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REVIEW

# Metabolic, autonomic and immune markers for cardiovascular disease in posttraumatic stress disorder

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## Abstract

Posttraumatic stress disorder (PTSD) has been associated with significantly greater incidence of heart disease. Numerous studies have indicated that health problems for individuals with PTSD occur earlier in life than in the general population. Multiple mechanistic pathways have been suggested to explain cardiovascular disese (CVD) risk in PTSD, including neurochemical, behavioral, and immunological changes. The present paper is a review of recent research that examines cardiovascular and immune risk profiles of individuals with PTSD. First, we address the relatively new evidence that the constellation of risk factors commonly experienced in PTSD fits the profile of metabolic syndrome. Next we examine the findings concerning hypertension/blood pressure in particular. The literature on sympathetic and parasympathetic responsivity in PTSD is reviewed. Last, we discuss recent findings concerning immune functioning in PTSD that may have a bearing on the high rates of CVD and other illnesses. Our primary goal is to synthesize the existing literature by examining factors that overlap mechanistically to increase the risk of developing CVD in PTSD.



**Key words:** Cardiovascular; Posttraumatic stress; Metabolic syndrome; Autonomic; Immune

**Core tip:** Research has documented a significantly increased cardiovascular disese (CVD) risk in posttrauamtic stress disorder. The present paper is a review of recent research that examines cardiovascular and immune risk profiles of individuals with posttraumatic stress disorder (PTSD). First, we address the relatively new evidence that the risk factors commonly experienced in PTSD fit the profile of metabolic syndrome. Next we examine the findings concerning hypertension/blood pressure in particular. The literature on sympathetic and parasympathetic responsivity in PTSD is reviewed. Last, we discuss recent findings concerning immune functioning in PTSD that may have a bearing on the high rates of CVD and other illnesses.

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## METABOLIC, AUTONOMIC AND IMMUNE MARKERS FOR CARDIOVASCULAR DISEASE IN POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD), a disorder of

extreme stress/anxiety responses to a psychologically traumatic experience, has been associated with significantly greater incidence of heart disease[1-4]. This effect has been demonstrated among combat Veterans[1,5,6], firefighters[7], and civilians[2]. The characteristics associated with PTSD include re-experiencing symptoms such as intrusive thoughts and nightmares, avoidance behaviors, and arousal symptoms such as anger and hyper-vigilance. Lifetime prevalence of PTSD is about 8%, with higher rates among trauma victims and women. Numerous studies have indicated that health problems for individuals with PTSD occur earlier in life than in the general population[6,8,9]. Further, there is limited evidence that the relationship of PTSD to physical health is independent of age, depression, or other comorbid anxiety disorders[10]. Adult health problems may also be related to childhood trauma. In two large epidemiological studies, relationships were observed between childhood trauma and cardiovascular disease (CVD) evidenced as adults[11,12], with up to 3 times greater risk of CVD. Multiple mechanistic pathways have been suggested to explain CVD risk in PTSD, including neurochemical[13,14], metabolic[15-17], and immunological changes[18-24].

The present paper is a review of recent research that examines cardiovascular and immune risk profiles of individuals with PTSD. First, we address the relatively new evidence that the constellation of risk factors commonly experienced in PTSD fits the profile of metabolic syndrome[25-28]. Next we examine the findings concerning hypertension/blood pressure (BP) in particular[29-31]. The literature on sympathetic and parasympathetic responsivity in PTSD is reviewed. Last, we discuss recent findings concerning immune functioning in PTSD that may have a bearing on the high rates of CVD and other illnesses. Our primary goal is to synthesize the existing literature by examining factors that overlap mechanistically to increase the risk of developing CVD in PTSD.

## METABOLIC SYNDROME AND PTSD

Most studies that have examined CVD risk factors in PTSD have not examined more than 1 or 2 risk variables, such as obesity or lipids. A study of police officers[27] reinforced the importance of studying multiple CVD risk factors-this study revealed that those with the highest levels of PTSD symptoms (severe category) were 3 times more likely to exhibit 3 or more metabolic syndrome criteria [waist circumference, BP, high-density lipoprotein cholesterol, triglycerides, and glucose levels] than officers in the lowest PTSD symptom category (subclinical)].

The Violanti *et al*[27] findings are consistent with a recent study indicating Gulf War Veterans with higher severity of PTSD (measured on a continuum using the Clinician Administered Posttraumatic Stress Scale) were more likely to meet 3 or more of the CVD risk criteria for defining metabolic syndrome[26]. Further analyses of these data by Heppner *et al*[32] indicated that antipsychotic medication use did not explain the increased risk for metabolic syndrome in severe PTSD. Similarly, among 245 low-socioeconomic-status subjects from general medical clinics in an inner-city hospital, significantly higher rates of metabolic syndrome were identified among patients with current PTSD, independent of antipsychotic medication use[28].

Subsequent studies added to the literature providing evidence for the association of PTSD with metabolic syndrome. In one study, the prevalence of metabolic syndrome and its components were compared between patients with chronic war-related PTSD in Bosnia and Herzegovina *vs* patients without PTSD who underwent treatment for somatic problems[33]. A significantly higher rate of metabolic syndrome was evident in patients with PTSD relative to the patients without PTSD, with hyperglycemia and abdominal obesity being more prevalent in patients with PTSD[33]. Additionally, in a large retrospective database study of 207954 veterans[25], metabolic syndrome was significantly higher in PTSD as compared to non-PTSD individuals. The results suggest PTSD accounted for 41% of the risk for metabolic syndrome[25].

## BLOOD PRESSURE AND PTSD

Early studies revealed elevated BP among combat veterans with PTSD[34-36]. However, recent studies and meta-analytic reviews have reflected mixed findings[29,30,37,38], raising doubt about the extent to which elevations in BP are consistently related to PTSD and might be a factor in CVD risk. Results of the meta-analyses by Buckley *et al*[29] and Pole[30] suggested elevations in both resting systolic blood pressure (SBP) and resting diastolic blood pressure (DBP) for individuals with PTSD, when examining unweighted effect sizes. However, examination of weighted effect sizes produced much more circumscribed findings for BP in PTSD; the weighted effect sizes appeared to be conservative adjustments, as the mean effect sizes were reduced considerably relative to the unweighted means. In these meta-analyses, most studies of resting BP were fairly homogenous in terms of sample size, with only one study having a sample size greater than 115 ($n$ = 991 for Keane *et al*[39]). This one very large study, which is weighted heavily for the meta-analyses, resulted in null effects for resting SBP and DBP. A potential methodological limitation in interpreting this large study is that only a single Dinamap reading was utilized for assessment of baseline BP (as opposed to multiple averaged readings and/or the gold standard sphygmomanometer-based casual BP assessments). In addition, the Keane *et al*[39] had a mean age of approximately 44 years-as most participants appeared to have a BP that was well within the normal range, it is possible that the BP assessment may have been affected by a limited range or floor effect.

Research conducted in our laboratory has supported relationships between PTSD and elevated BP. In a recently completed project, several CVD risk factors were assessed among relatively young women with PTSD (mean ± SD, age = 30 ± 8 years), and compared with

two demographically similar groups with depression and no mental illness[40]. Analyses revealed that SBP levels in the PTSD group were higher than in the no mental illness ($P < 0.001$) and depression ($P < 0.05$) groups. The DBP levels in the PTSD group were greater than the no mental illness group ($P < 0.05$), but were not significantly different than the depression group. This project utilized three standard sphygmomanometer-determined readings to calculate resting BP. The absolute levels of BP were generally in the normal range.

In another study we analyzed data from the United States National Comorbidity Survey to examine whether PTSD is significantly associated with hypertension, and whether this association is independent of depression[31]. The study sample ranged in age from 15-54 years and was designed to be representative of the United States population. A total of 4008 respondents were identified who fit into one of four diagnostic groups: (1) history of PTSD diagnosis (lifetime) and no history of major depression ($n = 219$); (2) a lifetime history of both PTSD and major depression ($n = 210$); (3) a history of major depression (lifetime) and no PTSD ($n = 785$); and (4) no history of mental illness ($n = 2794$). The sample was 45% male. In this relatively young sample, the rate of hypertension was modest (7.8% overall). The group with a history of PTSD and no history of depression had the highest rate of hypertension (14.5%), and this rate was significantly higher than the rate in the no mental illness group (6.5%) and the group with history of depression and no PTSD (9.7%). These differences in hypertension rates were significant when controlling for the relationship between age and hypertension rate. The observation that the rate of hypertension between the PTSD no depression group and the PTSD plus depression group (13.9%) was not significantly different, suggested that the relationship of PTSD to high BP is independent of comorbid depression.

## STRESS REACTIVITY AND PTSD

Exaggerated cardiovascular reactivity (CVR) in response to psychological stress is associated with markers for CVD such as hypertension, endothelial dysfunction, autonomic nervous system (ANS) dysregulation, and hypothalamic-pituitary-adrenal axis (HPA) alterations[41-45]. Evidence of physiological reactivity in individuals with PTSD, during trauma reminders, points to CVR as one of the intervening variables between PTSD and the development of CVD[46,47].

The literature provides evidence for the role of the sympathetic and parasympathetic nervous system dysregulation in PTSD. The roles of PTSD-related hyperarousal and re-experiencing symptoms in producing exaggerated CVR have been a central focus of PTSD/CVD research[46]. Tucker *et al*[48] found greater autonomic reactivity in participants with PTSD than gender-matched trauma exposed controls. In this study[48], SBP after trauma script delivery was the best measure for classification of patients with PTSD (75% sensitivity) and trauma exposed controls (100% specificity).

Chronic autonomic activation leads to dysregulation of the HPA axis in PTSD, which may begin a cascade of physiological responses increasing allostatic load and promoting CVD[42,49,50]. In response to acute stress, glucocorticoids (GC), primarily cortisol, are involved in both mobilization of defensive resources and in helping the body to return to homeostasis[50]. Additionally, lowered cortisol levels shortly after traumatic events have been linked to increased risk of developing PTSD following a traumatic event[51-54]. A recent meta-analysis[53] of HPA function in PTSD identified significant differences in both basal cortisol and GC receptor sensitivity among individuals with PTSD relative to both trauma-exposed (TC) and non-TC controls (NTC). Specifically, individuals with PTSD showed reduced morning cortisol levels (compared with both TC and NTC), and enhanced GC sensitivity (compared to NTC) as measured by cortisol levels following the dexamethasone suppression test.

Implication of reduced parasympathetic control in individuals with PTSD is evidenced by the negative association between baroreceptor sensitivity and basal HR[47,55]. Findings of lower HR variability among PTSD groups may provide evidence of autonomic dysregulation due to increased sympathetic hyperactivation and reduced parasympathetic activity[55-58].

## IMMUNE FUNCTIONING IN PTSD

Chronic alterations of neuroendocrine and inflammatory processes have been posited as one mechanism through which risk for CVD is elevated in PTSD. In addition to sympathetic nervous system (SNS) components such as epinephrine and norepinephrine, two interrelated stress-response systems-the HPA axis and the immune system-have been studied in relationship to traumatic stress and posttraumatic outcomes. Both the SNS and HPA axis modulate immune function through several mechanisms, including stimulating proliferation of T-cells and inducing the release of signaling proteins known as Interleukins (IL) or cytokines[59]. Elevations of pro-inflammatory cytokines, such as IL-6, tumor necrosis factor-α, IL-1β, and IL-2, as well as downstream acute-phase hepatic proteins such as C-reactive protein (CRP) and fibrinogen, are known to be involved in promoting inflammation, and chronic elevations have been linked to cardiovascular disease risk and other chronic diseases[42,60,61]. A 2012 review of the literature[62] indicated that, despite methodological and measurement differences, most studies reported positive associations between pro-inflammatory cytokine concentrations and PTSD symptomatology. Since this review, several studies have provided additional evidence of increased pro-inflammatory cytokines in PTSD[63-66], although others have reported either no significant relationship[21,67] or a negative association[68,69] with PTSD symptoms. The findings related to CRP have been more equivocal, with

recent results ranging from decreased CRP[70] or no difference[71] to increased CRP in PTSD as compared with healthy controls[38,72].

In addition to measuring basal cytokine levels, several recent studies have tested stimulated cytokine levels in PTSD either *in vivo,* through hydrocortisone administration[18], or through *in vitro* cytokine production by immune cells, whether spontaneous, stimulated using a chemical such as phytohemagglutinin A or lipopolysaccharide, or suppressed using an exogenous GC such as dexamethasone[20,21,68,73]. Promising new areas of research have also begun to identify genetic and epigenetic changes in DNA methylation[73] and inflammatory pathways (*e.g.*, nuclear factor-κB[73,74]) that may be involved in the risk of PTSD and inflammation-related chronic disease.

Although PTSD seems to be linked to a variety of inflammatory biomarkers, limited preliminary evidence suggests that successful psychological and/or pharmacological treatment of PTSD may result in an abatement of systemic inflammatory responses. Tucker *et al*[75] first described significant decreases in circulating pro-inflammatory IL-1β and increases in anti-inflammatory soluble IL-2 receptors after treatment with one of two SSRI medications or placebo. However, another SSRI treatment study did not find any significant post-treatment changes in cerebrospinal fluid levels of IL-6[76], despite achieving complete remission of PTSD symptoms. A cross-sectional study comparing women in recovery from PTSD to NTC and participants with current PTSD found elevated circulating IL-6 and CRP in current PTSD but identical levels for the recovery and NTC groups[66]. A longitudinal case-study of one year of psychotherapy also found decreases in excreted IL-6 over time, which seemed to correspond with gradual symptom improvements[77]. Additionally, following a four-week stress management intervention for survivors of childhood sexual abuse, Wilson[78] found a modest but statistically significant increase in salivary secretory Immunoglobulin A, a secreted biomarker involved in viral and bacterial immunity[79].

## CONCLUSION

Considering the evidence reviewed in the present article, there appears to be considerable metabolic, autonomic and immune involvement in the elevated CVD risk among individuals with PTSD. There is a high level of agreement among studies that PTSD is positively associated with metabolic syndrome. Stress-related cellular dysfunction may contribute to metabolic syndrome in PTSD[80]. Dysfunction related to stress-induced dysregulation of telomere/telomerase maintenance, mitochondria, and endoplasmic reticular stress may result in metabolic syndrome[81-83]. Conceptualizing the CVD risk factors from the standpoint of metabolic syndrome allows one to fully appreciate the clinical significance of multiple interacting physiological risks in PTSD[26,28]. In short, the impact of multiple risk factors is synergistic, resulting in a magnitude of risk greater than the sum of the individual risk factors.

Although findings concerning BP in PTSD are mixed, the overall direction of this relationship appears to be positive, with greater rates of hypertension in PTSD. Methodological factors in the study of resting BP in PTSD may have masked the extent of this problem. Additional studies across the range of BP levels (*i.e.*, normal, elevated, and high) may provide more insight into the extent of BP differences and prevalence of elevated BP in PTSD, as well as the mechanisms by which BP elevation occurs in early age.

The available evidence also suggests a positive relationship between PTSD and autonomic reactivity. Although further research is needed to fully elucidate the role of ANS stress reactivity in PTSD, recent advances suggest that sympathetic and parasympathetic dysfunction in PTSD may be evident through some reactivity paradigms[56,57]. The burgeoning literature on immune functioning in PTSD is rapidly providing insights into additional mechanisms (*e.g.*, proinflammatory cytokines and other immune biomarkers) that assist in understanding the relationships of PTSD to illnesses such as CVD[21,62,66]. In all, the available studies indicate a significant relationship between PTSD and immune dysfunction. With regard to future directions in the area of PTSD and CVD risks, further research on the role of ANS reactivity in PTSD-related CVD risk, as well as approaches to prevention and management of CVD risk factors in this population, would represent advanced directions in the field.

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