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Gender Difference in Cardiovascular Risk Indicator and Cardiovascular Disease Among Veterans with PTSD

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ABSTRACT

Using the allostatic load model of disease processes, this study investigated gender differences on cardiovascular risk and cardiovascular disease among PTSD and MDD veterans. Cross-sectional analysis of 884 de-identified veterans' data from four VISN7 primary care clinics was completed via ANCOVAs and binary logistic regression analyses. Veterans with PTSD had significantly higher levels of SBP. Among female veterans without PTSD, MDD was associated with increased DBP. Among veterans with neither PTSD nor MDD, male veterans had higher levels of DBP. Veterans without PTSD and men had higher rates of cardiovascular disease. Study results support continued focus on gender differences in the primary care setting.

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INTROCUTION

Women currently comprise 20% of the United States' Armed Forces and approximately 10% of all U.S. military veterans are women. (Frayne et.al., 2007; Fontana, 2006). The number of female soldiers has continued to rise over the last two decades resulting in an increasing female presence within the historically male dominated Veterans health care system (Fontana, 2006). Although representing only a small percentage of the total veteran population, there are approximately 1.7 million female veterans in the United States, accounting for approximately one in every 100 adult female patients seen in primary care clinics (Murdoch, 2006). In conjunction with the growing number of females in the military -14.3% of Army Active Duty in 2005- women soldiers are increasingly deployed to combat zones or engaged in dangerous military operations (Pereira, 2002) representing 10 % of the troops returning from OIF deployment in 2003-2004 (Murdoch, 2006; Felker, et.al., 2008).

Posttraumatic Stress Disorder (PTSD) is a complex anxiety disorder that develops after an individual is exposed to a traumatic event such as those frequently occurring during military combat (American Psychological Association, 2000). Empirical projections estimate that female veterans will constitute up to half of the victims of war-related PTSD from the current conflict (Sheeley, 1991 as cited in Pereira, 2002). Individuals suffering with PTSD are commonly afflicted with co-occurring mental and physical disorders with differing disease trajectories for men and women that are not well understood. The goal of the current analysis is to explore gender differences in physical

manifestations of stress - specifically cardiovascular health- among veterans with PTSD. The study aims to examine gender differences in cardiovascular risk indicators and cardiovascular disease among veterans with PTSD. Results will contribute to the body of knowledge indispensable in the treatment of veterans encountered at the intersection of primary physical and mental health care, which is at the center of current VA healthcare initiatives (Weaver, Thompson, 2008).

Epidemiological Background

From May through July 2005, 296 soldiers deployed at the U.S. Military Hospital Kuwait mental health clinic consented to having their intake mental health screening and demographic information included in an epidemiological study. Of these, 78 (27%) were female, and 214 (73%) were male. Nineteen percent screened positive for PTSD related symptoms, including 35% screening positive for Major Depressive Disorder (MDD) (Felker, et.al., 2008).

Epidemiological studies estimate lifetime prevalence rate of PTSD to be between 10.4% and 12.3% for women and 5.0% and 6.0% for men (Breslau, Davis, Andreski, & Peterson, 1991; Kessler, Sonnega, Bromet, Hughes, et.al., 1995). With the exception of sexual assault, women are significantly less likely to experience trauma in their lifetime. However, women are twice as likely as men to have a lifetime diagnosis of PTSD and are generally more likely to develop PTSD after traumatic exposure (Kessler, et al., 1995).

In contrast to epidemiological data, a recent study within the Veterans Health Administration found that male veterans were 3.4 times more likely to be diagnosed with PTSD than female veterans. Furthermore, the association between PTSD symptom

presentation and the subsequent diagnosis of PTSD was three times stronger for men than women (Pereira, 2002). In other words, unlike the civilian population, male veterans, not female veterans are more likely to have a diagnosis of PTSD.

A study of recently returned combat male and female veterans from a South Carolina VA found that 19.8% of female veterans were diagnosed with PTSD by VAMC (Veterans Administration Medical Center) psychiatrists. But, according to a structured PTSD interview, (the Clinician Administered PTSD Scale (CAPS)), 40.1% of women reported a score in the diagnostic PTSD range. Disparate from the civilian population, VAMC psychiatrists diagnosed a higher rate of PTSD for male veterans (59.1%) with a commensurate 62.7% endorsing a score in the diagnostic PTSD range on the CAPS (Benda, House, 2003). This study highlights a discrepancy between diagnosis and the presence of PTSD symptoms, which although present for both genders, appears to be more pronounced in female than in male veterans.

One explanation for the gender discrepancy is that although women have been shown to experience greater levels of distress when exposed to trauma, the two diagnoses most commonly used to identify psychological problems among female veterans - depression and borderline personality disorder - share many common symptoms with PTSD. This leads to misidentification of PTSD symptoms. Despite recent attempts to explore the experience of women within the VA health care system, a comprehensive explanation for the gender discrepancy remains unclear. Subsequently, PTSD continues to be under diagnosed in female veterans (Pereira, 2002).

Gender disparity in PTSD, the central focus of the current study, may also be due to: fundamental differences in how men and women are exposed to, perceive, and

experience traumatic events; perception and actual level of social support; biological and physiological variability in stress responses; and/or other traumatic vulnerability mediators such as co-occurring depression (Weissman, et al., 2005). Historically, explanations of the human stress response fail to explain this complex relationship between stress and mind-body health.

Theoretical & Biological Models of PTSD

For a normally functioning human being, sensory input from a traumatic event is transmitted via the amygdala subsequently activating the sympathetic nervous system and suppressing the parasympathetic nervous system. This initial response happens in conjunction with hypothalamic-pituitary-adrenal (HPA) axis stimulation and adrenal gland stimulation that releases cortisol into the blood stream. After resolution of the stressful exposure, cortisol functions as part of the feed back loop to down-regulate the "fight-or-flight" sympathetic nervous system response (Davidson, Stein, Shalev, Yehuda, 2004). Therefore, the usual outcome of trauma exposure and stress is adaptation and not pathology (Christopher, 2004).

Allostasis and allostatic load are relatively new concepts proposed to explain physiological responses to multi-system stress including physical, psychosocial, and environmental stressors (Logan, & Barksdale, 2008). Allostasis, or functional adaptation, continues as long as the body's collective stress response remains below an individual's subjective allostatic load threshold. Allostatic load is the cost to the body of adaptation to chronic stress conditions. Among individuals with PTSD, the body's ability to down-regulate or turn off the "fight-or- flight" response malfunctions. With ensuing chronic

stress exposure, the body becomes over burdened by circulating hormonal mediators of the endocrine system and the allostatic load is breached. Over time, the allostatic breach and disrupted diurnal rhythm (biological circadian rhythm synchronizing day-night cycle) lead to deterioration of bodily systems and an increasing occurrence of disease manifestation such as cardiovascular disease. For those with PTSD, an allostatic load breach means an increased sympathetic nervous system arousal to future traumatic exposure, enhanced startle response to both neutral and trauma related cues, and a lack of habituation of skin conductance to any repetition of loud startling noises suggesting that the central nervous system is continuing to classify loud noises as a sign of threat (Taylor, et al. 2000).

Clinically the allostatic load model provides a theoretical foundation from which to base primary and mental health care outcome treatment decisions. For the purposes of the current analysis, PTSD was defined as a disease state developing when the allostatic load is breached within the bounds of the biological, psychological, and sociological dynamics of an individual's subjective environment.

Stress Response, PTSD, & Gender Differences

Literature examining the relationship between gender and stress is not consistent. Numerous studies have determined that women find themselves in stressful circumstances more often than men (Almeida & Kessler, 1998; McDonough & Walters, 2001). Research also purports that women appraise threatening events as more stressful (Miller & Kirsch, 1987, Ptacek, Smith, & Zanas, 1992) and have more chronic stress than men. Women are exposed to more daily stress associated with female role functioning

(McDonough & Walters, 2001). Women are more likely to report home and family life events as stressful (Oman & King, 2000) and to experience gender specific stressors such as gender violence and sexist discrimination (Heim et.al., 2000; Klonoff, Landrine, &Campbell, 2000). More often than men, women perceive inadequate resources for coping with threatening situations, see stressful situations as unchangeable, and turn toward others for support (Pilar, 2004). Furthermore, research suggests that women are more affected than men by stress because women tend to have greater emotional involvement in social and family relationships (Kessler & McLeod, 1984; Turner et al, 1995).

Taylor, et al. (2000) offer insight into the disparate rates of PTSD among men and women. The article suggests that the naturally occurring female response to threat is best characterized by "tend-and-befriend" and *not* "fight-or-flight". The "tend-and-befriend" hypothesis is supported by the evolutionary theory that survival for women is driven by a strong parental investment. The female stress response may be designed to ensure woman's personal safety and to maximize offspring survival. Taylor et al. (2000) suggest that women are more likely than men to respond to stress by nurturing others and to exhibit behaviors reducing the usual neuroendocrine stress response as it may be harmful to an offspring's health. Additionally, women are more likely than men to affiliate with other social groups - especially other women - to maximize coping and management of a stressful situation. Therefore, a woman's natural response to stress maximizes resiliency factors for both herself and her children. To "tend" or nurture and to "befriend" or affiliate with others effectively down-regulates the sympathetic nervous system and HPA axis (Taylor, et.al, 2000). Given that women may be driven to respond differently than

men physiologically and psychologically to stress, the possibility that a disorder of the stress response system differs between genders is conceivable.

In order to investigate gender differences in posttraumatic vulnerability, a recent study of 250 male and 262 female Israeli civilians examined the effect of terrorism, a traumatic event which targets victims indiscriminately. The study results are supportive of a "tend- and-befriend" versus "fight or flight" variation in the human stress response among men and women. Consistent with epidemiological data from the United States, Israeli women were found to have lower rates of exposure to any act of terror but endorsed statistically higher numbers of stress related mental health symptoms than Israeli men. Women were more likely to report at least one symptom from the three DSM-IV PTSD symptom clusters (intrusive, avoidant, and hyper-arousal) and a significantly greater number of PTSD related dissociation symptoms than men. The study reported a diagnosis of PTSD to be six times more likely in women and more women than men reported feeling depressed after exposure to a traumatic terrorist act. Furthermore, women reported using a greater total number and different types of coping strategies than men. For example, women were more likely to cope through "checking on the whereabouts of friends and family" and men were more likely to cope through "talking about the situation and what could be done about it". Men reported being more optimistic than women with regards to their personal future and the future of their country. Women reported being more afraid for their own safety and the safety of those close to them (Solomn, Gelkopf, Bleich, 2005).

Although both men and women exposed to trauma present with increased mental and physical health disorders, research suggests that women exposed to trauma report

higher rates of mental and physical health problems and are diagnosed more often than men with physical health problems. Additionally, research suggests that the experience of stress is more predictive of health problems in women than in men (Wagner, Wolfe, Rotnitsky, Proctor, and Erickson 2000).

A study of Gulf War veterans post deployment found that out of ten health problems identified by the Health Symptom Checklist, female veterans endorsed a significantly greater number of headaches, aches/pains, upset stomach, and cold/flu symptoms than male veterans (Wagner, et al., 2000). In fact, men did not endorse *any* health symptoms significantly more than women.

Even after controlling for the effect of combat exposure, the above study found that PTSD symptomatology was significantly predictive of the level of self-reported health problems. Therefore, the study suggests that for both male and female veterans PTSD is a significant risk indicator of maladaptive physiological responses. However, the analysis did not report significant gender differences on PTSD and health outcomes (Wagner, et al., 2000).

Empirical studies are beginning to elucidate a profile for women in the military who have been exposed to trauma and subsequently developed PTSD. Dobie, et al. (2004) reported on 1,206 female veterans receiving care between October 1, 1996 and January 1, 1998 at the Puget Sound VAMC. The study found a 20% PTSD prevalence rate among female veterans, similar to that among male veteran outpatients. Controlling for age, female veterans with PTSD compared to those without PTSD were more likely to report health risks including substance use problems, smoking, multiple sexual partners, and a history of domestic violence. Female veterans with PTSD reported higher rates of

somatic distress and were more likely to screen positive for depression, eating disorders, and panic disorder than female veterans without PTSD. Among those medical conditions reported more frequently in female veterans with PTSD were obesity, fibromyalgia, irritable bowel syndrome, emphysema, and sexually transmitted diseases. Female veterans with PTSD also endorsed significantly lower scores on all eight subscales of the Medical Outcomes Study 36-Item Short Form Health Survey for Veterans (SF-36-V), indicating a lower subjective view of mental and physical health status across areas of functioning. Accordingly, the current study aims contribute to the developing female veteran profile.

Cardiovascular Risk Indicators & Cardiovascular Disease

According to the American Heart Association, approximately 72 million Americans (nearly one in three adults) age 20 or older have hypertension (Rosamond et. al 2007, as cited in Logan, Barksdale, 2008). There are many risk factors linked to cardiovascular disease including aging, obesity, smoking, genetic factors, and sedentary lifestyle but research has yet to advance a specific model to account for cardiovascular disease processes (Logan, Barksdale, 2008). The allostatic load model as defined by the current study attempts to theoretically account for the large degree of cardiovascular disease variability.

Post- war Vietnam veteran research reports that soldiers with PTSD, compared to those without PTSD, are significantly more likely to have abnormal electrocardiograph (ECG) results (28% vs. 14%), including atrioventricular conduction defects, and higher rates of myocardial infarction and abnormally high white blood cell and T-cell counts.

Furthermore, 20 years after military service, 25% of Vietnam veterans with PTSD had a physician-diagnosed circulatory disease compared to 13% in Vietnam veterans without PTSD (Boscarino, 1999, 2004). Buckely, Holohan, Greif, Bedard, et. al. (2004) reported that among 36 male Vietnam veterans, PTSD diagnostic status significantly accounted for an increase in heart rate beyond the effects of posture, body mass, smoking, ethnicity, and stress ratings. Buckely et al. (2004) also found that PTSD is significantly associated with elevated basal heart rate (HR) and greater blood pressure reactivity to stress. In other words, PTSD is most likely a significant indicator of cardiovascular disease and is significantly associated with elevated cardiovascular risk indicators.

Elevated cholesterol is a known risk factor for coronary artery disease (CAD). Kagan, Leskin, Haas, Wilkins, et.al. (1999) examined 73 male Vietnam veterans diagnosed with PTSD. These Vietnam veterans were admitted consecutively to the West Los Angeles VAMC. Veterans with chronic PTSD, versus those without chronic PTSD, were found to have a significantly higher mean cholesterol level, triglyceride level, and low-density lipoprotein (LDL) level in addition to a significantly reduced high-density lipoprotein (HDL) level. These results suggest that Vietnam veterans with chronic PTSD are at a significantly increased risk for CAD.

Further research examining the relationship of CAD risk factors found that among 103 Croatian male patients diagnosed with combat-related PTSD, versus 92 Croatian male patients diagnosed with MDD, the PTSD group had higher mean cholesterol, LDL levels, and triglyceride levels, and lower HDL levels, than the MDD group (Solter, Thaller, Karlovic, Crnkovic, 2002). Results from this study support a significant link between chronic PTSD and CAD risk factors but not between MDD and CAD risk

factors. For purposes of the current study, HDL and LDL triglyceride levels were unavailable. Instead, categorical cardiovascular disease outcomes such as elevated cholesterol, ischemic heart disease, hypertension, and diabetes were analyzed.

Vieweg, et al. (2006), from a database analysis of 221 male veterans from the Hunter Holmes McGuire VAMC in Richmond, Virginia, report on elevated body mass index (BMI) among veterans with PTSD. The study results report 82.8% of veterans diagnosed with PTSD had BMI values in the overweight or obese range. This is in contrast to the current US population of which 64.5% are either overweight or obese. The study results did not statistically explain disparate findings, and the relationship between BMI and PTSD is not fully understood. For the purposes of the current study, BMI was not available for analysis and the lack of BMI data may be considered a limiting factor.

Goodwin and Davidson (2005) examined data from the National Comorbidity Survey and found that compared to individuals in the general population without diabetes, self-reported diabetes was associated with a significantly increased likelihood (OR = 2.3, *95% CI*= 1.02, 5.21) of a PTSD diagnosis. Additionally, self-reported diabetes was not found to be significantly associated with any other mental disorder, including depression. Kinzie, et. al.(2008) reported on a group of 459 refugee psychiatric patients having experienced traumatic events in their native countries: Vietnam, Cambodia, Somali, and Bosnia. Among the refugees the prevalence of hypertension was 42% and the prevalence of diabetes was 15.5%. The rates of hypertension and diabetes are higher than population rates. According to the National Institute of Health, 14.7 % of Americans have hypertension. In 2007 11.2% of men and 10.2% of women age 20 and older were

diagnosed with diabetes (American Diabetes Association; Ostchega, Dillon, Hughes, Carroll, et.al., 2007).

In addition to the studies from Vietnam Veterans, research examining World War II (WWII) and Korean Veterans found that veterans with PTSD, compared to those without PTSD, had significantly increased risks for cardiovascular diseases including hypertension, all circulatory diseases and chronic ischemic heart disease (Kang, Bullman, Taylor, 2006). A study of Dutch resistance fighters during WWII found that individuals with PTSD had increased rates of angina pectoris (chest pain or discomfort due to coronary heart disease) compared with resistance fighters without PTSD (Falger, Op den Velde, Hovens, 1992 as cited in Kang, Bullman, Taylor, 2006). Studies examining veterans from the Beirut Civil War and the Croatia War report that individuals exposed to combat and trauma manifested significantly increased rates of coronary heart disease, cardiovascular disease mortality, and acute myocardial infarction compared to individuals not exposed to these conflicts (Boscarino, 2004).

As described above, research suggests the onset of cardiovascular disease processes among individuals with PTSD to be a result of recurrent adrenergic responses and chronic physiological hyperactivity generating functional and morphological changes in the cardiovascular system (Boscarino, 2004). Almost exclusively, research examining cardiovascular risk indicators and disease has focused on men and male veterans. Therefore, the current study aims to examine gender differences among male *and* female veterans on cardiovascular risk indictors and cardiovascular disease.

Cardiovascular Risk Indicators & Gender

There is a distinct paucity of research examining cardiovascular risk indicators and cardiovascular disease among women with PTSD. One study examined physiological arousal among 92 female veterans and found a statistically higher mean baseline heart rate in female veterans with PTSD compared to female veterans without PTSD. Elevated resting heart rate has been empirically associated with hypertension which often results in greater incidence of cardiovascular morbidity and mortality (Forneris, Butterfield, Bosworth, 2004).

To date, only two studies -both examining Israeli civilian population- have examined physiologic responses by gender among individuals with PTSD. The first study reported this trend: Israeli women with PTSD were found to have higher physiological responses, including increased heart rate, than Israeli men with PTSD (Shalev, Orr, Pittman, 1993). The second study examined Israeli civilians following Iraqi missile attacks during the Gulf War (Laor et al., 1999). The results revealed neither a main effect of gender nor an interaction of PTSD and gender on psychophysiological responses to a trauma related task. In other words, no mediating influence of gender upon PTSD psychophysiology was discovered. Because empirical evidence is limited to two Israeli civilian studies, the current study aims to better quantify gender differences on cardiovascular risk indicators.

It is important to note that results from the above study by Boscarino and Chang (1999) indicate that veterans with PTSD show ECG evidence of AV conduction defects and myocardial infarctions while veterans diagnosed with depression demonstrate evidence of arrhythmias. These associations between PTSD and AV conduction defects

and infarction remained significant even after controlling for anxiety, depression, and smoking history. Given the differential cardiovascular risk factors among individuals with PTSD and depression, the high rates of comorbidity between PTSD and depression, and the inconclusive evidence of the role of smoking in the allostatic load model, the current study proposed a more parsimonious model including MDD as a predictor variable and excluding smoking.

PTSD & Depression

Among women with PTSD the lifetime prevalence rate for co-occurring depression ranges from 42-49%. Among men with PTSD the lifetime prevalence rate for co-occurring depression ranges from 26-70% (Kimerling, Ouimette, Wolf, 2002, p. 212). There are three theories suggested by the literature to explain the high rates of diagnostic comorbidity between PTSD and MDD: 1) PTSD and MDD both develop out of the complex grieving process and human reactions to experiences associated with traumatic loss; 2) MDD develops as a reaction to the severity and chronicity associated with PTSD; 3) symptom overlap accounts for the co-occurrence and high rates of comorbid diagnosis between PTSD and MDD (Franklin, & Zimmerman, 2001).

A study by Franklin and Zimmerman (2001) specifically addresses the third possibility that symptom overlap between PTSD and MDD accounts for the high rates of comorbidity. The three overlapping DSM-IV diagnostic symptoms are loss or diminished interest in activities, sleep disturbance, and difficulty concentrating. Franklin and Zimmerman (2001) found that the overlapping symptoms did not significantly account for the high rates of comorbidity. In fact, the study results confirmed that the co-

occurrence of PTSD and MDD reflects two unique symptom patterns and that the overlapping symptom explanation for high PTSD/MDD comorbidity may be rejected.

From an epidemiological study of young adults in southeast Michigan, Breslau, Davis, Peterson, and Schultz (2000) report that individuals with existing depression, versus those without depression, are at a significantly higher risk for exposure to a traumatic event and for developing PTSD. Therefore, depression dually acts as a risk indicator for trauma exposure and the subsequent development of PTSD. Results support the hypothesis that PTSD and co-occurring MDD may result from similar vulnerabilities. In other words, PTSD and MDD develop out of the complex grieving process associated with traumatic loss. Specifically among women, PTSD has been found to be a significant risk indicator for first-onset MDD (Breslau, et al., 1997). These results are supportive of Franklin and Zimmerman's (2001) second hypothesis explaining the high prevalence of co-occurrence. In other words, MDD may develop as a reaction to the severity and chronicity associated with PTSD.

Historically, analysis of PTSD and comorbid disorders has focused on men. Literature consistently reveals that civilian men diagnosed with PTSD are more likely to meet criteria for substance abuse and antisocial personality disorder than women diagnosed with PTSD (Benda, House, 2003). Only very recently have researchers begun to explore co-occurring PTSD and MDD in women and female veterans.

Dobie, et. al. (2006) found that among female veterans with PTSD, 75% screened positive for depression. This is a significant and highly meaningful percentage given the myriad of symptom presentations among female veterans with PTSD. Of note, results indicate that female veterans endorsing co-occurring PTSD and depression report a

significantly greater burden from medical illness than women screening positive for depression alone. The 1999 Veterans health survey found that across age strata, female veterans with PTSD had a significantly greater number of medical illnesses and poorer physical functioning than female veterans with depression alone. Additionally, co-occurring PTSD and MDD was associated with a greater burden of medical illness among female veterans than PTSD or MDD alone. Therefore, among female veterans comorbid PTSD and depression denotes a greater significant risk for medical morbidity and functional disability than the risk associated with depression alone. (Frayne, Seaver, Loveland, Christiansen, et.al., 2004).

Study Aims & Hypothesis

For the purposes of the proposed study PTSD was considered a disease state developing when the allostatic load is breached within the bounds of the biological, psychological, and sociological dynamics of an individual's subjective environment. Allostatic load was the conceptual framework from which the aims of the proposed study were derived. In other words, cardiovascular indicators are elevated and cardiovascular disease occurs among veterans with PTSD because the body fails to down-regulate the stress response (McEwen, 2003).

The primary aim of the proposed study was an exploratory analysis of the relationship between PTSD and the cardiovascular risk indicators [Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Hemoglobin A1C (HGBA1C)] and specifically whether there are group differences by gender and depression.

Aim I, hypothesis I stated that after controlling for history of cardiovascular disease and socio-demographic variables, veterans with PTSD would have higher levels of cardiovascular risk indicators than veterans without PTSD. Aim I, hypothesis II stated that after controlling for history of cardiovascular disease and socio-demographic variables, female veterans with PTSD would have higher levels of cardiovascular risk indicators than male veterans with PTSD.

The secondary aim of the study was an additional exploratory analysis of the relationship between PTSD and cardiovascular disease, specifically whether there are group differences by gender and depression. The cardiovascular diseases of interest included elevated cholesterol, Diabetes Mellitus (DM), hypertension (HTN), and ischemic heart disease (IHD). Aim II, hypothesis I stated that after controlling for socio-demographic variables, veterans with PTSD would have greater frequency of cardiovascular disease than veterans without PTSD. Aim II, hypothesis II stated that after controlling for socio-demographic variables, female veterans with PTSD would have greater frequency of cardiovascular disease than male veterans with PTSD.

METHODS

The data were obtained through an approved Veterans Administration data share stewarded by Kathy Magruder, Ph.D. and Lori Davis, M.D. The original data were collected through a cross-sectional survey of veterans attending primary care clinics at four Veterans Affairs Medical Centers within Veterans Integrated Services Network-7 (VISN7; Charleston and Columbia, South Carolina; Tuscaloosa and Birmingham, Alabama). These cross-sectional data were augmented with a 12-month retrospective chart review and a diagnostic telephone interview. All procedures in the original study were approved by institutional review boards at the Medical University of South Carolina, University of South Carolina, Birmingham VA and Tuscaloosa VA. Procedures for the current data analysis were approved by institutional review boards at the Birmingham VA, Tuscaloosa VA, and University of Alabama at Birmingham, and by the Research and Development Committee at the Medical University of South Carolina (Magruder et.al., 2005). The study data were de-identified, which means the data did not contain any of the 18 HIPAA protected identifiers.

Participants

Eligible patients were identified from 229,780 veterans having had at lease one primary care visit during the fiscal year (FY) 1999. From this larger population, 1,198 patients were randomly identified and invited at the time of their primary care visit, either by letter on in person, to participate in the study.

Relative to the larger population, the randomly selected veterans (1,198) had fewer females (6.2% vs. 10.9%), were slightly older (average age 60 vs. 59) and had more outpatient visits during FY 1999 (average of 20 visits vs. 14). Out of the 1,198 randomly selected veterans, 981 (74.1%) signed informed consent. Those that consented, versus those that did not consent, were similar with regard to gender (6.8% vs. 4.2%) and had the same number of outpatient visits during FY 1999 (20 visits). Those that consented were slightly younger (average age 59 vs. 64).

From the randomly selected veterans, two study groups were recruited. For group 1, a master list of eligible patients was generated. Stratifying per hospital, each patient was assigned a random patient number. The master list was ordered according to these random numbers. According to this list, researchers sent blocks of 200 patients to each hospital. Dr. Magruder's research team at the Medical University of South Carolina then checked the primary care appointment lists. For group 1, when the randomly-selected veteran scheduled a primary care visit, the veteran was sent a letter of invitation in advance of his/her visit to explain the study.

Group 2 consisted of an oversample of female veterans. These female veterans were patients in the same primary care clinics. The researchers randomly identified additional female veterans from the original master list. At all four VA sites, the female veterans were approached during their primary health care visit. The female veterans did not receive letters in advance; instead they were approached directly and recruited to participate in the study. Study procedures were otherwise identical for the two groups of veterans.

Prior to veteran participation in the study, informed consent was signed during the primary care visit. At the time of the clinic visit, the veteran was informed that the study was examining stress-related disorders in primary care. If the veteran consented, sociodemographic data were collected and PTSD screening tools were administered. At the time of the clinic visit, veterans were informed they would be contacted by telephone for a follow-up interview.

Each telephone interview took place within two months of the clinic interviews. Masters level trained clinicians or higher administered the trauma assessment form Clinician-Administered PTSD Scale, (CAPS; Blake et. al., 1995) and the MINI International Neuropsychiatric Interview (Sheehan, 1997) evaluating for common psychiatric diagnoses. CAPS interviewers were blinded to the initial PTSD screening results. For both groups, telephone interviews were conducted in the same manner. For a more complete description of the original data collection see Magruder, et. al. (2005).

Variable Definition and Measurement

All sociodemographic information (gender, ethnicity, education) was coded into dichotomous variables except for age which served as a continuous variable. Exclusion criteria (yes/no) were determined based on clinical interviews and a 12-month retrospective chart review, both conducted by trained research assistants blinded to PTSD status. Exclusion criteria included current or lifetime history of schizophrenia, bipolar, any psychotic disorder; organic psychotic conditions; current or lifetime history of any cognitive disorder or history of Alzheimer's disease or any other dementia; or history of traumatic brain injury (Appendix A).

PTSD (yes/no) was coded based on the CAPS interview that diagnoses PTSD according to DSM-IV criteria and utilizes a cut-off score of >50 (Blake et. al., 1995). Veterans were coded positive for PTSD if the CAPS interview revealed a *current* diagnosis of PTSD. There was no rating of PTSD severity included in the data analysis. MDD (yes/no) was coded based on the MINI which diagnoses major depression based on DSM-IV criteria.

Cardiovascular Disease

From the 12-month retrospective chart review, ICD-9 (International Statistical Classification of Diseases and Related Health Problems-9th edition) codes for cardiovascular disease were identified. Elevated cholesterol (yes/no) was defined when an ICD-9 code for pure hypercholesterolemia, pure hyperglyceridemia, mixed hyperlipidemia, hyperchylomicronemia, or other and unspecified hyperlipidemia was identified in the veteran's chart. Diabetes Mellitus (yes/no) was defined when an ICD-9 code for diabetes was found in the veteran's chart. Hypertension (yes/no) was defined when an ICD-9 code for essential hypertension, hypertensive heart disease, hypertensive kidney disease, hypertensive heart & kidney disease, or secondary hypertension was found in the veteran's chart. Ischemic Heart Disease (yes/no) was defined when an ICD-9 code for acute myocardial infarction, other acute and subacute forms of ischemic heart disease, intermediary coronary syndrome, old myocardial infarction, angina pectoris, or other forms of chronic ischemic heart disease was found in the veteran's chart. An additional variable, CVD, was created identifying "any cardiovascular disease" (yes/no).

Cardiovascular Risk Indicators

From the 12-month retrospective chart review, values for systolic blood pressure (SBP), diastolic blood pressure (DBP), and hemoglobin A1C (HGBA1C) were obtained. Systolic blood pressure is the pressure generated when the heart contracts and diastolic blood pressure is the blood pressure generated when the heart relaxes. The American Heart Association identifies average normal blood pressure to be 120(SD=10) SBP over 80(SD = 10) DBP. HGBA1C is a test value used to assess blood glucose control over time and represents an average blood glucose level. The American Diabetes Association states that a non-diabetic range is 4-6. For adults, elevated HBA1C levels of seven or above indicate an increased risk for health complications due to diabetes. If a veteran had multiple SBP, DBP, or HGBA1C values listed, an average value was calculated.

Statistical Analysis

Sample characteristics were examined with Pearson's chi-square and one-sample t-tests. Three separate ANCOVAs (univariate analysis of covariance) were used to test the hypothesis that veterans with PTSD would have greater cardiovascular risk indicators (SBP, DBP, and HGBA1C) than veterans without PTSD and the hypothesis that female veterans with PTSD would have higher levels of cardiovascular risk indicators than male veterans with PTSD. One-way ANOVAs were conducted to determine covariate variable entry. If a potential covariate was significant at the p=0.10 level or below for any of the three predictor variables (SBP, DBP, HGBA1C) then the covariate was included in the ANCOVA model (Schneider, Bigelow, & Amoroso, 2000). The resulting significant

covariates were age, education, ethnicity, and “any cardiovascular disease”. Follow-up analysis of significant interactions was completed with simple main effects.

The data were evaluated for satisfaction of ANCOVA assumptions (Appendix B). After examining the standardized residuals and utilizing +/- 3.0 cut-off value as an outlier indicator, no outliers in the data set were identified. All additional assumptions for ANCOVA were found to be met except that HGBA1C could not be assumed to come from a normal distribution. Due to the fact that ANCOVA is robust in the face of violations of the assumption of normality, and to facilitate interpretation of findings, HGBA1C was not transformed.

Binary Logistic Regression was used to test the hypotheses that veterans with PTSD would have greater frequency of cardiovascular disease than veterans without PTSD and that female veterans with PTSD would have greater frequency of cardiovascular disease than male veterans with PTSD. Binary dependent variables were elevated cholesterol, diabetes, hypertension, ischemic heart disease, and “any cardiovascular disease”. PTSD, gender, and MDD, as well as age, education and ethnicity effects were tested individually. An additional analysis entered predictor variables (age, education, ethnicity, gender, PTSD, MDD) in one step to determine the unique contribution of each variable.

RESULTS

Of those who consented, 97 (9.9%) were excluded for any of the following: current or lifetime history of schizophrenia, bipolar, or any psychotic disorder; organic psychotic conditions; current or lifetime history of any cognitive disorder or history of Alzheimer's disease or any other dementia; or history of traumatic brain injury (Appendix A). Of the remaining 884 veterans, 147 (16.6%) were women, 79 (8.9%) received a current PTSD diagnosis by CAPS interview (PTSD-CAPS), and 121 (13.7%) received a current MDD diagnosis by MINI interview (MDD-MINI). Out of the 79 veterans diagnosed with PTSD, ten (6.8%) were women. Out of the 121 veterans diagnosed with MDD, 32 (21.8%) were women.

Table 1 lists the characteristics of the 884 individuals included in the analysis by gender. Overall, the study participants appear representative of a typical Southeastern veteran population (Magruder et. al, 2005). The average age was 59.6 (SD = 12.1) years. The majority of the veterans were male (83.4%), Caucasian (61.0%), high-school educated (61.9%), and married (64.4%). Table 1 also lists comorbidities as determined by CAPS and MINI clinical interviews. The prevalence of PTSD was slightly higher in males than females (9.4% vs. 6.8%; X^2 (1) = 1.04, p = .308) though not significantly. The prevalence of MDD was significantly higher in females than males (21.8% vs. 12.1%; X^2 (1) = 4.57, p<.05).

Examination of Cardiovascular Risk Indicators

The mean cardiovascular risk indicator values are presented in Tables 2, 3, and 4. In comparison to the American Heart Association's ideal blood pressure of 120 SBP over 80 DBP, the average SBP was significantly higher [136.0 (SD = 14.5); t(882) = 32.72, p <.001)] and the average DBP was significantly lower [77.3 (SD = 8.3); t(882) = -9.77, p<c.001)]. In comparison to the American Diabetes Association's maximum acceptable HGBA1C value (range of 4-6), the average sample's HGBA1C value was significantly higher [7.0 (SD = 1.8); t (362) = 10.31, p <.001].

Table 2 presents average SBP values for each gender, PTSD, and MDD group. Veterans with PTSD had higher levels of SBP than veterans without PTSD, F(1,724) = 4.589, p = .033. However, there were no significant differences in levels of SBP between male and female veterans, F(1,724) = 1.154, p = .283.

Table 3 presents average DBP values for each gender, PTSD, and MDD group. Among female veterans without PTSD, DBP was significantly higher if the female veteran was diagnosed with MDD, F(1,724) = 6.126, p = .014. Diagnosis of MDD did not have a significant effect on DBP for female veterans with PTSD, F (1,724) = 1.993, p = .158. Neither did MDD affect DBP among male veterans with, F (1,724) = .000, p = .995, or without PTSD, F(1,724) = .392, p = . 532; Gender*PTSD*MDD F(1,724) = 4.205, p = .041. Among veterans without PTSD or MDD male veterans had significantly higher DBP than female veterans, F (1,724) =23.302, p<.001. Among veterans with PTSD, MDD, or comorbid PTSD and MDD, being male did not significantly affect DBP, all F's < 1. Furthermore, there were no significant differences in levels of DBP between male and female veterans averaged across diagnostic categories, F<1.

Table 4 presents average HGBA1C values for each gender, PTSD, and MDD group. Although mean HGBA1C levels were higher on average for female veterans compared to male veterans, and for veterans with versus those without PTSD, neither of these differences was statistically significant, Fs $\leq$ 1.949, p $\geq$.164.

In summary, veterans with PTSD had higher levels of systolic blood pressure than veterans without PTSD. Additionally, results found that among female veterans without PTSD, DBP was higher if the female veteran was diagnosed with MDD; and among veterans without PTSD or MDD, DBP was higher in male veterans. The hypothesis that female veterans with PTSD would have greater levels of cardiovascular risk indicators than male veterans with PTSD was not supported.

Examination of Cardiovascular Disease

Table 5 presents overall frequencies of cardiovascular disease. Within the sample, the highest frequency of cardiovascular disease was hypertension (74.0%), followed by elevated cholesterol (58.3%), diabetes (32.4%) and ischemic heart disease (27.4%). Male veterans had significantly higher frequencies than female veterans of elevated cholesterol (61.3% vs. 42.9%; X^2 (1) = 70.98, p<.001), diabetes (34.3% vs. 22.4%; X^2 (1) = 13.74, p<.001), hypertension (76.8%, 59.9%; %; X^2 (1) = 173.95, p<.001), ischemic heart disease (30.8%, 10.2%; X^2 (1) = 5.272, p<.05), and "any cardiovascular disease" (90.0% vs. 77.6%; X^2 (1) = 392.63, p<.001).

Binary logistic regression results in the prediction of elevated cholesterol are presented in Table 6. When the model was adjusted for the other variables, ethnicity and gender maintained unique contributions in the prediction of elevated cholesterol.

Caucasian veterans were significantly more likely than non-Caucasian veterans to have elevated cholesterol (63.3% vs. 50.8%, adjusted *OR* = 1.567, *95% CI* = 1.129, 2.174); and male veterans were significantly more likely than female veterans to have elevated cholesterol (Table 5; adjusted *OR* = 1.997, *95% CI* = 1.276, 3.125).

Binary logistic regression results in the prediction of diabetes are presented in Table 7. After adjustment for the other variables, Caucasian veterans were significantly less likely than non-Caucasian veterans the have diabetes (28.2% vs. 39.8%, adjusted *OR* = .475, *95% CI* = .338, .666).

Binary logistic regression results in the prediction of hypertension are presented in Table 8. After adjustment, older veterans were significantly more likely than younger veterans to have hypertension (adjusted *OR* = 1.050, *95% CI* = 1.032, 1.067); and Caucasian veterans were significantly less likely than non-Caucasian veterans to have hypertension (70.1% vs. 79.9%, adjusted *OR* = .384, *95% CI* = .255, .576).

Binary logistic regression results in the prediction of ischemic heart disease are presented in Table 9. After adjustment, older veterans were significantly more likely than younger veterans to have ischemic heart disease (adjusted *OR* = 1.045, *95% CI* = 1.027, 1.063). Additionally, after adjustment Caucasian veterans were significantly more likely than non-Caucasian veterans to have ischemic heart disease (33.4% vs. 17.6%, adjusted *OR* = 1.684, *95% CI* = 1.142, 2.485). Furthermore, male veterans were significantly more likely than female veterans to have ischemic heart disease (adjusted *OR* = 2.294, *95% CI* = 1.184, 4.445).

Binary logistic regression results in the prediction of "any cardiovascular disease" are presented in Table 10. After adjustment, older veterans were significantly more likely than younger veterans to have "any cardiovascular disease" (adjusted *OR* = 1.063, *95% CI* = 1.039, 1.087); and Caucasian veterans were significantly less likely than non-Caucasian veterans to have "any cardiovascular disease" (87.0% vs. 89.1%, adjusted *OR* = .459, *95% CI* = .268, .788).

In contrast to the study hypothesis, a diagnosis of PTSD did not significantly increase the likelihood of having elevated cholesterol, diabetes, hypertension, ischemic heart disease, or "any cardiovascular disease". Also in contrast to the study hypothesis, male veterans were actually more likely to have cardiovascular disease than female veterans.

DISCUSSION

Veterans with PTSD were found to have significantly higher levels of SBP supporting the hypothesis that veterans with PTSD would have higher levels of cardiovascular risk indicators than veterans without PTSD. However, despite theoretical suggestions that allostatic load processes would vary between women (tend and befriend) and men (fight or flight), there were no significant differences in SBP, DBP, or HGBA1C between male and female veterans. Although mean HGBA1C levels were higher on average for female veterans compared to male veterans the difference was not statistically significant. One limitation in extrapolating these findings to the veteran population is the small number of female veterans in the study and the relatively small proportion of variance accounted for by the predictor variables (gender, PTSD, MDD) in the model. Future prospective research will benefit greatly from the ability to acquire larger samples of female veterans and conduct power analysis before beginning study recruitment.

Among veterans with neither PTSD nor MDD, male veterans had significantly higher DBP levels than female veterans. This result is not surprising as it is consistent with results of epidemiological studies published by the American Heart Association; on average, men have higher blood pressure than women (Reckelhoff, 2001). For female veterans without PTSD, DBP was significantly higher if the female veterans were diagnosed with MDD. Given the allostatic load theory of disease processes - that allostatic load is the cost to the body of adaptation to chronic stress conditions such as those associated with MDD - these results are not surprising. However, MDD did not

differentiate DBP among female veterans with PTSD. Given that the sample did not account for PTSD severity, it is possible that among a veteran population with a larger range of PTSD severity, a diagnosis of MDD would add to the body's allostatic load and significantly affect blood pressure.

Surprisingly, results found that PTSD did not significantly increase the likelihood of having cardiovascular disease. This finding is not fully understood. It is likely that the method of study recruitment, the non-war era status, and unreliable disease documentation in the veteran's chart played a role in the unexpected findings (Magruder & Yeager, 2008). Additionally, it is possible that PTSD severity played a mediating role. A severe presentation of PTSD would be more likely to trigger a physician to make a diagnosis resulting in more accurate chart recording of PTSD and co-occurring physical illness. However, PTSD severity and was not available for analysis in the current study (Magruder et. al., 2005).

Another study limitation may be the dichotomous categorization of cardiovascular disease, PTSD, and MDD. Future research will benefit from the prospective ability to select methods of measurement to include continuous variables and account for diagnostic severity and chronicity.

In the current study, male veterans were found to have slightly higher rates of cardiovascular disease then female veterans. Although this finding is consistent with epidemiological data, it is inconsistent with study hypothesis. Perhaps, as research suggests, as women age their risk of cardiovascular disease becomes equal to and may even surpass the risk of cardiovascular disease in men (Morgan, Colling, & Fye, 1996).

Therefore it is possible that the younger and more restricted age range of the female veterans played a role in the cardiovascular disease findings.

The demographics of the study sample are representative of veterans in the VISN7 (Magruder, et.al., 2005). However, other studies estimating prevalence rates among the current veteran population found higher rates for PTSD (19% vs. 8.9% in the current sample), MDD (35% vs. 13.7%), and Alcohol Abuse (11% vs. 1.7%; Felker, et.al., 2008). Furthermore, recent VA population research indicates that male veterans are 3.4 times more likely to be diagnosed with PTSD than female veterans (Pereira, 2002). In contrast, in the current sample population the prevalence of PTSD was only slightly higher in male than female veterans (9.4% vs. 6.8%; X2 (1) = 1.04, p = .308) and the difference in the rate of PTSD was not significant. Therefore, the study results may be less generalizable to the current OIF/OEF veteran population.

The reasons for the study population having lower prevalence rates of mental illness are not fully understood. The fact that veterans were recruited from primary care and not from mental health care may have contributed to these discrepant findings. Additionally, the veterans were recruited during a non war-era which could account for lower PTSD, MDD, and substance abuse prevalence rates. The veterans in the sample were older [59.6 (SD =12.1)] and therefore more likely than younger, post-deployment veterans to be in remission from substance dependence or receiving effective treatment for PTSD and MDD, thus minimizing current diagnoses. Therefore, it is possible that the sample prevalence rates were lower because the study only captured symptoms present in the last month (Magruder, et. al, 2005).

The study's proposed model was parsimonious in predicting gender differences in SBP, DBP, and HGBA1C among veterans with PTSD. Although significant, the model reflects a poor goodness of fit with only 10-20% of the variability in the cardiovascular risk indicators accounted for by the predictor variables (gender, PTSD, MDD) and covariates (age, education, ethnicity, and "any cardiovascular disease"). The low level of variability accounted for indicates that the model is unable to comprehensively explain the allostatic load process leading to cardiovascular disease. However, even given the low level of variability accounted for, the significant result –that female veterans had higher levels of DBP than male veterans, clearly indicate gender differences in cardiovascular risk indicators and between male and female veterans.

Of note, 69 male veterans met criteria for current PTSD according to the CAPS interview. The 12-month retrospective chart review identified 58 male veterans diagnosed with PTSD. Only 30 (43.5%) male veterans meeting criteria for PTSD by CAPS interview also had PTSD identified by chart review. Therefore, 48.3% (28) of male veterans identified as having PTSD by chart review did not meet criteria for PTSD by CAPS interview. Ten female veterans met criteria for current PTSD according to the CAPS interview. The 12-month retrospective chart review identified 13 female veterans with PTSD. Only two (20%) female veterans meeting criteria for PTSD by CAPS interview also had PTSD identified by chart review. Therefore, 84.6% of female veterans identified as having PTSD by chart review did not meet criteria for PTSD by CAPS interview. The discrepancy between chart review and CAPS diagnosis raises questions about the validity of relying upon chart review to accurately identify PTSD when conducting retrospective PTSD research among veterans.

Recent research suggests that mental health care needs are not being fully met within the primary care setting alone (Calhoun, Bosworth, Grambow, Dudley, et.al., 2002). Magruder et. al. (2005) reports on the original population of the current study. Of patients diagnosed with PTSD- CAPS, the 12-month chart review identified only 46.5% with a diagnosis of PTSD. Additionally, only 47.7% of those veterans diagnosed with PTSD-CAPS had utilized mental health services. Calhoun, et.al. (2002) reports on 996 veterans seeking an evaluation at a VA Medical Center PTSD clinic between March 1992 and September 1998. Veterans with PTSD had a median seven mental health care clinic appointments. These same PTSD veterans had a median 18 general physical health encounters where predominantly medical rather than mental health care services are provided.

Furthermore, due to the historic underuse of VA facilities by female veterans (Hoff & Rosenheck, 1998) and the growing cohort of female veterans returning from the current conflict (women currently constitute 20% of the Armed Forces), VA facilities need to create integrated programs targeting female veterans across all levels of mental and physical health care (Frayne et.al., 2007). The findings from the current study are clinically relevant because the use of cardiovascular risk indicators in the primary care setting could increase the identification and treatment of PTSD.

The current study documents the higher levels of systolic blood pressure among veterans with PTSD versus veterans without PTSD. These results support the hypothesis that veterans with PTSD will have significantly higher levels of cardiovascular risk indicators than veterans without PTSD. Results also found that among female veterans without PTSD, DBP was higher if the female veteran was diagnosed with MDD.

Furthermore, among veterans without PTSD or MDD, DBP was higher in male veterans. However, despite stress response differences between men and women (fight or flight vs. tend and befriend), and that HGBA1C levels on average were higher for female versus male veterans, there were no significant gender differences in cardiovascular risk indicators. Study limitations included the small number of female veterans in the study, and the low amount of variance accounted for by the predictor variables (gender, PTSD, MDD).

Results did not support the hypothesis that veterans with PTSD would have higher rates of cardiovascular disease than veterans without PTSD, nor did results support the hypothesis that female veterans with PTSD would have higher rates of cardiovascular disease than male veterans with PTSD. These unexpected results are likely attributable to the method of study recruitment from a primary care setting, the non-war era status of the veterans, unreliable disease documentation in the veteran's chart, the lack of PTSD severity analysis, and the relatively younger cohort of female veterans, versus male veterans, included in the study. Due to the historic underuse of VA facilities by female veterans and the growing cohort of female veterans returning from the current conflict, VA facilities need to create integrated programs targeting female veterans across all levels of mental and physical health. Although the current study results did not find gender differences in cardiovascular risk indicators and cardiovascular disease among veterans with PTSD, results argue for continued focus on gender differences to improve detection and treatment of PTSD in an integrated primary and mental health care setting.

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Table 1. Characteristics of 884 Veterans who Participated in a Study on Prevalence of PTSD in Primary Care Clinics

Characteristic	Overall N= 884		Female N= 147 (16.6%)		Male N= 737 (83.4%)	
Mean Age (SD)	59.6 (12.1)		49.3 (11.5)		61.6 (11.1)	
Age Categories	N	%	N	%	N	%
18-39 [34.3 (3.5)]	44	5.0	26	17.7	18	2.4
40-54 [48.6 (4.0)]	286	32.4	82	55.8	204	27.7
55-69 [62.5 (4.6)]	334	37.8	26	17.7	308	41.8
70 and over [74.7 (3.1)]	218	24.7	11	7.5	207	28.1
Race/Ethnicity[a]						
Caucasian	539	61.0	65	44.2	474	64.3
African American	324	36.7	79	53.7	245	33.2
Hispanic & Other	5	0.6	0	0.0	5	0.7
Education[b]						
Primary	182	20.6	4	2.7	178	24.2
Secondary	547	61.9	100	68.0	447	60.7
University	155	17.5	43	29.3	112	15.2
Married	569	64.4	60	40.8	509	69.1
PTSD-CAPS[c]	79	8.9	10	6.8	69	9.4
ICD-9 code identification						
PTSD	71	8.0	13	8.8	58	7.9
Acute Stress Disorder	2	0.2	1	0.7	1	0.1
Adjustment Disorder	88	10.0	19	12.9	69	9.4
Anxiety Disorder	139	15.7	40	27.2	99	13.4
Mood Disorder	184	20.8	51	34.7	133	18.0
Borderline Personality Disorder	4	0.5	3	2.0	1	0.1

Antisocial Personality Disorder	1	0.1	0	0	1	0.1
Substance Abuse Disorder	37	4.2	2	1.4	35	4.7
Tobacco Use Disorder	146	16.5	26	17.7	120	16.3
Any of the Above Comorbidities	209	23.6	42	28.6	167	22.7
Diagnosis by MINI						
Drug Dependence	2	0.2	34	23.1	2	0.3
Alcohol Dependence	15	1.7	1	0.7	14	1.9
Panic Disorder	52	5.9	8	5.4	44	6.0
Generalized Anxiety Disorder	89	10.1	17	11.6	72	9.8
Major Depressive Disorder	121	13.7	32	21.8	89	12.1
Dysthymia	82	9.3	4	2.7	78	10.6
Mania	0	0	0	0	0	0
Over sample[d]	93	10.5	93	63.3	0	0

[a] Ethnicity entered as a dichotomous variable: Caucasian & Non-Caucasian

[b] Education entered as dichotomous variable: Primary/Secondary & University

[c]PTSD as diagnosed by CAPS interview

[d] Number of female patients randomly recruited from Group II, oversampling for female veterans

Table 2. Gender differences in SBP Among Veterans with PTSD and MDD				
	PTSD+ 137.03 (13.63)* (n =79)		PTSD – 136.45 (14.87) (n = 805)	
	Female Veterans	Male Veterans	Female Veterans	Male Veterans
	PTSD + (n = 10)	PTSD + (n = 69)	PTSD – (n = 137)	PTSD – (n = 668)
MDD + 134.52 (13.35) (n = 121)	135.00 (16.84) (n=7)	137.33 (13.3) (n=45)	131.93 (13.88) (n=23)	132.88 (12.49) (n=43)
MDD – 136.47 (14.83) (n = 736)	153.12 (16.63) (n=2)	135.69 (13.3) (n=24)	131.14 (14.73) (n=78)	137.27 (14.74) (n=404)

*p<.05

Table 3. Gender differences in DBP Among Veterans with PTSD and MDD				
	PTSD+ 79.80 (8.20) (n =79)		PTSD – 76.74 (8.21) (n = 805)	
	Female Veterans	Male Veterans	Female Veterans	Male Veterans
	PTSD + (n = 10)	PTSD + (n = 69)	PTSD – (n = 137)	PTSD – (n = 668)
MDD + 78.83 (7.39) (n = 121)	79.05(10.10) (n=7)	79.77 (6.66) (n=45)	79.22(8.45)* (n=23)	77.60 (7.14) (n=43)
MDD – 76.87 (8.23) (n = 736)	85.78 (2.01) (n=2)	79.30 (8.35) (n=24)	75.24 (8.64) (n=78)	76.97(8.13)* (n=504)

p<.05

Table 4. Gender differences in HGBA1C Among Veterans with PTSD and MDD				
	PTSD+ 6.91 (2.63) (n =79)		PTSD – 6.95 (1.74) (n = 805)	
	Female Veterans	Male Veterans	Female Veterans	Male Veterans
	PTSD + (n = 10)	PTSD + (n = 69)	PTSD – (n = 137)	PTSD – (n = 668)
MDD + 6.82 (1.91) (n = 121)	8.49 (3.95) (n=2)	6.30 (1.31) (n=21)	6.13 (1.72) (n=8)	7.50 (2.17) (n=19)
MDD – 6.94 (1.78) (n = 736)	7.63 (2.72) (n=2)	6.75(2.75) (n=9)	7.51 (2.24) (n=33)	6.86 (1.64) (n=215)

Table 5. Cardiovascular Disease

	Overall N=884		Female N= 147 (16.6%)		Male N= 737 (83.3%)		X^2 (p-value) [e]
Cardiovascular Disease	N	%	N	%	N	%	
Elevated Cholesterol[a]	515	58.3	63	42.9	452	61.3	70.98 (.000)
Diabetes Mellitus [b]	286	32.4	33	22.4	253	34.3	13.74 (.000)
Hypertensive Disease [c]	654	74.0	88	59.9	566	76.8	173.95 (.000)
Ischemic Heart Disease [d]	242	27.4	15	10.2	227	30.8	5.272 (.022)
"Any cardiovascular disease"	777	87.9	114	77.6	663	90.0	392.63 (.000)

[a] According to ICD-9 codes for Cholesterol

[b] According to ICD-9 codes for Diabetes Mellitus

[c] According to ICD-9 codes for Hypertensive disease

[d] According toICD-9 codes for Ischemic Heart Disease

[e] df = 1

Table 6. Prediction of Elevated Cholesterol: Unadjusted and Adjusted OR								
VARIABLE	B	Unadjusted[a] OR	95%CI		B	Adj. OR	95%CI	
AGE	.021	1.021*	1.010	1.033	.005	1.005	.991	1.019
EDUCATION	.106	1.111	.783	1.577	.071	1.074	.719	1.603
ETHNICITY	.513	1.671*	1.265	2.206	.449	1.567*	1.129	2.174
GENDER	.749	2.115*	1.477	3.027	.692	1.997*	1.276	3.125
PTSD-CAPS	.533	1.704*	1.067	2.722	.333	1.395	.805	2.420
MDD-MINI	.621	1.860*	1.257	2.754	.352	1.423	.893	2.266

[a] Variables entered individually
[b] Variables entered in one step
* $p < .05$

Table 7. Prediction of Diabetes: Unadjusted and Adjusted OR								
VARIABLE	B	Unadjusted[a] OR	95%CI		B	Adj.[b] OR	95%CI	
AGE	.010	1.010	.998	1.022	.012	1.012	.997	1.027
EDUCATION	-.101	.904	.627	1.304	-.275	.759	.506	1.140
ETHNICITY	-.521	.594*	.444	.793	-.745	.475*	.338	.666
GENDER	.591	1.806*	1.191	2.738	.449	1.566	.956	2.565
PTSD-CAPS	.217	1.242	.745	2.072	.253	1.288	.712	2.329
MDD-MINI	.107	1.113	.733	1.692	-.055	.947	.578	1.550

[a] Variables entered individually
[b] Variables entered in one step
* $p < .05$

Table 8. Prediction of Hypertension: Unadjusted and Adjusted OR								
VARIABLE	B	Unadjusted[a] OR	95%CI		B	Adj. [b] OR	95%CI	
AGE	.042	1.043*	1.030	1.057	.048	1.050*	1.032	1.067
EDUCATION	.027	1.028	.693	1.523	-.259	.772	.484	1.230
ETHNICITY	-.529	.589*	.425	.817	-.958	.384*	.255	.576
GENDER	.797	2.219*	1.531	3.218	.463	1.589	.982	2.569
PTSD-CAPS	-.017	.983	.575	1.681	-.251	.778	.407	1.487
MDD-MINI	.263	1.301	.846	2.001	.148	1.160	.686	1.959

[a] Variables entered individually
[b] Variables entered in one step
* $p < .05$

Table 9. Prediction of Ischemic Heart Disease: Unadjusted and Adjusted OR								
VARIABLE	B	Unadjusted[a] OR	95%CI		B	Adjusted[b] OR	95%CI	
AGE	.059	1.060*	1.045	1.076	.044	1.045*	1.027	1.063
EDUCATION	.488	1.629*	1.065	2.492	.494	1.639	1.011	2.658
ETHNICITY	.851	2.343*	1.675	3.276	.521	1.684*	1.142	2.485
GENDER	1.365	3.917*	2.245	6.833	.830	2.294*	1.184	4.445
PTSD-CAPS	.561	1.752	.974	3.150	.600	1.823	.904	3.673
MDD-MINI	.412	1.510	.946	2.409	-.201	.818	.463	1.446

[a] Variables entered individually
[b] Variables entered in one step
* $p < .05$

Table 10. Prediction of "Any Cardiovascular Disease": Unadjusted and Adjusted OR								
VARIABLE	B	Unadjusted[a] OR	95%CI		B	Adjusted[b] OR	95%CI	
AGE	.061	1.063*	1.044	1.082	.061	1.063*	1.039	1.087
EDUCATION	.226	1.253	.757	2.076	-.275	.760	.399	1.446
ETHNICITY	-.195	.823	.537	1.263	-.778	.459*	.268	.788
GENDER	.953	2.594*	1.644	4.091	.423	1.526	.837	2.783
PTSD-CAPS	.370	1.448	.748	2.803	-.097	.907	.400	2.057
MDD-MINI	.674	1.961*	1.154	3.333	.467	1.595	.833	3.054

[a] Variables entered individually
[b] Variables entered in one step
* $p < .05$

APPENDIX A

EXCLUSION CRITERIA

Exclusion Criteria				
	Female Veterans N= 169		Male Veterans N= 809	
	N	%	N	%
Current or lifetime history of schizophrenia	4	2.4	19	2.3
Bipolar	12	7.1	12	1.5
Any psychotic disorder	2	1.2	13	1.6
Organic Psychotic Conditions	5	3.0	34	4.2
Current or lifetime history of any cognitive disorder/ history of Alzheimer's disease or any other dementia	3	1.8	27	3.3
History of a traumatic brain injury	5	3.0	9	1.1

APPENDIX B

STATISTICAL ASSUMPTIONS FOR GLM ANALYSIS

1. The sample is random, and observations were made independent of one another.
2. The independent variables are categorical
3. The dependent variables are continuous and interval.
4. Equal group sizes. Due to the smaller sample size and the lower baseline rates of women, data had some relatively unequal group sizes. Type III sums of squares was used in the univariate analysis to aid in balancing the model. There are no empty cells in the design.
5. The sample size is relatively small, therefore there is lower power and an increased risk type II error.
6. Homogeneity of Regression Slopes
7. Homoscedasticity of error and error variance

Levene's Test of Equality of Error Variances(a)

Dependent Variable: SBP

F	df1	df2	Sig.
.948	7	718	.468

Tests the null hypothesis that the error variance of the dependent variable is equal across groups.
a Design: Intercept+AGE+EDUCATIO+ETHNICIT+"ANY CARDIOVASCULAR DISEASE"+GENDER+CAPS_PTS+MDD_MINI+GENDER * CAPS_PTS+GENDER * MDD_MINI+CAPS_PTS * MDD_MINI+GENDER * CAPS_PTS * MDD_MINI

Levene's Test of Equality of Error Variances(a)

Dependent Variable: DBP

F	df1	df2	Sig.
1.393	7	718	.205

Tests the null hypothesis that the error variance of the dependent variable is equal across groups.
a Design: Intercept+AGE+ED2+ETH2+"ANY CARDIOVASCULAR DISEASE"+GENDER+CAPS_PTS+MDD_MINI+GENDER * CAPS_PTS+GENDER * MDD_MINI+CAPS_PTS * MDD_MINI+GENDER * CAPS_PTS * MDD_MINI

Levene's Test of Equality of Error Variances(a)

Dependent Variable: HGBA1C

F	df1	df2	Sig.
3.049	7	301	.004

Tests the null hypothesis that the error variance of the dependent variable is equal across groups.
a Design: Intercept+AGE+ED2+ETH2+"ANY CARDIOVASCULAR DISEASE"+GENDER+CAPS_PTS+MDD_MINI+GENDER * CAPS_PTS+GENDER * MDD_MINI+CAPS_PTS * MDD_MINI+GENDER * CAPS_PTS * MDD_MINI

According the Levene statistic, this assumption of homoscedasticity of error variance is met for SBP and DBP but not for HGBA1C.

Brown-Forsythe. Calculates the Brown-Forsythe statistic to test for the equality of group means.
Although, DBP tests indicate unequal group means, the group sizes are acceptable for interpretation of three-way interaction.

Robust Tests of Equality of Means by Gender

SBP

	Statistic(a)	df1	df2	Sig.
Brown-Forsythe	13.433	1	200.829	.000

a Asymptotically F distributed.

Robust Tests of Equality of Means by PTSD

SBP

	Statistic(a)	df1	df2	Sig.
Brown-Forsythe	.086	1	100.025	.770

a Asymptotically F distributed.

Robust Tests of Equality of Means by MDD

SBP

	Statistic(a)	df1	df2	Sig.
Brown-Forsythe	2.216	1	181.499	.138

a Asymptotically F distributed.

Robust Tests of Equality of Means by Gender

DBP

	Statistic(a)	df1	df2	Sig.
Brown-Forsythe	.021	1	196.622	.885

a Asymptotically F distributed.

Robust Tests of Equality of Means by PTSD

DBP

	Statistic(a)	df1	df2	Sig.
Brown-Forsythe	8.373	1	101.824	.005

a Asymptotically F distributed.

Robust Tests of Equality of Means by MDD

DBP

	Statistic(a)	df1	df2	Sig.
Brown-Forsythe	7.176	1	181.592	.008

a Asymptotically F distributed.

Robust Tests of Equality of Means by Gender

HGBA1C

	Statistic(a)	df1	df2	Sig.
Brown-Forsythe	1.317	1	62.989	.255

a Asymptotically F distributed.

Robust Tests of Equality of Means by PTSD

HGBA1C

	Statistic(a)	df1	df2	Sig.
Brown-Forsythe	.867	1	39.711	.357

a Asymptotically F distributed.

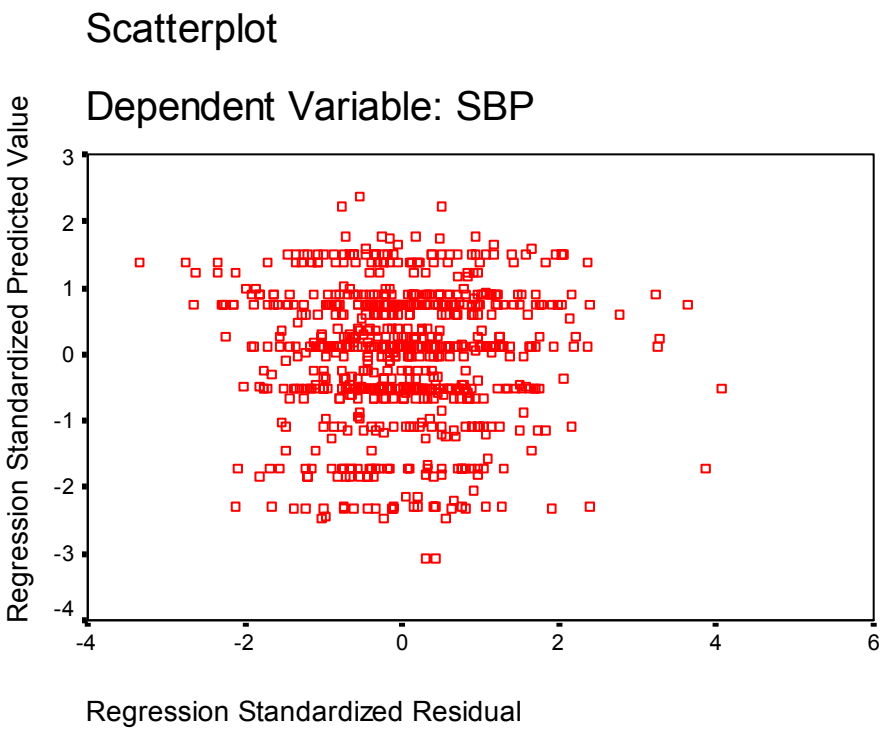
Robust Tests of Equality of Means by MDD

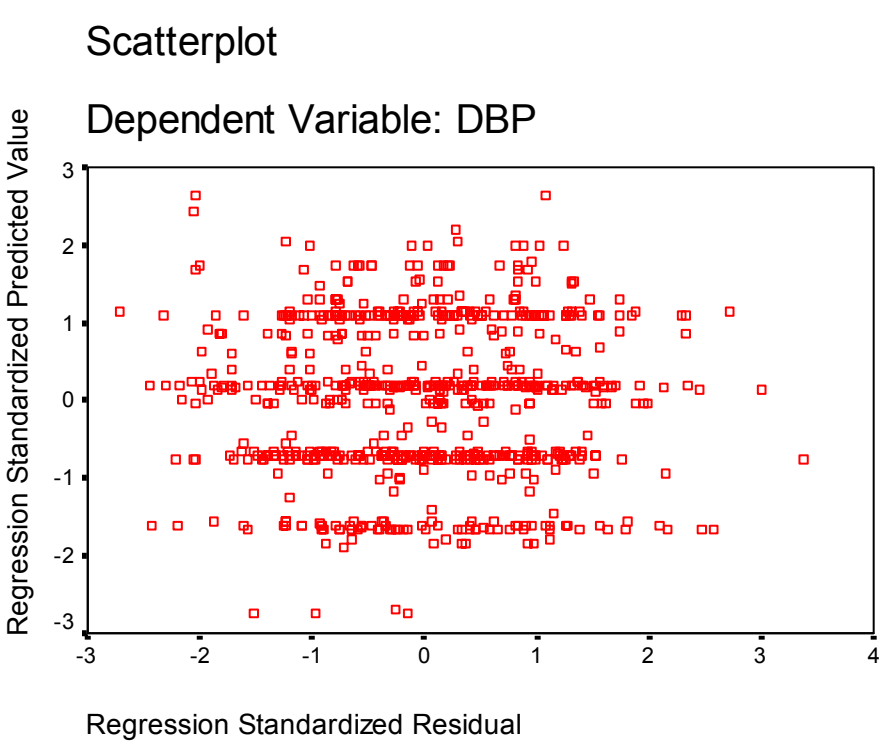
HGBA1C

	Statistic(a)	df1	df2	Sig.
Brown-Forsythe	.285	1	68.118	.595

a Asymptotically F distributed.

8a. Furthermore, in the standardized by predicted residuals scatterplots below one can see the desired random pattern, supporting the fulfillment of the assumption of randomly distributed residuals.


Scatterplot
Dependent Variable: SBP
Regression Standardized Predicted Value
Regression Standardized Residual
3
2
1
0
-1
-2
-3
-4
-4
-2
0
2
4
6


Scatterplot
Dependent Variable: DBP
Regression Standardized Predicted Value
Regression Standardized Residual
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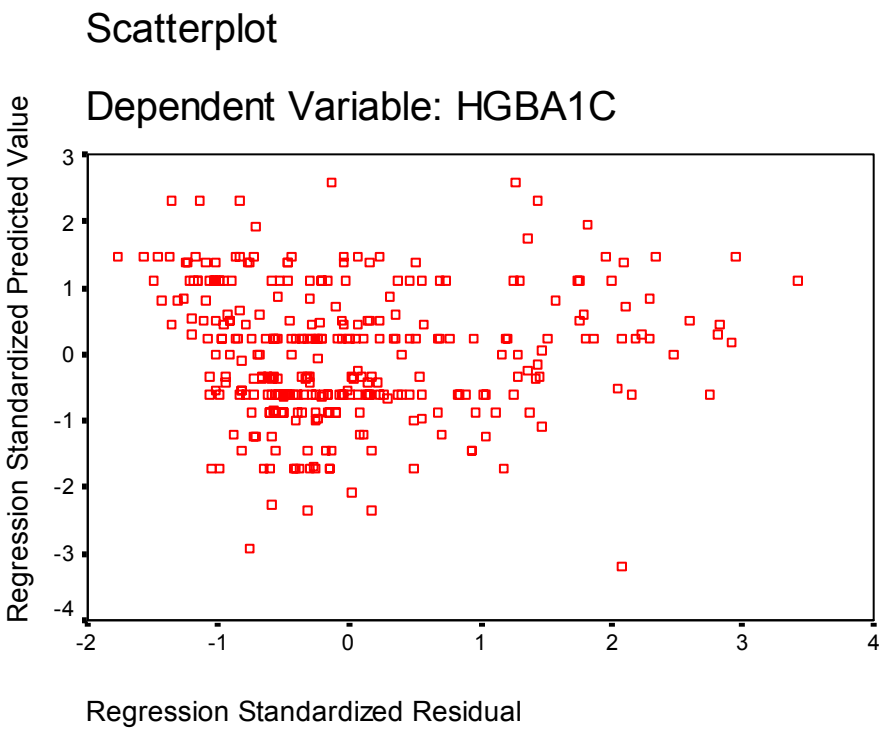

8b. Due to the fact that ANCOVA is robust in the face of violation of the assumption of homoscedasticity of error and error variance (www2.chass.ncsu), HGBA1C was not transformed.

9. Non-significant outliers

After examining the standardized residuals for IVs and DVs, and utilizing a +/- 3.0 cut off as an outlier indicator, it was determined that there were no outliers in the data set.

10. Homogeneity of Regression

	Unstandardized Coefficients		t	Sig.	Collinearity Statistics	
	B	Std. Error			Tolerance	VIF
(Constant)	112.868	3.428	32.925	.000		
AGE	.210	.048	4.378	.000	.800	1.250
EDUCATION	-.220	.857	-.257	.798	.939	1.065
ETHNICITY	5.700	1.045	5.453	.000	.904	1.106
collapsed cardiovascular disease	9.862	1.655	5.959	.000	.944	1.060
CAPS_PTS	2.644	1.880	1.407	.160	.772	1.295
MDD_MINI	-1.827	1.596	-1.145	.253	.755	1.325

a Dependent Variable: SBP

	Unstandardized Coefficients		t	Sig.	Collinearity Statistics	
	B	Std. Error			Tolerance	VIF
(Constant)	83.597	1.851	45.154	.000		
AGE	-.194	.026	-7.482	.000	.800	1.250
EDUCATIO	.151	.463	.326	.744	.939	1.065
ETHNICIT	2.965	.564	5.252	.000	.904	1.106
collapsed cardiovascular disease	4.252	.894	4.756	.000	.944	1.060
CAPS_PTS	2.081	1.015	2.050	.041	.772	1.295
MDD_MINI	.005	.862	.005	.996	.755	1.325

a Dependent Variable: DBP

	Unstandardized Coefficients		t	Sig.	Collinearity Statistics	
	B	Std. Error			Tolerance	VIF
(Constant)	1.802	.105	17.152	.000		
AGE	-.003	.001	-2.123	.035	.818	1.222
EDUCATIO	.017	.022	.779	.437	.951	1.052
ETHNICIT	.091	.026	3.499	.001	.888	1.126
collapsed cardiovascular disease	.227	.076	2.987	.003	.916	1.092
CAPS_PTS	-.051	.047	-1.073	.284	.752	1.329
MDD_MINI	-.008	.041	-.203	.840	.716	1.396

a Dependent Variable: LGHGBA1C

There is an acceptable level of intercorrelation among independent variables, all Tolerance values are above the suggested cut off value of .20 (www2.chass.ncsu.edu). In other words, the independent variables and covariate variables are not significantly intercorrelated. The assumption of homogeneity of regression is upheld.