CARDIOVASCULAR RISK INDICATORS AND HEALTH-RELATED QUALITY OF LIFE

IN WOMEN VETERANS WITH PTSD

APPROVED BY SUPERVISORY COMMITTEE

Alina M. Surís, Ph.D., ABPP (Chair)

Qi Fu, MD, PhD

Anushka Pai, PhD

Geetha Shivakumar, MD, MS

Julia Smith, PsyD

DEDICATION

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ELIZABETH HALLEN ANDERSON

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Elizabeth Hallen Anderson, PhD, MRC, 2018

The University of Texas Southwestern Medical Center at Dallas, 2018

Supervising Professor: Alina M. Surís, Ph.D., ABPP

Posttraumatic stress disorder (PTSD) is one of the most prevalent disorders among women veterans treated at the Veterans Health Administration and is associated with a wide range of negative physical health outcomes, including the development of cardiovascular disease. In addition, PTSD has a negative impact on an individual's subjective perception of the health-related quality of his or her own life. The majority of studies examining the complex relationship between PTSD and health have utilized primarily male populations. To better understand the impact of PTSD on laboratory-based and self-reported measures of health in women veterans, this study used multivariate analyses of variance to compare cardiovascular

risk indicators (resting heart rate, blood pressure, and muscle sympathetic nerve activity) and physical and mental health-related quality of life (SF-36) in a sample of women veterans with PTSD to a sample of nonveteran women without PTSD. In addition, hierarchical multiple regression analyses were used to examine the relationship between PTSD symptom criteria groups and sympathetic nervous system activity indicators and physical and mental health-related quality of life. Results revealed no significant differences between women veterans with PTSD and healthy controls in regards to cardiovascular risk indicators, however women veterans with PTSD reported significantly worse physical and mental health related quality of life. Contrary to expectations, the hyperarousal symptom criteria group was not found to be a significant and unique predictor of sympathetic nervous system activity indicators nor health related quality of life. However, clinician-rated non-hyperarousal PTSD symptom severity was found to be a significant and unique predictor of physical health-related quality of life. Further analysis demonstrated that, of the four PTSD symptom criteria groups, only clinician-rated re-experiencing symptom severity approached being a significant predictor of worse physical health-related quality of life. Since re-experiencing symptoms appear to be an important mechanism by which women veterans make judgments about their physical health, clinically targeting such symptoms in PTSD interventions may result in improved health-related quality of life. Given the relatively young state of research in women veterans with PTSD, it is important to confirm and build on previous research findings for this unique population.

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LIST OF DEFINITIONS

BPM – Beats per Minute

BP – Blood Pressure

CAPS-5 – Clinician – Administered PTSD scale for DSM-5

CHRT – Concise Health Risk Tracking

CVD – Cardiovascular Disease

DoD – Department of Defense

DSM – Diagnostic and Statistical Manual

ECG – Electrocardiography

HR – Heart Rate

HRQOL – Health-Related Quality of Life

IEEM – Institute for Exercise and Environmental Medicine

LEC – Life Events Checklist

MCS – Mental Component Summary from SF-36

MINI – Mini-Neuropsychiatric Interview

MSNA – Muscle Sympathetic Nerve Activity

MST – Military Sexual Trauma

MVC - Maximal Voluntary Contraction

NVVRS – National Vietnam Veterans' Readjustment Study

OEF – Operation Enduring Freedom

OIF – Operation Iraqi Freedom

OND – Operation New Daw

PCL – PTSD Checklist

PCS – Physical Component Summary from SF-36

PTSD – Posttraumatic Stress Disorder

Q-LES-Q-SF – Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form

SF-36 – Short Form Health Survey (36)

SOCOM – Special Operation Command

UTSWMC – University of Teas Southwestern Medical Center

VA – Veterans Affairs

VANTHCS – VA North Texas Health Care System

VHA – Veteran's Health Administration

CHAPTER ONE
Introduction

Posttraumatic stress disorder (PTSD) is one of the most prevalent disorders among women veterans treated at the Veterans Health Administration (VISN Support Services Center, 2010). Among women veterans of Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND), nearly 20% have been diagnosed with PTSD (United States Government Accountability Office, 2009). PTSD is associated with a wide range of negative physical health outcomes that are documented by laboratory measures (Boscarino, 2004; Vaccarino et al., 2013), physician diagnosis (Boscarino, 2004; Schnurr, Spiro III, & Paris, 2000), and self-reports of physical health status and functioning (Pacella, Hruska, & Delahanty, 2013; Pagotto et al., 2015). There is particularly strong evidence for the association between PTSD and the development of cardiovascular disease (Boscarino, 2008; Beth E. Cohen, Edmondson, & Kronish, 2015; Kubzansky, Koenen, Spiro, Vokonas, & Sparrow, 2007; Vaccarino et al., 2013). For example, in a study of male Vietnam-era veteran twins, PTSD was associated with more than twice the risk of coronary heart disease based on clinical diagnosis as well as objective quantitative measures of coronary perfusion and myocardial blood flow (Vaccarino et al., 2013). This increased risk remained after controlling for coronary heart disease risk factors, negative health behaviors, and familial risk factors. Although the mechanisms underlying the increased risk of cardiovascular disease in individuals with PTSD are not fully understood, changes in the autonomic nervous system and dysregulation of the neuroendocrine system are believed to be

contributing factors (J. D. Bremner, 2012; Krystal et al., 1989; Paulus, Argo, & Egge, 2013; Yehuda, 2002)

Cardiovascular disease (CVD) is one of the leading causes of death for women in the United States and accounted for 414,191 deaths for this demographic in 2015 (Benjamin et al., 2018). Between 2011 and 2014, the prevalence of CVD in women in the United States was 35.9% (Benjamin et al., 2017). Even though one in three women are diagnosed with CVD, women are diagnosed with PTSD at higher rates than men, and there appears to be a relationship between the two disorders, there is a shortage of research examining the association between PTSD and cardiovascular disease in women veterans (Benjamin et al., 2017; Kubzansky, Koenen, Jones, & Eaton, 2009; Tolin & Foa, 2006; World Health Organization, 2013). The majority of studies examining the relationship between PTSD and CVD have been limited to male populations. Of the two prospective studies in the literature examining the link between PTSD and CVD in women, both demonstrated that higher PTSD symptoms were associated with increased risk of CVD incidence (Kubzansky et al., 2009; Sumner et al., 2015). Although the women in these studies were civilians and no similar study exists for women veterans with PTSD, a large scale 2009 study found that veterans, both male and female, with mental health diagnoses had a significantly higher prevalence of all cardiovascular risk factors, including tobacco use, hypertension, dyslipidemia, obesity, and diabetes (Beth E Cohen, Marmar, Ren, Bertenthal, & Seal, 2009).

In addition, women veterans experience more chronic medical conditions, greater incidence of health risk behaviors, and worse health-related quality (HRQOL) of life than civilian women (Frayne et al., 2006; Lehavot, Hoerster, Nelson, Jakupcak, & Simpson,

2012). Women veterans with PTSD report significantly worse health-related quality of life than their counterparts without PTSD (Dobie et al., 2004). Regarding specific symptom criteria of PTSD, Kimerling et al. (2000) found that hyperarousal alone was significantly associated with higher levels of physical health symptoms and poorer health perception. It has been hypothesized that the physiological correlates of hyperarousal symptoms may be interpreted as evidence of physical illness (Litz, 1992; Zoellner, Goodwin, & Foa, 2000).

These findings suggest that women veterans with PTSD are at a heightened risk for experiencing health problems in general, particularly CVD. Due to the rapidly increasing number of women veterans and the high prevalence rate of PTSD in this population, it is important to understand CVD and risk factors in this population.

CHAPTER TWO
Review of the Literature

History of Women in the Military

While women have consistently served their country in the military since the American Revolution, the degree of their involvement, integration, and militarization has undergone significant change. Although formal inclusion in the United States Armed Forces began with the establishment of the Army Nurse Corps in 1901, women have informally served since the creation of our nation's military (Kamarck, 2016). In 1948, the Women's Armed Services Integration Act allowed women to become permanent members of the Armed Forces, but restricted the proportion of women in the military to 2% of the enlisted force and 10% of officers (National Center for Veterans Analysis and Statistics, 2017). The Women's Armed Services Integration Act removed limitations on the number and ranks of women in the military in 1967. The combination of the movement for equal rights for women and the military's difficulty recruiting and retaining an adequate number of qualified men following the end of conscription and creation of the All-Volunteer Force in 1973 led to a significant increase of the role of women in the Armed Forces (Kamarck, 2016). In 2016, there were 204,628 women in the Department of Defense (DOD) Active Duty Force (Army, Navy, Air Force, and Marine Corps) and 158,173 women in the Reserve and National Guard, representing 17.2% of the total military force (Department of Defense, 2016).

Women Veterans

Of the approximately 20.8 million living veterans, an estimated 8.7% (1.8 million) are women (National Center for Veterans Analysis and Statistics, 2018). Women are currently the fastest growing demographic within the veteran community (National Center for Veterans Analysis and Statistics, 2017). Projected growth of women in the military is expected to increase from 6% in 2000 to 16% in 2040. Overall, female veterans are younger than male veterans, with a median age of 50 compared to a median age of 65 for male veterans (National Center for Veterans Analysis and Statistics, 2018). In 2015, 23.4 % of women veterans had a service connected disability, with the five most prevalent being PTSD (11.8%), major depressive disorder (6.5%), migraine (5.9%), lumbosacral or cervical strain (5.5%), and complete removal of uterus and ovaries (3.1%; National Center for Veterans Analysis and Statistics, 2017).

Trauma in Women Veterans

Women veterans endorse higher rates of trauma exposure than their civilian counterparts (Zinzow, Grubaugh, Monnier, Suffoletta-Maierle, & Frueh, 2007). Experiencing traumatic events, regardless of trauma type, is associated with an increased risk of mental health disorders in women veterans, including PTSD, depression, and substance abuse (Hassija, Jakupcak, Maguen, & Shipherd, 2012; Luxton, Skopp, & Maguen, 2010; S. Maguen et al., 2012; Suffoletta-Maierle, Grubaugh, Magruder, Monnier, & Frueh, 2003; Zinzow et al., 2007). The majority of the literature regarding trauma in female veterans has focused on combat exposure, sexual trauma, and physical violence.

Combat Exposure

The presence of female service members in combat zones during Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn has been unmatched in terms of both the number of women deployed and their exposure to combat during deployment (Street, Vogt, & Dutra, 2009). Approximately 299,548 female service members were deployed for these operations between September 2001 and February 2012, resulting in over 800 wounded and 130 deaths (Burrelli, 2013). Prior to 1994, Department of Defense (DoD) policy under the Risk Rule did not allow women in the battlefield to prevent risk of exposure to direct combat, hostile fire, or capture (Beckett & Chien, 2002). The Risk Rule was replaced by the direct ground combat exclusion assignment rule in January of 1994. This new policy stated that the DoD could assign personnel to all position for which they are qualified in support units, but women would be excluded from assignment to units, below the brigade level, whose primary mission was to engage in direct on the ground combat (Beckett & Chien, 2002). This meant that women were banned from infantry, armor, artillery, combat engineers, and special operations units of battalion size or smaller. Despite these restrictions, the nonlinear battlefields of Iraq and Afghanistan meant that noncombat support units, which included women, regularly engaged in direct combat to carry out their mission (Burrelli, 2013). A study of 7,251 active duty soldiers deployed in support of the wars in Afghanistan and Iraq between 2006 and 2009 found that women reported the following combat exposures: being exposed to death (31.0%), witnessing killing (9.0%), being injured in a war zone (7.2%), and killing (4%; Maguen, Luxton, Skopp, & Madden, 2012). Another study of 54 active duty women returning from deployment to Iraq in support of Operation Iraqi Freedom found that 73.5% belonged to a unit that experienced hostile or incoming fire,

20.8% went on combat patrols/missions, 18.9% belonged to a unit that engaged in battle in which it suffered casualties, and 7.5% fired a weapon (Dutra et al., 2011). In January 2013, then Secretary of Defense Leon Panetta announced that the DoD would rescind the rule restricting women from serving in direct combat positions and instructed military departments and services to review their occupational standards and assignment policies and to make recommendations for opening all combat roles to women no later than January 1, 2016 (Kamarck, 2016). Following extensive studies conducted by military departments and Special Operations Command (SOCOM) on issues such as unit cohesion, equipment, women's health, then-Secretary of defense Ashton Carter directed the military to open all combat jobs without exception (Kamarck, 2016). In March of 2016, implementation plans for the integration of women into direct ground combat roles were approved (Kamarck, 2016). Given the recent significant changes in policy, it is reasonable to anticipate a significant growth in combat exposure among female service members in the coming years.

Sexual Assault

Sexual assault, particularly in the context of military service, has been the most widely studied type of trauma occurring in women veterans. Research examining the prevalence childhood sexual abuse among women who have served in the military have found rates ranging from 27% to 49% (Benda, 2006; Sadler, Booth, Mengeling, & Doebbeling, 2004; Schultz, Bell, Naugle, & Polusny, 2006; Suris, Lind, Kashner, Borman, & Petty, 2004; Zinzow, Grubaugh, Frueh, & Magruder, 2008). In comparison, rates of childhood sexual abuse in civilian women ranged from 27% to 32.3% (Briere & Elliott, 2003; Finkelhor, Hotaling, Lewis, & Smith, 1990). In regards to rates of adult sexual assault

in female veterans that did not take place during their military service, previous research reported prevalence rates of 24% to 49% (Benda, 2006; Campbell & Raja, 2005; Schultz et al., 2006; Suris et al., 2004; Zinzow et al., 2008). In contrast, estimates of adult sexual assault in civilian women have been reported in the ranges of 13% to 27.6% (Elliott, Mok, & Briere, 2004; Masho & Ahmed, 2007; Tjaden & Thoennes, 1998).

Military sexual trauma (MST) is currently defined as "… psychological trauma, which in the judgment of a Veterans Health Administration (VHA) mental health professional, resulted from a physical assault of a sexual nature, battery of a sexual nature or sexual harassment which occurred while the veteran was serving on active duty, active duty for training, or inactive duty training" ("Counseling and treatment for sexual trauma," 2012). As summarized by Surís and Lind (2008), there are unique characteristics of sexual trauma associated with military service that differentiate it from civilian sexual trauma. Because MST typically occurs where a person lives and work, he or she often has to continue to working and living (e.g. on base) with the perpetrator. The perpetrator of MST may be another service member, supervisor, or higher-ranking official and the victim may rely on him or her for services, security, evaluations, or promotion. Strong unit cohesion may contribute to a victim feeling like he or she cannot speak up about the assault or harassment for fear of being ostracized.

The reported prevalence rates of military sexual trauma vary greatly due to factors such as the definition of MST used, the manner of obtaining the data (e.g., database, mailed survey, telephone survey, in-person), the purpose of the study for which the data was gathered (e.g., descriptive, diagnostic, etc.), and the respondent sample (e.g., treatment

seeking, compensation seeking, service era, active duty vs. veteran status, etc.; Surís & Smith, 2011). To gain a better understanding of the prevalence of MST, Wilson (2016) conducted meta-analysis of 69 studies reporting lifetime prevalence of MST using different definitions of MST, methodologies, and populations samples. When the definition of MST included assault and harassment, 15.7% of military personnel and veterans reported MST (38.4% of women, 3.9% of men). Using definitions from Allard et al. (2011), sexual assault was defined as "an act that involved unwanted, nonconsensual, forced, or coerced touching of sexual body parts or sexual intercourse" and harassment was defined as "an act of unwanted, nonconsensual verbal or physical contact that was sexual in nature, such as sexual comments or sexual touching on nonsexual body parts." The presence of either force or the involvement of sexual body parts were the primary characteristics used to separate sexual assault from harassment. When the definition of MST was limited to assault, 13.9% reported MST (23.6% of women, 1.9% of men); when the definition was limited to harassment, 31.2% reported MST (52.5% of women, 8.9% of men; Wilson, 2016). In contrast to the lifetime prevalence rate of civilian sexual assault, MST prevalence rates are typically based on a time period of two to six years during which the service member is on active duty. Rates of sexual assault during these limited years are considerably higher than civilian lifetime rates, suggesting an increased risk for sexual assault among active duty military personnel (Anderson & Surís, 2013).

Physical Violence

Research indicates that 46.0% to 51.0% of women veterans experience some form of physical violence during their lifetime, a rate which is significantly higher than most

estimates of physical violence among women in the general population (R. Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Lang et al., 2003; Norris, 1992; Resnick, Kilpatrick, Dansky, Saunders, & Best, 1993; Stein et al., 2004; Zinzow et al., 2007). The few studies examining childhood physical violence in women veterans found rates ranging from 16.5% to 35.2% (Benda, 2006; Hassija et al., 2012; Sadler et al., 2004). In comparison, similar studies of general population samples found rates from 14.1% to 19.5% (Briere & Elliott, 2003; McCauley et al., 1997). Sadler et al. (2004) reported the prevalence of premilitary domestic violence in a sample of women veterans selected form VA health care registries to be 19.0%. The same author also found that 49% of those who endorsed premilitary violence (physical or sexual) reported joining the military to leave an abusive or difficult home. Physical assault during military service was found to occur at a rate of 30% in a sample of women veterans (Sadler, Booth, Cook, Torner, & Doebbeling, 2001). Twenty-three percent of the assaults were carried out solely by an intimate partner and 21% of the assaults were exclusively in the context of rape. In comparison, Tjaden & Thoennes (1998) found a lifetime prevalence 22.1% of physical assault by an intimate partner for women in the general population. Lower rates of physical assault were reported by women following their military service, with 22% reporting post-discharge physical assault (Sadler et al., 2004).

Posttraumatic Stress Disorder

PTSD, a psychiatric disorder that may develop following exposure to one or more traumatic events, is widely considered a “signature diagnosis” of trauma (American Psychiatric Association, 2013; C. North, 2017). This disorder is characterized by symptoms,

including intrusive re-experiencing of the traumatic events, avoidance, negative changes to mood and cognitions, and hyperarousal, associated with the traumatic event that last for at least one month and cause clinically significant distress or impairment.

The codification of symptoms and inclusion of PTSD in the third edition of the Diagnostic and Statistical Manual (DSM) of Mental Disorders in 1980 was driven by the large number of Vietnam veterans seeking treatment (American Psychiatric Association, 1980). At the time, PTSD was thought of as a rare disorder that was caused by "a recognizable stressor that would evoke significant symptoms of distress in almost everyone" (American Psychiatric Association, 1980). Such stressors were believed to be an atypical occurrence and, as clarified the DSM-III-R, "outside the range of usual human experience" (American Psychiatric Association, 1987). Subsequent epidemiological studies contradicted the DSM-III and DSM-III-R definition of a traumatic event by revealing a high prevalence of trauma exposure in the general population (R. Kessler et al., 1995). The DSM-IV diagnostic criterion for a traumatic event was changed to "an event or events that involved actual or threatened death, or serious injury, or a threat to the physical integrity of self or others" (American Psychiatric Association, 1994). Additionally, a subjective element was added to the criteria of the traumatic event, stating that the person's response to the event involved fear, helplessness, or horror. In the most recent edition of the DSM, this subjective response was removed from the definition of trauma (American Psychiatric Association, 2013).

The majority of the population experience at least one traumatic event during their lifetime, but only a minority of those who experience trauma will develop PTSD (Breslau, 2009). It is normal to experience change in one's cognitions, mood, and behavior in reaction

to a trauma and most individuals eventually recover from this experience. An individual with PTSD has been unable to recover from the trauma and continues to experience the psychological effects of the event (Yehuda, 2002).

PTSD is characterized by the onset of persistent re-experiencing of the event, avoidance, negative alterations to mood and cognition, and hyperarousal symptoms following the trauma (American Psychiatric Association, 2013). These symptoms cause clinically significant distress or impairment in functioning. According to the DSM-5, a diagnosis of PTSD (for individuals over the age of six years old) is met by the following criteria:

A. Exposure to actual of threatened death, serious injury, or sexual violence in one (or more) of the following ways:

    1. Directly experiencing the traumatic event(s).

    2. Witnessing, in person, the event(s) as it occurred to others.

    3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member of friend, the event(s) must have been violent or accidental.

    4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g. first responders collecting human remains, police officers repeatedly exposed to details of child abuse).

    Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.

B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:

1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).

Note: In children older than 6 years, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.

2. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).

Note: In children, there might be frightening dreams without recognizable content.

3. Dissociative reactions (e.g. flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.)

Note: In children, trauma-specific reenactment may occur in play.

4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

5. Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic events(s).

C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:

1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).

2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is completely ruined").

3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.

4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).

5. Markedly diminished interest or participation in significant activities.

6. Feelings of detachment or estrangement from others.

7. Persistent inability to experience positive emotions (e.g. inability to experience happiness, satisfaction, or loving feelings).

E. Marked alteration in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.
2. Reckless or self-destructive behavior.
3. Hypervigilance.
4. Exaggerated startle response.
5. Problems with concentration.
6. Sleep disturbance (e.g. difficulty falling or staying asleep or restless sleep).

F. Duration of the disturbance (Criteria B, C, D, and E) is more than one month.

G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

H. The disturbance is not attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition. (American Psychiatric Association, 2013, pp. 271-272)

Prevalence

A national representative study of 9,282 English-speaking adults in the United States found a lifetime prevalence rate of 6.8% using DSM-IV PTSD criteria (R. Kessler et al., 2005). A smaller, but more recent, study administered an internet-based survey to 2,953 adults in the United States that utilized DSM-5 criteria for PTSD found a lifetime prevalence of 8.3% (Kilpatrick et al., 2013). Women and girls have consistently been found to be more

likely than men and boys to meet criteria for PTSD, but less likely to experience potentially traumatic events overall (Tolin & Foa, 2006). However, women have been found to be more likely than men to experience a trauma associated with a high probability of PTSD (R. Kessler et al., 1995). Traumas with a high probability of PTSD for men include rape, combat exposure, childhood neglect, and physical abuse (R. Kessler et al., 1995). Among women, traumas with a high probability of PTSD include rape, sexual molestation, physical attack, being threatened with a weapon, and childhood physical abuse (R. Kessler et al., 1995). When researchers examined sex differences within the same categories of potentially traumatic events, female participants were more likely than male participants to meet criteria for PTSD and also reported greater symptom severity (Tolin & Foa, 2006).

Military/Veteran Prevalence

Numerous studies have examined the prevalence of PTSD in military/veteran populations during different eras. Based on interviews with a sample of 3,016 American veterans, the National Vietnam Veterans Readjustment Study (NVVRS) estimated the lifetime prevalence of PTSD to be 30.9% for men and 26.9% for women who served in the military during the Vietnam era (Kulka et al., 1990). The prevalence of current PTSD in a sample of 11,441 veterans of the Gulf War was reported to be 12.1% (Kang, Natelson, Mahan, Lee, & Murphy, 2003). Reviews of the literature examining the prevalence of PTSD among OEF/OIF/OND veterans found that most studies report rates between 5% and 30% (Ramchand, Rudavsky, Grant, Tanielian, & Jaycox, 2015; Ramchand et al., 2010). Researchers note that the widely varying estimates of prevalence may be explained by methodological differences and limitations in study design, such as different methods of

defining PTSD, selection bias, and the use of screening instruments in lieu of more complete diagnostic assessments (Ramchand et al., 2010). A 2015 meta-analysis of 33 studies estimated PTSD prevalence among Operations Enduring Freedom and Iraqi Freedom (EOF/OIF) to be 23%, however, the authors noted that the majority of the studies included in the analysis utilized VA database samples and determined prevalence of PTSD via ICD-9 codes in medical records (Fulton et al., 2015). Another study by Koo et al. (2016) analyzed records of OEF/OIF/OND veterans enrolled in VA care and found that 28% of men and 23% of women were diagnosed with PTSD between 2001 and 2013. Another study that examined gender differences in OEF/OIF/OND PTSD prevalence rates reported symptoms of probable PTSD at approximately equal rates of 20% among men and women veterans (Street, Gradus, Giasson, Vogt, & Resick, 2013). A 2009 government report stated that approximately 20% of OEF/OIF women Veterans have received a diagnosis of PTSD (United States Government Accountability Office, 2009). To this author's knowledge, there are no publications reporting PTSD criterion A trauma types for these veterans.

Course

PTSD may develop at any age following the first year of life (American Psychiatric Association, 2013). Symptoms of PTSD usually develop during the first three months following the trauma, however, it is possible for months, possibly years, to pass before an individual meets full PTSD symptom criteria (American Psychiatric Association, 2013). If there is a delay in meeting full diagnostic criteria of at least six months, the diagnosis of PTSD has a specifier of "with delayed expression" (American Psychiatric Association, 2013). In a large survey of PTSD in the general population, Kessler et al. (1995) found that

PTSD survival curves decreased most sharply in the first 12 months after the start of symptoms for both individuals who received mental health treatment and those who did not. The survival curves demonstrated a more gradual decrease for roughly six years after the start of PTSD symptoms. An estimated 82% of individuals with PTSD experience symptoms for at least three months and approximately 74% continue to have symptoms for at least six months (Breslau, 2001). Kessler et al. (1995) reported a median time to remission was 36 months for participants who pursued mental health treatment and 64 months for participants who did not. Furthermore, approximately one third of participants, both treatment-receiving and non-treatment receiving, did not achieve remission after many years.

Course for Veterans

Longitudinal studies demonstrate that the trajectory of PTSD symptoms in those who have served in the military is variable. In their study of veterans of the Vietnam era with chronic PTSD, Bremner et al. (1996) showed that the onset of symptoms typically occurred at the time of the trauma. Symptoms increased during the first few years following trauma exposure and then plateaued. At this point, symptoms became chronic, with no evidence of remission or relapse. Orcutt, Erickson, and Wolfe (2004) studied 2,949 veterans (2,702 men and 240 women) of the Gulf War and found that the course of PTSD symptoms in this sample was best represented by either: (a) low PTSD symptom levels that showed little increase over time, or (b) high initial PTSD symptom levels that increased significantly over time. Research examining the course of PTSD for OEF/OIF/OND veterans, as well as gender differences in course of the illness, is lacking.

Comorbidity

There is a high prevalence of comorbid psychiatric disorders among individuals with PTSD. In fact, comorbidity is said to be the rule rather than the exception for individuals with PTSD (Brady, Killeen, Brewerton, & Lucerini, 2000). Epidemiological studies of PTSD in the general population have documented more than 80%-90% lifetime psychiatric comorbidity (R. Kessler et al., 1995; Sareen, 2014). In the general population, the most prevalent lifetime psychiatric disorders comorbid with a lifetime history of PTSD are major depression, substance use disorders, conduct disorder, and anxiety disorders (R. Kessler et al., 1995). Among women, the prevalence of specific comorbidities were: major depression (49%), alcohol use disorder (28%), drug use disorder (27%), conduct disorder (15%), and specific anxiety disorders (13%-29%) (R. Kessler et al., 1995).

Comorbidity in Veterans

Over 80% of combat veterans diagnosed with PTSD meet diagnostic criteria for at least one additional comorbid diagnosis (Ginzburg, Ein-Dor, & Solomon, 2010; Kulka et al., 1990). A large study of male and female Vietnam Veterans found the most prevalent comorbid diagnoses to be substance abuse, antisocial personality disorder, and depression (Kulka et al., 1990). Deering et al. (1996) observed that combat veterans with PTSD had the highest prevalence of comorbidity compared to other trauma types and noted different rates of comorbid disorders compared to individuals with PTSD from other trauma types. For example, combat veterans with PTSD demonstrate a higher prevalence of comorbid substance use and personality disorders when compared to other populations (Brady et al., 2000; J Douglas Bremner et al., 1996; Deering et al., 1996; Keane & Kaloupek, 1997).

Few studies have examined gender differences in prevalence of comorbid psychiatric disorders in veterans. A study by Maguen et al. (2012) of 74,493 male and female OEF/OIF veterans with PTSD found that women were more likely to have received a comorbid diagnosis of depression, anxiety disorder, and eating disorder. The authors note that 70% of women veterans with PTSD were diagnosed with depression. In contrast, male veterans were more likely to have a comorbid diagnosis of alcohol and other substance use disorders. Women veterans were also found to be more likely to have received three or more comorbid psychiatric diagnoses while male veterans were more likely to have been given a single psychiatric diagnosis.

Cardiovascular Disease

Cardiovascular disease is a class/group of disorders of the heart and blood vessels (Mendis, Puska, Norrving, & Organization, 2011). These disorders include, but are not limited to:

- Coronary heart disease: diseases of the blood vessels supplying the heart muscle, such as myocardial infarction, sudden coronary death, and angina pectoris (Wong, 2014). This is the most common type of CVD in the United States (Centers for Disease Control and Prevention, 2017).
- Cerebrovascular disease: diseases of the blood vessels supplying the brain, including strokes.
- Peripheral artery disease: diseases of the blood vessels supplying the limbs.

- Deep vein thrombosis and pulmonary embolism: blood clots, typically from leg veins, which can dislodge and move to the heart and lungs (World Health Organization, 2017).

CVD accounted for 836,546 deaths in the United States in 2015, which was more than deaths related to all forms of cancer and chronic lower respiratory disease combined (Benjamin et al., 2018). In the US, coronary heart disease is the leading cause of deaths attributed to CVD (43.8%), followed by stroke (16.8%), hypertension (9.4%), heart failure (9.0%), diseases of the arteries (3.1%) and other CVDs (17.9%; Benjamin et al., 2018). Hypertension has been found to be the single largest risk factor for CVD related deaths (Danaei et al., 2009). Based on 2011 to 2014 data, an estimated one in three US adults (92.1 million) has one or more types of CVD (Benjamin et al., 2017). Rates of CVD increase with age and differ within racial, ethnic, geographic, and sociodemographic groups (Mensah & Brown, 2007). Direct and indirect costs of total CVD in the US are estimated to be in excess of 329.7 billion, including both health expenses and lost productivity (Benjamin et al., 2018). For individuals with disabilities in the US, heart disease, stroke, and hypertension ranked among the top 15 conditions that caused those disabilities (Centers for Disease Control and Prevention, 2009). The American Heart Association has estimated that 45.1% of the US population will have some form of CVD by 2035, with total costs related to CVD projected to reach 1.1 trillion (Khavjou, Phelps, & Leib, 2016).

CVD is one of the leading causes of death for women in the United States and, between 2011 and 2014, the prevalence of CVD in women in the United States was 35.9% (Benjamin et al., 2017). A woman's lifetime risk of developing CVD by the age of 50 is

estimated to be 39% (D'Agostino et al., 2008). Compared to men, women with coronary heart disease are typically older, have more comorbidities, present more frequently with atypical symptoms, postpone seeking treatment at a significantly higher rate, and are more prone to complications (Papakonstantinou, Stamou, Baikoussis, Goudevenos, & Apostolakis, 2013). Research has found that while mortality rates for coronary heart disease in older adults in the US have dramatically fallen over the past several decades, decreases in young adults, particularly young adult women, have been modest (Wilmot, O'Flaherty, Capewell, Ford, & Vaccarino, 2015). In addition, the prevalence of myocardial infarction is increasing in women aged 35 to 54 (Towfighi, Zheng, & Ovbiagele, 2009).

PTSD And Cardiovascular Disease

PTSD is associated with a wide range of negative physical health outcomes that are documented by laboratory measures (Boscarino, 2004; Vaccarino et al., 2013), physician diagnosis (Boscarino, 2004; Schnurr et al., 2000), and self-reports of physical health status and functioning (Pacella et al., 2013; Pagotto et al., 2015). For example, a study of Vietnam era veterans assessed 20 years after service found that theater veterans who were diagnosed with PTSD had a higher lifetime prevalence of circulatory, respiratory, musculoskeletal, digestive, and neurological diseases (Boscarino, 1997).

There is particularly strong evidence for the association between PTSD and the development of cardiovascular disease (Boscarino, 2008; Beth E. Cohen et al., 2015; Kubzansky et al., 2007; Vaccarino et al., 2013). In a study of male Vietnam-era veteran twins, PTSD was associated with more than twice the risk of coronary heart disease based on clinical diagnosis as well as objective quantitative measures of coronary perfusion and

myocardial blood flow (Vaccarino et al., 2013). This increased risk remained after controlling for coronary heart disease risk factors, negative health behaviors, and familial risk factors.

Another study prospectively examining early-age heart disease among a national sample of male Vietnam veterans who did not have heart disease at baseline found that having a diagnosis of PTSD at baseline doubled the risk of death from early onset heart disease at 20-year follow-up (Boscarino, 2008). In addition, a 5-point increase in PTSD symptom severity demonstrated a 20% increase in the risk of death from heart disease at follow up. Controlling for lifetime depression or combat exposure did not significantly change these results. A similar prospective cohort study of male veterans found that for each standard deviation increase in scores on the Mississippi Scale for Combat-Related PTSD, the relative risk of total coronary heart disease (nonfatal myocardial infarction and fatal coronary heart disease) was 1.26, although, after controlling for standard coronary risk factors, this relationship was only marginally significant (Kubzansky et al., 2009). A 2010 prospective cohort study of patients receiving care in the VA healthcare system who were free of cardiovascular disease at baseline found that a diagnosis of PTSD resulted in an increased risk for incident myocardial infarction (HR = 1.39, 95% CI: 1.33-1.46; Scherrer et al., 2010) .

PTSD and Risk for Cardiovascular Disease in Women

Despite the fact that cardiovascular disease is one of the leading causes of death in women, there is a lack of research examining the relationship between PTSD and cardiovascular disease in women veterans (Kubzansky et al., 2009; World Health Organization, 2013). The majority of studies examining the relationship between PTSD and

CVD have been limited to male populations. Of the two prospective studies in the literature examining the link between PTSD and CVD in women, both demonstrated that higher PTSD symptoms were associated with increased risk of CVD incidence (Kubzansky et al., 2009; Sumner et al., 2015). In the first study to examine PTSD as a risk factor coronary heart disease in women, Kubzansky et al. (2009) studied a cohort of community dwelling civilian women who had experienced at least one traumatic event during the past year prior to PTSD assessment. Based on incident coronary heart disease during the 14-year follow-up period, women with five or more symptoms of PTSD were at over three times the risk of incident coronary heart disease compared to women reporting no symptoms (age-adjusted OR = 3.21, 95% CI: 1.29 – 7.98). A more recent study examined trauma exposure and PTSD symptoms and their relationship to incident cardiovascular disease in 49,978 women over a 20-year period. Compared to women who denied trauma exposure, endorsing over four symptoms of PTSD was associated with an increased risk of cardiovascular disease after adjusting for age, family history, and childhood factors (HR = 1.60, 95% CI: 1.20-2.13; Sumner et al., 2015) . Trauma exposure alone (no symptoms of PTSD endorsed) was also associated with an increased risk of cardiovascular disease (hazard ratio, 1.45; 95% confidence interval, 1.15 – 1.83). Health behaviors and medical risk factors accounted for approximately 14% of the association between cardiovascular disease and trauma exposure alone and approximately 47% of the association between cardiovascular disease and trauma exposure paired with endorsing at least four symptoms of PTSD.

Potential Mechanisms Linking PTSD to CVD

Biological Mechanisms

Proposed biological mechanisms explaining the relationship between PTSD and CVD include autonomic nervous system dysfunction, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and inflammation. The autonomic nervous system, consisting of the sympathetic and parasympathetic nervous system, is a division of the peripheral nervous system that regulates body functions such as heart rate, blood pressure, digestion, and respiratory rate (Lovallo & Sollers III, 2007). The autonomic nervous system is also one of the key physiological systems involved in the acute stress response (Pacak & McCarty, 2007). Overactivation of the sympathetic nervous system plays a major role in the development and maintenance of hypertension, a significant risk factor for CVD, as well as the development arrhythmias, heart failure, and atherogenesis (Erami, Zhang, Ho, French, & Faber, 2002; Grassi, 2004, 2009; Julius, 1993).

A study that directly measured sympathetic nerve activity using microneurography found that individuals with PTSD had significantly increased muscle sympathetic nerve activity (MSNA) during combat-related and non-combat related mental stress, but did not demonstrate significant differences in baseline MSNA compared to non-PTSD controls (Park et al., 2017). Research has also provided indirect evidence, including decreased heart rate variability and higher resting heart rate and blood pressure, that suggests chronic sympathetic nervous system overactivity in individuals with PTSD (Bedi & Arora, 2007; Buckley & Kaloupek, 2001). In addition, research has shown increased levels of urinary noradrenaline and decreased levels of low frequency heart rate variability in individuals with PTSD, both of which are indicative of heightened sympathetic nervous system activity (Chang et al., 2013;

H. Cohen et al., 1998; Shah et al., 2013; Wingenfeld, Whooley, Neylan, Otte, & Cohen, 2015).

The release of catecholamines, such as the neurotransmitters epinephrine and norepinephrine, is part of the stress response. Increased levels of catecholamines directly affect the heart, blood vessels, and platelets and may lead to elevations in blood pressure and increases in coagulation (Bedi & Arora, 2007; Brotman, Golden, & Wittstein, 2007). Research has demonstrated elevated 24-hour urine catecholamine excretion in individuals diagnosed with PTSD (Southwick, Paige, Bremner, Krystal, & Charney, 1999). Norepinephrine and dopamine levels have also been found to be significantly correlated with PTSD symptom severity (Yehuda, Southwick, Giller, Ma, & Mason, 1992).

Numerous studies have found evidence of HPA axis dysregulation in individuals with PTSD (Wentworth et al., 2013). The HPA axis performs a key role in the adaptive response to stressors (Yehuda, 2001). Acute stress typically triggers a cascade of biochemical activity, including the release of cortisol, a glucocorticoid, which regulates numerous metabolic, neuronal, and immune reactions to mobilize energy to cope with the stressor and restore homeostasis (Meewisse, Reitsma, de Vries, Gersons, & Olff, 2007). The effects of cortisol may become maladaptive during chronic and excessive activation of the HPA axis (Dallman et al., 2004).

Levels of cortisol are frequently found to be lower than normal in individuals with PTSD, but may also be similar to or higher than those in a non-PTSD comparison group (J Douglas Bremner et al., 2003; Lemieux & Coe, 1995; Maes et al., 1998; Pitman & Orr, 1990; Rasmusson et al., 2001; Yehuda, 2006). Studies have also consistently shown an enhanced

negative feedback inhibition of cortisol in response to dexamethasone suppression tests (Yehuda, 2006; Yehuda et al., 1993). Yehuda et al (1996) examined circadian rhythm parameters of cortisol and found that individuals with PTSD exhibited a greater dynamic range of cortisol, suggesting a capacity for greater system reactivity (Yehuda et al., 1996). In explaining disparate findings, Yehuda (2006) stresses the recognition that "the components of the HPA axis are not uniformly regulated (e.g., circadian rhythm patterns, tonic cortisol secretion, negative feedback inhibition, and the cortisol response to stress are differentially mediated)…the HPA axis is a fundamentally dynamic system that may show transient increases or hyperresponsivity under certain environmental conditions." (158).

Dysregulation of the HPA axis may cause excessive inflammation through poor regulation of immune function (J. M. Gill, Saligan, Woods, & Page, 2009). If cortisol levels are low, inadequate glucocorticoid signaling may result in high levels of cell-mediated and pro-inflammatory cytokines (Elenkov, Iezzoni, Daly, Harris, & Chrousos, 2005; McEwen, 2007; Raison & Miller, 2003). Conversely, chronically high levels of cortisol can lead to the dominance of humoral immune actions, increasing susceptibility to encountered antigens (McEwen, 2007). Chronic inflammation has been identified as key factor in the development and progression of cardiovascular disease (Ridker, 2005; Ridker, Hennekens, Buring, & Rifai, 2000). A review of the literature of immune function in individuals with PTSD found that PTSD is associated with excessive inflammatory actions of the immune system, particularly in chronic cases of PTSD (J. M. Gill et al., 2009). In addition, a recent study reported a dose-response relationship between PTSD symptom severity and inflammation (von Känel et al., 2010; von Känel et al., 2007). Specifically, the authors found higher levels

of interleukin 1β and tumor necrosis factor α coupled with lower levels of the antiflammatory cytokine interleukin 4.

Behavioral Risk Factors

Research has demonstrated that individuals with PTSD have higher rates of tobacco use and alcohol and substance dependence compared to the individuals without PTSD, even when the individuals without PTSD have been exposed to trauma (Breslau, Davis, & Schultz, 2003; R. Kessler et al., 1995). There is also evidence that individuals with PTSD experience greater difficulties when attempting to decrease their use of such substances. A study by Dedert et al. (2011) of tobacco cessation found that individuals with PTSD had significantly higher cravings and withdrawal symptoms following overnight abstinence. PTSD has also been significantly correlated with obesity, both in the general population and in OEF/OIF veterans enrolled at the VA, which may reflect additional lifestyle factors such as poor eating habits and lack of exercise (Beth E Cohen et al., 2009; Scott, McGee, Wells, & Browne, 2008). A review of the literature published between 1980 and 2014 provided mixed results, but, overall, pointed to the presence of a negative association among PTSD, eating behavior, and physical activity (Hall, Hoerster, & Yancy Jr, 2015). A review of the literature by Vancampfort et al. (2016) found that hyperarousal symptoms specifically were associated with lower participation in physical activity in individuals with PTSD.

Of the symptoms that make up the diagnostic criteria for PTSD, sleep disturbance, including nightmares and difficulties with sleep onset and/or maintenance, is one of the most prevalent (Green, 1993). In a survey of Vietnam era male veterans, Neylan et al. (1998) reported prevalence rates of 44.0% for difficulty falling asleep, 90.7% for staying asleep, and

52.4% for nightmares in combat veterans with PTSD, which was significantly higher than combat veterans without PTSD or civilians. Cappuccio (2011) found that individual who sleep six hours per night or less have a greater risk of coronary heart disease and stroke than individuals sleeping seven to eight hours per night. Although the mechanisms that underlie this relationship are not fully understood, research has linked short sleep duration to alterations in circulating levels of the hormones leptin and ghrelin, increased inflammation, and changes in cortisol secretion and growth hormone metabolism (Copinschi, 2005; Spiegel, Knutson, Leproult, Tasali, & Cauter, 2005; Spiegel, Tasali, Penev, & Van Cauter, 2004; Taheri, Lin, Austin, Young, & Mignot, 2004). While poor sleep duration and/or quality leads to neuroendrocrine alterations that contribute to CVD risk, it also contributes to other behavioral risk factors. For example, Talbot, Neylan, Metzler, and Cohen (2014) found that poor sleep quality predicted lower physical activity in individuals with PTSD. In addition, preliminary research indicates that behaviors such as disinhibited eating in the context of poor sleep may also be a factor in negative health outcomes (Chaput, Després, Bouchard, & Tremblay, 2011).

Psychosocial Risk Factors

The risk of developing CVD in individuals with PTSD may also be increased by comorbid psychiatric disorders and impairments in social functioning (Edmondson & Cohen, 2013). Although several studies have shown that the association between PTSD and CVD remains significant after adjusting for depression, the presence of depression, particularly clinically diagnosed major depressive disorder, remains a risk factor for the development of CVD (Van der Kooy et al., 2007). A meta-analysis of 39 studies demonstrated that anger and

hostility are significantly associated with PTSD in trauma-exposed adults (Orth & Wieland, 2006). Research has also found a significant positive association between anger and myocardial infarction, symptoms of angina, and angiographic severity of CVD (Kawachi, Sparrow, Spiro, Vokonas, & Weiss, 1996). PTSD symptoms such as avoidance and negative alterations in cognition and mood, including feelings of detachment from others, may result in decreased social networks and support. Research has found that individuals with PTSD report significantly lower levels of social support (Davidson, Hughes, Blazer, & George, 1991). In addition, a 2006 longitudinal study found that chronic symptoms of PTSD erodes social support over time (King, Taft, King, Hammond, & Stone, 2006). Social isolation has been found to have a negative impact on general health, including an increased risk for cardiovascular mortality (S. Cohen, 1988; Kawachi, Colditz, et al., 1996).

Socioeconomic status has consistently been found to be one of the most important determinants of health and lower socioeconomic status has been reported to be associated with an increase in CVD risk factors, such as smoking and diabetes (Kanjilal et al., 2006; Kaplan & Keil, 1993; G. D. Smith & Egger, 1993). In addition, a prospective analysis reported that higher socioeconomic status, as indicated by income and education, was associated with a decrease in incident CVD (Albert, Glynn, Buring, & Ridker, 2006). Although literature describing differences in socioeconomic variables in individuals with PTSD is limited, there is more extensive research on related topics such as employment and homelessness. A study of veterans with PTSD found that those with more severe symptoms were more likely to work part-time or not at all (M. W. Smith, Schnurr, & Rosenheck, 2005). Another study of PTSD in a community sample found individuals with PTSD to have greater

job instability (Davidson et al., 1991). PTSD was found to increase the risk of homelessness among women veterans (Washington et al., 2010). In addition, a study of the impact of the collaborative Housing and Urban Development-Veterans Affairs Supported Housing initiative reported that veterans with PTSD had an 85% increased risk of returning to homelessness after obtaining housing (O'connell, Kasprow, & Rosenheck, 2008).

PTSD And Health-Related Quality Of Life

The concept of quality of life was first used in medical practice to evaluate if available cancer treatments could, in addition to increasing survival time, improve a patient's sense of well-being (W. O. Spitzer et al., 1981). Although there is not single universal definition of quality of life, there is general agreement regarding what an operationalized definition should entail (T. M. Gill & Feinstein, 1994). Experts generally agree that the concept should (a) emphasize the individual's subjective perception of the quality of his or her own life, (b) be multidimensional, and (c) focus on characteristics of personal experience that are related to health and health care (Gerin, Dazord, Boissel, & Chifflet, 1992; Larson, 1978; Palmore & Luikart, 1972; Ware, 1987). Patrick and Erickson (1988) proposed the following definition of health-related quality of life (HRQOL): "the value assigned to the duration of life as modified by the social opportunities, perceptions, functional states, and impairments that are influenced by disease, injuries, treatments, or policies."

Psychiatric disorders have a significant impact on HRQOL. In fact, such disorders have been found to account for substantially more impairment in HRQOL than common medical disorders such as diabetes, arthritis, and cardiac disease (R. L. Spitzer et al., 1995). Available evidence demonstrates that PTSD can substantially impair an individual's

functioning and overall well-being (Zatzick, Marmar, et al., 1997). Data from the National Vietnam Veterans Readjustment Study (NVVRS) found that PTSD was associated with worse perceived health status for both men and women (Kulka et al., 1990). After controlling for psychiatric and other medical comorbidities, PTSD was associated with diminished well-being, physical limitations, and increased reports of fair or poor health in male veterans; among women veterans, a diagnosis of PTSD was associated with increased reports of fair or poor physical health and staying in bed for all or part of the day for a physical health problem one or more times within the past three months (Zatzick, Marmar, et al., 1997; Zatzick, Weiss, et al., 1997). Data from a more recent study of male and female OEF/OIF veterans indicated that PTSD was significantly associated with greater functional impairment and lower mental HRQOL in both genders, while PTSD was associated with lower physical HRQOL in women only (Fang et al., 2015). The severity of PTSD symptoms has been found to predict worse HRQOL, even after controlling for depression and anxiety symptoms, as well as the number of comorbid psychiatric disorders (Araujo et al., 2014; Pagotto et al., 2015).

Summary

Women have long served in the military and are a rapidly expanding demographic within the veteran community (National Center for Veterans Analysis and Statistics, 2017). Women veterans endorse higher rates of trauma exposure than civilian women and experience rates of PTSD on par with male veterans (Street et al., 2013; Zinzow et al., 2007). One in three US women will develop CVD, which accounted for 414,191 deaths in women in the US in 2015 (Benjamin et al., 2017; Benjamin et al., 2018). PTSD is associated with a

wide range of negative physical health outcomes and there is a strong evidence for the association between PTSD and the development of CVD (Boscarino, 2004, 2008; Beth E. Cohen et al., 2015). The majority of studies examining the link between PTSD and CVD have utilized male samples, however the findings of the two prospective studies in the literature utilizing female samples support the association between PTSD and the development of CVD, as well (Kubzansky et al., 2009; Sumner et al., 2015). The mechanisms underlying the development of CVD in individuals with PTSD are not well understood, but evidence points to the involvement of biological risk factors, including overactivation of the sympathetic nervous system, behavioral risk factors, and psychosocial risk factors (Edmondson & Cohen, 2013). In addition to an individual's disease status, PTSD has a negative impact on an individual's subjective perception of the health-related quality of his or her own life (Fang et al., 2015; Pagotto et al., 2015).

CHAPTER THREE
Aims & Hypotheses

To better understand the impact of PTSD on laboratory-based and self-reported measures of health, the current study has three aims: 1) validate previous findings that women veterans with PTSD have greater cardiovascular risk indicators (i.e. higher resting heart rate, blood pressure, and MSNA) and report worse health-related quality of life compared to non-veteran women without PTSD; 2) investigate the relationship between PTSD symptom criteria and cardiovascular risk indicators; and 3) investigate the relationship between PTSD symptom criteria and HRQOL.

Aim One

Compare cardiovascular risk indicators (baseline heart rate, blood pressure, MSNA) and HRQOL in a sample of women veterans with PTSD to a non-veteran sample of women without PTSD (healthy controls).

Rationale for Aim One

Previous research has been suggestive of chronic overactivity of the sympathetic nervous system in PTSD based on findings of higher resting heart rate (Buckley & Kaloupek, 2001), higher resting blood pressure (Buckley & Kaloupek, 2001), decreased low frequency heart rate variability (Chang et al., 2013; H. Cohen et al., 1998), and increased urinary noradrenaline levels (Wingenfeld, Whooley, Neylan, Otte, & Cohen, 2015). A recent study directly assessing sympathetic nerve activity via microneurography in a sample of veterans with PTSD, consisting of ten males and two females, found heightened MSNA and diastolic

blood pressure responses during combat and non-combat related mental stress compared to healthy veteran controls, but not at baseline (Park et al., 2017). Previous research has consistently reported poorer HRQOL in veterans with PTSD, however the majority of these studies were carried out in predominantly male populations (Fang et al., 2015). Given the relatively young state of research in women veterans with PTSD, it is important to confirm and build on previous research findings in a sample of women veterans.

Hypothesis I

Female veterans with PTSD will exhibit higher baseline heart rate, systolic blood pressure, diastolic blood pressure and MSNA compared to a sample of healthy controls.

Hypothesis II

Female veterans with PTSD will report worse physical and mental HRQOL compared to a sample of healthy controls.

Aim Two

Examine the relationship between measures of PTSD symptoms criteria and laboratory measures of sympathetic nervous system activity in women veterans with PTSD.

Rationale for Aim Two

Previous research has found higher resting heart rate and higher resting systolic and diastolic blood pressures in individuals with PTSD, which indicates overactivation of the sympathetic nervous system in this population (Buckley & Kaloupek, 2001; Park et al., 2017). Given the relationship of overactivation of the sympathetic nervous system with the development of CVD, it is important to know if clinician- or patient-rated symptoms of

PTSD are predictive of sympathetic overactivity. A review of the literature did not reveal prior studies investigating the association between PTSD symptom groups and measures of physiological arousal. It is probable that, compared to the other PTSD symptom groups, hyperarousal will be the most predictive of higher physiological activity at baseline.

Hypothesis III

In women veterans with PTSD, symptoms of hyperarousal will be a significant predictor of higher baseline heart rate, systolic and diastolic blood pressure, and muscle sympathetic nerve activity.

Aim 3

Examine the relationship between measures of PTSD symptom criteria and health-related quality of life in women veterans with PTSD.

Rationale for Aim 3

Compared to women veterans not endorsing significant symptoms of PTSD, women veterans who screened positive for PTSD reported significantly worse HRQOL, as evidenced by significantly lower mean scores on all eight subscales and both composite scales (PCS and MCS) of the SF-36 (Dobie et al., 2004). Two studies examining self-reported physical symptoms and health perception in women with PTSD, both veterans (Kimerling, Clum, & Wolfe, 2000) and civilians (Clum, Nishith, & Resick, 2001), found that, of the different PTSD symptoms groups (using DSM-III-R and DSM-IV symptom criteria groups [re-experiencing, numbing/avoidance, and hyperarousal]), only hyperarousal symptoms were significantly associated with both greater levels of physical symptoms and worse health

perception. There is a lack of research examining the relationship between the DSM-5's four PTSD symptom criteria groups and health-related quality of life.

Hypothesis IV

In women veterans with PTSD, symptoms of hyperarousal will be a significant predictor of worse physical and mental health-related quality of life.

CHAPTER FOUR
Methodology

Study Design

The current study will utilize baseline data from a larger, controlled study investigating the role of the sympathetic nervous system and cardiac-vascular function in women veterans diagnosed with PTSD. The parent study also examined whether lifestyle modifications would be effective in reducing sympathetic activity, improving cardiovascular function, and improving psychiatric symptoms and quality of life outcomes in women veterans with PTSD. This parent study was a collaborative study between VA North Texas Healthcare System (VANTHCS) and the Institute for Exercise and Environmental Medicine (IEEM). Recruitment and psychological assessment of women veterans with PTSD was completed at VANTHCS and recruitment and psychological assessment of healthy controls, as well as physiological testing of both the PTSD group and healthy controls, was completed at the IEEM. The VANTHCS is the second largest VA health care system in the country and a major research center. The IEEM is a joint program between Texas Health Presbyterian Hospital Dallas and the University of Texas Southwestern Medical Center (UTSWMC) that houses several laboratories devoted to using an integrative approach to the study of human physiology and medicine. All procedures were conducted in compliance with the Institutional Review Board (IRB) of the VANTHCS, the UTSWMC, and Texas Health Presbyterian Hospital Dallas.

Participants

Participants with PTSD were recruited from the VANTHCS and healthy controls were recruited from the Dallas-Fort Worth area. Participants for the PTSD study group were identified through clinician referrals, by recruiting in veteran therapy groups, IRB-approved advertising, and by reviewing and calling potential participants from an IRB-approved research database of veterans interested in participating in PTSD research. All participants were individually screened for eligibility and given a detailed description of the study before providing informed consent.

Inclusion/Exclusion Criteria:

To be included in the study, participants were required to meet the following criteria:

a. Be either a female veteran with a current diagnosis of PTSD (for the PTSD group) or be a female non-veteran without a current diagnosis of PTSD (for the healthy control group).

Both groups, women veterans with PTSD and health controls without PTSD had to meet the following criteria:

b. Be between the ages of 18-65.
c. Sedentary (exercises less than three times a week for thirty minutes or less).

Participants were excluded from participation in the study for any of the following:

a. Any evidence of cardiopulmonary and neurological diseases by history or by physical examination.
b. Chronic kidney disease (serum creatine > 1.5 mg/dL).
c. Peripheral vascular disease.
d. Peripheral neuropathy.

e. Current substance use disorder other than tobacco related.
f. Endurance-trained athletes due to the effects of exercise training on sympathetic neural control and cardiac-vascular function.
g. Current pregnancy.

Measures

Baseline assessment included measures of PTSD symptomatology, depression, suicidality, quality of life, trauma history, psychiatric comorbidity, sympathetic neural control, and cardiac-vascular function. Basic demographic information and medical history was also collected during the baseline sessions. Please see Table 1 for a full list of baseline assessment measures for the parent study. Assessments utilized in the present study include the Clinician Administered PTSD Scale (CAPS; Blake et al., 1990), used to confirm PTSD diagnosis and assess symptom profile, including symptom severity; the PTSD Checklist-5 (PCL-5; Weathers et al., 2013), used to assess self-reported symptoms of PTSD; and the Short Form Health Survey (SF-36; Ware Jr. & Sherbourne, 1992), used to assess health related quality of life. Physiological measurements utilized in the present study include: MSNA, heart rate, and blood pressure, all used to assess the function of the sympathetic nervous system.

Clinician Administered PTSD Scale-5 (CAPS)

The CAPS-5 (DSM-5 version) was administered to confirm diagnosis of PTSD or, for participants in the healthy control group, to confirm the absence of a PTSD diagnosis. The CAPS was also used to assess severity of PTSD symptoms. The CAPS is highly validated diagnostic interview for PTSD that is used extensively in both clinical and research settings.

Originally developed in 1989 at the National Center for PTSD, the CAPS was recently revised to reflect changes to the PTSD criteria in the DSM-5 (American Psychiatric Association, 2013; D. D. Blake et al., 1990; Weathers et al., 2018). The CAPS-5 is a 30-item semi-structured clinical interview that measures the severity of 20 PTSD symptoms using a behaviorally anchored 5-point rating scale. Severity ratings range from zero ("absent") to four ("extreme/incapacitating"). The CAPS-5 total severity score has shown high internal consistency ($\alpha = .88$) and good test-retest reliability (intraclass correlation = .78). Diagnosis with the CAPS-5 showed strong interrater reliability ($\kappa = .78$ to 1.00, depending on the scoring rule; Weathers et al., 2018) and test-retest reliability ($\kappa = .83$; Weather et al. 2018).

PTSD Checklist for DSM-5 (PCL-5)

The PCL-5 was administered to participants in the PTSD group to assess self-reported PTSD symptom severity. The PCL is a widely used self-report measure of PTSD that was recently revised to mirror DSM-5 changes to the PTSD criteria (Blevins, Weathers, Davis, Witte, & Domino, 2015). The PCL consists of 20 items that correspond to the PTSD symptom criteria in the DSM-5 (American Psychiatric Association, 2013). Respondents indicate the extent to which they have been bothered by each PTSD symptom during the past month using a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). Item scores are summed to generate a continuous measure of PTSD symptom severity. The PCL-5 scores demonstrated internal consistency ($\alpha = .94$ to .95) and test-retest reliability ($r = .82$; Blevins et al., 2015). The PCL-5 scores exhibited good convergent (rs = .74 to .85) and discriminant (rs = .31 to .60) validity, as well (Blevins et al., 2015).

36-Item Short Form Health Survey (SF-36)

The SF-36 was administered to all participants to assess health-related quality of life. The SF-36 is a multipurpose health survey of physical health functioning across different areas of physical, mental, and social health (John E. Ware Jr & Sherbourne, 1992). The SF-36 measures eight health domains: physical functioning, social functioning, physical roles, emotional roles, general health, mental health, general health, bodily pain, and vitality. In addition, two aggregate summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS), are also produced. The response scales vary across and within the scales, with the number of responses ranging from two to six. The raw scores for each scale items are added and then transformed to a 0-100 scale, with higher scores indicating better health (John E Ware Jr, Kosinski, & Gandek, 2005). Scoring algorithms are used to calculate the PCS and MCS summary scores, as well as generate norm-based T scores for each scale. The domains of the SF-36 have good internal consistency as measured by Cronbach's α: physical functioning (.88 to .93), social functioning (.60 to .80), physical roles (.76 to .90), emotional roles (.80 to .96), general health (.80 to .95), mental health (.67 to .90), bodily pain (.79 to .86), and vitality (.62 to .96; McHorney, Ware & Raczek, 1993).

Physiological Measures

Physiological assessments were measured in both the PTSD veteran and healthy control groups in the same manner. Please see the Procedures section and Table 1 for a description of the physiological sessions and procedures. Only baseline MSNA, heart rate, and blood pressure will be used for the current study.

Muscle Sympathetic Nerve Activity (MSNA)

Microneurography is an electrophysiological method used to directly record the post-ganglionic efferent sympathetic action potentials in the peripheral nerves via intraneural microelectrodes. (Macefield, 2013; Mano, Iwase, & Toma, 2006). Microneurography was initially developed at the department of clinical neurophysiology at the Academic Hospital in Uppsala, Sweden between 1965 and 1966 (Ake B Vallbo, Hagbarth, & Wallin, 2004). A recording tungsten microelectrode is inserted through the skin and into a peripheral nerve (e.g., peroneal, tibial, radial, or median nerve) and a reference microelectrode is placed a short distance from the recording electrode. Nerve signals are recorded as voltage differences between the intraneural and reference electrodes (Mano, 1998). The multiunit nerve signals are processed by a bio-amplifier and band-pass filtered between 700-2,000 Hz before being rectified and integrated (using a leaky integrator; 0.1 second time constant) to obtain a mean voltage neurogram (Ake B Vallbo et al., 2004). In the current study, the raw, filtered and integrated MSNA signals were collected and stored for offline analysis (*AcqKnowledge*; Biopac System, Santa Barbara, CA).

Heart Rate (HR)

Heart rate refers to the speed of the heartbeat determined by the number contractions of the heart per minute. Heart rate is controlled by sympathetic and parasympathetic input to the sinoatrial node. The American Heart Association defines normal resting heart rate for adults as 60 to 100 beats per minute (American Heart Association, 2018a). For the present study, heart rate was determined via lead II of the electrocardiogram (ECG; Hewlett Packard Model 78352C, Whittemore Enterprises, Inc., Rancho Cucamonga, CA).

Blood Pressure (BP)

Blood pressure, the pressure of circulating blood on the walls of blood vessels, is typically expressed as the systolic pressure (pressure blood exerts against artery walls when the heart beats) over diastolic pressure (pressure blood exerts against artery walls while the heart rests between beats). In adults, normal resting blood pressure is less than 120 millimeters of mercury systolic and less than 80 millimeters of mercury diastolic (120/80 mmHg; American Heart Association, 2018b.). Arm-cuff blood pressure was measured by electrosphygmomanometry (model 4240; SunTech Medical Instruments Inc., Raleigh, NC, USA) with a microphone placed over the brachial artery to detect Korotkoff sounds.

Procedures

All participants were seen on an outpatient basis. See Table 2 for a summary of the parent study procedures.

Psychological Screening/Baseline Visit for PTSD group

After successful completion of preliminary screening and VANTHCS informed consent, participants were enrolled in the VANTHCS portion of the study and administered baseline assessments. Participants were administered the Life Events Checklist (LEC) and Clinician Administered PTSD Scale for DSM-5 (CAPS-5) structured interview to verify the diagnosis of PTSD and determine symptom severity. The Mini International Neuropsychiatric Interview (MINI) for DSM-5 was administered to assess for comorbid psychiatric disorders. Four self-report surveys were then completed by participants: PTSD Checklist for DSM-5 (PCL-5), Quick Inventory of Depressive Symptomatology (QIDS-16), Concise Health Risk Tracking Scale (CHRT-self report module only), and the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF). These self-report

measures assessed symptoms of PTSD, depression, suicidality, and quality of life. Participants also completed a demographics questionnaire. If a participant's diagnosis of PTSD was verified by the CAPS-5, a VA research coordinator provided the participants name and phone number to an IEEM research coordinator to set up an initial appointment at the IEEM.

IEEM Screening Visit for PTSD and healthy control groups

After successful completion of preliminary screening and UTSW informed consent, participants were enrolled in the IEEM portion of the study. Participants were screened with a careful medical history and review of medications, sitting blood pressure, 12-lead ECG, and 24-hour ambulatory blood pressure monitoring. Participants in the health control group were completed the LEC and CAPS-5 to confirm that they did not have a diagnosis of PTSD, as well as the MINI to screen for psychiatric disorders.

IEEM Visit One for PTSD and healthy control groups

Experimental procedures took place in the morning at least two hours after a light breakfast and at least eight hours after the last caffeinated or alcoholic beverage, in a quiet laboratory. A urine pregnancy test was performed for participants of childbearing potential to confirm that a participant was not pregnant. Quality of life and health status was assessed by using the SF-36 and the Q-LES-Q-SF.

Participants were positioned in a supine position and an intravenous catheter was inserted into an antecubital vein on the non-dominant arm for blood draws. Resting cardiac output was assessed using the modified acetylene rebreathing method (Triebwasser et al., 1977), baseline blood sample was collected for measurements of plasma catecholamine

concentration, cortisol, plasma renin activity and aldosterone, and left ventricular function was evaluated by echocardiography (Philips Medical Systems, Andover, MA, USA). Participants performed three maximal contractions for approximately three seconds with the dominant hand to determine her maximal voluntary contraction (MVC) force by using a handgrip dynamometer prior to microneurography. The highest value of these three contractions was used during testing.

A recording microelectrode was then inserted through the skin and into the peroneal nerve located on the upper outward side of the calf. A reference microelectrode was placed a short distance away from the recording electrode. Small adjustments in the electrode position were made to get a satisfactory recording of the nerve signals. Criteria for adequate MSNA recording included the following: (1) pulse synchrony; (2) facilitation during the hypotensive phase of the Valsalva maneuver, and suppression during the hypertensive overshoot after release; (3) increases in response to breath holding; and (4) insensitivity to a gentle skin touch or a loud shout (A B Vallbo, Hagbarth, Torebjork, & Wallin, 1979). At least 10 minutes after an acceptable recording of the nerve signal was achieved, baseline data (including heart rate, blood pressure, MSNA, respiratory waveform, and cerebral blood flow) was collected during spontaneous breathing and controlled breathing (0.2 Hz, 12 breaths per minute) for six minutes each. A Stroop color-word test was administered to assess cognitive function. A Valsalva maneuver at 40 mmHg expired pressure was performed to assess sympathetic and cardiovagal baroreflex sensitivities and the straining period lasted for 20 seconds. A cold pressor test was then performed to assess the integrity of central vasomotor processes and their efferent pathways. Baseline measurements were made for one minute,

and then the participant's dominant hand was placed into an ice water bath (50% ice and 50% water, about 4°C) for two minutes, followed by three minutes of recovery. After a recovery period, static handgrip was performed using the dominant hand at 40% of MVC until fatigue, followed by 2 minutes of post-exercise circulatory arrest with an upper arm cuff inflated to 250 mmHg. This test was used to assess the exercise pressor reflex. The participant was presented with a bar graph display that was proportionate to the achieved force, with a color-coded target of 40% of MVC. When the achieved force declined to less than 80% of this target for at least two seconds, the cuff was inflated manually. After a sufficient recovery period (e.g., ≥15 minutes), a graded upright tilt was performed to assess sympathetic neural and hemodynamic responses during orthostatic stress. Participants were tilted to 30° and 60° for five minutes each. Cardiac output was measured at the end of 30° and 60° upright tilt. Blood samples were taken during the 5th minute of 60° tilt. The Stroop color-word test was repeated at the end of tilting. After that, participants were returned to the supine position for recovery. After a recovery period, the microneurographic electrodes were removed.

IEEM Visit Two for PTSD and healthy control groups

Vascular function was assessed at the beginning of the visit. Arterial tonometry with simultaneous ECG was obtained from the radial, femoral, and carotid arteries using a pencil-sized probe over the maximal pulsation of the artery. Endothelium-dependent flow-mediated dilation of the brachial artery was assessed using a high-resolution Doppler ultrasound machine. A blood pressure cuff was placed on the subject's left forearm. The brachial artery was scanned longitudinally for 1 minute, and the end-diastolic diameter and blood velocity was measured. The blood pressure cuff was then inflated to a pressure of 250 mmHg for 5

min and then deflated rapidly. Images were recorded for 90 seconds before cuff deflation and continuously for two minutes after cuff deflation.

For participants in the PTSD group only, submaximal and maximal treadmill exercise tests were performed to assess peak oxygen uptake (VO_{2peak}) and peak exercise capacity. Quiet standing cardiac output, heart rate, blood pressure and VO_2 were first collected. Next, two submaximal steady-state workloads were determined based on individual fitness level so that about 30% and 60% of VO_{2peak} could be achieved at each level. Each workload lasted five minutes, and steady-state variables were collected during the last minute. After a short break, a maximal exercise test was performed by using a modified Astrand-Saltin incremental treadmill protocol (Balke, Nagle, & Daniels, 1965). Patients walked or jogged at a constant speed, which was determined based on individual fitness level and submaximal steady-state data, to achieve a peak work rate at 10-12 minutes. The grade was subsequently increased by 2% until exhaustion. Douglas bags were collected in the second minute of each stage with consecutive 45 seconds collections when the participant was nearing maximal effort. Cardiac output, blood pressure, and heart rate were measured during the final 20 seconds of maximal exercise.

Group Assignment and Intervention for PTSD group only

Participants in the PTSD group were assigned to one of two 12-week intervention groups: Lifestyle Modifications (exercise training and healthy eating) or contact control. The group assignments, exercise training, and dietary advice provided by the staff of the IEEM. Participants assigned to both the Lifestyle modifications and Contact Control Group completed brief phone assessments conducted by VANTHCS research coordinators every

two weeks during the 12-week intervention period. Phone assessments consisted of the PCL-5, QIDS-16, CHRT, and Q-LES-Q-SF.

Lifestyle Modification Group:

Exercise Training: A "personalized" training program was developed for each participant in the PTSD group assigned to the Lifestyle Modifications group. Using the maximal steady state heart rate and resting heart rate, three training zones (recovery, base pace, and maximal steady state) were determined. The target heart rate for each training zone was set for each patient. The majority of training sessions during the early phase of the program were "base pace" with target heart rate equivalent to about 75% of maximal. Initially, patients exercised three times per week for 20-30 minutes per session by walking, jogging or cycling. As the participants became more fit, the duration of the base training sessions increased in duration and intensity. Heart rate was monitored during every session using a Polar monitor. Files from the heart rate monitor were downloaded and the training progress was evaluated weekly by an IEEM research coordinator.

Healthy Eating: Participants in the PTSD group assigned to the Lifestyle Modifications group were provided with dietary advice consistent with the American Heart Association guidelines. The D.A.S.H. diet eating plan recommends eating vegetables, fruits and whole grains; including fat-free or low-fat dairy products, fish, poultry, beans, nuts, and vegetable oils; limiting foods that are high in saturated fat, such as fatty meats, full-fat dairy products, and tropical oils such as coconut, palm kernel, and palm oils; and limiting sugar-sweetened beverages and sweets. Patients met with an IEEM research staff and received a personalized diet booklet outlining daily meals using many of the participant's own

preselected favorite foods and recipes. The diets were planned for balanced nutrition with the goal of controlling body weight. Patients were also provided online resources such as "D.A.S.H. for Health" and "My Plate", which offer education and behavioral tools for healthy eating. A dietary risk assessment was performed prior to and following the intervention.

Contact Control

Participants in the PTSD group assigned to the contact control group continued with their usual visits and general advice from their health care providers. Participants were not discouraged from exercising and/or healthy eating on their own, but were not provided the exercise and healthy eating program and counseling given to the Lifestyle Modifications group. Participants in the Control group wore a physical activity monitor for seven days prior to and following the intervention. A dietary risk assessment was also performed prior to and following the intervention.

Post-Intervention Assessments for PTSD group

After 12 weeks of lifestyle modifications or contact control, IEEM researchers re-assessed sympathetic neural control and cardiac-vascular function in all participants in the PTSD group using the procedures described for IEEM Visit One and Two. Participants in the PTDS group return to the VANTHCS and were readministered the CAPS-5, PCL-5, QIDS-16, CHRT, and Q-LES-Q-SF.

CHAPTER FIVE
Results

Sample Characteristics

The study sample consisted of 17 women veterans with a diagnosis of PTSD and 9 civilian women without PTSD. One participant in the PTSD group had missing data for the SF-36. Table 3 lists sample characteristics for the PTSD and control groups. The mean age for participants in the PTSD group was 42.59 (SD=11.17) with a mean 14.94 years of education (SD=1.68). For participants in the control group, the mean age was 40.56 (SD=9.06) with a mean 15.33 years of education (SD=2.24). In the PTSD group, 47.1% (n=8) of the participants were Black, 35.3% (n=6) were White, 11.8% (n=2) were Hispanic, and 5.9% (n=1) were Asian. In the control group, 66.7% (n=6) of the participants were White, 22.2% (n=2) were Black, and 11.1% (n=1) were Asian. In the PTSD group, the mean BMI was 29.03 (SD=6.13) and 11.8% (n=2) currently used tobacco products. In the control group, the mean BMI was 27.41 (SD=5.01) and 11.1% (n=1) currently used tobacco products. In regards to symptoms of criteria, 58.8% (n=10) of the PTSD group currently met criteria for major depressive disorder while no one in the control group currently met criteria. There were no significant differences between the PTSD and control groups with regard to age, ethnicity, educational level, BMI, and smoking status ($p > .05$ for all these comparisons). A significant difference was found between the two groups for current major depressive disorder ($p = .004$), which not unexpected as the civilian control group was a healthy sample that was screened for mental illness.

In the PTSD group, 64.7% (n=11) of the participants served in the Army, 17.6% (n=3) served in the Navy, 11.8% (n=2) were Marines, and 5.9% (n=1) served in the Air Force. Regarding service era, 64.7% (n=11) were veterans of the OEF/OIF/OND era, 17.6% (n=3) were veterans of Desert Storm/Bosnia/Somalia, 11.8% (n=2) were veterans of multiple service eras, and 5.9% (n=1) were veterans of the post-Vietnam/pre-Desert Storm era. In the PTSD group, 52.9% (n=9) of participants' index trauma for their PTSD diagnosis was MST, 29.4% (n=5) had an index trauma that was combat-related, and 17.6% (n=3) had an index trauma of intimate partner violence.

Aim One

Compare cardiovascular risk indicators (baseline heart rate, blood pressure, MSNA) and health-related quality of life in a sample of women veterans with PTSD to a nonveteran sample of women without PTSD.

Hypothesis I

Female veterans with PTSD will exhibit higher baseline heart rate, systolic blood pressure, diastolic blood pressure and MSNA compared to a sample of healthy controls.

A one-way between groups multivariate analysis of variance was performed to assess differences in cardiovascular indicators. Four dependent variables were used: baseline heart rate, systolic blood pressure, diastolic blood pressure, and MSNA. The independent variable was study group (PTSD group versus healthy control). Preliminary assumption testing was conducted to check for normality linearity, univariate and multivariate outliers, homogeneity of variance-covariance matrices, and multicollinearity, with no serious violations noted. There was no statistically significant difference between the PTSD and healthy control

groups on the combined dependent variables, F (4, 21) = 0.97, p = .45; Wilks' Lambda = 0.84; η_p^2 = 0.16 (see Table 4).

Hypothesis II

Female veterans with PTSD will report worse physical and mental health-related quality of life compared to a sample of healthy controls.

A one-way between groups multivariate analysis of variance was performed to assess the differences in health-related quality of life. Two dependent variables were used: MCS and PCS from the SF-36. The independent variable was study group (PTSD group versus healthy control). Preliminary assumption testing was conducted to check for normality linearity, univariate and multivariate outliers, homogeneity of variance-covariance matrices, and multicollinearity, with no serious violations noted. There was a statistically significant difference between the PTSD and healthy control study groups on the combined dependent variables, F (2, 22) = 11.40, p < .001; Wilks' Lambda = 0.49; η_p^2= 0.51 (see Table 4). Results of two one-way ANOVAS showed that both PCS, F (1, 23) = 7.08, p = .014, η_p^2 = 0.24, and MCS, F (1, 23) = 16.88, p < .001, η_p^2 = .42, reached statistical significance, using a Bonferroni adjusted alpha level of 0.025 to control for multiple analyses. An inspection of the mean scores indicated that women veterans in the PTSD group had lower SF-36 PCS scores (M = 45.74, SD = 10.16) than women in the healthy control group (M = 55.32, SD = 4.60). Women veterans in the PTSD group also had lower SF-36 MCS scores (M = 35.48, SD = 12.23) compared to women in the healthy control group (M = 53.37, SD = 5.75).

Aim Two

Examine the relationship between measures of PTSD symptom criteria groups and laboratory measures of sympathetic nervous system activity in women veterans with PTSD.

Hypothesis III

In women veterans with PTSD, symptoms of hyperarousal will be a significant predictor of higher baseline heart rate, systolic and diastolic blood pressure, and muscle sympathetic nerve activity.

Eight hierarchical multiple regressions were used to assess the ability of PTSD hyperarousal symptom severity to predict baseline heart rate, systolic blood pressure, diastolic blood pressure, and MSNA, after controlling for the influence of non-hyperarousal PTSD symptom severity (calculated as total symptom severity minus hyperarousal symptom severity). One set of analyses was run using clinician-rated symptoms of PTSD (CAPS-5 scores) and another set of analyses was run using self-rated symptoms of PTSD (PCL-5 scores). To protect against Type I error due to multiple comparisons, a Bonferroni adjusted *p*-value of 0.0125 was used. Analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity, homoscedasticity, and independence of errors, as appropriate.

Analysis of Clinician-Rated PTSD Symptoms and Baseline Heart Rate

Clinician-rated non-hyperarousal PTSD symptom severity was entered at Step 1, F (1,15) = .44, p = .52, R^2 adjusted = -.04. Clinician-rated PTSD hyperarousal symptom severity were entered at Step 2, F (2, 14) = 0.32, p = .73, R^2 adjusted = -.09. In the final model, neither clinician-rated hyperarousal symptom severity (*beta* = -.14, p = .64) nor non-

hyperarousal PTSD symptoms severity (*beta* = -.12, *p* = .69) was statistically significant. The results of the regression analysis are detailed in Table 5.

Analysis of Clinician-Rated PTSD Symptoms and Baseline Systolic Blood Pressure

Clinician-rated non-hyperarousal PTSD symptom severity was entered at Step 1, *F* (1,15) = 3.7, *p* = .08, R^2 adjusted = .14. Clinician-rated PTSD hyperarousal symptom severity at Step 2, *F* (2, 14) = 1.86, *p* = .19, R^2 adjusted = .10. In the final model, neither clinician-rated hyperarousal symptom severity (*beta* = -.12, *p* = .64) nor non-hyperarousal PTSD symptoms severity (*beta* = -.40, *p* = .15) was statistically significant. The results of the regression analysis are detailed in Table 5.

Analysis of Clinician-Rated PTSD Symptoms and Baseline Diastolic Blood Pressure

Clinician-rated non-hyperarousal PTSD symptom severity was entered at Step 1, *F* (1,15) = 1.00, *p* = .33, R^2 adjusted = .000. Clinician-rated PTSD hyperarousal symptom severity was entered at Step 2, *F* (2, 14) = 1.91, *p* = .19, R^2 adjusted = .10. In the final model, neither clinician-rated hyperarousal symptom severity (*beta* = -.43, *p* = .12) nor non-hyperarousal PTSD symptoms severity (*beta* = -.08, *p* = .76) was statistically significant. The results of the regression analysis are detailed in Table 5.

Analysis of Clinician-Rated PTSD Symptoms and Baseline MSNA

Clinician-rated non-hyperarousal PTSD symptom severity was entered at Step 1, *F* (1,15) = .02, *p* = .90, R^2 adjusted = -.07. Clinician-rated PTSD hyperarousal symptom severity at Step 2, t*F* (2, 14) = .21, *p* = .81, R^2 adjusted = -.11. In the final model, neither clinician-rated hyperarousal symptom severity (*beta* = .18, *p* = .53) nor non-hyperarousal

PTSD symptoms severity (*beta* = -.04, *p* = .90) was statistically significant. The results of the regression analysis are detailed in Table 5.

Analysis of Self-Rated PTSD Symptoms and Baseline Heart Rate

Self-rated non-hyperarousal PTSD symptom severity was entered at Step 1, *F* (1,15) = 1.04, *p* = .32, R^2 adjusted = .003. Self-rated PTSD hyperarousal symptom severity at Step 2, *F* (2, 14) = 0.71, *p* = .51, R^2 adjusted = -.04. In the final model, neither self-rated hyperarousal symptom severity (*beta* = .21, *p* = .53) nor non-hyperarousal PTSD symptoms severity (*beta* = -.38, *p* = .26) was statistically significant. The results of the regression analysis are detailed in Table 6.

Analysis of Self-Rated PTSD Symptoms and Baseline Systolic Blood Pressure

Self-rated non-hyperarousal PTSD symptom severity was entered at Step 1, *F* (1,15) = .68, *p* = .42, R^2 adjusted = -.02. Self-rated PTSD hyperarousal symptom severity was entered at Step 2, *F* (2, 14) = 0.43, *p* = .66, R^2 adjusted = -.08. In the final model, neither self-rated hyperarousal symptom severity (*beta* = -.15, *p* = .65) nor non-hyperarousal PTSD symptoms severity (*beta* = -.11, *p* = .74) was statistically significant. The results of the regression analysis are detailed in Table 6.

Analysis of Self-Rated PTSD Symptoms and Baseline Diastolic Blood Pressure

Self-rated non-hyperarousal PTSD symptom severity was entered at Step 1, *F* (1,15) = .1.18, *p* = .29, R^2 adjusted = .01. Self-rated PTSD hyperarousal symptom severity were entered at Step 2, *F* (2, 14) = 1.49, *p* = .26, R^2 adjusted = .06. In the final model, neither self-rated hyperarousal symptom severity (*beta* = -.41, *p* = .21) nor non-hyperarousal PTSD

symptoms severity (*beta* = -.01, *p* = .97) was statistically significant. The results of the regression analysis are detailed in Table 6.

Analysis of Self-Rated PTSD Symptoms and Baseline MSNA

Self-rated non-hyperarousal PTSD symptom severity was entered at Step 1, *F* (1,15) = .000, *p* = .99, R^2 adjusted = -.07. Self-rated PTSD hyperarousal symptom severity were entered at Step 2, *F* (2, 14) = .04, *p* = .96. In the final model, neither self-rated hyperarousal symptom severity (*beta* = .10, *p* = .29) nor non-hyperarousal PTSD symptoms severity (*beta* = -.06, *p* = .86) was statistically significant. The results of the regression analysis are detailed in Table 6.

Aim Three

Examine the relationship between measures of PTSD symptom criteria and health-related quality of life in women veterans with PTSD.

Hypothesis IV

In women veterans with PTSD, symptoms of hyperarousal will be a significant predictor of worse physical and mental health-related quality of life.

Four hierarchical multiple regressions were used to assess the ability of PTSD hyperarousal symptom severity to predict SF-36 PCS and MCS scores, after controlling for the influence of non-hyperarousal PTSD symptom severity (calculated as total symptom severity minus hyperarousal symptom severity). One set of analyses was run using clinician-rated symptoms of PTSD (CAPS-5 scores) and another set of analyses was run using self-rated symptoms of PTSD (PCL-5 scores). To protect against Type I error due to multiple comparisons, a Bonferroni adjusted *p*-value of 0.025 was used. Analyses were conducted to

ensure no violation of the assumptions of normality, linearity, multicollinearity, and homoscedasticity.

Analysis of Clinician-Rated PTSD Symptoms and SF-36 PCS

Clinician-rated non-hyperarousal PTSD symptom severity was entered at Step 1, explaining 49% of the variance in SF-36 PCS, F (1,14) = 15.15, p = .002, R^2 adjusted = .49. After entry of the clinician-rated PTSD hyperarousal symptom severity at Step 2, the total variance explained by the model as a whole was 52.3%, F (2, 13) = 9.22, p = .003, R^2 adjusted = .52. Hyperarousal symptom severity explained an additional 6.7% of the variance in baseline heart rate, after controlling for non-hyperarousal PTSD symptom severity, R^2 change = .067, F change (1, 13) = 2.10, p = .17. In the final model, non-hyperarousal PTSD symptoms severity (*beta* = -.83, p = .001) was statistically significant, but clinician-rated hyperarousal symptom severity (*beta* = .28, p = .17) was not. The results of the regression analysis are detailed in Table 7.

An exploratory standard multiple regression analysis was performed with SF-36 PCS as the dependent variable and the four clinician-rated PTSD symptom criteria group severity scores as the predictor variables. Table 8 displays results for this analysis. R for the regression model was significantly different from zero, F (4,11) = 3.55, p = .04. The adjusted R^2 value .41 indicated that more than a third of the variability on SF-36 PCS scores was predicted by the four clinician-rated PTSD symptom criteria group scores. Re-experiencing symptom severity (*beta* = -.52, p = .051) was the only predictor variable to approach significance. The results of the regression analysis are detailed in Table 8.

Analysis of Clinician-Rated PTSD Symptoms and SF-36 MCS

Clinician-rated non-hyperarousal PTSD symptom severity was entered at Step 1, F (1,14) = .08, p = .79, R^2 adjusted = -.07. Clinician-rated PTSD hyperarousal symptom severity was entered at Step 2, F (2, 13) = .19, p = .83, R^2 adjusted = -.12. In the final model, neither clinician-rated hyperarousal symptom severity (*beta* = .16, p = .59) nor non-hyperarousal PTSD symptoms severity (*beta* = .001, p = .98) was statistically significant. The results of the regression analysis are detailed in Table 7.

Analysis of Self-Rated PTSD Symptoms and SF-36 PCS

Self-rated non-hyperarousal PTSD symptom severity was entered at Step 1, F (1,14) = .39, p = .55, R^2 adjusted = -.04. Self-rated PTSD hyperarousal symptom severity at Step 2, F (2, 13) = .18, p = .84, R^2 adjusted = -.12. In the final model, neither self-rated hyperarousal symptom severity (*beta* = .01, p = .98) nor non-hyperarousal PTSD symptoms severity (*beta* = -.17, p = .64) was statistically significant. The results of the regression analysis are detailed in Table 7.

Analysis of Self-Rated PTSD Symptoms and SF-36 MCS

Self-rated non-hyperarousal PTSD symptom severity was entered at Step 1, F (1,14) = .03, p = .86, R^2 adjusted = -.07. Self-rated PTSD hyperarousal symptom severity was entered at Step 2, F (2, 13) = .02, p = .99, R^2 adjusted = -.15. In the final model, neither self-rated hyperarousal symptom severity (*beta* = -.01, p = .97) nor non-hyperarousal PTSD symptoms severity (*beta* = -.04, p = .91) was statistically significant. The results of the regression analysis are detailed in Table 7.

CHAPTER FIVE
Conclusions and Recommendations

The current study had three aims: 1) validate previous findings that women veterans with PTSD have greater cardiovascular risk indicators (baseline heart rate, blood pressure, and MSNA) and worse health-related quality of life compared to non-veteran women without PTSD; 2) investigate the relationship between PTSD symptom criteria groups, and sympathetic nervous system activity indicators; and 3) investigate the relationship between PTSD symptom criteria groups and HRQOL. Results revealed no significant differences between women veterans with PTSD and healthy controls in regards to cardiovascular risk indicators, however women veterans with PTSD reported significantly worse physical and mental health related quality of life. Contrary to expectations, the hyperarousal symptom criteria group was not found to be a significant and unique predictor of sympathetic nervous system activity indicators nor health related quality of life. However, clinician-rated non-hyperarousal PTSD symptom severity was found to be a significant and unique predictor of physical health-related quality of life. Further analysis demonstrated that, of the four PTSD symptom criteria groups, only clinician-rated re-experiencing symptom severity approached being a significant predictor (p = .051) of worse physical health-related quality of life.

The finding that women veterans with PTSD did not significantly differ on baseline cardiovascular risk indicators differs from previous research examining baseline heart rate and blood pressure (Buckley & Kaloupek, 2001), but is consistent with the findings of Park et al. (2017), who did not find a difference in baseline heart rate, blood

pressure, and MSNA. In a meta-analysis of basal cardiovascular activity, Buckley et al. (2001) found that individuals with PTSD have higher resting heart rate and, to a lesser degree, blood pressure, compared to both trauma-exposed individuals without PTSD or non-trauma exposed individuals. It was reported that individuals in the PTSD group had an average resting heart rate that was approximately five beats faster than the heart rate found in the comparison groups. In contrast, Park et al. (2017) found no significant differences between resting heart rate, blood pressure, or MSNA between a sample of OEF/OIF/OND veterans with PTSD (n = 14) and OEF/OIF/OND veterans without PTSD (n = 14), although they did find that that individuals in the PTSD group had significantly greater MSNA responses during both combat-related and non-combat-related mental stress. Park and colleagues (2017) also found diastolic blood pressure to be greater during non-combat-related mental stress compared to the control group. The sample size of the current study (n = 26) was closer to that of the study by Park et al. (n = 24; 2017), while the average sample size in the meta-analysis by Buckley (2001) was 82. Characteristics of the various study samples did not provide a clear explanation for observed differences. The mean age of participants in the current study (42.59 ± 11.17) was approximately eight years older than that of the participants in the study by Park et al. (34.14 ± 1.7; 2017), but similar to the average age of 40 found across studies analyzed by Buckley et al. 2001). The individuals in the study by Park et al. (2017) and meta-analysis by Buckley (2001) were predominantly male. Although the majority individuals in the current study (both in the PTSD and control groups) had blood pressure that fell in the normal range, this was also true of the meta-analysis by Buckley et al. (2001) that did find significant

differences between PTSD and comparison groups. It is possible that the sample size in the current study did not provide adequate power to detect any differences between the groups, however it is also possible that no significant differences exist.

The finding that women veterans with PTSD report worse physical and mental health-related quality of life that nonveteran woman without PTSD is consistent with previous research that finds that women with PTSD report worse physical and mental health related quality of life compared to women without a diagnosis of PTSD. Although it is not surprising that women veterans with PTSD report worse physical and mental health-related quality of life compared to a healthy control group, the majority of research examining health-related quality of life in individuals with PTSD has been carried in predominantly male samples and it is important to confirm findings for the smaller but growing research base reporting similar findings in women. The current study also adds to previous published findings by using a study sample from more recent conflicts (Gulf War/Kosovo/Somalia and OEF/OIF/OND) and the use of DSM-5 diagnostic criteria for PTSD. Another strength of the current study is that the CAPS-5 was used to confirm a diagnosis of PTSD in participants rather than using screening cut-off scores as other studies have done.

Results from the current study did not find PTSD hyperarousal symptom group severity or non-hyperarousal PTSD symptom group severity to be a unique and significant predictor of sympathetic nervous system activity indicators, including baseline heart rate, blood pressure, and MSNA. Given the earlier finding that there was not significant baseline difference between the PTSD group and healthy controls, this finding

is not surprising. To this author's knowledge, this is the first study to examine the relationship between PTSD criteria symptom groups and such physiological measures. In light of the findings by Park et al. (2017) that demonstrated augmented MSNA and diastolic blood pressure during stressors, future research might examine the relationship between PTSD symptom criteria groups and the degree of response during stressors.

Results from the current study did not support the hypothesis that PTSD symptoms of hyperarousal would be a unique or significant predictor of physical or mental health-related quality of life. Exploratory analysis revealed that only the clinician-rated re-experiencing symptom criteria group approached significance in its ability to predict physical health-related quality of life. Although a limited number of studies have examined the relationship between PTSD symptom criteria groups and health-related quality of life and the findings have been somewhat mixed, the majority found hyperarousal to be a significant predictor of health-related quality of life. A review of the literature of re-experiencing symptoms found them to be unique predictors of worse scores on the SF-36 physical functioning and bodily pain subscales (Asnaani, Reddy, & Shea, 2014). Another study found that re-experiencing symptoms were related to a greater report of physical symptoms on the Quality of Life Self-Report Health Subsection (Zoellner et al., 2000). There is little data regarding the mechanisms by which individual PTSD symptom criteria groups impact health-related quality of life, particularly physical health-related quality of life, which makes it difficult to determine why re-experiencing symptoms might impact physical health. One possible hypothesis is that the re-experiencing symptom group is the only symptom group category that specifically refers

to physiological reactions (symptom B5: Marked physiological reaction to internal or external cues that symbolize or resemble an aspect of the traumatic event). In addition, the mean time since index trauma for individuals in the PTSD group was 16 years; it is possible that these individuals have become accustomed to chronic levels of hyperarousal, but not to the acute increase in physiological symptoms, such as heart racing, difficulty breathing, or feeling shaky, which may occur in response to a trauma reminder. It would be beneficial for future studies with larger sample sizes to examine the relationships between the PTSD symptom criteria groups and the eight subscales of the SF-36 that make up of the physical and mental component summaries to gain a better understanding of what specific components of health-related quality of life are being impacted by which symptom criteria groups.

Another factor that may be muddying the interpretation of the data is the fact that some of the prior studies examining the relationship between PTSD symptom criteria groups on health-related quality of used trauma samples in which not all participants had a diagnosis of PTSD. For example, in the study by Kimerling et al. (2000), the sample (n=50) consisted of 12 women meeting full criteria for current PTSD, five women meeting criteria for "partial PTSD" (i.e., met criteria for the majority, but not all of the symptom criteria), and 40 women who did not meet full PTSD criteria. Posttraumatic stress disorder and "PTSD symptoms" are distinct entities and one must be careful not to confuse normal reactions to trauma with psychopathology (C. S. North, Suris, Davis, & Smith, 2009). Hyperarousal and re-experiencing symptoms are relatively common in individuals who have experienced trauma. For example, in a study of 130 survivors of the

Northridge, California, earthquake, 13% of the sample met full PTSD criteria when assessed three months following the trauma, however 48% of participants met both the hyperarousal and re-experiencing symptom criteria (McMillen, North, & Smith, 2000). Perhaps studies utilizing samples that include both traumatized individuals with posttraumatic stress symptoms, but no PTSD diagnosis, and individuals with a diagnosis of PTSD, is inflating the importance of certain PTSD symptom criteria groups, such as hyperarousal.

Limitations

Limitations of this study include the small sample size. It is possible that significant between group differences in cardiovascular risk indicators would have been found if a larger sample size had been studied. In addition, the small sample size limited the ability to control for factors such as age, depression, childhood trauma, and overall trauma load, which may impact both cardiovascular risk indicators and health-related quality of life. Another important limitation of the study was that medications, including antidepressants, anxiolytics, and antihypertensives, were not held prior to physiological testing. There is evidence for antidepressants, anxiolytics medication inhibiting physiological measures such as MSNA, blood pressure, and hear rate. (Blankestijn, 2004; Kitajima et al., 2004; Scalco et al., 2009). Further, the PTSD group sample was limited to women veterans who utilize the Veteran's Administration for treatment and may not be representative of women veterans in general.

Conclusion/Future Research

In summary, the results of this study indicate that women veterans with PTSD report worse physical and mental health-related quality of life compared to nonveteran women without PTSD, but there is not a significant difference in baseline cardiovascular risk indicators such as heart rate, blood pressure, and MSNA. The hyperarousal symptom criteria group was not found to be a significant and unique predictor of cardiovascular risk indicators nor health related quality of life, however clinician-rated non-hyperarousal PTSD symptom severity was found to be a significant and unique predictor of physical health-related quality of life. Further analysis showed that, of the four PTSD symptom criteria groups, only clinician-rated re-experiencing symptom severity approached being a significant predictor ($p = .051$) of worse physical health-related quality of life. Since re-experiencing symptoms appear to be an important mechanism by which women veterans make judgments about their physical health, clinically targeting such symptoms in PTSD interventions may result in improved health-related quality of life.

It is important to continue building the research base for women veterans with PTSD, due to their growth in population and unique mental and physical health needs. Future studies examining the complex relationship between PTSD and health should include women in their study population. In regards to investigating the relationship between PTSD symptom criteria groups and sympathetic nervous system activity indicators and health-related quality life, future research should utilize larger samples that meet full diagnostic criteria for a current diagnosis of PTSD to help delineate the difference between individuals with posttraumatic stress disorder versus PTSD symptoms. Larger samples would also allow exploration of the relationship between

PTSD symptom criteria groups and the eight SF-36 subscales. Such investigations would help pinpoint in what areas of physical and mental health-related quality of life different symptoms criteria groups are influencing. In addition, it would be beneficial to examine the relationship between PTSD symptom criteria groups and hemodynamic and sympathetic responses to mental stress. Future research should also investigate the mechanisms by which different PTSD symptom criteria groups influence health-related quality of life.

APPENDIX A
Tables

Table 1

Summary of Study Assessments

	Assessments/Measurements	Domain	Assessment Period			
			Baseline		12-Week Intervention (PTSD group only)	Post-Intervention (PTSD group only)
			PTSD	Control		
Psychological Measures	Life Events Checklist (LEC)	Trauma inventory	X	X		X
	Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)	PTSD symptoms (clinician-rated)	X	X		X
	Mini International Neuropsychiatric Interview for DSM-5 (MINI)	Diagnostic screen	X	X		X
	PTSD Checklist for DSM-5 (PCL-5)	PTSD symptoms (patient-rated)	X		X	X
	Quick Inventory of Depressive Symptomatology (QIDS SR-16)	Depression symptoms	X		X	X
	Concise Health Risk Tracking (CHRT; self-report module only)	Suicidality	X		X	X
	Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q-SF)	Quality of life	X	X	X	X
	36-Item Short Form Health Survey (SF-36)	Health-related quality of life/physical function	X	X		X

(continued)

Table 1. (continued)

		Assessments/Measurements		Domain	Assessment Period			
					Baseline		12-Week Intervention (PTSD group only)	Post-Intervention (PTSD group only)
					PTSD	Control		
Autonomic Function		**Muscle Sympathetic Nerve Activity (MSNA; assessed via microneruography**	Experimental Protocols: Resting spontaneous and controlled breathing; Valsalva maneuver, Stroop color-word test; Cold pressor test; Static handgrip exercise; Graded upright tilt	Sympathetic outflow to skeletal muscle vasculature	X	X		X
		Heart rate (assessed via electrocardiogram)		Number of contractions of the heart per minute	X	X		X
		Blood pressure		Pressure of circulating blood on the walls of the blood vessels	X	X		X
		Respiration (via nasal cannula)		Respiration	X	X		X
		Cardiac Output (modified acetylene rebreathing)		Amount of blood the heart pumps each minute	X	X		X
		Stroke Volume (cardiac output divided by heart rate)		Amount of blood pumped by the left ventricle of the heart in one contraction	X	X		X
		Total Peripheral Resistance (mean blood pressure divided by cardiac output)		Resistance to blood flow offered by all of the systemic vasculature, excluding the pulmonary vasculature	X	X		X
		Cerebral Blood Flow (transcranial Doppler)		Blood supply to the brain in a given period of time	X	X		X
Cardiovascular Function	Cardiac Function	Left ventricular systolic function (echocardiography)		Heart (left ventricular) function via assessment of wall movements, blood flow, and valve movements	X	X	X	X
		Left ventricular diastolic function (echocardiography)		Heart (left ventricular) function via assessment of wall movements, blood flow, and valve movements	X	X		X
	Vascular Function	Endothelium-dependent flow-mediated vasodilation (ultrasound Doppler)		Endothelial function	X	X		X
		Carotid-femoral and carotid-radial pulse wave velocity (arterial tonometry)		Central and peripheral arterial stiffness	X	X		X
		Augmentation pressure and index (arterial tonometry)		Central arterial stiffness/compliance	X	X		X

(continued)

Table 1. (continued)

	Assessments/Measurements		Domain	Assessment Period			
				Baseline		12-Week Intervention (PTSD group only)	Post-Intervention (PTSD group only)
				PTSD	Control		
Physical Fitness Assessment	Peak oxygen uptake (Douglas bag method)	Experimental Protocols: Resting hemodynamics; Steady-state 1; Steady-state 2; Maximal treadmill test	Indication of physical fitness	X			X
	Heart rate (ECG)		Number of contractions of the heart per minute	X			X
	Blood pressure (SunTech)		Pressure of circulating blood on the walls of the blood vessels	X			X
	Cardiac Output (modified acetylene rebreathing)		Amount of blood the heart pumps each minute	X			X
	Blood lactate		Lactic acid that appears in the blood	X			X

Note. Bolded assessments were used in the current study

Table 2

Overview of Parent Study

Study Phase	Visit	Location/Staff	Group	Procedures/Assessments	Time Length	Compensated
Determining Eligibility	Psychological Screen/Baseline Assessment	VANTHCS	PTSD	Demographics	1.5 -2 Hours	No
				LEC/**CAPS-5**		
				MINI		
				PCL-5		
				QIDS-16		
				CHRT		
				Q-LES-Q-SF		
	Physical Screen	IEEM	PTSD & Control	Demographics	1.5-2 Hours	No
				Vital Signs		
				12-lead ECG		
				24 hour ambulatory BP monitoring		
				LEC/CAPS-5 (Control only)		
				MINI (Control only)		
Pre-Intervention Testing	IEEM Visit 1	IEEM	PTSD & Control	**SF-36** & Q-LES-Q-SF	4-5 Hours	$25/hour
				Cardiac Output		
				Echocardiogram		
				HR & **BP**		
				Microneurography		
				Spontaneous & Controlled breathing		
				Stroop test		
				Valsalva Maneuver		
				Cold Pressor Test		
				Static Handgrip		
				Graded Upright Tilt		
	IEEM Visit 2	IEEM	PTSD & Control	Flow Mediated Dilation of the Brachial Artery	3 Hours	$25/hour
				Arterial Tonometry		
			PTSD	Submaximal Treadmill Test		
				Maximal Treadmill Test		

(continued)

Table 2. (continued)

Study Phase	Visit	Location/Staff	Group	Procedures/Assessments	Time Length	Compensated
12-Week Intervention (Lifestyle Modification or Contact Control)	Biweekly Phone Assessments (VANTHCS) & Check ins with IEEM staff	VANTHCS/IEEM	PTSD	Biweekly phone assessments (VANTHCS) PCL-5 QIDS-16 CHRT Q-LES-Q-SF Check in with IEEM Staff (Lifestyle Modification Group only) Exercise HR Exercise Diary	15 minutes x 5	Fitness Center Membership
Post-Intervention Testing	IEEM Visit 3	IEEM	PTSD	See IEEM Visit 1 Procedures	4-5 Hours	$25/Hour
	IEEM Visit 4	IEEM	PTSD	See IEEM Visit 2 Procedures	3 Hours	$25/Hour
	Psychological Assessment	VANTHCS	PTSD	CAPS-5 PCL-5 QIDS-16 CHRT Q-LES-Q-SF	1.5-2 Hours	No

Note. Bolded assessments were used in the current study.

Table 3

Sample Characteristics

Sample Characteristics	PTSD Group (n = 17)	Healthy Control (n = 9)	p value
Age (M±SD)	42.59 (11.17)	40.56 (9.06)	0.64
Ethnicity (*n* [%])			
White	6 (35.3)	6 (66.7)	0.22
Black	8 (47.1)	2 (22.2)	0.40
Hispanic	2 (11.8)	0 (0)	0.53
Asian	1 (5.9)	1 (11.1)	1.00
Years of Education (M±SD)	14.94 (1.68)	15.33 (2.24)	0.62
BMI kg/m^2 (M±SD)	29.03 (6.13)	27. 41 (5.01)	0.50
Elevated or High Blood Pressure	7 (41.2)	2 (22.2)	0.42
Current Tobacco Use (*n* [%])	2 (11.8)	1 (11.1)	1.00
Past Tobacco Use (*n* [%])	4 (23.5)	2 (22.2)	1.00
Current MDD (*n* [%])	10 (58.8)	0 (0)	0.004
Current GAD (*n* [%])	5 (29.4)	0 (0)	0.13
Current Panic Disorder (*n* [%])	4 (23.5)	0 (0)	0.26
Current Medication			
Antihypertensive	4 (23.5)	0 (0)	0.26
Antidepressant	8 (47.1)	0 (0)	0.02
Anxiolytic	5 (29.4)	0 (0)	0.13
Service Branch (*n [*%])			
Air Force	1 (5.9)	N/A	
Army	11 (64.7)	N/A	
Marines	2 (11.8)	N/A	
Navy	3 (17.6)	N/A	
Service Era (*n* [%])			
OEF/OIF/OND	11 (64.7)	N/A	
Desert Storm/Kosovo/Somalia	3 (17.6)	N/A	
Multiple	2 (11.8)	N/A	
Other	1 (5.9)	N/A	
PTSD Index Trauma (*n* [%])			
Combat	5 (29.4)	N/A	
Intimate Partner Violence	3 (17.6)	N/A	
Military Sexual Trauma	9 (52.9)	N/A	
Years since Index Trauma (M±SD)	16.09 (9.88)	N/A	
CAPS-5 Total Score (M±SD)	33.24 (8.47)	N/A	
PCL-5 Total Score (M±SD)	46.41 (15.52)	N/A	

Table 4

Comparisons of Cardiovascular Risk Indicators and Health-Related Quality of Life Among Women Veterans with PTSD and Health Controls

MANOVA: Group Differences in Cardiovascular Risk Indicators						
Effect	Value	*F*	*df*	*Error df*	*p*	η_p^2
Wilks' Λ	0.84	0.97	4	21	0.45	0.16
MANOVA: Group Differences in Health-Related Quality of Life						
Effect	Value	*F*	*df*	*Error df*	*p*	η_p^2
Wilks' Λ	0.49	11.4	2	22	<.001	0.51

	Mean (SD)		Between-subject effects		
	PTSD Group	Healthy Control Group	*F*	*p*	η_p^2
Baseline HR	77.69 (11.43)	74.79 (10.58)	0.39	0.54	0.02
Baseline Systolic Blood Pressure	120.29 (14.52)	112.44 (8.13)	2.23	0.15	0.09
Baseline Diastolic Blood Pressure	72.00 (7.12)	70.00 (4.90)	0.56	0.46	0.02
Baseline MSNA	23.06 (18.33)	13.67 (9.51)	2.04	0.17	0.08
SF-36 PCS	45.74 (10.16)	55.32 (4.60)	7.08	0.01	0.24
SF-36 MCS	35.48 (12.23)	53.37 (5.75)	16.88	<.001	0.42

Table 5

Hierarchical Multiple Regression Analyses of Clinician-Rated PTSD Symptom Criteria Groups as Predictors of SNS Outcomes

Dependent Variable	Model	Predictor Variable	*B*	*SE B*	β	*p*	Partial Correlation	Part Correlation	R^2 change
Baseline Heart Rate	1	Non-hyperarousal PTSD Symptom Severity (Clinician-Rated)	-0.27	0.406	-0.17	0.52	−.17	−.17	0.028
	2	PTSD hyperarousal symptom severity (Clinician-rated)	−.52	1.09	−.14	0.64	−.13	−.11	0.015
Baseline Systolic Blood Pressure	1	Non-hyperarousal PTSD Symptom Severity (Clinician-Rated)	−.84	0.438	−.45	0.07	−.45	−.45	0.2
	2	PTSD hyperarousal symptom severity (Clinician-rated)	−.55	1.18	−.12	0.65	−.12	−.11	0.01
Baseline Diastolic Blood Pressure	1	Non-hyperarousal PTSD Symptom Severity (Clinician-Rated)	−.23	0.23	−.25	0.33	−.25	−.25	0.06
	2	PTSD hyperarousal symptom severity (Clinician-rated)	−.95	0.58	−.43	0.12	−.40	−.39	0.15
Baseline MSNA	1	Non-hyperarousal PTSD Symptom Severity (Clinician-Rated)	0.09	0.61	0.04	0.89	0.04	0.04	0.001
	2	PTSD hyperarousal symptom severity (Clinician-rated)	1.04	1.63	0.18	0.53	0.17	0.17	0.03

Table 6

Hierarchical Multiple Regression Analyses of Self-Rated PTSD Symptom Criteria Groups as Predictors of SNS Outcomes

Dependent Variable	Model	Predictor Variable	*B*	*SE B*	β	*p*	Partial Correlation	Part Correlation	R^2 change
Baseline Heart Rate	1	Non-hyperarousal PTSD Symptom Severity (Self-Rated)	−.20	0.2	−.23	0.32	−.26	−.26	0.07
	2	PTSD hyperarousal symptom severity (Self-Rated)	0.5	0.78	0.21	0.53	0.17	0.16	0.03
Baseline Systolic Blood Pressure	1	Non-hyperarousal PTSD Symptom Severity (Self-Rated)	−.2	0.24	−.21	0.42	−.21	−.21	0.04
	2	PTSD hyperarousal symptom severity (Self-Rated)	−.43	0.94	−.15	0.65	−.12	−.12	0.01
Baseline Diastolic Blood Pressure	1	Non-hyperarousal PTSD Symptom Severity (Self-Rated)	−.13	0.12	−.27	0.3	−.27	−.27	0.07
	2	PTSD hyperarousal symptom severity (Self-Rated)	−.57	0.43	−.41	0.21	−.332	−.32	0.1
Baseline MSNA	1	Non-hyperarousal PTSD Symptom Severity (Self-Rated)	0.003	0.3	0.002	0.99	0.002	0.002	0
	2	PTSD hyperarousal symptom severity (Self-Rated)	0.35	1.2	0.1	0.78	0.08	0.08	0.01

Table 7

Hierarchical Multiple Regression Analyses of PTSD Symptom Criteria Groups as Predictors of SF-36 PCS and MCS

Dependent Variable	Model	Predictor Variable	*B*	*SE B*	β	*p*	Partial Correlation	Part Correlation	R^2 change
SF-36 PCS	1	Non-hyperarousal PTSD Symptom Severity (Patient-Rated)	−1.01	0.26	−.72	0.002	−.72	−.72	0.52
	2	PTSD hyperarousal symptom severity (Patient-Rated)	0.95	0.655	0.28	0.17	0.37	0.26	0.07
SF-36 MCS	1	Non-hyperarousal PTSD Symptom Severity (Patient-Rated)	0.14	0.52	0.07	0.79	0.07	0.07	0.005
	2	PTSD hyperarousal symptom severity (Patient-Rated)	0.77	1.4	0.16	0.59	0.15	0.15	0.02
SF-36 PCS	1	Non-hyperarousal PTSD Symptom Severity (Self-Rated)	−.11	0.18	−.16	0.54	−.16	−.16	0.03
	2	PTSD hyperarousal symptom severity (Self-Rated)	0.02	0.73	0.01	0.98	0.01	0.01	0
SF-36 MCS	1	Non-hyperarousal PTSD Symptom Severity (Self-Rated)	−.05	0.26	−.05	0.86	−.05	−.05	0
	2	PTSD hyperarousal symptom severity (Self-Rated)	−.04	1.03	−.01	0.97	−.01	−.01	0

Table 8

Standard Multiple Regression Analysis of PTSD Symptom Criteria Groups as Predictors of SF-36 PCS Outcomes

Dependent Variable	Predictor Variables	*B*	*SE B*	β	*p*	Partial Correlation	Part Correlation
SF-36 PCS	Re-experiencing Symptom Severity	−1.26	0.58	−.52	0.051	−.55	−.43
	Avoidance Symptom Severity	−1.54	1.85	−.21	0.42	−.24	−.17
	Cognitions & Mood Symptom Severity	−.92	.6-	−.34	0.15	−.42	−.31
	Hyperarousal Symptom Severity	1.04	0.8	0.31	0.22	0.37	0.26

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