Posttraumatic Stress Disorder and Incident Heart Failure in U.S. Veterans

THESIS

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By

Samit Sunny Roy, B.A.

Graduate Program in Public Health

The Ohio State University

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Master's Examination Committee:

Dr. Randi E. Foraker, PhD, Advisor
Dr. Randall E. Harris, MD, PhD
Dr. Alyssa Mansfield, PhD, MPH
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Abstract

**Introduction:** Veterans are a population at increased risk of developing posttraumatic stress disorder (PTSD). Evidence suggests PTSD is a causal determinant for adverse physical health outcomes, specifically cardiovascular disease (CVD). However, there exists a gap in the literature regarding the association between PTSD and heart failure (HF). The purpose of this study was to determine whether Veterans with diagnosed PTSD are at increased risk for developing heart failure (HF) compared to Veterans without PTSD after adjusting for known risk factors for PTSD and HF.

**Methods:** We examined the association between PTSD and HF in a sample of 11,864 Veterans using medical records from 2002-2012 obtained from the Veterans Affairs Pacific Islands Healthcare System (VAPIHCS). We assessed for continuous use of VAPIHCS services throughout the study period to construct the study cohort. We included Veterans free of HF at study baseline (2005) and assessed for PTSD and presence of service-related and clinical covariates at that time. Multivariable Cox regression was used to estimate hazard ratios and 95% confidence intervals (HR; 95% CI) and to account for known risk factors for PTSD and HF.

**Results:** Over a mean follow-up of 7.2 years, Veterans with PTSD were at significantly increased risk for developing HF (1.47; 1.13-1.92) compared to Veterans without PTSD in a model including age, gender, diabetes, hyperlipidemia, hypertension, combat service,
period of military service, and body mass index (BMI). Other significant predictors of HF included age (1.05; 1.03-1.07), diabetes (2.54; 2.02-3.20), hypertension (1.87; 1.42-2.46), combat service (4.99; 1.29-19.38), and BMI (Overweight: 1.72; 1.25-2.36; Obese: 3.43; 2.50-4.70).

**Discussion:** Our study is the first large-scale longitudinal study to investigate the association between PTSD and incident HF among Veterans. We found that PTSD is associated with increased risk of developing HF in Veterans, and this association persisted after controlling for known risk factors related to PTSD and HF. Our findings suggest that prevention and treatment efforts for CVD and its associated risk factors should be redoubled among Veterans with PTSD.
Dedication

This document is dedicated to my family, without whose support this would have been impossible.
Acknowledgments

The Acknowledgments page is optional. This page includes a brief, sincere, professional acknowledgment of the assistance received from individuals, advisor, faculty, and institution.
Vita

2007 ......................................................... Troy High School

2011 ............................................................ B.A. Psychology, New York University

Fields of Study

Major Field: Public Health
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Introduction

Posttraumatic Stress Disorder (PTSD) is a psychiatric illness that may result after the experience of severe trauma. The United States (US) Census Bureau has estimated that approximately 7.7 million Americans over the age of 18 are currently afflicted (US Census Bureau 2005). While PTSD can result from many forms of trauma, one subpopulation at elevated risk for this disease is Veterans. While figures vary slightly, estimates for PTSD in male Veterans have been reported as high as 30% (Kulka et al., 1990). Given the US’ ongoing military operations over the last decade in Afghanistan and Iraq, a better understanding of the disease burden faced by those with PTSD is vital.

There has been a growing amount of scientific evidence to support the role of psychiatric illness, specifically PTSD, in adverse health outcomes. For example, PTSD has been linked to significantly higher rates of arthritis (Qureshi et al., 2009), liver disease (Spitzer et al., 2009), digestive disease (Norman et al. 2006), and cancer (Norman et al. 2006). One of the most consistent findings suggests detrimental effects of PTSD on cardiovascular health, leading to cardiovascular disease (CVD; Ahmadi et al., 2011; Kang et al., 2006; Kubzansky et al., 2007). While many studies have found higher rates of CVD in people with PTSD, there are significant gaps in the literature regarding the effect of PTSD on cardiovascular outcomes such as heart failure (HF). While there exists few studies on the topic (Spitzer et al., 2009, Glaesmer et al., 2011), PTSD has been
linked with significantly increased odds [OR=3.4; 95% CI: 1.4-6.0] of developing HF in both the general population (Spitzer et al., 2009) and in a sample of the elderly [OR=2.9; 95% CI: 1.7-5.2] (Glaesmer et al., 2011). While these preliminary findings suggest an association between PTSD and HF, both studies reporting this association were limited due to cross-sectional study design, small sample sizes of people with PTSD, and as well as reliance on self-reported measures for both PTSD and HF (Spitzer et al., 2009, Glaesmer et al., 2011). Due to the scarcity of large-scale prospective studies investigating the association between PTSD and HF, we undertook a study to further elucidate the role of PTSD in incident HF.

Thus, we investigated the role of PTSD in incident HF in a sample of Veterans from the Veterans Affairs Pacific Islands Health Care System (VAPIHCS). After reviewing the extant literature on the subject, we believe that PTSD is a significant risk factor for development of HF even after controlling for other known risk factors for HF. Our study, being the first longitudinal prospective study on the subject, contributed to the evolving understanding of the total HF disease burden faced by those with PTSD by adding evidence of the relationship between PTSD and HF based on a strong study design, well-characterized clinical measures, and a large sample of Veterans.

**Posttraumatic Stress Disorder**

PTSD is a psychiatric illness that may result after an individual experiences severe trauma. The newly released fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), published by the American Psychiatric Association, categorizes PTSD as a ‘Trauma- and Stressor- Related Disorder’. The diagnostic criteria
of PTSD are outlined by eight criteria, A-H (American Psychiatric Association 2013). Criterion A states that for an adult to be diagnosed with PTSD, that individual must have had exposure to a traumatic event involving actual or threatened death, serious injury, or sexual violence. Criterion A lists four ways in which this exposure may occur: (1) direct experience of a traumatic event, (2) witnessing of a traumatic event, (3) learning of the occurrence of a traumatic event to a close family member or friend, and (4) repeated experience or exposure to the aversive details of a traumatic event.

The remaining seven criteria B-H are concerned with the symptoms of PTSD. The hallmark symptoms of PTSD are (B) intrusive recollection, (C) avoidance, (D) negative alterations in cognition and mood, (E) alterations in arousal and reactivity, (F) duration of symptoms, (G) clinical significance of impairment, and (H) symptoms not attributable to effects of substance use or another medical condition. Intrusive recollection refers to a persistent re-experiencing of the trauma, which can manifest itself through memories, dreams, thoughts, recollections, images, perceptions, illusions, hallucinations, dissociative flashback episodes, or reenactment. Avoidance refers to persistent avoidance of stimuli associated with the traumatic event. Negative alterations in cognition and mood is characterized through a range of symptoms including inability to recall an important aspect of the trauma, exaggerated negative beliefs or expectations, persistent distorted cognition, persistent negative emotional state, diminished interest or participation in significant activities, feeling of detachment or estrangement from others, and inability to experience positive emotions. Alterations in arousal and reactivity refers to symptoms of, irritability, outbursts of anger, reckless or self-destructive behavior, hypervigilance,
exaggerated startle response, problems with concentration, and sleep disturbance.

The final three criteria of PTSD (F-H) are duration, which states that symptoms must be experienced more than one month following the trauma, functional significance which states that the symptoms must cause significant distress or impairment in social, occupational, or other important areas of functioning, and the final criterion states that the disturbance is not attributable to the physiological effects of a substance or another medical condition. The DSM-V states that for a diagnosis of PTSD, at least one of the aspects of intrusive recollection, one aspect of avoidance, two aspects of negative cognition and mood, two aspects of alteration in arousal and reactivity, and the final three criteria of duration, functional significance, and non-attributability to another substance or medical condition must be present (American Psychiatric Association 2013).

The prevalence of PTSD in the general population has been reported to be 6.8% (Kessler et al., 2005). This summary statistic is slightly misleading, however, as there are segments of the population that are at increased risk for PTSD. For example, the lifetime prevalence of PTSD was estimated to be 3.6% in males but 9.7% in females (National Comorbidity Survey 2005). Another sub-population at elevated risk for PTSD is military Veterans. The National Vietnam Veterans Readjustment Study (NVVRS) was a study conducted in the 1980s on over 3,000 Veterans who served in Vietnam. NVVRS reported lifetime rates of PTSD to be 30.9% in men and 26.9% in women, and among those who served in the Vietnam theatre, the prevalence of PTSD in men was reported at 15.2% and 8.1% in women at the time of the study (Kulka et al., 1990). Given the significantly elevated rates of PTSD among Veterans from earlier service periods, and the United
States’ military conflicts of the last decade including Operation Enduring Freedom (OEF) in Afghanistan, Operation Iraqi Freedom (OIF), and Operation New Dawn (OND) in Iraq, PTSD is a significant issue that warrants thorough scientific investigation.

The role of PTSD as a causal determinant for adverse physical health outcomes has been investigated in numerous studies that have reported significant associations between PTSD and future detrimental health outcomes as diverse as arthritis (Qureshi et al., 2009), CVD (Ahmadi et al., 2011; Kang et al., 2006; Kubzansky et al., 2007), liver disease (Spitzer et al., 2009), digestive disease (Norman et al., 2006), and cancer (Norman et al., 2006). Furthermore, PTSD has been linked to increased all-cause mortality (Boscarino, 2006) and increased healthcare usage (O’Toole & Catts, 2008).

When the post-war health status of Vietnam veterans was examined, those with PTSD had substantially higher rates of many major chronic diseases including circulatory, nervous system, digestive, musculoskeletal, and respiratory disease, even after controlling for major risk factors associated with these conditions (Boscarino, 1997). While these studies are contributing to a more complete understanding of PTSD and the disease burden faced by those with the disease, significant gaps remain in the literature regarding some health outcomes. The following study was undertaken to determine the effect of PTSD on the development of HF.

Biological Plausibility: Mood, Anxiety, Stress, & Cardiovascular Disease

There is an ever-growing body of literature that has examined the role of mood, anxiety, and stress disorders in CVD. CVD is a broad term used to describe any disease that affects the cardiovascular system including coronary heart disease (CHD),...
cardiomyopathy, hypertensive heart disease, cor pulmonale, cardiac dysrhythmia, inflammatory heart disease, valvular heart disease, peripheral arterial disease, stroke, and HF (Maton, 1993). It is hypothesized that stressful events influence physical disease through negative affective states (such as depression or anxiety) that in turn directly affect biological processes or behavior that influences disease risk (Cohen 1995). Chronic stress exposure is considered especially detrimental because it may lead to permanent changes in emotional, behavioral, and biological responses that affect the cardiovascular system (Cohen et al., 1995, McEwan, 1998).

HF is a chronic disease that results from the heart being unable to sufficiently pump enough blood to meet the body’s needs. This can result in shortness of breath, leg swelling, and intolerance of exercise. HF is generally detected clinically with an echocardiogram. HF affects roughly one to two percent of the population but is most common in people over the age of 65 (McMurray & Pfeffer, 2005). The annual age-adjusted incidence rate of HF among those 45 years or older was 7.2 per 1,000 men and 4.7 per 1,000 women, and the prevalence was similar between genders: 24 per 1,000 men and 25 per 1,000 women (Ho et al., 1993).

There have been a number of studies exploring risk factors for the development of HF. Old age, male sex, hypertension, diabetes, obesity, valvular heart disease, and CHD are important risk factors for HF (Kannel et al., 1999, Levy et al., 1996, Chen et al., 1999). Furthermore, behavioral factors such as tobacco use, physical inactivity, and low educational attainment have also been shown to be associated with increased risk for development of HF (He et al., 2001). More recent research has implicated a role of
psychiatric conditions such as depression and anxiety in HF (Williams et al., 2002), however the mechanisms by which these psychiatric comorbidities influence HF risk remains unclear and requires further exploration (O’Connor & Joynt 2004).

Epidemiologic studies have consistently demonstrated a significant prospective relationship between depression and negative cardiac events in both healthy patients (Arooma et al., 1994, Wasserthal-Smoller et al., 1996, Pratt et al., 1996) as well as patients with pre-existing CVD (Carney et al., 1988, Barefoot et al., 1996). A few studies have also reported a gradient between the magnitude of depressive symptoms and future cardiac events (Pratt et al., 1996, Anda et al., 1993, Everson et al., 1996). Anxiety-related psychiatric diagnoses have also been found to be associated with cardiac death (Haines et al., 1987, Kawachi et al., 1994). The Northwick Park Heart Study followed 1,457 men over ten years and reported a significant association between self-reported phobic anxiety symptoms and fatal CHD (Haines et al., 1987). Although these studies suggest a relationship between anxiety and detrimental cardiovascular outcomes, the number of studies investigating this association has been sparse, and more research is needed to elucidate the specific mechanisms involved in the atherosclerotic process (Rozanski, Blumenthal, & Kaplan, 1999).

Finally, negative cardiovascular outcomes have been found in research focused on stress. The INTERHEART study of over 25,000 participants in 52 countries found that people reporting ‘permanent stress’ at work or home were more than twice as likely to develop CVD (Rosengren et al., 2004). Another study looking at the long-term effects of the siege of Leningrad found that even 50 years after the siege, citizens who lived
through the siege had elevated blood pressures and were more likely to die from CVD than Russians who were not in the besieged city (Sparen et al., 2004).

Mood, anxiety, and stress disorders are thought to influence cardiovascular outcomes by way of two distinct mechanisms—behavioral and physiological. Behavioral changes in response to psychological illness often manifests in lifestyle factors that increase risk for CVD, such as smoking (Zigelstein et al., 1998, Kawachi et al., 1994, Twisk et al., 1999). Biologically, there have been a number of hypothesized mechanisms by which each type of psychiatric illness affects cardiovascular health. In depression, physiological changes are believed to induce hypercortisolemia (Carroll et al., 1976), and increased platelet reactivity (Musselman et al., 1996). Anxiety and stress have been linked to various hemodynamic, neuroendocrine, and immune responses. These responses include release of catecholamines and corticosteroids resulting in increased heart rate, cardiac output, and elevated blood pressure (Krantz & Manuck 1984), changes to haemostatic and thrombotic processes such as coronary vasoconstriction, platelet aggregation, or plaque rupture (Muller et al., 1989, Patterson et al., 1995), increased inflammation and hypercoagulation (Jain et al., 2007), increased fibrinogen (Steptoe et al., 2003), and a blunted baroreflex sensitivity, which refers to an inability to adjust heart rate when blood pressure increases (Thomas et al., 2004). While many of these hypotheses require more research to determine exact mechanistic processes, it is clear from the extant literature that mood, anxiety, and stress play a significant role in development of CVD outcomes.

Posttraumatic Stress Disorder, Cardiovascular Disease, and Heart Failure
The evidence linking PTSD to CVD is also substantial and supported by epidemiologic and clinical data. A study of Veterans found that those with PTSD were significantly more likely to have an abnormal electrocardiograph results than those without PTSD (28% vs. 14%) including a higher prevalence of myocardial infarctions and atrioventricular conduction deficits (Boscarino & Chang, 1999). A study of World War II and Korean War veterans also found higher rates of diagnosed cardiovascular disease among Veterans with PTSD compared to those without PTSD (Schnurr, Spiro, & Paris, 2000). A study of adults exposed to the disaster at Chernobyl found increased rates of heart disease up to ten years after the event (Cwikel et al., 1997), and studies of the Civil War in Beirut found increases in arteriographically confirmed CHD and CVD mortality (Sibai et al., 1989, Sibai et al., 2001).

A recent review of PTSD in development of CVD examined a number of current hypotheses thought to play a role in this association (Wentworth et al., 2013). Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS) dysfunction are commonly observed in people with PTSD (Friedman & Schnurr, 1995). These changes lead to a variety of physiological changes that may potentially damage the cardiovascular function. Increased inflammation (von Kanel et al., 2007), dysfunctions of valvular endothelium (von Kanel et al., 2008), hypercoagulability (von Kanel et al., 2006), and cardiac hyperreactivity (Sloan et al., 1999) have all been noted physiological effects presenting in patients with PTSD. Altered neurochemistry, such as increased arginine vasopressin (de Kloet et al., 2008), and elevated prevalence of metabolic syndrome (Dedert et al., 2010) may also contribute to adverse cardiac events.
While there have been studies showing PTSD to be related to various types of CVD, very few studies have shown a direct relationship between PTSD and incident HF. The only two studies we found that specifically looked at this association reported in the general population those who had PTSD were 3.4 times (95% CI [1.9, 6.0]) as likely to develop HF compared to participants who reported not having PTSD (Spitzer et al 2009). The second study was a population-based study of the German elderly that also reported that patients who reported having PTSD had significantly increased odds of developing HF [OR=2.9; 95%CI: 1.7-5.2] (Glaesmer et al., 2011). While these findings helped shape our initial hypothesis regarding the role of PTSD in HF, we acknowledge that the previous studies were both limited due to the cross-sectional study design, reliance on self-reported medical information for both PTSD and HF, and very small number of participants with diagnosed PTSD (Spitzer et al. 2009: n=62 participants with reported PTSD, Glaesmer et al. 2011: n=67 participants with reported PTSD).

Based on the information presented it can be seen that PTSD and HF are important medical and public health issues individually, but there is a strong case, supported by extant literature, to suspect that those with PTSD are at higher risk for development of incident HF than those without PTSD. To investigate this association, we conducted a study to determine the underlying relationship between PTSD and incident HF in a high-risk population of Veterans.
Methods

Study Design

This study utilized a cohort design using data obtained from the Veterans Affairs Pacific Islands Healthcare System (VAPIHCS). VAPIHCS spans an area of 4.8 million square miles, serving approximately 130,000 Veterans in the Pacific basin, and stretches from Hawaii in the east to Guam in the west. We queried the medical records for eligible Veterans between January 1\textsuperscript{st}, 2002 and December 31\textsuperscript{st}, 2012. Due to the fact that the researchers only had access to data from Veterans in the Pacific Islands region, the possibility existed that Veterans were treated elsewhere and later relocated to the Pacific Islands. The implication of this is that there may have been Veterans in the study that had been diagnosed with HF or PTSD and it would not be immediately apparent in the VAPIHCS system. To combat this, the period between January 1\textsuperscript{st}, 2002 and December 31\textsuperscript{st}, 2004 was used as a ‘buffer’ period to ensure that the Veterans accurate medical information was included within the VAPIHCS system. Thus, the study has an 8-year follow-up period (January 1\textsuperscript{st}, 2005 to December 31\textsuperscript{st}, 2012) for the ascertainment of incident HF.

Eligibility
To be considered eligible for the study, Veterans must have met the following two inclusion criteria. All Veterans included in the study must have received medical care through VAPIHCS during the complete study period beginning January 1st 2002 and ending December 31st 2012. While the possibility of patients being lost to follow up due to relocation, or utilization of non-VA healthcare services may have occurred, the assumption that Veterans were not lost to follow-up represents an administrative limitation. The second criteria for inclusion was that Veterans must have been at least age 45 as of January 1st 2005, and no older than 89 years old by the study end point. The decision to only include Veterans at least 45 years old was made based on the fact that HF primarily affects older people. The upper age limit was chosen due to additional Institutional Review Board (IRB) restrictions on human participants above 89 years of age. The sole exclusion criterion applied was that all Veterans included in the study could not have a diagnosis of HF in the administrative record as of baseline assessment. This was done to ensure that all cases of HF in our study comprised incident cases.

Cohort Construction

We began assembling the cohort for analysis by querying the medical records for all Veterans with a VAPIHCS visit before January 1st, 2002, yielding a total of 43,286 participants. After applying our age criteria, we excluded 12,234 Veterans, leaving 31,052 Veterans in our cohort. We then excluded 1,952 Veterans who died before January 1st, 2005, resulting in 29,100 individual records. Our final step was exclusion of all Veterans without a VAPIHCS visit after January 1st, 2005 as well as those Veterans
with prevalent HF at baseline. The result was our final cohort consisting of 11,864 Veterans.

Institutional Review Board Approval

The current study was approved by the Veterans Affairs Pacific Islands Healthcare System Institutional Review Board (Project Number: 2012-15/AJM/Promise 0003) and The Ohio State University Institutional Review Board (Protocol Number: 2013B0059).

Outcome Measure: Incident Heart Failure

The outcome of interest for this study was development of incident HF between baseline and study end. This measure was coded dichotomously such that all Veterans with a noted HF diagnosis code were considered to have developed HF and all other Veterans were considered free of HF. The following ICD-9 diagnosis codes were used to indicate presence of HF: 428.00, 428.10, 428.20-428.23, 428.30-428.33, 428.40-428.43, and 428.9.

The records used for this analysis also included a Veteran’s date of death if applicable. We took into account patient deaths in our analysis by adjusting the time contributed to the study; however, we did not assess death as a competing risk to HF.

Exposure Measure: Posttraumatic Stress Disorder

To assess exposure status for Veterans, the records of all PTSD diagnosis dates were obtained. The exposure was coded dichotomously such that all Veterans with a
diagnosis code of 309.81 were considered to have PTSD and all Veterans without a PTSD diagnosis code were considered free of PTSD.

Potential Effect Measure Modifiers

Two potential effect measure modifiers (EMMs) were considered in the analysis. We hypothesized that Veterans with PTSD would be more likely to be tobacco users and substance users than Veterans without PTSD. Furthermore, both of these behaviors are known risk factors for HF. This relationship indicates that both tobacco use and substance use lie on the causal pathway between PTSD and HF, and should therefore be considered potential EMMs.

Tobacco use was classified as having tobacco use noted in the patient record as of baseline assessment. We used the categories of “current tobacco user” and “not current tobacco user” according to data available in the medical record. This variable was not based off a diagnosis code but was noted in patient records.

Substance use disorder was classified as having a noted substance use disorder diagnosis in the patient record as of baseline assessment. Each veteran was classified as having a current substance use disorder or not according to the medical record data. The following diagnosis code were used to determine presence of substance use disorder: 304.00-304.3, 304.10-304.13, 304.20-304.23, 304.30-304.33, 304.40-304.43, 304.50-304.53, 304.60-304.63, 304.70-304.73, 304.80-304.83, 304.90-304.93, 305.20-305.23, 305.30-305.33, 305.40-305.43, 305.50-305.53, 305.60-305.63, 305.70-305.73, 305.80-305.83, and 305.90-305.91.

To test these EMMs, interaction variables were created between PTSD and both
possible EMMs. This interaction term represented the risk for Veterans who were in the highest risk category for PTSD and each of the EMMs tested compared to the referent group. For example, the interaction term between PTSD and tobacco use represented the risk of Veterans with PTSD who were tobacco users compared to veterans without PTSD who were not tobacco users. Likewise, the interaction term for substance use represented the risk of Veterans with PTSD who also had substance use disorder listed in their record compared to veterans without PTSD who did not have substance use disorder in their record. A likelihood ratio test was used to test significance of the interaction terms and a p-value less than or equal to 0.2 was used a cutoff. The increased p-value cutoff represents an acknowledgement of reduced power in testing interaction terms. The null hypothesis was that the hazard ratio for the high-risk categories was not equal to zero.

Potential Confounders

Four categories of covariates were included to adjust for the potential confounding of the association between PTSD and HF. These four categories were (1) demographics, (2) known risk factors for HF, (3) comorbid psychiatric diagnoses, and (4) military service variables.

Demographics

(i) Age: Due to our inability to collect patient date of birth due to patient privacy concerns, the variable age was collected as a whole number as of baseline. If a patient’s age was unavailable at baseline, the closest available age occurring before January 1st, 2005 was used in these analyses.
(ii) Gender

(iii) Race / ethnicity – While data were obtained for patient’s race/ethnicity, preliminary analysis showed that there were extremely high levels (over 80%) of missing and/or unknown data. We made the decision to not use this variable due to this high percentage of missing data.

(iv) Marital Status – Data on the patient’s most current marital status (as of May 2013) were obtained. Veterans who were noted as being married in the record were assigned to the married category, and all other Veterans were assigned to the non-married category.

Known Risk Factors for Heart Failure

(i) Diagnosed Diabetes: This measure relied on the Veteran having a noted diagnosis code for diabetes in the medical record. The following diagnosis codes were used as indication of diagnosed diabetes: 250.00-250.03, 250.10-250.13, 250.20-250.23, 250.30-250.33, 250.40-250.43, 250.50-250.53, 250.60-250.63, 250.70-250.73, 250.80-250.83, and 250.90-250.93.

(ii) Diagnosed Hyperlipidemia - This measure relied on a Veteran’s record having a noted hyperlipidemia diagnosis code 272.0.

(iii) Diagnosed Hypertension - This measure relied on a Veteran’s record having a noted hypertension diagnosis code 401.9.

(iv) Body Mass Index (BMI) – While this variable was collected in the initial dataset, preliminary analysis found high levels (approximately 30%) of missing and/or
unknown data. Due to this incomplete data, BMI was not considered in the initial analysis of the data, however, after obtaining an initial model, BMI was evaluated in later sensitivity analyses, as it is a well-noted risk factor for HF. We created three categories for BMI. Veterans with a BMI less than 25.0 were considered ‘Normal BMI’, Veterans with a BMI between 25.0 and 29.9 were considered ‘Overweight’ and Veterans with a BMI over 30.0 were considered ‘Obese’.

Comorbid Psychiatric Disorders

(i) Depression - This measure relied on a Veteran’s record having a noted diagnosis of depression 296.20-296.26, 296.30-296.36, 300.4, 309.0, 309.1, 309.2, and 311.

(ii) Adjustment Disorder - This measure relied on a Veteran’s record having a noted diagnosis of adjustment disorder 309.0, 309.1, 309.2, 309.4, 309.82, 309.83, 309.89, 309.9

(iii) Anxiety Disorder other than PTSD - This measure relied on a Veteran’s record having a noted diagnosis of anxiety disorder other than PTSD 300.00, 300.01, 300.02, 300.09, 300.20, 300.21-300.23, 300.29, 300, 300.3, 300.4, 300.9.

Military Service Variables:

(i) Period of military service – We used categories to indicate in which U.S. military conflict or era the Veteran served. This variable was coded categorically based on chronology. The earliest conflict noted in the record was World War II, and all Veterans with a noted World War II period of service were assigned the referent group value. We then grouped all Veterans with a noted Korean War period of service, those
with a noted Post-Korean War period of service, Veterans who served during Vietnam, those with a Post-Vietnam period of service, Veterans with a Persian Gulf War period of service, and Veterans with unknown or with a designated ‘Other’ period of service into separate categories.

(ii) Combat Exposure Indicated during Military Service – This measure relied upon combat service being indicated on the Veteran’s record.

Time to Event Analyses

We estimated hazard ratios and 95% confidence intervals (HR, 95% CIs) for the association between PTSD and HF using time-to-event analysis and a Cox proportional hazards model. A major component of this type of analysis is the variable time. As noted above, the study period included the 8 years between January 1st, 2005 and December 31st, 2012. For each Veteran, a variable ‘time’ was created that represented the number of days that Veteran was in the study without being censored. Censoring refers to the process of removing participants from the analysis who no longer contribute time to the study. In this study, we used three types of censoring. We censored Veterans who developed HF during the study period because after developing HF, these Veterans were no longer at risk for developing HF. These Veterans contributed the number of days between the study period and their HF diagnosis date. We also censored Veterans who died during the study period, at the time of their death, because these Veterans were also no longer at risk for developing HF after they died. These Veterans contributed the amount of time between the study’s start point and their date of death as noted in the record. The last group of censored Veterans was those who reached the study end point.
without developing HF or dying.

To compensate for the potential for changing exposure status, time was recalculated for these Veterans who were diagnosed with PTSD during the study period. For example, if a Veteran was diagnosed with PTSD at any point during the study period, then that Veteran’s study time was recalculated from the diagnosis date. From the Veteran’s PTSD diagnosis date, time was calculated as the number of days until that Veteran developed HF, died, or reached the study end. We recognized that this choice creates a slight problem in that all covariates were assessed as of baseline (January 1st 2005) and that covariates may have changed between baseline and a later PTSD diagnosis date. This fact was outweighed due to the fact that while the number of Veterans with PTSD diagnosed after baseline was a small fraction of the total sample (~5%) these Veterans represented roughly one third of the total PTSD group. Furthermore, due to the fact that HF was a rare occurrence in the sample, the choice was made to ensure that a relatively large portion of the main outcome variable was considered. Post-hoc sensitivity analyses were conducted excluding these Veterans with PTSD diagnoses after study assessment to ensure that this choice did not substantively change the direction or magnitude of the association.

Cox Regression Proportional Hazards Model

Cox regression is a semi-parametric proportional hazards model that uses a quantity known as the hazard function. In this analysis, the hazard function represents the rate of incident HF for Veterans. From determining the hazard function of each group, the hazard ratio (HR) can be calculated by dividing the estimated hazard function from group
one (the exposed group) by the estimated hazard function from group two (the referent, or unexposed, group). In this analysis we assigned Veterans with PTSD as group one and Veterans without PTSD as group two. The resulting HR is equivalent to the relative risk of developing HF between those Veterans with PTSD compared to those Veterans without PTSD.

The Cox model is based on four assumptions. The first is that each participant has independent event times. In other words, this assumption states that each participant who develops HF does so independently of other participants who develop HF, with respect to time. This assumption is satisfied by the current study as time to incident HF is determined by individual participant factors. The second assumption is that censoring times are independent for each participant in the study. This assumption states that after adjustment for all relevant factors, censoring is unrelated to risk of HF. The third assumption is that the natural log of the hazard ratio \( \ln(\text{HR}) \) is a linear function of the predictors. This assumption is a statement of the semi-parametric nature of the Cox model. The final assumption is proportional hazards. This assumption states that the HR is constant in with respect to time. This final assumption must be tested for each predictor and can be tested both graphically and through hypothesis testing.

We investigated the proportional hazards of variables by conducting individual likelihood ratio tests for each predictor. The null hypothesis tested was that the coefficient of each covariate interacted with a log-transformed function of time was equal to zero. All tests that yielded p-values greater than 0.1 signified that predictor being independent of time and satisfying the proportional hazards assumption. If the variable
violated the proportional hazards assumption we included the significant interaction between the variable and log-transformed time. We used backwards selection to build our final regression model. We removed variables consecutively if the p-value exceeded 0.05. Finally, we conducted sensitivity analyses to characterize significant time-varying covariates and determine the influence of diagnosis dates and missing data.

Sample Size & Power

Based on a Type I error rate (\( \alpha \)) of 0.05 and power (1 - \( \beta \)) of 0.80 and previous estimates used in a similar study of PTSD and coronary artery disease of ‘survival’ of the control group (0.90) and the PTSD group (0.83) (Ahmadi 2011), the required sample size needed with an expected ratio of control Veterans to Veterans with PTSD of 5 is 2,836. We were able to ascertain records for 11,864 Veterans for this study, providing ample power to detect a difference between groups.
Results

A total of 11,864 Veterans were followed for an average of 2,633 days (7.2 years). Of the total sample, 2,240 were diagnosed with PTSD (18.9%). Table 1 shows the baseline characteristics of Veterans without diagnosed PTSD compared to Veterans with diagnosed PTSD. Veterans with diagnosed PTSD were much more likely to have tobacco use (25.6%) and substance use (26.8%) noted in their record compared to Veterans without a PTSD diagnosis (9.4% and 9.6% respectively). Veterans with PTSD were also much more likely to have combat service indicated (19.4%) compared to Veterans without a PTSD diagnosis (8.3%). Rates of comorbid depression (20.4%), anxiety disorder (11.7%), and adjustment disorder (17.8%) were also considerably higher in the PTSD group compared to the non-PTSD group (5.1%, 2.1%, and 3.5% respectively). Differences between the two groups in biological risk factors of HF such as diabetes, hyperlipidemia, and hypertension were modest in comparison.

Over the study period, 477 Veterans developed HF and 1,719 Veterans died. There were 376 (3.9%) cases of HF among Veterans without PTSD and 101 (4.5%) cases of HF among Veterans with PTSD. There were 1,495 (15.5%) deaths in the non-PTSD group and 224 deaths (10.0%) in the PTSD group. Figure 1 shows the Nelson-Aalen estimated cumulative hazard functions for the each group. A log-rank test evaluating the
difference in hazard rates of developing HF between the two groups was significant ($\chi^2(1) = 5.54; p = 0.0186$).

**Figure 1: Estimated Cumulative Hazard Plot**

![Nelson-Aalen Cumulative Hazard Estimates](image)

**Testing the Proportional Hazards Assumption**

Appendix A shows the likelihood ratio test of the proportional hazards assumption for each predictor. The only predictors that violated proportional hazards were Combat Service ($\chi^2(1) = 11.72; p = 0.0006$) and Hypertension ($\chi^2(1) = 4.04; p = 0.0445$).
<table>
<thead>
<tr>
<th>Covariate</th>
<th>No PTSD (n=9624)</th>
<th>PTSD (n=2240)</th>
<th>Total (N=11864)</th>
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</thead>
<tbody>
<tr>
<td>HF</td>
<td>376 (3.91)</td>
<td>101 (4.51)</td>
<td>477 (4.02)</td>
</tr>
<tr>
<td>Age (Mean +/- SE)</td>
<td>64 +/- 11.04</td>
<td>59 +/- 7.77</td>
<td>63 +/- 10.67</td>
</tr>
<tr>
<td>Male</td>
<td>9204 (95.64)</td>
<td>2156 (96.25)</td>
<td>11360 (95.75)</td>
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<tr>
<td>Race</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1103 (11.46)</td>
<td>481 (21.47)</td>
<td>1584 (13.35)</td>
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<tr>
<td>Asian</td>
<td>1498 (15.57)</td>
<td>552 (24.64)</td>
<td>2050 (17.28)</td>
</tr>
<tr>
<td>Missing</td>
<td>7023 (72.97)</td>
<td>1207 (53.69)</td>
<td>8230 (69.37)</td>
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<tr>
<td>Body Mass Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>1972 (20.49)</td>
<td>629 (28.08)</td>
<td>2601 (21.92)</td>
</tr>
<tr>
<td>Overweight</td>
<td>2571 (26.71)</td>
<td>656 (29.29)</td>
<td>3227 (27.20)</td>
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<tr>
<td>Normal</td>
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<td>2420 (20.40)</td>
</tr>
<tr>
<td>Missing</td>
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<td>528 (23.57)</td>
<td>3616 (30.48)</td>
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<tr>
<td>Married</td>
<td>5729 (59.53)</td>
<td>1190 (53.13)</td>
<td>6919 (58.32)</td>
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<tr>
<td>Diabetic</td>
<td>917 (9.53)</td>
<td>249 (11.12)</td>
<td>1166 (9.83)</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>4199 (43.63)</td>
<td>1001 (44.69)</td>
<td>5200 (43.83)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>3271 (33.99)</td>
<td>914 (40.80)</td>
<td>4185 (35.27)</td>
</tr>
<tr>
<td>Depression</td>
<td>495 (5.14)</td>
<td>457 (20.40)</td>
<td>952 (8.02)</td>
</tr>
<tr>
<td>Adjustment Disorder</td>
<td>337 (3.50)</td>
<td>399 (17.81)</td>
<td>736 (6.20)</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>195 (2.03)</td>
<td>262 (11.70)</td>
<td>457 (3.85)</td>
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<tr>
<td>Period of Service</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>World War II</td>
<td>1120 (11.64)</td>
<td>75 (3.35)</td>
<td>1195 (10.07)</td>
</tr>
<tr>
<td>Korean War</td>
<td>1439 (14.95)</td>
<td>117 (5.22)</td>
<td>1556 (13.12)</td>
</tr>
<tr>
<td>Post-Korean</td>
<td>671 (6.97)</td>
<td>27 (1.21)</td>
<td>698 (5.88)</td>
</tr>
<tr>
<td>Vietnam Era</td>
<td>4215 (43.80)</td>
<td>1680 (75.00)</td>
<td>5895 (49.69)</td>
</tr>
<tr>
<td>Post-Vietnam</td>
<td>1350 (14.03)</td>
<td>169 (7.54)</td>
<td>1519 (12.80)</td>
</tr>
<tr>
<td>Persian Gulf</td>
<td>729 (7.57)</td>
<td>167 (7.46)</td>
<td>896 (7.55)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>100 (1.04)</td>
<td>5 (0.22)</td>
<td>105 (0.89)</td>
</tr>
<tr>
<td>Combat Service Indicated</td>
<td>799 (8.30)</td>
<td>435 (19.42)</td>
<td>1234 (10.40)</td>
</tr>
<tr>
<td>Smoker</td>
<td>902 (9.37)</td>
<td>574 (25.63)</td>
<td>1476 (12.44)</td>
</tr>
<tr>
<td>Substance Use Disorder</td>
<td>928 (9.64)</td>
<td>601 (26.83)</td>
<td>15.29 (12.89)</td>
</tr>
</tbody>
</table>
Assessing Effect Measure Modification

Our tests to assess effect measure modification due to tobacco use ($\chi^2(1) = 0.02; p = 0.8838$) and substance use ($\chi^2(1) = 0.04; p = 0.8512$) both failed to achieve statistical significance. Having failed as potential EMMs, both the variables tobacco use and substance use were removed from further models.

Backwards Selection of Significant Predictors

Appendix B shows the backwards selection process. The preliminary model obtained contained 16 predictors, including PTSD, age, gender, anxiety disorder, diabetes, combat service indicated, hypertension, period of service (categorized into 6 variables), and two interaction terms: (1) combat status and log-transformed time, and (2) hypertension and log-transformed time. Appendix C shows the complete output. After constructing this model, the proportional hazards assumption was again tested to ensure the new model still satisfies this assumption. The variables combat service ($\chi^2(1) = 11.43; p = 0.0007$) and hypertension ($\chi^2(1) = 3.51; p = 0.0608$) violated the proportional hazards assumption justifying the inclusion of terms in the model to capture the interaction with log-transformed time. The whole model did not violate the proportional hazards assumption ($\chi^2(1) = 7.22; p = 0.8907$). This output is also included in Appendix C.

Sensitivity Analyses & Final Model Determination
As mentioned earlier, post-hoc sensitivity analyses were conducted to support the validity of research decisions made in the study design, and the results contributed to determining the final model. First we looked at whether our decision to recalculate time for Veterans who were diagnosed with PTSD during the study period negatively affected the direction or magnitude of the association. To investigate this possibility, the exact same analysis as outlined above was run on the dataset excluding those Veterans who were diagnosed with PTSD during the study period. These Veterans had to be excluded, as they could not be considered in either the PTSD group or the non-PTSD group. The output of this analysis have not been shown because it resulted in an unstable model. We believe this occurred primarily due to the thinning of the number of Veterans in the PTSD group as well as the reduction of the number of incident HF diagnoses.

The second post-hoc analysis conducted was in regards to BMI. Of the initial 11,864 Veteran records collected, 3,616 records did not have a recorded BMI. BMI is considered an extremely important risk factor for consideration when looking at HF. Our analysis investigated the change in estimates produced by a model including BMI compared to our preliminary model. The complete output is listed in Appendix D. Both our preliminary and final models are presented for comparison in Table 2. When a model was created excluding those Veterans with missing BMI, the variable hypertension no longer violated the proportional hazards assumption ($\chi^2 (1) = 0.57; p = 0.4522$). The model, consisting of 8,248 Veterans with a listed BMI, did not differ significantly in regards to the estimates for the main effects from our original model with the exception of anxiety disorder. This covariate, which was significant in our original model, was
insignificant in a model adjusting for BMI. The results of this analysis were encouraging, and we decided to include BMI in our final model.

The last post-hoc analysis conducted was an analysis that looked at the comorbid illnesses (diabetes, hypertension, hyperlipidemia, depression, anxiety disorder, and adjustment disorder) in a slightly broader context. Instead of using only official diagnosis as an indicator for each of these covariates, this last analysis re-coded these variables such that either diagnosis or current medication for treatment of these covariates would be considered in the assessment of whether each Veteran had the disease. Diagnosis is considered the gold standard when assessing comorbid conditions due to off-label use of medications. For example, it is possible that a person without a diagnosis of depression could be taking anti-depressants for an unrelated illness such as migraine prophylaxis. While this effect differs from illness to illness we believed that it could help solidify our initial conclusions. The complete results have not been shown, but the final model created using this reclassification can be seen in Appendix E. Of importance is the result that anxiety disorder is again became insignificant (p=0.369) and hyperlipidemia remained insignificant (p=0.136). All other conclusions are in line with our initial results.

Final Model

Our final model in the investigation of incident HF in Veterans with and without PTSD is listed below (Table 2). Due to our decision to include BMI in our model, our final model included 8,248 veterans with non-missing BMI. We made the decision to drop the covariate anxiety disorder from the model primarily because results from two of our post-hoc analyses suggested that the relationship might be spurious as it ceases to be
significant upon addition of BMI. As BMI is a more accepted risk factor for HF, we believed it was best to include it over anxiety disorder. Similarly, we also decided to keep hyperlipidemia in the model because even though it did not turn out to be a significant predictor of incident HF. We made this choice because hyperlipidemia is considered an extremely important risk factor for HF and is thus important to control for in the model.

Our final results indicate that PTSD is a significant risk factor for development of incident HF after controlling for known risk factors such as age, gender, hyperlipidemia, diabetes hypertension, BMI, service-connected disability percentage, combat service, and period of military service. Our study shows that over the study period, the relative risk of developing HF in Veterans with PTSD was 1.47 times the risk of developing incident HF in Veterans without PTSD (95% CI 1.13-1.92).

Our final model is consistent with existing literature on HF risk and confirms that variables such as age, diabetes, and hypertension are all significant risk factors for incident HF. We found that the relative risk for developing HF increased by approximately 5% (HR=1.05; 95% CI: 1.03-1.07) for each additional year of age. The relative risk of HF for Veterans diagnosed with diabetes was 2.54 times (95% CI: 2.02-3.20) the risk of developing HF for Veterans without diagnosed diabetes, and similarly, the relative risk for Veterans with diagnosed hypertension was 1.87 times (95% CI: 1.42-2.46) the risk of HF for Veterans without diagnosed hypertension. While the effect of gender in our model (HR=1.95; 95% CI: 0.92-4.15) did not reach statistical significance, the estimate was trending towards significance in favor of the accepted belief that men are at greater risk for developing incident HF than women. Our analysis of the
hyperlipidemia as a predictor for incident HF did not reach statistical significance (HR=0.83; 95% CI: 0.66-1.01). We also found that having combat service indicated in a Veteran’s record was significantly associated with development of HF (HR=4.99 95% CI: 1.29-19.38). However, this covariate did not satisfy the proportional hazards assumption, and investigation into this violation found that over the course of the study period, Veterans with combat service indicated were at substantially higher risk for development of HF up until 2,100 days of follow-up. After 2,100 days, the risk of HF was lower in these Veterans than in Veterans without combat service indicated.

<table>
<thead>
<tr>
<th>Table 2 – Comparison of Models Predicting Incident HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary Model</td>
</tr>
<tr>
<td>(n=11,864)</td>
</tr>
<tr>
<td>Incident HF</td>
</tr>
<tr>
<td>PTSD</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Combat Service</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Period of Military Service</td>
</tr>
<tr>
<td>World War II</td>
</tr>
<tr>
<td>Korean War</td>
</tr>
<tr>
<td>Post-Korean War</td>
</tr>
<tr>
<td>Vietnam Era</td>
</tr>
<tr>
<td>Post Vietnam Era</td>
</tr>
<tr>
<td>Gulf War</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Body Mass Index</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Overweight</td>
</tr>
<tr>
<td>Obese</td>
</tr>
<tr>
<td>Time Varying Covariates</td>
</tr>
<tr>
<td>Combat * log(time)</td>
</tr>
<tr>
<td>Hypertension * log(time)</td>
</tr>
</tbody>
</table>

Data are presented as Hazard Ratios [95% Confidence Interval]

Preliminary Model did not include BMI; hypertension did not violate Proportional Hazards in Final Model.
The results of our analysis on period of military service found that the referent group considered—Veterans of World War II—were much more likely to develop HF than Veterans who served in any other period. This is most likely due to a cohort effect in which Veterans of World War II are older than Veterans of subsequent periods and thus may capture the effect of age on HF development. Other than this, there were no discernible trends in period of military service and risk of incident HF.

Finally, we found that over the course of the study period, Veterans with a BMI that was considered ‘overweight’ had a relative risk of developing HF 1.72 times (95% CI: 1.25-2.36) the risk of Veterans who had a ‘normal’ BMI, and Veterans who had a BMI that was considered ‘obese’ had a relative risk of developing HF that was 3.43 times (95% CI: 2.50-4.70) the risk of Veterans who had a ‘normal’ BMI.

Regression Diagnostics

After running our models, we ran diagnostics to determine how well the model fit the data and to determine the effect of outliers. The first diagnostic we ran was the Cox-Snell Residual Plot, as seen in Figure 2. The plot is a graph of the cumulative hazard rate against a line representing the residuals, or deviance from predicted values. The results from this diagnostic showed that the model fit these data fairly well, although there were some significant deviations at some of the higher estimated cumulative hazard rates.
The second regression diagnostic we performed on the data was a plot of the Martingale Residuals vs. the predicted risk score. We constructed this plot by predicting a risk score for HF for each Veteran in the data and plotting the residuals, or deviance, from this predicted value. As can be seen in Figure 3, most of the deviations are randomly scattered, which shows that there are no significant systematic flaws in the prediction model. This further confirms that our model, while not a perfect predictive index for HF, fit these data fairly accurately. It is generally believed that residuals greater than 2 or less than negative 2 are significant errors in the predictive model.
Figure 3 – Plot of Martingale Residuals vs. Predicted Risk Score.
Discussion

In this study we conclude that PTSD is a significant risk factor for development of HF. Using time-to-event analysis we found that over the course of our study period, the risk of developing HF in Veterans with PTSD was 1.47 times (95% CI: 1.13-1.92) the risk of developing HF in Veterans without PTSD even after controlling for known risk factors such as age, gender, hyperlipidemia, diabetes, hypertension, and BMI as well as military-specific factors such as combat service, and period of military service. Our study was focused on development of incident HF.

While the variable gender did not reach statistical significance in our analysis, we believe this was primarily due to the fact that the sample used in this study was overwhelmingly male (>95%). We believe the low numbers of women in the sample reduced the power to be able to detect differences across gender. Our finding of a dose-response relationship across categories of BMI is consistent with the literature in suggesting that obesity is a risk factor for development of HF.

There were a few unexpected results from our analysis, such as hyperlipidemia trending towards being a protective factor (HR=0.83, 95% CI: 0.66-1.01). While this result is in contrast to the widely accepted idea that hyperlipidemia is a risk factor for HF, we suspect that the estimate was biased from inclusion of related factors such as BMI, hypertension, and diabetes. Exploration into this finding found that hyperlipidemia is a
significant predictor of HF when these other variables are not included, supporting our hypothesis. Another unexpected finding was that combat service was in significant violation of the proportional hazards assumption. As noted in our results, we found that there was significant divergence in the effect of combat service in regards to HF between baseline and 2,100 days of follow up time, and from 2,100 days of follow-up and study period conclusion. We believe this may have been a spurious result, but further research is needed in determining the effect of combat service in development of HF.

This study had many strengths such as the longitudinal study design, large sample size, and use of time-to-event analysis in elucidating the underlying relationship between PTSD and HF. Furthermore, the large number of covariates we were able to analyze including military-specific variables bolstered this study. While we believe that this study many benefits, it was not without limitations.

One of the major limitations of this study came from the use of VAPIHCS administrative data. VAPIHCS does not operate its own inpatient medical facility in the Pacific Islands. As a result, all Veterans receiving inpatient care from VAPIHCS are treated at Tripler Army Medical Center (TAMC) in Hawaii. Due to the use of separate administrative systems between TAMC and VAPIHCS, certain outcomes, including HF, only appear in the record for Veterans if an outpatient VAPIHCS physician subsequently treats them. The result of this administrative difference is the potential for underreporting of HF, since we were unable to ascertain hospitalized HF cases unless they were subsequently seen as an outpatient. Furthermore, use of administrative data in our study design meant that we were unable to assess changing covariates. For example, covariates
such as tobacco use, substance use, BMI, and marital status may have changed over the course of our study period, and we were unable to adjust for these changes. Another limitation we experienced was that of missing data, particularly in regards to race/ethnicity and BMI. We were unable to analyze these data in regards to racial and ethnic differences because almost 70% of the participants had missing data for this variable. There may be some significant underlying differences by race and ethnicity, and further research should be conducted to determine these effects. Given the unique racial and ethnic populations in the Pacific Islands we were disappointed at being unable to draw any conclusions regarding these differences. Finally, there was an administrative limitation in assessment of military service period. We were unable to distinguish Veterans who had served in the Persian Gulf Operation Desert Storm (1990-1991) from Veterans who have served in the more recent Persian Gulf Operations in Afghanistan and Iraq (2001-present). It would have been very interesting to analyze differences in these Veterans as PTSD awareness and screening are on the rise coupled with decreasing stigma associated with PTSD.

Another limitation of this study was the inability to acquire data regarding history of myocardial infarction (MI). This variable has been implicated both as a risk factor for HF as well as a possible cause of PTSD and should be considered in future analysis of this association. Finally, the last limitation of this study was the fact that all covariates were collected as of baseline but we had to recalculate time for Veterans diagnosed with PTSD during the study period. It is likely that some of the covariates changed during the period between baseline and subsequent PTSD diagnosis, and our analysis was unable to
account for these changes.

Our results have strong clinical and public health implications for Veterans with PTSD. The VA can use this knowledge to target screenings, interventions, and treatment programs for this high-risk population. From a public health perspective, the results contribute to both the overall understanding of the total disease burden faced by those with PTSD and help substantiate the claim that psychological illness can be detrimental to physical health.

As this study is one of the first to look at this association, there are many possible future research directions that should be taken to better understand the role of PTSD in HF, and PTSD and CVD in general. This study was focused on Veterans who represent a focused sub-population. Research should be conducted on other populations to determine if the relationship reported here is consistent. Furthermore, our analysis only looked at one outcome—the development of HF. Future studies should consider HF and competing risks such as other CVD outcomes or death. Even though this study is one of the first prospective studies examining the role of PTSD in development of HF, it is consistent with the newly emerging scientific picture that implicates a significant role of psychological illness in physical health.
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Pratt LA, Ford DE, Crum RM, Armenian HK, Gallo JJ, Eaton WW. Depression, psychotropic medication, and risk of myocardial infarction: prospective data from the


Steptoe A, Kunz-Ebrecht S, Owen N, Feldman PJ, Rumley A, Lowe GD, Marmot M.


Appendix A: Testing the Proportional Hazards Assumption

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Likelihood Ratio Test Statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD:</td>
<td>$\chi^2(1) = 0.38$</td>
<td>$p = 0.5373$</td>
</tr>
<tr>
<td>AGE:</td>
<td>$\chi^2(1) = 0.71$</td>
<td>$p = 0.4010$</td>
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<tr>
<td>MARITAL STATUS:</td>
<td>$\chi^2(1) = 2.27$</td>
<td>$p = 0.1315$</td>
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<tr>
<td>GENDER:</td>
<td>$\chi^2(1) = 0.30$</td>
<td>$p = 0.5837$</td>
</tr>
<tr>
<td>ADJUSTMENT DIS.:</td>
<td>$\chi^2(1) = 0.05$</td>
<td>$p = 0.8300$</td>
</tr>
<tr>
<td>ANXIETY DIS.:</td>
<td>$\chi^2(1) = 0.45$</td>
<td>$p = 0.5044$</td>
</tr>
<tr>
<td>DEPRESSION:</td>
<td>$\chi^2(1) = 0.53$</td>
<td>$p = 0.4685$</td>
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<tr>
<td>DIABETES:</td>
<td>$\chi^2(1) = 0.08$</td>
<td>$p = 0.7753$</td>
</tr>
<tr>
<td>HYPERLIPIDEMIA:</td>
<td>$\chi^2(1) = 0.85$</td>
<td>$p = 0.3566$</td>
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<td>$p = 0.1442$</td>
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<td>TOBACCO USE:</td>
<td>$\chi^2(1) = 2.28$</td>
<td>$p = 0.1307$</td>
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<tr>
<td>*COMBAT SERVICE:</td>
<td>$\chi^2(1) = 11.72$</td>
<td>$p = 0.0006$</td>
</tr>
<tr>
<td>*HYPERTENSION:</td>
<td>$\chi^2(1) = 4.04$</td>
<td>$p = 0.0445$</td>
</tr>
<tr>
<td>PERIOD OF SERVICE:</td>
<td>$\chi^2(1) = 2.50$</td>
<td>$p = 0.8685$</td>
</tr>
</tbody>
</table>

* A p-value less than or equal to 0.1 was considered a significant violation of the Proportional Hazards Assumption.
### Appendix B: Backwards Selection of Predictors

<table>
<thead>
<tr>
<th>Covariate</th>
<th>L.R. Test p-value</th>
<th>L.R. Test p-value</th>
<th>L.R. Test p-value</th>
<th>L.R. Test p-value</th>
<th>L.R. Test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD</td>
<td>( \chi^2(1) = 9.27 ) p=0.0023</td>
<td>( \chi^2(1) = 9.55 ) p=0.0020</td>
<td>( \chi^2(1) = 10.66 ) p=0.0011</td>
<td>( \chi^2(1) = 10.73 ) p=0.0011</td>
<td>( \chi^2(1) = 8.97 ) p=0.0027</td>
</tr>
<tr>
<td>AGE</td>
<td>( \chi^2(1) = 15.49 ) p=0.0001</td>
<td>( \chi^2(1) = 15.49 ) p=0.0001</td>
<td>( \chi^2(1) = 15.27 ) p=0.0001</td>
<td>( \chi^2(1) = 14.23 ) p=0.0002</td>
<td>( \chi^2(1) = 15.03 ) p=0.0001</td>
</tr>
<tr>
<td>GENDER</td>
<td>( \chi^2(1) = 5.92 ) p=0.0150</td>
<td>( \chi^2(1) = 5.92 ) p=0.0150</td>
<td>( \chi^2(1) = 5.92 ) p=0.0159</td>
<td>( \chi^2(1) = 5.36 ) p=0.0206</td>
<td>( \chi^2(1) = 5.46 ) p=0.0194</td>
</tr>
<tr>
<td>DIABETES</td>
<td>( \chi^2(1) = 72.40 ) p=0.0000</td>
<td>( \chi^2(1) = 72.41 ) p=0.0000</td>
<td>( \chi^2(1) = 72.81 ) p=0.0000</td>
<td>( \chi^2(1) = 72.78 ) p=0.0000</td>
<td>( \chi^2(1) = 73.16 ) p=0.0000</td>
</tr>
<tr>
<td>HYPERTENSION</td>
<td>( \chi^2(2) = 41.69 ) p=0.0000</td>
<td>( \chi^2(2) = 41.73 ) p=0.0000</td>
<td>( \chi^2(2) = 42.19 ) p=0.0000</td>
<td>( \chi^2(2) = 42.54 ) p=0.0000</td>
<td>( \chi^2(2) = 42.14 ) p=0.0000</td>
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<tr>
<td>HYPERLIPIDEMIA</td>
<td>( \chi^2(1) = 3.99 ) p=0.0457</td>
<td>( \chi^2(1) = 3.99 ) p=0.0458</td>
<td>( \chi^2(1) = 3.91 ) p=0.0481</td>
<td>( \chi^2(1) = 3.96 ) p=0.0467</td>
<td>( \chi^2(1) = 4.35 ) p=0.0370</td>
</tr>
<tr>
<td>PERIOD OF SERVICE</td>
<td>( \chi^2(6) = 16.63 ) p=0.0107</td>
<td>( \chi^2(6) = 16.64 ) p=0.0107</td>
<td>( \chi^2(6) = 16.73 ) p=0.0103</td>
<td>( \chi^2(6) = 16.97 ) p=0.0094</td>
<td>( \chi^2(6) = 17.15 ) p=0.0087</td>
</tr>
<tr>
<td>COMBAT SERVICE</td>
<td>( \chi^2(2) = 15.64 ) p=0.0004</td>
<td>( \chi^2(2) = 15.64 ) p=0.0004</td>
<td>( \chi^2(2) = 15.67 ) p=0.0004</td>
<td>( \chi^2(2) = 15.90 ) p=0.0004</td>
<td>( \chi^2(2) = 16.21 ) p=0.0003</td>
</tr>
<tr>
<td>ANXIETY DISORDER</td>
<td>( \chi^2(1) = 3.79 ) p=0.0517</td>
<td>( \chi^2(1) = 3.82 ) p=0.0506</td>
<td>( \chi^2(1) = 3.52 ) p=0.0607</td>
<td>( \chi^2(1) = 3.40 ) p=0.0651</td>
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</tr>
<tr>
<td>MARITAL STATUS</td>
<td>( \chi^2(1) = 1.43 ) p=0.2314</td>
<td>( \chi^2(1) = 1.44 ) p=0.2307</td>
<td>( \chi^2(1) = 1.53 ) p=0.2166</td>
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<tr>
<td>DEPRESSION</td>
<td>( \chi^2(1) = 0.35 ) p=0.5520</td>
<td>( \chi^2(1) = 0.40 ) p=0.5271</td>
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<td></td>
</tr>
<tr>
<td>ADJUSTMENT DISORDER</td>
<td>( \chi^2(1) = 0.00 ) p=0.9600</td>
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<td></td>
</tr>
</tbody>
</table>
Appendix C: Preliminary Model

No. of subjects = 11864  
Number of obs = 11864
No. of failures = 477  
Time at risk = 30759034  
LR chi2(15) = 263.95
Log likelihood = -4290.857  
Prob > chi2 = 0.0000

| Covariate | Haz. Ratio | Std. Err. | z   | P>|z|    | [95% CI] |
|------------|------------|-----------|-----|--------|---------|
| ptsd       | 1.450189   | .1750809  | 3.08| 0.002  | 1.144615 1.837342 |
| age        | 1.03085    | .0079117  | 3.96| 0.000  | 1.015459 1.046473 |
| gender     | 2.105041   | .7566118  | 2.07| 0.038  | 1.040673 4.25801  |
| diabetes   | 2.812166   | .3173331  | 9.16| 0.000  | 2.254182 3.508271 |
| hyperlip   | .8089031   | .0823246  | -2.08| 0.037 | .6626238 .9874748 |
| combat     | 6.869941   | 4.326982  | 3.06| 0.002  | 1.999079 23.60892 |
| hyperT     | 5.55637    | 3.27414   | 2.91| 0.004  | 1.750706 17.63474 |

Period of Military Service
| Korean     | .8153593   | .1368969  | -1.22| 0.224 | .5867246 1.133088 |
| Post-Kor   | .5149724   | .1394684  | -2.45| 0.014 | .3028696 .8756131 |
| Vietnam    | 1.026527   | .1991211  | 0.13| 0.893 | .7018725 1.501353 |
| PostViet   | .9752302   | .2712701  | -0.09| 0.928 | .5653753 1.682199 |
| Gulf War   | .5731906   | .2041887  | -1.56| 0.118 | .2851505 1.15219  |
| Other      | 1.405213   | .498875   | 0.96| 0.338 | .7007299 2.817951 |

Time Varying Covariate Interactions
| combat_logT | .7024863 | .06924  | -3.58| 0.000 | .5790817 .852189 |
| htn_logT    | .8589913 | .0725861 | -1.80| 0.072 | .7278819 1.013  |

** CHECKING PROP. HAZARDS OF MODEL **

1 - CHECKING P.H. FOR COMBAT SERVICE:
Likelihood-ratio test  LR chi2(1) = 11.49  
(Assumption: . nested in final)  
Prob > chi2 = 0.0007

2 - CHECKING P.H. FOR HYPERTENSION:
Likelihood-ratio test  LR chi2(1) = 3.47  
(Assumption: . nested in final)  
Prob > chi2 = 0.0624

3 - GLOBAL TEST FOR OTHER PREDICTORS:
Likelihood-ratio test  LR chi2(13) = 4.12  
(Assumption: final nested in all_ints)  
Prob > chi2 = 0.9661
Appendix D: Final Model

No. of subjects = 8248  Number of obs = 3223539
No. of failures = 371
Time at risk = 21199276
LR chi2(16) = 287.36
Log likelihood = -3159.8757  Prob > chi2 = 0.0000

| Covariate | Haz. Ratio | Std. Err. | z    | P>|z|  | [95% CI] |
|------------|------------|-----------|------|------|---------|
| ptsd       | 1.473927   | .1980754  | 2.89 | 0.004 | 1.132625 1.918075 |
| age        | 1.046355   | .0095182  | 4.98 | 0.00  | 1.027865 1.065178 |
| gender     | 1.950913   | .750856   | 1.74 | 0.082 | .9175544 4.148044 |
| hyperlip   | .8159507   | .0885115  | -1.88| 0.061 | .6596727 1.009251 |
| diabetes   | 2.542878   | .297736   | 7.97 | 0.00  | 2.021443 3.198818 |
| combat     | 4.991163   | 3.454068  | 2.32 | 0.020 | 1.285698 19.37602 |
| hyperT     | 1.871117   | .2622162  | 4.47 | 0.00  | 1.421721 2.462563 |

Period of Military Service
- Korean | .7065622   | .1308775  | -1.88| 0.061 | .4914521 1.015827 |
- Post-Kor | .4811799  | .1403194  | -2.51| 0.012 | .2716965 .852179 |
- Vietnam  | .8871383   | .1954274  | -0.54| 0.587 | .5760768 1.366162 |
- PostViet | .971187    | .3063684  | -0.09| 0.926 | .523341 1.802275 |
- Gulf War | .4646848   | .1987665  | -1.79| 0.073 | .2093778 1.074622 |
- Other    | 1.483489   | .5322228  | 1.10 | 0.272 | .7343506 2.99685 |

Body Mass Index
- Overwt  | 1.717373   | .2768101  | 3.36 | 0.001 | 1.252178 2.355393 |
- Obese   | 3.425759   | .5541091  | 7.61 | 0.000 | 2.495035 4.703669 |

Time-Varying Covariate Interaction
- combat_logT | .7323864 | .0796478 | -2.86 | 0.004 | .5917949 .906378 |

** CHECKING PROP. HAZARDS OF FINAL MODEL **

1 - CHECKING P.H. FOR COMBAT SERVICE:
Likelihood-ratio test LR chi2(1) = 7.35
(Assumption: . nested in final) Prob > chi2 = 0.0067

2 - GLOBAL TEST FOR OTHER PREDICTORS:
Likelihood-ratio test LR chi2(13) = 14.34
(Assumption: final nested in all_ints) Prob > chi2 = 0.4244
Appendix E: Analysis with Reclassified Covariates

| Covariates    | Haz. Ratio | Std. Err. | z     | P>|z|  | [95% CI]     |
|---------------|------------|-----------|-------|------|----------------|
| ptsd          | 1.396      | .1689626  | 2.76  | 0.006| 1.101188 - 1.769739 |
| age           | 1.029836   | .0079206  | 3.82  | 0.000| 1.014429 - 1.045478 |
| gender        | 2.038378   | .732752   | 1.98  | 0.048| 1.007619 - 4.123566 |
| hyperlip      | .8453878   | .0857994  | -1.65 | 0.098| .6928935 - 1.031443 |
| diabetes      | 2.411903   | .2595384  | 8.18  | 0.000| 1.953279 - 2.97821 |
| combat        | 7.288519   | 4.590339  | 3.15  | 0.002| 2.121041 - 25.04549 |
| hyperT        | 2.087842   | .2410325  | 6.38  | 0.000| 1.66506 - 2.617973 |
| Period of Military Service | | | | | |
| Korean        | .8263642   | .1387879  | -1.14 | 0.256| .5945826 - 1.148499 |
| Post-Kor      | .526319    | .142394   | -2.37 | 0.018| .3097126 - .894415 |
| Vietnam       | 1.084907   | .2106026  | 0.42  | 0.675| .7415777 - 1.587187 |
| PostViet      | 1.056543   | .2937286  | 0.20  | 0.843| .6126966 - 1.821919 |
| Gulf War      | .6117686   | .2180839  | -1.38 | 0.168| .3041935 - 1.230338 |
| Other         | 1.517137   | .5381646  | 1.18  | 0.240| .7569778 - 3.040648 |
| Time-Varying Covariate Interaction | | | | | |
| Combat_logT   | .7003043   | .0690197  | -3.61 | 0.000| .5772915 - .8495295 |