IS INSOMNIA AN INDEPENDENT PREDICTOR OF INCIDENT ATHEROSCLEROTIC CARDIOVASCULAR DISEASE AMONG HIV-INFECTED VETERANS?

by

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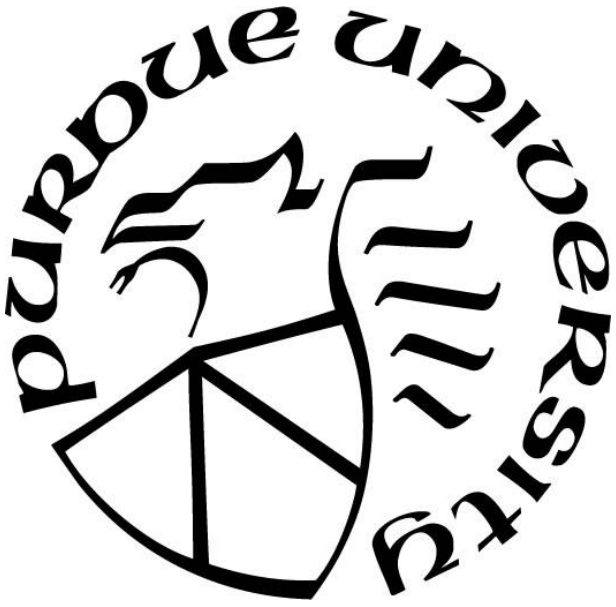
A Thesis

Submitted to the Faculty of Purdue University

In Partial Fulfillment of the Requirements for the degree of

Master of Science



Department of Psychology

Indianapolis, Indiana

December 2017

THE PURDUE UNIVERSITY GRADUATE SCHOOL
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ABSTRACT

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Title: Is Insomnia an Independent Predictor of Incident Atherosclerotic Cardiovascular Disease Among HIV-Infected Veterans?
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While insomnia/sleep disturbance has been identified as an independent predictor of cardiovascular disease in the general population, no studies have examined whether insomnia contributes to the elevated cardiovascular disease (CVD) risk in people with human immunodeficiency virus (HIV). Thus, the current study examined whether insomnia symptoms predict incident atherosclerotic CVD in the Veterans Aging Cohort Study 9 (VACS9), a prospective cohort of HIV-infected (n = 3,138) and uninfected (n = 3,010) Veterans utilizing self-report measures and administrative data. In partial support of my hypotheses, I found that HIV-infected Veterans bothered a lot by difficulty falling or staying asleep have greater CVD risk than HIV-infected Veterans without these symptoms. This study failed to replicate previous findings that insomnia symptoms are predictive of incident CVD in uninfected adults, which may be due to issues related to the validity of the insomnia symptoms assessment. A number of methodological issues are identified and considered in the interpretation of the current study results. Given the novelty of examining insomnia as a predictor of incident CVD in HIV-infected adults and the limitations of the present study, future research is needed to better elucidate the association between insomnia and future CVD in this population.

CHAPTER 1. INTRODUCTION

The American Heart Association's 2015 update of heart disease and stroke statistics indicates that cardiovascular disease (CVD) remains the leading cause of death of men and women in the U.S. (Mozaffarian et al., 2015). In the general population, psychosocial factors, including insomnia, have been identified as predictors of CVD onset above and beyond the risk attributable to traditional CVD risk factors. Of relevance to the present study, adults infected with the human immunodeficiency virus (HIV) are more likely to report insomnia symptoms and develop CVD than adults from the general population. To date, however, no studies have examined whether insomnia is a risk factor for CVD in the HIV-infected population. The present study seeks to address this important gap in knowledge.

In this thesis, I present several topics before discussing the present study's methodology. First, I review research examining insomnia, CVD, and the insomnia-CVD relationship in the general population. Second, I review the same literatures in the HIV-infected population. Third, I present the rationale for and hypotheses of the present study. Fourth, I review the results of the present study. Lastly, I discuss limitations and interpretive issues, fit with literature, directions for future research, and final conclusions of the present study.

Insomnia

Epidemiology. Insomnia, as a symptom and a disorder, has only recently been recognized as an independent concern from other mental and physical conditions. This shift in attention is reflected in the ICSD-3's (International Classification of Sleep Disorders-3;

American Academy of Sleep Medicine, 2014) and the DSM-5's (Diagnostic and Statistical Manual of Mental Disorders-5; American Psychiatric Association, 2013) acknowledgment of insomnia as a disorder irrespective of its manifestation as either a primary disorder or a disorder secondary to a mental or physical comorbidity (Morin & Jarrin, 2013). Insomnia symptoms include: (1) a subjective complaint of poor sleep quantity or quality (e.g., difficulty initiating, maintaining, or returning to sleep), (2) significant distress or impairment in functioning, and (3) the presence of insomnia symptoms for at least three nights per week for at least 3 months (American Academy of Sleep Medicine, 2014; American Psychiatric Association, 2013).

The prevalence and incidence rates of insomnia vary widely depending upon the study design, sample, and follow-up length. Prevalence rates of insomnia symptoms (i.e., sleep disturbance) range from 5-50% (Ohayon, 2002). However, when using criteria set by either the ICSD or DSM (i.e., insomnia diagnosis), the prevalence rate range is a more conservative 6-10% (Jansson-Frojmark & Linton, 2008; Morin, LeBlanc, Bélanger, Ivers, & Mérette, 2011; Morin, LeBlanc, Daley, Gregoire, & Merette, 2006; Ohayon & Reynolds, 2009; Roth et al., 2006). A prospective population-based study in Canada estimated the 1-year incidence of insomnia to be 7.3%. This estimate dropped to 3.9% when limited to those without a lifetime history of insomnia episodes (LeBlanc et al., 2009).

There is mixed evidence regarding racial/ethnic differences in insomnia. One study reported that the prevalence of insomnia disorder did not differ between Caucasian and African American adults (Kalmbach, Pillai, Arnedt, & Drake, 2016). Although few investigations have focused on insomnia disorder, many studies have examined racial/ethnic differences in insomnia symptoms and sleep duration. A 2010 meta-analysis

found that Caucasians report higher rates of insomnia symptoms than African Americans (Ruiter, DeCoster, Jacobs, & Lichstein, 2010). This conflicts with studies that have since observed either no difference in insomnia symptoms between Caucasian, African American, and Hispanic adults (Baldwin et al., 2010) or a higher rate of poor sleep quality in African Americans than in Caucasians (Chen et al., 2015). Similarly, there does not appear to be a difference in insomnia symptoms between Caucasian or Hispanic Americans (Baldwin et al., 2010). Evidence also suggests a consistent pattern of shorter sleep duration in African Americans than in Caucasians (Chen et al., 2015; Ruiter, DeCoster, Jacobs, & Lichstein, 2011), an association that may be mediated by socioeconomic factors (Stamatakis, Kaplan, & Roberts, 2007).

Research supports sex differences in insomnia. In a large community-based sample of U.S. adults, it was found that women comprise the majority of adults with current insomnia disorder and normal sleep duration (12% vs. 6%) and with current insomnia disorder and short sleep duration (12% vs. 8%; Kalmbach et al., 2016). Concerning insomnia symptoms, a meta-analysis reported that women were 41% more likely than men to report insomnia symptoms and that this sex difference exists in young, middle, and late adulthood, with the greatest sex difference observed among the elderly (Zhang & Wing, 2006). Others have found that elderly women were more likely than elderly men to report difficulty initiating sleep and early morning awakening (Jaussent et al., 2011). Thus, it appears that women are more prone than men to experiencing both insomnia disorder and symptoms.

There are mixed results regarding age differences in insomnia. Several studies have reported that older adults have a higher prevalence of insomnia symptoms than younger

adults (Leger, Guilleminault, Dreyfus, Delahaye, & Paillard, 2000; Sivertsen, Krokstad, Øverland, & Mykletun, 2009; Terzano et al., 2004). However, there is debate regarding whether this relationship can be explained by other conditions common among older adults that disrupt sleep (e.g., chronic pain, dementia, and other medical comorbidities; Foley, Ancoli-Israel, Britz, & Walsh, 2004; Taylor et al., 2007; Tractenberg, Singer, & Kaye, 2005) or by changes in sleep architecture with aging (e.g., phase advance of normal circadian rhythm, reduced total sleep time, and reduced delta sleep; Wolkove, Elkholy, Baltzan, & Palayew, 2007).

Pathophysiology. Although there is no universally accepted model of insomnia, a common conceptualization is the 3P stress-diathesis model. This model proposes three levels of factors thought to cause and maintain insomnia: (1) predisposing factors, (2) precipitating factors, and (3) perpetuating factors (Spielman, Caruso, & Glovinsky, 1987). Predisposing factors are biopsychosocial characteristics predisposing an individual to the development of insomnia, such as genetic factors, trait sleep reactivity, and cognitive intrusions (Drake, Pillai, & Roth, 2014; LeBlanc et al., 2009; Vgontzas et al., 2001). Precipitating factors are usually acute events that interact with predisposing factors, resulting in a transient insomnia episode. Examples of precipitating factors are stressful life events, medical conditions, and psychiatric disorders (LeBlanc et al., 2009). Perpetuating factors include beliefs and compensatory behaviors adopted by the individual to cope with insomnia in the short-term, inadvertently perpetuating sleep disturbances and leading to chronic insomnia. For example, excessive time in bed, napping, deconditioning of the bedroom for sleep, and sleep worry are all factors that can perpetuate a disrupted sleep cycle (Espie, 2007; Stepanski & Wyatt, 2003).

In line with the National Institute of Mental Health's "Research Domain Criteria" (RDoC), a more biologically comprehensive model has recently been proposed to complement the 3P model (Levenson, Kay, & Buysse, 2015). This model adds that insomnia is likely to develop in those with a genetic predisposition for atypical neurobiological processes, producing a trait disposition for insomnia (i.e., predisposing factor) that is then triggered by precipitating factors and continues as a result of biological and psychological processes (i.e., perpetuating factors). Identified candidate genes of insomnia include Apoε4, $PER3^{4/4}$, HLA DQB1 * 0602, homozygous Clock gene 3111C/C Clock, and the short (s-) allele of the 5-HTTLPR (Levenson et al., 2015; Palagini, Biber, & Riemann, 2014). It is proposed that these genetic factors produce a trait disposition for insomnia through atypical neurobiological processes, such as dysregulated wake-promoting/sleep-suppressing and sleep-promoting/wake-suppressing substances (e.g., γ-aminobutyric acid [GABA] and cortisol). Finally, chronic insomnia is thought to result from continuous dysregulation of these wake- and sleep-regulating substances and brain changes (e.g., increased high-frequency electroencephalogram [EEG] activity near sleep onset, increased sensory information processing, and EEG arousal during REM sleep; Levenson et al., 2015), as well as the psychological and behavioral perpetuating factors included in the 3P model.

Cardiovascular Disease

Epidemiology. CVD is an umbrella term capturing coronary artery disease (CAD), cerebrovascular disease, and peripheral arterial disease, among other conditions (World Health Organization, 2015). Atherosclerotic CVD, or CAD, is a disease affecting the major blood vessels of the heart. The present study will focus on acute myocardial infarction

(AMI), coronary revascularization, and stroke, which are clinical manifestations of atherosclerotic CVD. An AMI occurs as a result of prolonged ischemia (i.e., inadequate blood supply) to heart muscles, leading to cell death (Thygesen et al., 2012). Prolonged ischemia is primarily caused by two types of events: (1) a blood clot could become lodged in a coronary artery, blocking blood flow, or (2) an atherosclerotic plaque in a coronary artery could rupture, spilling its contents into the artery and blocking blood flow. Coronary revascularization is used to treat CAD and includes percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). PCI, also known as angioplasty, is a non-surgical intervention option for the widening of narrowed or blocked coronary arteries. This group of procedures involves threading a catheter through the coronary arteries to the narrowed blood vessel, inflating the balloon to widen the vessel and push any existing plaque or blood clot into the artery walls, and placing a stent into the newly widened blood vessel in order to keep the vessel from narrowing in the future (American Heart Association, 2017). CABG is a surgical intervention option for the bypassing of narrowed or blocked coronary arteries. This group of procedures involves harvesting a vein from another part of the body to be placed into the heart as a means of bypassing, or going around, the narrowed or blood vessels (American Heart Association, 2017). A stroke also occurs as a result of prolonged ischemia leading to cell death. Unlike ischemia leading to AMI, ischemia leading to stroke is localized in the blood vessels of the brain and leads to cell death of brain tissue. In stroke, prolonged ischemia is primarily caused by a blood clot or other debris becoming lodged in an artery that feeds the blood vessels of the brain (Moskowitz, Lo, & Iadecola, 2010). A small percentage of strokes are caused by hemorrhaging or a rupturing of the blood vessels in the brain.

CAD's estimated prevalence is 6.2% in Americans over the age of 20 (7.6% in men and 5.0% in women), and AMI's estimated prevalence is 2.8% (4.0% in men and 1.8% in women; Mozaffarian et al., 2015). The incidence of CAD increases with age and differs by sex (Mozaffarian et al., 2015). Specifically, first cardiac events for women are, on average, about 10 years later than those for men (Ferreira-Gonzalez, 2014). The delay in incidence of CAD between the sexes increases to 20 years for AMI only (Mozaffarian et al., 2015). Due to an increase in CVD primary prevention efforts over the last decade, there has been a shift in the prevalence of coronary revascularization procedures. One study examining the trends of PCI and CABG among Medicare patients between 2001 and 2009 found that, (1) while PCI use showed a mean annual increase of 1.3% per 1,000 Medicare beneficiaries during 2001-2009, this primarily occurred between 2001-2004 as PCI use showed a decrease of 5% during 2004-2009, and (2) CABG use showed a mean annual decreased of 5% during 2001-2009 (Riley, Don, Powell, Maynard, & Dean, 2011). Stroke's estimated prevalence is 2.6% in Americans over the age of 20 (Mozaffarian et al., 2015). The incidence of stroke increases with age, with men showing a higher incidence rate in younger and middle adulthood; this gender gap narrows in the oldest age groups, with the incidence of stroke in women becoming equal or higher than that of men (Mozaffarian et al., 2015).

Pathophysiology. The underlying condition that causes CAD and stroke is atherosclerosis, which refers to the thickening and hardening of the artery walls due to the accumulation of lipids, leukocytes, calcium, and smooth muscle cells (Libby, 2006). The development of atherosclerosis occurs through two mechanisms acting simultaneously: (1) a traditional circulatory process and (2) an inflammatory process (Libby, 2003, 2006). The

traditional circulatory process is characterized by the accumulation of lipids in the endothelium, the single layer of cells that lines the blood vessels (Weber & Noels, 2011). Lipids trapped in the artery wall are then vulnerable to oxidative changes. Triggers of this process include a diet high in saturated fat, smoking, hypertension, obesity, and insulin resistance.

Endothelial damage resulting from this circulatory process initiates the inflammatory process through the expression of adhesion cells (Libby, 2006). These adhesion cells bind with passing leukocytes (i.e., monocytes and T lymphocytes), which then enter the artery wall. Monocytes in the artery wall mature into macrophages tasked with ingesting foreign substances, including the accumulated lipids. As the macrophages work, they become packed with lipids and resemble foam and, thus, are named foam cells. T lymphocytes are also attracted to lipids in the artery wall. Together with the foam cells, they make up what is called the fatty streak. The macrophages and T lymphocytes multiply, amplifying the inflammatory response by releasing cytokines and growth factors. The smooth muscle cells of the artery also migrate to the surface of the fatty streak to replicate and form a fibrous cap in an attempt to heal the artery wall and protect the flow of blood. The lesion has now progressed to an atheromatous plaque. Once the fatty streak is sealed off, some foam cells die and release their lipids, which is why the core of the plaque has been termed the lipid or necrotic core.

The interaction between circulatory and inflammatory processes can spiral into a vicious cycle, which can ultimately lead to thrombotic complications. A severe thrombotic complication of CAD is AMI (Thygesen et al., 2007). One way an AMI can occur is through excessive plaque build-up in a coronary artery that eventually blocks blood flow

to the heart muscle. However, the majority of AMIs (60-70%) are the result of plaque ruptures (Falk, Shah, & Fuster, 1995). When a plaque ruptures, the necrotic core is suddenly released into the blood stream. T lymphocytes released from the core then stimulate foam cells to produce high levels of tissue factor to form a blood clot and release chemicals to impede the body's attempts to decompose the clot. The clot, in turn, blocks blood flow to the heart muscle, resulting in cell death. A severe complication of cerebrovascular disease, another form of CVD, is stroke. The majority of strokes occur as a result of a blood clot or debris that build up and block the blood flow in the brain (Moskowitz et al., 2010). Blood clots can originate in the brain or may travel from atherosclerotic plaques in the coronary arteries. A small portion (~15%) of strokes occur as a result of the rupturing of the artery wall (Moskowitz et al., 2010).

Insomnia-Cardiovascular Disease Relationship

Epidemiology. The literature examining insomnia as a risk factor of CAD has grown steadily over the past few decades. A meta-analysis of 10 studies published in 1999 found a significant pooled odds ratio of 1.70 for the relationship between subjective sleep complaints and CAD events (Schwartz et al., 1999). A more recent meta-analysis of 13 prospective cohort studies confirmed these results, as a significant pooled odds ratio of 1.45 was found for the relationship between subjective sleep complaints and total CVD events (i.e., acute myocardial infarction, coronary artery disease, stroke, or death from any of these conditions; Sofi et al., 2014). Although the Sofi et al. (2014) meta-analysis did not include studies published after 2011, another meta-analysis published that same year did and examined the prospective associations between subjective sleep complaints/insomnia diagnosis and various types of CVD events (Li, Zhang, Hou, & Tang, 2014). Li and

colleagues (2014) found significant pooled relative risk ratios of 1.33 for CVD mortality (13 studies), 1.55 for stroke (2 studies), 1.28 for CAD (3 studies), and 1.41 for myocardial infarction (7 studies). Thus, accumulating evidence suggests that self-reported sleep disturbance may increase the risk of CVD events, including AMIs and strokes.

To date, only one study has examined insomnia disorder as a predictor of CVD events. Hsu et al. (2015) prospectively examined the association between insomnia diagnoses (i.e., diagnostic codes in Taiwan's National Health Insurance Research Database) and CVD outcomes among 44,080 Taiwanese adults and observed hazard ratios of 1.81 for total CVD events, 1.85 for stroke, and 1.68 for AMI after adjustment for age, sex, some traditional CVD risk factors, and select medical conditions. Thus, insomnia, operationalized as a clinical diagnosis in the medical record, may also be a risk factor for CVD events, including AMI. However, further studies are needed to examine if this association holds after accounting for other potential confounders, including race/ethnicity, socioeconomic status, and other CVD risk factors (i.e., smoking, body mass index, poor diet, physical inactivity, and family history of CVD).

Related literature exists examining the prospective relationship between short sleep duration and incident CVD. Short sleep duration, typically defined as ≤ 6 hours of sleep per night, is related to the insomnia diagnostic criterion of subjective complaint of poor sleep quantity but does not include subjective perception of sleep quality or significant distress or impairment in functioning. A 2011 meta-analysis of 15 studies examining the prospective association between short sleep duration and incident CVD found significant pooled relative risk ratios of 1.48 for CAD and 1.15 for stroke, but no significant association was observed for total CVD (Cappuccio, Cooper, D'Elia, Strazzullo, & Miller,

2011). Most epidemiologic studies conducted since that meta-analysis also report significant associations between short sleep duration and incident CVD (Michal et al., 2014; Rod et al., 2014; Sands-Lincoln et al., 2013; Westerlund et al., 2013). However, one recent epidemiology study found a significant association between short sleep duration and incident CVD only among participants classified as unhealthy (i.e., current/past cancer, stroke, or diabetes; Holliday, Magee, Kritharides, Banks, & Attia, 2013).

Candidate mechanisms. Insomnia could lead to the development of CVD through both behavioral and biological pathways. Regarding behavioral candidate mechanisms, insomnia has been related to physical inactivity, excessive alcohol use (Haario, Rahkonen, Laaksonen, Lahelma, & Lallukka, 2013; Hoefelmann et al., 2012), smoking (Htoo, Talwar, Feinsilver, & Greenberg, 2004), and poor diet (Hoefelmann et al., 2012). Regarding biological candidate mediators, insomnia has been linked to hypothalamic-pituitary-adrenal axis (Balbo, Leproult, & Van Cauter, 2010) and autonomic nervous system (Calandra-Buonaura, Provini, Guaraldi, Plazzi, & Cortelli, 2016) dysregulation, chronic inflammation (Irwin, Olmstead, & Carroll, 2015), altered coagulation (Jackowska & Steptoe, 2015), and endothelial dysfunction (Kohansieh & Makaryus, 2015). Additionally, insomnia has been associated with traditional CVD risk factors, such as obesity (Janson, Lindberg, Gislason, Elmasry, & Boman, 2001; Lyytikainen, Lallukka, Lahelma, & Rahkonen, 2011), hypertension (Fernandez-Mendoza et al., 2012; Vgontzas, Liao, Bixler, Chrousos, & Vela-Bueno, 2009), and diabetes (Hoefelmann et al., 2012; Vgontzas, Calhoun, et al., 2009), which have both behavioral and biological aspects.

Human Immunodeficiency Virus

Epidemiology. It has been estimated that HIV, an infectious disease that is the precursor to acquired immunodeficiency syndrome (AIDS), affects 2.3 million people in high-income countries, which represents only 6.7% of the global total of people living with HIV (Sullivan, Jones, & Baral, 2014). HIV infection can be acquired through the sharing of bodily fluid (e.g., via a blood transfusion, needle sharing, or unprotected sex (Patel et al., 2014). The prevalence of HIV is increasing in nearly every country, largely due to averted HIV/AIDS-related deaths by antiretroviral therapy (ART; UNAIDS, 2013). While the HIV prevalence rate is on the rise, the incidence rate for ages 15 to 59 has decreased from 0.11% in 1996 to 0.05% in 2012 worldwide (UNAIDS, 2013). Current ART treatment guidelines recommend a combination of two nucleoside reverse transcriptase inhibitors (NRTI) plus a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI; Tseng, Seet, & Phillips, 2015). These regimens are typically referred to as either highly active antiretroviral therapy (HAART) or combination antiretroviral therapy (cART).

Pathophysiology. Once the body is infected with HIV, the virus targets and kills a multitude of cells throughout the body. The infection targets CD4+ T cells throughout the body; monocytes and macrophages in the spleen, brain, liver, and lungs; and dendritic cells in germinal centers such as the vagina, tonsils, and rectum (Lucas & Nelson, 2015). Such extreme cell death leads to subsequent HIV-related disease in three main ways: (1) reduction of CD4+ T cells resulting in compromised immune function and increased risk of opportunistic infections, (2) mononuclear cell activation (e.g., monocytes, lymphocytes, and dendritic cells) resulting in direct tissue damage, and (3) endothelial cell dysfunction

and chronic immune activation resulting in indirect tissue damage. The use of ART suppresses the HIV-1 RNA viral load circulating in the blood and allows for the repopulation of CD4+ T cells (Tseng et al., 2015). However, the HIV-1 RNA viral load in the central nervous system (CNS) is not well controlled by ART (Dahl et al., 2014).

Insomnia in HIV

Epidemiology. Sleep disturbance and insomnia symptoms are highly prevalent in the HIV-infected population. The first qualitative review of sleep disturbance among HIV-infected individuals examined 29 studies and identified sleep disturbance as a frequent complaint and present during all stages of HIV infection (Reid & Dwyer, 2005). A more recent qualitative review of 19 studies reported sleep disturbance prevalence estimates between 29-97% (Low, Goforth, Preud'homme, Edinger, & Krystal, 2014). This was followed by a meta-analysis reporting the prevalence of sleep disturbance to be 58% in an accumulated sample of 9,246 HIV-infected adults from 27 studies (Wu, Wu, Lu, Guo, & Li, 2015), much higher than the 36% reported in the general population (Roth et al., 2006).

Despite evidence indicating that sleep disturbance is a prevalent problem among HIV-infected individuals, only one study has examined the prevalence of insomnia based on diagnostic criteria. Using a structured interview for sleep disorders, a small study of 29 HIV-infected and 19 uninfected African Americans observed an insomnia disorder prevalence of 56% (Gamaldo et al., 2013). Thus, the prevalence of insomnia disorder is unknown in the HIV-infected population (Low et al., 2014).

Pathophysiology. Evidence suggests that traditional insomnia risk factors or precipitating factors – e.g., stress, fatigue, substance use, depression, and anxiety (Allavena et al., 2016; Jabbari, Dabaghzadeh, Khalili, & Abbasian, 2015; Jean-Louis et al., 2012) –

are also operating in the HIV-infected population. In addition, HIV-specific insomnia risk factors have been identified and include duration HIV infection (Allavena et al., 2016), advanced disease stage, cognitive impairment (Rubinstein & Selwyn, 1998), and use of the NNRTI efavirenz (Allavena et al., 2016; Low et al., 2014). CD-4^+ T cell count and HIV-1 RNA viral load do not appear to be associated with insomnia risk (Low et al., 2014). Thus, traditional risk factors and HIV-specific factors may contribute to the development of insomnia among people with HIV.

However, serum levels of CD-4^+ T cell count and HIV-1 RNA viral load do not reflect the viral burden in the central nervous system (CNS), which ART regimens do not efficiently infiltrate due to their inability to penetrate the blood brain barrier (Dahl et al., 2014). Because of this, the CNS is viewed as a reservoir of HIV infection, leading to the following consequences: (1) a release of viral products (neurotoxins) from infected cells in the CNS; (2) an inducement of the inflammatory response; and (3) a positive feedback cycle produced by the neurotoxins and inflammatory mediators, causing escalating damage, especially to dopaminergic and glutamatergic systems, which are both implicated in sleep/wake functioning (Low et al., 2014). Thus, the mechanisms by which HIV affects sleep may also lie in the neurotoxic effects of HIV on the CNS.

Cardiovascular Disease in HIV

Epidemiology. The recent decrease in HIV/AIDS-related deaths in people with HIV has been accompanied by an increase in non-HIV/AIDS-related deaths, particularly deaths due to cardiovascular disease (Feinstein et al., 2016). In fact, in the HIV population, CVD is currently among the leading causes of death (Gill et al., 2010). HIV-infected individuals exhibit a 48-111% higher risk of AMI than uninfected individuals, even after

controlling for traditional CVD risk factors (Durand, Sheehy, Baril, Lelorier, & Tremblay, 2011; Freiberg et al., 2013; Triant, Lee, Hadigan, & Grinspoon, 2007). A 2012 meta-analysis found the overall relative risk of CVD among HIV-infected individuals naïve to ART to be 61% higher than uninfected individuals and this risk increases to 200% when comparing HIV-infected individuals on ART to uninfected individuals (Islam, Wu, Jansson, & Wilson, 2012). Even among those without CVD risk factors, HIV-infected persons continue to exhibit double the risk of AMI compared to uninfected persons (Paisible et al., 2015).

Pathophysiology. The increased CVD risk in the HIV population is thought to be due to both traditional and HIV-specific mechanisms. Regarding traditional mechanisms, people with HIV exhibit elevated rates of smoking, hypertension, diabetes, and dyslipidemia (Klein, Hurley, Quesenberry, & Sidney, 2002; Triant et al., 2007). In addition, evidence of chronic inflammation and altered coagulation have also been observed in the HIV-infected individuals. A recent review found that 75% of studies report a significant association of inflammatory and coagulation biomarkers with incident CVD in people with HIV, independent of traditional CVD risk factors (Vos, Idris, Barth, Klipstein-Grobusch, & Grobbee, 2016).

Regarding HIV-specific mechanisms, several factors related to HIV infection and treatment have been implicated in increasing CVD risk. First, viral replication, a low CD-4^+ T cell nadir, and a high CD8 T-cell count have been associated with increased risk of MI, independent of traditional CVD risk factors and ART regimen (Lang et al., 2012; Silverberg et al., 2014). These results have been experimentally supported by the Strategies for Management of Antiretroviral Therapy (SMART) trial, which compared conservative

ART (i.e., ART used when $CD4^+$ cell count <250/mm^3 and stopped when $CD4^+$ cell count >350/mm^3) to continuous ART. This trial found HIV-infected individuals in the conservative group had an 80% greater risk of CVD than the continuous ART group (El-Sadr et al., 2006), suggesting that a less than optimal $CD\text{-}4^+$ T cell count and a higher viral load contribute to CVD risk. Second, evidence suggests the HIV infection itself affects many stages of the atherosclerotic process (Lang, Boccara, Mary-Krause, & Cohen, 2015; Longenecker, Sullivan, & Baker, 2016). Specifically, HIV infection enhances monocyte activation and systemic inflammation and alters cholesterol metabolism. Third, some ART regimens are thought to contribute to the elevated CVD risk in HIV. PIs and NRTIs have been associated with 11% and 5% increases in CVD risk per exposure year, respectively (Islam et al., 2012). The Islam et al. (2012) meta-analysis previously mentioned also reports an overall relative risk of incident CVD among HIV-infected adults on ART to be 51% higher than HIV-infected adults naïve to ART. In addition, ART regimens have also been associated with increasing the likelihood of some traditional CVD risk factors, such as dyslipidemia (Crowe et al., 2010).

The Present Study

Given that (1) insomnia/sleep disturbance is a predictor of CVD in the general population and that (2) insomnia/sleep disturbance is highly prevalent in the HIV population, a key next step is to examine whether insomnia, in part, contributes to the elevated CVD risk of people with HIV. Identifying novel and treatable risk factors for CVD in HIV could inform the development of new interventions to prevent CVD in this vulnerable population. To date, however, no studies have examined whether insomnia

predicts incident CVD in people with HIV. Accordingly, the present study sought to address this important gap in knowledge.

CHAPTER 2. METHODS

The proposed project required significant modifications following our team's preliminary analyses of the *International Classification of Diseases, Ninth Revision* (ICD-9) codes for insomnia disorder, which revealed unacceptably low sensitivity. While the proposed project was approved by the Veterans Aging Cohort Study (VACS) principal investigator (Dr. Amy Justice) and relevant VACS workgroups, it was on the condition that our team perform preliminary analyses examining the sensitivity and specificity of the ICD-9 insomnia disorder codes before conducting hypothesis-testing analyses. Members of the VACS Cardiovascular Disease and Pulmonary Disease Core Workgroup suspected that the ICD-9 codes may have low sensitivity, which was confirmed by our preliminary analyses (see Baseline Insomnia Symptoms section). Thus, it was not appropriate to use the ICD-9 insomnia disorder codes to determine baseline insomnia status. Nonetheless, my hypotheses could still be tested by using an assessment of insomnia symptoms in the VACS questionnaire data, which was the alternative approach recommended by Dr. Justice. The change in the definition of baseline insomnia resulted in a number of necessary modifications to the methods. These changes are detailed in the sections below following descriptions of the originally proposed methods. The only modification that was necessary to the hypotheses was replacing "insomnia disorder" with "insomnia symptoms". The updated hypotheses are:

Hypothesis 1: Baseline insomnia symptoms will be an independent predictor of incident atherosclerotic CVD among all Veterans in the VACS9 cohort (N = 6,148).

Hypothesis 2: Baseline insomnia symptoms will be an independent predictor of incident atherosclerotic CVD among uninfected Veterans in the VACS9 cohort (n = 3,010).

Hypothesis 3: Baseline insomnia symptoms will be an independent predictor of incident atherosclerotic CVD among HIV-infected Veterans in the VACS9 cohort (*n* = 3,138).

Exploratory Hypothesis: Baseline insomnia symptoms will be a stronger predictor of incident atherosclerotic CVD among HIV-infected Veterans than among uninfected Veterans.

Study Design and Sample

I originally proposed to test my hypotheses in VACS Virtual Cohort (VACS-VC), a prospective, multisite cohort of HIV-infected veterans and age-, race/ethnicity-, and clinical site-matched uninfected Veterans (Fultz et al., 2006; Justice et al., 2006). In brief, VACS-VC participants have been continuously selected for study enrollment since 1998 using a validated algorithm of the VA national electronic record system (Fultz et al., 2006). However, due to concerns regarding the validity of ICD-9 insomnia disorder codes, my hypotheses has to be tested in the VACS9 cohort instead. VACS9, a subsample of the VACS-VC cohort, is comprised of Veterans who completed a battery of self-report questionnaires at their time of enrollment (Womack et al., 2017). As with other VACS9 projects, the baseline period for this project was defined as –ever to +6 months of the enrollment date. Of note, specific dates are not used to define the baseline period, as VACS9 undergoes continuous enrollment throughout the entire study period starting in June of 2002. In this study, all participants were followed until the occurrence of an atherosclerotic CVD event or the end of the follow-up period (December 31, 2011). VACS has been approved by the University of Pittsburgh, Yale University, and West Haven VA Medical Center institutional review boards.

VACS9 utilizes data from a number of sources. All variables originated from either the VA self-report battery or the VA laboratory, pharmacy, clinical, administrative, or immunology case registry data. The one exception to this was the outcome variable, which originated from VA and Medicare administrative data and the VA fee-for-service data.

A total of 7,515 Veterans have been enrolled in VACS9. To this cohort, our team applied the following exclusion criteria: (1) pre-existing CVD (n = 1,178), defined as the presence of an ICD-9 code for AMI, unstable angina, cardiovascular revascularization, stroke or transient ischemic attack, peripheral vascular disease, or heart failure during the baseline period (Armah et al., 2014; Freiberg et al., 2013); (2) uninfected participants with at least one of viral load, CD4 cell count, or ART regimen present (n = 43); (3) participants with a baseline date after December 28, 2011 (n = 20); (4) coding errors (i.e., the last follow-up date on or before the enrollment date (n = 11); and (5) participants missing insomnia questionnaire data (n = 115). Thus, the final sample consisted of 6,148 Veterans.

Although originally proposed, I was unable to exclude Veterans with baseline sleep apnea because the performance of the ICD-9 sleep apnea codes (327.20, 327.21, 327.23, 327.24, 327.26, 327.27, 327.29, 780.51, 780.53, 780.57) against the VACS9 yes-no sleep apnea item ("Has a doctor ever told you that you have any of the following lung or breathing conditions? Sleep apnea?") indicated high specificity for the uninfected (99.4%) and HIV-infected (99.6%) cohorts but unacceptably low sensitivity for these groups (22.2% and 11.7%, respectively).

Measures and Procedures

Baseline Insomnia Symptoms. Originally, I planned to classify participants as having a baseline insomnia disorder if they have at least one inpatient or two outpatient

ICD-9 codes for insomnia disorder (307.40, 307.41, 307.42, 307.49, 327.00, 327.01, 327.02, 327.09, 780.50, 780.52, 780.59) in VA administrative data during the baseline period. Our preliminary analyses evaluating the performance of the ICD-9 insomnia disorder codes against the VACS9 insomnia item (i.e., the presence of difficulty falling or staying asleep during the past four weeks) indicated high specificity; however, these analyses also revealed unacceptably low sensitivity of the ICD-9 codes. In the uninfected cohort, the ICD-9 codes had a specificity of 97.2% and a sensitivity of 7.8%. In the HIV-infected cohort, they had a specificity of 98.0% and a sensitivity of 4.3%. These results indicate that the ICD-9 insomnia disorder codes identified only 7.8% and 4.3% of participants with self-reported difficulty falling or staying asleep in the past month in the uninfected and HIV-infected cohorts, respectively. Our team and the VACS investigators agreed that using the ICD-9 codes would result in an unacceptably high degree of misclassification (i.e., participants with insomnia symptoms coded as no for insomnia status).

Consistent with the recommendation of the VACS principal investigator, the present study instead used the insomnia symptoms item from the VACS HIV Symptom Index, which was included in VACS9 self-report battery administered at the time of enrollment. The HIV Symptom Index is a 20-item, self-report questionnaire designed to assess the frequency and bother of common symptoms in HIV-infected patients exposed to multidrug ART and protease inhibitors (Justice et al., 2001). Participants were asked to indicate what response best described their experience of each symptom over the past four weeks using the following options: 0 = “I do not have this symptom” or “I have this symptom and…” 1 = “it doesn’t bother me”, 2 = “it bothers me a little”, 3 = “it bothers

me", 4 = "it bothers me a lot". In the present study, responses to the insomnia item – "Difficulty falling or staying asleep?" – were used to create a 5-level insomnia symptoms variable. From this variable, four dummy coded variables were created with the "no symptoms" group as the reference category.

Baseline HIV Status. Consistent with prior VACS reports, participants were classified as HIV-infected if one inpatient or two outpatient ICD-9 codes for AIDS (042), asymptomatic HIV (V08), and related diagnostic code groups (488-490) were present in the VA administrative data and confirmed in the VA Immunology Case Registry during the baseline period (Fultz et al., 2006). All other veterans were classified as uninfected.

Incident Atherosclerotic CVD. In the original proposal, incident AMI was the outcome variable. However, due to the smaller sample size of VACS9, there was a low number of AMIs (<10) in several of the cells (see Table 1), raising concerns about low power and unstable regression coefficients (Concato, Peduzzi, Holford, & Feinstein, 1995; Peduzzi, Concato, Feinstein, & Holford, 1995). To increase event counts to acceptable levels, the outcome variable was broadened to incident atherosclerotic CVD.

TABLE 1. Frequencies for Incident Acute Myocardial Infarction by Insomnia Symptoms Level in the VACS9 Cohort (N = 6,148)

	I do not have this symptom.	It doesn't bother me.	It bothers me a little.	It bothers me.	It bothers me a lot.
Entire Cohort	60	10	36	25	15
Uninfected Cohort	33	3	13	14	6
HIV-Infected Cohort	27	7	23	11	9

Incident atherosclerotic CVD is a composite variable that counts any of the following as events during the follow-up period: AMI, coronary artery revascularization, or stroke. Data for these events originated from VA and Medicare administrative data and VA fee-for-service data. First, incident AMI was defined using ICD-9 410.X codes. The use of AMI code 410 has shown strong agreement with adjudicated AMI outcomes in the Cardiovascular Health Study (Ives et al., 1995). Second, incident coronary artery revascularization was defined using ICD-9 procedural codes for PCI (00.66, 36.01, 36.02, 36.06, 36.07, 92977, 92978, 92980, 92981, 92982, 92995) or CABG (33510, 33517, 33518, 33519, 33533, 33534, 33535). Third, incident stroke was defined using the following ICD-9 codes: 433.01, 433.11, 433.91, 434.01, 434.11, 434.91, 436.00, 438.00, 438.11, 438.19, 438.20, 438.21, 438.22, 438.41, 438.50, 438.60, 438.81, 438.82, 438.84, 438.89, 438.90.

Covariates. Analyses included covariates from five categories: demographic variables, cardiovascular risk factors, additional potential confounders, depressive symptoms and medications, and HIV-specific factors.

Demographic variables are age (years), sex (0 = male; 1 = female), and race/ethnicity (0 = White, Hispanic, and Other; 1 = African American). These variables were computed from the VACS9 self-report questionnaire data obtained at enrollment (Justice et al., 2006).

Cardiovascular risk factors are hypertension, diabetes, body mass index (BMI), smoking, total cholesterol, and statin use. Hypertension was defined using VA clinical (systolic and diastolic blood pressures) and pharmacy data (antihypertensive medication) pulled from the encounter closest to the enrollment date during the baseline period.

Hypertension was coded as no hypertension (<140/90 mmHg and no antihypertensive medication [reference]), controlled hypertension (<140/90 mmHg with antihypertensive medication), or uncontrolled hypertension (≥140/90 mmHg; Chobanian et al., 2003). Diabetes was defined using VA laboratory, pharmacy, and administrative data based on a previously validated metric incorporating glucose measurements, diabetes medication use, and/or at least one inpatient or two outpatient ICD-9 codes for diabetes during the baseline period (Butt et al., 2004). BMI was defined using VA clinical data pulled from the encounter closest to the enrollment date during the baseline period. Smoking (never [reference], current, and former smoker) was computed from the VACS9 self-report questionnaire data obtained at enrollment. Total cholesterol was defined using VA laboratory data and statin use was defined using VA pharmacy data from the encounter closest to the enrollment date during the baseline period.

Additional potential confounders are hepatitis C infection, renal disease, anemia, alcohol use, and cocaine use. Hepatitis C infection was defined using VA laboratory data (hepatitis c virus antibody test) or VA administrative data (ICD-9 codes) during the baseline period. Hepatitis C infection was coded as present if a participant had a positive hepatitis c virus antibody test or at least 1 inpatient or 2 outpatient ICD-9 codes for hepatitis c infection (Butt et al., 2009). Renal disease was defined using VA laboratory data for glomerular filtration rate (eGFR), an indicator of kidney function, from the encounter closest to the enrollment date during the baseline period. Anemia was defined using VA laboratory data for hemoglobin from the encounter closest to the enrollment date during the baseline period. Alcohol use was defined using self-report questionnaire data obtained at enrollment (Alcohol Use Disorders Identification Test [AUDIT]) and VA administrative

data (ICD-9 codes) during the baseline period (Crawford, Fulton, Swinkels, Beckham, & Calhoun, 2013). Alcohol use was coded 0 = no current use or non-hazardous use or 1 = hazardous use or alcohol abuse/dependence disorder (291.0, 291.2, 291.3, 291.8, 291.81, 291.89, 303.00, 303.01, 303.02, 303.03, 303.90, 303.91, 303.92, 303.93, 305.0, 305.01, 305.02, 305.03, 357.5, 571.1, 571.2, 571.3, V11.3). Cocaine use was defined using responses to the enrollment questionnaire item, "For each of the following drugs, please mark the box that best indicates how often in the past year you used each drug. Cocaine or crack," as 0 = never tried or no use in last month or 1 = less than once a month, 1-3 times a month, 1-3 times a week, 4-6 times a week, or every day. In addition, participants with an ICD-9 code for cocaine use disorder (304.20, 304.21, 304.22, 304.23, 305.60, 305.61, 305.62, 305.63) during the baseline period were also coded as 1.

Depressive symptoms and medications were also included as covariates. Originally, I proposed to include the following in a prescription sleep medication use variable: non-benzodiazepines, benzodiazepines, serotonin receptor agonists, dibenzothrazepines, and miscellaneous other medications used to treat insomnia. However, after re-reviewing the medication lists, the team decided to focus solely on non-benzodiazepines, given their higher specificity for sleep problems than the other medication categories. Non-benzodiazepine sleep medication use was defined using VA pharmacy data from the encounter closest to the enrollment date during the baseline period (see Table 2). I originally proposed to define depressive disorders using ICD-9 codes for major depressive disorder and dysthymia. However, because the VACS9 self-report questionnaire battery included the reliable and valid Patient Health Questionnaire-9 (PHQ-9; Kroenke, Spitzer, & Williams, 2001), I decided to use the PHQ-9 total score, as it provided a continuous

measure of depressive symptoms and should capture participants with undiagnosed depression. The team also added antidepressant medication use as a covariate, which was defined using VA pharmacy data for the encounter closest to the enrollment date during the baseline period. Three separate dichotomous variables were computed based on the type of antidepressant medication – selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressant (TCA), and miscellaneous other antidepressants.

TABLE 2. List of Non-Benzodiazepine Prescription Sleep Medications

Generic Name	Brand Name
Zolpidem	Ambien, Ambien CR, Edluar, Intermezzo, Stilnox, Stilnoct, Sublinox, Hypnogen, Zonadin, Sanval, Zolsana, Zolpimist, Zolfresh
Zaleplon	Sonata, Starnoc, Andante
Eszopiclone	Estorra, Lunesta
Indiplon-IR, Indiplon-MR	--

HIV-specific factors are HIV-1 RNA levels, CD-4$^+$ T cell count, and ART regimen. HIV-1 RNA levels and CD-4$^+$ T cell count were defined using VA laboratory data from the encounter closes to the enrollment date during the baseline period. ART regimen was defined using VA pharmacy data from the encounter closest to the enrollment date during the baseline period. ART regimen was coded as 0 = no ART regimen or 1 = any type of ART regimen (e.g., NRTI plus PI, NRTI plus NNRTI, or other regimen).

Data Analysis

VACS9 is a federally protected data source with access granted only to those working on-site within the VACS team. Due to this added security, I did not have direct access to the VACS9 dataset or new data that was pulled for the proposed project (e.g.,

sleep disorder diagnoses and prescription sleep medication use). Instead, I worked closely with VACS biostatisticians by designing and directing all data pulls and statistical analyses, interpreting outputs and results, and constructing tables. Communication with the VACS team occurred via bimonthly calls and emails between calls during the project period.

Frequencies for categorical variables and medians and 1st and 3rd quartiles for continuous variables were examined to assess whether values were within expected ranges (see Table 3). Chi-square tests were conducted to determine whether there were differences between uninfected and HIV-infected Veterans in insomnia symptoms and incident atherosclerotic CVD. A chi-square test was also conducted to determine whether there were differences between Veterans with and without non-benzodiazepine sleep medication use in insomnia symptoms. Significant chi-square tests were followed by examining the contributions (i.e., [observed – expected]^2/expected) of each cell to the total chi-square (i.e., sum of each cells contribution). This approach was recommended over the use of post-hoc pairwise comparisons by the VACS biostatisticians.

TABLE 3. Characteristics of the VACS9 Participants Stratified by HIV Status

	Entire Cohort (N = 6,148)	Uninfected Cohort (n = 3,010)	HIV-infected Cohort (n = 3,138)
Demographic Variables			
Age, Years	49.2	49.6	49.0
	[43.7, 54.7]	[44.0, 54.9]	[43.4, 54.6]
Sex, % Male	5,794 (94.2)	2,747 (91.3)	3,047 (97.1)
Race/ethnicity, % African American	4,012 (65.3)	1,936 (64.3)	2,076 (66.2)
Income, < $12,000/year	2,703 (45.5)	1,195 (41.3)	1,508 (49.4)
Cardiovascular Risk Factors			
Hypertension[a]			
% None	2,408 (39.2)	1,023 (34.1)	1,385 (44.2)
% Controlled	2,162 (35.2)	1,115 (37.1)	1,046 (33.4)
% Uncontrolled	1,571 (25.6)	866 (28.8)	705 (22.5)
Diabetes, %	992 (16.1)	557 (18.5)	435 (13.9)
Body Mass Index,[a] % ≥ 30 kg/m^2	1,648 (26.9)	1,190 (39.8)	458 (14.6)
Smoking[a]			
% Current	3,033 (49.8)	1,395 (47.1)	1,638 (52.4)
% Former	1,463 (24.0)	731 (24.7)	732 (23.4)
% Never	1,592 (26.1)	838 (28.3)	754 (24.1)
Total Cholesterol,[a] % ≥ 200 mg/dL	1,789 (31.1)	973 (35.0)	816 (27.4)
Statin Use, %	1,130 (18.4)	659 (21.9)	471 (15.0)
Additional Potential Confounders			
Hepatitis C infection, %	2,116 (34.4)	730 (24.3)	1,386 (44.2)
Renal Disease,[a] eGFR < 60 mL/min/1.73m^2	308 (5.1)	132 (4.5)	176 (5.6)
Anemia,[a] % Hemoglobin < 12 g/dL	539 (9.0)	142 (4.9)	397 (12.7)

TABLE 3. continued

Alcohol use,[a] % Hazardous/Abuse/Dependence	2,446 (39.9)	1,237 (41.2)	1,209 (38.7)
Cocaine Use,[a] %	1,199 (20.1)	508 (17.4)	691 (22.7)
Depressive Symptoms and Medications			
Non-benzodiazepine Sleep Medication	406 (6.6)	196 (6.5)	210 (6.7)
PHQ-9,[a] % Total Score ≥ 10	1,284 (21.1)	602 (20.2)	682 (21.9)
Antidepressant Medication			
% SSRI	2,003 (32.6)	950 (31.6)	1,053 (33.6)
% Tricyclic	1,061 (17.3)	430 (14.3)	631 (20.1)
% Miscellaneous	2,044 (33.2)	1,014 (33.7)	1,030 (32.8)
HIV-Specific Factors			
HIV-1 RNA Levels,[a] % ≥ 500 copies/mL	--	--	1,515 (48.4)
CD-4$^+$ T cell count [a]			
% < 200 mm^3	--	--	695 (22.2)
% 201-499 mm	--	--	1,445 (46.3)
% ≥ 500 mm^3	--	--	984 (31.5)
ART regimen, %	--	--	2,504 (79.8)

Note. Continuous variables are presented as median [first quartile, third quartile], and categorical variables are presented as *n* (%).
VACS = Veterans Aging Cohort Study; HIV = human immunodeficiency virus; PHQ-9 = Patient Health Questionnaire-9; SSRI = selective serotonin reuptake inhibitor; ART = antiretroviral therapy.
[a]The following variables had fewer than 6,148 participants due to missing data (*n* missing, %): income (200, 3.3), hypertension (8, 0.1), BMI (28, 0.5), smoking (60, 1.0), total cholesterol (390, 6.3), renal disease (90, 1.5), anemia (131, 2.1), alcohol use (17, 0.3), cocaine use (189, 3.1), PHQ-9 total score (50, 0.8), HIV-1 RNA levels (5, 0.1), and CD-4$^+$ T cell count (14, 0.4).

Cox proportional hazards models were constructed to test whether baseline insomnia symptoms independently predicted incident atherosclerotic CVD in the entire VACS9 cohort (Hypothesis 1). Cox models examine the effect of the independent variable, in the presence of covariates, on the *time* to the dependent variable or event. The models were structured in such a way that Models 1-3 hierarchically added the main covariates. Models 4a-4c each added one additional covariate to Model 3, and Model 5 included all three additional covariates. Specifically, Model 1 (demographic variables) included age, sex, and race/ethnicity. Model 2 (cardiovascular risk factors) included the Model 1 covariates plus hypertension, diabetes, BMI, smoking, total cholesterol, and statin use. Model 3 (additional potential confounders) included the Model 2 covariates plus hepatitis C infection, renal disease, anemia, alcohol use, and cocaine use. Model 4's included the Model 3 covariates plus non-benzodiazepine sleep medication use (4a), PHQ-9 total score (4b), or the three antidepressant medication use variables (4c). Lastly, Model 5 (all covariates) included the Model 3 covariates plus non-benzodiazepine use, PHQ-9 total score, and antidepressant use variables.

Cox proportional hazards models were also used to test whether baseline insomnia symptoms independently predicted incident atherosclerotic CVD in the VACS9 uninfected (Hypothesis 2) and HIV-infected (Hypothesis 3) cohorts. The modeling for Hypothesis 2 is identical to that of Hypothesis 1, while the modeling for Hypothesis 3 included one additional set of main covariates. Specifically, Model 4 (HIV-specific factors) included the Model 3 covariates plus HIV-1 RNA levels, CD-4^+ T cell count, and ART regimen. Consequently, Model 5's included the Model 4 covariates plus non-benzodiazepine sleep medication use (5a), PHQ-9 total score (5b), or the three antidepressant medication use

variables (5c). Lastly, Model 6 (all covariates) included the Model 4 covariates plus non-benzodiazepine use, PHQ-9 total score, and antidepressant use variables.

To evaluate whether baseline insomnia symptoms were a stronger predictor of incident atherosclerotic CVD among HIV-infected Veterans than uninfected Veterans (Exploratory Hypothesis), the HIV status main effect and HIV status x insomnia symptoms cross-product interaction term were added to Model 3 involving the entire VACS9 cohort.

For Hypothesis 1-3, I present the overall *p*-value and pairwise comparison hazard ratios (*HR*s) and *p*-values for insomnia symptoms predicting incident atherosclerotic CVD. The overall *p*-values are omnibus tests of the association of insomnia symptoms, across all levels of the variable, with incident atherosclerotic CVD. The pairwise comparison *p*-values are tests of whether the *HR*s for each level of insomnia symptoms (doesn't bother, bothers a little, bothers, and bothers a lot) significantly differs from the *HR*s for the no symptoms reference group. Pairwise comparisons were performed regardless of the overall *p*-value because the bothers and bothers a lot groups may best capture Veterans with insomnia disorder, which was the original predictor variable of interest. It is plausible that the degree of bother reflects the degree of distress and/or impairment due to insomnia symptoms. For the Exploratory Hypothesis, I present the *p*-value for the HIV status x insomnia symptoms cross-product interaction term. This *p*-value is a test of whether the *HR*s for baseline insomnia symptoms predicting incident atherosclerotic CVD are significantly different between uninfected and HIV-infected participants.

To handle missing data, two data imputation approaches were utilized. First, within-person mean imputation was used in the computation of the PHQ-9 total score when only one item was missing (n = 243). Second, multiple imputation was used in the Cox

models to handle missing data for the covariates (see footnote *a* to Table 3 for the extent of missingness). Multiple imputation is three-step process in which missing values are estimated based on a missing-at-random assumption. First, each missing value is estimated from a vector of possible values to create a complete dataset. This process is repeated *n* times to create multiple datasets with the first dataset utilizing the first vector value, the second utilizing the second vector value, and so on. Using five to ten datasets is typical (Horton & Kleinman, 2007). Second, each of the created datasets are analyzed separately, resulting in *n* number of point estimates and standard errors. Third, the results from *n* datasets are combined to create a single point estimate, standard error, and confidence interval. The major advantage of multiple imputation over single imputation is the allowance of uncertainty in the imputation values, reflected by the combination of multiple potential estimated values (Horton & Kleinman, 2007)

The event-to-predictor ratio was examined for each model to assess for possible overfitting. An event-to-predictor ratio of 10:1 is desirable; lower ratios suggest potentially unstable or biased estimates and should be interpreted with caution (Concato et al., 1995; Peduzzi et al., 1995). Models involving the entire cohort had the following event-to-predictor ratios: 52:1 (Model 1), 24:1 (Model 2), 18:1 (Model 3), 17:1 (Model 4a), 17:1 (Model 4b), 16:1 (Model 4c), and 14:1 (Model 5). Models involving the uninfected cohort only had the following ratios: 26:1 (Model 1), 12:1 (Model 2), 9:1 (Model 3), 9:1 (Model 4a), 9:1 (Model 4b), 8:1 (Model 4c), and 7:1 (Model 5). Models involving the HIV-infected cohort only had the following ratios: 26:1 (Model 1), 12:1 (Model 2), 9:1 (Model 3), 8:1 (Model 4), 8:1 (Model 5a), 8:1 (Model 5b), 7:1 (Model 5c), and 6:1 (Model 6).

CHAPTER 3. RESULTS

Participant Characteristics

The entire VACS9 cohort consisted of 6,148 Veterans (n = 3,010 uninfected, n = 3,138 HIV-infected; see Table 3 for participant characteristics). Of note, the median age was 49 years. Most participants were men (94%), and a majority of participants were African Americans (65%). The prevalence of cardiovascular risk factors was generally high, with 61% of participants with hypertension, 16% with diabetes, 27% with obesity, 50% current smokers, 31% high cholesterol, and 18% on a statin. The prevalence of additional potential confounders was also generally high, with 34% of participants with hepatitis C infection, 5% with renal disease, 9% with anemia, 40% with hazardous alcohol use, and 20% with cocaine use. In terms of medications, 7% of participants were using non-benzodiazepine sleep medications, while 33% and 17% were using SSRI or TCA antidepressants, respectively. 21% of the sample scored ≥10 on the PHQ-9, a cut-off score indicative of a potential depressive disorder (Manea, Gilbody, & McMillan, 2012). Additionally, in the HIV-infected cohort, 48% had an HIV-1 RNA level ≥ 500, 22% a CD-4^+ T cell count < 200, and 80% on an ART regimen.

Baseline Insomnia Symptoms

The participant distribution across levels of insomnia symptoms is displayed in Table 4. For both cohorts, the highest frequency was in the no symptoms group, and the lowest frequency was in the doesn't bother group. A chi-square test revealed that there were significant differences between uninfected and HIV-infected Veterans in insomnia symptoms (χ^2 = 11.019, p = .026). Examining the cell contributions to the chi-square total

indicated that uninfected participants had slightly higher rates of no symptoms (43.9% vs. 40.7%) and slightly lower rates of doesn't bother (7.4% vs. 9.2%) than HIV-infected participants. Another chi-square test revealed that there were significant differences between Veterans with and without non-benzodiazepine sleep medication use in insomnia symptoms (χ^2 = 192.93, p < .001). Examining the cell contributions indicated that participants with non-benzodiazepine use had much lower rates of no symptoms (17.4% vs. 44.0%) and much higher rates of bother (24.6% vs. 14.5%) and bothers a lot (32.3% vs. 12.9%) than those without non-benzodiazepine use, as was expected.

TABLE 4. Frequencies for Insomnia Symptoms Levels and Incident Atherosclerotic CVD Events in the VACS9 Cohort

Insomnia Symptoms	**Total Cases**		**Incident Atherosclerotic CVD Cases**	
	No.	**%**	**No.**	**%**
Entire Cohort (N = 6,148)	--	--	362	5.9
No Symptoms	2,598	42.3	155	6.0
Doesn't Bother	513	8.3	22	4.3
Bothers a Little	1,231	20.0	78	6.3
Bothers	932	15.2	53	5.7
Bothers a Lot	874	14.2	54	6.2
Uninfected Cohort (n = 3,010)	--	--	181	6.0
No Symptoms	1,321	43.9	85	6.4
Doesn't Bother	224	7.4	8	3.6
Bothers a Little	582	17.5	40	6.9

TABLE 4. continued

Bothers	460	15.3	28	6.1
Bothers a Lot	423	14.1	20	4.7
HIV-Infected Cohort (n = 3,138)	--	--	181	5.8
No Symptoms	1,277	40.7	70	5.5
Doesn't Bother	289	9.2	14	4.8
Bothers a Little	649	20.7	38	5.9
Bothers	472	15.0	25	5.3
Bothers a Lot	451	14.4	34	7.5

Note. CVD = cardiovascular disease; VACS = Veterans Aging Cohort Study; HIV = human immunodeficiency virus.

Incident Atherosclerotic CVD Events

The median follow-up time was 8.2 years (1st quartile: 4.7, 3rd quartile: 8.9). During this follow-up period, 362 atherosclerotic CVD events were identified – 181 in the uninfected cohort and 181 in the HIV-infected cohort. A chi-square test revealed that the CVD event rate did not differ between uninfected (6.0%) and HIV-infected (5.8%) participants (χ^2 = .125, p = .723). As can be seen in Table 4, only one cell had CVD event counts <10. Consequently, caution should be used when interpreting comparisons involving the doesn't bother group in the uninfected cohort, given that this estimate may not be stable. CVD event rates ranged from 3.6% to 7.5% (see Table 4), with lowest rate in the doesn't bother group in the uninfected cohort and the highest rate in the bothers a lot group in the HIV-infected cohort.

Hypothesis 1: Entire VACS9 Cohort

My first hypothesis that baseline insomnia symptoms will be an independent predictor of incident atherosclerotic CVD in the entire VACS9 cohort was not supported (see Table 5). The omnibus test of the association of insomnia symptoms, across all levels, with incident atherosclerotic CVD (overall *p*-value) was not significant for Models 1 (p = .175), 2 (p = .286), 3 (p = .203), 4a (p = .242), 4b (p = .288), 4c (p = .274), and 5 (p = .268). Similarly, for Models 1-5, none of the pairwise comparisons between no symptoms and the other four insomnia symptom levels (doesn't bother, bothers a little, bothers, and bothers a lot) were significant. An unexpected, though non-significant (*p*-value range: .055-.191), observation is that the *HR*s for the doesn't bother-no symptoms comparison tended to fall below 1.00, suggesting that the doesn't bother group may have a lower risk of atherosclerotic CVD than the no symptoms group.

TABLE 5. Baseline Insomnia Symptoms Predicting Incident Atherosclerotic CVD in the Entire VACS9 Cohort (N = 6,148)

Factor	*HR* (95% *CI*)	*p*-value
Model 1: Demographic Variables		.175
No Symptoms	1.00	--
Doesn't Bother	0.74 (0.47-1.16)	.191
Bothers a Little	1.18 (0.90-1.55)	.243
Bothers	1.10 (0.80-1.50)	.569
Bothers a Lot	1.28 (0.94-1.75)	.120
Model 2: Cardiovascular Risk Factors		.286
No Symptoms	1.00	--
Doesn't Bother	0.70 (0.45-1.10)	.123
Bothers a Little	1.09 (0.82-1.43)	.557

TABLE 5. continued

Bothers	0.99 (0.72-1.35)	.930
Bothers a Lot	1.19 (0.87-1.63)	.288
Model 3: Additional Potential Confounders		.203
No Symptoms	1.00	--
Doesn't Bother	0.67 (0.73-1.05)	.083
Bothers a Little	1.09 (0.82-1.43)	.560
Bothers	0.98 (0.71-1.34)	.881
Bothers a Lot	1.19 (0.87-1.63)	.285
Model 4a: Non-Benzodiazepine Medication		.242
No Symptoms	1.00	--
Doesn't Bother	0.67 (0.43-1.05)	.083
Bothers a Little	1.07 (0.81-1.41)	.625
Bothers	0.96 (0.69-1.32)	.784
Bothers a Lot	1.16 (0.84-1.60)	.372
Model 4b: PHQ-9 Total Score		.288
No Symptoms	1.00	--
Doesn't Bother	0.65 (0.41-1.02)	.063
Bothers a Little	1.04 (0.78-1.38)	.790
Bothers	0.89 (0.63-1.26)	.502
Bothers a Lot	1.02 (0.69-1.50)	.933
Model 4c: Antidepressant Medication		.274
No Symptoms	1.00	--
Doesn't Bother	0.66 (0.42-1.03)	.066
Bothers a Little	1.04, (0.79-1.38)	.765
Bothers	0.90 (0.65-1.25)	.536
Bothers a Lot	1.07 (0.76-1.49)	.709

TABLE 5. continued

Model 5: All Covariates			.268
	No Symptoms	1.00	
	Doesn't Bother	0.64 (0.41-1.01)	.055
	Bothers a Little	1.01 (0.76-1.34)	.948
	Bothers	0.84 (0.59-1.20)	.336
	Bothers a Lot	0.95 (0.64-1.42)	.814

Note. Incident atherosclerotic CVD events = 362. The overall *p*-value is displayed in respective model row.
CVD = cardiovascular disease; VACS = Veterans Aging Cohort Study; HR = hazard ratio; CI = confidence interval.

Hypothesis 2: VACS9 Uninfected Cohort

My second hypothesis that baseline insomnia symptoms will be an independent predictor of incident atherosclerotic CVD in the VACS9 uninfected cohort was also not supported (see Table 6). Once again, the omnibus test (overall *p*-value) was not significant for Models 1 ($p = .291$), 2 ($p = .361$), 3 ($p = .350$), 4 ($p = .349$), 5 ($p = .110$), 6 ($p = .312$), and 7 ($p = .102$). Similarly for Models 1-4, none of the pairwise comparisons between no symptoms and the other four insomnia symptom levels (doesn't bother, bothers a little, bothers, and bothers a lot) were significant (*p*-value range: .051-.811). An unexpected, significant result was observed in Model 5 for the pairwise comparison between bothers a lot-no symptoms ($p = .041$). The associated *HR* suggests that Veterans bothered a lot by difficulty falling or staying asleep are at 48% lower risk of incident atherosclerotic CVD than Veterans without these symptoms, which was unexpected. However, there is little evidence of this inverse association in the simpler models with fewer covariates, which major raises concerns about the reproducibility and meaning of this result. Once again, the *HR*s for the doesn't bother-no symptoms comparison tended to fall below 1.00 (*p*-value

range: .073-.151). Of note, there were only eight cases of incident atherosclerotic CVD in the doesn't bother group, which raises concerns about the stability of these estimates.

TABLE 6. Baseline Insomnia Symptoms Predicting Incident Atherosclerotic CVD in the Uninfected Cohort (*n* = 3,010)

Factor	*HR* (95% *CI*)	*p*-value
Model 1: Demographic Variables		.291
No Symptoms	1.00	--
Doesn't Bother	0.59 (0.28-1.21)	.151
Bothers a Little	1.25 (0.86-1.82)	.249
Bothers	1.14 (0.74-1.76)	.547
Bothers a Lot	0.94 (0.57-1.54)	.811
Model 2: Cardiovascular Risk Factors		.361
No Symptoms	1.00	--
Doesn't Bother	0.58 (0.28-1.19)	.136
Bothers a Little	1.14 (0.78-1.66)	.503
Bothers	1.02 (0.66-1.58)	.937
Bothers a Lot	0.82 (0.50-1.34)	.430
Model 3: Additional Potential Confounders		.350
No Symptoms	1.00	--
Doesn't Bother	0.56 (0.27-1.15)	.115
Bothers a Little	1.11 (0.75-1.62)	.607
Bothers	0.98 (0.63-1.53)	.933
Bothers a Lot	0.79 (0.48-1.30)	.348
Model 4a: Non-benzodiazepine Medication		.349
No Symptoms	1.00	--
Doesn't Bother	0.56 (0.27-1.15)	.115

TABLE 6. continued

Bothers a Little	1.09 (0.74-1.61)	.648
Bothers	0.97 (0.62-1.51)	.885
Bothers a Lot	0.78 (0.47-1.28)	.322
Model 4b: PHQ-9 Total Score		.110
No Symptoms	1.00	--
Doesn't Bother	0.51 (0.25-1.07)	.075
Bothers a Little	1.01 (0.68-1.49)	.969
Bothers	0.80 (0.50-1.30)	.370
Bothers a Lot	0.55 (0.30-1.00)	0.51
Model 4c: Antidepressant Medication		.312
No Symptoms	1.00	--
Doesn't Bother	0.55 (0.26-1.14)	.105
Bothers a Little	1.07 (0.73-1.58)	.728
Bothers	0.95 (0.60-1.49)	.809
Bothers a Lot	0.73 (0.43-1.25)	.255
Model 5: All Covariates		.102
No Symptoms	1.00	--
Doesn't Bother	0.51 (0.24-1.07)	.073
Bothers a Little	0.98 (0.66-1.46)	.928
Bothers	0.78 (0.48-1.28)	.333
Bothers a Lot	0.52* (0.28-0.97)	.041

Note. Incident atherosclerotic CVD events = 181. The overall *p*-value is displayed in respective model row.
CVD = cardiovascular disease; VACS = Veterans Aging Cohort Study; HR = hazard ratio; CI = confidence interval.
*$p < .05$

Hypothesis 3: VACS9 HIV-Infected Cohort

My third hypothesis that baseline insomnia symptoms will be an independent predictor of incident atherosclerotic CVD in the VACS9 HIV-infected cohort was partially supported (see Table 7). Again, the omnibus test (overall *p*-value) was not significant for Models 1 ($p = .169$), 2 ($p = .146$), 3 ($p = .085$), 4 ($p = .115$), 5a ($p = .170$), 5b ($p = .210$), 5c ($p = .332$), and 6 ($p = .325$). Similarly, for Models 1-6, none of the pairwise comparisons between no symptoms and three of the insomnia symptom levels (doesn't bother, bothers a little, and bothers) were significant (*p*-value range: .473-.982). In contrast, for Models 1-5b, a significant result was observed for the pairwise comparison between bothers a lot-no symptoms (*p*-value range: .010-.045). The associated *HR* suggests that Veterans bothered a lot by difficulty falling or staying asleep are at 64-77% greater risk of incident atherosclerotic CVD than Veterans without these symptoms. Of note, for Models 5c and 6, this relationship slightly attenuated (48 and 54% greater risk) and became nonsignificant ($p = .094$ and .112) after adjustment for antidepressant medication use.

TABLE 7. Baseline Insomnia Symptoms Predicting Incident Atherosclerotic CVD in the HIV-infected Cohort (*n* = 3,138)

Factor	*HR* (95% *CI*)	*p*-value
Model 1: Demographic Variables		.169
No Symptoms	1.00	--
Doesn't Bother	0.88 (0.49-1.56)	.653
Bothers a Little	1.12 (0.75-1.66)	.578
Bothers	1.07 (0.67-1.69)	.787
Bothers a Lot	1.66* (1.10-2.51)	.016
Model 2: Cardiovascular Risk Factors		.146
No Symptoms	1.00	--
Doesn't Bother	0.82 (0.46-1.46)	.506
Bothers a Little	1.04 (0.69-1.55)	.859
Bothers	1.01 (0.63-1.60)	.982
Bothers a Lot	1.64* (1.08-2.50)	.020
Model 3: Additional Potential Confounders		.085
No Symptoms	1.00	--
Doesn't Bother	0.80 (0.44-1.46)	.473
Bothers a Little	1.11 (0.73-1.67)	.631
Bothers	1.09 (0.68-1.74)	.722
Bothers a Lot	1.77* (1.15-2.73)	.010
Model 4: HIV-Specific Factors		.115
No Symptoms	1.00	--
Doesn't Bother	0.82 (0.45-1.50)	.519
Bothers a Little	1.11 (0.74-1.68)	.608
Bothers	1.10 (0.69-1.75)	.702
Bothers a Lot	1.73* (1.12-2.68)	.013

TABLE 7. continued

Model 5a: Non-benzodiazepine Medication		.170
No Symptoms	1.00	--
Doesn't Bother	0.82 (0.45-1.49)	.514
Bothers a Little	1.10 (0.73-1.65)	.665
Bothers	1.07 (0.67-1.71)	.781
Bothers a Lot	1.66* (1.07-2.59)	.023
Model 5b: PHQ-9 Total Score		.210
No Symptoms	1.00	--
Doesn't Bother	0.82 (0.45-1.49)	.514
Bothers a Little	1.11 (0.73-1.69)	.631
Bothers	1.09 (0.66-1.79)	.748
Bothers a Lot	1.71* (1.01-2.88)	.045
Model 5c: Antidepressant Medication		.332
No Symptoms	1.00	--
Doesn't Bother	0.80 (0.44-1.45)	.454
Bothers a Little	1.04 (0.69-1.58)	.847
Bothers	0.96 (0.59-1.55)	.862
Bothers a Lot	1.48 (0.94-2.33)	.094
Model 6: All Covariates		.325
No Symptom	1.00	--
Doesn't Bother	0.80 (0.44-1.47)	.481
Bothers a Little	1.05 (0.69-1.60)	.818
Bothers	0.98 (0.59-1.63)	.940
Bothers a Lot	1.54 (0.90-2.62)	.112

Note. Incident atherosclerotic CVD events = 181. The overall *p*-value is displayed in respective model row.
CVD = cardiovascular disease; VACS = Veterans Aging Cohort Study; HR = hazard ratio; CI = confidence interval.
*$p < .05$

Entire VACS9 Cohort – Exploratory Hypothesis

My exploratory hypothesis that insomnia symptoms will be a stronger predictor of incident atherosclerotic CVD among HIV-infected Veterans than among uninfected Veterans was not supported. When added to Model 3 in the entire cohort, the HIV status x insomnia symptoms interaction term was not significant (p = .128), indicating that the overall association of insomnia symptoms with incident atherosclerotic CVD was not significantly different in the uninfected and HIV-infected cohorts.

CHAPTER 4. DISCUSSION

Summary of Results

The overall aim of this study was to examine whether insomnia symptoms are an independent predictor of incident atherosclerotic CVD in uninfected and HIV-infected Veterans. First, chi-square tests revealed that there were minimal, although significant, differences in insomnia symptoms and no differences in incident CVD between uninfected and HIV-infected Veterans. Second, Cox models indicated that Hypotheses 1 and 2 were not supported; baseline insomnia symptoms did not predict incident CVD in the entire VACS9 cohort or in the uninfected cohort. Unexpectedly, uninfected Veterans bothered a lot by difficulty falling or staying asleep exhibited a 48% lower risk of incident CVD than uninfected Veterans without these symptoms in the model including all covariates. Third, Cox models indicated that Hypothesis 3 was partially supported, as HIV-infected Veterans bothered a lot by difficulty falling or staying asleep exhibited a 64-77% greater risk of incident CVD than HIV-infected Veterans without these symptoms, independent of demographic variables, cardiovascular risk factors, additional potential confounders, HIV-specific factors, non-benzodiazepine sleep medication use, and depressive symptoms. However, this relationship was attenuated (48-54% greater risk) and became nonsignificant in the presence of antidepressant medication use. No other differences in incident CVD were detected between the no symptoms group and the other insomnia symptoms groups in the HIV-infected cohort. Lastly, my exploratory hypothesis was not supported. The interaction testing whether insomnia symptoms were a stronger predictor of incident CVD in the HIV-infected versus uninfected cohort was not significant. Taken together, the

present results provide preliminary support that highly bothersome insomnia symptoms may be an independent predictor of incident atherosclerotic CVD among HIV-infected adults.

Limitations and Interpretive Considerations

The present results should be interpreted with caution for a number of reasons. First, the insomnia symptoms item was taken from the HIV Symptom Checklist, a questionnaire validated in a small sample of 113 HIV-infected Veterans at one VA site (Justice et al., 2001). This questionnaire was designed to assess the frequency and bother of common symptoms in HIV-infected patients exposed to multidrug ART and protease inhibitors; thus, it is unclear whether this questionnaire functions similarly in uninfected Veterans. Two plausible explanations exist for the null findings in the uninfected cohort. First, the HIV Symptom Checklist is not appropriate for and may not be valid in uninfected Veterans. Second, it is possible that uninfected and HIV-infected Veterans use the response options differently. Specifically, insomnia severity may need to be higher for HIV-infected Veterans to give a rating of "bothers a lot", given that they are likely coping with many other bothersome symptoms related to HIV. These response option issues could have contributed to the differential associations of insomnia symptoms with incident atherosclerotic CVD observed in uninfected and HIV-infected Veterans. Furthermore, in the HIV Symptom Checklist validation study (Justice et al., 2001), the psychometric properties of the insomnia symptoms item were not directly evaluated. Thus, it is unclear whether this item provides a valid assessment of insomnia symptoms in uninfected or HIV-infected Veterans. Despite these potential issues with the insomnia symptoms assessment, the item (1) was deemed preferable to ICD-9 insomnia disorder codes because of their

unacceptably low sensitivity and (2) was strongly associated with non-benzodiazepine sleep medication use in the expected direction.

Second, using a single item is not sufficient to capture all of the important aspects of insomnia. While the VACS9 insomnia symptoms item assesses difficulty initiating and maintaining sleep and distress (i.e., bothersomeness), it misses other insomnia symptoms, such as early morning awakening and functional impairment, and it does not measure symptom frequency and duration. These issues with content validity could lead to misclassification (e.g., coding a Veteran with insomnia symptoms as not having them), which could contribute to null results or the underestimation of effect sizes. Single-item assessments also tend to have lower reliability than multi-item questionnaires (DeVellis, 2016), which can make it more difficult to detect true associations. Thus, the null findings of the present study may be partially due to the use of a single-item insomnia measure. However, the majority of studies involving uninfected adults have used single-item insomnia measures (most often, difficulty falling asleep) and have observed positive associations with CVD-related outcomes (Li et al., 2014).

Third, because the most complex Cox models included a large number of covariates, some event-to-predictor ratios were lower than the recommended 10:1 (i.e., Models 3-5 for the uninfected cohort and Models 3-6 for the HIV-infected cohort). These lower ratios suggests that the listed models may be overfitted, which raises concerns about the reproducibility of the results in future studies. Overfitted models have a high risk of producing unstable regression coefficients, meaning that estimates are based on the idiosyncrasies of the original sample and will likely fluctuate with repeated sampling (Babyak, 2004). Thus, the unexpected result that uninfected Veterans bothered a lot by

difficulty falling or staying asleep are at a lower risk of incident CVD (Model 5 only) may be a true finding of an overfitted model in the current VACS9 dataset but may not replicate in other datasets. This finding also contradicts the existing literature on the insomnia-CVD relationship in the uninfected population (Li et al., 2014; Schwartz et al., 1999; Sofi et al., 2014), further building the case that this result may be due to overfitting. In contrast, it is unlikely that the finding in the HIV-infected cohort are attributable to overfitted models, as the result that HIV-infected Veterans bothered a lot by difficulty falling or staying asleep are at a higher risk of incident CVD was also detected in simpler, non-overfitted models (i.e., Models 1 and 2).

Fourth, the present study performed a large number of statistical tests with no correction for multiple testing applied. Our team decided against applying a correction because our power for many comparisons is likely low due to lower CVD event counts. Nonetheless, some detected relationships could be type 1 errors. This issue is particularly applicable to the uninfected cohort bothers a lot-no symptoms comparison that only became significant in Model 5. It is less likely that this issue is of concern for the HIV-infected findings as the bothers a lot-no symptoms comparison was consistent across Models 1-5b.

Fifth, despite changing the outcome variable from AMI to the broader atherosclerotic CVD, event counts were still low in some insomnia symptoms groups. In particular, the number of events per insomnia symptoms group in the uninfected cohort was less than the suggested ≥10 (Concato et al., 1995; Peduzzi et al., 1995) for the doesn't bother group (8). This raises concern about whether estimates for this group are stable and unbiased.

Sixth, it is worth noting that including insomnia symptoms, depressive symptoms, and their corresponding medications in the most extensively adjusted models may represent overadjustment. Removal of the shared variance among these variables could have reduced the ability to detect the hypothesized relationships. Thus, the nonsignificant findings for HIV-infected Veterans in the bothers a lot-no symptoms comparison in Models 5c and 6 may be due to overadjustment.

Seventh, the included sample was made up entirely of Veterans and largely included African American males. Such a sample could impede our ability to generalize our findings to other populations and could affect our ability to replicate previous literature findings. For instance, the existing literature does not include studies of Veterans. In addition, little is known about whether psychosocial risk factors, such as insomnia symptoms, contribute to CVD risk differentially in African American versus Caucasian or Hispanic Americans. It is also important to note that the VACS9 cohort includes high rates of substance use diagnoses and a large number of adults with an income <$12,000, which could contribute to sample differences that may have affected my ability to replicate the results of previous studies. However, it is unlikely that our disproportionately higher numbers of males negatively affected the ability to observe the insomnia-CVD relationship as previous studies of largely male samples find significant, positive associations between subjective sleep complaints and CVD events (Li et al., 2014).

Fit With Literature and Leading Explanations

Uninfected Adults. The lack of significant relationships between baseline insomnia symptoms and incident atherosclerotic CVD among uninfected Veterans was surprising and contrasts with the existing literature. To illustrate, a 1999 meta-analysis

found that adults with versus without sleep complaints are 70% more likely to experience a CAD event (Schwartz et al., 1999). Similarly, two 2014 meta-analyses found that adults with sleep complaints are 45% more likely to experience a total CVD event (AMI, CAD, stroke, or CVD-related mortality; Sofi et al., 2014) and that adults with sleep complaints are at a 41% increased risk for AMI, a 28% increased risk for CAD, a 55% increased risk for stroke, and a 33% increased risk for CVD-related mortality (Li et al., 2014). In addition, the one study that examined insomnia disorder found that adults with insomnia disorder are at an 81% increased risk of total CVD events (AMI and stroke), a 68% increased risk of AMI, and an 85% increased risk of stroke (Hsu et al., 2015). To my knowledge, this is the first study to examine the association of insomnia symptoms or insomnia disorder with incident CVD in a Veteran sample.

Conflicting with the existing literature for the uninfected population, I did not observe a positive relationship between insomnia symptoms and incident CVD. There are at least five plausible explanations for this discrepancy. First, the VACS9 insomnia symptoms assessment was from the HIV Symptom Checklist, which may not be appropriate or valid for uninfected Veterans. Second, uninfected and HIV-infected Veterans may be using the response options of the HIV Symptom Checklist differently. Third, it is unknown whether the HIV Symptom Checklist insomnia item provides a valid assessment of insomnia symptoms in either uninfected or HIV-infected Veterans. Fourth, a single item is insufficient to capture all of the important aspects of insomnia. Fifth, the included uninfected sample was made up entirely of Veterans and largely included African American males. These possible explanations are discussed in detail in the previous section.

Also conflicting with the existing literature, I observed an inverse relationship between insomnia symptoms and incident CVD in Model 5 for the uninfected Veterans. However, this finding was not observed in Models 1-4c and, thus, could be due to an overfitted model or a type 1 error. Given that previous literature reports a positive, rather than an inverse, relationship and that statistical concerns may be contributing factors, it is unlikely that this result will replicate in future studies involving uninfected cohorts.

HIV-Infected Adults. For the HIV-infected cohort, the present study reports findings that conflict with existing literature. Previous reviews have reported a high prevalence of sleep disturbance and insomnia symptoms (29-97%) in people with HIV (Low et al., 2014; Reid & Dwyer, 2005). In addition, a meta-analysis found the prevalence of sleep disturbance to be 58% in the HIV-infected population (Wu et al., 2015), which was suspected to be greater than that in the uninfected population (36%; Roth et al., 2006). In the present study, I found a significant difference in insomnia symptoms; however, this difference was minimal and not as large as expected, given past findings. One potential explanation for the smaller than expected difference is that the VACS9 insomnia item did not assess some important aspects of insomnia (e.g., early morning awakening, functional impairment, symptom frequency and duration), which could limit the ability to detect true differences in insomnia prevalence between uninfected and HIV-infected adults. In support of this explanation, the Low et al. (2014) meta-analysis found that studies of HIV-infected samples using the 19-item Pittsburgh Sleep Quality Index reported higher prevalence rates (66-97%) than studies using other measures of sleep disturbance (29-76%).

The present study also reports findings that are novel. Specifically, the results provide preliminary evidence that highly bothersome insomnia symptoms may be an

independent predictor of incident atherosclerotic CVD among HIV-infected adults. To my knowledge, this is the first study to examine insomnia symptoms as a predictor of CVD-related events in HIV. While little is known about potential mechanisms underlying the insomnia-CVD relationship in the HIV-infected population, research from the uninfected population suggests both behavioral (physical inactivity, excessive alcohol use, smoking, poor diet) and biological pathways (hypothalamic-pituitary adrenal axis and autonomic nervous system dysregulation, chronic inflammation, altered coagulation, and endothelial dysfunction; Balbo et al., 2010; Calandra-Buonaura et al., 2016; Haario et al., 2013; Hoefelmann et al., 2012; Htoo et al., 2004; Irwin et al., 2015; Jackowska & Steptoe, 2015; Kohansieh & Makaryus, 2015). Thus far, research in people with HIV has focused solely on inflammation as a biological mechanism and suggests that insomnia is linked to higher levels of inflammatory markers implicated in CVD (Gay et al., 2015; Lee et al., 2014; Wirth et al., 2015). Research examining the link between insomnia and the other potential pathways in HIV is lacking.

Rather than finding a dose-response relationship between insomnia symptoms and incident CVD, I observed a threshold effect, with only the highest level of insomnia symptoms exhibiting an increase in CVD risk. The leading potential explanation for this finding is that (a) the bothered a lot group may have the highest rate of insomnia disorder and that (b) it is insomnia disorder, versus subclinical insomnia symptoms, that is related to elevated CVD risk. Supporting this notion, Veterans bothered a lot by difficulty falling or staying asleep had the highest rate of non-benzodiazepine sleep medication use (32.3%).

I also found that the insomnia symptoms-incident CVD relationship in HIV was attenuated after adjustment for antidepressant medication use. The leading potential explanation for this result, as noted above, is overadjustment. Several antidepressants captured by the antidepressant use variables (amitriptyline, doxepin, nortriptyline, trimipramine, nefazodone, trazodone, and mirtazapine) are also used to treat insomnia. Thus, the antidepressant variables may be additional markers of the presence of insomnia disorder (Buysse, 2013; Wichniak, Wierzbicka, & Jernajczyk, 2012; Wilt et al., 2016).

Finally, the present results suggests that insomnia symptoms are not a stronger predictor of incident CVD in HIV-infected versus uninfected Veterans. To my knowledge, there are not existing studies that have examined whether the risk of CVD conferred by insomnia is different between HIV-infected and uninfected adults. As is discussed above, because there are a number of methodological issues with the VACS9 insomnia assessment, it is unclear whether this result will replicate in future studies utilizing different insomnia assessments.

Future Directions

The present investigation has important limitations to be addressed in future research. Specifically, future prospective studies should: (1) use a comprehensive insomnia symptom measure (e.g., Insomnia Severity Index (Morin, Belleville, Belanger, & Ivers, 2011) or a structured diagnostic interview assessment (e.g., Structured Interview for Sleep Disorders [SIS-D]; Schramm et al., 1993), ideally validated specifically in people with HIV; (2) examine measures of subclinical atherosclerosis (e.g., carotid intima-media thickness or coronary artery calcification), which would provide continuous outcome variables allowing for shorter follow-up periods; (3) utilize samples with greater

generalizability (e.g., non-Veteran samples with a greater representation of women); (4) exclude participants with sleep apnea to help isolate the insomnia-CVD association (sleep apnea is also linked with elevated CVD risk. In addition to these recommendations, future studies should address the literature gap regarding potential mechanisms underlying the insomnia-CVD relationship in HIV. To address this need, I plan to pursue a dissertation with the overall aim of examining the associations of insomnia symptoms with three potential biological pathways of CVD in HIV – systemic inflammation, altered coagulation, and endothelial dysfunction.

Conclusion and Implications

In sum, this prospective cohort study provides preliminary support that highly bothersome insomnia symptoms are an independent predictor of incident atherosclerotic CVD among HIV-infected Veterans. I found that HIV-infected Veterans bothered a lot by difficulty falling or staying asleep have greater CVD risk than HIV-infected Veterans without these symptoms. This study failed to replicate previous findings that insomnia symptoms are predictive of incident CVD in uninfected adults, which may be due to issues related to the validity of the insomnia symptoms assessment. Given the novelty of examining insomnia as a predictor of incident CVD in HIV and the limitations of the present study, future research is needed to better elucidate the association between insomnia and future CVD in this population. Ultimately, research examining the insomnia-CVD relationship in people with HIV could lead to the identification of a novel and treatable risk factor for CVD in HIV and could inform the development of new interventions to prevent CVD in this vulnerable population.

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