

# Posttraumatic Stress Disorder and Cardiometabolic Disease

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## Key Words

Cardiovascular disease · Hypothalamic-pituitary-adrenal axis · Inflammation · Insulin resistance · Metabolism · Sympathetic nervous system

## Abstract

The need for addressing posttraumatic stress disorder (PTSD) among combat veterans returning from Afghanistan and Iraq is a growing public health concern. Current PTSD management addresses psychiatric parameters of this condition. However, PTSD is not simply a psychiatric disorder. Traumatic stress increases the risk for inflammation-related somatic diseases and early mortality. The metabolic syndrome reflects the increased health risk associated with combat stress and PTSD. Obesity, dyslipidemia, hypertension, diabetes mellitus, and cardiovascular disease are prevalent among PTSD patients. However, there has been little appreciation for the need to address these somatic PTSD comorbidities. Medical professionals treating this vulnerable population should screen patients for cardiometabolic risk factors and avail themselves of existing preventive diet, exercise, and pharmacologic modalities that will reduce such risk factors and improve overall long-term health outcomes and quality of life. There is the promise that cardiometabolic preventive therapy complementing psychiatric intervention may, in turn, help improve the posttraumatic stress system dysregulation and favorably impact psychiatric and neurologic function.

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## Introduction

Exposure to traumatic stressors is widespread. Short-term severe traumatic stress may severely compromise an individual's long-term psychological health. However, there is increasing evidence that posttraumatic stress disorder (PTSD) is not just a 'mental illness' but is also associated with an increased risk for somatic diseases and early mortality [1, 2].

Current management of PTSD focuses on the psychiatric parameters of this condition with little emphasis on addressing the comorbid cardiometabolic risk factors that impair overall long-term health outcomes.

## Posttraumatic Stress Disorder

PTSD is a severely disabling neuropsychiatric anxiety disorder that develops in civilians, police officers, combat soldiers, and others as a result of experiencing horrifying trauma/stress [3].

## History

Combat-related stress responses have been mentioned as early as in the 19th century BCE by an Egyptian named Hori, in the 5th century BCE by the Greek historian Herodotus [4], and in the 11th century by the *Anglo-Saxon Chronicle* [5]. Lady Percy's soliloquy in *Henry IV*, written around 1597, appears to describe PTSD symptoms

[6]. During the siege of Gibraltar in 1727, a soldier's diary made note of affected soldiers killing or wounding themselves [5].

Different names have described this condition. In the 17th century, Swiss and German military physicians found soldiers to be suffering from 'nostalgia' and 'Heimweh', respectively. In the early 19th century, military doctors diagnosed battle-stressed soldiers with 'exhaustion'. Civil War combatants suffered from 'soldier's heart'. During the Russo-Japanese War (1905–1906), battle stress was treated as a mental disease. World War I had many soldiers disabled by 'railway spine', 'stress syndrome', 'traumatic war neurosis', or 'shell shock'. Following prolonged combat, enlisted men suffered 'battle fatigue' in World War II and a 'gross stress reaction' during the Korean War. The modern understanding of PTSD evolved as a result of the 'post-Vietnam syndrome' or 'stress response syndrome' experienced by Vietnam veterans in the 1970s, largely due to the efforts of groups, such as the Vietnam Veterans against War working in conjunction with psychiatrist Dr. Chaim F. Shatan. The Diagnostic and Statistical Manual (DSM) of Mental Disorders III incorporated PTSD as a psychiatric diagnosis in 1980 [5, 7].

#### PTSD Diagnosis

The 4th edition of the DSM of Mental Disorders (text rev., DSM-IV-TR) [8] has several criteria for the diagnosis of PTSD, encompassing

- (1) A: trauma history;
  - (2) B–D: behavioral PTSD symptom clusters: intrusion (B), avoidance (C), and arousal (D);
  - (3) E: duration, and
  - (4) F: severity.
- *Criterion A: prior exposure to traumatic events*, a sine qua non for PTSD diagnosis [9].

Such trauma, as distinguished from ordinary stress, posed a perceived physical threat to life or the physical integrity of oneself or others and may range from a

- one-time catastrophic event, to
  - chronic severe stresses.
- Examples are
- combat- or war-related trauma;
  - torture;
  - physical and sexual abuse;
  - natural disasters;
  - criminal or terrorist physical violence;
  - exposure to atrocities or their sequelae, or
  - overwhelming untreated pain.

– *A2: an individual's emotional response at the time.*

During the trauma event, the affected individual must have experienced intense

- fear;
  - helplessness, or
  - horror.
- *B: intrusion symptoms.*  
Emotionally intrusive hypermnesia of the trauma manifests via one or more of the following:
- flashback memories;
  - subjective reexperiencing of the traumatic event(s);
  - recurring distressing dreams, or
  - intense negative psychological or physiological response to any subjective or objective reminder of the traumatic event(s).
- *C: avoidance and emotional numbing.*  
This involves a sufficient level and frequency of
- avoidance of any trauma-related stimulus since the associated, aroused feelings are overwhelming;
  - avoidance of any trauma reminders that might evoke disturbing memories; flashbacks, nightmares, or intense psychological and physiological distress;
  - inability to recall major parts of the trauma;
  - decreased capacity, down to complete inability, to experience certain feelings, due to numbness, detachment, or lack of emotion;
  - withdrawal and estrangement from family and friends;
  - abusive 'self-medication' via alcohol/drugs, and
  - an expectation that one's future will be constrained relative to that of others [10].

– *D: increased arousal and reactivity.*

These are new-onset cognitive, emotional, behavioral, and physiological issues, including

- impaired concentration and memory;
- persistent anxiety, phobic reactions;
- feeling 'on guard', hypervigilance;
- hyperactivity, obsession;
- excessive physical reactivity, increased startle reactions;
- irritability, anger with outbursts;
- physiologic symptoms of autonomic hyperarousal, and
- insomnia [3, 11].

– *E: duration.*

Symptom duration >1 month.

– *F: symptom impact.*

Symptoms must be clinically significantly distressing or impair important life functions, such as social relations and occupational activities, for example [12, 13].

The composition and severity of PTSD symptoms vary among individuals. Established PTSD symptomatology can fluctuate over time, often in response to life stresses [14, 15].

### Complex PTSD

The 'simple' PTSD diagnosis may not fully capture the severe psychological symptoms that may arise in survivors of prolonged, repeated, severe trauma lasting months to years. Examples of such trauma include:

- concentration or prisoner-of-war (POW) camps;
- political torture;
- long-term domestic violence;
- long-term physical and/or sexual child abuse;
- prostitution/brothels, or
- organized child exploitation rings [16].

The concept of complex PTSD was first described by Herman [17] who described this aspect of the spectrum of traumatic disorders which may present with multiple symptoms, excessive somatization, dissociation, affect changes, and pathological changes in relationships and in self-identity.

### Traumatic Brain Injury

A companion condition to PTSD, traumatic brain injury (TBI), is also a mental health problem, given the large number of soldiers wounded in improvised explosive device attacks. The term describes a range of injuries from mild concussions to severe, penetrating head wounds. Described by Bhattacharjee [18] as 'shell shock revisited', the condition presents itself in similar ways to PTSD. US military service members are returning from the wars in Iraq and Afghanistan with elevated rates of TBI and PTSD. Nineteen percent of returning service members, a total of about 320,000, report that they experienced a possible TBI while deployed, with 7% reporting both probable TBI and concurrent PTSD or major depression [19, 20].

### Evolutionary Context

Mammals, as prey, have evolved to acutely appraise the degree to which a threat taxes their resources. They respond with physiological reactions, including increased heart rate and blood pressure. They react emotionally with fear, terror, or anger. They embrace a range of defensive behaviors as a function of the proximity of the threat, including vigilance, avoidance, withdrawal, aggressive defense, appeasement, or tonic immobility. Cognitively, mammals may respond with dissociation or with heightened memorization of the threat in order to avoid similar threats in the future [21].

Bracha [21] has posited that PTSD may reflect ongoing overactivation of these mammalian threat responses. PTSD-related trauma hypermnnesia relates to threat memorization; PTSD-related hyperarousal reflects hypervigilance and aggressive defense under threat, and PTSD-re-

lated avoidance behaviors may correspond to mammalian avoidance of, and withdrawal from, threats. Complex PTSD may, in part, correspond to the appeasement and, possibly, the tonic immobility stage [21, 22].

### Diagnostic Assays

Several validated trauma assessments allow quantification of trauma symptomatology via clinician-administered symptom checklists or patient self-report [7].

PTSD can be assessed using the Clinician-Administered PTSD Scale, the Short PTSD Rating Interview, the Mississippi Scale for Combat-Related PTSD, the Watson PTSD Inventory, the Computerized Diagnostic Interview Schedule for DSM-IV, the PTSD Checklist and the PTSD Checklist-Military Version, or the Keane PTSD scale. High PTSD symptomatology can be defined via a high Impact of Event Scale score  $\geq 26$  compared to  $< 26$  for low PTSD symptomatology [23].

### Course of PTSD

PTSD can be categorized into

- acute (symptoms lasting 1–3 months), and
- chronic (symptoms persisting  $> 3$  months) [24].

PTSD onset can be

- early (the majority of PTSD cases developing shortly after the experienced traumatic event);
- delayed (4–6% of trauma victims develop PTSD months, years, or even decades later), and
- slowly developing (gradual emergence of symptoms that progressively escalate with the passage of time, most likely in response to further traumatizing stressors) [24].

PTSD may go into partial remission; however, there may be long-lasting alterations of the primary stress pathways of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), as well as changes in the brain, even after clinical symptoms have subsided. Reexposure to reminders of the original trauma, or to recurrent trauma, may trigger reemergence of the same problems, or increase PTSD symptom severity, due to underlying neuroplastic and cognitive changes [25, 26].

### Incidence of PTSD

Up to 50–90% of humans will experience trauma in their lifetime [27]. Most individuals exposed to comparable trauma are resilient and do not develop PTSD [7].

During the early hours and days following a highly traumatizing event, the majority of people experience at least some symptoms of an acute stress disorder. Although 20–30% may develop PTSD-like symptoms, more

than half of such trauma survivors completely recover within 1–3 months in the absence of any intervention [24]. Seven to 12% of PTSD-afflicted individuals fail to recover without therapy [27, 28].

PTSD affects at least 13 million Americans. According to the US National Comorbidity Survey Replication, the adult PTSD lifetime prevalence was approximately 6.8% [29]. The Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions found a prevalence of 4.5% [30]. The variability in PTSD prevalence reports may, in part, arise as a function of the reported functional impairment.

As elucidated in a 2011 study from the Georgia State University and San Diego State University, people currently most at risk for developing PTSD are Army and Marine military/combat servicemen exposed to a high operation tempo and tours of duty exceeding a year [31].

In a recent study by the Department of Veterans Affairs (VA), close to 30% of 834,463 Iraq/Afghanistan veterans seen at VA facilities had PTSD [32], and PTSD rates among these veterans may reach approximately 35% [33].

Nonmilitary individuals at risk for developing PTSD are Holocaust survivors, victims of war, natural disasters, or criminal/terrorist attacks, or rape/child abuse victims. Twelve to 15% of patients with acute coronary syndromes (ACS) or myocardial infarctions (MI) develop PTSD as a result of their ACS event [34]. Even elephants, dogs, rats, and other mammals experience PTSD.

PTSD was originally thought to be an ordinary reaction to an extraordinary event, attributing the cause for this disorder to environmental factors, as stated by the psychiatrist and concentration camp survivor Victor Frankl: ‘an abnormal response to an abnormal situation is normal behavior’. A subsequent emphasis on vulnerability/resiliency factors suggested that genetic factors dominated the expression of the disorder. For example, the reported prevalence of PTSD tends to be twice as common in women compared to men [7, 35]. Most likely, a balance between nature and nurture underlies the development of PTSD [36].

### *Costs of PTSD*

PTSD carries a devastating toll. The individual may be plagued by waking nightmares and insomnia, and succumb to alcoholism, drug abuse, and suicidal thoughts. PTSD is associated with marked deficits in social functioning, disrupting families and relationships. Hyperarousal can impair concentration and occupational performance. The inability to hold a job contributes to an epidemic of homelessness among combat veterans.

The societal toll associated with PTSD entails economic costs due to lost productivity, work absenteeism, suicide, and increased mental health care costs [24]. A RAND study noted that the societal costs of PTSD and major depression for 2 years after deployment range from about 6,000 to >25,000 USD/case. The total PTSD- and major depression-related costs for the US in 2007 may range from 4.0 to 6.2 billion USD over 2 years [19]. The societal cost of caring for veterans with stress-related mental health disorders is expected to surpass that of the Global War on Terror, which is estimated at 600 billion USD [37].

## **PTSD and Health**

### *Mental Health*

PTSD is associated with poor mental health, including elevated odds of lifetime mood, anxiety, borderline, and narcissistic personality disorders, drug and alcohol use, and decreased psychosocial functioning. PTSD is often accompanied by other comorbid anxiety disorders and depression [30].

### *Neurological Changes*

PTSD is associated with long-lasting dysregulation of neural networks involved in stress responsivity, learning, and memory [7, 38]. There is chronic sympathetic and renin-angiotensin-aldosterone system (RAAS) hyperarousal,

- glutamatergic excitotoxicity,
  - alterations in neuropeptide Y (NPY), the neuroactive glucocorticoid systems, and brain-derived neurotrophic factor (BDNF), and
  - underactivity of the parasympathetic, serotonergic, dopaminergic, and GABAergic system, the primary inhibitory neurotransmitter system,
- which all contribute to neurometabolic changes, synaptic loss, neuronal dysfunction, and loss, engendering structural brain changes [39, 40].

Brain imaging studies reveal marked reductions in gray matter volumes in memory-/anxiety-relevant brain regions, such as the hippocampus, insula, orbito-/prefrontal cortex, anterior cingulate gyrus, and caudate in PTSD patients [41, 42].

The limbic-neuronal structural abnormalities contribute to cognitive/emotional/behavioral symptoms and disorders [39, 40]. They may underlie the pathophysiology of PTSD and exist on a continuum with PTSD symptoms [43].



## Pain Syndrome

PTSD victims experience an enhanced rate of chronic pain [26], including headaches, and back, neuropathic [44], and temporomandibular joint pain [45]. Pain and PTSD involve similar brain regions – the amygdala, hippocampus, insula, and the anterior cingulate gyrus. As in anxiety dysregulation, deficient extinction rather than enhanced acquisition of pain responses is a core deficit [26].

## Physical Health

After controlling for major depression, alcohol, nicotine, and substance abuse/dependence, PTSD-affected individuals have a higher incidence of various disorders, including

- increased waist-hip ratio, obesity, hypertension, dyslipidemia, cardio- and cerebrovascular disease, tachycardia, metabolic syndrome, noncirrhotic liver disease, diabetes mellitus (DM), and premature death;
- impaired immunity with increased susceptibility to infections, stomach ulcers, and human immunodeficiency virus seropositivity;
- autoimmune conditions, such as rheumatoid arthritis, psoriasis, and thyroid disease, and
- chronic pain, fibromyalgia, chronic fatigue syndrome, chronic musculoskeletal disorders, bone demineralization, and osteoarthritis [2, 46–50].

## PTSD-Related Risk Factors for Cardiometabolic Disease

PTSD arises in response to overwhelming external stress, but it engenders tremendous ongoing internal distress [49]. Chronic exposure to PTSD-stress-related biochemical pathways accelerates physiologic aging that underlies an increased risk for age-related diseases and early mortality [45].

In a vicious circle, the systemic trauma/stress manifestations may further worsen stress-related structural and functional CNS changes.

## Cellular Processes

PTSD-related cellular dysfunction may arise from stress-induced dysregulation of telomere/telomerase maintenance [39], mitochondria, and endoplasmic reticular (ER) stress.

## Telomere Dysfunction

Shalev et al. [51] have undertaken pivotal studies suggesting that stress accelerates telomere erosion beginning

very early in life and highlighting the linkage of stress and mental illnesses with telomere erosion. PTSD-stress-related accelerated cell aging is indexed by telomere attrition [52]. Telomerase activity under stress can be low, accentuating telomere loss and stress-related replicative senescence [53]. PTSD patients have shorter age-adjusted leukocyte telomere lengths than controls [54, 55].

## Mitochondrial Dysfunction

Work in animal models has shown that exposure to chronic mild stress inhibits mitochondrial respiration rates and dissipates mitochondrial membrane potential [56]. Mitochondria are highly susceptible to damage due to their finite DNA and protein repair mechanisms. Chronically activated stress pathways elicit a prooxidant and proinflammatory milieu that accelerates not only telomere attrition but also mitochondrial dysfunction. Failing mitochondria contribute to cell dysfunction by inducing

- a bioenergetic deficit,
- oxidative stress, and
- a proinflammatory state.

Impaired mitochondrial performance leads to cell senescence and cell death processes. The cumulative cellular losses provoke organ dysfunction, organismal aging, and age-dependent cardiometabolic diseases [57].

## ER Stress

Stress-related mitochondrial dysfunction is intimately linked to ER stress, allowing for deleterious crosstalk between both organelles.

ER stress leads to the misfolding of nascent proteins and the accumulation of such unfolded proteins in the ER lumen. ER stress also promotes chronic oxidative stress [58, 59] and inflammatory and degenerative processes, leading to cell pathology, apoptotic cell death, tissue dysfunction, and age-related cardiometabolic diseases [57].

## Neuroendocrine Activation

PTSD-related neurohormonal activation affects not only structural/functional brain changes but also systemic metabolism.

## Glucocorticoids

In a challenge to traditional stress research findings, Yehuda [60] noted that urinary and plasma cortisol levels were considerably lower in PTSD patients than in non-PTSD trauma survivors and normal controls. There is enhanced inhibition of the HPA axis in PTSD patients [41], and both hypocortisolism [46] and reduced responsive-

ness to glucocorticoids are found in PTSD victims [61]. Hypocortisolism is characterized by a symptom triad of

- pain,
- fatigue, and
- enhanced stress sensitivity [62],

to the extent that low cortisol levels may be a trait that predisposes individuals to the development of PTSD [63]. It may also contribute to alterations in insulin sensitivity [64].

#### Neurosteroids

Rasmusson et al. [65] have been involved in pivotal studies on diverse neuroendocrinologic disturbances elicited by PTSD and the link to metabolic syndrome. PTSD is associated with decreased levels of neurosteroids, such as dehydroepiandrosterone (DHEA), allopregnanolone, and pregnanolone, in corticolimbic neurons.

Allopregnanolone and pregnanolone are  $3\alpha$ -reduced progesterone derivatives that equipotently and positively modulate the action of GABA at GABA<sub>A</sub> receptors. Since expression of the  $3\alpha$ -hydroxysteroid dehydrogenase gene is upregulated by cortisol, PTSD-afflicted individuals with deficient cortisol during stress may not appropriately upregulate allopregnanolone levels. The resulting increased NPY levels have adverse cardiometabolic effects [65].

Increasing DHEA/sulfated DHEA (DHEAS) levels in the face of stress appears to confer psychological resilience, and increased DHEA responses are associated with lower PTSD symptoms [65]. In some individuals, stress may decrease DHEA/DHEAS levels [65], and PTSD victims may have reduced DHEA levels [46]. Low DHEA/DHEAS levels have been associated with the metabolic syndrome [65].

#### Sympathetic Arousal

Kosten et al. [66] noted high urinary norepinephrine/epinephrine excretion in PTSD patients relative to patients with other mental health diagnoses. There is chronic, high-level SNS arousal in PTSD patients relative to controls, which is evidenced by elevated plasma and 24-hour urinary catecholamine levels [67, 68]. PTSD is characterized by tremor and other symptoms of autonomic arousal. PTSD patients exhibit cardiovascular sympathetic activation with significantly higher heart rates and blood pressure levels relative to controls, even during sleep, with lower respiratory sinus arrhythmia [69, 70]. Corrected for age, PTSD patients, relative to non-trauma-exposed controls, have a high prevalence of lower heart rate variability, consistent with increased sympathetic and attenuated parasympathetic tone at

baseline and throughout different affective conditions [71–73].

Sympathetic arousal plays a key role in RAAS activation and the pathogenesis of hypertension, cardiovascular remodeling, and insulin resistance, the magnitude of the sympathetic response to mental stress being associated with increasing insulin resistance. Crosstalk between the catecholamine and insulin signaling pathways establishes the metabolic milieu that blunts insulin sensitivity and is conducive to the development of the metabolic syndrome and type 2 DM in susceptible persons.  $\alpha$ - and  $\beta$ -adrenergic receptor mechanisms are implicated [57].

#### Neuropeptide Y

NPY is a sympathetic neurotransmitter involved in stress regulation [74], being anxiolytic and neuroprotective against hippocampal excitotoxicity [75]. It is also involved in learning, memory, and cognition [76].

NPY is released during intense SNS activation. Once released, NPY amplifies norepinephrine effects to increase overall blood pressure while inhibiting vagal action to facilitate stress-related heart rate increases. NPY increases high blood pressure maintenance via mitogenic induction of vascular smooth muscle cell hypertrophy and vasoconstrictor hyperresponsivity to NPY [65].

NPY promotes recovery from stress-induced energy depletion via intracellular, central, and peripheral tissue effects on metabolism and feeding behavior, thus helping to maintain energy balance [74]. Chronic stress-induced NPY release amplifies and accelerates diet-induced obesity and the metabolic syndrome [77].

Male combat veterans with PTSD have reduced resting, as well as stress-activated, plasma NPY levels [78], thus forfeiting its anxiolytic effects. Such individuals, therefore, have a lower stress threshold, paradoxically prompting an increase in the frequency of stress-induced NPY release. In PTSD, lower amplitude NPY stress responses will thus be triggered at higher frequency, not only by exposure to serious stressors in objectively threatening environments, but also repeatedly in reaction to over-generalized, conditioned threat cues in objectively safe environments [65].

In PTSD, the frequency, as well as the amplitude, of NPY release into fat may critically contribute to the risk of developing obesity, hypertension, and the metabolic syndrome [65].

#### Inflammation

Multiple factors promote a milieu of systemic inflammation in PTSD. Telomere, mitochondrial, and ER stress

pathways of cellular senescence promote inflammation [57].

In addition, neuroendocrine and immune systems form an integrated early host response to trauma/stress. PTSD-associated hypocortisolism may fail to contain inflammatory reactions [79], which would, from an evolutionary perspective, foster immune readiness and increased arousal [63]. Since cortisol is normally important for restoring homeostasis after the stress response, insufficient glucocorticoid signaling in PTSD may impair feedback regulation of relevant stress responses, including the SNS [64]. Sympathetic excitotoxicity entails neurogenic priming of the systemic proinflammatory response. PTSD-associated SNS arousal may also activate the RAAS and promote inflammatory pathways [80].

In addition, PTSD stress may alter gene-specific DNA methylation, effecting persistent epigenetic gene function changes, with many of the affected genes being associated with inflammation [81]. Among PTSD patients, the methylation level of such genes is significantly and negatively correlated with trauma/burden [82].

von Känel et al. [83] have been instrumental in elucidating the linkage of PTSD with a proinflammatory state and many of its attendant cardiometabolic sequelae. PTSD patients do have activation of innate immune responses and a low-grade systemic proinflammatory state [84] with increased circulating proinflammatory markers [85] and cytokine serum levels positively related to PTSD scores [86].

Inflammation alters vascular function as well as carbohydrate, protein, and lipid metabolism in order to benefit the host response, but with adverse effects on cardiometabolic health. In order to prioritize energy provisioning to the immune system, proinflammatory cytokines impair non-immune organ insulin sensitivity, engendering insulin resistance. As a result, whereas glucose availability for the insulin-independent immune cells is enhanced, glucose uptake by 'nonessential' insulin-dependent tissues is compromised [57].

Chronic PTSD stress effects may constitute one pathophysiologic link between stress and the development of somatic disorders with an inflammatory etiology, as clustered in cardiometabolic pathologies [49, 64, 65, 68, 87, 88].

#### Oxidative Stress

Mitochondrial dysfunction, ER stress, and RAAS- and inflammation-associated chronic prooxidant stress leads to vascular dysfunction and insulin resistance in a number of tissues, including the vasculature, skeletal and car-

diac muscles, fibroblasts, and adipose tissue. Oxidative stress importantly contributes to cardiometabolic disease [57].

#### Weight Gain

Stress pathways can induce weight loss due to catabolic and anorexic responses in some individuals [77] but weight gain in others. PTSD groups tend to have an elevated body mass index (BMI) [89].

PTSD is associated with limbic-neuronal structural/functional abnormalities. Fehm et al. [90] have elucidated central mechanisms of body weight regulation. Hippocampal structures determine the set point for body weight regulation. This hippocampal set point can be permanently displaced by trauma/stress situations. As a result, the energy supply of the stressed organism may predominantly depend on increased new fuel revenue via orexigenic stimuli and metabolic rate dampening rather than on redistributive glucose allocation. This favors stress-induced ponderosity in susceptible individuals and may be a primary disturbance in stress-related obesity [91].

Excess body weight may also stem from a degradation of hippocampal inhibitory learning and memory processes that help regulate energy intake and that normally function to inhibit nonhomeostatic eating behavior [92].

In addition, stress hormone activation significantly reduces food reward sensitivity in the amygdalar/hippocampal/cingulate cortex reward areas. Diminished food reward perception may engender nonhomeostatic consumption of sugar- and fat-rich 'comfort foods' favoring weight gain [77, 93].

#### Obesity

There is a strong association between PTSD and the risk of central obesity [94]. The prevalence of obesity in the veteran population continues to increase, as documented extensively by Vieweg et al. [95].

In a PTSD program database analysis, the 82.8% prevalence of overweight/obesity among PTSD veterans (mean BMI =  $30.2 \pm 5.8$ ) exceeded the contemporaneous 64.5% US population findings and those of veteran groups without PTSD [95].

In a sample of randomly selected veterans from the national database, the BMI of male military PTSD veterans ( $n = 1,819$ ; BMI:  $29.28 \pm 6.09$ ) exceeded that of non-PTSD veterans ( $n = 44,959$ ;  $27.61 \pm 5.99$ ;  $p < 0.0001$ ) [96].

In a local database of male military PTSD veterans, mean BMI was in the obese range ( $30.00 \pm 5.65$ ) and did not vary by age [96] or use of psychotropic drugs associated with weight gain [97].

In logistic regression analyses of 20,013 participants weighted to represent the general US adult population, obesity rates were 24.1% for persons without lifetime PTSD and 32.6% among persons with PTSD in the past year. After adjustment for sociodemographics, gender, depression, substance and alcohol abuse/dependence, and psychotropic medication status, past-year PTSD was associated with greater likelihood of obesity [odds ratio (OR) = 1.51] [98].

In multivariate analyses of health information data from 15,000 Gulf War veterans and 15,000 contemporaneous veterans, PTSD was positively associated with obesity after adjustment for age, sex, Gulf deployment status, rank, income, education, and current smoking (OR = 1.5) [99].

In turn, in a survey of 12,992 participants  $\geq 16$  years, obesity was significantly associated with PTSD (OR = 2.64) [100].

#### Insulin Resistance

PTSD patients have consistent activation of stress pathways. Obesity exacerbates stress activation, facilitating systemic inflammatory activation [91]. As adipose tissue, particularly visceral adiposity, becomes secondarily inflamed and dysfunctional, it amplifies the systemic pro-inflammatory milieu via massive deleterious systemic free fatty acid and adipocytokine release [57].

Although, in general,

the greater BMI  $\rightarrow$  the higher insulin resistance,

adipose inflammation, rather than ponderosity alone, constitutes the link between obesity, insulin resistance, and PTSD-associated cardiometabolic risk [57, 91]. Bays [101] has been at the forefront elucidating the linkage between 'sick fat' (or adiposopathy) and cardiometabolic risk.

In individuals chronically stressed by PTSD, poor health behavior and eating pathology conspire with neuroendocrine mechanisms to promote obesity and attendant cardiometabolic abnormalities [100, 102].

#### Sleep Debt

Short sleep duration is associated with symptoms of PTSD, high health risk behaviors, and suicide attempts [103]. PTSD symptom severity is related to the degree of sleep disturbance [104, 105]. There is fragmentation of rapid eye movement sleep in developing and chronic PTSD and reduced deep slow wave sleep in chronic PTSD [106]. van Liempt et al. [70] and Germain [107] have published extensively on sleep disturbances and PTSD.

#### Insomnia

Insomnia is defined as

- an impaired ability to initiate or maintain sleep,
- early awakening, and
- interrupted, nonrestorative, poor-quality sleep, followed by significantly impaired daytime function not attributable to other conditions [8]. Clinically significant insomnia presents  $>3$  times weekly, and chronic insomnia persists for  $>6$  months. Insomnia is a core component of PTSD (DSM IV criterion D) [108]. Seventy to 91% of patients with PTSD report insomnia symptoms. Hyperarousal is a hallmark of PTSD, and insomnia is but a manifestation of continuous PTSD hyperarousal rather than a state of sleep loss [109].

#### Sleep-Disordered Breathing

PTSD hyperarousal also appears related to sleep-disordered breathing and impaired sleep maintenance [104, 105, 110]. Sleep-disordered breathing, as well as sleep movement disorders, frequently manifest in PTSD patients at a higher-than-expected prevalence than in the general population [109, 111].

#### Nightmares

PTSD patients are plagued by posttraumatic trauma-related distressing dreams (DSM IV criterion B) [112]. Nightmares are reported by 19–71% of PTSD patients, depending on PTSD severity [109]. Dream content may vary between trauma replay, non-replay, or mixed replay/non-replay, the affect reflecting the terror experienced at the time of trauma [113].

#### Cardiometabolic Disease

Chronic sleep loss accelerates age-related chronic cardiometabolic disorders and increases their severity [114]. Epidemiologic studies indicate a causal link between sleep deprivation and

- obesity,
- metabolic syndrome,
- type 2 DM,
- hypertension,
- atherosclerosis,
- stroke,
- heart failure,
- cardiac arrhythmias,
- sudden death, and
- reduced lifespan [57].



### Worsening PTSD

Sleep problems, especially if associated with nightmares,

- worsen neurocognitive functions,
- negatively impact on PTSD development, severity, and outcome [107],
- adversely affect the efficacy of first-line PTSD treatments [115], and
- are a unique predictor of suicide attempt longitudinally in young military personnel [116].

### Metabolic Syndrome

The metabolic syndrome is defined in an individual by the presence of three out of five modified National Cholesterol Education Program (NCEP): Adult Treatment Panel (ATP) III criteria:

- waist circumference  $\geq 102$  cm in men and  $\geq 88$  cm in women;
- serum triglycerides (TG)  $\geq 150$  mg/dl (1.69 mmol/l);
- high-density lipoprotein (HDL) cholesterol level  $< 40$  mg/dl (1.04 mmol/l) in men and  $< 50$  mg/dl (1.29 mmol/l) in women;
- blood pressure  $\geq 130/85$  mmHg, and
- serum glucose level  $\geq 110$  mg/dl (6.1 mmol/l) [57].

The metabolic syndrome mediates significant long-term health risks. Insulin resistance itself, defined as TG/HDL  $\geq 3.8$ , as well as the metabolic syndrome, is associated with an elevated risk of type 2 DM and cardiovascular disease [117].

The prevalence of insulin resistance, metabolic syndrome, and type 2 DM continues to rise, and nonwhite populations are at the greatest risk. Other contributing factors include mitochondrial dysfunction, aging, chronic infection/inflammation, oxidative stress, inflamed adiposity, physical inactivity, certain medications, genetics, stress, and mental disorders [118]. As noted in a 2006 hearing before the Committee on VA House of Representatives, of the current VA patient population, 2,000,000 have the metabolic syndrome [119].

Traumatic-stress populations display an increased propensity for glucose metabolism disorders [120]. The rate of the metabolic syndrome is especially high among persons with anxiety [121] and psychiatric disorders [122], including PTSD, as outlined in work by Pervanidou and Chrousos [68] as well as Rasmussen et al. [65]. PTSD patients with comorbid depression appear to be at even greater risk for the metabolic syndrome [65, 123].

### Risk Factors

The adverse metabolic consequences of the distress-altered HPA, SNS, and RAAS stress responses are additive and complementary. These pathways directly induce insulin resistance.

Trauma/stress pathways impair systemic insulin sensitivity also indirectly via systemic proinflammatory activation and oxidative stress, comorbid inflamed adiposity, posttraumatic insomnia, and sleep-disordered breathing, which facilitate the evolution of insulin resistance and metabolic syndrome in susceptible individuals.

Unhealthy lifestyles prevalent in PTSD compound the development of visceral adiposity, insulin resistance, metabolic syndrome, and DM [89].

In addition, atypical antipsychotics employed for long-term PTSD treatment promote the metabolic syndrome [124]. Among outpatients treated with atypical antipsychotics for various mental health disorders, PTSD patients nevertheless had the highest risk of the metabolic syndrome (72%) [89].

### Prevalence/Incidence

Metabolic syndrome criteria, albeit prevalent, vary among PTSD patients, suggesting that individually variable neurobiological processes also underlie variations in nonpsychiatric manifestations [65].

In a crossover design study, 15 overweight, male war refugees with PTSD (mean age  $44 \pm 11$  years, BMI  $29.3 \pm 4.3$ ), responded to acute stress exposure with significantly raised postprandial blood glucose and insulin levels [125].

In a cross-sectional survey of 118 active duty, male police officers, those afflicted with PTSD, after controlling for sociodemographics, BMI, and tobacco, alcohol and medication use, exhibited significantly higher serum cholesterol and TG levels than those without PTSD [126].

Among 245 subjects with a low socioeconomic status from medical clinics in Atlanta, the prevalence of the metabolic syndrome was 33.2%, but it was 47.8% ( $p = 0.006$ ) among PTSD patients [127].

A peer-reviewed literature search (1966 onward) reported a 31.9–35% prevalence of the metabolic syndrome in combat PTSD patients [128].

According to the modified NCEP:ATP III criteria, 25–35% of male PTSD combat veterans had the metabolic syndrome [123, 124, 129].

Forty percent of 253 veterans (average age 51.5 years, 92% male) at the Cincinnati VA Medical Center met the criteria for the metabolic syndrome, versus 43% of PTSD veterans ( $n = 139$ ), while controlling for variables includ-

**Table 1.** Incidence of insulin resistance and metabolic syndrome with and without PTSD at 2-year follow-up

Variable	PTSD (n = 11,420)	No PTSD (n = 196,534)	p value
TG, mg/dl	139±90	129±72	0.001
HDL mg/dl	42±15	45±13	0.006
TG/HDL ratio	4.3±3.8	3.3±1.9	0.0001
Insulin resistance, %	34.8	19.3	0.00001
Fasting blood sugar	114±41	110±38	0.008
Metabolic syndrome	52.5	37.3	0.0001

ing sociodemographics, BMI, alcohol/substance/nicotine/medication use, and depression [130].

Ahmadi et al. [131] have shown PTSD to be independently associated with an increased incidence of insulin resistance and metabolic syndrome. In a VA study of electronic medical records of 207,954 veterans in Southern California and Nevada [age  $60 \pm 14$  years, 93% male, no known coronary heart disease (CHD)/DM], there were no significant baseline differences in age, gender, lipids, fasting blood sugar, and conventional risk factors among individuals with and without PTSD. At the 2-year median follow-up, the incidence of insulin resistance, defined as TG/HDL  $\geq 3.8$ , was higher among PTSD than non-PTSD veterans (34.8 vs. 19.3%;  $p = 0.00001$ ). Similarly, the metabolic syndrome, defined by NCEP:ATP III criteria, was higher among PTSD than non-PTSD veterans (52.5 vs. 37.3%;  $p = 0.00001$ ; table 1). Adjusted for age, gender, and conventional risk factors, the excess incidence of insulin resistance and metabolic syndrome was 14.20 (17.83–18.53;  $p = 0.0001$ ) and 12.07% (13.73–14.42;  $p = 0.0001$ ) in PTSD veterans and non-PTSD veterans ( $p < 0.05$ ), respectively. The population risk of insulin resistance and metabolic syndrome attributable to PTSD was 49 and 41%, respectively [131].

#### PTSD Severity

The metabolic syndrome and PTSD intensity are significantly related.

After controlling for relevant demographic, somatic, and behavioral/psychiatric factors, veterans with higher PTSD severity were significantly more likely to meet diagnostic criteria for the metabolic syndrome. Each 1-point increase in PTSD symptom severity, as measured by the Clinician-Administered PTSD Scale [132], conferred a 1-point increase in the risk for the metabolic syndrome [130].

The rate of the metabolic syndrome among police officers with the most severe PTSD exceeded that of officers with the lowest PTSD severity category threefold despite adjustments for age and several demographic and lifestyle factors (age, education, smoking, and alcohol intake) [133].

The metabolic syndrome was identified in 66.7% of high-intensity PTSD combat veterans relative to 23.3% of low-intensity PTSD veterans [124].

#### Diabetes Mellitus

The metabolic syndrome is associated with an elevated risk for DM. Of the current VA patient population, 1,000,000 (20%) veterans have DM. Thirty percent of VA health care costs go to diabetic veterans. As noted by Boscarino [46], PTSD patients, in particular, have an increased risk of insulin-dependent DM.

There is an association between DM and PTSD [134]. In a comparison of 80 PTSD patients and 70 matched non-PTSD controls, PTSD patients had a significantly higher prevalence of fasting blood glucose  $>5.6$  mmol/l and DM (26.3 vs. 11.4%;  $p < 0.05$ ) [135]. In 44,754 military Millennium Cohort Study participants (median age 36 years), after adjustment for age, sex, BMI, education, ethnicity, military service, and mental health, only baseline PTSD symptoms, but not other mental health symptoms or deployment experience, were significantly associated with a future risk of DM (OR = 2.07) [136]. Among low-income minorities with DM, lifetime PTSD symptoms were significantly associated with hemoglobin A<sub>1C</sub>  $>7\%$  [137].

#### Neuropathophysiology

Insulin resistance, metabolic syndrome, and DM, in turn, can worsen structural/functional brain abnormalities in a vicious circle. As pointed out by Reagan [138], Stranahan and Mattson [139] and others [140, 141], there are significant pathophysiological similarities between obesity-/DM-, and stress-related mood disorders. Common mechanisms may include mitochondrial dysfunction, insulin resistance, neuroinflammation, oxidative stress, abnormal brain lipid metabolism, or BDNF deficits. The long-term consequence of both entails accelerated brain aging that increases the risk for psychiatric comorbidities, neurocognitive deficits, and neurodegenerative disorders [142, 143].

The National Comorbidity Survey of US adults (15–54 years) found DM to be associated with an increased likelihood of PTSD (OR = 2.3), which persisted after adjusting for differences in sociodemographics [134].

## Cardiovascular Disease and Mortality

A number of epidemiologic studies support an association of trauma-/stress-related disorders, including PTSD, with increased cardiovascular risk, hypertension, and CHD [144, 145].

In 2005, the VA affirmed hypertension, atherosclerosis, and stroke to be service connected in former POW [146]. In VA and non-VA healthcare data (1991–2000) for 19,442 former World War II POW and 9,728 non-POW controls, POW had a significantly higher risk of PTSD, and PTSD POW had significantly higher risks of hypertension and CHD compared to non-POW and non-PTSD POWs [147]. In a review of 11 studies, PTSD patients had increased rates of physician-rated and self-reported cardiovascular diseases [148].

Boscarino [149] and others [131] have brought to the fore the notion that PTSD constitutes a potent risk factor for cardiovascular disease.

### *Mechanisms*

Trauma-/stress-related anxiety disorders, particularly PTSD, confer SNS hyperarousal, HPA axis dysregulation, proinflammatory activation, obesity, and sleep disturbances, conditions conducive not only to the development of the metabolic syndrome but also of CHD [144, 150].

Inflammation may link PTSD with an increased risk of cardiovascular events [83]. Numerous molecular and cellular proinflammatory pathways promote atherosclerosis [151].

Metabolically, inflammation entails insulin resistance and underlies the development of the metabolic syndrome. The metabolic syndrome constitutes a clustering of cardiovascular risk factors that directly and indirectly hasten cardiovascular disease and predict CHD-related morbidity and premature mortality [152].

### Risk Perception

The association between PTSD and increased cardiometabolic disease is often complicated by a co-occurrence of multiple health risk behaviors or comorbid psychiatric conditions.

Many PTSD patients significantly reduce their sport participation following onset of PTSD symptomatology [153].

The Large Health Survey of Veterans (n = 501,161) showed a statistically increased (OR = 1.26) co-occurrence of obesity, current tobacco use, and absence of regular exercise among PTSD veterans [154]. Among CHD

patients, those with PTSD are more likely to report physical inactivity, medication nonadherence, and smoking. Adjustment for comorbid depression and lower income explain some of these associations [155].

ACS patients with PTSD have significantly greater optimistic bias regarding their ability to control their CHD on their own than do controls after adjustment for demographics, ACS severity, medical comorbidities, depression, and self-confidence [156]. Since patients with PTSD tend to avoid stress, PTSD symptoms among ACS patients are independently associated with significantly longer prehospital delays [157].

Following ACS/MI, PTSD symptoms predict nonadherence to medical advice and treatments, with a higher likelihood of ACS recurrence, cardiovascular morbidity, and readmission during the 1-year follow-up [156, 158].

### Dyslipidemia

PTSD may promote an unfavorable lipid profile, specifically low HDL and elevated TG plasma levels comprising two modified NCEP:ATP III metabolic syndrome criteria. Such dyslipidemia may contribute to PTSD-related atherosclerotic risk [159].

In a mouse model with features of PTSD and major depression, a Western-style diet increased non-HDL cholesterol and intrahepatic TG accumulation [160].

In a comparison of 80 PTSD patients and 70 non-PTSD controls, PTSD patients had a higher prevalence of HDL <1.0 mmol/l (31.3 vs. 8.6%; p = 0.0006) and TG >2.3 mmol/l (62.5 vs. 21.4%; p = 0.001) [135]. In a comparison of 50 PTSD veterans with non-PTSD veterans, PTSD veterans had lower HDL (0.96 ± 0.18 vs. 1.15 ± 0.24 mmol/l; p < 0.001) but higher TG (2.55 ± 0.68 vs. 1.73 ± 0.77 mmol/l; p < 0.001) [161], with similar findings in other studies [162, 163]. Patients with PTSD caused by MI had significantly lower HDL than patients with subsyndromal or no PTSD after controlling for sex, BMI, and statin-equivalent dosage. HDL levels were significantly inversely associated with total PTSD symptoms, reexperiencing, and avoidance [159].

### Vascular Dysfunction

Psychological distress can result in arterial endothelial injury. Inflammation and insulin resistance entail endothelial dysfunction [164].

PTSD has a continuous relationship with indices of endothelial dysfunction, such as soluble tissue factor and von Willebrand factor [165]. PTSD is associated with higher levels of circulating cellular adhesion molecules, greater PTSD severity correlating with significantly high-

er resting levels of soluble vascular cellular adhesion molecule-1 and soluble P-selectin [166].

In the Buffalo Cardio-Metabolic Occupational Police Stress study of 100 randomly selected police officers, who were compared to similarly aged populations, police officers had higher rates of PTSD, depression, and elevated BMI with lower flow-mediated dilation [167].

PTSD is associated with decreased compliance of large arteries. Pulse wave velocity measures of arterial stiffness increased with PTSD severity ( $p = 0.001$ ) [135].

In a review of electronic medical records of 896 patients 1 year before until 4 years after the disaster, after adjusting for demographics, smoking, and physical health before the disaster, disaster-related PTSD was significantly associated with newly recorded vascular problems (OR = 1.92) [168].

Erectile dysfunction can be multifactorial and caused by the use psychotropic medications. It is also a symptom of endothelial dysfunction. PTSD is associated with pervasive sexual dysfunction [169]. Erectile difficulties are common among PTSD-afflicted Vietnam veterans [170]. PTSD combat veterans experience a significantly higher rate (85%) of sexual dysfunction than do non-PTSD veterans (22%). Moderate-to-severe erectile dysfunction is present in 45% of PTSD patients versus 13% of controls [171].

### Hypertension

Vascular dysfunction is a risk factor for hypertension. The prevalence of hypertension, a modified NCEP:ATP III metabolic syndrome criterion, appears to be increased in PTSD [172, 173].

Altered neurochemistry, most notably perturbations in norepinephrine and NPY function [78, 174], and increased arginine-vasopressin levels may contribute to hypertension in PTSD [175].

PTSD is characterized by the absence of normal nocturnal blood pressure dipping and elevated nocturnal blood pressure [176]. PTSD patients have significantly higher diastolic blood pressure compared with patients afflicted by other psychiatric disorders [89]. Data from the US National Comorbidity Survey suggest PTSD to be related to hypertension independently of depression [177].

In a comparison of 80 elderly PTSD patients with 70 non-PTSD controls, PTSD patients had a higher prevalence of blood pressure  $>140/90$  (86.0 vs. 65.7%;  $p = 0.003$ ) [135]. In a comparison of 1,381 Gulf War veterans with non-PTSD veterans, adjusted OR for hypertension was 2.90 in the past 12 months and 2.27 for lifetime prevalence in PTSD veterans. Hypertension was  $>7$  times more

likely among PTSD veterans than among those free of mental illness [178].

### Hypercoagulability

Platelet activation and hypercoagulability occur in the metabolic syndrome and contribute to coronary atherothrombosis.

Platelet reactivity in PTSD may be exaggerated [179] by SNS hyperarousal, and altered adenylate cyclase and platelet  $\alpha_2$ -adrenoreceptor expression [145]. Platelet reactivity was higher in PTSD war veterans than in healthy controls and correlated with the severity of PTSD symptoms [145].

PTSD may elicit subthreshold hypercoagulability [180], but hypercoagulability may become exacerbated by anticipatory stress [181]. PTSD patients are at higher risk of arterial and venous thromboembolic events [181]. Von Willebrand factor antigen levels and factor VIII activity were significantly increased in severe chronic PTSD patients compared to controls [182].

### Coronary Heart Disease

Dyslipidemia, vascular dysfunction, hypertension, and hypercoagulability are all manifestations of the metabolic syndrome that contribute to CHD, a serious comorbidity of the metabolic syndrome.

There is a substantial link between PTSD and CHD. PTSD is a risk factor for atherogenesis and cardiovascular disease [149, 175, 183].

In a comparison of 50 PTSD veterans with 50 non-PTSD veterans, the 10-year ATP III CHD risk was higher in the PTSD group ( $19.44 \pm 7.27$  vs.  $9.74 \pm 4.10\%$ ;  $p < 0.001$ ) [161]. The 10-year ATP III CHD risk was also higher in 103 combat-related PTSD patients versus 92 depressed patients [163]. Higher measured PTSD symptomatology increases the incident CHD risk. In a study of 179 patients (mean age = 63 years, 68% men) with psychotic symptoms but without known CHD/stroke at baseline, PTSD increased the Framingham 10-year CHD risk by 72% relative to the general Framingham Heart Study population [184].

PTSD was associated with premature atherosclerosis of coronary, cerebral, and peripheral blood vessels in the veterans of special risk subdivisions [185].

PTSD correlates with the presence and severity of coronary atherosclerosis as reflected by the coronary artery calcium (CAC) score. In a study of 637 veterans without known CHD ( $61 \pm 9$  years, 12.2% women), CAC was more prevalent in the PTSD cohort than the non-PTSD cohort (76.1 vs. 59%;  $p = 0.001$ ), and their CAC scores



were significantly higher in each Framingham risk score category compared to the non-PTSD group. Multivariable generalized linear regression analysis identified PTSD as an independent predictor of the presence and extent of atherosclerotic CHD ( $p < 0.01$ ) [186].

In a comparison of 80 PTSD patients with 70 non-PTSD controls, PTSD patients had a higher prevalence of CHD (71.3 vs. 44.3%;  $p < 0.001$ ). Stepwise logistic regression showed PTSD to be a strong factor promoting the appearance of CHD (OR 3.80;  $p = 0.002$ ) [135].

The prevalence of MI and stroke is increased in PTSD [172, 173, 186]. In a study of 4,462 nonhospitalized male veterans (mean age = 38) about 20 years following military service, after controlling for multiple biases, confounders, current anxiety, and depression, PTSD was significantly associated with resting 12-lead electrocardiographic findings of atrioventricular conduction defects (OR = 2.81) and infarctions (OR = 4.44) [164].

PTSD symptoms occur in 10–25% of patients presenting with ACS. In turn, PTSD is an important compounding factor for the genesis of future cardiovascular disease [187]. PTSD is prospectively associated with an increased risk of cardiovascular readmission in post-MI patients [148]. In a meta-analysis of 24 studies including 2,383 ACS patients, developing PTSD due to ACS doubled the risk of having recurrent ACS or dying within 1–3 years compared with cardiac patients who did not develop PTSD [188].

#### *Premature Mortality*

PTSD is a risk factor for increased premature mortality independent of age, gender, and conventional risk factors [186]. PTSD is prospectively associated with an increased risk of cardiovascular mortality in combat veterans [148]. PTSD is a strong and independent predictor of an elevated risk for major adverse cardiac events and all-cause mortality (adjusted hazard ratio 3.38;  $p = 0.015$ ), and should be considered in ACS patient risk stratification [34].

During a mean follow-up of 42 months of 637 veterans without known CHD (age =  $61 \pm 9$  years), the death rate in the PTSD cohort exceeded that of the non-PTSD group (17.1 vs. 10.4%;  $p = 0.003$ ). Multivariable survival regression analyses revealed a significant PTSD mortality and CAC mortality linkage. After adjustment for risk factors, relative risk of death was 1.48 ( $p = 0.01$ ) in subjects with PTSD and CAC score  $>0$  compared to subjects without PTSD and CAC score = 0. For each non-zero CAC category, the relative risk of death of PTSD subjects exceeded that of matched non-PTSD subjects (1.23 for CAC scores 1–100, 1.51 for CAC scores 101–400, and 1.81 for CAC scores  $\geq 400$ ;  $p < 0.05$  for all comparisons) [186].

PTSD symptoms adversely affect long-term mortality risk in implantable cardioverter-defibrillator (ICD)-treated cardiac event survivors, independent of disease severity. In 5.1-year follow-up data derived from the Living with an Implanted Cardioverter-Defibrillator-Study of 211 patients with ICDs, PTSD patients had no differences in left ventricular ejection fraction status or extent of ICD discharges compared with non-PTSD patients. The relative mortality risk (multivariate adjusted for age, sex, DM, left ventricular ejection fraction,  $\beta$ -blocker prescription, prior resuscitation, ICD shocks received, depression, and anxiety) hazard ratio was 3.45 ( $p = 0.002$ ) for the PTSD group [189].

There is also a higher risk of mortality following surgery in PTSD patients [46, 173, 190].

#### *Sympathetic Activity*

Heart rate variability is reduced with PTSD. Low heart rate variability is a robust predictor of cardiac mortality [191].

In 891 veterans, 91 with PTSD (age  $67 \pm 12$  years), presenting for routine echocardiography and followed for  $\leq 7.5$  years, midregional proadrenomedullin, a marker of sympathetic activation, was an independent predictor of all-cause mortality after adjusting for B-type natriuretic peptide, cardiovascular risk factors, cancer, and sleep apnea ( $p = 0.007$ ) [192].

Basal heart rate may be elevated in PTSD, reflecting not only elevated sympathetic but also abnormally low tonic parasympathetic cardiac activity [193]. An elevated resting heart rate is associated with reduced survival [194] and is a risk factor for mortality independent of physical fitness, physical activity, and other major cardiovascular risk factors [195].

#### *Suicide*

PTSD is a major suicide risk factor [116, 196], especially if left untreated. PTSD suicidality may be associated with a decrease in BDNF functioning [197].

#### **Conclusion**

The need for addressing PTSD among returning combat veterans is a growing public health concern. Untreated or undertreated PTSD entails a cascading set of problems, with drug use, suicide, marital problems, unemployment, and homelessness being just some of the consequences.

PTSD is treatable. Current PTSD management addresses psychiatric parameters of this condition primarily via the use of cognitive behavioral therapy in conjunction with available anti-anxiety medications, antidepressants, and antipsychotics, which only partially reduce symptoms.

Efforts are underway both to lower susceptibility to PTSD through greater stress resilience training and to lessen its advent or severity via immediate posttraumatic psychological and pharmacological intervention. Ongoing studies that focus on the (epi)genetic and neurobiologic underpinnings of the stress response may bring about targeted therapies that focus on restoring normal hippocampal function and the extinction of learned fear responses in PTSD, particularly during the posttraumatic neuroplastic 'window of opportunity'.

However, PTSD is not simply a psychiatric disorder. Traumatic stress deleteriously increases the risk for inflammation-related somatic diseases and early mortality, but little emphasis has been placed on addressing these somatic PTSD comorbidities.

PTSD is a substantial risk factor for the metabolic syndrome and cardiovascular disease that warrants increased screening and clinical intervention to predict and prevent the onset of cardiometabolic disease in PTSD patients. Insulin resistance, metabolic syndrome, and CHD can be reversed during their early stages. Advising patients of existing preventive diet, exercise, and pharmacologic modalities in conjunction with PTSD-related psychiatric therapy will reduce cardiometabolic risk factors to lessen long-term adverse health outcomes, such as DM, heart attack, stroke, and death, and will improve quality of life. Such an approach has been shown to be effective in the management of patients with clinical depression for whom guideline-based, collaborative managed care, aiming to treat depression as well as chronic systemic disease, provided significantly improved control of both medical disease (CHD and/or DM) and depression relative to usual care controls [198].

There is the promise that current cardiometabolic preventive therapy may also help improve the posttraumatic dysregulation of cortical arousal and neurohormonal abnormalities, thus favorably impacting neuropsychologic function:

- Regular physical exercise may enhance executive function, hippocampus-dependent learning and memory, neuroprotection, neurogenesis, synaptic plasticity, neurotransmission, prefrontal cortex blood flow, and hippocampal volume, in part by increasing the expression of BDNF. It may ameliorate PTSD symptomatology.
- Dietary n-3 polyunsaturated fatty acids may protect hippocampal plasticity, help prevent neuroinflammation, and enhance resistance to oxidative stress, while normalizing BDNF levels and improving learning ability, with potential benefit for PTSD symptoms.
- Angiotensin receptor blockers may lower brain inflammation, be neuroprotective, increase BDNF signaling, improve cognition, and decrease PTSD symptomatology.
- Statins may enhance BDNF signaling, induce brain plasticity, and have neuroprotective and neurorestorative effects.
- Metformin may recruit neural stem cells, promote neurogenesis, improve neuronal function, and enhance spatial memory formation.
- Centrally acting  $\alpha_1$ -adrenoceptor antagonists appear promising for their capacity to reduce PTSD-related nightmares and insomnia.
- Successful treatment of sleep-disordered breathing improves insomnia, nightmares, and PTSD symptoms independent of psychiatric interventions.

We have a clear moral duty to ensure that our fighting men and women receive comprehensive care for all the injuries they sustained while serving our nation. Their sacrifices should not be in vain. The therapeutic effort must comprehensively address both psychiatric and cardiometabolic disease. High-quality prevention and treatment could save close to 2 billion USD within 2 years by substantially reducing indirect PTSD costs [19].

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