging from 1.69 to 2.08 (small and medium effect size, respectively). When the All CVD

outcome was separated into two categories (Hypertension Only and Other CVD diagnoses), sleep disorder diagnoses remained a significant predictor for each CVD outcome. The odds ratio for Hypertension Only remained significant with a small effect size (OR = 1.68), consistent with the All CVD dependent variable. The odds ratio of an individual with a sleep disorder diagnosis having a diagnosis of Other CVD diagnosis was 1.82 (small to medium effect size), with a wider confidence interval than seen on the other odds ratios within Aim 3.

Overall, sleep disorder diagnoses remained a significant predictor of all CVD diagnoses in each of the logistic regression analyses presented in Aim 3, although the odds ratio for PTSD decreased as covariates were entered into the logistic regression model (Table 14).

Aim 4

Aim 4 explored the relationship between PTSD and sleep disorder diagnoses with CVD diagnoses while controlling for a series of covariates. The first set of analyses included both PTSD and sleep disorder variables as independent variables. As demonstrated by the forest plot above (Figure 3), PTSD remained a significant predictor of all CVD diagnoses as more covariates were added to the logistic regression model, with odds ratios ranging from 1.79 to 2.18 (small-medium to medium effect sizes). Sleep disorder diagnoses also remained a significant predictor of CVD diagnoses as more covariates were added to the logistic regression model, with odds ratios ranging from 1.58 to 1.84 (small to small-medium effect sizes).

Overall, both PTSD and sleep disorder diagnoses remained significant predictors of All CVD diagnoses in each of the analyses presented in Aim 2, although the odds ratio

both for PTSD and sleep disorder diagnoses decreased as more covariates were entered into the logistic regression model (Table 16). With both PTSD and sleep disorders in the logistic regression model, the medical risk factor variable and PTSD had a small-medium effect size for All CVD diagnoses, sleep disorders had a small effect size, and lastly behavioral risk factors and depression had less than small effect sizes.

Aim 4 – Additive Analyses

Additive analyses for Aim 4 created a 4-category PTSD-Sleep disorder variable to assess the independent and additive contributions of PTSD and sleep disorder diagnoses. This final model showed diagnoses of both PTSD and a sleep disorder was a significant predictor of all CVD diagnoses with a medium-large effect size, with all covariates added to the model (OR = 2.55). These results were consistent for Hypertension Only and Other CVD diagnoses, analyzed separately (Table 17). Comparisons of the odds ratios among PTSD-Sleep variable 4-categories revealed that the odds of CVD associated with Both PTSD and Sleep Disorder, a comorbid diagnosis, was greater than that associated with presence of each diagnosis alone.

CHAPTER 4: Discussion

General Summary of Results

The results of this dissertation demonstrate that a diagnosis of PTSD and a diagnosis of a sleep disorder in active duty Army soldiers are both independent and additive predictors of CVD. These results remained significant after accounting for other medical, behavioral, and psychological risk factors. Within the Army enlisted population studied in the present analyses, hypertension was the prominent CVD diagnosis, and results were evident for hypertension considered as a separate endpoint as well as when more severe, non-hypertension CVD diagnoses (CAD, MI, stroke) were considered as its own "Other CVD" composite endpoint. Most of the effects for hypertension vs. Other CVD endpoints were similar, with the exception of some differences in the relationships with sleep disorders.

To test the study hypotheses, the strategy was to present a series of models with each successive model adding the covariates MRF, BRF, and depression to the model. In all analyses, when PTSD and sleep disorders were entered independently, both a diagnosis of PTSD and a diagnosis of a sleep disorder significantly predicted CVD outcomes. To determine the impact of soldiers having both a diagnosis of PTSD and a diagnosis of a sleep disorder, we defined a 4-category variable that assessed the presence/absence of PTSD with and without a sleep disorder diagnosis, and compared groups. These analyses indicated that odds of CVD associated with having both a PTSD diagnosis and sleep disorder diagnosis was significantly greater than odds associated with having either of these diagnoses alone.

DISCUSSION OF RESULTS BY AIM

Aim 1: Relationships Among Predictor Variables

The goal of Aim 1 was to assess the relationship between each of the variables we planned to enter subsequently into our regression models. Hypothesis 1a predicted that a diagnosis of PTSD would be positively associated with a CVD diagnosis, MRF (obesity, DM2), BRF for CVD (smoking, alcoholism), and a diagnosis of depression. Results from these correlation analyses supported this hypothesis, indicating that a diagnosis of PTSD was significantly related to our dependent variable (CVD) and to MRF, BRF, and depression. Hypothesis 1b predicted that sleep disorder diagnoses would also be positively associated with CVD diagnoses, MRF for CVD, BRF for CVD, and a diagnosis of depression. Results from the correlation analysis also were supportive of this hypothesis, indicating that sleep disorder diagnoses were significantly related to our dependent variable (CVD) and covariates (MRF, BRF, and depression).

Evidence for Study's Conceptual Model

The present study findings provide support for the conceptual model presented on page 4. Specifically, findings from these analyses demonstrated that all of the variables included in the conceptual model are significantly related to one another, and therefore appropriate for inclusion in the study's model. First, we established that a diagnosis of PTSD and a diagnosis of a sleep disorder were significantly predictive of a CVD diagnosis. The next step was to determine if MRF diagnoses and BRF diagnoses were related to a PTSD diagnosis, sleep disorder diagnosis, and a CVD diagnosis. Next, by examining all variables in the model together, we observed that each of the variables

included in the conceptual model contribute to the development of CVD and may represent potential mechanisms linking a diagnosis of PTSD and a sleep disorder diagnosis to CVD diagnostic risk.

It is important to note the difference between risk factors and risk markers when assessing a variable that contributes to the development of a disease or disorder. Risk markers are variables that are associated with a disease but is not causally associated with the risk of the disease. Simply, a risk marker is an indicator of risk for a disease but it is not causal. On the other hand, a risk factor is a variable that is thought to have a causal role in the development of the disorder. Throughout this study, the variables have been referred to as risk factors for CVD and thus viewed as having a causal role in the development of CVD. Based on the known mechanisms of the independent and covariate variables, although not directly studied within this dissertation, that directly impact the cardiovascular system, these variables would be considered risk factors rather than risk markers.

Consistency with Prior Studies and Possible Mechanisms

The relationships among the covariates and independent variables within this study are consistent with the prior literature. Prior literature has identified that individuals diagnosed with PTSD have higher rates of obesity, DM2, nicotine use and alcohol abuse (419) (212) (130) (212).

Although the present study is not designed to assess mechanisms, the relationship of PTSD to CVD in the present study after the medical and behavioral covariates are entered into the model is consistent with this dissertation's conceptual model since they reveal a direct relationship between PTSD and CVD. It is also important to note that the

covariates in this study were also related to one another. These relationships between all variables within the model illustrates the complexity of the relationship between PTSD and CVD.

Aim 2: Independent Effects of PTSD on CVD Risk

The goal of Aim 2 was to assess the CVD risk associated with a diagnosis of PTSD after accounting for known medical, behavioral, and psychological risk factor diagnoses for CVD. Aim 2 had 4 hypotheses, with each hypothesis tested by adding another set of relevant variables or covariates to the logistic regression examining relationships between a diagnosis of PTSD and a CVD diagnosis. In each of the 4 hypotheses and respective logistic regressions, a diagnosis of PTSD remained the strongest significant predictor of CVD diagnoses. As more covariates were added to the logistic regression, the risk of CVD associated with a diagnosis of PTSD somewhat decreased. Although the odds associated with a diagnosis of PTSD decreased as more covariates were added to the logistic regression model, a diagnosis of PTSD still remained over 2 times an increased odds for a CVD diagnosis.

Although these results were supportive of the conclusion that PTSD is an independent predictor of CVD, this association was at least partially explained by the MRF's and BRF's. This finding indicates that these covariates (e.g., MRF, BRF, depression) were not sufficient to account for the relationship between a diagnosis of PTSD and a CVD diagnosis, and that a diagnosis of PTSD continues to be related to an increased odds of CVD even after these variables were controlled for in the analyses. However, although they do not account for the PTSD-CVD relationship, analyses indicated that the variables themselves (MRF, BRF, and depression) are predictive of

CVD diagnoses independent of a PTSD diagnosis. With respect to the MRFs explored in this study (diagnoses of obesity and/or DM2), prior research has shown that obesity (64; 184) and diabetes (34; 445) are significant, independent predictors of CVD diagnoses, and the present study replicates the relationships in a largely younger age Army enlisted population. Similarly, for BRFs (diagnoses of nicotine use and/or alcohol abuse), prior studies indicate that increased consumption of nicotine (162) and alcohol (127; 312) is related to increased risk of adverse cardiovascular health. Depression is another important psychological risk factor for CVD, and the present results demonstrate that the effects of a PTSD diagnosis on CVD diagnoses are independent of a depression diagnosis, even though a depression diagnosis is a significant risk factor in the present data.

One shortcoming of this study is that the risk factors for CVD that were used were limited to medical diagnoses. There are many other known risk factors for CVD that are not medical diagnoses such as diet, exercise, family history, and cholesterol level that were not examined in this study. Thus, the strict hypothesis that a diagnosis of PTSD remains a risk factor independent of effects of all relevant MRF's and BRF's was not tested completely in the study. However, the particular MRF's and BRF's chosen for examination in the present study were done so specifically because of evidence for their prior associations with PTSD (34; 64; 127; 184; 220; 292; 445). Therefore, controlling for the diagnostic risk factors for CVD in this study provided stringent test of the potential independent impact of a diagnosis of PTSD.

Possible Mechanisms Accounting for Hypothesis 2 Results.

PTSD's independent effects on CVD may be related to the dysregulation of the HPA axis (102; 117). Physiologic dysregulation associated with PTSD also is related to

excessive SNS activation and autonomic nervous system dysregulation, high levels of catecholamines (norepinephrine, epinephrine), overproduction of cortisol, and changes in immune system function and glucose metabolism (232; 502). SNS activation is also related to the hyperarousal symptomology of PTSD, and is directly linked to increased catecholamines in the bloodstream. Research further shows that consistently high levels of catecholamines can impact the cardiovascular system by causing increased heart rate and blood pressure (254). The physiological dysregulation associated with PTSD can also directly increase risk for CVD by increasing resting heart rate and blood pressure, decreasing vagal tone, and causing metabolic changes (208; 276; 501).

Comparison with Prior Research

Results of the present study are particularly relevant to one recent study of PTSD as an independent risk factor (391). Because this study explored issues related to the present study hypothesis, and will be discussed in some detail. Specifically, the present findings are not consistent with findings their findings suggesting that when CVD risk factors that are associated with PTSD are controlled, there is no longer an independent contribution of PTSD to CVD risk (391). This is of interest as this study and the Scherrer (391)et al, study utilized electronic medical record data and were limited to ICD-9 diagnostic codes.

There are many possible explanations for the differences between the results of these two studies. Easily identified are the age range of the populations and size of the sample used in the two studies. This dissertation looked at active duty enlisted Army Soldiers (age range 17 – 40+), whereas the Scherrer et al. study (391) looked at Veterans of all services between the ages of 30-70 years old. There is a significant difference in

sample analysis between the two studies with Scherrer utilizing 4,178 veterans, and this study assessing over 28 million person-months. Additionally, the criteria for PTSD in the Scherrer et al. (391) study required 2 visits with an ICD-9 code for PTSD and the criteria for CVD included not only ICD-9 codes but CPT codes and ICD-9 procedure codes. Lastly, the covariates used in the Scherrer et al. (391) study included DM2, obesity, hypertension, hyperlipidemia, depression, anxiety, substance use disorder, sleep disorders and demographic variables. Most of these covariates were based on ICD-9 diagnostic coding but some included data from screening questionnaires (nicotine).

Perhaps because of the different populations studied, the prevalence of CVD diagnoses also differed between the two studies. This dissertation identified the majority of CVD cases as hypertension (95%), whereas the other study had a majority of "other heart disease diagnoses" and hypertension only represented 10% of their population. In addition, depending on the analysis, Scherrer et al.'s study included hypertension both as a predictor and as an outcome. (391).

Lastly, in the Scherrer study, in the case of multiple CVD events, it is not clear which of several possible CVD events (i.e., initial onset of any CVD event vs. most severe CVD event) was used as the CVD outcome. This is in contrast to the present study, which used the subject's most severe diagnosis of CVD within the time period of the study if subjects had multiple CVD endpoints. Given all the differences in methodology between the present study and the Scherrer et al. study, it remains for future research to determine which, if any, of the above differences may account for the divergent findings.

Aim 3: Sleep Disorders and CVD Risk

The goal of Aim 3 was to assess the CVD risk associated with sleep disorders after accounting for known medical, behavioral, and psychological risk factors for CVD that also are associated with PTSD. Additionally, these medical and behavioral risk factors for CVD are known implications and outcomes of sleep disorders. Therefore, these medical and behavioral risk factors could account for possible mechanisms between sleep disorders and the development of CVD.

Aim 3 had 4 hypotheses, with each hypothesis tested by adding an additional covariate to the logistic regression examining relationships between sleep disorders and CVD. In each of the respective logistic regressions, diagnoses of a sleep disorder remained a significant predictor of CVD diagnoses. As more covariates were added to the logistic regression, the risk of CVD associated with sleep disorders decreased from a medium to a small effect size. Diagnoses of medical risk factors, behavioral risk factors, and depression also were found to be significant independent predictors of CVD diagnoses in US Army enlisted soldiers.

Although the present results were supportive of the conclusion that sleep disorders are independent predictors of CVD, these associations were at least partially explained by the MRF's and BRF's. Thus, although they do not fully account for the sleep disorders-CVD relationship, analyses indicated that the covariates themselves (MRF, BRF, and depression) are predictive of CVD diagnoses independent of sleep disorder diagnosis. Nevertheless, consistent with prior research, a sleep disorder diagnosis did remain a significant independent predictor of CVD diagnoses (both hypertension and Other CVD) in all analyses.

Mechanisms of Associations of Sleep Disorders and CVD

Sleep disruptions and disorders are associated with multiple biological mechanisms that impact an individual's cardiovascular health. These mechanisms include increased inflammation, autonomic nervous system activation, and metabolic changes (164). (See also section on associations between sleep disorders and obesity and DM2 in discussion of Hypothesis 1b results). Since metabolic changes would likely be associated with obesity and DM2, the independent risk associated with sleep disorders in the present results may be due to their impact on inflammation and autonomic nervous system. Similar to PTSD, sleep disorders result in an increase in SNS activity and increased circulating catecholamines in the bloodstream, both of which directly impact the cardiovascular system by causing increased heart rate and blood pressure. Increased sympathetic activity is also likely associated with a decrease in parasympathetic activity and lowered vagal tone (270). As noted previously, sleep disorders have been found to increase inflammation markers (IL-6, CRP) (63; 188). These inflammation markers are known to increase the thickness in artery walls resulting in increased risk of CVD (225; 484).

Obstructive sleep apnea (OSA) is a sleep disorder that has specific consequences for, and particular mechanisms of association with CVD. OSA and sleep-disordered breathing involve numerous physiologic mechanisms, including increased SNS activation, inflammation, metabolic dysregulation, as well as direct impact to the cardiovascular system through endothelial dysfunction and increased coagulation. There are also particular relationships of OSA and sleep disordered breathing to blood pressure

and hypertension (408). Based on the multi-fold impact of OSA on cardiovascular health, it is important for future research to study OSA separately from other sleep disorders.

Aim 4: Independent and Additive Effects of PTSD and Sleep Disorders on CVD

The goal of Aim 4 was to assess the CVD risk associated with PTSD and sleep disorders independently, after accounting for known medical, behavioral, and psychological risk factors for CVD. Aim 4 had 4 hypotheses, with analyses for each hypothesis adding an additional covariate to the analyses. For 3 out of the 4 hypotheses and their respective logistic regressions, a diagnosis of PTSD remained the strongest significant predictor of CVD diagnoses. For Hypothesis 4d, when depression diagnoses were added to the model, a diagnosis of PTSD became the second strongest predictor of CVD diagnoses after MRF's. A sleep disorder diagnosis continued to significantly predict CVD diagnoses in each of hypothesis 4 analyses. However, a sleep disorder diagnosis was not one of the stronger predictors of CVD diagnoses in the various logistic regression models. That being said, both a PTSD diagnosis and a sleep disorder diagnosis remained significant independent predictors of CVD diagnoses when all other risk factors were added to the model.

These results were supportive of research that indicates that diagnoses of PTSD and sleep disorders are independent predictors of CVD diagnoses. As covariates MRF, BRF, and depression diagnoses were added to the regression model, these variables also were found to be significant independent predictors of CVD diagnoses in Army enlisted soldiers.

Aim 4 – Additive PTSD and Sleep Disorder Effects

The goal of Aim 4 was to assess the additive impact of a PTSD diagnosis and a sleep disorder diagnosis on cardiovascular health. This aim was examined using individual comparisons among 4 groups formed by combinations of the presence/absence of a PTSD diagnosis and a sleep disorder diagnosis: PTSD diagnosis only, sleep disorder diagnosis only, PTSD and sleep disorder diagnoses, and neither PTSD nor sleep disorder diagnoses. Results indicated that a sleep disorder diagnosis alone and PTSD diagnosis alone groups demonstrated higher rates of CVD diagnoses compared to the group with neither PTSD nor sleep disorder diagnoses. The group with both PTSD and sleep disorder diagnoses were at greater risk than all of the other groups. These results supported the additive relation of PTSD and sleep disorder diagnoses to cardiovascular disease risk. Moreover, the increased risk associated with both PTSD and a sleep disorder diagnoses combined were at a higher risk of CVD diagnoses, even when all of the other variables were included in the model.

Why Additive Effects of PTSD and Sleep Disorders?

Much of the emphasis in this dissertation and in the literature has been on shared physiological and behavioral mechanisms between PTSD and sleep disorders. Although there has not been a body of research specifically investigating independent and/or additive physiological effects of sleep disorders and PTSD, PTSD and sleep disorders each likely affects the cardiovascular system via medical and behavioral mechanisms assessed in this dissertation. With PTSD and sleep disorders affecting similar medical and behavioral mechanisms, we would expect an increase in the extent or magnitude of

these mechanisms affecting the cardiovascular system when both PTSD and sleep disorders occur comorbidly. Additionally, since PTSD and sleep disorder impact different physiological systems that also are associated with poor cardiovascular health (see below), if they occur comorbidly, the separate mechanisms of action would also be expected to contribute to an independent and additive increased risk for CVD.

As noted previously in a prior section of this discussion, it is also possible that that there are mechanisms that are specific to specific to sleep disorders that affect the cardiovascular system. Specifically, there may be particularly important physiological effects of obstructive sleep apnea and disordered breathing on the autonomic nervous system and on blood pressure regulation (336; 408; 471). As described above in the section on Aim 3, the effects of OSA include increased SNS activation, inflammation, metabolic dysregulation, as well as direct impact to the cardiovascular system through endothelial dysfunction and increased coagulation (408). Although the possible independent mechanisms of PTSD and sleep disorders is not resolved, it nevertheless is intriguing and warrants future research.

Lastly, as mentioned previously, sleep disruptions are found in two of the diagnostic criteria for PTSD, specifically sleep difficulties and nightmares (9; 209). The shared symptomology between sleep disorder diagnoses and a PTSD diagnosis is important to acknowledge as this may account for some of the shared mechanisms. However, although there are shared symptomology between PTSD and sleep disorder diagnoses, the present study showed that both diagnoses contributed independently as well as additively when both diagnoses occurred simultaneously.

Associations of PTSD & Sleep Disorders with Hypertension

Results of exploratory analyses in this study indicate that most of the relationships found for total CVD in the sample also apply to hypertension alone and to other CVD diagnoses (CAD, MI, stroke, and CHF) considered separately. These analyses were undertaken because many studies of PTSD and CVD do not include hypertension as a CVD outcome. We included hypertension as an outcome because of the younger age of the present sample, and the fact that other manifestations of CVD usually occur at older ages (75). Studies have shown that PTSD is associated with a 2-fold increased risk of hypertension (62; 334) in both civilian (213; 214) and military populations (82).

With regard to possible mechanisms linking PTSD to hypertension, excessive sympathetic activation and repeated acute blood pressure increases may be particularly relevant (452). In this regard, stressful circumstances and transient periods of stress are thought to be involved in chronic blood pressure elevations (432).

Associations of sleep disorders with hypertension have been reported in many studies. For example, evidence indicates that surges in blood pressure are associated with obstructive sleep apnea, and that these increases may keep blood pressure levels elevated at night. Blood pressure levels are also increased in many individuals with OSA during the day (111). A meta-analysis of 11 studies also found that short sleep duration, broken sleep due to awakenings, and early morning awakening increased the risk of hypertension by an average of 20% (284). Specifically, studies found that sleep durations of less than 7 hours of sleep (157) had an increased prevalence of hypertension. These findings were consistent with findings in veteran populations (455).

STRENGTHS OF THIS STUDY

Major strengths of this dissertation are the sample size, and the fact that the study sample was representative of all enlisted service members of the US Army. This dissertation utilized the Army STARRS HADS database, allowing for analyses of every soldier on active duty between the years 2004 and 2009. This resulted in a total of over 29 million data points used in the analyses. The Army STARRS HADS database also allowed access to all medical and mental health diagnoses for every Army soldier within this 6-year window.

Another strength of this dissertation and the dataset used, is the relatively young age of the sample. Since the Army STARRS HADS database included those individuals on active duty during the time of the study, this population is significantly younger than most studies assessing the relationship between PTSD and CVD. The majority of studies to date have assessed the relationship between PTSD and CVD in veteran populations (43; 45; 47; 203; 242; 414). Veterans are an older population and, therefore, are at an increased risk of CVD due to age and higher rates of other CVD risk factors (76). By assessing the relationship between PTSD and CVD in a younger active duty population, the study identified that there are implications of PTSD for CVD earlier in a Soldier's life.

The use of ICD-9 diagnostic codes is both a strength and weakness of the study. By utilizing diagnostic codes, the medical and mental health variables within the study were at a clinically significant level. This means that each of the variables were diagnosed by a medical or mental health provider. This is different from some studies that utilize self-report measures which do not ensure clinical diagnoses of disorders. On

the other hand, a weakness is that individuals with diagnoses are confined to those who seek medical care.

Yet another strength of this study was the examination of hypertension alone, which is more likely to occur early in life than more severe manifestations of CVD. By examining hypertension alone, this study was able to evaluate an earlier stage of CVD development which is important due to the younger age range of the study's population. Additionally, by examining hypertension alone, this study, unlike most research evaluating the association between PTSD and CVD, was able to the strength of the relationship between different levels of development of CVD. Also examined separately were those more severe diagnoses such as atherosclerosis, peripheral artery disease, stroke, and congestive heart failure. Future studies utilizing this dataset could examine all 5 categories of the CVD diagnosis separately in order to better understand the impact of PTSD and sleep disorders on different manifestations of severity of CVD.

LIMITATIONS OF THIS STUDY

Although a strength of the study, the large sample size allowed for detection of very small differences that might not be clinically or practically meaningful. In interpreting the present study results, it is important to examine the effect sizes and confidence intervals of the findings. Statistically, odds ratios effect sizes are considered to be small (OR=1.5), medium (OR=2.0), and large (OR=3.0) (218). For our study, most of the odds ratios meet criteria for a small effect size, although a few of the predictors of CVD met criteria for a medium effect size and none met criteria for a large effect size (see Figure 3).

As noted above, although the utilization of ICD-9 codes can be a strength, it can also be a weakness. That is because ICD-9 relies on medical or mental health provider diagnostic coding practices. Relying on ICD codes limits the study to those soldiers who sought medical or mental health care and who received a diagnosis. Additionally, by relying on ICD codes, this limits the inclusion of biopsychosocial risk factors for CVD. As a result, risk factors for CVD such as diet and physical activity levels were not included within this study.

The study is also limited by the years of the study, 2004-2009. Since the data collection period, mental health diagnostic criteria and medical diagnostic codes have been updated to ICD-10, and DSM-5 is now the standard for diagnosis of PTSD. This means that the study is based on diagnostic criteria and medical codes that may be out of date or no longer in use. For example, the PTSD diagnostic criteria under the DSM-IV in use during the study period is significantly different (an additional criterion category has been added) then the DSM-5 PTSD criteria currently utilized. This limitation may affect the direct application and implementation of the present results in clinical care

Finally, it is important to consider the effect of the providers' clinical judgment on the composition of the present study's groups. First, there is an overlap in diagnostic criteria between certain sleep disorders and PTSD, thus it is possible not all patients experiencing both clinically significant PTSD and sleep disturbance would receive both diagnoses. Specifically, the diagnostic criteria for PTSD includes trauma-related nightmares and difficulty falling and staying asleep, which are also diagnostic criteria for some sleep disorders such as insomnia. Thus, it is not clear how providers made clinical decisions regarding diagnoses of sleep difficulties above and beyond symptoms of PTSD.

Due to potential career implications (perceived and actual) for a military member receiving mental health diagnoses including PTSD, depression, and alcohol use disorder (AUD) (97), there is a possibility that these diagnoses may be under-diagnosed in the study's data. Providers may experience pressure to down-code or refrain from these diagnoses due to the military stigma of mental health diagnoses. For example, there may be hesitation to diagnose AUD because of its known military repercussions. Additionally, there is the chance that PTSD could have been down-coded as an adjustment disorder.

CLINICAL SIGNIFICANCE

This study has several implications for clinical practice. A major implication is the observation that even in this relatively young population of soldiers, PTSD and sleep disorders may directly impact cardiovascular health. Thus, if an individual is diagnosed with PTSD and/or a sleep disorder, providers should monitor and consider treatment options for cardiovascular health. In addition to treatment for PTSD, medical and mental health providers should monitor and treat known risk factors for CVD as a preventative measure. Some risk factors that could be easily discussed with the member include obesity, poor diet, lack of exercise, sleep, tobacco use, and alcohol use. Although not examined in the present study, another implication of the present findings is the possibility of potential benefits and drawbacks of psychological and pharmacological treatments for PTSD on cardiovascular health.

Additionally, analyses in this study also revealed significant impacts of medical and behavioral risk factors for CVD, including obesity and DM2, depression, alcoholism, smoking. Therefore, if an individual is diagnosed with PTSD and/or sleep disorders, providers also should monitor DM2, obesity, nicotine use, and alcohol use, especially

since PTSD and sleep disorders are known to negatively affect metabolic function (79; 427) as well as affective coping via substance abuse (29; 53; 274). In addition, there are clinical implications of the observation that cardiovascular risk was greater for individuals with comorbid PTSD and sleep disorders compared to individuals with only PTSD or only a sleep disorder. This finding suggests that it is crucial for behavioral and medical providers to monitor and consider appropriate treatments for PTSD and sleep disorders.

A recent review of the psychotherapeutic and pharmacological interventions for comorbidity of PTSD and insomnia, nightmares, and OSA found mixed results on the treatment approach (86). Specifically, research has shown that PTSD treatment decrease nightmare frequency, but do not resolve insomnia or OSA. Improvements in sleep quality and quantity may lead to improvements in other biopsychosocial areas such as mood due to emotional processing during sleep (104), anxiety and stress responses due to SNS regulation (511), and metabolic state due to glucose and lipid storage (424). Due to these biopsychosocial benefits to improved sleep, theoretically treating sleep disorders prior to the treatment of PTSD could allow the individual to be in a healthier state to tackle some of the more intricate symptomology of PTSD. However, research is unclear if insomnia on negatively impacts PTSD treatment or if there is an ideal order of treatment of PTSD and insomnia (86). Research does show that untreated OSA does interfere with the treatment of PTSD; therefore, those individuals with OSA and PTSD should receive treatment for OSA prior to their PTSD treatment (86).

Implications for Future Research

The present study demonstrated the independent and additive effects of PTSD and sleep disorders on CVD. However, as previously noted, this study only examined the diagnoses of these variables and did not investigate possible mechanisms that link these disorders. It is important for future research to identify shared and unique mechanisms between PTSD and sleep disorders and their role in the development of CVD. Additionally, this study's conceptual model presents like a mediation model; however, mediation was not analyzed but rather odds of CVD when other variables in the model. Future research could take the analyses for this model a step further by testing whether the CVD biopsychosocial risk factors mediate the relationship between PTSD and CVD as well as sleep disorders and CVD.

Another avenue for future research is to examine the progression and timeline of the association of PTSD with particular diagnoses of CVD. Future prospective cohort studies should examine the progression of the development of more severe CVD diagnoses, specifically if individuals with PTSD had a different pattern of CVD diagnoses. It would also be important to understand the timeline from initial PTSD diagnosis to the development of hypertension and/or other CVD diagnoses to identify differences in disease progression compared to those without a PTSD diagnosis. This would help identify PTSD risk windows, and ultimately treatment windows in individuals who may develop a CVD diagnoses.

This study did not consider whether an individual was receiving mental health treatment (psychotherapy and/or pharmacological) or treatment for CVD diagnoses. An important direction for future research on prevention of early CVD in military

populations is to examine possible preventive effects of various PTSD and sleep disorder treatment approaches.

Additionally, this study combined sleep disorder diagnoses together and did not distinguish between different sleep disorders. Because of the different mechanisms associated with different sleep disorders (i.e. insomnia vs. OSA), each of the various sleep disorders effect on CVD should be examined independently, as well as comorbid with PTSD. This would allow identification of particular sleep disorders which may have a more severe impact on an individual's cardiovascular health.

Lastly, CVD risk factors are not limited to an individual's physical or mental health. Other factors that could impact an individual's cardiovascular health include genetics, environment, race/ethnicity, and childhood adversity or trauma. These risk factors have been found to impact physical and mental health to include the diagnostic risk factors assessed within this study.

MILITARY SIGNIFICANCE

Prior research has found the both PTSD and sleep disorders are prevalent in military populations. Due to shifting work schedules, 24-hour operations, and changing sleep cycles with missions and travel (31; 140; 246; 317), military members are also known to have a higher prevalence of sleep disorders compared to non-military populations (177; 302), especially OSA (313). This dissertation identified that within the military population, having one or both diagnoses (PTSD, sleep disorders) significantly increases the odds of the development of CVD. This suggests that more resources and attention should be directed to prevention of CVD in military populations with PTSD and/or sleep disorders.

With the inclusion of behavioral health providers within primary care clinics, the military has begun to integrate and identify the overlap and inter-relationships between physical health and mental health (139). Typically, primary care providers refer patients with mental health issues to the embedded behavioral health providers in the clinic. It is very rare to see primary care providers, other than psychiatrists, embedded in behavioral health settings. With the identification of significant physical health impacts of PTSD and sleep disorders, the military may need to better integrate mental health and physical health care delivery. Modifying health care delivery in this way might prove to be effective in better monitoring and treating individuals with comorbid mental health diagnoses, including PTSD, who are at higher risk for physical health problems.

With this study's findings, there are multiple potential policy changes that would help address CVD risk in patients with PTSD and/or sleep disorders. As discussed in the paragraph above, increased integration and collaboration between medical and mental health clinics would allow for comprehensive patient care. An addition of a requirement for regularly (monthly, quarterly, etc.) scheduled interdisciplinary case review meetings to ensure patients with a diagnosis of PTSD and/or a sleep disorder are receiving the appropriate care (medical and mental health) as well as preventative measures for CVD and CVD's associated risk factors. Another way to increase medical and mental health care providers' awareness to these patients, a "flag" could be place in their medical record. "Flags" notify the provider of special circumstances associated with the patient, to include arming status, flying status, and risk of harm to self. An additional "flag" identifying a mental health condition that warrants reoccurring (i.e. annual) CVD health screenings that would include assessment and monitoring of CVD risk factors such as

BMI, DM2, level of physical activity, diet, smoking, and alcohol use. Another option for reoccurring assessment and monitoring of CVD health and risk factors for individuals diagnosed with PTSD and/or sleep disorders could be added to the annual Physical Health Assessment (PHA) each military member is required to complete and have reviewed by their primary care provider.

SUMMARY

The present study is the first study to the CVD impact of PTSD and sleep disorders in Active Duty service members. This study is also the first study to demonstrate PTSD's 2-fold independent risk of CVD within Active Duty service members. This study is also the first study to assess the additive effects of comorbid diagnoses of PTSD and sleep disorders. This study is also the first study to assess the impact of a diagnosis of PTSD and/or sleep disorders on not only the range of CVD diagnoses but also hypertension, a preliminary development of CVD, independently. Each of these results were identified after controlling for known biopsychosocial risk factors for CVD. This novel study demonstrates that PTSD independently and comorbid with a sleep disorder is not only a psychological concern, but also has significant physical health consequences that cannot go unaddressed.

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