

Post-traumatic Stress Disorder and Cardiovascular Disease

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Abstract: This review provides an up-to-date summary of the evidence from clinical and epidemiologic studies indicating that persons with post-traumatic stress disorder (PTSD) may have an increased risk of coronary heart disease and possibly thromboembolic stroke. Persons with PTSD, a common anxiety disorder in both veteran and nonveteran populations, have been reported to have an increased risk of hypertension, hyperlipidemia, obesity, and cardiovascular disease. Increased activity of the sympathoadrenal axis may contribute to cardiovascular disease through the effects of catecholamines on the heart, vasculature, and platelet function. Reported links between PTSD and hypertension and other cardiovascular risk factors may partly account for reported associations between PTSD and heart disease. The associations observed between PTSD and cardiovascular diseases have implications for cardiology practice and research.

Keywords: Anxiety disorders, coronary heart disease, hypertension, hyperlipidemia, post-traumatic stress disorder, stroke, veterans.

INTRODUCTION

An increasing body of evidence indicates that post-traumatic stress disorder, a common anxiety disorder in both veteran and nonveteran populations, is associated with major forms of cardiovascular disease including those attributed to atherosclerosis such as coronary heart disease and thromboembolic stroke. Persons with PTSD have also been reported to be more likely to have hypertension, hyperlipidemia, obesity, and cardiovascular disease [1]. These findings are important to the field of cardiology since coronary heart disease may develop over time as a result of hemodynamic factors (for example, elevated blood pressure with turbulence and shear stress within coronary arteries), hyperlipidemia, and events such as the rupture of atherosclerotic plaques and thrombus formation [2]. This review summarizes cardiovascular alterations linked to PTSD including results from epidemiologic and clinical studies and possible biological mechanisms.

BACKGROUND

Individuals may develop PTSD after being exposed to a traumatic event such as combat experiences, a motor vehicle crash, or sexual assault [3]. Symptoms of PTSD may include nightmares, intrusive thoughts, or other re-experiencing phenomena, the avoidance of situations that remind the person of the traumatic event, a feeling of numbness or being socially detached from family and friends, and hyper-arousal (for example, feeling angry, irritable and "on edge," or having difficulty concentrating). Hyper-arousal or hypervigilance includes a rapid and pronounced reaction to

stressors which may lead to a preoccupation with signs of threat and emotional distress. Persons with PTSD may have other challenges such as difficulties with employment, relationships, or other health conditions (for example, depression, alcohol abuse or drug dependency).

Effective psychological and medical treatments for PTSD include group or individual psychotherapy (for example, cognitive-behavioral therapy) and pharmacotherapy such as the use of selective serotonin reuptake inhibitors [4]. Cognitive-behavioral therapy helps patients to address their traumatic memories and distorted cognitions (for example, by providing education about the nature of PTSD and stress responses and helping the individual with the integration of the traumatic events).

CARDIOVASCULAR ALTERATIONS ASSOCIATED WITH PTSD

Cardiovascular alterations associated with autonomic arousal and cardiovascular health outcomes have long been reported to be associated with PTSD or wartime traumatic exposure [1, 5]. Persons suffering from PTSD and chronic PTSD have been shown to have increases in basal heart rate and blood pressure and increased heart rate and blood pressure in response to stimuli such as loud sounds and visual slides that remind them of the trauma [6-9]. In clinical studies involving small samples of veterans, plasma norepinephrine and 24-hour urine norepinephrine levels have been reported to be elevated among veterans with PTSD as compared to those without PTSD [10]. The increases in plasma norepinephrine are more pronounced when PTSD patients are exposed to trauma-related stimuli such as loud tones [11]. Stress and anxiety have been associated with increased plasma and urinary norepinephrine, epinephrine, and their metabolites, which are peripheral measures of the noradrenergic system, in healthy adults [8, 12].

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The effects of traumatic exposures or chronic stress on the hypothalamic pituitary adrenal axis (HPA) and the autonomic nervous system have been examined in clinical studies and in animal models. The results of these studies indicate that PTSD can result in important neurobiologic and psychophysiological changes [1]. Physiological dysregulation of the HPA axis and altered autonomic function may contribute to increases in cardiovascular risk factors reported in persons with PTSD. Increased activity of the sympathoadrenal axis might contribute to cardiovascular disease through the effects of catecholamines on the heart, vasculature, and platelet function [8]. Platelet function is altered by elevated levels of circulating catecholamines. Catecholamines act on alpha-2a receptors on platelet membranes leading to increased platelet aggregation and other changes in platelet function [8, 13]. Catecholamine-induced alterations of platelet activity have been hypothesized to be a link between chronic stress, increased sympathoadrenal activation, and cardiovascular disease [13, 14].

Studies have shown that patients with PTSD have higher heart rates at rest and reduced heart rate variability which is consistent with increased sympathetic activity [8, 15]. The finding that baseline heart rate is higher among veterans suffering from PTSD than among those without PTSD is consistent with chronic hyperstimulation of the autonomic nervous system. Alternatively, the finding could be an artifact due to the research participants being anxious about the impending psychophysiological assessment [16]. The individuals who participated in the studies may have experienced anxiety because they were anticipating exposure to stimuli that would remind them of traumatic events [8]. McFall *et al.* [17] examined basal heart rates, systolic and diastolic blood pressures among veterans with and without PTSD over an extended period and did not find any significant differences between the two groups. However, in a separate study by Gerardi *et al.* [6] which included 32 Vietnam veterans with combat-related PTSD and 26 Vietnam era veterans with no combat exposures, those with PTSD had significantly higher heart rate, systolic and diastolic blood pressure. Buckley and Kaloupek [18] completed a meta-analysis of reported studies of basal heart rate and blood pressure among persons with and without PTSD. A total of 34 studies were included with a total sample size across studies of 2,670 subjects. Their results suggested that, on average, persons with PTSD have an elevated basal heart rate as compared with persons without PTSD or those who were not exposed to trauma [18]. The average difference in resting heart rate between persons with or without PTSD was 5 beats per minute. Their meta-analysis also suggested that PTSD is associated with blood pressure elevations [18].

STUDIES OF PTSD AND HYPERTENSION

PTSD was associated with an increased risk of hypertension in the National Comorbidity Survey and in an epidemiologic study of Vietnam veterans from Australia [19, 20]. Since elevated diastolic and systolic blood pressure are established risk factors for cardiovascular disease, the apparent link between PTSD and hypertension may partly account for reported associations between PTSD and heart disease [1]. Cohen *et al.* [15] examined associations between PTSD and hypertension and other cardiovascular risk factors using national data from veterans of Operation Enduring Freedom

and Operation Iraqi Freedom (OEF/OIF) who sought care at VA health care facilities. The majority of the PTSD patients in their cross-sectional study had comorbid mental health diagnoses including depression (53%), other anxiety disorder (29%), substance abuse disorder (10%) and other psychiatric diagnoses (33%). Veterans with mental health diagnoses had a significantly higher frequency of hypertension and other cardiovascular disease risk factors [15]. For example, among 65,603 male OEF/OIF veterans who had PTSD with or without other mental health diagnoses, the adjusted odds ratio for the association between PTSD and hypertension was 2.88 (95% confidence interval 2.79-2.97) after controlling for age, race (white, black, Hispanic, or other), component type, rank, branch of service, and multiple deployments [15]. Among 6,964 female OEF/OIF veterans who had PTSD with or without other mental health diagnoses, the adjusted odds ratio for the association between PTSD and hypertension was 2.88 (95% confidence interval 2.79-2.97) after controlling for age, race/ethnicity (white, black, Hispanic, or other), component type, rank, branch of service, and multiple deployments [15].

PTSD AND HYPERLIPIDEMIA

There is increasing evidence from clinical studies that PTSD may have effects on lipid metabolism [21, 22]. Karlovic *et al.* [23] examined total cholesterol, LDL and HDL cholesterol, and triglycerides in Croatian war veterans with PTSD and patients with major depression. Those with PTSD had higher levels of cholesterol and LDL cholesterol, and triglycerides, on average, and lower HDL cholesterol levels as compared with the patients with major depression. In the study by Cohen *et al.* [15] of associations between PTSD and cardiovascular risk factors among OEF/OIF veterans who sought care at VA health care facilities, veterans with mental health diagnoses had a significantly higher frequency of dyslipidemia [15]. For example, among 65,603 male OEF/OIF veterans who had PTSD with or without other mental health diagnoses, the adjusted odds ratio for the association between PTSD and dyslipidemia was 2.70 (95% confidence interval 2.63-2.78) after controlling for age, race/ethnicity (white, black, Hispanic, or other), component type, rank, branch of service, and multiple deployments [15]. Among 6,964 female OEF/OIF veterans who had PTSD with or without other mental health diagnoses, the adjusted odds ratio for the association between PTSD and dyslipidemia was 2.68 (95% confidence interval 2.44-2.95) after controlling for age, race/ethnicity (white, black, Hispanic, or other), component type, rank, branch of service, and multiple deployments [15]. Elevated levels of total cholesterol and triglycerides have also been observed among Brazilian police officers with PTSD [24].

STUDIES OF PTSD AND CORONARY HEART DISEASE

Positive associations between PTSD and cardiovascular disease (particularly coronary heart disease) have been observed in a growing number of studies of veterans and civilians who were exposed to combat or other traumatic experiences, as summarized in Table 1. Some of these studies were retrospective, relied upon self-reported information about cardiovascular disease, or had other design limitations [2, 25-31, 35, 36]. Nevertheless, an increasing number of

Table 1. Studies of PTSD and Cardiovascular Disease among Veterans and Civilian Populations Exposed to Traumatic Experiences

Study	Sample	Study Design	Results	Limitations	Other Information
Falger <i>et al.</i> (1992)	Male WW II Dutch Resistance veterans (n=147), aged 60-65 years, and age and sex-matched controls with recent hospitalization for MI (n=65) or surgery (n=79).	Clinical interviews of surviving veterans conducted more than 4 decades after the war had ended. PTSD was assessed using structured interviews based on DSM-III.	The Resistance veterans, especially those with PTSD, scored higher than the matched controls on angina pectoris, type A behavior, life stressors, and vital exhaustion. About 10% of the veterans reported having had an MI in the past 15 years. About 56% percent of the veterans were currently suffering from PTSD.	The use of controls with recent MI may have partly obscured associations with cardiovascular risk factors. History of MI was based on self-reported information.	Half of these Resistance veterans had been arrested and incarcerated in Nazi prisons and forced labor and death camps. All were exposed to extraordinary war-time trauma.
Boscarino (1997)	National sample of male Vietnam veterans (n=1,399) who served in the U.S. Army.	In-person interviews conducted about 20 years post combat exposure. Circulatory diseases were assessed retrospectively.	After controlling for age, race, region of birth, enlistment status, volunteer status, Army marital status, Army medical profile, smoking history, substance abuse, education, income, and other factors, lifetime PTSD status was associated with reported circulatory diseases (OR = 1.62, p = .007) and other illnesses after military service. About 63% (n=332) had a lifetime history of PTSD.	Self-reported information about disease history was used in the analysis. The response rate was 65%.	
Boscarino and Chang (1999)	National sample of male U.S. Army veterans who served in theatre during the Vietnam war (n=2,490) or during the same era (n=1,972).	Medical examinations (conducted about 17 years after combat exposures for Vietnam theatre veterans). Psychiatric evaluations included the Diagnostic Interview Schedule based on DSM-III.	After controlling for age, place of service, illicit drug use, medication use, race, body mass index, alcohol use, cigarette smoking, and education, PTSD was associated with ECG findings including atrioventricular conduction defects (OR =2.81, 95% CI 1.03-7.66, p < 0.05) and infarctions (OR=4.44, 95% CI 1.20-16.43, p < 0.05).	The overall participation rate was 60%. Soldiers who served in theatre may have had greater exposure to toxic chemicals.	The average age of first onset of PTSD was 21 years.
Boscarino (2006)	National sample of male U.S. Army veterans (n=15,288) who served during the Vietnam War era.	Cohort mortality study with 16 years of follow-up following completion of a telephone survey (or about 30 years after their military service).	After controlling for race, Army volunteer status, entry age, and discharge status, Army illicit drug abuse, age, and other factors, PTSD among Vietnam theatre veterans was associated with cardiovascular mortality (hazards ratio = 1.7, p = 0.034), all-cause mortality, cancer, and external causes of death.	Adjustment was made for pack-years of cigarette smoking only when looking at cancer mortality.	
Boscarino (2008)	National sample of male Vietnam veterans (n=4,328) who served in the U.S. Army. The men were < 65 years of age at follow-up.	Cohort mortality study	PTSD was assessed using two measures include one based on DSM-III. Having more PTSD symptoms was positively associated with early-age heart disease mortality.		
Dobie <i>et al.</i> (2004)	Female veterans (n=1,259) who received care at the VA Puget Sound Health Care System between October 1996 and January 1998	Cross-sectional postal survey	Of the eligible women who completed the survey, 21% screened positive for current PTSD (PTSD Checklist-Civilian Version score \geq 50). A statistically nonsignificant association was observed with myocardial infarction or coronary artery disease (OR = 1.8, 95% CI 0.9-3.6).	Study limitations include the cross-sectional design and the reliance on self-reported information about medical conditions.	

Table 1. contd....

Study	Sample	Study Design	Results	Limitations	Other Information
Kang <i>et al.</i> (2006)	Former WW II prisoners of war (n=19,442) and non POW controls (n=9,728)	Review of healthcare utilization data for 10 years (1991-2000) from VA and non-VA healthcare providers.	After adjustment for age and race, former POWs with PTSD had statistically significant increased risks of CVD, including ischemic heart disease and hypertension, as compared with both non-POWs and POWs without PTSD. The magnitude of the increased risk of ischemic heart disease was modest.	POWs might be more likely than the study controls to be in VA medical treatment files.	
Schnurr <i>et al.</i> (2000)	Male combat veterans of WW II and the Koren conflict (n=605). The average age at study entry was 43.9 years. The majority of the men (98%) were white.	Follow-up study. Medical examinations were performed periodically beginning in 1960. PTSD symptoms were assessed in 1990.	PTSD was assessed using the Mississippi Scale for Combat-Related PTSD. PTSD symptoms were positively associated with the onset of arterial disorders (hazard ratio =1.3, 95% CI 1.2-1.5) after controlling for age, smoking, alcohol consumption, and body mass index. The hazard ratios for hypertensive and ischemic cardiovascular disease were not significantly different than one.	PTSD was not measured at the beginning of the study but rather in 1990 after many of the outcomes had already occurred.	
Kubzansky <i>et al.</i> (2007)	Community dwelling men (n=1,002) from the greater Boston, Massachusetts area who were aged 21 to 80 years in 1961. Over 90% of the men are veterans and most were white. Men with preexisting coronary heart disease or diabetes	Prospective cohort study.	PTSD was assessed using the Mississippi Scale for Combat-Related PTSD. For each standard deviation increase in PTSD symptom level, the age-adjusted relative risk for nonfatal and fatal myocardial infarction combined was 1.3 (95% CI 1.05-1.5).		The data were from the VA Normative Aging Study.
Kubzansky <i>et al.</i> (2009)	were excluded. Community dwelling women who participated in the Baltimore cohort of the Epidemiologic Catchment Area Study (n=1,059)	Prospective cohort study that assessed incident coronary heart disease over a 14-year period	Past year trauma and associated PTSD symptoms were assessed using the NIMH Diagnostic Interview Schedule. Women with 5 or more symptoms of PTSD were over three times more likely to develop coronary heart disease than those with no symptoms (age-adjusted OR = 3.2, 95% CI 1.3-8.0). The association persisted after further adjustment was made for coronary risk factors and depression or trait anxiety.		
Dirkzwager <i>et al.</i> (2007)	Sample of adult survivors (n=896) of a fire disaster in Enschede, Netherlands that killed 23 persons and destroyed or damaged almost 1,500 houses.	Longitudinal design. Electronic medical records from family practitioners (1 year and 4 years post disaster) were used. Survey data were also collected at 3 weeks and 18 months post disaster to assess PTSD and physical health.	The Self-Rating Scale for PTSD was used to assess the condition. After controlling for demographic factors, smoking, and predisaster physical health, PTSD was positively associated with risk of new vascular problems (OR = 1.9, 95% CI 1.04-3.6).		

Table 1. contd....

Study	Sample	Study Design	Results	Limitations	Other Information
Spitzer <i>et al.</i> (2009)	Community dwelling adults in Germany (n=3,171)	Cross-sectional survey	PTSD was assessed using the Structured Clinical Interview for DSM-IV. After controlling for demographic factors, smoking, body mass index, blood pressure, depression, and alcohol use disorders, PTSD was positively associated with angina (OR = 2.4, 95% CI 1.3-4.5), heart failure (OR = 3.4, 95% CI 1.9-6.0), and peripheral arterial disease.	Study limitations include the cross-sectional design and the reliance on self-reported information about medical conditions.	
Johnson <i>et al.</i> (2010)	Male residents of four U.S. communities (n=5,347)	Population-based study of the prevalence of subclinical atherosclerosis (carotid intima thickness and carotid plaque) measured noninvasively at two study visits (1987-1989 and 1990-1992).	Compared to non-combat veterans, non-veterans and combat veterans had higher age-adjusted mean carotid intima thickness. Differences remained for combat veterans after adjustment for race, father's education, and age at service entry but not years of service. No differences in carotid plaque were noted.	PTSD was not assessed in this study.	The data were from the Atherosclerosis Risk in Communities (ARIC) Study.

studies have prospectively examined PTSD as a predictor of physician-diagnosed cardiovascular disease [32-34]. Taken overall, these results from observational research provide considerable evidence that persons with PTSD have an increased risk of coronary heart disease morbidity and mortality.

PTSD AND CEREBRAL VASCULAR DISEASE

There is some evidence from epidemiologic studies of an association between PTSD and cerebrovascular disease. Brass and Page [37] found that former World War II prisoners of war (POWs) had a statistically nonsignificant increased risk of stroke. Among the 475 former POWs, 12.7% (20 of 158) of those with PTSD had strokes, compared with 7.6% (24 of 317) without PTSD (relative risk = 1.7, 95% confidence interval 0.95 to 2.9). In a cross-sectional survey of female veteran's who received care at the VA Puget Sound Health Care System, Dobie *et al.* [29] found an association between PTSD and self-reported history of stroke. About 5% (13 of 256) of the female veterans with PTSD reported a history of stroke as compared with 3% (28 of 905) of those without PTSD (age-adjusted odds ratio = 2.9, 95% confidence interval 1.4-6.0) [29]. A study of trauma and PTSD among 3,171 male and female adults living in the general population of a German community found that persons with a history of trauma had a higher odds of stroke (odds ratio = 1.2, 95% confidence interval 1.0-1.5), angina pectoris, and heart failure after adjustment for demographic factors, blood pressure, smoking, body mass index, depression, and alcohol-related disorders [35].

DISCUSSION

This review of the published literature highlights evidence from epidemiologic and clinical studies that persons

with PTSD are at increased risk of cardiovascular disease including coronary heart disease and possibly stroke. These findings have several implications for cardiologists and cardiovascular researchers. Anxiety disorders such as PTSD are common in the general population [4]. In addition, combat veterans have an increased risk of PTSD [3, 4]. Clinicians who see patients in primary care practice or in cardiology clinics should be aware that longstanding PTSD may have deleterious effects on the cardiovascular system including increased risk of coronary heart disease and hypertension. Cardiologists routinely talk with patients about alcohol drinking and cigarette smoking, both of which may be more frequent among persons suffering from PTSD. Effective evidence-based treatments are available for persons with PTSD including those who suffer from dual diagnoses such as PTSD and alcohol dependence [4].

The biological mechanisms that account for the observed associations between PTSD and cardiovascular disease may relate to the effects of traumatic exposures and chronic stress on the HPA axis and the autonomic nervous system [8]. Dysregulation of the HPA axis and chronic over-stimulation of the autonomic nervous system may contribute to the increases in blood pressure and lipid levels that have been observed in PTSD patients. Catecholamine-induced alterations of platelet activity may also contribute to the apparent link between PTSD and cardiovascular disease. Changes in immune function seen in some PTSD patients may also have a role including circulating levels of interleukin-6 (IL-6), IL-1, tumor necrosis factor, and C-reactive protein [38]. Inflammatory mediators such as IL-6, tumor necrosis factor, and C-reactive protein have been reported to stimulate atherosclerosis [38]. Interactions among the immune and neuroendocrine systems may partly account for associations between PTSD and chronic disease outcomes.

Previous authors have proposed general models of possible mechanisms underlying the relationship between PTSD and physical health including cardiovascular disease [31]. The models take into account biological function (e.g., HPA axis, heightened noradrenergic function, immune function), psychological comorbidities such as depression, health risk behaviors, symptom reports and functional status, and disease morbidity and mortality. A similar model of PTSD outcomes proposed by Boscarino accounts for different pathways leading to changes in health status; the influences of heredity, shared environment, history of trauma, behavior and perceptions, biological changes, and stressful life event exposures are taken into account in the model [5].

In conclusion, persons with PTSD have been reported to have an increased risk of hypertension, hyperlipidemia, obesity, and cardiovascular disease. Such persons have been observed to have an increased risk of coronary heart disease and possibly thromboembolic stroke. The reported link between PTSD and hypertension and other cardiovascular risk factors may partly account for the observed associations between PTSD and heart disease.

ABBREVIATIONS

- DSM = Diagnostic and Statistical Manual of Mental Disorders
- LDL = Low Density Lipoprotein
- HPA = Hypothalamic Pituitary Adrenal Axis
- IL-6 = Interleukin-6
- LDL = Low Density Lipoprotein
- OR = Odds Ratio
- OEF/OIF = Operation Enduring Freedom/Operation Iraqi Freedom
- POWs = Prisoners of War
- PTSD = Post-traumatic Stress Disorder
- VA = Department of Veterans Affairs

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