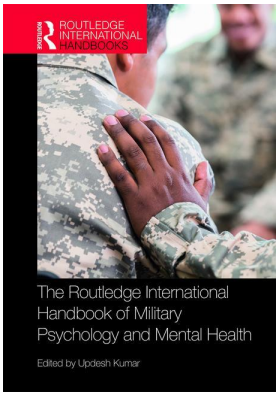

The Routledge International Handbook of Military Psychology and Mental Health

Updesh Kumar

Neuroendocrine and immune biomarkers of posttraumatic stress disorder in combat veterans

Publication details
https://test.routledgehandbooks.com/doi/10.4324/9780429281266-32
Nela Pivac, Marcela Konjevod, Marina Sagud, Suzana Uzun, Oliver Kozumplik
Published online on: 19 Dec 2019

32

NEUROENDOCRINE AND IMMUNE BIOMARKERS OF POSTTRAUMATIC STRESS DISORDER IN COMBAT VETERANS

Nela Pivac, Marcela Konjevod, Marina Sagud, Suzana Uzun, and Oliver Kozumplik

Posttraumatic stress disorder

Posttraumatic stress disorder (PTSD) is a trauma- and stress-related disorder, frequent in modern society in civilians as well as in soldiers. It develops as a consequence of the exposure to a traumatic event(s), usually combat in military personnel, but only in a portion of vulnerable soldiers. Risk factors for PTSD include different neuroanatomical, neuroendocrine, immune, psychological, molecular, genetic, cognitive, emotional, environmental and psychosocial factors and the interaction between them. Therefore, biomarkers of vulnerability to develop PTSD in soldiers and different symptoms and comorbidities that occur in combat related PTSD are important research targets in military medicine. The quest to identify biomarkers is a major question in PTSD research, i.e. to detect and identify factors of vulnerability (risk factors) or factors of resilience (protective factors) in military veterans. This issue is especially important in the military, since there is still an unfulfilled goal to find validated and confirmed biomarkers that would predict PTSD development in soldiers exposed to combat trauma, which might also foresee the behaviour and responses in soldiers under combat stress (Frank, Zamorski, Lee & Colman, 2018).

Diagnostic criteria for PTSD according to the DSM-5 (American Psychiatric Association, 2013; Ito, Takebayashi, Suzuki & Horikosh, 2018; Rosebrock, Arditte Hall, Rando, Pineles & Liverant, 2018) are: Criterion A: stressor; Criterion B: intrusion symptoms; Criterion C: avoidance; Criterion D: negative alterations in cognition and mood; Criterion E: alterations in arousal and reactivity; Criterion F: duration of more than 1 month; Criterion G: functional significance (symptoms create distress or functional impairment) and Criterion H: exclusion (symptoms are not due to medication, substance use or other illness). There are two subtypes of PTSD: (1) dissociative subtype: in addition to meeting criteria for diagnosis, an individual experiences high levels of depersonalization and derealization. Depersonalization is an experience of being an outside observer of or detached from oneself (e.g., feeling as if "this is not happening to

me" or one were in a dream). Derealization is an experience of unreality, distance or distortion (e.g., "things are not real") and (2) delayed subtype is presented when full diagnostic criteria are not met until at least six months after the trauma(s), although onset of symptoms may occur immediately (Weathers, 2017; Yehuda et al., 2015). The diagnosis of PTSD has been criticized on numerous grounds, but principally for three reasons: (1) the alleged pathologizing of normal events, (2) the inadequacy of Criterion A and (3) symptom overlap with other disorders. The diagnosis of PTSD also represents a challenge since in the military, due to malingering (Ali, Jabeen & Alam, 2015); veterans might exaggerate or describe false symptoms because of the possible benefits, i.e. financial or personal gains, or forensic purposes. On the other hand, PTSD might be under-diagnosed due to denial or minimalizing of symptoms since a diagnosis of PTSD might affect veterans' employment status and/or promotion in military service and later in civilian life (Lehrner & Yehuda, 2014).

Although exposure to trauma is common throughout the world (Bisson, Cosgrove & Roberts, 2015), the majority of people will not develop PTSD; the prevalence of PTSD development differs among different populations, while the type of traumatic exposure significantly affects its development (Kessler et al., 2017). The lifetime prevalence of PTSD in the general population is 1.3%–8.8% (Atwoli, Stein, Koenen & McLaughlind, 2015). The prevalence of PTSD is much higher in the military. A prevalence of 11%–30% of war-related traumatic experiences has been recorded among U.S. combat veterans (Dursa, Reinhard, Barth & Schneiderman, 2014; Kang, Natelson, Mahan, Lee & Murphy, 2003). This prevalence differs according to the area of service, and the estimated prevalence of PTSD is 30% in Vietnam veterans, 10% in Gulf War veterans, 15% in veterans serving in Iraq and 11% in veterans returning from Afghanistan (Kintzle, Barr, Corletto & Castro, 2018). The estimated prevalence of PTSD in Croatian veterans is 18%–40% (Komar & Vukusic, 1999; Priebe et al., 2010).

Biomarkers in posttraumatic stress disorder

PTSD is associated with diverse symptoms, and these different symptoms are all linked with disturbances in different biological, psychological, social and neurological functions. Combat-related PTSD has some special characteristics since it is associated with higher total PTSD severity and arousal symptom intrusions (Guina, Nahhas, Suttom & Farnsworth, 2018), often with traumatic brain injury and other blast injuries, resulting in the "poly-trauma" concept and treatment resistance (Corvalan & Klein, 2011). Dysregulation of many biological systems is associated with PTSD, but to date, there are still no specific, validated or sensitive biomarkers for PTSD (Lehrner & Yehuda, 2014).

Biomarkers are non-invasive and objective measures of patient diagnosis, prognosis and treatment (Nikolac Perkovic et al., 2017). They should be determined in easily available fluids such as in saliva, blood, urine and cerebrospinal fluid. However, there are no valid biomarkers for PTSD, and some proposed biomarkers (Lehrner & Yehuda, 2014) still lack specificity and sensitivity. Therefore, there is a high priority for clearly defined and replicated valid biomarkers to discriminate between persons susceptible or resilient to the development of PTSD. Such biomarkers might provide insights into the disease pathogenesis, and can be used for prevention (if related to vulnerability to develop PTSD). In the military, they might even help in selection of resilient individuals who are less likely to develop PTSD when exposed to combat stressors. Biomarkers might also be used for development of targeted treatments and interventions. Biomarkers of PTSD related to the neuroendocrine system (the hypothalamic-pituitary-adrenal [HPA] axis), are CRH, ACTH and cortisol; biomarkers of the immune system are C-reactive protein /CRP/ and other cytokines: interleukin 6 /IL-6/, interferon-γ) (Kao, Stalla, Stalla,

Wotjak & Anderzhanova, 2015; Konjevod et al., 2019; Nedic Erjavec et al., 2018; Olff & van Zuiden, 2017; VanDyke, Burton, Hanidovic & Burke, 2017).

Biomarkers of posttraumatic stress disorder comorbid with cardiovascular diseases

Reliable diagnosis of PTSD is sometimes difficult to achieve (Lehrner & Yehuda, 2014) since PTSD is rarely an isolated disorder and is frequently comorbid with other somatic (Britvic et al., 2015) and psychiatric (Flory, 2015) disorders. In the military, PTSD is very often associated with mild traumatic brain injury (TBI) (Lehrner & Yehuda, 2014). Among the somatic comorbidities in veterans, the most frequent are: cardiovascular, dermatological, musculoskeletal, pulmonary and metabolic diseases (Britvic et al., 2015). Therefore, combat-related PTSD increases the likelihood of developing somatic diseases (Britvic et al., 2015). In Croatia, PTSD veterans with cardiovascular diseases (CVD), myocardial infarction, arrhythmia and other CVD were more common than in general population (Britvic et al., 2015). It has been known for a long time that severe trauma, such as combat stress, affects the heart and cardiovascular system (Tennant, 1982). Prospective studies have consistently found that individuals with PTSD, without known CVD, have increased risk of future CVD events. These findings are evident for both war-related (Ahmadi et al., 2015; Beristianos, Yaffe, Cohen & Byres, 2016; Britvic et al., 2015; Scherrer et al., 2010) and civilian PTSD (Gradus et al., 2015; Jordan et al., 2013). Middle-aged American war veterans with PTSD had higher risk for congestive heart failure, myocardial infarction and peripheral vascular disease than veterans without PTSD (Beristianos et al., 2016). Patients from the Veteran's Administration diagnosed with PTSD were at increased risk of incident myocardial infarction (Scherrer et al., 2010). Similarly, PTSD was associated with myocardial infarction, stroke, ischaemic stroke and venous thromboembolism in a Danish population, with the strongest association in the youngest age group of up to 39 years of age (Gradus et al., 2015). This association existed in the absence of depression, alcohol abuse or other substance dependences (Gradus et al., 2015). Veterans without known coronary heart disease (CHD) had the highest risk of cardiovascular mortality, especially if they had PTSD comorbid with mild TBI (Ahmadi et al., 2015). The presence of PTSD was associated with myocardial ischemia in a large cohort of otherwise asymptomatic veterans (Turner, Neylan, Schiller, Li & Cohen, 2013). PTSD was most strongly associated with incident CVD among veterans of 50 to 59 years of age (Scherrer et al., 2019). Despite large advances in prevention and early recognition and treatment of CVD, these conditions are still the leading cause of death worldwide, while PTSD is considered a fast-track to a premature CVD (Wentworth et al., 2013; Wolf & Schnurr, 2016). These results demonstrate the importance for physicians and healthcare providers to regularly assess cardiovascular (CV) health in combat veterans and other populations with high levels of trauma exposure, regardless of the age or other demographic variables. The connection between PTSD with the increased CVD is still not clear. Risk factors for CVD are numerous and interrelated (Sagud et al., 2017), and CVD biomarkers are elevated in patients with PTSD. Common pathways for both PTSD and CVD include sympathetic over-activation and inflammation (Brudey et al., 2015). Hypertension is related to chronic autonomic activation and HPA axis dysregulation (Kibler, Tursich, Ma, Malcolm & Greenbarg, 2014). Hypertension was found to be the most common component of the metabolic syndrome in middle-aged veterans with PTSD (Rosenbaum et al., 2015). Subjects with PTSD, including both war-related and civilian PTSD, had almost twice the risk for metabolic syndrome than individuals from the general population (Rosenbaum et al., 2015), and this was evident even in young veterans (Blessing et al., 2017). The presence of metabolic syndrome was also associated with a severity of PTSD symptoms (Heppner et al.,

2012). Individuals with PTSD also manifested other indicators of autonomic over-activity, such as increased muscle sympathetic nerve activity in response to virtual reality combat exposure (Park et al., 2017). The association between PTSD and incident CVD might be explained by the presence of numerous comorbid conditions, such as obesity, dyslipidaemia, hypertension, smoking, depression and sleep disturbances (Scherrer et al., 2019). In Croatian war veterans with PTSD, increased median BMI, cholesterol and triglyceride levels were found in individuals with the median age of 56 years who did not have any CVD and who were not taking cardiovascular drugs or statins (Tudor et al., 2018).

Chronic peripheral, low-grade inflammation is manifested in elevated circulatory levels of CRP and pro-inflammatory cytokines, suggesting immune dysfunction in PTSD (Hori & Kim, 2019; Kibler et al., 2014; Lindqvist et al., 2017). Several cross-sectional studies reported an association between elevated CRP levels and PTSD (Canetti, Russ, Luborsky, Gerhart & Hobfoll, 2014; Farr et al., 2015), particularly with re-experiencing and avoiding symptoms (Canetti et al., 2014; Rosen et al., 2017), overall PTSD severity (Farr et al., 2015; Michopolus et al., 2015; Rosen et al., 2017) and chronicity (Solomon et al., 2017). Meta-analysis confirmed higher IL-6, interleukin 1β (IL-1β), tumour necrosis factor-α (TNF-α) and interferon γ levels in a PTSD group compared to healthy controls (Passos et al., 2015). The duration of PTSD was positively correlated with IL-1β and PTSD severity with IL-6 levels (Passos et al., 2015). These findings show bidirectional association, since PTSD is associated with immune activation, and chronicity and severity of PTSD contribute to more pronounced inflammation. The link between increased levels of pro-inflammatory cytokines and CVD is, among others, increased platelet and endothelial activation (Michaud et al., 2013). Moreover, endothelial activation and/or endothelial damage contribute to the increased risk of arterial thrombosis in PTSD patients (Robicsek, Makhoul, Klein, Brenner & Sarig, 2011). The particularly important substances in the development and acceleration of atherosclerosis are IL-1β and IL-6 (Loppnow, Buerke, Werdan & Rose-John, 2011). This association might be in part explained by risk habits such as smoking and alcohol abuse (Dennis et al., 2014).

Brain-derived neurotropic factor (BDNF), although not a conventional CVD risk factor, has also drawn attention. Namely, low peripheral levels of BDNF were associated with an increased risk of stroke (Pikula et al., 2013) and were proposed as a biomarker of heart failure (Takashio et al., 2015). In line with this, higher serum BDNF levels were protective, suggesting decreased risk of CVD (Kaess et al., 2015). The most frequently studied polymorphisms on the BDNF gene, Val66Met and C270T, were not significantly associated with BMI or plasma lipid levels in Croatian war veterans with combat-related PTSD (Tudor et al., 2018). Namely, there was no association between BDNF Val66Met and BMI values, as well as plasma total cholesterol, triglycerides, HDL and LDL cholesterol levels in veterans with PTSD (Tudor et al., 2018).

All these studies delineated the need to advance our understanding of the underlying mechanisms by which PTSD contributes to the development of CVD. Unhealthy lifestyle, such as smoking, poor diet and physical inactivity, substantially contributes to increased CVD risks. The well-established association between PTSD and CVD may be at least partly due to poor diet, sedentary lifestyle, obesity and smoking (van den Berk-Clark et al., 2018). Patients with PTSD had higher smoking rates (Kelly, Jensen & Sofuoglu, 2015; Sagud et al., 2018) and nicotine dependence levels (Sagud et al., 2018), more difficulties in smoking cessation and stronger withdrawal symptoms than individuals not diagnosed with PTSD (Kelly et al., 2015). Moderate/heavy nicotine dependence was associated with more severe negativity, hyper-arousal and depression in veterans with PTSD (Sagud et al., 2018). Veterans with PTSD were also more frequently smokers (Dennis et al., 2014) and had higher prevalence of nicotine dependence when compared to veterans without PTSD (Beristianos et al., 2016). This was confirmed in

twin studies, where twins with PTSD were more frequently smokers than twins without PTSD, despite no differences in BMI, HDL cholesterol and systolic blood pressure (Goetz et al., 2014). In addition, patients with PTSD frequently abuse alcohol, mainly to self-medicate anxiety and hyper-arousal (Edmondson, Kronish, Shaffer, Falzon & Burg, 2013). Other life-style risk factors include sedentary life-style and consumption of unhealthy food. Sedentary behaviour is related to other CVD risk factors, such as increased blood pressure, insulin resistance and high cholesterol levels (Brock, King, Wofford & Harell, 2005). Decreased physical activity and unhealthy eating habits in patients with PTSD were related to obesity (Hall, Hoerster & Yancy, 2015). In Croatian war veterans, BMI did not differ between veterans with or without PTSD and age-matched healthy control subjects (Kozaric Kovacic et al., 2009), but this study detected a high prevalence of obesity in a healthy group, and therefore veterans with PTSD and healthy groups had similar BMI values in the overweight range (Kozaric Kovacic et al., 2009). Recent meta-analysis confirmed the association between PTSD and increased BMI (Suliman et al., 2016). Although the aforementioned studies reveal increased CVD risk factors in individuals with PTSD, this relationship appears to be complex and not fully elucidated. The severity, symptom clusters and duration of PTSD symptoms, but not a PTSD diagnosis, contribute to increased CVD risks (Sagud et al., 2017).

To the best of our knowledge, there are no data on the effects of common treatment methods to decrease CVD risk markers in patients with PTSD. Unlike in the PTSD population, current literature provides evidence of effectiveness of different interventions, such as CBT and transcendental meditation, on reducing recurrent CVD events in cohorts with CHD, while data on primary prevention are lacking (Cohen, Edmondson & Kronish, 2015). Specifically, despite the well-known relationship between the presence of PTSD and increased CVD risk, there are no data on the influence of any treatment on CVD risk factors in patients with PTSD, which is recognized in the current literature as an impetus for the future research (Koenen et al., 2017). Progressive muscular relaxation had beneficial effects on sleep and depression in a small study on patients with PTSD (Blanaru et al., 2012). While establishing efficacious treatment for PTSD is an important goal, showing that such treatment would also improve cardio-metabolic health is a key outstanding question in the literature (Koenen et al., 2017).

Early detection and effective management of hypertension, type 2 diabetes mellitus, depression, anxiety, sleep disorders and other CVD risk factors, particularly smoking, might help to mitigate the risk of CVD in patients with PTSD. Thus, the recognition of CVD risk markers which might cause silent ischemia is important to prevent its further progression to potentially fatal CVD events. All aforementioned risk markers might be modifiable risk factors for CHD (Edmondson et al., 2013). Since at present it is unknown that any specific treatment which targets PTSD symptoms might alleviate CVD risks, future treatment trials addressing both PTSD symptoms and markers of CVD are urgently needed.

Biomarkers of the hypothalamic-pituitary-adrenal axis in posttraumatic stress disorder

PTSD is associated with disturbed regulation and altered function of the major stress response system, the hypothalamic–pituitary–adrenal (HPA) axis (VanDyke et al., 2017; Yehuda et al., 2015). Release of all hormones of the HPA axis activation cascade, i.e. CRH, ACTH and glucocorticoid hormones (cortisol), is altered in PTSD. Although acute stress elicits an increase in these hormones, in PTSD there are heterogeneous and divergent findings regarding basal measurements of CRH, ACTH and cortisol (VanDyke et al., 2017). In normal conditions (stress-free conditions), the sympathetic nervous system (SNS) interacts with the HPA axis to produce

response to external stimuli: the HPA axis is activated with the subsequent release of CRH, arginine vasopressin, ACTH and cortisol, and these hormones control their release via negative feedback. In situations of extreme stress and trauma, the SNS response activates fast release of noradrenaline, adrenaline and dopamine, with activation of the HPA axis and increased cortisol release. Cortisol binds in normal stress-free conditions to mineralocorticoid receptors and exerts negative feedback of CRH, arginine vasopressin and ACTH, but in stressful situations, it also binds to glucocorticoid receptors (Daskalakis, McGill, Lehrner & Yehuda, 2015; de Kloet et al., 2007). In extreme stress situations and in PTSD, this negative feedback control is disturbed and the whole system is out of balance, which leads to exaggerated responses to normal stimuli and disturbed glucocorticoid and CRH signalling (Osório, Probert, Jones, Young & Robbins, 2017; VanDyke et al., 2017; Yehuda et al., 2015). This insufficient signalling is responsible for diverse effects such as the inability of HPA downregulation and increased negative feedback sensitivity in PTSD but also consolidation of the traumatic memories and deficits in fear conditioning and inability of fear extinction (Osório et al., 2017; Yehuda et al., 2015).

Conclusions of literature review regarding HPA axis alterations in PTSD are mixed, but most of the studies reveal attenuated cortisol in subjects with PTSD; however, these findings depend on the time of the day when cortisol was measured, on the biological fluid in which cortisol was measured and confounding variables such as age, sex, and medication use, as well as the time past after traumatic experience (VanDyke et al., 2017). In contrast, in Croatian war veterans, plasma cortisol levels were increased both in veterans with PTSD as well as in veterans who did not develop PTSD but were exposed to the same traumatic experiences when compared to non-exposed healthy control subjects (Pivac, Muck-Seler, Jakovljevic, Ljubicic & Crncevic-Orlic, 1998). Contrarily to these data, no significant differences in basal blood concentrations of cortisol and ACTH were found in subjects with current PTSD, lifetime PTSD, trauma controls and healthy subjects (Savic, Knezevic, Damjanovic, Spiric & Matic, 2012). ACTH levels did not differ between subjects with or without PTSD (Kellner, Yassouridis, Hubner, Baker & Wiedemann, 2003; Muhtz, Wester, Yassouridis, Wiedemann & Kellner, 2008). The data using salivary cortisol in PTSD are more uniform, since most of the data detected decreased salivary cortisol in PTSD compared to control subjects (Pan, Wang, Wu, Wen & Liu, 2018; VanDyke et al., 2017). CRH has numerous roles in the CNS, and it modulates glutamatergic, dopaminergic, serotonergic and noradrenergic neurotransmission (Risbrough & Stein, 2006). CRH was found to be elevated in cerebrospinal fluid (CSF) of Vietnam veterans with PTSD as compared to healthy controls after single sampling (Bremner et al., 1997). This result was confirmed later after serial CSF sampling (Baker et al., 1999), but there is a lack of novel studies that would corroborate these findings. Increased CRH concentrations might be associated with hyper-arousal in PTSD patients (Bremner et al., 1997). Higher CRH in PTSD contributes to various disturbances and symptoms due to the widespread localization of CRH neurons and CRHR1 and CRHR2 receptors in different brain regions; there are complex and bidirectional interactions between glucocorticoids and CRH that are responsible for the disturbed fear and stress responses and divergent symptoms in PTSD (Raglan, Schmidt & Schulkin, 2017).

Components of the HPA axis are regulated by a number of genes, and their polymorphisms might affect HPA axis activity and the cascade of events that happens if this regulation is disturbed in PTSD (Mehta & Binder, 2012). The most common risk genetic variants associated with PTSD are the gene variants encoding glucocorticoid receptors (NR3C1). These polymorphisms (TthIII I, ER22/23EK, N363S, BclI and GR-9 beta) are important since they affect cortisol release and glucocorticoid receptor sensitivity and resistance. Genetic variants of the mineralocorticoid receptors (NR3C2), I180V and -2G/C, affect stress response and

plasma cortisol level. A SNP within the CRH binding protein (CRHBP) locus, rs10473984, was significantly associated with higher plasma ACTH levels and increased dexamethasone suppression of ACTH (Binder et al., 2010). Other frequently studied genetic variants are those coding for CRHR1R and a co-chaperone of the glucocorticoid receptors (FKBP5), encoding FK506-binding protein 5 (Yehuda et al., 2015). An association between a SNP within the CRHR1 gene, rs110402, and cortisol levels was detected in subjects traumatized in childhood (Osório et al., 2017). FKBP5 is important since it regulates glucocorticoid receptor sensitivity and elicits less efficient nuclear translocation: after it binds to the receptor complex, cortisol binds with lower affinity to this receptor (Yehuda et al., 2015). PTSD is associated with downregulation of FKBP5 gene expression (Daskalakis et al., 2015). Genetic variants of FKBP5 are linked with increased FKBP5 protein expression, resulting in impaired binding of glucocorticoids to glucocorticoid receptors and consequently in disrupted negative feedback of the HPA axis. A recent meta-analysis confirmed the significant gene-by environment (GxE) effects of the FKBP5 variants (rs1360780, rs3800373, rs9296158, rs9470080) with traumatic event exposure on PTSD (Hawn et al., 2019).

Therefore, these data suggest that PTSD is associated with imbalance and dysregulation of the HPA axis and consequently with altered homeostasis: blunted cortisol secretion; low glucocorticoid signalling; impaired negative feedback, leading to the allostatic load and overreactions to moderate stressful stimuli (Daskalakis et al., 2015). All these alterations result in altered neurotransmission regulated by dopamine, noradrenaline, serotonin, brain derived neurotrophic factor (BDNF), and others, and in altered immune response.

Biomarkers of the immune system in PTSD

Besides dysregulation of the HPA axis, PTSD is also associated with low-level chronic inflammation, and altered cytokine levels (Gill, Saligan, Woods & Page, 2009; Gola et al., 2013; Altemus, Dhabhar & Yang, 2006). Such dysregulation of immune system represents a risk for several metabolic disorders, including diabetes type 1 and 2, arthritis, cardiovascular and autoimmune diseases (Gill et al., 2009; Britvic et al., 2015). The interaction between stress and alterations in inflammatory response system (Maes et al., 1999a,b) leads to altered levels of humoral and cell-mediated cytokines (Altemus et al., 2006). Cytokines have multiple roles as the signalling molecules that mediate cross-talk between the peripheral immune system and central nervous system (Furtado & Katzman, 2015). Therefore, normal cytokine function is important for maintaining homeostasis. The immune system is associated with the HPA axis, as it maintains homeostasis and protects against inflammatory processes. Thus, dysregulation of the HPA axis and macrophage activation both stimulate pro-inflammatory cytokines that promote inflammation. Several studies showed that pro-inflammatory cytokines, including TNF-α, interleukin-1α (IL-1α), IL-1β and IL-6, are associated with PTSD (Altemus, Dhabhar & Yang, 2006; Neigh & Ali, 2016; Wang et al., 2019). TNF-α and IL-6, which are responsible for symptoms associated with infection, can pass through the blood brain barrier and affect the HPA axis (Gill et al., 2009; Rohleder, Joksimovic, Wolf & Kirscbaum, 2004). There are mixed results on the role of cytokines in PTSD. Individuals with PTSD of both genders showed increases of IL-6 and TNF-α levels, while PTSD patients with comorbidities, such as depression, had even greater HPA axis dysregulation compared to controls (Gill et al., 2009). In addition, interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-8 (IL-8) and interleukin-10 (IL-10) were also significantly increased in individuals with PTSD compared to healthy controls (Furtado & Katzman, 2015). However, opposite results are also reported. IL-4 was decreased in PTSD subjects, while TNF-α and interferon-γ were increased in female but not in male PTSD patients

(Furtado & Katzman, 2015; Gill, Vythilingam & Page, 2008). Cytokines IL-1β, IL-6 and TNF-α are released after stimulation of microglia or macrophages and have a major role in acute phase reaction. IL-1β is a cytokine that plays an important role in the inflammatory and immune system. It is associated with several behavioural impairments, including sleep alterations, eating disorders and lack of energy (Maes et al., 1999a,b). In addition, it has a role in regulation of the HPA axis, expression of serotonin transporter and catecholaminergic system (Maes et al., 1999a,b). IL-1β is positively correlated with several PTSD symptoms, including avoidance and re-experiencing, and with certain comorbidities (Spivak et al., 1997; Waheed, Dalton, Wesemann, Ibrahim & Himmerich, 2018). IL-1β is a crucial cytokine since it is released and promotes release of other cytokines, including IL-6 (Jones & Thomsen, 2012). Increased levels of IL-6 are associated with PTSD development and vulnerability (Gill, Luckenbaugh, Charney & Vythilingam, 2010). IL-6 has a major role in dopamine regulation in the hippocampus and maintains the survival of dopaminergic neurons (Gill et al., 2009). Increased levels of IL-6 affect vascular endothelium and may be associated with stroke, myocardial infarction, arrhythmias or cardiac death (Gil et al., 2010). As PTSD is frequently comorbid with different psychiatric and somatic disorders, comorbidities might affect IL-6 levels. Namely, patients with PTSD without depression had a different IL-6 profile compared to patients with PTSD comorbid with depression (Gil et al., 2010). Pro-inflammatory cytokines, IL-1β and IL-6, affect the HPA axis, stimulate its activity and alter cortisol levels (Gill et al., 2008). T-helper cell 1 (Th1) cytokines IL-2 and IFN-γ are increased among PTSD patients, while inhibitory mediators TGF-β, IL-4 and IL-10 levels were decreased among PTSD patients (Wang, Mandel, Levingston & Young, 2016; Wang & Young, 2016). However, several studies found that IL-4 and IL-10 levels were increased in PTSD patients (Guo et al., 2012; Wang & Young, 2016). Out of the inflammatory mediators, TNF-α, IL-1, IL-17 and IL-6 were increased (Hoge et al., 2009; Wang et al., 2016; Wang & Young, 2016). It is proposed that Th1 and inflammatory cytokines are increased, while inhibitory mediators are decreased in patients with PTSD (Wang et al., 2016). Levels of IL-6, IL-1β and TNF-α were elevated in PTSD patients even months after traumatic events (Jones & Thomsen, 2012). However, a similar level of inflammatory cytokines in women that recovered from PTSD and non-traumatized women was also observed (Wang & Young, 2016). Cytokine levels can be altered due to certain health conditions, including cancer or other neuropsychiatric disorders, such as depression (Wang et al., 2016). Alterations in the immune system are reflected not only in the impaired cytokine levels, but also in the composition of immune cells. Th1 and Th17 pro-inflammatory cells are increased, while anti-inflammatory cells, CD4+PD-L1+ cells, were decreased in patients with PTSD (O'Donovan et al., 2015). PTSD is associated with enhanced risk for development of autoimmune disorders due to biological impairments caused by chronic low-level inflammation (O'Donovan et al., 2015). Patients with PTSD have reduced gene methylation and impaired gene expression in immune cells (O'Donovan et al., 2015). Moreover, genes that encode for TNF- IL-16 and Il-18 had enhanced expression in PTSD patients compared to healthy controls, while genes that encode for IL-8 were demethylated in PTSD patients (Zass, Hart, Seedat, Hemmings & Malan-Müller, 2017). Chronic inflammation characteristic of PTSD stimulates the immune system to release CRP. CRP is released as a result of the acute stress, infection or impairments in the immune system. However, chronic stress and depression might also cause release of CRP due to chronic inflammation (Heath et al., 2013). Typical PTSD symptoms, such as re-experiencing/flashbacks, might affect CRP levels, which are increased in PTSD subjects (Heath et al., 2013). An altered immune system, together with an altered HPA axis, increases the risk for autoimmune diseases in PTSD. Individuals with PTSD have a higher risk to develop autoimmune disorders compared to subjects without psychiatric disorder, while females are

more prone to developing autoimmune disorder compared to males (O'Donovan et al., 2015). Chronic inflammation characteristic of PTSD stimulates reactive oxygen species that cause accelerated aging through telomere impairment (Passos et al., 2015).

In brief, the immune system, together with the HPA axis, is dysregulated in PTSD, and although the results from the literature are inconsistent, immune alterations in PTSD reveal immunological imbalance and a low grade pro-inflammatory state in PTSD (Wang, Caughron & Young, 2017).

Most of the reported data reveal increased plasma levels of pro-inflammatory cytokines such as IFN-γ, IL-6, TNF-α, and IL-17 (Wang et al., 2017).

Conclusion

Pronounced dysregulation of the HPA axis and immune system is present in PTSD. PTSD is often comorbid with other psychiatric as well as somatic disorders. Among the somatic comorbidities, cardiovascular and metabolic are the most frequent, and the most serious, since severe trauma, such as combat stress, affects the cardiovascular system. This review focused on the neuroendocrine and immune markers, which are common for PTSD as well as in PTSD comorbid with CVD. Biomarkers should be easily accessible and determined in easily available body fluids such as blood, saliva or urine. They might help in improving clinical care and treatment. Since PTSD is a complex and polygenic disorder, associated with different comorbid disorders, impaired stress response and altered immune systems might only describe part of the potential patho-mechanisms underlying PTSD.

Note: The work was supported by the Croatian Science Foundation, project number IP-2014-09-4289.

References

Ahmadi, N., Hajsadeghi, F., Yehuda, R., Anderson, N., Garfield, D., Ludmer, C., & Vaidya, N. (2015). Traumatic brain injury, coronary atherosclerosis and cardiovascular mortality. *Brain Injury*, *29*(13–14), 1635–1641.

Ali, S., Jabeen, S., & Alam, F. (2015). Multimodal approach to identifying malingered posttraumatic stress disorder: A review. *Innovations in Clinical Neurosciences*, *12*(1–2), 12–20.

Altemus, M., Dhabhar, F.S., & Yang, R. (2006). Immune function in PTSD. *Annals New York Academy of Sciences*, *1071*, 167–183.

American Psychiatric Association. (2013) *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Washington, DC: American Psychiatric Press Inc.

Atwoli, L., Stein, D.J., Koenen, K.C., & McLaughlind, K.A. (2015). Epidemiology of posttraumatic stress disorder: Prevalence, correlates and consequences. *Current Opinion in Psychiatry*, *28*(4), 307–311.

Baker, D.G., West, S.A., Nicholson, W.E., Ekhator, N.N., Kasckow, J.W., Hill, K.K., … Geracioti, T.D. (1999). Serial corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. *American Journal of Psychiatry*, *156*, 585–588.

Beristianos, M.H., Yaffe, K., Cohen, B., & Byers, A.L. (2016). PTSD and risk of incident cardiovascular disease in aging veterans. *American Journal of Geriatric Psychiatry*, *24*(3), 192–200.

Binder, E.B., Owens, M.J., Liu, W., Deveau, T.C., Rush, A.J., Trivedi, M.H., … Nemeroff, C.B. (2010). Association of polymorphisms in genes regulating the corticotropin-releasing factor system with antidepressant treatment response. *Achieves in General Psychiatry*, *67*(4), 369–379.

Bisson, J.I., Cosgrove, S., & Roberts, N.P. (2015). Post-traumatic stress disorder. *British Medical Journal*, *351*, h6161.

Blanaru, M., Bloch, B., Vadas, L., Arnon, Z., Ziv, N., Kremer, I., & Haimov, I. (2012). The effects of music relaxation and muscle relaxation techniques on sleep quality and emotional measures among individuals with posttraumatic stress disorder. *Mental Illness*, *4*(2), e13.

Blessing, E. M., Reus, V., Mellon, S. H., Wolkowitz, O.M., Flory, J. D., Bierer, L., … Marmar, C.R. (2017). Biological predictors of insulin resistance associated with posttraumatic stress disorder in young military veterans. *Psychoneuroendocrinology*, *82*, 91–97.

Bremner, J. D., Licinio, J., Darnell, A., Krystal, J. H., Owens, M. J., Southwick, S. M., … Charney, D. S. (1997). Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. *American Journal of Psychiatry*, *154*, 624–629.

Britvic, D., Anticevic, V., Kaliterna, M., Lusic, L., Beg, A., Brajevic-Gizdic, I., … Pivac, N. (2015). Comorbidities with PTSD among combat veterans; 15 years postwar analysis. *International Journal of Clinical and Healthy Psychology*, *15*, 81–92.

Brock, C. M., King, D. S., Wofford, M. R., & Harrell, T. K. (2005). Exercise, insulin resistance, and hypertension: A complex relationship. *Metabolic Syndrome and Related Disorders*, *3*, 60–65.

Brudey, C., Park, J., Wiaderkiewicz, J., Kobayashi, I., Mellman, T. A., & Marvar, P. J. (2015). Autonomic and inflammatory consequences of posttraumatic stress disorder and the link to cardiovascular disease. *American Journal of Physiology – Regulatory, Integrative and Comparative Physiology*, *309*(4), 315–321.

Canetti, D., Russ, E., Luborsky, J., Gerhart, J. I., & Hobfoll, S. E. (2014). Inflamed by the flames? The impact of terrorism and war on immunity. *Journal of Traumatic Stress*, *27*, 345–352.

Cohen, B. E., Edmondson, D., & Kronish, I. M. (2015). State of the art review: Depression, stress, anxiety, and cardiovascular disease. *Americal Journal of Hypertension*, *28*(11), 1295–1302.

Corvalan, J. C., & Klein, D. (2011). PTSD: Diagnosis, evolution, and treatment of combat-related psychological/psychiatric injury. *Missouri Medicine*, *108*(4), 296–303.

Daskalakis, N. P., McGill, M. A., Lehrner, A., & Yehuda, R. (2015). Endocrine aspects of PTSD: Hypothalamic-pituitary-adrenal (HPA) axis and beyond. In C. R. Martin, V. R. Preedy, & V. B. Patel (Eds.), *Comprehensive Guide to Post-Traumatic Stress Disorder* (pp. 245–260). Switzerland: Springer International Publishing.

De Kloet, C. S., Vermetten, E., Heijnen, C. J., Geuze, E., Lentjes, E. G., & Westenberg, H. G. (2007). Enhanced cortisol suppression in response to dexamethasone administration in traumatized veterans with and without posttraumatic stress disorder. *Psychoneuroendocrinology*, *32*, 215–226.

Dennis, P. A., Ulmer, C. S., Calhoun, P. S., Sherwood, A., Watkins, L. L., Dennis, M. F., & Beckham, J. C. (2014). Behavioural health mediators of the link between posttraumatic stress disorder and dyslipidemia. *Journal of Psychosomatic Research*, *77*(1), 45–50.

Dursa, E. K., Reinhard, M. J., Barth, S. K., & Schneiderman, A. I. (2014). Prevalence of a positive screen for PTSD among OEF/OIF and OEF/OIF-era veterans in a large population-based cohort. *Journal of Traumatic Stress*, *27*, 542–549.

Edmondson, D., Kronish, I. M., Shaffer, J. A., Falzon, L., & Burg, M. M. (2013). Posttraumatic stress disorder and risk for coronary heart disease: A meta-analytic review. *American Heart Journal*, *166*, 806–814.

Farr, O. M., Ko, B. J., Joung, K. E., Zaichenko, L., Usher, N., Tsoukas, M., … Mantzoros, C. S. (2015). Posttraumatic stress disorder, alone or additively with early life adversity, is associated with obesity and cardiometabolic risk. *Nutrition, Metabolism & Cardiovascular Diseases*, *25*, 479–488.

Flory, J. D. (2015). Comorbidity between post-traumatic stress disorder and major depressive disorder: Alternative explanations and treatment considerations. *Dialogues in Clinical Neuroscience*, *17*, 141–150.

Frank, C., Zamorski, M. A., Lee, J. E., & Colman, I. (2018). Deployment-related trauma and post-traumatic stress disorder: Does gender matter?. *European Journal of Psychotraumatology*, *9*(1), Advance online publication. doi: 10.1080/20008198.2018.1486123

Furtado, M., & Katzman, M. A. (2015). Neuroinflammatory pathways in anxiety, posttraumatic stress, and obsessive compulsive disorders. *Psychiatry Research*, *229*, 37–48.

Gill, J., Luckenbaugh, D., Charney, D., & Vythilingam, M. (2010). Sustained elevation of serum interleukin-6 and relative insensitivity to hydrocortisone differentiates posttraumatic stress disorder with and without depression. *Biological Psychiatry*, *68*, 999–1006.

Gill, J. M., Saligan, L., Woods, S., & Page, G. (2009). PTSD is associated with an excess of inflammatory immune activities. *Perspectives in Psychiatric Care*, *45*(4), 262–277.

Gill, J., Vynthilingam, M., & Page, G. G. (2008). Low cortisol, high DHEA, and high levels of stimulated TNF-α, and IL-6 in women with PTSD. *Journal of Traumatic Stress*, *21*(6), 530–539.

Goetz, M., Shah, A., Goldberg, J., Cheema, F., Shallenberger, L., Murrah, N. V., … Vaccarino, V. (2014). Posttraumatic stress disorder, combat exposure, and carotid intima-media thickness in male twins. *American Journal of Epidemiology*, *180*(10), 989–996.

Gola, H., Engler, H., Sommershof, A., Adenauer, H., Kolassa, S., Schedlowski, M., … Kolassa, I-T. (2013). Posttraumatic stress disorder is associated with an enhanced spontaneous production of pro-inflammatory cytokines by peripheral blood mononuclear cells. *BMC Psychiatry*, *13*(1), 40. doi: 10.1186/1471-244X-13-40.

Gradus, J. L., Farkas, D. K., Svensson, E., Ehrenstein, V., Lash, T. L., Milstein, A., … Sørensen, H. T. (2015). Associations between stress disorders and cardiovascular disease events in the Danish population. *British Medical Journal*, *5*(12), e009334.

Guina, J., Nahhas, R.W., Sutton, P., & Farnsworth, S. (2018). The influence of trauma type and timing on PTSD symptoms. *The Journal of Nervous and Mental Disease*, *206*, 72–76.

Guo, M., Liu, T., Guo, J. C., Jiang, X. L., Chen, F., & Gao, Y. S. (2012). Study on serum cytokine levels in posttraumatic stress disorder patients. *Asian Pacific Journal of Tropical Medicine*, *5*(4), 323–325.

Hall, K.S., Hoerster, K. D., & Yancy, W. S. (2015). Post-traumatic stress disorder, physical activity, and eating behaviors. *Epidemiologic Reviews*, *37*, 103–115.

Hawn, S. E., Sheerin, C. M., Lind, M. J., Hicks, T. A., Marraccini, M. E., Bountress, K., … Amstadter, A. B. (2019). GxE effects of FKBP5 and traumatic life events on PTSD: A meta-analysis. *Journal of Affective Disorders*, *243*, 455–462.

Heath, N.M., Chesney, S.A., Gerhart, J.I., Goldsmith, R.E., Luborsky, J.L., Stevens, N.R., & Hobfoll, S.E. (2013). Interpersonal violence, PTSD and inflammation: Potential psychogenic pathways to higher C-reactive protein levels. *Cytokine*, *63*, 172–178.

Heppner, P.S., Lohr, J.B., Kash, T.P., Jin, H., Wang, H., & Baker D.G. (2012). Metabolic syndrome: Relative risk associated with post-traumatic stress disorder (PTSD) severity and antipsychotic medication use. *Psychosomatics*, *53*(6), 550–558.

Hoge, E.A., Brandstetter, K., Moshier, S., Pollack, M.H., Wong, K.K., & Simon, N.M. (2009). Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. *Depression and Anxiety*, *26*, 447–455.

Hori, H., & Kim, Y. (2019). Inflammation and post-traumatic stress disorder. *Psychiatry and Clinical Neurosciences*, *73*(4), 143–153.

Ito, M., Takebayashi, Y., Suzuki, Y., & Horikoshi, M. (2018). Posttraumatic stress disorder checklist for DSM-5: Psychometric properties in a Japanese population. *Journal of Affective Disorders*, *247*, 11–19.

Jones, K.A., & Thomsen, C. (2012). The role of innate immune system in psychiatric disorders. *Molecular and Cellular Neuroscience*, *53*, 52–62.

Jordan, H.T., Stellman, S.D., Morabia, A., Miller-Archie, S.A., Alper, H., Laskaris, Z., … Cone, J.E. (2013). Cardiovascular disease hospitalizations in relation to exposure to the September 11, 2001 World Trade Center disaster and posttraumatic stress disorder. *Journal of the American Heart Association*, *2*(5), e000431.

Kaess, B. M., Preis, S. R., Lieb, W., Beiser, A. S., Yang, Q., Chen, T. C., … Stewart, A. F. (2015). Circulating brain-derived neurotrophic factor concentrations and the risk of cardiovascular disease in the community. *Journal of the American Heart Association*, *4*, e001544.

Kang, H.K., Natelson, B. H., Mahan, C.M., Lee, K.Y., & Murphy, F. M. (2003). Post-traumatic stress disorder and chronic fatigue syndrome-like illness among Gulf War veterans: A population-based survey of 30,000 veterans. *American Journal of Epidemiology*, *157*, 141–148.

Kao, C.Y., Stalla, G., Stalla, J., Wotjak, C.T., & Anderzhanova, E. (2015). Norepinephrine and corticosterone in the medial prefrontal cortex and hippocampus predict PTSD-like symptoms in mice. *European Journal of Neuroscience*, *419*, 1139–1148.

Kellner, M., Yassouridis, A., Hübner, R., Baker, D. G., & Wiedemann, K. (2003). Endocrine and cardiovascular responses to corticotropin-releasing hormone in patients with posttraumatic stress disorder: A role for atrial natriuretic peptide? *Neuropsychobiology*, *47*, 102–108.

Kelly, M.M., Jensen, K.P., & Sofuoglu, M. (2015). Co-occurring tobacco use and posttraumatic stress disorder: Smoking cessation treatment implications. *The American Journal on Addictions*, *24*, 695–704.

Kessler, R.C., Aguilar-Gaxiola, S., Alonso, J., Benjet, C., Bromet, E.J., Cardoso, G., … On behalf of the WHO World Mental Health Survey Collaborators. (2017). Trauma and PTSD in the WHO World Mental Health Surveys. *European Journal of Psychotraumatology*, *8*(5). doi: 10.1080/20008198

Kibler, J. L., Tursich, M., Ma, M., Malcolm, L., & Greenbarg, R. (2014). Metabolic, autonomic and immune markers for cardiovascular disease in posttraumatic stress disorder. *World Journal of Cardiology*, *6*, 455–461.

Kintzle, S., Barr, N., Corletto, G., & Castro, C.A. (2018). PTSD in U.S. veterans: The role of social connectedness, combat experience and discharge. *Healthcare (Basel)*, *6*(3), 102. doi: 10.3390/healthcare6030102.

Koenen, K.C., Sumner, J.A., Gilsanz, P., Glymour, M.M., Ratanatharathorn, A., Rimm, E. B., … Kubzansky, L.D. (2017). Post-traumatic stress disorder and cardiometabolic disease: Improving causal inference to inform practice. *Psychological Medicine*, *47*(2), 209–225.

Komar, Z., & Vukusic, H. (1999). Post-traumatic stress disorder in Croatian war veterans; incidence and psychosocial features. In D. Dekaris, & A. Sabioncello (Eds.), *New Insights in Post-Traumatic Stress Disorder (PTSD)* (pp. 42–44). *Proceedings (Abstracts, references and illustrations)*. Croatian Academy of Science and Arts, Zagreb.

Konjevod, M., Tudor, L., Svob Strac, D., Nedic Erjavec, G., Barbas, C., Zarkovic, N., … Pivac, N. (2019). Metabolomic and glycomic findings in posttraumatic stress disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *88*, 181–193.

Kozaric-Kovacic, D., Ilic, M.G., Romic, Z., Vidovic, A., Jendricko, T., & Pivac N. (2009). Body mass index in male Caucasian veterans with or without posttraumatic stress disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *33*, 1447–1450.

Lehrner, A., & Yehuda, R. (2014). Biomarkers of PTSD: Military applications and considerations. *European Journal of Psychotraumatology*, *5*. Online publication. doi: 10.3402/ejpt.v5.23797

Lindqvist, D., Mellon, S.H., Dhabhar, F.S., Yehuda, R., Grenon, S.M., Flory, J.D., … Wolkowitz, O.M. (2017). Increased circulating blood cell counts in combat-related PTSD: Associations with inflammation and PTSD severity. *Psychiatry Research*, *258*, 330–336.

Loppnow, H., Buerke, M., Werdan, K., & Rose-John, S. (2011). Contribution of vascular cell-derived cytokines to innate and inflammatory pathways in atherogenesis. *Journal of Cellular and Molecular Medicine*, *15*, 484–500.

Maes, M., Lin, A., Delmeire, L., Van Gastel, A., Kenis, G., De Jongh, R., & Bosman, E. (1999a). Elevated serum interleukin-6 (IL-6) and IL-6 receptor concentrations in posttraumatic stress disorder following accidental man-made traumatic events. *Biological Psychiatry*, *45*, 833–839.

Maes, M., Lin, A. H., Verkerk, R., Delmeire, L., Van Gastel, A., Van der Planken, M., & Scharpé, S. (1999b). Serotonergic and noradrenergic markers of post-traumatic stress disorder with and without major depression. *Neuropsychopharmacology*, *20*(2), 188–197.

Mehta, D., & Binder, E.B. (2012). Gene x environment vulnerability factors for PTSD: The HPA-axis. *Neuropharmacology*, *62*, 654–662.

Michaud, M., Balardy, L., Moulis, G., Gaudin, C., Peyrot, C., Vellas, B.,… Nourhashemi, F. (2013). Proinflammatory cytokines, aging, and age-related diseases. *Journal of the American Medical Directors Association*, *14*, 877–882.

Michopoulos, V., Rothbaum, A.O., Jovanovic, T., Almli, L.M., Bradley, B., Rothbaum, B.O., … Ressler, K.J. (2015). Association of CRP genetic variation and CRP level with elevated PTSD symptoms and physiological responses in a civilian population with high levels of trauma. *American Journal of Psychiatry*, *172*, 353–362.

Muhtz, C., Wester, M., Yassouridis, A., Wiedemann, K., & Kellner, M. (2008). A combined dexamethasone/corticotropin-releasing hormone test in patients with chronic PTSD–first preliminary results. *Journal of Psychiatric Research*, *42*, 689–693.

Nedic Erjavec, G., Konjevod, M., Nikolac Perkovic, M., Svob Strac, D., Tudor, L., Barbas, C., … Pivac, N. (2018). Short overview on metabolomic approach and redox changes in psychiatric disorders. *Redox Biology*, *14*, 178–186.

Neigh, G.N., & Ali, F.F. (2016). Co-morbidity of PTSD and immune system dysfunction: Opportunities for treatment. *Current Opinion in Pharmacology*, *29*, 104–110.

Nikolac Perkovic, M., Nedic Erjavec, G., Svob Strac, G., Uzun, S., Kozumplik, O., & Pivac, N. (2017). Theranostic biomarkers for schizophrenia. *International Journal of Molecular Sciences*, *18*(4), 733. doi: 10.3390/ijms18040733

O'Donovan, A., Cohen, B.E., Seal, K.H., Bertenthal, D., Margaretten, M., Nishimi, K., & Neylan, T.C. (2015). Elevated risk for autoimmune disorders in Iraq and Afghanistan veterans with posttraumatic stress disorder. *Biological Psychiatry*, 77(4), 365–374.

Olff, M., & van Zuiden, M. (2017). Neuroendocrine and neuroimmune markers in PTSD: Pre-, peri- and post-trauma glucocorticoid and inflammatory dysregulation. *Current Opinion in Psychology*, *14*, 132–137.

Osório, C., Probert, Z., Jones, E., Young, A.H., & Ian Robbins, I. (2017). Adapting to stress: Understanding the neurobiology of resilience. *Behavioral Medicine*, *43*(4), 307–322.

Pan, X., Wang, Z., Wu, X., Wen, S.W., & Liu, A. (2018). Salivary cortisol in post-traumatic stress disorder: A systematic review and meta-analysis. *BioMed Central Psychiatry*, *18*(1):324.

Park, J., Marvar, P.J., Liao, P., Kankam, M.L., Norrholm, S.D., Downey, R.M., … Rothbaum, B.O. (2017). Baroreflex dysfunction and augmented sympathetic nerve responses during mental stress in veterans with post-traumatic stress disorder. *The Journal of Physiology*, *595*(14), 4893–4490.

Passos, I.C., Vasconcelos-Moreno, M.P., Costa, L.G., Kunz, M., Brietzke, E., Quevedo, J., … Kauer-Sant'Anna, M. (2015). Inflammatory markers in post-traumatic stress disorder: A systematic review, meta-analysis, and meta-regression. *Lancet Psychiatry*, *2*, 1002–1012.

Pikula, A., Beiser, A.S., Chen, T.C., Preis, S.R., Vorgias, D., DeCarli, C., … Seshadri, S. (2013). Serum brain-derived neurotrophic factor and vascular endothelial growth factor levels are associated with risk of stroke and vascular brain injury: Framingham Study. *Stroke*, *44*, 2768–2775.

Pivac, N., Muck-Seler, D., Jakovljevic, M., Ljubicic, D., & Crncevic-Orlic Z. (1998). Hypothalamic-pituitary-adrenal axis function in posttraumatic stress disorder in Croatian war veterans. *Psychiatria Danubina*, *10*, 103–104.

Priebe, S., Bogic, M., Ajdukovic, D., Franciskovic, T., Galeazzi, G.M., Kucukalic, A., … Schutzwohl, M. (2010). Mental disorders following war in the Balkans: A study in 5 countries. *Archives of General Psychiatry*, *67*, 518–528.

Raglan, G.B., Schmidt, L.A., & Schulkin J. (2017). The role of glucocorticoids and corticotropin-releasing hormone regulation on anxiety symptoms and response to treatment. *Endocrine Connections*, *6*, 1–7.

Risbrough, V.B., & Stein, M.B. (2006). Role of corticotropin releasing factor in anxiety disorders: A translational research perspective. *Hormones and Behavior*, *50*(4), 550–561.

Robicsek, O., Makhoul, B., Klein, E., Brenner, B., & Sarig, G. (2011). Hypercoagulation in chronic post-traumatic stress disorder. *The Israel Medical Association Journal*, *13*(9), 548–552.

Rohleder, N., Joskimovic, Lj., Wolf, J.M., & Kirschbaum, C. (2004). Hypocortisolism and increased glucocorticoid sensitivity of pro-inflammatory cytokine production in Bosnian war refuges with posttraumatic stress disorder. *Biological Psychiatry*, *55*, 745–751.

Rosebrock, L.A., Arditte Hall, K.A., Rando, A., Pineles, S.L., & Liverant, G.I. (2018). Rumination and its relationship with thought suppression in unipolar depression and comorbid PTSD. *Cognitive Therapy and Research*, *43*(1), 226–235.

Rosen, R.L., Levy-Carrick, N., Reibman, J., Xu, N., Shao, Y., Liu, M., … Galatzer-Levy, I.R. (2017). Elevated C-reactive protein and posttraumatic stress pathology among survivors of the 9/11 World Trade Center attacks. *Journal of Psychiatric Research*, *89*, 14–21.

Rosenbaum, S., Vancampfort, D., Steel, Z., Newby, J., Ward, P. B., & Stubbs, B. (2015). Physical activity in the treatment of Post-traumatic stress disorder: A systematic review and meta-analysis. *Psychiatry Research*, *230*, 130–136.

Sagud, M., Jaksic, N., Vuksan-Cusa, B., Loncar, M., Loncar, I., Mihaljevic Peles, A.M., … Jakovljevic, M. (2017). Cardiovascular disease risk factors in patients with posttraumatic stress disorder (PTSD): A narrative review. *Psychiatria Danubina*, *29*(4), 421–430.

Sagud, M., Petrovic, B., Vilibic, M., Mihaljevic Peles, A., Vuksan-Cusa, B., Rados, I., … Trkulja, V. (2018). The relationship among psychopathology, religiosity, and nicotine dependence in Croatian war veterans with posttraumatic stress disorder. *Croatian Medical Journal*, *59*(4), 165–177.

Savic, D., Knezevic, G., Damjanovic, S., Spiric, Z., & Matic, G. (2012). The role of personality and traumatic events in cortisol levels–where does PTSD fit in?. *Psychoneuroendocrinology*, *37*, 937–947.

Scherrer, J.F., Chrusciel, T., Zeringue, A., Garfield, L.D., Hauptman, P.J., Lustman, P.J., … True, W.R. (2010). Anxiety disorders increase risk for incident myocardial infarction in depressed and nondepressed Veterans administration patients. *American Heart Journal*, *159*(5), 772–779.

Scherrer, J.F., Salas, J., Cohen, B.E., Schnurr, P.P., Schneider, F.D., Chard, K.M., … Lustman, P.J. (2019). Comorbid conditions explain the association between posttraumatic stress disorder and incident cardiovascular disease. *Journal of the American Heart Association*, *8*(4): e011133.

Solomon, Z., Levin, Y., Assayag E.B., Furman, O., Shenhar-Tsarfaty, S., Berliner, S., & Ohry, A. (2017). The implication of combat stress and PTSD trajectories in metabolic syndrome and elevated C-reactive protein levels: A longitudinal study. *The Journal of Clinical Psychiatry*, *78*(9), 1181–1186.

Spivak, B., Shohat, B., Mester, R., Avraham, S., Gil-Ad, I., Bleich, A., … Weizman, A. (1997). Elevated levels of serum interleukin-1β in combat-related posttraumatic stress disorder. *Biological Psychiatry*, *42*, 345–348.

Suliman, S., Anthonissen, L., Carr, J., du Plessis, S., Emsley, R., Hemmings, S.M., … Seedat, S. (2016). Posttraumatic stress disorder, overweight, and obesity: A systematic review and meta-analysis. *Harvard Review of Psychiatry*, *24*(4), 271–293.

Takashio, S., Sugiyama, S., Yamamuro, M., Takahama, H., Hayashi, T., Sugano, Y., … Ogawa, H. (2015). Significance of low plasma levels of brain-derived neurotrophic factor in patients with heart failure. *American Journal of Cardiology*, *116*, 243–249.

Tennant, C. (1982). Psychosocial stress and ischaemic heart disease: An evaluation in the light of the diseases' attribution to war service. *Australian New Zeland Journal of Psychiatry*, *16*(2), 31–36.

Tudor, L., Konjevod, M., Nikolac Perkovic, M., Svob Strac, D., Nedic Erjavec, G., Uzun, S., … Pivac, N. (2018). Genetic variants of the brain-derived neurotrophic factor and metabolic indices in veterans with posttraumatic stress disorder. *Frontiers in Psychiatry*, *9*, 637.

Turner, J.H., Neylan, T.C., Schiller, N.B., Li, Y., & Cohen, B.E. (2013). Objective evidence of myocardial ischemia in patients with posttraumatic stress disorder. *Biological Psychiatry*, *74*, 861–866.

van den Berk-Clark, C., Secrest, S., Walls, J., Hallberg, E., Lustman, P.J., Schneider, F.D., & Scherrer, J.F. (2018). Association between posttraumatic stress disorder and lack of exercise, poor diet, obesity, and co-occuring smoking: A systematic review and meta-analysis. *Health Psychology*, *37*(5), 407–416.

VanDyke, L.M., Burton, E., Hamidovic, A., & Burge, M.R. (2017). Hormonal aspects of post-traumatic stress disorder. *Endocrinology Diabetes and Metabolism Journal*, *1*(2), 1–10.

Waheed, A., Dalton, B., Wessemna, U., Ibrahim, M.A.A., & Himmerich, H. (2018). A systematic review of interleukin-1β in post-traumatic stress disorder: Evidence from human and animal studies. *Journal of Interferon & Cytokine Research*, *38*(1), 1–11.

Wang, Z., Caughron, B., & Young, M.R.I. (2017). Posttraumatic stress disorder: An immunological disorder? *Frontiers in Psychiatry*, *8*, 222.

Wang, Z., Mandel, H., Levingston, C.A., & Young M.R.I. (2016). An exploratory approach demonstrating immune skewing and a loss of coordination among cytokines in plasma and saliva of Veterans with combat PTSD. *Human Immunology*, *77*, 652–657.

Wang, W., Wang, L., Xu, H., Cao, C., Liu, P., Luo, S., … Zhang, X. (2019). Characteristics of pro- and anti-inflammatory cytokines alteration in PTSD patients exposed to a deadly earthquake. *Journal of Affective Disorders*, *248*, 52–58.

Wang, Z., & Young, M.R.I. (2016). PTSD, a disorder with and immunological component. *Frontiers in Immunology*, *7*(219), 1–6.

Weathers, F.W. (2017). Redefining posttraumatic stress disorder for DSM-5. *Current Opinion in Psychology*, *14*(122), 122–126.

Wentworth, B.A., Stein, M.B., Redwine, L.S., Xue, Y., Taub, P.R., Clopton, P., … Maisel, A.S. (2013). Post-traumatic stress disorder: A fast track to premature cardiovascular disease? *Cardiology in Review*, *21*, 16–22.

Wolf, E.J., & Schnurr, P.P. (2016). PTSD-related cardiovascular disease and accelerated cellular aging. *Psychiatric Annals*, *46*, 527–532.

Yehuda, R., Hoge, C.W., McFarlane, A.C., Vermetten, E., Lanius, R.A., Nievergelt, C.M., … Hyman, S.E. (2015). Post-traumatic stress disorder. *Nature Review*, *15057*.

Zass, L.J., Hart, S.A., Seedat, S., Hemmings, S.M.J., & Malan-Müller, S. (2017). Neuroinflammatory genes associated with post-traumatic stress disorder: Implications for comorbidity. *Psychiatric Genetics*, *27*(1), 1–16.