An Evaluation of Insomnia Treatment to Reduce Cardiovascular Risk in Patients With Posttraumatic Stress Disorder

NCT04498754

Study Protocol and Statistical Analysis Plan
Document Date: 8/26/2024

Full Protocol: An evaluation of insomnia treatment to reduce cardiovascular risk in patients with posttraumatic stress disorder
Principal Investigators: Jean C. Beckham, Ph.D. and Andrew Sherwood, Ph.D.

SPECIFIC AIMS

Posttraumatic stress disorder (PTSD) is a disabling, chronic, and costly psychiatric disorder that is estimated to occur in 20% of individuals who are exposed to a traumatic event (Kessler, Chiu, Demler, & Walters, 2005). In addition to its negative impact on quality of life, there is substantial evidence that PTSD is associated with a markedly increased risk of morbidity and mortality due to cardiovascular disease (CVD) even after controlling for depression and other risk factors (Flood et al., 2010; Dedert et al., 2012; Edmondson, Kronish, Shaffer, Falzon, & Burg, 2013). Although the mechanisms for the association between PTSD and CVD risk are not well understood, sleep quality (insomnia, sleep efficiency, reduced wake after sleep onset and/or sleep duration) has emerged as being strongly associated with many atherosclerotic CVD risk factors (Irwin, Omstead, & Carroll, 2016; Irwin et al., 2014; Carroll et al., 2015; Meng, Zheng, & Hui, 2013; Li, Zhang, Hou, & Tang, 2014; Aziz et al., 2016; Sofi et al.., 2014; Matthews et al., 2014; Hoevenaar-Blom, Spijkerman, Kromhount, van den Berg, & Verschuren, 2011; Haack et al., 2013; Ferrie et al., 2007; Wang, Xi, Liu, Zhang, & Fu, 2012), and is a prominent complaint among those with PTSD. In fact, most individuals with PTSD also meet criteria for co-morbid Insomnia Disorder. Our pilot data, as well as the work of others, suggest that sleep may mediate the association between PTSD and CVD biomarkers (Irwin, Omstead, & Carroll, 2016; Irwin et al., 2014; Carroll et al., 2015; Meng, Zheng, & Hui, 2013; Li, Zhang, Hou, & Tang, 2014; Aziz et al., 2016; Sofi et al.., 2014; Matthews et al., 2014; Hoevenaar-Blom et al., 2011; Haack et al., 2013; Ferrie et al., 2007; Wang et al., 2012).

Our *long-term goal* is to understand how PTSD increases risk of CVD morbidity and mortality so that preventative and therapeutic strategies can be developed. Impaired sleep is a hallmark symptom of PTSD (American Psychiatric Association, 2013), with insomnia reported by as many as 90% of patients who have received first-line PTSD treatment (Zayfert & DeViva, 2004; Ohayon & Shapiro, 2000). It is well established that insomnia is associated with increased CVD risk (Bonnet & Arand, 2007), but this association has not been studied in those with PTSD (Sofi et al., 2014). The *objective* of this application is to establish the contribution of insomnia to the markedly increased atherosclerotic CVD risk among those with PTSD, and to examine whether this risk can be ameliorated.

Based upon recent evidence, including our own preliminary data, our central hypothesis is that insomnia in those with PTSD is a potentially modifiable feature of PTSD that contributes to CVD. Unfortunately, even following intensive evidence-based psychotherapy for PTSD, insomnia typically remains an unresolved problem (Belleville, Guay, & Marchand, 2011). Recent evidence suggests that a behavioral sleep intervention, Cognitive Behavioral Therapy for Insomnia (CBT-I), can increase improve sleep quality and duration, and promote consolidated sleep among individuals with PTSD (Talbor et al., 2014); however, it is currently unknown whether these improvements would have a favorable impact on CVD risk.

We will test our central hypothesis in a randomized controlled trial (RCT) designed to determine if reduced insomnia symptoms result in improved CVD risk among those with co-morbid PTSD and Insomnia Disorder (ID). Specific and established CVD morbidity and mortality biomarkers of risk will be examined, including vascular endothelial function measured by brachial artery flow-mediated dilation (FMD), nighttime blood pressure (BP) dipping measured using 24-hour ambulatory blood pressure monitoring (ABPM), arterial stiffness measured by central pulse wave velocity (PWV), and atherosclerotic cardiovascular disease (ASCVD) risk score (Bonnet & Arand, 2007; Bonnet & Arand, 2010; Routledge & McFetridge-Durdle, 2007; Tsuji et al., 1996; Verdecchia, Angeli, Gentile, Mazzotta, & Reboldi, 2011). Insomnia will be measured *via* a multi-modal assessment strategy, including self-report and actigraphy. The *rationale* for the proposed research is if it is established that insomnia-related sleep impairment is a modifiable CVD risk factor among those with PTSD, new innovative approaches to integrating sleep treatment with PTSD focused interventions can be developed and implemented.

We will randomize 150 individuals with co-morbid PTSD and ID to either an 8-week CBT-I intervention or to a minimal contact control condition. Insomnia severity and objective sleep parameters, quality of life measures, and biomarkers of CVD risk will be assessed at baseline, post-intervention, and at a 6-month follow-up. Specific Aims include:

AIM 1: Determine whether CBT-I improves (a) CVD risk biomarkers, (b) 10-year ASCVD risk, and (c) quality of life (QoL) in persons with PTSD. *Hypothesis 1*: Compared to the control condition, CBT-I will be associated with increased sleep-efficiency and decreased insomnia severity (manipulation check), improved CVD risk biomarkers (Hypothesis 1a) including (i) lower nighttime BP and enhanced nighttime BP dipping, (ii) augmented vascular endothelial function (FMD), (iii) reduced sympathetic nervous system (SNS) activity (catecholamines), lower 10-year ASCVD risk score (Hypothesis 1b) and improved quality of life (Hypothesis 1c).

AIM 2: Determine whether within-person changes in sleep efficiency are accompanied by improved CVD risk biomarkers and 10-year ASCVD risk. *Hypothesis 2*: Within-person improvements in sleep efficiency (N=150) will be associated with improvements in CVD risk biomarkers and reduced ASCVD risk score.

Supplemental Aim: Explore the heterogeneity of CBT-I treatment response on sleep and CVD risk. We will explore moderators of improvements in sleep and CVD risk biomarkers following CBT-I including primary trauma type, insomnia disorder phenotype (objectively measured short sleep duration vs. objective normal sleep duration), medication use, biological sex, and minority status.

With respect to *expected outcomes*, the proposed work should establish whether unconsolidated sleep contributes to mechanisms conveying CVD risk burden in persons with PTSD. Identification of modifiable determinants of the relationship between PTSD and CVD risk is expected to have an important *positive impact* on the medical management of PTSD.

A. RESEARCH STRATEGY: SIGNIFICANCE AND INNOVATION

Several studies have now linked PTSD to increased cardiovascular disease (CVD) morbidity and

mortality (Boscarino, 2006; Edmondson et al., 2013; Flood et al., 2010), including a two-fold increase in the risk of premature death from CVD (Boscarino, 2008). While the distinct mechanisms underlying this association remain unclear, evidence suggests that PTSD contributes to CVD morbidity and mortality independent of health risk behaviors (e.g., smoking) and comorbid depression (Boscarino, 2008; Vaccarino et al., 2013). A recent review of the available evidence described PTSD as "a fast-track to premature cardiovascular disease" concluding that there was a lack of mechanistic evidence regarding the progression of atherosclersosis in PTSD, and a need to examine CVD risk biomarkers (Wentworth et al., 2013). Establishing the mechanism(s) linking PTSD to CVD is an essential next step in identifying therapeutic targets to reduce cardiovascular risk in this vulnerable population (Committee on Veterans' Affairs House of Representatives Subject, 2010).

We hypothesize that deficits in sleep are causally related to increased CVD risk in persons with PTSD and expect that improving sleep in this population will significantly improve quality of life and cardiovascular risk parameters. The potential benefit of demonstrating that CBT-I is an effective treatment for insomnia in PTSD (AIM 1), and a treatment that also improves QoL (AIM 2) and reduces CVD risk (AIM 3) in this vulnerable population, could be tremendous. The scientific premise of the proposed project is built solidly upon evidence that (1) PTSD is associated with increased rates of insomnia and sleep disturbance even after successful PTSD treatment, (2) insomnia is associated with increased CVD risk in non-clinical populations, and (3) our preliminary data and that from others (Irwin, Omstead, & Carroll, 2016; Irwin et al., 2014; Carroll et al., 2015; Meng, Zheng, & Hui, 2013; Li, Zhang, Hou, & Tang, 2014; Aziz et al., 2016; Sofi et al.., 2014; Matthews et al., 2014; Hoevenaar-Blom et al., 2011; Haack et al., 2013; Ferrie et al., 2007; Wang et al., 2012; McCubbin et al., 2016) suggest that the association between PTSD and CVD risk parameters is mediated by poor sleep. Note that:

- An estimated 7.7 million adults age 18 or older in the United States suffer from PTSD in a given year (Kessler et al., 2005).
- In addition to the deleterious impact of PTSD on emotional, occupational and social functioning, PTSD is a significant risk factor for poor physical health (Beckham et al., 1998; Friedman & Schnurr, 1995; Schnurr & Green, 2004; Spiro, Hankin, Mansell, & Kazis, 2006).
- Studies have linked PTSD to increased cardiovascular disease (CVD) morbidity and mortality (Boscarino, 2006; Edmondson et al., 2013; Flood et al., 2010) including a two-fold increase in the risk of premature death from CVD (Boscarino, 2008).
- PTSD and insomnia are twice as likely to occur in women compared to men (Krishnan & Collop, 2006; Perkonigg, Kessler, Storz, & Wittchen, 2000).
- Over $57 billion is spent annually on mental illness in medical costs, disability payments, and lost productivity (Soni, 2009); the healthcare costs of PTSD exceed costs associated with major depressive disorder (Ivanova et al., 2011).
- Sleep disturbance has been labeled the "hallmark of PTSD" (Ross, Ball, Sullivan, & Caroff, 1989).
- Insomnia among persons with PTSD is associated with increased physical health complaints (Clumb, Nishith, & Resick, 2011; Mohr et al., 2003), and is characterized by self-reported poor sleep quality, objectively measured short sleep duration, increased intermittent wakefulness, and decreased sleep efficiency.
- Insomnia persists following evidence-based PTSD treatments that have otherwise been successful in improving PTSD symptoms (Ohayon & Shapiro, 2000; Belleville, Guay, & Marchand, 2011).

- Our preliminary studies, as well as data from others (McCubbin et al., 2016), suggest that poor sleep is a significant mediator of the relationship between PTSD and CVD risk biomarkers.

Most of the previous work examining insomnia and CVD risk in individuals with PTSD has relied on cross-sectional designs, thus limiting the ability to establish a temporal relationship between PTSD sleep-related symptoms and CVD risk biomarkers. Despite compelling evidence of the link between insomnia and CVD risk, no studies have been specifically designed to examine the role that insomnia plays in the link between PTSD and CVD risk. Further, the current study provides a novel and innovative approach to assessing the direct effect of impaired sleep on CVD risk biomarkers. Since the majority of individuals with PTSD also meet criteria for co-morbid Insomnia Disorder (Talbot et al., 2014), we propose to use CBT-I to treat insomnia with the hypothesis that among those receiving CBT-I, improvements in sleep will result in improved diurnal blood pressure regulation and biomarkers of CVD risk compared to individuals receiving either sleep education alone or usual care. These findings would establish for the first time a direct link between insomnia symptoms (total sleep time [TST], wake after sleep onset [WASO], and sleep efficiency [SE]) and CVD risk among individuals with co-morbid PTSD and ID independent of other symptoms and health risk behaviors. The innovative use of CBT-I to specifically target CVD risk stands to make considerable contributions to research in other at-risk populations (e.g., depression). It is expected that insomnia treatment may be a novel and cost effective approach to reducing the CVD risk burden evident in this population.

B. RESEARCH STRATEGY: APPROACH

B.1. Insomnia and CVD risk

The *scientific premise* for this work is based in part on a growing body of evidence that insomnia is associated with increased CVD risk (Aziz et al., 2016; Carroll et al., 2015; Ferrie et al., 2007; Haack et al., 2013; Hoevenaar-Blom et al., 2011; Li et al., 2014; Matthews et al., 2014; Meng, Zheng, & Hui, 2013; Sofi et al., 2014; Wang et al., 2012). Observational studies employing objective sleep measures are consistent with this larger literature as well, and show that those with insomnia have higher CVD, even after controlling for co-morbid sleep disorders, depression and anxiety (Taylor et al., 2007). Short sleep duration, in either insomniacs or healthy adults, has also been associated with an increased risk of heart disease, higher blood pressure, metabolic syndrome, greater coronary calcification, and higher levels of stress hormones (Bonnet & Arand, 2007).

B.2. Insomnia and PTSD

Sleep disturbance has been labeled the “hallmark of PTSD” (Ross et al., 1989) Insomnia Disorder is defined as difficulty initiating or maintaining sleep (Motivala, 2011), is the most frequently reported symptom of PTSD, and is reported by up to 90% of individuals with PTSD. Insomnia among persons with PTSD is associated with increased physical health complaints (Mohr et al., 2003; Clum, Nishith, & Resick, 2001), and is characterized by self-reported poor sleep quality, objectively measured short sleep duration, increased intermittent wakefulness, and decreased sleep efficiency.

Importantly, insomnia typically persists following evidence-based PTSD treatments that have otherwise been successful in improving PTSD symptoms (Belleville, Guay, & Marchand, 2011; Zayfert & DeViva,

2004). Although most RCTs of PTSD treatments have failed to report effects on sleep, there is increasing evidence that insomnia remains prevalent among patients who were otherwise successfully treated for PTSD (Galovski, Monson, Bruce, & Resick, 2009; Spoormaker & Montgomery, 2008; Zayfert & DeViva, 2004).

B.3. Insomnia Symptoms Fail to Remit Following PTSD Treatment

Importantly, considerable insomnia symptoms persist following evidence-based PTSD treatments that have otherwise been successful in improving PTSD symptoms (Belleville, Guay & Marchand, 2011; Zayfert & DeVIva, 2004). Although most RCTs of PTSD treatments have failed to report effects on sleep, there is increasing evidence that insomnia remains prevalent among patients who were otherwise successfully treated for PTSD (Galovski, Monson, Bruce & Resick, 2009; Spoormaker & Mongomery, 2008; Zayfert & DeVIva, 2004). For example, in an important trial comparing two evidence-based therapies for PTSD, none of the participants randomized to prolonged exposure therapy or cognitive processing therapy achieved reductions in sleep quality on the Pittsburgh Sleep Quality Index (PSQI) that placed them below clinical cutoffs, suggesting none of the sample returned to normal sleep functioning despite treatment gains (Galovski et al., 2009). These results are consistent with prior trials that suggest the majority of patients successfully treated for PTSD (who are no longer reporting nightmares and hypervigilance) still report clinically significant insomnia (Schnurr & Lunney, 2019; Zafert & DeViva, 2004).

B.4. Insomnia may be a Modifiable CVD Risk Factor in those with PTSD

Based upon recent evidence, including our own preliminary data, our central hypothesis is that sleep disturbance in those with PTSD is a potentially modifiable feature of PTSD that contributes to CVD risk. While the evidence that insomnia is a risk for CVD is convincing, the scientific premise for this work is further supported by two recent studies conducted in our laboratory, indicating that impaired sleep was a significant mediator of the association between PTSD and cardiovascular risk mechanisms (see C.8. Preliminary Studies). In order to demonstrate mediation with high scientific rigor, however, randomized trials are needed (Kraemer, 2016). With few exceptions, randomized studies designed to examine physiological response to insomnia treatment are largely absent from the literature. We propose to move the field forward by improving insomnia symptoms via CBT-I in an at-risk population and measuring changes in key cardiovascular risk biomarkers. We expect that improvements in objectively measured sleep efficiency will be accompanied by reduced cardiovascular risk in individuals with PTSD. This premise is supported by recent evidence that improved sleep can reduce blood pressure. In a randomized trial among prehypertensive or Stage 1 hypertensive adults, improved sleep was associated with a concurrent reduction in both systolic and diastolic blood pressure (Haack et al., 2013). Importantly, another recent trial of adults (N=123; aged 55+), has demonstrated that CBT-I treatment results in significant reductions in CVD risk biomarkers (Irwin et al., 2014; Irwin, Olmstead, & Carroll, 2016) including a multisystem CVD risk score (Carroll et al., 2015) where effects persisted at 16-months post-intervention.

B.5. Cognitive Behavioral Therapy for Insomnia (CBT-I) CBT-I has well-established efficacy in improving sleep (Edinger et al., 2001; Geiger-Brown et al., 2015; Morin et al., 2006; Morin et al., 2015; Morin, Culbert, & Schwartz, Morin, Vallieres, & Guay, 2009; 1994; Murtagh & Greenwood, 1995) and can be

delivered by nonspecialist providers (Buysse, Germain, & Moul, 2011; Manber, Carney, & Edinger, 2012; Neylan, 2011). CBT-I is delivered as a short-term intervention and produces long term gains in sleep (Morin et al., 1999; Murtagh & Greenwood, 1995). CBT-I has been shown to be effective even among individuals with other medical and psychiatric morbidity including cancer, depression, alcohol dependence and chronic pain (Smith, Huang, & Maber, 2005). Theoretically, a behavioral model of sleep is applicable to PTSD in that the traumatic event can serve as an initiating event for insomnia while behavioral factors (e.g., time in bed extension) may lead to chronic insomnia(Spielman, Saskin, & Thorpy, 1987). An 8-week course of CBT-I has recently been shown to improve objective and subjective sleep in individuals with PTSD (Talbot et al., 2004), and gains were maintained at 6-months. Bonnet and Arand (2007) have recommended that future research is needed to determine whether sleep interventions that result in improved sleep are also temporally related to reduced CVD risk**.**

B.6. Biomarkers of Cardiovascular Risk

The logistical and financial obstacles (e.g., large sample sizes, extended follow-up periods of years) associated with infrequent "hard" clinical endpoints (e.g., myocardial infarction, stroke, death) has proven to be a major challenge to furthering our understanding of the optimal ways to treat vulnerable patients because of the obvious logistical and financial obstacles such investigations present. One solution to this problem is to first study intermediate markers of risk in vulnerable patients to untoward cardiac events (Rozanski, Blumenthal, Davidson, Saab, & Kubzansky, 2005). Examination of changes in intermediate endpoints can provide important insights into the mechanisms and potential value of clinical interventions and has a number of important advantages over “hard endpoints,” in that fewer patients are required to detect treatment effects and changes in cardiac risk can be reliably and objectively measured over short follow-up intervals. Following the guidelines advanced by a panel of prominent cardiovascular scientists (Naghavi et al., 2003), we propose to examine intervention effects on biomarkers of atherosclerotic cardiovascular risk (i.e., "intermediate endpoints") in “vulnerable” PTSD patients with insomnia**.**

B.6.1. Ambulatory Blood Pressure (ABP) and Blunted Nighttime Blood Pressure (BP) Dipping.

Measurement of BP throughout the day and night by 24-hour ABP monitoring has been shown to be of superior diagnostic and prognostic value than multiple clinic BP readings (Clement, De Buyzere, & De Bacquer, 2003; Dolan, Stanton, & Thom, 2009; Pickering, Schwartz, & James, 1995; Staesson, Asmar, & De Buyzere, 2001;White, Giles, Bakris, Neutel, Davidai, & Weber, 2006). Twenty-four-hour ABP monitoring also allows characterization of the diurnal pattern of BP variation, including daytime BP, nighttime BP, and BP “dipping” (the relative fall in BP from day to night). Nighttime BP is a stronger predictor of cardiovascular risk than clinic or daytime ABP (Hanson, Li, Boggia, Thijs, Richart, & Staessen, 2001). Blunted nighttime BP dipping, including BP non-dipping (typically defined as <10% fall in systolic BP from day to night), is a strong independent prognostic indicator of cardiovascular morbidity and mortality for both hypertensive and non-hypertensive individuals (Ben-Dov, Kark, Ben-Ishay, Mekler, Ben-Arie, & Bursztyn, 2007; Clement, De Buyzere, & De Bacquer, 220; Dolan, Stanton, & Thom, 2009; Fagard, Celis, Thijs, Staessen, Clement, & De Buyzere, 2008; Hansen et al., 2011; Ingelssson, Bjorklund-Bodegard, Lind, Arnlov, & Sundstrom, 2006; Mancia, Facchetti, Bombelli, Grassi, & Sega, 2006; Ohkubo et al., 2002; Staessen et al., 1999). Despite the established adverse consequences of blunted nighttime BP dipping, its causes are less well understood. In terms of

modifiable causes, a number of studies have now shown that impaired sleep quality and insomnia are accompanied by blunted nighttime BP dipping (Hinderliter et al., 2013; Hughes, 2007; Lanfranchi et al., 2009; Loredo, Neleson, Ancoli-Israel, & Dimsdale, 2004; Routledge & McFetridge-Durdle, 2007; Sherwood, Bower, & Routledge, 2012; Sherwood et al., 2011; Ulu, Ulu, & Ulasli, 2013). A recent study linked poor sleep quality to high levels of stress, with both factors contributing to blunted BP dipping (Huang, Mai, & Hu, 2011). PTSD is characterized by both sleep impairment and high levels of stress, but to our knowledge, only two studies have evaluated nighttime BP dipping in individuals with PTSD. Mellman and colleagues (2009) studied 30 young African American men and women with a history of trauma, including 17 individuals with full or sub-threshold lifetime PTSD, with the remainder never having evidenced significant PTSD symptoms. PTSD was found to be associated with nighttime BP non-dipping. A second study by our group (Ulmer, Calhoun, Bosworth, Dennis, & Beckham, 2013) found that sleep quality mediated the association between PTSD symptoms and nighttime BP non-dipping.

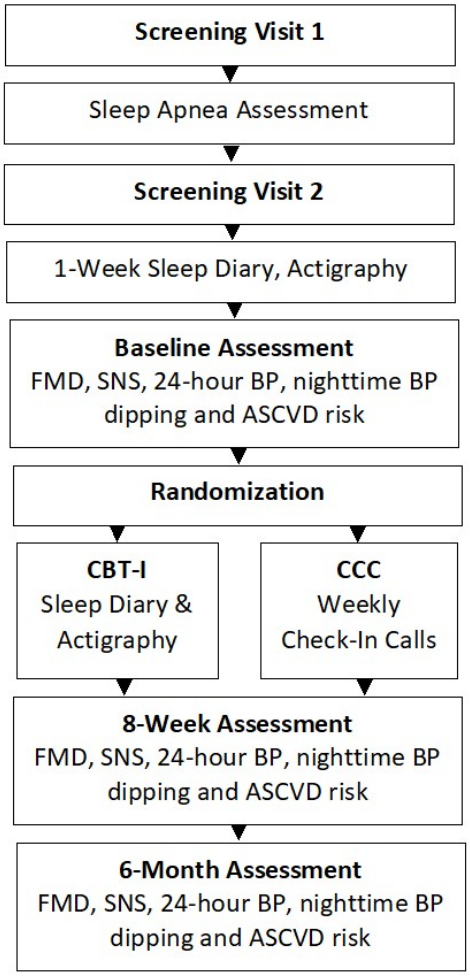
B.6.2. Vascular Endothelial Function assessed by Flow Mediated Dilation (FMD). Vascular endothelial dysfunction plays a vital role in the development, progression, and clinical manifestations of atherosclerosis (Bonetti, Lerman, & Lerman, 2003; Brevetti, Silvestro, Schiano, & Chiariello, 2003). It can be assessed non-invasively using standardized vascular ultrasound techniques to determine FMD of the brachial artery (Celermajer, Sorenson, Bull, Robinson, & Deanfield, 1994; Corretti et al., 2002), , and is prognostic of the clinical manifestation of CVD. It has recently been identified as a mechanism by which posttraumatic stress could contribute to atherosclerosis (Von Kanel et al., 2006). Also, in a recently published study of 496 men and women, impaired FMD was related to poor sleep quality and insomnia (Routledge et al., 2015). Impaired FMD has been linked to elevated depression symptoms (Sherwood, Hinderliter, Watkins, Waugh, & Blumenthal, 2005), elevated anxiety symptoms (Munk et al., 2012), acute mental stress (Ghiadoni et al., 2000; Lind, Johansson, & Hall, 2002; Jambrik, Sebastiani, Picano, Ghelarducci, & Santarcangelo, 2005), and most recently to insomnia (Routledge et al., 2015). Impaired FMD is responsive to treatments designed to reduce CVD risk, and behavioral interventions designed to reduce stress have resulted in improved FMD (Blumenthal et al., 2005).

B.6.3 24-hour Urinary Catecholamines (Epinephrine and Norepinphrine). The SNS is involved in the pathogenesis of hypertension, as well as various manifestations of CBD (Esler, Lambert, Schlaich, & Navar, 2010; Grassi, Mark, & Esler, 2015). SNS activity can be assessed noninvasively by the measurement of catecholamines (epinephrine and norepinephrine) excreted in the urine. Using 24-hour urinary catecholamine assays, partitioned in awake and nighttime sleep-period samples, our own work has shown that blunted nighttime BP dipping is related to nighttime SNS hyperactivity in men and women with hypertension (Sherwood, Steffen, Blumenthal, Kuhn, & Hinderliter, 2002; Sherwood et al., 2011). Data from the Multi-Ethnic Study of Atherosclerosis (MESA) suggest that heightened SNS activity is linked to low sleep efficiency (Castro-Diehl et al., 2016). SNS hyperactivity assessed by 24-hour urinary catecholamine excretion has been found to be associated with low sleep efficiency, measured by actigraphy, in healthy middle-aged men and women (Zhang et al., 2011). These observations are consistent with our hypothesis that SNS hyperactivity is a potential mechanism of CVD risk related to low sleep efficiency. Urinary catecholamines have also been used to document that insomnia disorder is often characterized by a state of hyperarousal (Roehrs & Roth, 2016).

B.6.. 10-year Atherosclerotic Cardiovascular Disease (ASCVD) Risk. ASCVD risk will be based on the Pooled Cohort Equations recently validated and recommended by the clinical practice guideline expert panel of the American College of Cardiology/American Heart Association (Goff et al., 2013). These equations estimate the 10-year risk of a primary ASCVD event (including myocardial infarction and stroke) among patients without pre-existing CVD who are between 40 and 79 years of age. Patients are considered to be at "elevated" risk if the Pooled Cohort Equations predicted risk is ≥ 7.5%. Because several large population studies have shown that insomnia and short sleep duration are linked to hyperlipidemia (Lin, Tsai, & Yeh, 2016), the CBT-I intervention holds promise for both lowering BP and improving the abnormal lipid profiles seen in PTSD (Solter, Thaller, Karlovic, & Crnkovic, 2002).

C. RESEARCH DESIGN AND METHODS

Figure 1. Study Design



C.1. Study Design Overview

In an innovative use of an established and well validated intervention for insomnia, we propose to examine the direct effects of sleep on biomarkers of CVD risk outcomes among persons with PTSD and comorbid insomnia disorder (ID; see Figure 1). In this 2-arm RCT, 150 participants with PTSD and ID will be randomized at a 2:1 ratio to either CBT-I, or a minimal contact control condition (CCC). We anticipate that we may need to consent and screen as many as 500 participants to reach this goal. Sleep efficiency as measured by actigraphy will be the primary sleep outcome measure. Other parameters [total sleep time (TST) wake after sleep onset (WASO), sleep fragmentation) will be measured with a multi-modal assessment strategy including validated self-report measures, sleep diaries collected *via* Qualtrics, and objective sleep measurement (i.e., actigraphy). Sleep diaries and actigraphy will be continuously collected for 10-weeks (including a week-long baseline, 8-week period for CBT-I or CCC, and one-week post treatment) and for a week-long period at the 6-month follow-up. The primary outcomes for this clinical trial are established biomarkers of CVD risk, including flow mediated dilation, SNS activity, nighttime BP, nighttime BP dipping, and ASCVD risk. These biomarkers will be assessed at three time points: baseline, post-intervention (8-weeks), and 6-month follow-up. The 6-month follow-up period will allow us to evaluate whether the intervention effects on CVD risk are sustained beyond the immediate post-intervention period. Timing for the 6-month follow-up visit will be 6 months after the baseline assessment or three months after the post-intervention assessment, whichever is later. Participants in both arms will continue with usual medical care.

C.2. Recruitment

Participants (N=150) will be recruited from among outpatients in the primary care and PTSD clinics at the Duke University Medical Center (DUMC), and in the community. This procedure has been used in our previous studies with strong success for recruitment of individuals with PTSD. Over the past five years, approximately 1,200 males and females have participated in our ongoing clinical research studies and there has never been difficulty with recruitment of PTSD participants for our studies. The samples we have collected include men and women with and without PTSD; men and women who have trauma exposure but no PTSD; PTSD resulting from a wide range of trauma exposures including sexual assault, physical assault, accidents, and combat; and significant minority representation.

On recruitment materials, we will plan to use an acronym to refer to the study. That acronym is UPLIFT, **U**nderstanding **P**TSD Risk by **L**essening **I**nsomnia **F**rom **T**reatment.

Recruitment materials such as IRB-approved study flyers and brochures will be placed in outpatient clinic areas at DUMC. In addition, study flyers will be placed throughout DUMC in centrally located posting areas. Study recruitment materials will advertise a research study that includes insomnia treatment for persons with PTSD. This recruitment method will be used over the course of the entire recruitment period. We will also contract with a third-party company, BuildClinical, to enhance recruitment. BuildClinical is a data-driven platform that helps academic researchers recruit participants for research studies more efficiently using social media, software, and machine learning. We have included for your review the recruitment materials that they have developed. BuildClinical utilizes study-specific advertisements to engage participants on digital platforms such as Facebook, Google, WebMD, etc., and redirect them to a study-specific landing page should they click it. On the landing page, the person can complete an online pre-screen questionnaire. Duke staff can log into the BuildClinical portal to retrieve information about potential participants.

We will identify potential participants using Duke's Deduce and Maestro Care systems. We will identify potentially eligible participants, using diagnostic and contact information in those systems. Potentially eligible participants will be sent information and invitation to participate via 1) MyChart, 2) an introductory letter, or 3) email asking them to consider participation, and they will be provided contact information for the study coordinator. Potential participants may also be called about a week after they are sent the letter to determine interest. Potential participants will be contacted no more than three times, as indicated by DOCR guidelines. They will also be provided information about how to opt out of additional contact from the study team re: this study.

We will also identify potential participants using University of North Carolina (UNC) medical center's messaging health care system, My UNC Care. Our team at UNC will use PHI including diagnostic information, medical record numbers, and participant names. In accordance with UNC's policies regarding this recruitment type, the UNC study team will reach out to potential participants via My UNC Chart to inform them of the Duke study, and to ask them to consider participation. Interested participants will be provided the name, telephone number, and email address of the study coordinator, and will be asked to contact them about participation. They will also be provided a link to a Qualtrics

survey that will screen them for participation. No staff at Duke will have access to the PHI of UNC patients unless those patients contact the study team about participation. Only UNC staff will access PHI of UNC patients. The UNC site will rely on Duke's IRB for oversight, please see the reliance agreement provided. Please note that Dr. Patrick Smith, the UNC investigator who will be assisting with this recruitment effort, is already listed on our project as key personnel outside Duke. Please note that although Dr. Smith will have access to the PHI of UNC patients, he will not have any access to Duke PHI after participants provide consent at Duke.

Maestro Care MyChart messaging: This study will use a MaestroCare MyChart recruitment invitation to help identify potential participants pre-consent. Potential participants are identified via a report generated within Maestro Care by the DOCR Maestro Care Analyst team. A recruitment invitation will be sent by a DOCR analyst to potential participants via MyChart. The patient will indicate if they are interested or not interested, and they will be asked to complete a survey designed to evaluate eligibility. The study coordinator will be sent an Inbasket message (Maestro Care internal message) indicating the response. Only key personnel who are delegated the task of patient identification/recruitment will have access to the Inbasket messages. Only patients who express interest and meet basic study eligibility will be contacted by key personnel, who will then follow the recruitment process approved by the IRB for this study. If a patient expresses interest and the study team determines the patient is not qualified for the study prior to contacting them, they will be sent an approved email letting them know. If a patient does not open their MyChart message, the Maestro or Epic Analyst can send up to two additional "tickler" notifications, at least a week apart, to let the patient know they have an unread message.

We will plan to use a recruitment method referred to as respondent-driven sampling, or "seed recruitment" (Christina Meade, Ph.D., personal communication). Seed recruitment is suitable for sampling "hidden populations" of participants who are best known by their own peers (Heckathorn, 1997). It includes providing incentives to participants for referral of other eligible participants. In our model, each participant, or seed, will receive three coupons to recruit other people in his/her social networks. The recruitment coupons will provide a brief description of the survey and a phone number for contacting the study coordinator. The coupon will be marked with a unique identification number (not the study identification number) so that when the coupons are returned to us, the ID number can be used to provide payment ($20) to the participant who made the referral. The key connecting the participant's study ID number with the seed ID number will be kept in a database separate from other PHI, creating two layers of separation between the seed ID and the already-participating person's identifying information. Any participant who does not wish to recruit in this manner will not be required to do so.

The study will be registered at clinicaltrials.gov, which will allow for online recruitment during the course of the study. As needed in years one through five, we will advertise the study in local area newspapers, on Duke University's clinical research website, and on online classified advertising websites such as Craigslist.com, DukeList, or JobFinder.com. In addition, we will post study recruitment materials at local community areas such as laundromats, Bull Connector bus lines, substance use treatment centers, rape crisis centers, battered women shelters/programs, restaurants, and grocery

stores.

Our study team will use social media to reach potentially eligible participants. We have developed a Facebook page for posting IRB-approved study flyers and information for this and other studies in the Traumatic Stress and Health Research Laboratory, https://www.facebook.com/Duke-Traumatic-Stress-and-Health-Research-Lab-379366159145563/. We plan to place pictures of our study flyers on the Facebook page, and use Facebook's post boost to draw attention to the post. The post itself will say "Enroll now!" or "Now enrolling!" We will also plan to use Facebook ads to target potential participants within a 50-mile radius of Duke. If any participant contacts the email associated with the Facebook page (TSHRLab@dm.duke.edu, he/she will be sent an automatic email response.

Any participant who contacts by telephone the study coordinator or other study staff regarding the study will be provided more information, and will be interviewed using an IRB-approved telephone screening. If a participant is deemed potentially eligible in the telephone screen, he/she will be scheduled to attend a formal screening visit. We will send, via Duke secured email, appointment reminders to any participant who wants to receive them. Prior to beginning study procedures, the study staff member obtaining consent will explain the study in detail, provide the participant with an IRB-approved written consent form explaining the procedures and risks, and answer any questions. The consent form will be signed via RedCap. Participants are given the chance to thoroughly read the consent prior to participation. Participants are given a copy of the signed informed consent form, and are given phone numbers to call if they have additional questions about the consent form or the research, if they have any problems during the study, or if they have questions about participating in research studies in general. With regards to determination of decision making capacity of potential participants, our laboratory has a standard procedure for determining understanding of the study procedures, risks, and benefits. We utilize this procedure if we have any reason to suspect that the participant may have difficulty in the consent process (e.g., traumatic brain injury impacting cognitive function, active psychotic symptoms). In this procedure, the study coordinator providing the informed consent information evaluates understanding of the procedures at several different time points during the process by asking questions like "Do you understand what we're asking you to do?" and "Do you have any questions about the risks of the study? Can you tell me what you understand the risks to be?" Prior to having a participant sign consent, the study coordinator, who has clinical experience in working with persons with psychotic disorders, may ask the potential participant to outline the study procedures, risks, and benefits so that he can make sure that the participant is aware of them. If the participant is unable to summarize these, he/she will not be allowed to sign the informed consent form, and may be referred for other treatment. No study procedures will begin until informed consent has been obtained.

C.3. Patient Eligibility and Randomization

Participants must meet each of the following inclusion criteria:

- Are between 40-59 years old;
- Has a current diagnosis of chronic PTSD (at least 3 months duration) based on the Clinician Administered PTSD Scale DSM-5 version (Weathers et al., 2013);
- Has a current diagnosis of ID as defined in the International Classification of Sleep Disorders

(ICSD-3; American Academy of Sleep Medicine, 2014)

Participants who meet any of the following criteria will be excluded from participation:

- Has a history of CVD events, including myocardial infarction, stroke, transient ischemic attack, or coronary revascularization;
- Has diagnosis of congestive heart failure or coronary artery disease based on results of diagnostic testing;
- Has a current alcohol use or substance use disorder (those who meet lifetime but not current alcohol or substance use disorder will be included);
- Is currently participating in an evidence-based trauma focused therapy for PTSD (i.e., Prolonged Exposure, Cognitive Processing Therapy, or Eye Movement Desensitization and Reprocessing);
- Has cognitive impairment as evidenced by <u>less than 20</u> on the Montreal Cognitive Assessment scale (M0CA; Nasreddine et al., 2005);
- Meets criteria for a psychotic spectrum disorder or bipolar disorder;
- Has severely impaired hearing or speech;
- Is pregnant;
- Does not use benzodiazepines for sleep, and if prescribed benzodiazepines for some other use (e.g., anxiety, panic attacks), uses them fewer than four times in a one month period.;
- Is not stable (medications and dose stable for one month) on any other current psychoactive and/or cardiovascular medications or will not be stable on these medications during the course of the study;
- Works night shift;
- Is participating in another interventional study to address insomnia;
- Has prominent suicidal or homicidal ideation (as assessed through a clinical interview);
- Has nonclinically significant or sub-threshold insomnia as indicated by a score of <8 on the Insomnia Severity Index;
- Has seizures (based on clinical interview and self-report);
- Has a body mass index of 45 or greater;
- Has sleep apnea (based on the overnight assessment described below) or a positive sleep apnea screen;
- Has restless leg syndrome (based on the *Duke Structured Interview for Sleep Disorders* (DSISD)*;* Edinger, Wyatt, & Olsen, 2009), and that sleep disorder is the primary cause of their sleep complaint (participants with restless legs syndrome who also have insomnia disorder can be included in the study);
- Has an organic cause of sleep disruption that cannot be addressed by cognitive-behavioral changes (e.g., hyperthyroidism), as determined by the DSISD;
- Has excessive daytime sleepiness, defined as a score >15 on the Epworth Sleepiness Scale (ESS) or as determined by the DSISD;
- Does not complete sleep diary assessments within 6 hours of rising on at least 5 of the 7 days of the initial assessment period; or
- Cancels or no-shows for two or more Time 1 assessment appointments

- Has uncontrolled hypertension (screening office BP > 160/100 mm Hg)

Participants who cannot complete study procedures may be withdrawn by the PIs. If any participant is excluded due to uncontrolled hypertension seeks treatment and their blood pressure becomes adequately controlled {e.g., with a stable antihypertensive medication regimen), they will become eligible to participate if their clinic/office blood pressure is lower than 160/100 mm Hg and they have been stable on their antihypertensive medication(s) for one month.

Because the physiological changes of pregnancy may impact study outcome, we will exclude women who self-report pregnancy. Urine samples will be assayed by a trained staff member using a Quidel QuickVue pregnancy test. These pregnancy tests will be completed for women of childbearing potential. We have developed a short interview for female participants; this interview will help us determine which female participants must have a urine pregnancy test, and when the test should be done. Female participants of childbearing potential who are not pregnant must agree to use appropriate contraception during the course of the study, and to notify study staff if they become pregnant during the study.

Dropout rates across psychological and pharmacologic studies in our clinic that involved 3 to 15 visits have ranged from 0 to 20%. Participants who drop out will receive partial reimbursement for the time they donate. Eligible participants will be randomized to either CBT-I, or CCC+ in a 2:1 ratio. Randomization will be stratified by gender and smoking. Participants will be paid $1060 for their complete participation.

During the study, study staff members will communicate with participants via phone, email, standard mail, or texts sent from a Duke-owned phone, based on participant preferences. Participants will be allowed to opt out of texting or emailing if they wish.

C.4. Interventions

C.4.1. Cognitive Behavior Therapy for Insomnia (CBT-I). The approach to CBT-I for the proposed study is based on CBT-I programs that have been practiced and studied by research team members (Karlin, Trockel, Tylor, Gimeno, & Manber, 2013; Manber, Carney, & Edinger, 2012). CBT-I is manualized in a session-by-session guide (Perlis, Jungquist, Smith, & Posner, 2005). Dr. Ulmer serves as a consultant and trainer on the nationwide dissemination of CBT-I. Dr. Ulmer will train study therapists to deliver CBT-I in accordance with the training approach adopted by the CBT-I dissemination effort (Karlin, Trockel, Tylor, Gimeno, & Manber, 2013). Further, Dr. Manber will be available for consultation regarding the training procedures and fidelity measures and methods.

C.4.2. Minimal Contact Control Condition. Participants assigned to the CCC will be contacted via WebEx or Zoom every week for eight weeks. To monitor their insomnia symptoms and mood, they will be asked to complete the PTSD Checklist and Insomnia Severity Index. Check-in calls will be audio-recorded. This will allow us to do fidelity ratings to ensure that participants are not receiving any sleep interventions, advice, etc. Please note that our lab has an SOP related to suicide risk assessment, and the study coordinator who makes the check-in calls has been trained in the use of the SOP. Participants

will be asked about any insomnia treatments they use/receive during usual care. At the end of the 6-month follow-up, participants randomized to this condition will be offered CBT-I.

C.4.3. Intervention Training and Fidelity. Study therapists will include Dr. Ulmer and two masters' level mental health providers. Each therapist will provide treatment in both arms. Masters' level therapists will be trained by Dr. Ulmer. Initial didactic training (covering session by session procedures, core components of CBT-I and SH+) will last three days and be followed by training cases. Therapists will be allowed to provide the intervention once they have demonstrated 100% competence and adherence with all required treatment elements. Therapists will meet weekly for supervision throughout the trial. All therapy sessions will be audio-recorded. A random selection of twenty percent will be rated for fidelity. In order to protect against drift, the frequency of fidelity checks will occur equally across the beginning, middle, and end of the intervention period. Dr. Ulmer will rate therapist treatment fidelity/adherence for recorded sessions using the adapted version of the *Yale Adherence and Competence Scale* (Carroll, 2000). In the CBT-I condition, recordings will be rated on the presence/absence of CBT-I elements. In the comparison condition, recordings will be rated on the presence of proscribed elements of CBT-I. In addition, recordings from both conditions will be rated on the presence/absence of nonspecific treatment elements (e.g., therapeutic alliance, patient expectancies). Feedback from fidelity checks will be provided to therapists. In addition, emergency procedures for suicidal and homicidal ideation have been well developed in our laboratory and these will be carefully followed for each participant. Dr. Manber will also provide consultation to Dr. Ulmer.

C.5. Measures

We have experience assessing all the proposed measures and items discussed below. Table 1 summarizes the measures and the timepoints at which they are given.

Table 2. Study Measures

Measure	Completer 1=Beckham team, 2=Sherwood team	Time			
		Screen*	Baseline	PostTxt	6-Mon
Clinician Administered PTSD Scale	Trained interviewer[1]	X[2]			
Structured Clinical Interview for DSM5	Trained interviewer[1]	X[2]			
Duke Structured Interview for Sleep Disorders	Trained interviewer[2]	X[1]			
Montreal Cognitive Assessment	Trained interviewer[1]	X[1]			
Traumatic Life Events Questionnaire	Participant	X[1]			
PTSD Checklist	Participant	X[1]	X	X	X
Beck Depression Inventory – II	Participant	X[1]	X	X	X
WHO Disability Assessment Schedule	Participant	X[1]			
WHO Quality of Life	Participant		X	X	X
Everyday Discrimination Scale	Participant	X[1]			
Short Form-36 Health Survey	Participant		X	X	X
Daily sleep diaries	Participant	X	X	X	X
Insomnia Severity Index	Participant	X[1]	X	X	X
Pittsburgh Sleep Quality Index with PTSD addendum	Participant		X	X	X

Epworth Sleepiness Scale	Participant	X[1]			
Medical Problems Checklist	Study coordinator[1]	X[1]			
STOP-BANG	Participant	X[1]			
Pre-Sleep Arousal Scale	Participant		X	X	X
Demographics measure	Participant	X[1]			
Fagerström Test for Nicotine Dependence	Participant	X[1]			
AUDIT-C	Participant	X[1]			
Leisure Time Exercise Questionnaire	Participant		X	X	X
Menopausal status	Participant		X		X
PEG	Participant	X[1]			
Medications List	Participant	X[1]	X	X	X
Insomnia Treatment Measure	Participant			X	Xau
Over-the-Counter Medications List	Participant	X[1]	X	X	X
Physiological Measures					
Actigraphy	Study staff[2]		X	X	X
WatchPAT One sleep apnea assessment	Participant	X[2]			
24-hour blood pressure assessment	Study staff[2]		X	X	X
Flow mediated dilation	Study staff[2]		X	X	X
24-hour urinary catecholamines	Participant[2]		X	X	X
ASCVD risk	Study staff[2]		X	X	X
Body Mass Index	Study staff[2]		X	X	X
* Superscript 1 indicates that these procedures are completed at the first screen visit, and superscript 2 items are completed at the second screen visit.					

C.5.1. PTSD, Depression, Alcohol Use Disorder and Quality of Life Measures. The *Clinician-Administered PTSD Scale* (CAPS; Weathers, Blake, et al., 2013) will be utilized to establish PTSD diagnosis. The CAPS is considered to be the gold standard for determining PTSD diagnosis. The Traumatic Life Events Questionnaire (TLEQ; Kubany, Hill, & Owens, 2003) is designed to assess exposure to traumatic events, and has an item to assess exposure to combat. Individual items/exposures can be summed to reflect a total exposure type score. PTSD symptom severity will be measured by the PTSD Checklist (PCL5) with criterion A (Weathers, Litz et al., 2013). Diagnoses other than PTSD will be assessed using the *Structured Clinical Interview for DSM-5* (SCID). The SCID has been shown to have good reliability (Williams, Gibbon, First, 1992) and includes modules that determine current and lifetime psychiatric disorders. PTSD symptom severity will be measured by the PTSD Checklist (PCL5 with criterion A; Weathers, Litz et al., 2013). The Everyday Discrimination Scale will measure the perceived frequency of chronic, routine and subtle experiences of unfair treatment that could be one dimension of perceived stress in our sample (Williams, Yu, Jackson, & Anderson, 1997).*Depressive symptoms* will be measured with the Beck Depression Inventory-II (Beck, Steer, & Brown, 1996). *Functional status* will be measured using the World Health Organization Disability Assessment Schedule 2.0 (WHO DAS-II), a 36-item self-report of functional disability designed to measure functioning and impairment over the past 30 days. The WHO DAS-II has exhibited excellent reliability and validity in prior research (Garin et al., 2010). *Quality of life* will be measured using the Short Form-36 Health Survey (SF-36; Ware & Sherbourne, 1992), which provides a physical health and mental health QoL summary score. The SF-36 has demonstrated reliability and validity in PTSD populations (Shiner, Watts, Pomerantz, Young-Xu, & Schnurr, 2011). We will also use the World Health Organization Quality of Life Scale, Brief Version (WHOQOL-BREF).

C.5.2. Insomnia and Sleep Measurement. Sleep measurement will include both subjective and objective measures. Subjective measures will include sleep diaries collected via interactive voice technology and self-report measures of sleep quality, insomnia severity, and perceived daytime sleepiness. Actigraphy will be employed as an objective measure of the sleep outcomes (TST, WASO, and SE).

C.5.2.1 Interview-Based Assessment. The *Duke Structured Interview for Sleep Disorders* (DSISD) is currently being revised to be consistent with DSM-V and the International Classification of Sleep Disorders, and will be administered to identify those meeting criteria for ID and rule out individuals having excluded co-morbid sleep disorders. The DSISD has been shown to have good reliability and validity (Edinger, Wyatt, & Olsen, 2009). The DSISD will be given during the first screening session.

C.5.2.2. Sleep Apnea Assessment. Following the DSISD and (completed at the enrollment visit), if a participant has scored a three or greater on the STOP BANG, the potential study participant will be sent home with a portable apnea screening device to wear for 1 complete night to rule out sleep apnea. The WatchPAT device (Itamar Medical) is a sensitive and specific assessment for identifying the presence of obstructive sleep apnea. The device requires that participants download an app that will sync with the device and transfer the data to WatchPAT's servers. Participants will be given the option of using their own personal phone or using a Duke-owned iPhone that they then return. In the event that the sleep evaluation reveals that a participant shows an apnea-hypopnea index (AHI) > 15 (i.e., more than 5 sleep apnea-hypopneas per hour of sleep) (Walczewska et al., 2011), participant will be notified that they are no longer eligible to continue, and will be encouraged to seek additional evaluation and treatment through their physician (Epstein et al., 2009).

In the event of any equipment malfunction, participants may be asked to repeat the WatchPAT home study. In order to reliably rule out obstructive sleep apnea, a minimum of 4 hours of recording time is required. Therefore, if participants notice any of the equipment coming off in the middle of the night, they will be instructed to reattach. If it is found that there is less than 4 hours of recording time, the participant will be asked to repeat the in-home study. To prevent this from occurring, participants will be given detailed instructions and staff will provide an in-person demonstration to show them how to properly use the device.

C.5.2.3. Actigraphy. Actiwatch Spectrum Plus® (Respironics, Inc.) are wristwatch style actigraphs containing a calibrated accelerometer that samples, digitizes, and stores movement activity. When interfaced with a computer, a scoring algorithm provides estimates of various sleep parameters. When costly PSG is not feasible and sleep staging outcomes are not the focus of research, wrist actigraphy is recommended as an essential measure of rest-activity patterns in insomnia research (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006). The following sleep metrics will be collected over a one week period at baseline, post-treatment, and 6-month follow-up: Time in Bed (TIB), TST, WASO, and sleep fragmentation (Ancoli-Israel, Cole, Alessi, Chambers, Moorcroft, & Pollack, 2003; Blackwell et al., 2008; Littner et al., 2003; Marino et al., 2013; Morgenthaler et al., 2007; Sadeh & Acebo, 2002; Sadeh, Hauri, Kripke, & Lavie, 1995; Thorpy et al., 1995). These parameters will also be collected during the entire 8-

week treatment period.

Sleep duration will be defined as TST (calculated by subtracting all periods of wakefulness from the time spent in bed). WASO is calculated by summing wakefulness periods after initial sleep onset and before final awakening. Sleep efficiency is defined as the ratio of total sleep time divided by TIB (TST/TIB). Sleep fragmentation (a secondary outcome) is defined as the sum of percent mobile and percent immobile bouts less than 1-minute duration to the number of immobile bouts for a given interval (Respironics Incorporated, 2008). Actigraphy will be used as the primary source for these variables (Lauderdale, Knutson, Yan, Liu, & Rathouz, 2008). Scoring of actigraphy data will proceed in accordance with the guidelines by the Society of Behavioral Sleep Medicine (Ancoli-Israel et al., 2015). The sleep diary will include queries about removal of the actigraphy watch from the wrist, and unusual activities during the monitoring period (e.g., travel), and these factors will be considered when scoring. The event marker will be used as the primary method for establishing "into bed" and "out of bed" times. However, when study participants fail to press the event marker, (i.e., no marker on actigraphy output), light sensor data and sleep diaries will be combined with accelerometery data to establish "into and out of bed" times.

C.5.2.4. Daily Sleep Diaries. Subjective sleep estimates will be obtained concurrent with actigraphy, using a Qualtrics survey. Participants will record their sleep using the recently developed consensus sleep diary (Carney et al., 2012) to assure comparability across insomnia research studies. Sleep diaries will be used to calculate averages for: TIB, sleep onset latency (SOL) (Marino et al., 2013), TST, WASO, and SE. The sleep diary is considered the gold standard of self-reported sleep (Buysse et al., 2006). We will use Duke Qualtrics to gather the daily sleep diaries.

C.5.2.5. Subjective Insomnia Severity Measures. Subjective insomnia severity will be evaluated utilizing the *Insomnia Severity Index* (Bastien, Vallieres, & Morin, 2001). The ISI provides a global measure of perceived insomnia severity. The total scores range from 0-28, with higher scores indicating higher severity. The ISI has excellent internal consistency (Cronbach alpha = 0.74) and temporal stability (r = 0.80). The ISI has been validated with sleep diaries and PSG (Bastien, Vallieres, & Morin, 2001). In clinical samples, a cut off score of 11 was shown to have the greatest sensitivity and specificity for correctly identifying study participants meeting criteria for insomnia diagnosis (Morin, Belleville, Belanger, & Ivers, 2011). Because we are using the ISI as an screening measure and as a within-subject outcome, we will use a cut score of 8, which is indicative of subthreshold insomnia. Diagnosis of insomnia will be determined by a structured sleep interview. Other sleep measures to be used, each of which has been shown to have internal consistency and validity, include the *Pittsburgh Sleep Quality Index* (*PSQI*; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), a 19-item measure of sleep quality and disturbances over the past month, the *Pittsburgh Sleep Quality Index-Addendum* (*PSQI-A*; Germain, Hall, Krakow, Katherine, & Buysse, 2005), which assesses other disruptive nocturnal behaviors related to PTSD including hot flashes, nightmares and episodes of terror during sleep; and the *Epworth Sleepiness Scale* (*ESS*; Johns, 1991), an 8-item measure of perceived daytime sleepiness.

C.5.2.6. Sleep-Related Arousal. The Pre-Sleep Arousal Scale (PSAS; Jansson-Fröjmark & Norell-Clarke, 2012) is a widely used measure of pre-sleep arousal with cognitive and somatic arousal subscales.

Scores on the 13-item measure range from 8-40. The PSAS demonstrated acceptable internal consistency on both the cognitive and somatic arousal subscales, and it effectively discriminated between normal sleepers, poor sleepers, and those with insomnia disorder. The PSAS demonstrated convergent validity with measures of sleep-related worry, sleep-related beliefs, anxiety, depression, sleep parameters, and daytime impairment.

C.5.3. Demographic Variables, Medical Screen and Health Risk Behaviors. Each participant's medical history will be reviewed, and clinic BP will be determined by standard sphygmomanometry. We will collect demographic, health risk, and other clinical information that will be used in part to characterize study participants' 10-year risk for ASCVD (Goff et al., 2013). Education, occupation and household income will be added to provide a composite measure. Education will be measured by highest degree earned. Occupation will be coded into three categories. This summary variable has been reported in studies examining the relationship between social status and psychological and physiological functioning (Adler, Epel, Castellazzo, & Ickovics, 2000). We will collect information about participants' current medications and current/lifetime medical diagnoses. In addition, we will collect data on body mass index (BMI), calculated using participant's weight and height. This measurement will be done at the baseline lab visit. The *Fagerström Test of Nicotine Dependence* (*FTND*; Heatherton, Kozlowski, Frecker, & Fagerström, 1991) and a smoking history questionnaire (e.g., number of cigarettes smoked/day, age of first smoking, number of previous quit attempts) will be used to measure smoking behaviors. Self-reported alcohol use will be assessed with the three-item AUDIT-C (Bush, Kivlanhan, McDonnel, Fihn, & Bradley, 1998), which has demonstrated reliability and validity (Crawford et al., 2013). The Leisure Time Exercise Questionnaire (Godin & Shephard, 1985) will be collected *via* Qualtrics during the day of ABP assessment). We will also check for the presence of cognitive impairment using the *Montreal Cognitive Assessment* (MoCA; Nasreddine et al., 2005). This tool has been used as a short cognitive screening tool for identifying impaired cognitive functioning in the general population; scores range from 0 to 30, and any individual who scores below 20 will be excluded from participation due to the presence of cognitive impairment (Gallagher et al., 2013). Although the cut score of 26 has good specificity and sensitivity to diagnose mild cognitive impairment (MCI; Hoops et al., 2009), we do not wish to rule out participants with MCI, but rather those with dementia. A cut score of 26 will likely otherwise suitable participants, as CPT has been successfully used in patients with traumatic brain injury (TBI) and MCI. Any participant who is excluded due to low MoCA scores will be informed of the results and encouraged to discuss the findings with their personal physician or care provider for further evaluation and treatment if necessary.

C.5.4. Measurement of Other Potential Covariates. Menopausal status will be documented by self-reported menstrual bleeding, using the criteria described by Tom and colleagues (2010). Status categories are postmenopausal (natural or surgical), perimenopausal, and premenopausal. Menopausal status and lifetime alcohol use disorder (as well as current alcohol consumption measured as drinks per week) will be considered as potential covariates in analytic models. Pain will be measured with the 3-item PEG, a reliable and valid brief version of the Brief Pain Inventory (Krebs et al., 2009). For descriptive and analytic purposes, each patient's medications will be recorded and classified as: anticholinergic; alpha-adrenergic blockade; beta-blockade and other anti-hypertensive medications (diuretics, ACE inhibitors, and calcium channel blockers); specific serotonin re-uptake inhibitor (SSRI);

heterocyclic antidepressant; lithium; MAOI anti-depressant; other antidepressant; neuroleptic; or sedative-hypnotic. This classification system is based on our previous work involving the input and consensus of our team physicians (Beckham et al., 2000).

C.6. Measures of Cardiovascular Disease Risk

C.6.1. Assessment of 24-hour Ambulatory Blood Pressure (ABP). We have experience measuring 24-hour ABP and will use the Oscar 2 ABP monitor (Suntech Medical Inc., Raleigh, NC), which has been validated by previous investigators (Goodwin, Bilous, Winship, Finn, & Jones, 2007; Jones, Bilous, Winship, Finn, & Goodwin, 2004). Clinic BP will be determined according to the new ACC/AHA guidelines (Whelton et al., 2018) with three readings taken after five minutes of quiet rest in a seated posture, each separated by 2 minutes, using the Oscar 2 BP monitor together with appropriate cuff size, and averaged to represent clinic BP. Subsequently, he ABP monitor will be programmed to take BP measurements every 20 minutes throughout the waking hours and every 30 minutes during the nighttime sleep period. We have used this procedure with excellent participant acceptability and compliance in numerous previous studies (Blumenthal, Sherwood, & Gullette, 2000; Carels, Sherwood, Szczepanski, & Blumenthal, 2000; Prather, Blumenthal, Hinderliter, & Sherwood, 2011; Sherwood et al., 2011; Sherwood, Thurston, Steffen, Blumenthal, Waugh, & Hinderliter, 2001). A successful 24-hour study will require at least 80% of the total readings to be valid, with no more than two consecutive hours lacking a valid reading (White et al., 2006). Unsuccessful ABP studies will be repeated.

In addition to mean 24-hour ABP, mean waking and nighttime ABP will be computed, with the nighttime sleep period defined by self-report and confirmed by actigraphy (Sherwood et al., 2001; Sherwood et al., 2011; Sherwood et al., 2002). Nighttime BP dipping will be defined as the percentage of the decline in nighttime systolic blood pressure (SBP) [(mean daytime SBP- mean nighttime SBP/mean daytime SBP) × 100]; SBP dipping defined in this way is a continuous variable that will be a primary outcome measure in this proposed RCT. In addition, for descriptive purposes, a SBP dip ≥ 10% will be classified as normal “dipper”, while <10% will be classified as “non-dipper”, with secondary analyses evaluating intervention effects on dipping status. Twenty-four-hour ABP assessments will be obtained at pre-randomization baseline, upon completion of the 8-week intervention, and at 6-month follow-up, in order to evaluate intervention effects on ABP and nighttime BP dipping.

C.6.2. Flow Mediated Dilation (FMD). Our approach for assessing endothelial function conforms to the recently published guidelines for assessment of flow-mediated arterial vasodilatation (Thijssen et al., 2011). Longitudinal B-mode ultrasound images of the brachial artery, 4-6 cm proximal to the antecubital crease, will be obtained at end-diastole (ECG R-wave gated digital image capture) using a dedicated Acuson Aspen ultrasound platform. All images will be acquired with participants supine, utilizing an 11 MHz linear array probe with stereotactic holder in our temperature-controlled clinical research laboratory, by Michael Ellis, RDMS, RVT, who has over 15 years of experience performing the standardized image acquisition protocols for our ultrasound FMD assessments. In an unpublished evaluation of 20 healthy men and women who underwent our FMD assessment protocol on two consecutive days, repeat FMD values showed a correlation of r=0.81, p<.001, a mean absolute difference of 0.64%. Images will be obtained and stored digitally at resting baseline, as well as during and following inflation to 250 mm Hg of an occlusion cuff placed around the forearm, 2 cm below the

elbow. All arterial diameter measurements will be performed by the same experienced member of the research team (AS), blinded to participant identity and treatment condition, using edge detection software (Brachial Analyzer, MIA-LLC, Coralville, IA). FMD response will be assessed from 10-120 seconds post-deflation of the forearm cuff, with peak arterial diameter quantified using polynomial curve fitting, and FMD thereby defined as the maximum percent change in arterial diameter relative to pre-inflation resting baseline. As others have reported, using this rigorous standardization of FMD methodology, our FMD assessments will be obtained with optimal reproducibility, reflected in a coefficient of variation of approximately 10% or less (Donald et al., 2008; Ghiadoni et al., 2012; Charakida et al., 2013). Peak hyperemic flow and shear stress will be derived by standard formulae based upon Doppler velocity measurements during the first 10 seconds following deflation of the occlusion cuff (Mitchell et al., 2004; Pyke, Hartnett, & Tschakovsky, 2008).

***C.6.3. 24-hour Urinary Catecholamines (Epinephrine and Norepinephrine)*.** Patients will be asked to collect urine over a 24-hour period (Blumenthal, Sherwood, & Gullette, 2000; Hughes, Watkins, Blumenthal, Kuhn, & Sherwood, 2004; Sherwood, Steffen et al., 2002; Zhang et al., 2011, White, Brunner, & Barron, 1995;. Urine samples will be kept cold by storage in a portable cooler throughout each 24-hour sample period. Urine will be collected in three containers provided to each participant in a portable cooler, with careful instructions to collect daytime/awake urine in containers labeled accordingly, including the last collection before bedtime; any nighttime/sleep period urine collection will be collected in the container labelled "nighttime", and participants will be instructed to void using that collection container as soon as they get up in the morning. Samples will be assayed for norepinephrine, epinephrine, and creatinine. Catecholamine levels will be expressed as urine concentration (µg/ml) per urine concentration of creatinine (mg/ml), yielding norepinephrine and epinephrine values of µg per mg creatinine for each sample. This provides catecholamine excretion indices that are corrected for individual differences in body size and urine volume (White, Brunner, & Barron, 1995). In prior studies of circadian changes in sympathetic activity, urinary catecholamine data have proven informative, with low subject burden and excellent compliance (Blumenthal, Sherwood, & Gullette, 2000; Hughes et al., 2004; Sherwood, Steffen et al., 2002; Steffen, Hinderliter, Blumenthal, & Sherwood, 2001). 24-urinary catecholamines (epinephrine and norepinephrine) have also been shown to be inversely related to sleep efficiency measured by actigraphy (Zhang et al., 2011).

C.6.4. ASCVD – 10-Year Consensus Markers. We will collect demographic and clinical information required to characterize study participants' 10-year risk for ASCVD, and calculate it at baseline, post CBT-I, and at 6-month follow-up. The variables that are included in risk assessment equations are age, race, total and HDL-cholesterol, systolic BP (including treated or untreated status), diabetes, and current smoking status. Information on age, gender, race, and treatment of hypertension will be collected. Clinical information will be obtained from medical record review. Lipids and glucose levels will be determined from blood specimens drawn between 8:00-10:00 am following overnight fasting. All blood samples will be kept refrigerated until transfer to the appropriate laboratories. Lipids will be determined by enzymatic methods.

C.7. Risk/Benefit Ratio and Protections Against Risk

C.7.1. Study Risks. In both conditions, with regards to completing study measures, there is a risk of

discomfort or distress in answering questions, especially questions related to traumatic experiences. However, distress and discomfort related to questionnaire completion are usually temporary and well-tolerated. With the blood draw, there is a risk of bruising at the site of the draw and rarely, fainting and/or infection. There is a minimal risk of disrupted sleep associated with the sleep apnea assessment. The Oscar 2 ABPM has built in safe-guards to avoid over-inflation or prolonged inflation of the cuff, as well as a measurement abort key that can be activated by the participant. The FMD assessment will include blood pressure cuff inflation for 5 minutes, which has the risk of causing tingling and discomfort in the arm. There are no known risks associated with use of the actigraphy or the Qualtrics sleep diary. There is a potential risk associated with the loss of confidentiality of study data, although all due precautions will be taken to minimize such risk. Participants are provided information during the informed consent process about risks inherent with mobile app download and use, and use of a Duke-owned, loaned device.

C.7.2. Potential Benefits. While participants may benefit from improved sleep and/or reduced insomnia complaints, there are no guaranteed benefits to the individual participant and no immediate benefits of the proposed research to others. Information gathered from participants may help us to establish a link between sleep impairment and autonomic and inflammatory markers of CVD risk among individuals with PTSD. In our opinion, the anticipated benefits of this study outweigh the potential risks.

C.7.3. Protection from Risk. Participants are informed clearly during the initial informed consent process that the study is completely voluntary, and that they may refuse to answer any items that they do not wish to answer on the questionnaires and interviews. They are also informed that they are free to decline participation in any procedure and can withdraw from the study at any time. Potential risks will be minimized by carefully screening potential participants according to the inclusion/exclusion criteria, closely monitoring symptom levels, and following established laboratory procedures. Patients will complete the MoCA to assess cognitive function. Patients who score <20, which suggests the presence of cognitive impairment, will be informed of the results and encouraged to discuss the findings with their personal care physician for further evaluation and treatment if necessary. With regards to determination of decision making capacity of potential participants, our laboratory has a standard procedure for determining understanding of the study procedures, risks, and benefits. We utilize this procedure if we have any reason to suspect that the participant may have difficulty in the consent process (e.g., traumatic brain injury impacting cognitive function, active psychotic symptoms). In this procedure, the study coordinator providing the informed consent information evaluates understanding of the procedures at several different time points during the process by asking questions like “Do you understand what we’re asking you to do?” and “Do you have any questions about the risks of the study? Can you tell me what you understand the risks to be?”

C.7.4. Data Storage and Security. Data that links participants to information collected in the course of a given study will be kept separately from identifying information in an electronic, password-protected MS Access database stored at duhsnas-pri\dusom_psych\private\irb\beckham\PTSD Insomnia; the key connecting identifying information and data will be stored here as well. Hard copy paper records will be stored in a locked filing cabinet in the study coordinator’s locked office within Dr. Beckham’s

laboratory space at Duke University Medical Center. Information from the interview and/or questionnaires may be entered into a computerized database that will be stored on the DUMC server at duhsnas-pri\dusom_psych\private\irb\beckham\PTSD Insomnia in a password-protected database. This database is accessible only by Dr. Beckham, Dr. Sherwood, and study staff. Any staff members who leave the study for any reason will have access to study resources, including data, removed immediately.

Audio recordings of therapy sessions and check-in calls will be made via Duke Zoom or WebEx. We will record directly to a Duke-owned laptop, and then transfer recordings to the Duke shared server In the event that we move back to in-person visits post-pandemic, we will use a Duke-owned iPhone or iPad that is encrypted at levels compliant with FIPS 140-2 standards. The device to be used will be hardened such that only the recording capability will remain. Recordings will be moved from the device to the Duke shared server (file path above) as soon as possible after the recordings have been made, and will then be deleted from the mobile device. Any device that is not in use will be stored in a locked filing cabinet in the study coordinator's office. Recordings will remain on the Duke shared drive until they are reviewed for fidelity by Dr. Ulmer. The recordings will be copied to an encrypted hard drive for permanent storage, and the copies on the Duke shared drive will be deleted. The encrypted hard drive will be stored in a locked file cabinet in Dr. Beckham's lab space at Duke. Only the key personnel listed on the staff listing will have access to the encryption password and/or the hard drive.

C.7.5. Data and Safety Monitoring Plan

We believe that provision of treatment for insomnia should enhance rather than jeopardize health status, and potential serious adverse events (SAEs) for participants in this project are not expected. Regardless, we will minimize potential risk by carefully screening potential participants and following established laboratory procedures for physiological data acquisition and data safety monitoring. The individuals responsible for data safety and monitoring will be the PIs, the co-Investigators, and the study coordinator.

Dr. Beckham will serve as the primary safety monitor for the proposed study. There will be several ongoing mechanisms for monitoring and reporting of adverse events (AEs), including serious adverse events (SAEs): 1) ongoing participant contact via study personnel; 2) a telephone number provided to participants to report concerns related to study participation; 3) weekly meetings between Dr. Beckham and study personnel. In order to monitor possible adverse events, participants will be instructed to report any adverse effects of study participation as soon as possible to research staff; they will have contact information needed to report these problems to study personnel. The PI will meet at least weekly with study personnel to discuss participants' reactions to the intervention, proper delivery of the intervention, and any adverse events or unanticipated problems. Monthly meetings between the investigators and the study coordinator will allow for ongoing progress reports, including the number of participants currently involved in the study groups, attrition rates, and scheduled data collection from participants, as well as notification and review of any AEs. Safety monitoring for adverse events will be conducted in real time by Dr. Beckham and/or study coordinator. The following information about adverse events will be collected: 1) the onset and resolution of the AE, 2) an

assessment of the severity or intensity, 3) an assessment of the relationship of the event to the study (definitely, probably, possibly or not related), and 4) action taken (e.g., none, referral to physician, start or increase concomitant medication). Dr. Beckham will determine the severity of the event, will assign attribution to the event, and will monitor the event until its resolution.

Any adverse events (AEs) will be reported to the Duke University Medical Center (DUMC) Institutional Review Board (IRB) in accordance with the local Human Research Protection Program's Standards of Practice. These guidelines require immediate reporting of any SAEs that are potentially study related. All research projects conducted at DUMC are required to have yearly IRB review. Reports of non-serious AEs or unanticipated problems that may increase risk for study participants or others are required as part of the annual progress reports. Additionally, any changes to the project between review periods must be approved by the IRB prior to implementation. All communication with the DUMC IRB will occur using Duke's electronic IRB system (IRIS).

C.7.6. Plans for Responding to Psychiatric Emergencies. Given the nature of PTSD symptoms, it is not unexpected that participants will experience increased distress associated with the assessment procedures and diagnostic clinical interviews. Our extensive clinical and research experience suggest that there is no serious risk in these patients associated with assessment and interview procedures as proposed. Over the past several years, several hundred patients with PTSD have participated in our research team's clinical trials, and there have been only rare occurrences of serious adverse events (i.e., hospitalization only) due to PTSD symptom increases.

The Traumatic Stress and Health Research Laboratory (TSHRL) has established, IRB-approved standards of practice (SOP) for the evaluation of risk of suicide and homicide. All study staff members are trained in use of the psychiatric emergencies SOP by a Ph.D. or Masters' level clinician with years of experience in working with persons with PTSD. The SOP includes a thorough risk assessment including evaluation of risk factors and protective factors associated with both suicide and homicide. Also included in the policy are differential recommendations for action based on determinations of low, moderate, or high risk. Any staff member conducting an interview in which moderate or high risk is determined will contact a senior staff person with clinical expertise in risk assessment [including the PI, co-investigator(s), and/or DUMC's Emergency Room]. At several time points throughout the study, participants are reminded that they are asked to inform the study therapist, study coordinator, or study PI if they experience a psychiatric emergency such as homicidal or suicidal ideation. In addition, participants are provided the telephone number of study staff who they can call in the case of psychiatric emergencies, including an after-hours contact number.

C.7.7. Post-Study Referrals for Participants. It is not unexpected that participants in both conditions may complete the study with residual PTSD and/or major depressive disorder symptoms. Because participants complete the PTSD Checklist (PCL5) and the Beck Depression Inventory-II (BDI-II) at multiple time points, we will refer to these scores at the end of the study as a gauge of residual symptoms. We will provide referrals for continued treatment to anyone with a score of 38 or higher on the PCL5 and/or a BDI-II score of 20 or higher (i.e., moderate to severe depression range). Additionally, referrals will be provided to participants who self-report distress at symptoms of PTSD or depression

(regardless of measure scores) and wish to continue with another form of treatment. The TSHRL has developed patient educational materials regarding available resources, including portable resource cards for participants. Participant resources may include local community mental health centers, local private mental health providers, Duke Adult Psychiatry Clinic, Duke's Psychology Clinic, and other resources such as emergency clinics and substance abuse treatment centers. Where applicable and convenient to the participant, direct referral will be made in addition to providing resource cards.

Table 2. Participant Reimbursement	
Task Completed	**Payment**
Screening Visit	Up to $75
Sleep Apnea Screen and Actigraphy Monitoring	$100
Baseline Labs (FMD, ABP)	$225
Treatment Sessions (8)	$0
Posttreatment Actigraphy Monitoring (1 week)	$50
Posttreatment Labs (FMD, ABP)	$250
Follow-up Actigraphy Monitoring (1 week)	$50
Follow-up Labs (FMD, ABP)	$250
Seed recruitment	$60
TOTAL	**$1060**

C.7.8. Subject Reimbursement.
Reimbursement to participants will offset the costs in time, effort, and possible lost wages associated with commitment to the study. Participants are paid as indicated in Table 2. Participants who are eligible for treatment will not receive payment for study participation until completion of the post-treatment actigraphy monitoring and labs. At that time, they will be paid $700. If participants are excluded prior to randomization, or withdraw from CBT-I, they will be paid for their study participation to date.

Participants will be provided parking passes and/or bus passes to encourage attendance at all sessions.

D. STATISTICAL ANALYSES

D.1. General Considerations and Descriptive Analyses

The study is designed as a two-arm trial to examine the effects of CBT-I on objective sleep parameters and CVD risk biomarkers. Statistical analyses will be performed using SAS, version 9.4 (SAS Institute, Cary, NC) and Mplus, version 7 (Muthén & Muthén, 2012). The first step in the analysis will be to calculate descriptive statistics, including graphical displays, to summarize all study variables. We will construct individual and mean trajectory plots of the longitudinal outcome variables to understand their general trends from baseline to post-intervention and 6-month follow-up. In addition, we will explore the variability and correlation structure of the longitudinal outcome variables. We will stratify by trauma exposure (combat or non-combat) and objectively measured sleep duration (<6 hours or $\geq$6 hours).

Each of the study hypotheses will be examined using data collected at baseline, immediately following the 8-week intervention phase (i.e., post-intervention), and again at 6-month follow-up. Given nesting of these multiple observations within each participant, multilevel modeling (MLM) will be used to examine each set of hypotheses. MLM is a technique for analyzing repeated observations of data across multiple individuals (Searle, Casella, & McCulloch, 1992). Unlike repeated-measures ANOVA,

MLM uses all available data and can handle data missing at random. MLM can also accommodate imbalanced data and unequal variances.

To manage the problem of random positive findings when making multiple comparisons within each hypothesis (i.e., random significant findings occurring due to multiple proposed analyses), we will correct alpha using the "false discovery rate approach" described by Glickman (Glickman, Rao, & Schultz, 2014). This methodology differentiates random findings from hypothesis-driven outcomes and is more powerful than Bonferroni-type alpha adjustments that control the false-positive rate (Benjamini, 2010; Glickman, Rao, & Schultz, 2014; Schafer & Olsen, 1988; Searle, Casella, & McCulloch, 1992; Simes, 1986). Specifically, alpha correction will be applied to Aims 1 and 2 but not to the Supplemental Aim, given that any exploratory hypothesis that is supported would require validation with further research.

D.2. Missing Data Considerations

MLM can accommodate data missing at random, using maximum likelihood-derived estimates based on all available data. That said, data may be missing not at random (MNAR). That is, the outcome data may be systematically missing, for instance, from participants who experience no benefit from CBT-I. Nevertheless, even in the case of MNAR data, estimates derived from analyses examining Hypothesis 2 (addressing the within-person associations of change in insomnia with change in CVD risk) and the Supplemental Aim are unlikely to be affected by data missingness. After all, even if participants who benefit the least from CBT-I drop out of the study, we still anticipate observing the same magnitude of association between improved sleep and changes in cardiovascular biomarkers and QoL. By contrast, Hypothesis 1, which examines clinical response to CBT-I, would be affected by MNAR data. As such, we will conduct sensitivity analysis on three missing data approaches for Aim 1. First, we will conduct a completer analysis, analyzing only data from participants who complete each of the three assessments. Second, we will allow the maximum-likelihood estimation to generate estimates for all available data. In a third approach, we will use an intent-to-treat approach, assuming that missing post-intervention and/or 6-month follow-up data are evidence of stagnation. Specifically, we will use last observation carried forward in the cases of missing data.

D.3. Primary and Secondary Analyses

To examine the degree to which CBT-I is associated with improved sleep efficiency and insomnia severity index score (manipulation check), linear MLM will be used to model sleep outcomes as a function of treatment (CBT-I, control), time (baseline, post-intervention, 6-month follow-up), and the interaction between treatment and time. Planned treatment contrasts in change from baseline to post-intervention and 6-month follow-up will be examined within the context of the model. To determine the degree to which CBT-I is associated with improved CVD risk biomarkers (Hypotheses 1a), each of the 6 CVD risk variables (24-hr SBP, nighttime SBP dipping, FMD, 24-hr epinephrine, and norepinephrine) will also be modeled as a function of treatment, time, and their interaction, with planned treatment contrasts in change from baseline at post-intervention and 6-month follow-up. Dichotomized 10-year ASCVD risk scores (Hypothesis 1b) and QoL scores (Hypothesis 1c) will similarly be modeled via logistic MLM.

To examine whether increased sleep efficiency is associated with decreased CVD risk (Hypothesis 2), lagged values will be used to create changes scores, defined by subtracting values for sleep efficiency and each of the CVD risk parameters measured at time *t-1* from those measured at time *t*. Thus, decreases will be reflected by negative change scores and increases by positive change scores. Linear MLM will then be used to model each of the change scores corresponding to the 6 aforementioned CVD risk variables using the general equation below:

$\text{CVD risk}_{\Delta t} = B0 + B1*\text{Sleep efficiency}_{\Delta t} + B2*\text{CVD risk}_{t-1} + B3*\text{Sleep efficiency}_{t-1}$

where change in the CVD risk outcome from *t-1* to *t* will be modeled as a function of corresponding change in sleep efficiency, covarying for sleep efficiency measured at *t-1* and the outcome in question measured at *t-1*. To explore the heterogeneity of CBT-I treatment response on sleep (Supplemental Aim), potential moderators (trauma type, insomnia phenotype, medication use, biological sex, and minority status) of the effect of CBT-I treatment on sleep outcomes will be examined via interaction effects. Specifically, sleep efficiency and sleep quality measured at baseline, post-intervention, and 6-month follow-up will be modeled in separate analyses as a function of treatment, time, a given moderator, and their second- and third-order interactions. To avoid the effects of multicollinearity, each moderator will be tested in a separate analysis. To determine whether the effect of changes in sleep efficiency on changes in CVD risk parameters vary by each of the aforementioned moderators, the analyses specified above for Hypothesis 2 will be modified to examine the main effect of a given moderator as well as the interaction effect of the moderator and sleep efficiency on each of the CVD risk variables.

D.4. Sample Size and Power Considerations

Calculations are based on Aims 1 and 2. Because each of the analyses will make use of repeated-measures data, statistical power will depend on the effective sample size (ESS). For Hypotheses 1, which will examine treatment effects associated with differences in sleep and cardiovascular outcomes, the ESS will be equivalent to the total number of observations (number of participants x number of data collections) adjusted for intra-individual correlations. As the intra-individual, or intra-class, correlation (ICC) decreases, the ESS increases. Given that we anticipate substantial intra-individual variability on account of the intervention, an ICC of .50, representing an equal allotment of variance attributable to inter-individual differences and intra-individual variability, provides a conservative estimate of the ESS. With a sample of 150 contributing 3-time points of data each and an ICC of .50, the ESS would be 225. Even with 10% attrition post-intervention and then again at the 6-month follow-up, the ESS would be 215. Assuming equivalent attrition rates among the 100 CBT-I participants and 50 controls, this would have 80% power to detect treatment effects equivalent to Cohen's *d* of 0.41 via a two-tailed test with an alpha of .05. For reference, a meta-analysis on CBT-I (Okajima, Komada, & Inoue, 2011) found 12-month treatment effects on SOL, WASO, and sleep efficiency equivalent to *d* = 0.45, 0.47, and 0.54, respectively. *Six-month follow-up CBT-I treatment effects in Talbot et al.'s (2014) RCT of CBT-I in persons with PTSD far exceeded these for SE (d = 1.48), SOL (d = 1.31), and TST (d = 0.76). Moreover, Talbot et al. (2014) recorded large effects of CBT-I on 6-month increases in psychosocial functioning (d = 1.02).* Although the specific impact of CBT-I on CVD risk remains untested, comparable behavioral-health interventions, such as stress management, have shown robust effects. For instance, in one study, 16 weeks of weekly 1.5-hour stress-management training compared to usual care was sufficient to achieve large increases in FMD (*d* = 2.32; Blumenthal,

Sherwood et al., 2005). In another study, a similar regimen of weekly group stress-management sessions was associated with significantly reduced time to adverse cardiac events, *HR* = 0.26 (95% CI: 0.07-0.90), in comparison to usual care. Given these effect sizes, the present study should have adequate power to detect treatment effects similar to those found in previous trials**.**

The second aim, which will examine within-person associations of changes in sleep efficiency with concomitant changes in cardiovascular indices, will have an ESS that is roughly equivalent to the total number of observations. With 150 participants contributing up to 2 change scores each, even with 10% attrition at each time point, the ESS is projected to be 256, which would have 80% power to detect an association equivalent to β = .15. A number of studies have established cross-sectional associations of sleep disturbance with cardiovascular risk factors (Spiegelhalder, Scholtes, & Riemann, 2010). In our own research, we have found that self-reported sleep disturbance is modestly associated with reduced heart-rate variability (β = -.18) and dyslipidemia (equivalent β = .11). We anticipate that these associations will be stronger in the proposed within-subjects analysis given the absence of random effects from between-person differences. Thus, the current trial should be sufficiently powered to detect even modest associations between concurrent changes in sleep efficiency and CVD risk parameters.

D.5. Data Sharing with Key Personnel Outside Duke

Patrick Smith, PhD, at University of North Carolina at Chapel Hill, will perform some of the above-described statistical analyses in accordance with a sub-award to him. De-identified data will be shared with Dr. Smith via Box@Duke. No PHI, including dates, will be shared with Dr. Smith.

E. STUDY TIMELINE

The overall data collection and analysis timeline is outlined in Table 3. Recruitment will occur in years 1 through 5. Intervention delivery and follow-ups will occur in years 1-5.

Table 3. Project Timeline

ACTIVITY	Year 1	Year 2	Year 3	Year 4	Year 5	Totals
Hiring/Training/Development	X					
Screening	26	48	47	47	31	199
Recruitment	20	35	35	35	25	150
DATA COLLECTION						
CVD & Sleep Measures	20	35	35	35	25	150
Treatment Waitlist	20	35	35	35	25	150
Post Assessment	15	38	34	32	23	142
6-month Assessment	0	40	38	41	23	142
Data Processing				X	X	
Data Analysis					X	

References

Adler, N.E., Epel, E.S., Castellazzo, G. & Ickovics, J.R. (2000). Relationship of subjective and objective social status with psychological and physiological functioning: Preliminary data in health white women. *Health Psychology,* 19, 586-92.

Alsaadi, S.M., McAuley, J.H., Hush, J.M., Bartlett, D.J., McKeough, Z.M., Grunstein, R.R., Dungan II, G.C. & Maher, C.G. (2014). Assessing sleep disturbance in low back pain: The validity of portable instruments. *PloS One,* 9, e95824.

American Academy of Sleep Medicine. (2014). *The International Classification of Sleep Disorders, 3rd ed*. Darien, IL: American Academy of Sleep Medicine.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Arlington, VA: American Psychiatric Association.

Ancoli-Israel, S., Cole, S., Alessi, C., Chambers, M., Moorcroft, W. & Pollak, C.P. (2003). The role of actigraphy in the study of sleep and circadian rhythms. *Sleep,* 26, 342-92.

Ancoli-Israel, S., Martin, J.L., Blackwell, T., Buenaver, L., Liu, L., Meltzer, L.J., Sadeh, A., Spira, A.P. & Taylor, D.J. (2015). The SBSM Guide to Actigraphy Monitoring: Clinical and Research Applications. *Behavioral Sleep Medicine,* 13 Suppl 1, S4-S38.

Aziz, M., Ali, S.S., Das, S., Younus, A., Malik, R., Latif, M.A., Humayun, C., Anugula, D., Abbas, G., Salami, J., Elizondo, J.V., Veledar, E. & Nasir, K. (2016). Association of subjective and objective sleep duration as well as sleep quality with non-invasive markers of sub-clinical cardiovascular disease (CVD): A systematic review. *Journal of Atherosclerosis and Thrombosis*.

Bastien, C.H., Vallieres, A. & Morin, C.M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Medicine,* 2, 297-307.

Beck, A.T., Steer, R.A. & Brown, G. (1996). *Beck Depression Inventory-II*. San Antonio, TX: The Psychological Corporation.

Beckham, J.C., Feldman, M.E., Barefoot, J.C., Fairbank, J.A., Helms, M.J., Haney, T.L., Hertzberg, M.A., Moore, S.D. & Davidson, J.R.T. (2000). Ambulatory cardiovascular activity in Vietnam combat veterans with and without posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology,* 68, 269-76.

Beckham, J.C., Moore, S.D., Feldman, M.E., Hertzberg, M.A., Kirby, A.C. & Fairbank, J.A. (1998). Health status, somatization, and severity of posttraumatic stress disorder in Vietnam combat veterans with posttraumatic stress disorder. *American Journal of Psychiatry,* 155, 1565-69.

Belleville, G., Guay, S. & Marchand, A. (2011). Persistence of sleep disturbances following cognitive-behavior therapy for posttraumatic stress disorder. *Journal of Psychosomatic Research,* 70, 318-27.

Ben-Dov, I.Z., Kark, J.D., Ben-Ishay, D., Mekler, J., Ben-Arie, L. & Bursztyn, M. (2007). Predictors of all-cause mortality in clinical ambulatory monitoring: Unique aspects of blood pressure during sleep. *Hypertension,* 49, 1235-41.

Blackwell, T., Redline, S., Ancoli-Israel, S., Schneider, J.L., Surovec, S., Johnson, N.L., Cauley, J.A. & Stone, K.L. (2008). For the study of Osteoporotic Fracture Research Group. Comparision of sleep parameters from actigraphy and polysomnography in older women: The soft study. *Sleep,* 31, 283-91.

Blumenthal, J.A., Sherwood, A., Babyak, M.A., Watkins, L.L., Waugh, R., Georgiades, A., Bacon, S.L.,

Hayano, J., Coleman, R.E. & Hinderliter, A. (2005). Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease: A randomized controlled trial. *Journal of the American Medical Association,* 293, 1626-34.

Blumenthal, J.A., Sherwood, A. & Gullette, E.C.D. (2000). Exercise and weight loss reduce blood pressure in men and women with mild hypertension. *Archive of Internal Medicine,* 160, 19942-1958.

Bonetti, P.O., Lerman, L.O. & Lerman, A. (2003). Endothelial dysfunction: A marker of atherosclerotic risk. *Arteriosclerosis, Thrombosis, and Vascular Biology,* 23, 168-75.

Bonnet, M.H. & Arand, D.L. (2007). Cardiovascular implications of poor sleep. *Sleep Medicine Clinics,* 2, 529-38.

Bonnet, M.H. & Arand, D.L. (2010). Hyperarousal and insomnia: state of the science. *Sleep Medicine Reviews,* 14, 9-15.

Boscarino, J.A. (2006). Posttraumatic stress disorder and mortality among U.S. Army veterans 30 years after military service. *Annals of Epidemiology,* 16, 248-56.

Boscarino, J.A. (2008). Psychobiologic predictors of disease mortality after psychological trauma: Implications for research and clinical surveillance. *Journal of Nervous & Mental Disease,* 196, 100-07.

Brevetti, G., Silvestro, A., Schiano, V. & Chiariello, M. (2003). Endothelial dysfunction and cardiovascular risk prediction in peripheral arterial disease: additive value of flow-mediated dilation to ankle-brachial pressure index. *Circulation,* 108, 2093-8.

Bush, K., Kivlahan, D.R., McDonell, M.B., Fihn, S.D. & Bradley, K.A. (1998). The AUDIT alcohol consumption questions (AUDIT-C): An effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). *Archives of Internal Medicine,* 158, 1789-95.

Buysse, D.J., Ancoli-Israel, S., Edinger, J.D., Lichstein, K.L. & Morin, C.M. (2006). Recommendations for a standard research assessment of insomnia. *Sleep,* 29, 1155-73.

Buysse, D.J., Germain, A. & Moul, D.E. (2011). Efficacy of brief behavioral treatment for chronic insomnia in older adults. *Archives of Internal Medicine,* 171, 887-95.

Buysse, D.J., Reynolds, C.F., Monk, T.H., Berman, S.R. & Kupfer, D.J. (1989). The Pittsburgh Sleep Quality Index: A new instrument of psychiatric practice and research. *Psychiatry Research,* 28, 193-213. PMCID: PMC2748771

Calabia, J., Torguet, P., Garcia, M., Garcia, I., Martin, N., Guasch, B., Faur, D. & Valles, M. (2011). Doppler ultrasound in the measurement of pulse wave velocity: Agreement with the Complior method. *Cardiovascular Ultrasound,* 9, 13. PMCID: PMC3098145.

Calhoun, P.S., Wiley, M., Dennis, M.F., Means, M.K., Edinger, J.D. & Beckham, J.C. (2007). Objective evidence of sleep disturbance in women with posttraumatic stress disorder. *Journal of Traumatic Stress,* 20, 1009-18.

Carels, R.A., Sherwood, A., Szczepanski, R. & Blumenthal, J.A. (2000). Ambulatory blood pressure and marital distress in employed women. *Behavioral Medicine,* 26, 80-85.

Carney, C.E., Buysse, D.J., Ancoli-Israel, S., Edinger, J.D., Krystal, A.D., Lichstein, K.L. & Morin, C.M. (2012). The consensus sleep diary: Standardizing prospective sleep self-monitoring. *Sleep,* 35, 287-302.

Carroll, J.E., Seeman, T.E., Olmstead, R., Melendez, G., Sadakane, R., Bootzin, R., Nicassio, P. & Irwin,

M.R. (2015). Improved sleep quality in older adults with insomnia reduces biomarkers of disease risk: Pilot results from a randomized controlled comparative efficacy trial. *Psychoneuroendocrinology,* 55, 184-92. PMCID: PMC4422640.

Carroll, K.M. (2000). A general system for evaluating therapist adherence and competence in psychotherapy research in the addictions. *Drug and Alcohol Dependence,* 57, 225-38.

Castro-Diehl, C., Diez Roux, A.V., Redline, S., Seeman, T., McKinley, P., Sloan, R. & Shea, S. (2016). Sleep duration and quality in relation to autonomic nervous system measures: The Multi-Ethnic Study of Atherosclerosis (MESA). *Sleep,* 39, 1927-40. PMCID: PMC5070747.

Celermajer, D.S., Sorenson, K.E., Bull, C., Robinson, J.H. & Deanfield, J.E. (1994). Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. *Journal of the American College of Cardiology,* 24, 1468-74.

Charakida, M., de Groot, E., Loukogeorgakis, S.P., Khan, T., Luscher, T., Kastelein, J.J., Gasser, T. & Deanfield, J.E. (2013). Variability and reproducibility of flow-mediated dilatation in a multicentre clinical trial. *European Heart Journal,* 34, 3501-7.

Chesnut, R.M., Temkin, N., Carney, N., Dikmen, S., Rondina, C., Videtta, W., Petroni, G., Lujan, S., Pridgeon, J., Barber, J., Machamer, J., Chaddock, K., Celix, J.M., Cherner, M., Hendrix, T. & Global Neurotrauma Research Group. (2012). A trial of intracranial-pressure monitoring in traumatic brain injury. *New England Journal of Medicine,* 367, 2471-81. PMCID: PMC3565432.

Chouchou, F., Pichot, V., Celle, S., Barthelemy, J.C., Gosse, P. & Roche, F. (2016). Sleep disruptions increase arterial stiffness. *International Journal of Cardiology,* 203, 744-5.

Cicek, Y., Durakoglugil, M.E., Kocaman, S.A., Cetin, M., Erdogan, T., Dogan, S., Ugurlu, Y. & Canga, A. (2013). Non-dipping pattern in untreated hypertensive patients is related to increased pulse wave velocity independent of raised nocturnal blood pressure. *Blood Pressure,* 22, 34-8.

Clement, D.L., De Buyzere, M.L. & De Bacquer, D.A. (2003). Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *The New England Journal of Medicine,* 24, 2407-15.

Clum, G.A., Nishith, P. & Resick, P.A. (2001). Trauma-related sleep disturbance and self-reported physical health symptoms in treatment-seeking female rape victims. *Journal of Nervous and Mental Disease,* 189, 618-22.

Cohen, J. (1988). *Statistical power analyses for the behavioral sciences*. 2nd ed. Hillsdale, NJ: Lawrence Earlbaum Associates.

Collins, L.M., Schafer, J.L. & Kam, C.M. (2001). A comparison of inclusive and restrictive strategies in modern missing data procedures. *Psychological Methods,* 6, 330-51.

Committee for Proprietary Medicinal, P. (2004). Committee for Proprietary Medicinal Products (CPMP): Points to consider on adjustment for baseline covariates. *Statistics in Medicine,* 23, 701-9.

Committee on Veterans' Affairs House of Representatives Subject. (2010). VA Health Care: Status of VA's Approach in Conducting the National Vietnam Veterans Longitudinal Study Washington, DC. Administration, V.H.

Crawford, E.F., Fulton, J.J., Swinkels, C.M., Beckham, J.C., VA Mid-Atlantic MIRECC OEF/OIF Registry Workgroup & Calhoun, P.S. (2013). Diagnostic efficiency of the AUDIT-C in U.S. veterans with military service since September 11, 2001. *Drug and Alcohol Dependence,* 132, 101-6.

Corretti, M.C., Anderson, T.J., Benjamin, E.J., Celermajer, D., Charbonneau, F., Creager, M.A., Deanfield, J., Drexler, H., Gernard-Herman, M., Herrington, D., Vallance, P., Vita, J. & Vogel, R. (2002).

Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force.[erratum appears in Journal of the American College of Cardiology, 39, 1082]. *Journal of the American College of Cardiology,* 39, 257-65.

Dedert, E.A., Calhoun, P.S., Harper, L.A., Dutton, C.E., McClernon, F.J. & Beckham, J.C. (2012). Smoking withdrawal in smokers with and without posttraumatic stress disorder. *Nicotine & Tobacco Research,* 14, 372-76. PMCID: PMC3281234.

de Vries, G.E., van der Wal, H.H., Kerstjens, H.A., van Deursen, V.M., Stegenga, B., van Veldhuisen, D.J., van der Hoeven, J.H., van der Meer, P. & Wijkstra, P.J. (2015). Validity and predictive value of a portable two-channel seep-screening tool in the identification of sleep apnea in patients with heart failure. *Journal of Cardiac Failure,* 21, 848-55.

Dolan, E., Stanton, A.V. & Thom, S. (2009). Ambulatory blood pressure monitoring predicts cardiovascular events in treated hypertensive patients--an Anglo-Scandinavian cardiac outcomes trial substudy. *Journal of Hypertension,* 27, 876-85.

Donald, A.E., Halcox, J.P., Charakida, M., Storry, C., Wallace, S.M., Cole, T.J., Friberg, P. & Deanfield, J.E. (2008). Methodological approaches to optimize reproducibility and power in clinical studies of flow-mediated dilation. *Journal of the American College of Cardiology,* 51, 1959-64.

Edinger, J.D., Wyatt, J.K. & Olsen, M.K. (2009). Reliability and validity of the Duke Structured Interview for Sleep Disorders for insomnia screening. *Sleep,* 32, A265.

Edinger, J.D., Wohlgemuth, W.K., Radtke, R.A., Marsh, G.R. & Quillian, R.E. (2001). Cognitive behavioral therapy for treatment of chronic primary insomnia: A randomized controlled trial. *Journal of the American Medical Association,* 285, 1856-64.

Edmondson, D., Kronish, I.M., Shaffer, J.A., Falzon, L. & Burg, M.M. (2013). Posttraumatic stress disorder and risk for coronary heart disease: A meta-analytic review. *American Heart Journal,* 166, 806-14. PMCID: PMC3815706.

Epstein, L.J., Kristo, D., Strollo, P.J., Friedman, N., Malhotra, A., Patil, S.P., Ramar, K., Rogers, R., Schwab, R.J., Weaver, E.M., Weinstein, M.D. & Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. (2009). Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *Journal of Clinical Sleep Medicine,* 5, 263-76. PMCID: PMC2699173.

Esler, M., Lambert, E., Schlaich, M. & Navar, L. (2010). The dominant contributor to systemic hypertension: Chronic activation of the sympathetic nervous system vs activation of the intrarenal renin-angiotensis system. *Journal of Applied Physiology,* 109, 1996-98.

Fagard, R.H., Celis, H., Thijs, L., Staessen, J.A., Clement, D.L. & De Buyzere, M.L. (2008). Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension,* 51, 55-61.

Ferrie, J.E., Shipley, M.J., Cappuccio, F.P., Brunner, E., Miller, M.A., Kumari, M. & Marmot, M.G. (2007). A prospective study of change in sleep duration: Associations with mortality in the Whitehall II cohort. *Sleep,* 30, 1659-66. PMCID: PMC2276139.

Flood, A.M., Boyle, S.H., Calhoun, P.S., Dennis, M.F., Barefoot, J.C., Moore, S.D. & Beckham, J.C. (2010). Prospective study of externalizing and internalizing subtypes of posttraumatic stress disorder and their relationship to mortality among Vietnam veterans. *Comprehensive Psychiatry,* 51, 236-42. PMCID: PMC2858053.

Friedman, M.J. & Schnurr, P.P. The relationship between trauma, PTSD, and physical health. In: Friedman, M.J., Charney, D.S. & Deutch, A.Y., eds. *Neurobiological and clinical consequences of stress: From normal adaptation to PTSD*. New York: Lippincott-Raven; 1995:507-24.

Galovski, T.E., Monson, C., Bruce, S.E. & Resick, P.A. (2009). Does cognitive-behavioral therapy for PTSD improve perceived health and sleep impairment? *Journal of Traumatic Stress,* 22, 197-204. PMCID: PMC2765684.

Garin, O., Ayuso-Mateos, J.L., Almansa, J., Nieto, M., Chatterji, S., Vilagut, G., Alonso, J., Cieza, A., Svetskova, O., Burger, H., Racca, V., Francescutti, C., Vieta, E., Kostanjsek, N., Raggi, A., Leonardi, M. & Ferrer, M. (2010). Validation of the "World Health Organization Disability Assessment Schedule, WHODAS-2" in patients with chronic diseases. *Health and Quailty of Life Outcomes,* 8, 51. PMCID: PMC2893517.

Geiger-Brown, J.M., Rogers, V.E., Liu, W., Ludeman, E.M., Downton, K.D. & Diaz-Abad, M. (2015). Cognitive behavioral therapy in persons with comorbid insomnia: A meta-analysis. *Sleep Medicine Reviews,* 23, 54-67.

Germain, A., Hall, M., Krakow, B., Katherine, S.M. & Buysse, D.J. (2005). A brief sleep scale for posttraumatic stress disorder: Pittsburgh sleep quality index addendum for PTSD. *Journal of Anxiety Disorders,* 19, 233-4.

Gheorghiade, M., Konstam, M.A., Burnett, J.C., Grinfeld, L., Maggioni, A.P., Swedberg, K., Udelson, J.E., Zannad, F., Cook, T., Ouyang, J., Zimmer, C., Orlandi, C. & Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan Investigators. (2007). Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: The EVEREST Clinical Status Trials. *Journal of the American Medical Association,* 297, 1332-43.

Ghiadoni, L., Donald, A.E., Cropley, M., Mullen, M.J., Oakley, G., Taylor, M., O'Connor, G., Betteridge, J., Klein, N., Steptoe, A. & Deanfield, J.E. (2000). Mental stress induces transient endothelial dysfunction in humans. *Circulation,* 102, 2473-8.

Ghiadoni, L., Faita, F., Salvetti, M., Cordiano, C., Biggi, A., Puato, M., Di Monaco, A., De Siati, L., Volpe, M., Ambrosio, G., Gemignani, V., Muiesan, M.L., Taddei, S., Lanza, G.A. & Cosentino, F. (2012). Assessment of flow-mediated dilation reproducibility: A nationwide multicenter study. *Journal of Hypertension,* 30, 1399-405.

Godin, G. & Shephard, R.J. (1985). A simple method to assess exercise behavior in the community. *Canadian Journal of Applied Sport Science, 10*, 141-146.

Goff, D.C., Jr., Lloyd-Jones, D.M., Bennett, G., O'Donnell, C.J., Coady, S., Robinson, J., D'Agostino, R.B., Sr., Schwartz, J.S., Gibbons, R., Shero, S.T., Greenland, P., Smith, S.C., Jr., Lackland, D.T., Sorlie, P., Levy, D., Stone, N.J. & Wilson, P.W. (2013). 2013 ACC/AHA guideline on the assessment of cardiovascular risk: A report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Journal of the American College of Cardiology,* 63, 3026.

Goodwin, J., Bilous, M., Winship, S., Finn, P. & Jones, S.C. (2007). Validation of the Oscar 2 oscillometric 24-h ambulatory blood pressure monitor according to the British Hypertension Society protocol. *Blood Pressure Monitoring,* 12, 113-17.

Grassi, G., Mark, A. & Esler, M. (2015). The sympathetic nervous system alterations in human hypertension. *Circulation Research,* 116, 976-90. PMCID: PMC4367954.

Haack, M., Serrador, J., Cohen, D., Simpson, N., Meier-Ewert, H. & Mullington, J.M. (2013). Increasing sleep duration to lower beat-to-beat blood pressure: A pilot study. *Journal of Sleep Research,*

22, 295-304. PMCID: PMC3582793.
Hansen, T.W., Li, Y., Boggia, J., Thijs, L., Richart, T. & Staessen, J.A. (2011). Predictive role of the nighttime blood pressure. *Hypertension,* 57, 3-10.
Hauri, P. Sleep hygiene. In: Hauri, P., ed. *Current Concepts: The Sleep Disorders*. Kalamazoo, MI: The Upjohn Company; 1977:21-35.
Heatherton, T.F., Kozlowski, L.T., Frecker, R.C. & Fagerström, K.O. (1991). The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction,* 86, 1119-27.
Hinderliter, A.L., Routledge, F.S., Blumenthal, J.A., Koch, G., Hussey, M.A., Wohlgemuth, W.K. & Sherwood, A. (2013). Reproducibility of blood pressure dipping: Relation to day-to-day variability in sleep quality. *Journal of the American Society of Hypertension,* 7, 432-9. PMCID: PMC3865136.
Hoevenaar-Blom, M.P., Spijkerman, A.M., Kromhout, D., van den Berg, J.F. & Verschuren, W.M. (2011). Sleep duration and sleep quality in relation to 12-year cardiovascular disease incidence: The MORGEN study. *Sleep,* 34, 1487-92. PMCID: PMC3198203.
Huang, P., Tilley, B.C., Woolson, R.F. & Lipsitz, S. (2005). Adjusting O'Brien's test to control type I error for the generalized nonparametric Behrens-Fisher problem. *Biometrics,* 61, 532-9. PMCID: PMC2827210.
Huang, Y., Mai, W. & Hu, Y. (2011). Poor sleep quality, stress status, and sympathetic nervous system activation in nondipping hypertension. *Blood Pressure Monitoring,* 16, 117-23.
Hughes, J.R. (2007). Measurement of the effects of abstinence from tobacco: A qualitative review. *Psychology of Addictive Behaviors,* 21, 127-37.
Ingelsson, E., Bjorklund-Bodegard, K., Lind, L., Arnlov, J. & Sundstrom, J. (2006). Diurnal blood pressure pattern and risk of congestive heart failure *Journal of the American Medical Association,* 295, 2859-66.
Irwin, M.R., Olmstead, R. & Carroll, J.E. (2016). Sleep disturbance, sleep duration, and inflammation: A systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biological Psychiatry,* 80, 40-52. PMCID: PMC4666828.
Irwin, M.R., Olmstead, R., Carrillo, C., Sadeghi, N., Breen, E.C., Witarama, T., Yokomizo, M., Lavretsky, H., Carroll, J.E., Motivala, S.J., Bootzin, R. & Nicassio, P. (2014). Cognitive behavioral therapy vs. Tai Chi for late life insomnia and inflammatory risk: A randomized controlled comparative efficacy trial. *Sleep,* 37, 1543-52. PMCID: PMC4153053.
Ivanova, J.I., Birnbaum, H.G., Chen, L., Duhig, A.M., Dayoub, E.J., Kantor, E.S., Schiller, M.B. & Phillips, G.A. (2011). Cost of post-traumatic stress disorder vs major depressive disorder among patients covered by medicaid or private insurance. *The American Journal of Managed Care,* 17, e314-23.
Jambrik, Z., Sebastiani, L., Picano, E., Ghelarducci, B. & Santarcangelo, E.L. (2005). Hypnotic modulation of flow-mediated endothelial response to mental stress. *International Journal of Psychophysiology,* 55, 221-7.
Johns, M.W. (1991). A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep,* 14, 540-5.
Jones, S.C., Bilous, M., Winship, S., Finn, P. & Goodwin, J. (2004). Validation of the OSCAR 2 oscillometric 24-hour ambulatory blood pressure monitor according to the International Protocol for the validation of blood pressure measuring devices. *Bood presure monitoring,* 9,

219-23.
Karlin, B.E., Trockel, M., Tylor, C.B., Gimeno, J. & Manber, R. (2013). National dissemination of cognitive behavioral therapy for insomnia in veterans: Therapist- and patient-level outcomes. *Journal of Consulting and Clinical Psychology,* 81, 912-17.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R. & Walters, E.E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archive of General Psychiatry,* 62, 593-602.
Kessler, R.C., Chiu, W.T., Demler, O. & Walters, E.E. (2005). Prevalence, severity and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry,* 62, 617-27.
Kobayashi, I., Boarts, J.M. & Delahanty, D.L. (2007). Polysomnographically measured sleep abnormalities in PTSD: A meta-analytic review. *Psychophysiology,* 44, 660-69.
Kraemer, H.C. (2016). Messages for clinicians: Moderators and mediators of treatment outcome in randomized clinical trials. *American Journal of Psychiatry,* 173, 672-9.
Kraemer, H.C., Kiernan, M., Essex, M. & Kupfer, D.J. (2008). How and why criteria defining moderators and mediators differ between the Baron & Kenny and MacArthur approaches. *Health Psychology,* 27, S101-8. PMCID: PMC3376898.
Krebs, E.E., Lorenz, K.A., Bair, M.J., Damush, T.M., Wu, J., Sutherland, J.M., Asch, S.M. & Kroenke, K. (2009). Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. *Journal of General Internal Medicine,* 24, 733–8.
Krishnan, V. & Collop, N.A. (2006). Gender differences in sleep disorders. *Current Opinion in Cardiology,* 12, 383-9.
Lanfranchi, P.A., Pennestri, M.H., Fradette, L., Dumont, M., Morin, C.M. & Montplaisir, J. (2009). Nighttime blood pressure in normotensive subjects with cronic insomnia: Implications for cardiovascular risk. *Sleep,* 32, 760-66.
Lauderdale, D.S., Knutson, K.L., Yan, L.L., Liu, K. & Rathouz, P.J. (2008). Self-reported and measured sleep duration: How similar are they? *Epidemiology,* 19, 838-45. PMCID: PMC2785092.
Laurent, S., Katsahian, S., Fassot, C., Tropeano, A.I., Gautier, I., Laloux, B. & Boutouyrie, P. (2003). Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. *Stroke,* 34, 1203-6.
Li, M., Zhang, X.W., Hou, W.S. & Tang, Z.Y. (2014). Insomnia and risk of cardiovascular disease: A meta-analysis of cohort studies. *International Journal of Cardiology,* 176, 1044-7. Meng, L., Zheng, Y. & Hui, R. (2013). The relationship of sleep duration and insomnia to risk of hypertension incidence: A meta-analysis of prospective cohort studies. *Hypertension Research,* 36, 985-95. PMCID: PMC3819519.
Lin, C.L., Tsai, Y.H. & Yeh, M.C. (2016). The relationship between insomnia with short sleep duration is associated with hypercholesterolemia: A cross-sectional study. *Journal of Advanced Nursing,* 72, 339-47.
Lind, L., Johansson, K. & Hall, J. (2002). The effects of mental stress and the cold pressure test on flow-mediated vasodilation. *Blood Pressure,* 11, 22-7.
Littner, M., Kushida, C.A., Anderson, W.M., Bailey, D., Berry, R.B., Davila, D.G., Hirshkowitz, M., Kapen, S., Kramer, M., Loube, D., Wise, M. & Johnson, S.F. (2003). Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms: An update for 2002. *Sleep,* 26, 337-41.

Loredo, J.S., Nelesen, R., Ancoli-Israel, S. & Dimsdale, J.E. (2004). Sleep quality and blood pressure dipping in normal adults. *Sleep,* 27, 1097-103.

Manber, R., Carney, C. & Edinger, J. (2012). Dissemination of CBTI to the non-sleep specialist: Protocol development and training issues. *Journal of Clinical Sleep Medicine,* 8, 209-18.

Mancia, G., Facchetti, R., Bombelli, M., Grassi, G. & Sega, R. (2006). Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure. *Hypertension,* 47, 846-53.

Marino, M., LiMarino, Y., Rueschman, M.N., Winkelman, J.W., Ellenbogen, J.M., Solet, J.M., Dulin, H., Berkman, L.F. & Buxton, O.M. (2013). Measuring sleep: Accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. *Sleep,* 36, 1747-55.

Matthews, K.A., Chang, Y., Kravitz, H.M., Bromberger, J.T., Owens, J.F., Buysse, D.J. & Hall, M.H. (2014). Sleep and risk for high blood pressure and hypertension in midlife women: The SWAN (Study of Women's Health Across the Nation) sleep study. *Sleep Medicine,* 15, 203-8. PMCID: PMC3946296.

Maxwell, S.E., Cole, D.A. & Mitchell, M.A. (2011). Bias in cross-sectional analyses of longitudinal mediation: Partial and complete mediation under an autoregressive model. *Multivariate Behavior Research,* 46, 816-41.

McCubbin, J.A., Zinzow, H.M., Hibdon, M.A., Nathan, A.W., Morrison, A.V., Hayden, G.W., Lindberg, C. & Switzer, F.S. (2016). Subclinical posttraumatic stress disorder symptoms: Relationships with blood pressure, hostility, and sleep. *Cardiovascular Psychiatry and Neurology,* 2016, 4720941. PMCID: PMC4925987.

Mellman, T.A., Brown, D.D., Jenifer, E.S., Hipolito, M.M. & Randall, O.S. (2009). Posttraumatic stress disorder and nocturnal blood pressure dipping in young adult African Americans. *Psychosomatic Medicine,* 6, 627-30.

Mitchell, G.F., Parise, H., Vita, J.A., Larson, M.G., Warner, E., Keaney, J.F., Jr., Keyes, M.J., Levy, D., Vasan, R.S. & Benjamin, E.J. (2004). Local shear stress and brachial artery flow-mediated dilation: The Framingham Heart Study. *Hypertension,* 44, 134-9.

Mohr, D.C., Vedantham, K., Neylan, T.C., Metzler, T.J., Best, S.R. & Marmar, C.R. (2003). The mediating effects of sleep in the relationship between traumatic stress and health symptoms in urban police officers. *Psychosomatic Medicine,* 65, 485-89.

Morgenthaler, T., Allesi, C., Friedman, L., Owens, J., Kapur, V., Boehlecke, B., Brown, T.A., Chesson, A., Coleman, J., Lee-Chiong, T., Pancer, J. & Swick, T. (2007). Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: An update for 2007. *Sleep,* 30, 519-29.

Morin, C.M., Belleville, G., Belanger, L. & Ivers, H. (2011). The Insomnia Severity Index: Psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep,* 34, 601-8. PMCID: PMC3079939.

Morin, C.M., Bootzin, R.R., Buysse, D.J., Edinger, J.D., Espie, C.A. & Lichstein, K.L. (2006). Psychological and behavioral treatment of insomnia: Update of the recent evidence (1998-2004). *Sleep,* 29, 1398-414.

Morin, C.M., Culbert, J.P. & Schwartz, S.M. (1994). Nonpharmacological interventions for insomnia: A meta-analysis of treatment efficacy. *American Journal of Psychiatry,* 151, 1172-80.

Morin, C.M., Drake, C.L., Harvey, A.G., Krystal, A.D., Manber, R., Riemann, D. & Spiegelhalter, K. (2015).

Insomnia disorder. *Primer,* 1, 1-18.
Morin, C.M., Hauri, P.J., Espie, C.A., Spielman, A.J., Buysse, D.J. & Bootzin, R.R. (1999). Nonpharmacologic treatment of chronic insomnia. An American Academy of Sleep Medicine review. *Sleep,* 22, 1134-56.
Morin, C.M., Vallieres, A. & Guay, B. (2009). Cognitive behavior therapy, singly ond combined with medication, for persistent insomnia: A randomized controlled trial. *Journal of American Medical Association,* 301, 2005-15.
Motivala, S.J. (2011). Sleep and inflammation: Psychoneuroimmunology in the context of cardiovascular disease. *Annals of Behavioral Medicine,* 42, 141-52.
Murtagh, D.R. & Greenwood, K.M. (1995). Identifying effective psychological treatments for insomnia: A meta-analysis. *Journal of Consulting and Clinical Psychology,* 63, 79-89.
Munk, P.S., Isaksen, K., Bronnick, K., Kurz, M.W., Butt, N. & Larsen, A.I. (2012). Symptoms of anxiety and depression after percutaneous coronary intervention are associated with decreased heart rate variability, impaired endothelial function and increased inflammation. *International Journal of Cardiology,* 158, 173-6.
Naghavi, M., Libby, P., Falk, E., Casscells, S.W., Litovsky, S., Rumberger, J., Badimon, J.J., Stefanadis, C., Moreno, P., Pasterkamp, G., Fayad, Z., Stone, P.H., Waxman, S., Raggi, P., Madjid, M., Zarrabi, A., Burke, A., Yuan, C., Fitzgerald, P.J., Siscovick, D.S., de Korte, C.L., Aikawa, M., Juhani Airaksinen, K.E., Assmann, G., Becker, C.R., Chesebro, J.H., Farb, A., Galis, Z.S., Jackson, C., Jang, I.K., Koenig, W., Lodder, R.A., March, K., Demirovic, J., Navab, M., Priori, S.G., Rekhter, M.D., Bahr, R., Grundy, S.M., Mehran, R., Colombo, A., Boerwinkle, E., Ballantyne, C., Insull, W., Jr., Schwartz, R.S., Vogel, R., Serruys, P.W., Hansson, G.K., Faxon, D.P., Kaul, S., Drexler, H., Greenland, P., Muller, J.E., Virmani, R., Ridker, P.M., Zipes, D.P., Shah, P.K. & Willerson, J.T. (2003). From vulnerable plaque to vulnerable patient: A call for new definitions and risk assessment strategies: Part I. *Circulation,* 108, 1664-72.
Nasreddine, Z.S., Phillips, N.A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L. & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society,* 53, 695-9.
Neylan, T.C. (2011). Time to disseminate cognitive behavioral treatment of insomnia. Comment on "Efficacy of brief behavioral treatment for chronic insomnia in older adults". *Archive of Internal Medicine,* 171, 895-6.
O'Brien, P.C. (1984). Procedures for comparing samples with multiple endpoints. *Biometrics,* 40, 1079-87.
Ohkubo, T., Hozawa, A., Yamaguchi, J., Kikuya, M., Ohmori, K., Michimata, M., Matsubara, M., Hashimoto, J., Hoshi, H., Araki, T., Tsuji, I., Satoh, H., Hisamichi, S. & Imai, Y. (2002). Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: The Ohasama study. *Journal of Hypertension,* 20, 2183-9.
Ohayon, M.M. & Shapiro, C.M. (2000). Sleep disturbances and psychiatric disorders associated with posttraumatic disorder in the general population. *Comprehensive Psychiatry,* 41, 469-78.
O'Kelly, M. & Ratitich, B. (2014). *Clinical trials with missing data: A guide for practitioners*. West Sussex, United Kingdom: John Wiley & Sons.
Okajima, I., Komada, Y. & Inoue, R. (2011). A meta-analysis on the treatment effectiveness of cognitive behavioral therapy for primary insomnia. *Sleep and Biological Rhythms,* 9, 24-34.

Olsen, M.K., Stechuchak, K.M., Edinger, J.D., Ulmer, C.S. & Woolson, R.F. (2012). Move over LOCF: Principled methods for handling missing data in sleep disorder trials. *Sleep Medicine,* 13, 123-32.

Pereira, T. & Maldonado, J. (2010). Comparative study of two generations of the Complior device for aortic pulse wave velocity measurements. *Blood Pressure Monitoring,* 15, 316-21.

Perkonigg, A., Kessler, R.C., Storz, S. & Wittchen, H. (2000). Traumatic events and posttraumatic stress disorder in the community: Prevalence, risk factors, and comorbidity. *Acta Psychiatrica Scandinavica,* 101, 46-59.

Perlis, M.L., Jungquist, C.R., Smith, M.T. & Posner, D. (2005). Cognitive-behavioral treatment of insomnia: A session-by-session guide. *NY: Springer Scinece + Bussiness Media*.

Pickering, T.G., Schwartz, J.E. & James, G.D. (1995). Ambulatory blood pressure monitoring for evaluating the relationships between lifestyle, hypertension and cardiovascular risk. *Clinical and Experimental Pharmacology and Physiology,* 22, 226-31.

Pyke, K.E., Hartnett, J.A. & Tschakovsky, M.E. (2008). Are the dynamic response characteristics of brachial artery flow-mediated dilation sensitive to the magnitude of increase in shear stimulus? *Journal of Applied Physiology,* 105, 282-92.

Prather, A.A., Blumenthal, J.A., Hinderliter, A.L. & Sherwood, A. (2011). Ethnic differences in the effects of the DASH diet on nocturnal blood pressure dipping in individuals with high blood pressure. *American Journal of Hypertension,* 24, 1338-13344.

Respironics Incorporated. (2008). *Actiware and Actiware CT Software Manual*. Murrysville, PA

Roehrs, T.A. & Roth, T. (2016). Hyperarousal in insomnia and hypnotic dose escalation. *Sleep Medicine,* 23, 16-20. PMCID: PMC5063239.

Ross, R.J., Ball, W.A., Sullivan, K.A. & Caroff, S.N. (1989). Sleep disturbance as the hallmark of posttraumatic stress disorder. *The American Journal of Psychiatry,* 146, 697-707.

Routledge, F.S., Dunbar, S.B., Higgins, M., Rogers, A.E., Feeley, C., Ioachimescu, O., Euwer, K., Eapen, D. & Quyyumi, A. (2015). Insomnia symptoms are associated with abnormal endothelial function. *Journal of Cardiovascular Nursing*.

Routledge, F.S. & McFetridge-Durdle, J. (2007). Nondipping blood pressure patterns among individuals with essential hypertension: A review of the literature. *European Journal of Cardiovascular Nursing: Journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology,* 6, 9-26.

Rozanski, A., Blumenthal, J.A., Davidson, K.W., Saab, P.G. & Kubzansky, L. (2005). The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: The emerging field of behavioral cardiology. *Journal of American College of Cardiology,* 45, 637-51.

Rumble, M.E., Keefe, F.J., Edinger, J.D., Affleck, G., Marcom, P.K. & Shaw, H.S. (2010). Contribution of cancer symptoms, dysfunctional sleep related thoughts, and sleep inhibitory behaviors to the insomnia process in breast cancer survivors: A daily process analysis. *Sleep,* 33, 1501-9. PMCID: PMC2954700.

Sadeh, A. & Acebo, C. (2002). The role of actigraphy in sleep medicine. *Sleep Medicine Reviews,* 6, 113-24.

Sadeh, A., Hauri, P.J., Kripke, D.F. & Lavie, P. (1995). The role of actigraphy in the evaluation of sleep disorders. *Sleep,* 18, 288-302.

Saeed, S., Wajea-Andreassen, U., Fromm, A., Oygarden, H., Naess, H. & Gerdts, E. (2015). 3d.04:

Blunted Nightly Blood Pressure Reduction Is Associated with Increased Arterial Stiffness in Ischemic Stroke Patients: A Norwegian Stroke in the Young Study. *Journal of Hypertension,* 33 Suppl 1, e41.

Saeed, S., Waje-Andreassen, U., Lonnebakken, M.T., Fromm, A., Oygarden, H., Naess, H. & Gerdts, E. (2015). Covariates of non-dipping and elevated night-time blood pressure in ischemic stroke patients: the Norwegian Stroke in the Young Study. *Blood Press,* 1-7.

Schnurr, P.P. & Green, B.L., eds. *Trauma and Health: Physical Health Consequences of Exposure to Extreme Stress*. Washington, DC: American Psychological Association; 2004.

Sherwood, A., Bower, J.K. & Routledge, F.S. (2012). Nighttime blood pressure dipping in postmenopausal woman with coronary heart disease. *American Journal of Hypertension,* 25, 1077-82.

Sherwood, A., Hinderliter, A.L., Watkins, L.L., Waugh, R.A. & Blumenthal, J.A. (2005). Impaired endothelial function in coronary heart disease patients with depressive symptomatology. *Journal of American College of Cardiology,* 46, 656-59.

Sherwood, A., Routledge, F.S., Wohlgemuth, W.K., Hinderliter, A.L., Kuhn, C.M. & Blumenthal, J.A. (2011). Blood pressure dipping: Ethnicity, sleep quality, and sympathetic nervous system activity. *American Journal of Hypertension,* 24, 982-88.

Sherwood, A., Steffen, P.R., Blumenthal, J.A., Kuhn, C. & Hinderliter, A.L. (2002). Nighttime blood pressure dipping: The role of the sympathetic nervous system. *American Journal of Hypertension,* 15, 111-18.

Sherwood, A., Thurston, R., Steffen, P., Blumenthal, J.A., Waugh, R.A. & Hinderliter, A.L. (2001). Blunted nighttime blood pressure dipping in postmenopausal women. *American Journal of Hypertension,* 14, 749-54.

Shiner, B., Watts, B.V., Pomerantz, A., Young-Xu, Y. & Schnurr, P.P. (2011). Sensitivity of the SF-36 to PTSD symptom change in veterans. *Journal of Traumatic Stress,* 24, 111-5.

Smith, M., Huang, M.I. & Maber, R. (2005). Cognitive behavior therapy for chronic insomnia occurring within the context of medical and psychiatric disorders. *Clinical Psychology Reviews,* 25, 559-92.

Sofi, F., Cesari, F., Casini, A., Macchi, C., Abbate, R. & Gensini, G.F. (2014). Insomnia and risk of cardiovascular disease: A meta-analysis. *European Journal of Preventive Cardiology,* 21, 57-64.

Solter, V., Thaller, V., Karlovic, D. & Crnkovic, D. (2002). Elevated serum lipids in veterans with combat-related chronic posttraumatic stress disorder. *Croatian Medical Journal,* 43, 685-89.

Soni, A. *The Five Most Costly Conditions, 1996 and 2006: Estimates for the U.S. Civilian Noninstitutionalized Population. Statistical Brief #248. July 2009*. Rockville, MD, Agency for Healthcare Research and Quality; 2009.

Spielman, A., Saskin, P. & Thorpy, M. (1987). Treatment of chronic insomnia by restriction of time in bed. *Sleep,* 10, 45-56.

Spiro, A., Hankin, C.S., Mansell, D. & Kazis, L.E. (2006). Posttraumatic stress disorder and health satus : The veterans health study. *Journal of Ambulatory care Management,* 29, 71-86.

Spoormaker, V.I. & Montgomery, P. (2008). Disturbed sleep in post-traumatic stress disorder: Secondary symptom or core feature? *Sleep Medicine Reviews,* 12, 169-84.

Staessen, J.A., Asmar, R. & De Buyzere, M. (2001). Task Force II: Blood pressure measurement and cardiovascular outcome. *Blood Pressure Monitoring,* 6, 355-70.

Staessen, J.A., Thijs, L., Fagard, R., O'Brien, E.T., Clement, D., de Leeuw, P.W., Mancia, G., Nachev, C.,

Palatini, P., Parati, G., Tuomilehto, J. & Webster, J. (1999). Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *Journal of the American Medical Association,* 282, 539-46.

Stepanski, E.J. & Wyatt, J.K. (2003). Use of sleep hygiene in the treatment of insomnia. *Sleep Medicine Reviews,* 7, 215-25.

Sunbul, M., Kanar, B.G., Durmus, E., Kivrak, T. & Sari, I. (2014). Acute sleep deprivation is associated with increased arterial stiffness in healthy young adults. *Sleep Breath,* 18, 215-20.

Talbot, K., Eidem, W.L., Tinsley, C.L., Benson, M.A., Thompson, E.W., Smith, R.J., Hahn, C.G., Siegel, S.J., Trojanowski, J.Q., Gur, R.E., Blake, D.J. & Arnold, S.E. (2004). Dysbindin-1 is reduced in intrinsic, glutamatergic terminals of the hippocampal formation in schizophrenia. *The Journal of Clinical Investigation,* 113, 1353-63.

Talbot, L.S., Maguen, S., Metzler, T.J., Schnitz, M., McDaslin, S.E., Richards, A., Perlis, M.L., Posner, D.A., Weiss, B., Ruoff, L., Varbel, J. & Neylan, T.C. (2014). Cognitive behavioral therapy for insomnia in posttraumatic stress disorder: A randomized controlled trial. *Sleep,* 37, 327-41.

Taylor, D.J., Mallory, L.J., Lichstein, K.L., Durrence, H.H., Riedel, B.W. & Bush, A.J. (2007). Comorbidity of chronic insomnia with medical problems. *Sleep,* 30, 213-18.

Thijssen, D.H., Black, M.A., Pyke, K.E., Padilla, J., Atkinson, G., Harris, R.A., Parker, B., Widlansky, M.E., Tschakovsky, M.E. & Green, D.J. (2011). Assessment of flow-mediated dilation in humans: A methodological and physiological guideline. *American Journal of Physiology - Heart and Circulatory Physiology,* 300, H2-12. PMCID: PMC3023245.

Thorpy, M., Chesson, A., Derderian, S., Kader, G., Millman, R., Potolicchio, S., Rosen, G. & Strollo, P. (1995). Practice parameters for the use of actigraphy in the clinical assessment of sleep disorders. *American Sleep Disorders Association. Sleep,* 18, 285-87.

Tilley, B.C., Marler, J., Geller, N.L., Lu, M., Legler, J., Brott, T., Lyden, P. & Grotta, J. (1996). Use of a global test for multiple outcomes in stroke trials with application to the National Institute of Neurological Disorders and Stroke t-PA Stroke Trial. *Stroke,* 27, 2136-42.

Tom, S.E., Kuh, D., Guralnik, J.M. & Mishra, G.D. (2010). Self-reported sleep difficulty during the menopausal transition: Results from a prospective cohort study. *Menopause,* 17, 1128-35. PMCID: PMC3151465.

Triantafyllidi, H., Tzortzis, S., Lekakis, J., Ikonomidis, I., Arvaniti, C., Trivilou, P., Kontsas, K., Siafakas, N., Zerva, L., Stamboulis, E., Kremastinos, D. & Anastasiou-Nana, M. (2010). Association of target organ damage with three arterial stiffness indexes according to blood pressure dipping status in untreated hypertensive patients. *American Journal of Hypertension,* 23, 1265-72.

Troendle, J.F. & Legler, J.M. (1998). A comparison of one-sided methods to identify significant individual outcomes in a multiple outcome setting: stepwise tests or global tests with closed testing. *Statistics in Medicine,* 17, 1245-60.

Tsuji, H., Venditti, F.J., Jr., Manders, E.S., Evans, J.C., Larson, M.G., Feldman, C.L. & Levy, D. (1996). Determinants of heart rate variability. *Journal of the American College of Cardiology,* 28, 1539-46.

Ulmer, C.S., Calhoun, P.S., Bosworth, H.B., Dennis, M.F. & Beckham, J.C. (2013). Nocturnal blood pressure non-dipping, posttraumatic stress disorder, and sleep quality in woman. *Behavioral Medicine,* 39, 111-21. PMCID: PMC3964784.

Ulu, S.M., Ulu, S. & Ulasli, S.S. (2013). Is impaired sleep quality responsible for a nondipping pattern even in normotensive individuals? *Blood Pressure Monitoring,* 4, 183-87.

Vaccarino, V., Goldberg, J., Rooks, C., Shah, A.J., Veledar, E., Faber, T.L., Votaw, J.R., Forsberg, C.W. & Bremner, J.D. (2013). Post-traumatic stress disorder and incidence of coronary heart disease: A twin study. *Journal of the American College of Cardiology,* 62, 970-8. PMCID: PMC3823367.

Verdecchia, P., Angeli, F., Gentile, G., Mazzotta, G. & Reboldi, G. (2011). Telmisartan for the reduction of cardiovascular morbidity and mortality. *Expert Review of Clinical Pharmacology,* 4, 151-61.

Von Kanel, R., Hepp, U., Buddeberg, C., Keel, M., Mica, L., Aschbacher, K. & Schnyder, U. (2006). Altered blood coagulation in patients with posttraumatic stress disorder. *Psychosomatic Medicine,* 68, 598-604.

Walczewska, J., Rutkowski, K., Wizner, B., Cwynar, M. & Grodzicki, T. (2011). Stiffness of large arteries and cardiovascular risk in patients with posttraumatic stress disorder. *Eur Heart J,* 32, 730-6.

Wang, Q., Xi, B., Liu, M., Zhang, Y. & Fu, M. (2012). Short sleep duration is associated with hypertension risk among adults: A systematic review and meta-analysis. *Hypertension Research,* 35, 1012-8.

Ware, J.E. & Sherbourne, C.D. (1992). The MOS 36-item Short-Form Helath Survey (SF-36): Conceptual framework and item selection. *Medical Care,* 30, 473-83.

Weathers, F.W., Blake, D.D., Schnurr, P.P., Kaloupek, D.G., Marx, B.P. & Keane, T.M. (2013). The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). Interview available from the National Center for PTSD at www.ptsd.gov.

Weathers, F.W., Litz, B.T., Keane, T.M., Palmieri, P.A., Marx, B.P. & Schnurr, P.P. (2013). The PTSD Checklist for DSM-5 (PCL-5). Scale available from the National Center for PTSD at www.ptsd.va.gov.

Wentworth, B.A., Stein, M.B., Redwine, L.S., Xue, Y., Taub, P.R., Clopton, P., Nayak, K.R. & Maisel, A.S. (2013). Post-traumatic stress disorder: A fast track to premature cardiovascular disease? *Cardiol Rev,* 21, 16-22.

White, A.R., Giles, T., Bakris, G.L., Neutel, J.M., Davidai, G. & Weber, M.A. (2006). Measuring the efficacy of antihypertensive therapy by ambulatory blood pressure monitoring in the primary care setting. *American Heart Journal,* 15, 176-84.

World Health Organization. Division of Mental Health. (1996). WHOQOL-BREF : Introduction, administration, scoring and generic version of the assessment: Field trial version, December 1996. World Health Organization.

Williams, J.B., Gibbon, M. & First, M.B. (1992). The Structured Clinical Interview for DSM-III-R (SCID): Multisite test-retest reliability. *Archives of General Psychiatry,* 49, 630-6.

Williams, D.R., Yu, Y., Jackson, J.S., & Anderson, N.B. (1997). Racial differences in physical and mental health: Socioeconomic status, stress, and discrimination. *Journal of Health Psychology, 2*, 335-351.

Zarcone, V.P. Sleep hygiene. In: Kryger, M.H., Roth, T. & Dement, W.C., eds. *Principles and Practice of Sleep Medicine. 3rd ed.* Philadelphia, PA2000:657-61.

Zayfert, C. & DeViva, J.C. (2004). Residual insomnia following cognitive behavioral therapy for PTSD. *Journal of Traumatic Stress,* 17, 69-73.

Zhang, J., Ma, R.C., Kong, A.P., So, W.Y., Li, A.M., Lam, S.P., Li, S.X., Yu, M.W., Ho, C.S., Chan, M.H., Zhang, B. & Wing, Y.K. (2011). Relationship of sleep quantity and quality with 24-hour urinary catecholamines and salivary awakening cortisol in healthy middle-aged adults. *Sleep, 34*, 225-

33. PMCID: PMC3022944.