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Post-Traumatic Stress Disorder (PTSD) as a Systemic Disorder: Pathways to Cardiovascular Disease

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Evidence indicates that post-traumatic stress disorder (PTSD) is a significant risk factor for the development and progression of cardiovascular disease (CVD). Most explanations for PTSD-CVD associations conceptualize PTSD as a stress-related mental health disorder that elicits physiological, behavioral, and psychological responses that are causal factors in the development of cardiovascular disorders. This article reviews evidence for the broader physical health consequences of PTSD, and presents a conceptual model based on research suggesting that PTSD is a systemic disorder. Specifically, research findings indicate that diagnostic criteria are just the "tip of the iceberg" of a broader systemic disorder with elements that are cardiovascular risk factors. These systemic physiological and behavioral elements therefore should not be regarded as accompanying but unrelated diseases or comorbidities, but as inherent components of PTSD that directly impact the development of CVD. The systemic disorder approach has implications for the conceptualization of PTSD as a cardiovascular risk factor, for needed research on PTSD and CVD, and for clinical efforts to reduce PTSD-associated cardiovascular risk. It is suggested that treatments that aim to reduce cardiovascular disease risk need to address both the PTSD diagnostic components and its associated cardiovascular risk factors. Further research is needed to test the applicability and implications of the systemic disorder perspective.

Keywords: post-traumatic stress disorder, cardiovascular disease, coronary heart disease, risk factors, comorbidities

Post-traumatic stress disorder (PTSD) is a heterogeneous, stress-related mental health disorder that results from direct or indirect exposure to trauma or highly stressful circumstances (American Psychiatric Association, 2013). The disorder is defined in terms of the presence of several clusters of psychological, behavioral, and physiological symptoms, including intrusive thoughts, avoidance, negative alterations in cognitions and moods, and arousal and stress reactivity (American Psychiatric Association, 2013). Moreover, PTSD often co-occurs with other psychological disorders and behavioral conditions, including psychiatric comorbidities such as depression, substance abuse disorders, and sleep disorders such as insomnia and obstructive sleep apnea (Bukhbinder & Schulz, 2016; Flory & Yehuda, 2015; Krakow et al., 2015; Ryder et al., 2018).

However, in the past decade, accumulated evidence indicates that, although it is typically defined as a psychological disorder, PTSD is associated with physiological changes and disorders in a variety of organ systems, including central nervous system (e.g., dementia, sleep disorders), autoimmune and inflammatory (e.g., rheumatoid arthritis), neuroendocrine and metabolic (e.g., diabetes, metabolic syndrome), and cardiovascular disorders (Koenen et al., 2017; McFarlane, 2017; Pacella et al., 2013; Qureshi et al., 2009; Ryder et al., 2018). The most widely-researched area of nonpsychiatric consequences of PTSD is cardiovascular health; PTSD has been shown to be a prospective risk factor for the development of coronary heart disease (CHD) and coronary artery disease (CAD; Burg & Soufer, 2016; Edmondson et al., 2013; Edmondson & von Känel, 2017), as well as hypertension and stroke (Burg et al., 2017; Rosman et al., 2019).

From the traditional perspective that defines PTSD in terms of its diagnostic psychological symptoms (American Psychiatric Association, 2013), the physical and psychological conditions that often co-occur with PTSD are considered to be comorbidities or multimorbidities, representing the co-occurrence of multiple different physical or psychological illnesses (Suls et al., 2019). The central nervous system (CNS) and peripheral effects of PTSD

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are recognized, but they are not considered to be a diagnostic feature, and attention is not directed toward explaining or treating comorbidities.

However, an emerging and broader view suggests that PTSD is a systemic metabolic disorder "in disguise" (Bukhbinder & Schulz, 2016; Michopoulos et al., 2016), involving CNS, neuroendocrine, metabolic, and inflammatory elements (Carvajal, 2018; Flory & Yehuda, 2018; McFarlane, 2017; Mellon et al., 2018; Michopoulos et al., 2016). This alternate perspective suggests that PTSD be reconceptualized as broader than a psychological disorder (McFarlane, 2017; Michopoulos et al., 2016). Using this approach, the co-occurring physical disorders associated with PTSD are seen as a direct manifestation of the mosaic of physiological systems affected in PTSD, rather than as related but independently developing comorbidities as is traditionally conceptualized. Whether PTSD is seen as a psychological stress disorder or as a systemic disorder encompassing many elements beyond mental health diagnostic descriptors has research implications for understanding the mechanisms and role of PTSD in cardiovascular and cardiometabolic health. These different approaches of conceptualizing PTSD and physical health also have direct clinical implications for identifying important targets for intervention.

This article will briefly review previous research on the consequences of PTSD for physical health, including the association between PTSD and CVD. In addition, we also provide a conceptual framework for understanding the associations between PTSD, CVD risk factors, and CVD based on the perspective that PTSD is a systemic disorder, and then discuss research and clinical implications of this perspective.

Physical Health Effects of Trauma and PTSD

A large body of research indicates that, even when PTSD symptoms are not present, acute and chronic environmental stressors, including traumas or extreme stressors, elicit a cascade of CNS, autonomic, neuroendocrine, immune, and cardiovascular responses, and are associated with the exacerbation and/or development of a range of physical and mental disorders (for reviews, see Cohen et al., 2019; Garfin et al., 2018; Holmes et al., 2006; McEwen & Akil, 2020; Nelson et al., 2020; O'Connor et al., 2021; Schnurr & Green, 2004). Much of this broad literature documents the effects of acute and chronic stress and trauma on cardiovascular outcomes (Dar et al., 2019; Godoy et al., 2021; Holmes et al., 2006; Osborne et al., 2020; Steptoe & Kivimäki, 2013). The biobehavioral pathways involved in the effects of psychosocial stress and in the effects of PTSD are overlapping, complementary, and have relevance to CVD, but exposure to trauma does not inevitably result in PTSD. In this regard, considerable research has identified risk and protective factors for the development of PTSD after trauma exposure. These include, but are not limited to, biological responses and biomarkers, genetics, childhood and mental health history, psychological traits, coping resources, and social support (Garfin et al., 2018; Kroll, 2003; Schnurr & Green, 2004; Yehuda et al., 2006). Because of these distinctions and differences between trauma exposure and PTSD, the present focus will be on PTSD and CVD, and a broader review of stress and trauma research is beyond the scope of this article.

When trauma does result in the development of PTSD, evidence for the physical health consequences of PTSD is also extensive. A growing number of prospective studies using objective disease measures have demonstrated predictive relationships between PTSD and poor physical health outcomes (for reviews, see Flory & Yehuda, 2018; Pacella et al., 2013; Qureshi et al., 2009; Ryder et al., 2018). Possible mechanisms mediating the relationships between PTSD and disease outcomes include changes in health behaviors, sympathetic nervous system activity, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and systemic inflammation (Bukhbinder & Schulz, 2016; Lee & Park, 2018; Michopoulos et al., 2016; Ryder et al., 2018). However, it has been noted that few studies have incorporated both measures of mechanisms and objective disease outcomes in the same study (Ryder et al., 2018).

PTSD as a Systemic Disorder in Disguise

The question arises as to the significance of these many physiological and disease correlates for the conceptualization and understanding of PTSD. From the point of view of clinical neuroscience, the brain and CNS effects of PTSD have received considerable attention (Bremner, 2016; Fenster et al., 2018; Sakellariou & Stefanatou, 2017). However, increasing evidence indicates that, because of its wide-ranging physiological effects, PTSD may be a whole-body, systemic disorder "in disguise" (Michopoulos et al., 2016), with the psychological diagnostic criteria being just "the tip of the iceberg." These systemic changes involve not just the brain and behavior, but have effects spanning multiple biological components (Bukhbinder & Schulz, 2016). Systems affected by PTSD include brain circuitry and neurochemistry, cellular, immune, endocrine and metabolic functions, as well as systems regulating behavioral and emotional characteristics (Flory & Yehuda, 2015; McFarlane, 2017). The approach to viewing PTSD in this manner, which is not limited to observable diagnostic criteria, is similar to the Research Domain Criteria (RDoC) strategy, which seeks to understand mental health and illness in terms of dysfunction in general psychological/biological systems (Cuthbert & Insel, 2013).

PTSD and Cardiovascular Disease (CVD)

Many of the physiological, psychological, and behavioral correlates of PTSD are cardiovascular risk factors, and among the most extensively documented physical health outcomes linked with PTSD are cardiovascular disorders (CVD), including coronary heart disease (CHD), hypertension, and stroke. Evidence for PTSD as a CVD risk factor includes cross-sectional and prospective epidemiological studies, clinical studies of associations between PTSD and intermediate markers of CHD, and studies of possible mechanisms linking PTSD with the development of CVD. The prospective association between PTSD and a variety of manifestations of CVD has been established in a wide variety of populations, and this literature has been consolidated in several review articles and meta-analyses (e.g., Arenson & Cohen, 2017; Burg & Soufer, 2016; Edmondson et al., 2013; Edmondson & von Känel, 2017; Vaccarino & Bremner, 2013).

To summarize, one meta-analysis (Edmondson et al., 2013) examined prospective studies of PTSD and CHD encompassing more than 400,000 participants with follow-up data ranging from 1 to 30 years. After adjusting for relevant demographic, clinical, and psychosocial factors, this analysis demonstrated significant associations between PTSD and CVD, with reported hazard ratios for CHD or cardiac mortality between 1.46 and 3.28. PTSD symptoms have been associated an increased risk of cardiovascular

disease roughly comparable to that conferred by risk factors such as smoking and cholesterol (Edmondson et al., 2013). Subsequent studies have strengthened these conclusions.

PTSD also appears to be associated with subclinical atherosclerosis, angina, myocardial ischemia (a functional manifestation of CHD), more rapid CHD progression (Ahmadi et al., 2011; Krantz & Burg, 2014; Lima et al., 2020; Turner et al., 2013; Vaccarino & Bremner, 2013), and with stroke (Rosman et al., 2019). In addition, it is estimated that PTSD is present in 25% of individuals after a stroke (Edmondson et al., 2013), and that PTSD after a cardiac event may be associated with worsened cardiovascular outcomes (Edmondson & von Känel, 2017). Although early studies included largely male populations, later research demonstrated that PTSD is also associated with CHD in both men and women (Ebrahimi et al., 2021; Kubzansky et al., 2009; Remch et al., 2018; Sumner et al., 2015, 2016).

The following sections will identify several of the relevant processes that are systemic physiological responses or disorders, and/or behavioral and psychological correlates of PTSD, that may account for associations between PTSD and CVD.

Physiological Mediators of PTSD-CVD Associations

Metabolic Syndrome and Type 2 Diabetes

Metabolic syndrome is a cluster of interrelated factors, including central obesity, hypertension, heightened high-density lipoprotein cholesterol, elevated triglycerides, elevated glucose levels, and/or dyslipidemia (Alberti et al., 2009). PTSD is associated with obesity, an association that may be due to biological mechanisms, eating habits, and/or alcohol dependence (Farr et al., 2014; Kubzansky et al., 2014); in turn, excess weight is associated with an increased risk of metabolic syndrome and type 2 diabetes (Farr et al., 2014). Metabolic syndrome is consistently associated with PTSD (Bukhbinder & Schulz, 2016; Koenen et al., 2017; Michopoulos et al., 2016). For example, in various populations, PTSD has been associated with elevated cholesterol levels, hyperglycemia, and abdominal obesity, as well as with type 2 diabetes (Roberts et al., 2015; Vaccarino et al., 2014; Vancampfort et al., 2016), and individuals with PTSD have double the risk for metabolic syndrome compared to population controls (Koenen et al., 2017; Michopoulos et al., 2016). Metabolic syndrome, glucose dysregulation, and diabetes are well-established risk factors for CVD and have also been associated with autonomic dysregulation (Michopoulos et al., 2016).

Inflammation

Long-term changes in inflammatory processes have also been posited as one of several mechanisms for the relationship between PTSD and increased risk for CVD (Brudey et al., 2015; Pollard et al., 2016; Quinones et al., 2020). Several proinflammatory cytokines have been implicated in the development of CVD (Hori & Kim, 2019; Sumner et al., 2018), and a meta-analysis concluded that individuals with PTSD exhibit elevated blood levels of inflammatory markers compared to healthy controls, such as interleukin-1β, interleukin-6, tumor necrosis factor alpha, and C-reactive protein (Passos et al., 2015). There is also emerging evidence that PTSD is associated with the composition of the gut microbiome. These gut microbiome effects are important determinants of immunoregulation, and may affect both PTSD and the inflammatory and metabolic sequelae of PTSD (Hemmings et al., 2017; Leclercq et al., 2016). In addition, the temporal relationship between PTSD and inflammation is not well understood (Hori & Kim, 2019). Increased levels of circulating proinflammatory cytokines have been associated with sympathetic nervous system activation and exaggerated cardiovascular reactions to mental stressors in individuals with PTSD (Hori & Kim, 2019; Sakellariou & Stefanatou, 2017). This provides support for a possible relationship between inflammation and cardiovascular and autonomic nervous system responses in PTSD.

Sympathetic Activation, Autonomic Balance, and HPA Activity

One of the hallmark characteristics of PTSD is chronic dysregulation of the neurohormonal systems that are part of the stress response (Bremner, 2016; Flory & Yehuda, 2018; Vaccarino et al., 2014). Relative to healthy controls, peripheral cortisol levels are reduced at rest; however, during trauma-related stimuli, cortisol release increases, and there is increased reactivity as measured by sympathetic activation, heart rate, catecholamine release, and blood pressure (Bremner, 2016; Sakellariou & Stefanatou, 2017). Among other CNS mechanisms and abnormalities in stress-related brain regions (e.g., the amygdala and hippocampus; Bremner, 2016), PTSD is also associated with alterations in the endocannabinoid system, which is involved in HPA axis responses to stress and the release of cortisol (Neumeister et al., 2013). High blood pressure, cardiovascular stress reactivity, and elevated catecholamines and sympathetic function may ultimately lead to premature development of cardiovascular disease, including dysfunction of the vascular endothelium (an early stage of atherosclerosis), and later to vulnerability to cardiac arrhythmias, myocardial ischemia or infarction, and sudden cardiac death (Bremner, 2016; Edmondson & von Känel, 2017; Krantz & Manuck, 1984; Steptoe & Kivimäki, 2013; Vaccarino & Bremner, 2013).

Sleep Disorders

Sleep disturbance and/or nightmares are part of the diagnostic criteria for PTSD (American Psychiatric Association, 2013), with up to 80–90% of patients with PTSD experiencing insomnia and/or nightmares (Koffel et al., 2016). Sleep disordered breathing, in the form of obstructive sleep apnea, is also disproportionately higher in individuals with PTSD than in the general population (Krakow et al., 2015). Evidence indicates that both short and long sleep duration as well as insomnia and poor sleep quality are associated with subclinical and clinical cardiovascular disease (Hall et al., 2018; Kwok et al., 2018). Plausible physiological mechanisms linking disturbed sleep and CVD risk have been identified, and include autonomic nervous system dysfunction, increased inflammation, and metabolic abnormalities (Hall et al., 2018).

Hypertension

Hypertension, an important cardiovascular disorder, is a major risk factor for coronary artery disease and stroke, and PTSD is associated with an increased risk of the development of hypertension

(Burg et al., 2017; Burg & Soufer, 2016; Persu et al., 2018). The renin-angiotensin system, which plays an important role in the development of hypertension and stroke (Brudey et al., 2015) is also associated with the regulation of stress response in patients diagnosed with PTSD (Terock et al., 2018). For example, among a large sample of veterans, there was also suggestive evidence that although incidence of hypertension was higher among individuals with PTSD, it was lower among those individuals receiving either behavioral or pharmacologic treatment for PTSD (Burg et al., 2017). An association of PTSD and incident hypertension also has been found in women, as well as men (Sumner et al., 2015).

Other Intermediate Pathophysiological Changes Associated With PTSD

Many of the aforementioned physiological alterations can contribute to intermediate pathophysiological changes that reflect early or beginning coronary artery disease processes. These include impairment in endothelial function, other markers of early atherosclerosis, or factors that may affect diseased coronary arteries and the triggering of acute coronary events (Dedert et al., 2010; Edmondson & Cohen, 2013; Lampert, 2014; Papademetriou et al., 1996; Turner et al., 2013). For example, research indicates that even among individuals without coronary artery disease symptoms, older veterans with PTSD demonstrated greater coronary calcification scores compared to matched controls without PTSD (Ahmadi et al., 2011). Other studies indicate that PTSD is associated with impaired endothelial function, an early stage in the development of atherosclerosis (Grenon et al., 2016; Sumner et al., 2018). With respect to functional manifestations of coronary heart disease, PTSD is associated with mental stress-induced myocardial ischemia (Krantz & Burg, 2014; Lima et al., 2020), which could increase the likelihood of subsequent cardiovascular events.

Behavioral and Psychosocial Mediators of PTSD-CVD Associations

In addition to its physiological correlates, numerous behavioral and psychological correlates of PTSD are also cardiovascular risk factors. These include smoking, substance abuse, other health behaviors, depression, and anger/hostility.

Smoking, Substance Abuse, and Health Behaviors

PTSD has been linked to multiple behavioral changes that are known to increase risk for CVD, such as decreased exercise, poorer adherence to treatment regimens, and sleep disruption (Burg & Soufer, 2016; Koffel et al., 2016). PTSD is also associated with increased tobacco use, potentially as an attempt to regulate negative affect (Pericot-Valverde et al., 2018), and smokers with PTSD report more withdrawal symptoms than those without PTSD (e.g., Dedert et al., 2012). Alcohol abuse and dependence is also common in men and women with PTSD, with a high prevalence of comorbid diagnoses of PTSD and substance use disorder (Kessler et al., 1995; Pietrzak et al., 2011). Both men and women with PTSD are 2–3 times more likely to meet diagnostic criteria for alcohol abuse or dependence than individuals without PTSD (Kessler et al., 1995). In turn, excessive alcohol consumption has been associated with an increased risk of hypertension, obesity, and coronary heart disease (Rehm & Roerecke, 2017). Taken together, these factors are likely to at least partially explain the relationship between PTSD and CVD.

Depression

PTSD is highly comorbid with depression, with estimates indicating a 52% comorbidity rate with PTSD (Flory & Yehuda, 2015; Rytwinski et al., 2013). Depression is itself associated with biological mechanisms and risk markers such as increased sympathetic activation and neuroendocrine changes, and vascular, metabolic, and immune effects (Arenson & Cohen, 2017; Edmondson & von Känel, 2017; Steptoe & Kivimäki, 2013). The extensive literature on depression and cardiovascular disease has been reviewed elsewhere (e.g., Cohen et al., 2015; Freedland & Carney, 2013; Penninx, 2017). In summary, prospective studies indicate that depression and depressive symptoms are risk factors for the development of CHD events in previously healthy patients, recurrent cardiovascular events in patients established CHD, and for adverse cardiovascular outcomes after coronary artery bypass grafting surgery (Freedland & Carney, 2013). Risk associated with depression appears to be independent of standard risk factors (Cohen et al., 2015; Freedland & Carney, 2013), and comorbid PTSD and depression appear to confer particularly high risk (Roberts et al., 2020).

Anger and Hostility

Irritability and outbursts of anger are included in the hyperarousal symptoms of PTSD (American Psychiatric Association, 2013). Accordingly, research indicates that traits of hostility and anger are strongly associated with PTSD (Jakupcak et al., 2007; Olatunji et al., 2010). Evidence further indicates that anger and hostility are predictive of incident CHD, cardiac symptoms, and poorer outcomes among men and women with preexisting cardiovascular disorders (for example, (Chida & Steptoe, 2009; Keith et al., 2017; Krantz et al., 2006).

Research on the Role of Mediators in the Cardiovascular Risk Associated With PTSD

Given the relationship of PTSD to known cardiovascular risk factors, it is important to examine whether PTSD as a mental health diagnosis contributes uniquely to CVD, over and above the contribution of other already established risk variables. If so, an independent relationship might direct attention away from these already established variables and toward other potential mechanisms to better elucidate PTSD as a unique risk factor. In public health research, a variable is called an "independent" risk factor if it maintains significant contribution to a health outcome in a statistical model that includes known risk factors (Brotman et al., 2005). However, concluding that a variable is an independent risk factor indicates that it is predictive, but not necessarily that it is causal. Therefore, if PTSD still predicts cardiovascular outcomes after adjusting for comorbidities and other known risk factors, this would support the notion that different or additional mechanisms, potentially inherent to a PTSD diagnosis, account for cardiovascular risk.

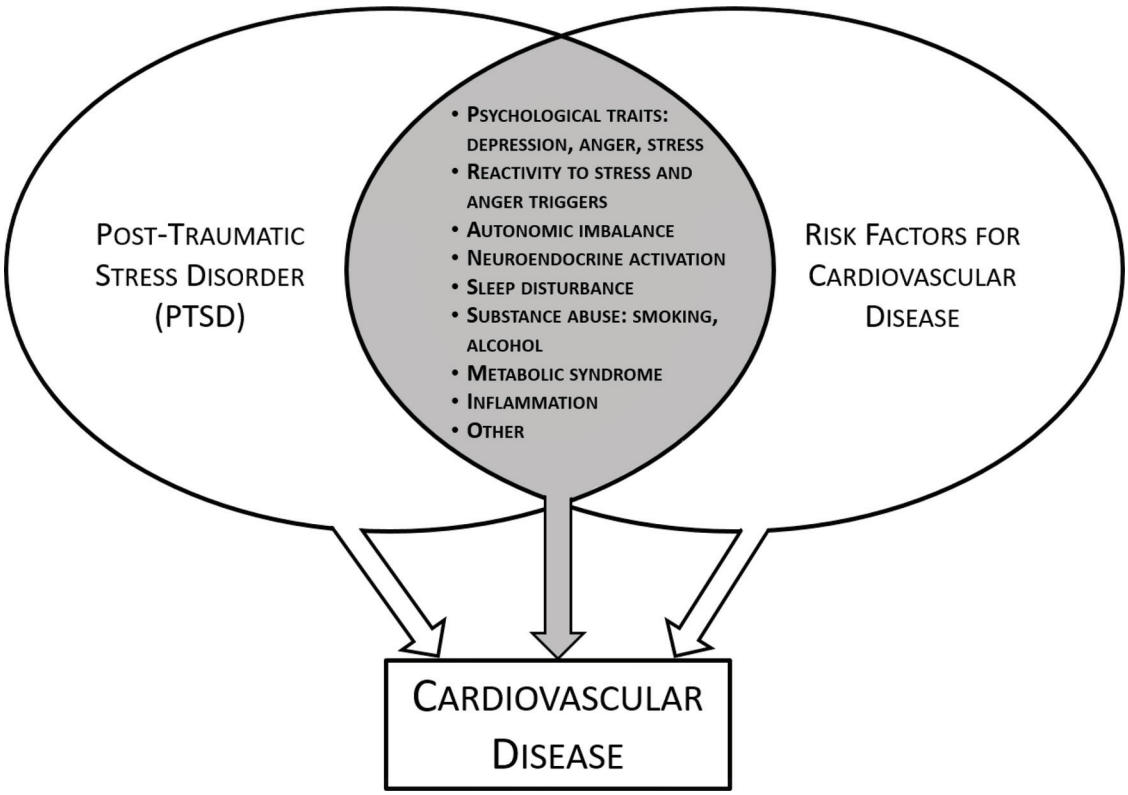
However, an alternative view is portrayed by the shaded area of overlapping circles in Figure 1. A set of possible overlapping risk factors, reviewed earlier in this paper, is presented in the shaded area. This alternative view suggests that the CVD risk associated with PTSD may, in whole or in part, be attributable to overlapping risk factors and/or comorbidities, rather than to unique features of PTSD as a psychological condition (Scherrer, Salas, Cohen, et al., 2019; Schnurr & Green, 2004).

Studies examining the independent contributions of PTSD to CVD after taking into account known risk factors have produced conflicting findings. Most prospective studies that have found significant associations between PTSD and cardiovascular endpoints have controlled for demographic factors (e.g., age, gender, education, race/ethnicity) and standard cardiovascular risk factors such as smoking, body mass index, and hypertension (for reviews, see Burg & Soufer, 2016; Edmondson & Cohen, 2013; Edmondson & von Känel, 2017). Several studies further indicate that the association of PTSD with CVD remains significant independent of the effects of depression, although the effect size of PTSD is somewhat diminished after adjusting for depressive symptoms (Belleau et al., 2020; Burg & Soufer, 2016; Edmondson et al., 2013). Other studies (e.g., Sumner et al., 2015) have also included adjustments diet, diabetes, hormone replacement, and antidepressant use, and found that associations between PTSD and cardiovascular outcomes remained significant after these adjustments.

In contrast, based on analyses of cardiovascular diagnoses in veterans with and without diagnosed PTSD, a recent study (Scherrer, Salas, Cohen, et al., 2019) reached a different conclusion that is consistent with is portrayed by the shaded area in Figure 1. Using a series of statistical models that adjusted for different cardiovascular risk factors, there was a significant association between PTSD and CVD after adjusting only for age. However, when a full set of covariates including metabolic disorders, smoking, sleep disorder, substance use disorder, anxiety and depression were added into the model, PTSD was no longer a significant predictor of incident CVD. These findings suggested that, in aggregate, the covariates might account for the association of PTSD with cardiovascular outcomes. However, in this sample, significant associations remained after adjusting for some of the metabolic covariates, and no single covariate alone accounted for PTSD as a predictor of CVD. Thus, the study provides some limited support for both perspectives, depending on the particular variables and number of variables included. Taken together with the prior body of research in this area, these findings indicate that more evidence

Figure 1

Illustration of the Overlap Between PTSD and Cardiovascular Risk Factors



Note. The shaded area represents and lists variables that are both correlates of PTSD and risk factors for cardiovascular disease. The notion of PTSD based on diagnostic criteria as an independent risk factor would suggest that there are unique elements of PTSD diagnosis associated with cardiovascular risk after statistically adjusting for known cardiovascular risk factors. An alternative hypothesis, indicated by the shaded arrow, would suggest that the CVD risk associated with PTSD may, in whole or in part, be attributable to these overlapping risk factors and/or comorbidities, rather than to unique features of PTSD as a psychological disorder.

is needed to determine the role of PTSD-associated comorbidities in accounting for CVD risk associated with PTSD.

Also relevant to the role of risk factors and comorbidities are several additional studies examining whether changes in PTSD over time are associated with changes in comorbid risk factors (Koenen et al., 2017; Scherrer et al., 2019). These studies provide information about the reversibility of the PTSD-CVD link, and about possible targets for treatment and prevention. In this regard, recent studies indicate that PTSD improvements are not significantly related to incident cardiovascular disease or to improvements in hypertension or hyperlipidemia (Scherrer et al., 2020); but are related to changes in risk of type 2 diabetes (Scherrer et al., 2019). Important information would be derived from further research to determine whether treatment of PTSD is associated with reductions in known risk factors (LoSavio et al., 2021).

Conceptualizing PTSD as a Cardiovascular Risk Factor

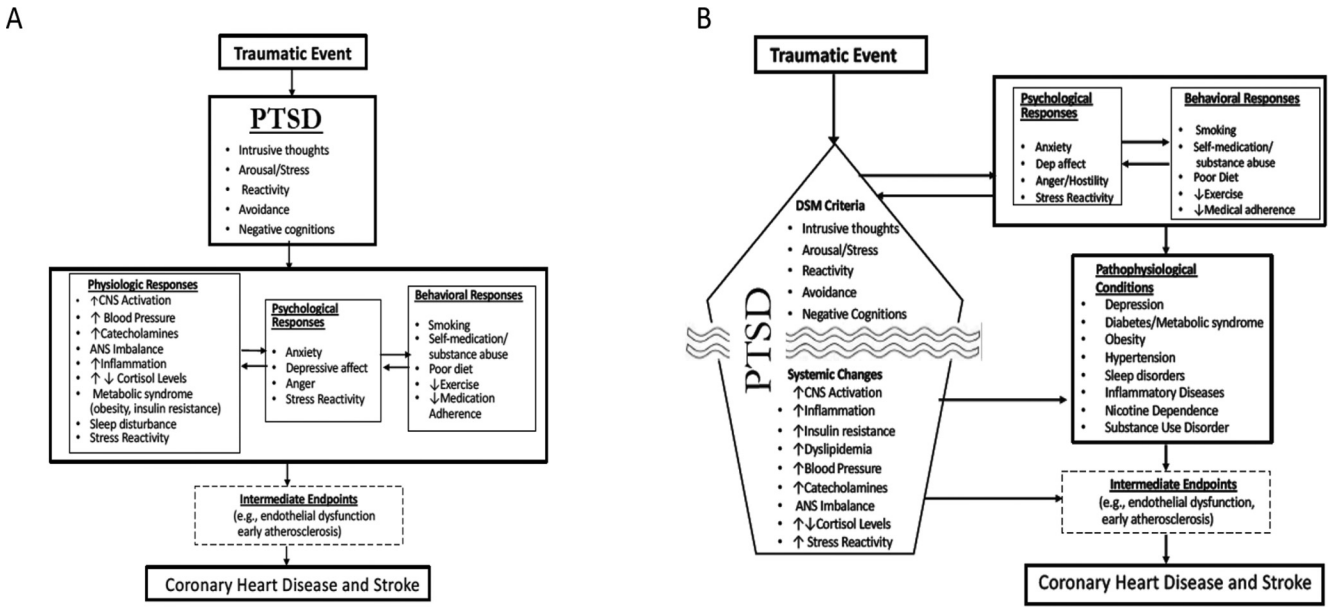
The recognition that PTSD is a systemic disorder, and questions about the role of known cardiovascular risk factors and comorbidities as risk mediators, raise questions about how to best conceptualize the associations between PTSD and CVD outcomes. Figure 2 presents two alternate approaches to conceptualizing the associations between PTSD and cardiovascular outcomes. Based on existing research, each model presupposes a causal relationship between PTSD and cardiovascular disease, but the pathways and mechanisms proposed for these associations differ between the two.

The model in Figure 2A views PTSD as a mental health disorder that elicits stress-related responses that are causal factors in the atherosclerotic process and the development of cardiovascular disorders. A similar causal sequence has been proposed in several prior models (e.g., Dedert et al., 2010; Schnurr & Green, 2004; Schnurr et al., 2014; Vaccarino & Bremner, 2013). In Figure 2A, PTSD elicits physiological, behavioral, and psychological responses similar to those associated with psychosocial stress (Cohen & Rodriguez, 1995; Holmes et al., 2006; O'Connor et al., 2021). For example, as a stress-related mental health disorder, PTSD is associated with emotional (e.g., anxiety, anger) and stress responses that initiate physiological (e.g., inflammatory, endocrine, sympathetic nervous system), behavioral (e.g., smoking, substance abuse), and emotional changes (e.g., anger, depressive affect). These responses, in turn, heighten cardiovascular risk via a variety of mechanisms.

In the medical literature, comorbidities are typically defined as other diseases that are present in addition to an index disease (Feinstein, 1970; Suls et al., 2019; Valderas et al., 2009). Since they are conditions or diseases separate from PTSD (the index disorder in question), comorbidities, as such, do not necessarily appear in the causal sequence in Figure 2A, even though they are associated with PTSD. Any role they play in the disease process is seen as involving a set of mechanisms that are not necessarily

Figure 2

Two Alternate Approaches to Conceptualizing the Associations Between PTSD and Cardiovascular Outcomes



Note. Each model presupposes a causal relationship between PTSD and cardiovascular disease, but the pathways and mechanisms proposed for these associations differ between the two. Panel A: The model in Figure 2A views PTSD as a mental health disorder that elicits stress-related responses that are causal factors in the atherosclerotic process and the development of cardiovascular disorders. In this figure, PTSD elicits physiological, behavioral, and psychological responses similar to those associated with psychosocial stress or allostatic load. These responses, in turn, heighten cardiovascular risk via a variety of mechanisms. Comorbidities do not necessarily appear in the causal sequence in Figure 2A, even though they are associated with PTSD. Panel B: Figure 2B, in contrast, displays a model of PTSD as a systemic disorder with biological as well as behavioral risk factor components. The diagnostic PTSD characteristics are just the "tip of the iceberg", and links between PTSD and co-occurring physical disorders or "pathophysiological conditions" are a direct result of the systemic changes intrinsic to PTSD. This systemic disorder model links physical health conditions that frequently occur together with PTSD with these systemic changes.

inherent to PTSD. The model in Figure 2A would suggest that efforts to reduce cardiovascular risk associated with PTSD might primarily be focused on directly treating PTSD as a psychological disorder via psychological/behavioral, stress-management, and/or pharmacological methods (e.g., LoSavio et al., 2021). Efforts at treating the comorbidities might involve separate clinical interventions that would not be seen as being related to PTSD.

In contrast, Figure 2B displays a "systemic disorder model" of PTSD as a systemic disorder with biological, as well as behavioral, risk factor components. In this model, the diagnostic PTSD characteristics are just the "tip of the iceberg." The links between PTSD and these accompanying co-occurring physical disorders are explained as being a direct result of the collection of systemic changes and the biological dysregulation intrinsic to PTSD (McFarlane, 2017). Since they are intrinsic to PTSD, strictly speaking, they are not seen as comorbidities or unrelated diseases, and are therefore labeled in Figure 2B as "pathophysiological conditions", rather than as comorbidities.

The systemic disorder model in Figure 2B has the advantage of linking correlated physical health conditions such as hypertension, diabetes, and inflammatory diseases, which develop later, to the systemic changes inherent to PTSD (e.g., autonomic nervous system imbalance, changes in cortisol levels), which develop earlier. This model also allows for an indirect relationship between PTSD and cardiovascular outcomes—specifically, that these later developing pathophysiological conditions are causally involved in the relationship between PTSD and CVD. Although both models allow for interactive effects, the systemic model would also allow for additive or interactive effects of PTSD diagnoses and these accompanying conditions (Belleau et al., 2020). Thus, this approach is relevant for the conceptualization of PTSD as a cardiovascular risk factor, for research on PTSD and CVD, and for clinical efforts to reduce PTSD-associated cardiovascular risk.

Research and Clinical Implications of PTSD as a Systemic Disorder

Conceptualizing PTSD as a systemic disorder has several additional research and clinical implications. For example, further research needs to investigate the unique contributions of PTSD to cardiovascular risk, and/or whether levels of other new or established risk variables additively increase risk (e.g., do PTSD and metabolic syndrome, or PTSD and sleep disorders represent additive risk factors). Such research would be helpful in identifying at-risk individuals as well as directing attention to possible mechanisms of disease.

Another important issue is determining the temporal sequence of relationships between psychological diagnoses and systemic changes. It is generally assumed that many of the systemic changes associated with PTSD occur after the behavioral and psychological symptoms that reflect the PTSD disorder (e.g., Vaccarino & Bremner, 2013). In addition, the manifestations of cardiovascular disease as well as some of the comorbid physical disorders associated with PTSD would presumably develop over a longer time period. However, there is some preliminary evidence that biomarkers and other earlier physiological and biobehavioral changes may also predispose individuals to the development of PTSD, and their presence might therefore precede the development of PTSD diagnoses (Garfin et al., 2018; Hori & Kim, 2019; Sumner et al., 2015). These issues are important in terms of defining optimal timing for prevention and intervention and would also inform the understanding of the development of systemic components of PTSD.

Clinical Relevance

Many current psychotherapy treatments for PTSD, such as prolonged exposure and cognitive processing therapy, focus on decreasing stress responses to trauma-related external and internal stimuli (Watkins et al., 2018). An elevated stress response would impact psychological, behavioral, and biological risk factors for cardiovascular disease, so it is not unreasonable to suggest that these therapies would reduce cardiovascular risk factors as well as PTSD symptoms (Garfin et al., 2018; LoSavio et al., 2021; Scherrer et al. 2020). For example, it has been suggested that evidence-based treatments for PTSD may produce positive cardiovascular effects due to a decrease in unhealthy behaviors such as smoking, eating behaviors, poor sleep, and alcohol use (LoSavio et al., 2021; Scherrer et al., 2019). Studies need to also evaluate whether there are changes in metabolic, inflammatory, and cardiovascular risk factors associated with standard treatments (e.g., LoSavio et al., 2021).

However, standard treatment options for PTSD are directed at reducing psychological and behavioral symptomatology and do not address most of the systemic changes or accompanying pathophysiological conditions associated with PTSD (Watkins et al., 2018). Therefore, the absence of changes, or small changes, in cardiovascular risk factors would not be surprising, but would direct attention to the need to develop or implement new or combined, multidisciplinary treatment approaches to both address PTSD symptoms and reduce cardiovascular risk factors among individuals with PTSD. Such combined treatments might amplify any beneficial effects of treatment on cardiovascular risk.

If the goal is to reduce the cardiovascular health risk associated with PTSD, the systemic disorder model would suggest that it would be important to closely monitor early changes such as weight and metabolic changes in individuals with PTSD. Early, nonspecific preventive interventions might specifically target the systemic changes inherent to PTSD reduce CVD. Importantly, additional behavioral and/or pharmacologic interventions would be recommended to simultaneously target PTSD, the systemic physiological changes, and the resulting pathophysiological conditions associated with the PTSD systemic disorder. Ideally, early treatment would focus on addressing the systemic physiological changes seen in PTSD (e.g., increased insulin resistance, inflammation), before the associated clinical pathophysiological conditions develop. Such an approach would theoretically prevent the development of these associated pathophysiological conditions, and ultimately CVD.

Pairing nonspecific dietary and lifestyle interventions, together with evidence-based treatments for PTSD, may prevent the development of many pathophysiological conditions. For example, interventions targeting weight loss/maintenance (e.g., U.S. Preventive Services Task Force, 2018), increased physical activity (e.g., Tsatsoulis & Fountoulakis, 2006), and diet quality (e.g., Shirani et al., 2013) may ameliorate the systemic changes associated with PTSD such as inflammation, insulin resistance, and changes in stress reactivity. Additionally, preliminary evidence suggests that increasing physical activity may directly reduce PTSD symptoms. Increasing

physical activity and targeting weight loss/maintenance may have the added benefit of reducing the risk of developing depression, obesity, metabolic syndrome, hypertension, and inflammatory disorders (Hall et al., 2015; Rosenbaum et al., 2015). While additional research is needed, other potentially promising behavioral interventions targeting the systemic changes in PTSD include mindfulness-based interventions and biofeedback (Boyd et al., 2018; Quinones et al., 2020). As these interventions are layered on top of evidence-based PTSD treatments, care must be taken to ensure patient buy-in, compliance, and to avoid overwhelming patients with complex changes (Stonerock & Blumenthal, 2017).

Notably, among those diagnosed with PTSD, most report a sleep complaint—primarily insomnia, but many also have obstructive sleep apnea (OSA; Brownlow et al., 2020). Insomnia is associated with an increased risk of the development or cardiac death (Javaheri & Redline, 2017), and severe OSA is associated with higher likelihood of developing CVD. Nonpharmacological interventions for insomnia such as Cognitive Behavioral Therapy for Insomnia [CBT-I] not only reduce insomnia symptoms (Wu et al., 2015), but also reduce PTSD symptoms (Colvonen et al., 2018; Ho et al., 2016). In contrast, treatments for PTSD result in some improvement in insomnia symptoms, but symptoms often persist after treatment (Colvonen et al., 2018). In a small pilot study of combined treatment for insomnia and PTSD, participants demonstrated clinically significant improvements in insomnia and PTSD symptoms (Colvonen et al., 2018). Treating obstructive sleep apnea (OSA) also results in small reductions in PTSD symptoms (Colvonen et al., 2018; Ullah et al., 2017). Thus, integrating direct treatments for sleep disorders with evidence-based PTSD treatment, and investigation of their effects on cardiovascular risk are important areas for further research (Colvonen et al., 2018; Hall et al., 2018).

In sum, subject to the results of ongoing (e.g., LoSavio et al., 2021) and future research, additional data on combined interventions will help evaluate whether treating PTSD alone is sufficient to maximize reduction of cardiovascular risk among individuals affected by trauma. Instead, a systemic biopsychosocial approach addressing both PTSD and cardiovascular risk factors may be necessary for maximizing the likelihood of success of efforts to prevent CVD. Such combined interventions would need to be developed so that they provide the necessary support to be feasible and acceptable to individuals who are coping with distressing symptoms associated with PTSD.

Conclusions and Closing Comments

This article has reviewed evidence for the physical health consequences of PTSD, including risk of CVD, and for the conceptualization of PTSD as broader than a mental health disorder defined by its diagnostic criteria. We propose a conceptual model for understanding PTSD as a cardiovascular risk factor. This model is based on the notion that diagnostic PTSD characteristics are just the "tip of the iceberg" for a set of systemic physiological (e.g., allostatic load, inflammation, metabolic changes), psychological (e.g., anger, depressive affect), and behavioral (e.g., smoking, substance abuse, health behaviors) processes. The systemic disorder model has the advantage of linking these correlated physical health conditions, such as hypertension, diabetes, and inflammatory diseases, which develop later, to the earlier systemic changes inherent to PTSD. The proposed relationships allow for indirect associations between PTSD and cardiovascular outcomes, namely, that these pathophysiological conditions are implicated in the relationship between PTSD and CVD. This approach also allows for additive effects of PTSD with other risk factors.

The perspective advocated in this article for understanding PTSD also raises the broader question of whether a systemic framework is relevant to other mental health disorders that are reliably associated with the development of CVD and with other physical health comorbidities. As one possible example, depression is a mental health diagnosis that might benefit from this type of conceptual approach, since extensive research indicates that it is a risk factor for coronary heart disease (e.g., Freedland & Carney, 2013). Depression is also associated with other physical comorbidities and with systemic biological changes (e.g., heightened inflammatory responses, reduced heart rate variability, etc.; Cohen et al., 2015; Freedland & Carney, 2013; Penninx, 2017; Read et al., 2017). These characteristics, as well as somatic or "vegetative" symptoms that are part of the mental health diagnostic criteria (American Psychiatric Association, 2013), might be seen as reflecting a broader systemic disorder. Determination of the relevance, applicability, and utility of this approach to depression or other mental health diagnoses associated with CVD would require further hypothesis development and research.

In conclusion, we have suggested that a systemic disorder perspective has implications for research on PTSD and cardiovascular disease, and for clinical efforts to reduce PTSD-associated cardiovascular risk. Further research is clearly needed to determine the validity and utility of this approach. However, regardless of whether the proposed pathways are ultimately supported, the research agenda outlined would lead to a fuller understanding of the relationships between PTSD, cardiovascular disease, and physical health outcomes.

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