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Posttraumatic Stress Disorder, Cardiovascular, and Metabolic Disease: A Review of the Evidence

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Abstract

Background Posttraumatic stress disorder (PTSD) is a significant risk factor for cardiovascular and metabolic disease.
Purpose The purpose of the current review is to evaluate the evidence suggesting that PTSD increases cardiovascular and metabolic risk factors, and to identify possible biomarkers and psychosocial characteristics and behavioral variables that are associated with these outcomes.
Methods A systematic literature search in the period of 2002–2009 for PTSD, cardiovascular disease, and metabolic disease was conducted.
Results The literature search yielded 78 studies on PTSD and cardiovascular/metabolic disease and biomarkers.
Conclusions Although the available literature suggests an association of PTSD with cardiovascular disease and biomarkers, further research must consider potential confounds, incorporate longitudinal designs, and conduct careful PTSD assessments in diverse samples to address gaps in the research literature. Research on metabolic disease and biomarkers suggests an association with PTSD, but has not progressed as far as the cardiovascular research.

Introduction

The past decade of research has provided evidence that individuals with posttraumatic stress disorder (PTSD) report more health complaints, suffer from more physician-diagnosed medical conditions [1], and exhibit higher health care utilization [2]. However, further evidence is needed to determine whether PTSD increases risk of physical illness. The present review focuses on research on other biomarkers and physiological mechanisms of the association between PTSD and physical illness. In particular, the review details results on two classes of disease commonly associated with PTSD: cardiovascular and metabolic disease. Despite treatment efforts, PTSD remains prevalent, and it is important to monitor the physical health implications of PTSD and inform prevention and treatment efforts. Because previous reviews of PTSD and cardiovascular disease [3] and hostility [4] have included comprehensive characterizations of the pre-2002 literature, we chose to update this literature by focusing our search on publications between 2002 and 2009. A number of recent reports have contributed to this quickly growing literature, and review of recent findings is needed to identify important research and clinical targets.

In this review, we propose a model of the relationship between PTSD and cardiovascular and metabolic disease. Although research has linked PTSD to a number of health problems, there has been a lack of specificity in terms of which disease processes may be most related to PTSD.

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Because different diseases may be related to PTSD through different mechanisms or pathways, this review focuses on cardiovascular and metabolic disease specifically. In addition, a previous review by Boscarino [5] detailed findings and mechanisms supporting the possibility that PTSD could alter disease outcomes through disrupted hypothalamic-pituitary-adrenal axis (HPA) and sympathoadrenomedullary (SAM) functioning, so this review focuses on cardiovascular and metabolic mechanisms. Because individuals with PTSD have been shown to exhibit higher levels of anger and hostility [6], we explore the role of mediators (e.g., hostility) of the relationship between PTSD and cardiovascular/metabolic disease. We also discuss the potential roles of moderators in cardiovascular/metabolic outcomes.

## Identification of Studies for Review

Articles examining PTSD, cardiovascular disease (CVD), and metabolic disease were identified by searching the Published International Literature on Traumatic Stress, MEDLINE, and Psychological Information databases for articles published between January 2002 and April 2009. Articles were included if they met the following criteria: (1) inclusion of at least one measure of cardiovascular- or metabolic-related disease, mortality, or biomarkers; (2) original data or a new analysis of previously published data, rather than a review of the literature; (3) focused on the development of disease or biomarkers in those with PTSD; and (4) availability in English language. Animal studies were excluded. Search terms included the following: PTSD, cardio*, diabet*, metabol*, heart rate, and

blood pressure. Studies focusing on the development of PTSD in response to medical trauma (e.g., PTSD developed with myocardial infarction as the index trauma or prevalence of PTSD in patients with diabetes), the prediction of PTSD by peritraumatic physical symptoms, or physiological response to treatment were not included in the primary literature search. Search terms were selected to focus on the diseases and biomarkers of primary interest and restricted this review from other worthy topics such as infectious disease. In addition to the examination of electronic databases, the references of all retrieved articles were reviewed to identify additional relevant investigations. These procedures yielded a total of 78 published reports. In addition to these articles, two studies were included because they were known to be in press and a number of references were included to provide historical or scientific context, as well as to review other critical variables in this field of research, including depression, behavioral health, and hostility.

Model of Posttraumatic Stress Disorder, Cardiovascular Disease, and Metabolic Disease

A substantial literature documents a potential relationship between PTSD and increased cardiovascular reactivity to trauma-related cues, disturbed sleep physiology, autonomic hyperarousal, and altered HPA activity [7]. A possible model to evaluate the relationships between PTSD and health is presented in Fig. 1. Originally presented by Schnurr and Jankowski [8], this model proposes that certain individuals are more likely to endure traumatic stress and that both traumatic stress and PTSD are directly related to

Fig. 1 Model of the influences of traumatic stress risk, PTSD, psychological states, and health behavior on pre-clinical disease markers. It is proposed that pre-clinical disease biomarkers then progress to cardiovascular/metabolic disease through autonomic dysregulation, endothelial dysfunction, metabolic syndrome, and insulin resistance. This figure is modified from Schnurr & Jankowski [8]
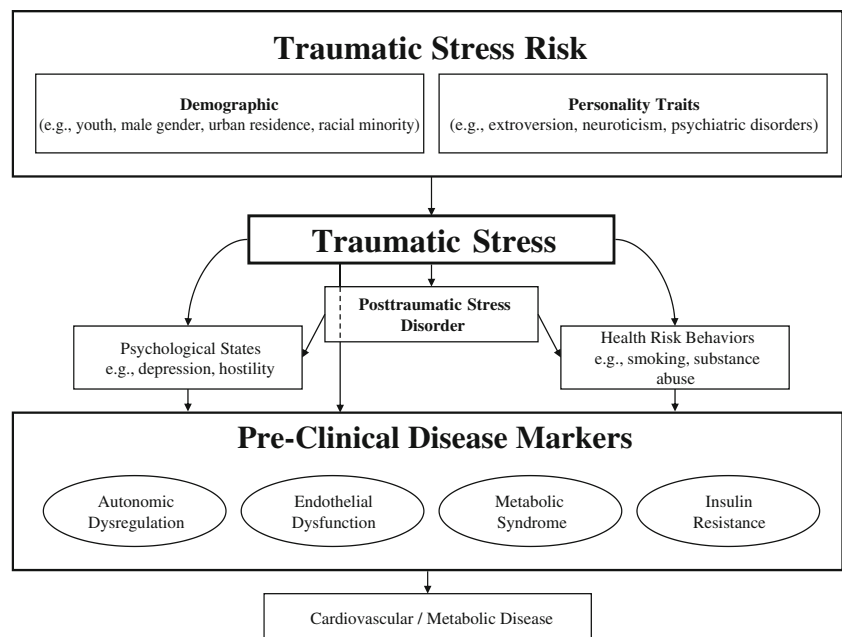
several physiological reactivity indices and disease biomarkers. In addition, the model conceptualizes PTSD as being indirectly related to reactivity and biomarkers through psychological states such as hostility and health risk behaviors commonly associated with PTSD. Finally, the model proposes several pre-clinical disease variables that convey the effects of physiological reactivity and disease biomarkers to medical morbidity and mortality. Given the differential prevalence rates in PTSD by gender, there may also be important gender differences in the trajectory of the disorder. However, because research in this area is lacking, gender is not proposed as a moderator in this model.

Cardiovascular and Metabolic Morbidity/Mortality in PTSD

PTSD and Morbidity and Mortality of Cardiovascular Disease

Initial evidence of a link between PTSD and CVD was drawn from investigations of CVD following traumatic stress. A longitudinal study of traumatic stress resulting from prolonged war in Beirut found that individuals with more war-related traumatic experiences were at greater risk for CVD-related mortality. The relationship between trauma and CVD differed by gender such that CVD-related mortality was more evident in women who suffered personal traumas, such as injuries or family deaths, while it was more prominent in men who had suffered property loss, work-related problems, or displacement from home [9]. In a study of cardiovascular morbidity in World War II prisoners of war, increased risk of CVD was present in those who developed PTSD [10]. A recent review summarizing the results of seven studies published between 1999 and 2006 found partial support for an association between PTSD and cardiovascular and metabolic disease [3]. PTSD was significantly associated with medical morbidity in four out of the six included studies on circulatory disorders [10–13]. A study of Vietnam veterans found that those veterans with PTSD exhibited elevated rates of CVD relative to combat-exposed veterans without PTSD [12]. In a review of medical records of male veterans who completed self-report measures of PTSD symptoms in 1990 and did not have coronary heart disease at the time of the baseline assessment, PTSD symptoms were associated with increased risk of experiencing either nonfatal myocardial infarction or onset of fatal coronary heart disease over an 11-year period [14]. A telephone-interview-based 30-year follow-up study with Vietnam era veterans noted that those veterans at PTSD were at increased risk of CVD-related mortality [15]. In a study of Australian veterans, PTSD was associated with increased risk of hypertension [16]. This study was unique and significant due to its use of the Structured Clinical Interview for the Diagnostic and Statistical Manual for PTSD diagnosis, interview assessment of medical disorders, and adjustment for demographic covariates, combat exposure, and peritraumatic dissociation.

While much of the research on medical morbidity has occurred in male veterans, there is preliminary evidence that those findings are present in other populations. A study of civilian survivors of a man-made disaster reported that vascular disorders were more common in those who developed PTSD [17]. In addition, data from the National Comorbidity Survey of United States civilians support an increased risk of hypertension in PTSD [18], a finding that was also evident in PTSD-diagnosed family members of soldiers killed in the wars in Bosnia and Herzegovina [19]. An association between PTSD and CVD was also observed in firefighters [20] and Native American Indians [21]. Prospective epidemiologic evidence from the Baltimore cohort of the Epidemiologic Catchment Area Survey indicates that this relationship might generalize to civilian women, as the presence of at least five PTSD symptoms was related to increased 14-year incidence of coronary heart disease in women [22].

Concordant with the evidence of a possible relationship between PTSD and CVD, available research supports a link to both CVD-related and all-cause mortality. Data analysis from a random sample of 4,462 Vietnam era veterans suggested that the predictive power of PTSD for mortality may be comparable to that of common disease indicators such as inflammation [23]. In fact, in models statistically controlling for demographic and military variables, behavioral health variables, substance abuse, depression, and baseline disease pathology measures, PTSD was associated with an approximate twofold increase in both all-cause and cardiovascular-related mortality [24]. Recent evidence suggests that subtypes of PTSD may be particularly associated with morbidity and mortality [25]. Subtypes of externalizing and internalizing have been identified in previous studies [7], and these subtypes may be significantly related to mortality compared to individuals with a low pathology subtype [25]. Investigations of PTSD and physical morbidity suggest an association between the two, but there is a clear need for epidemiologic research using longitudinal, prospective methods and investigation of potential moderating variables. Unfortunately, the examination of gender differences in the cardiovascular physiology of PTSD is also relatively understudied.

PTSD and Morbidity of Type 2 Diabetes

Although the research is not as extensive as that on CVD, there is evidence that PTSD is associated with the occurrence of Type 2 diabetes. A recent review found partial evidence for the relationship: of the four studies that included diabetes as an outcome, positive associations with PTSD were ob-

served in two [3, 11, 26]. After controlling for a range of covariates, including age, education, race, intelligence, income, geographic region, Army volunteer status, number of times married, and history of antisocial personality, alcohol abuse, drug abuse, and history of cigarette smoking, PTSD was associated with an adjusted odds ratio of 2.9 for insulin-dependent diabetes mellitus in veterans [5]. In men sampled from a primary care setting, trauma history was associated with diabetes, but PTSD was not [27]. PTSD was found to be related to increased risk of diabetes in a large primary care sample [26]. Medical eligibility data demonstrated a positive link in female children and adolescents between PTSD and problems in a combined category of endocrine, metabolic, and immune function [28]. The association between self-reported diabetes and PTSD appears to generalize at least somewhat to community population adults, although a large survey of Canadian civilians found no association between PTSD and diabetes after adjusting for demographic and psychiatric variables [11, 29, 30]. Unfortunately, there are no studies to date that longitudinally examine specific biomarkers of CVD and type 2 diabetes risk in individuals with PTSD. In addition, possible gender differences in PTSD and diabetes in adults have not yet been evaluated.

Biomarkers of Cardiovascular and Metabolic Disease in PTSD

Autonomic Dysregulation

The autonomic nervous system regulates vital body functions such as heart rate, respiration rate, digestion, and salivation. It includes the sympathetic nervous system (SNS), which promotes short-term adaptation to immediate stressors through the fight-or-flight response and the parasympathetic nervous system (PNS), which reduces heart and respiration rates in order to conserve and restore energy. Autonomic dysregulation can arise from disruption of either the sympathetic or parasympathetic nervous systems, or disruption of the interplay between these two systems. Not surprisingly, recent research examining both SNS and PNS suggests they combine to produce the autonomic dysregulation associated with PTSD [31]. Consequently, measurement and consideration of both the SNS and the PNS are critical to developing a complete understanding of PTSD and autonomic dysregulation. In addition, early research on autonomic dysregulation in PTSD compared Lebanon war veterans with PTSD to those without, noting that veterans with PTSD reported more cardiovascular symptoms and low effort tolerances during a cardiovascular task [32]. More extensive alteration of cardiovascular indicators has been observed in individuals with chronic PTSD [33].

Heart Rate

Although a few studies have not detected an association between trauma cues and heart rate for individuals with PTSD (compared to trauma-exposed individuals with no PTSD) [34, 35], most research has found that individuals with PTSD exhibit a more pronounced increase in heart rate in response to trauma cues [36–39]. This reactivity may be relevant to increased risk of cardiovascular disease, as elevated resting heart rate has been shown to be predictive of earlier mortality from CVD [40]. It should be noted that there is some intragroup variability in the relationship between PTSD and increased heart rate response to trauma cues: 23% of a sample of motor vehicle accident survivors with PTSD, for example, did not demonstrate a significant increase in heart rate when listening to an audio description of the accident [41]. A number of studies have also observed increased heart rate in people with PTSD when no traumatic stimulus is being presented [36, 42]. Meta-analyses of laboratory studies have found that both men and women with PTSD show increased basal heart rate and blood pressure compared to both trauma- and non-trauma-exposed individuals without PTSD [33]. A study of comparative laboratory assessments showed that civilians with PTSD had higher basal heart rates than their non-PTSD counterparts, while police officers with PTSD did not [43]. Buckley and colleagues [44] found that increased basal heart rates were independent of the contributions of behavioral health variables such as body mass index (BMI) and smoking. Laboratory assessments of heart rate have been complemented by clinical assessments. Retrospective chart reviews of female veterans found that although there were no group differences in blood pressure or BMI, those with PTSD had elevated resting heart rates [45]. Elevated basal heart rate in PTSD has also been evident in studies using ambulatory monitoring [44, 46–48].

While elevated heart rate in PTSD is generally interpreted as being a result of the disorder, it is possible that hyperarousal of the cardiovascular system promotes heightened vulnerability to the development of PTSD. This hypothesis was investigated in a monozygotic twins study in which only one of each pair had been exposed to combat in the Vietnam War. Approximately half of the Vietnam veterans had developed PTSD, resulting in a sample consisting of combat veterans with and without PTSD as well as people who had not been exposed to combat. Heart rate responses to loud noises were elevated in combat veterans with PTSD, but not in their twins or the combat-exposed non-PTSD group [49], which suggests that this physiological reactivity was influenced by the development of PTSD.

Research on stressor stimuli that are not trauma-specific has yielded conflicting results. This contrast was evident in

a study in which exaggerated heart rate reactivity to trauma cues was not mirrored by a larger increase in PTSD participant reactions to non-trauma negative cues in a sample of motor vehicle accident survivors [36]. A study of women who had survived assault found that those who developed PTSD did not exhibit an elevated heart rate response to a loud noise 1 month after the assault, but did 6 months after the assault [50]. Recent research in a sample of both men and women with various traumas found that both acute and chronic PTSD associated with an elevated heart rate response to trauma cues and an exaggerated startle response to loud noises [51]. While research to date indicates that people with PTSD have increased cardiovascular reactivity to trauma cues, the physiological response to general environmental stressors appears to be either similar or diminished relative to those without PTSD. When confronted with a cognitive challenge, a group of patients with PTSD responded with significantly higher cortisol, but similar heart rate and blood pressure compared to healthy controls [52]. In a study of general environmental stressors, participants with PTSD exhibited less physiological responsiveness to demands of laboratory tasks, relative to traumatized participants with no PTSD. When a response inhibition cue was added to the task, participants without PTSD exhibited the expected increases in SNS activity as indicated by skin conductance, but those with PTSD had smaller increases or no increase at all. Finally, while traumatized people without PTSD had increases in both heart rate and skin conductance when they could receive a monetary reward for performance on a lab task, those with PTSD exhibited a blunted physiological response [53]. Further evidence of physiological hyporeactivity to stressors was observed in a study of primarily female, non-veteran participants that compared people with PTSD to those with other anxiety disorders. Relative to other anxiety disorders, PTSD was associated with reduced eyeblink startle and heart rate increases to sentences designed to elicit physiological fear responses [54]. In a study of male and female Gulf War veterans with chronic fatigue, those with comorbid PTSD failed to exhibit the expected increase in blood pressure in response to speaking and mental arithmetic tasks requiring mental effort [55]. These results contradict observations suggesting general hyperarousal in people with PTSD and raise the possibility that physiological changes associated with PTSD could impair physiological responsiveness to non-trauma-related environmental stressors. It is possible that the characteristics of the stressor explain some of the inconsistencies in physiological responsiveness in PTSD. Nevertheless, given the conflicting nature of these results, further research is needed to establish that the physiological reactions noted in previous studies can be replicated and that the reactions are persistent across time in longitudinal studies.

In addition to the cardiovascular startle response, the time it takes for the cardiovascular system to recover to the baseline level following startle has also been used as a measure of dysfunction in PTSD. In a study using this methodology in a sample of combat veterans in treatment for PTSD, the severity of PTSD symptoms was related to delayed heart rate recovery following startle [56]. Although most of this research has been conducted in men, recent years have seen some research on the heart rate response to startle in women. In a study of women who served as nurses in Vietnam, those with current PTSD exhibited more dramatic startle responses, as measured by heart rate, than participants with either past or no history of PTSD [57]. However, skin conductance responses were not significantly larger in the current PTSD group. Because heart rate response is determined by both SNS and PNS components and the skin conductance response is primarily an indicator of SNS activity, the authors interpreted this discrepancy as an indication that the increased heart rate responses were due to decreased parasympathetic tone [57]. The autonomic trauma cue reactivity frequently observed in people with PTSD may be complicated by second-order conditioning of trauma cues. Due to repeated fear responses, cues related to the index trauma could function as unconditioned stimuli. However, evidence from heart rate conditioning paradigms has been inconsistent with regard to heart rate conditioning to non-trauma aversive stimuli [58, 59].

Blood Pressure

Although the effects are not as large or as consistent, findings of elevated blood pressure in PTSD have generally mirrored existing research on heart rate [33, 60]. Relative to traumatized individuals without PTSD, police officers with PTSD exhibited exaggerated blood pressure increases in response to trauma scripts [43]. In a study of eight male Vietnam veterans with combat-related PTSD, viewing videotapes of combat scenes induced negative mood and higher anxiety and was associated with increases in heart rate as well as both systolic and diastolic blood pressure [61]. A more dramatic blood pressure increase during affective distress has also been observed in studies monitoring ambulatory blood pressure [44]. Data from a small ($n=11$) sample of veterans with PTSD indicated no significant relationship between norepinephrine and blood pressure, which suggests that irregular blood pressure findings in PTSD may be due in part to an absence of regulation by norepinephrine [62]. In a study comparing participants with PTSD to those with borderline personality disorder who had suffered childhood traumatic events, PTSD was related to significantly greater systolic, but not diastolic, blood press response to trauma scripts [63]. That there was no between-group difference in blood pressure response to neutral or abandon-

ment scripts affirms a stronger cardiovascular response to trauma cues relative to the response to general stressors.

Meta-analysis has also suggested a trend toward higher basal blood pressure in PTSD [33]. Research on a sample of people with PTSD replicated previous observations of elevated baseline systolic and diastolic blood pressure [64]. Furthermore, these participants exhibited significantly greater increases in blood pressure following the administration of corticotrophin-releasing hormone [64].

Endothelial Dysfunction

Preliminary research has estimated the influence of PTSD on CVD by assessing endothelial dysfunction. Early research on medical morbidity from the Veterans Affairs Normative Aging Study suggested that self-reported PTSD symptoms were associated with increased risk of onset of arterial disorders [65]. Because endothelial dysfunction is recognized as the initial step in the atherosclerotic process and its progression [66, 67], assessment of endothelial functioning offers a potential pre-clinical marker of the development of arterial disorders as well as an additional method to utilize in research on CVD in PTSD. Endothelial dysfunction can be measured using flow-mediated dilation (FMD), which uses ultrasound images to follow changes in vessel diameter in response to increased blood flow. In arteries lined by healthy endothelium, increased flow causes dilatation of the vessel, but this response is compromised by endothelial dysfunction. FMD reveals the presence of endothelial dysfunction in individuals at high risk of atherosclerosis prior to the clinical manifestation of vascular disease [68, 69].

In a mixed sample of male and female police officers who completed the Impact of Event scale as a measure of PTSD symptomatology, FMD and carotid artery thickness were used to assess endothelial function. Compared to police officers with the lowest PTSD symptomatology, those in the severe range exhibited approximately half the brachial reactivity [70]. In contrast, carotid artery intima-media thickness did not differ by PTSD symptomatology. This study provides evidence that PTSD symptoms are related to pre-clinical markers of disease, but the study is limited due to the use of self-report measures rather than a clinician symptom rating sufficient for establishing a PTSD diagnosis.

Endothelial dysfunction can also be assessed by measuring circulating proteins that promote blood coagulation. In a small study comparing physically healthy patients with PTSD to traumatized controls, those with PTSD had higher levels of soluble tissue factor, although this effect was not independent of emotional distress and was not observed in two other endothelium-derived circulating proteins [71]. Another analysis of these data found some evidence for an association between an increase in blood clotting factors and PTSD symptom severity, although not PTSD diagnosis [72].

Baroreceptor Sensitivity

Mediated by central baroreceptor feedback loops, blood pressure variability is regulated by vagal control of heart rate and the direct effects of sympathetic activity on vasculature [73]. Individuals with reduced cardiac autonomic control, as indicated by reduced heart rate variability (HRV), have greater blood pressure variability due to a diminished buffering capacity [73, 74]. Baroreceptors are pressure-sensing nerves that regulate parasympathetic activity. Consequently, baroreceptor sensitivity has been used as a measure of PNS tone. Prominence of the PNS in cardiovascular symptoms in PTSD is derived from several studies in controlled laboratory conditions that have demonstrated a relationship between PTSD and reduced PNS control of the heart [75–77]. Parasympathetic components of cardiovascular functioning could also be influenced by the immediate environment, as illustrated by a study in which electrocardiogram assessments of children with PTSD were recorded while they interacted with parents [78].

An investigation of smokers with PTSD found that while baroreceptor sensitivity was not altered in men, it was significantly decreased in women [77]. Subsequent research extended these findings to a mixed sample of female smokers and non-smokers with PTSD in observing decreased baroreceptor sensitivity at rest. Furthermore, while baroreceptor sensitivity decreased for all participants during an anger recall task, the change was less dramatic for women with PTSD, possibly due to their lower resting values [76]. More recently, in a study of women with and without PTSD, an interaction was detected between baroreceptor sensitivity and objective sleep parameters [79]. Lower baroreceptor sensitivity was associated with poorer sleep in women with PTSD, but not in those without PTSD [79].

Parasympathetic Nervous System Measures

Because it is heavily influenced by the autonomic nervous system and involves both the SNS and PNS in its functioning, heart rate variability has often been used as an index of autonomic function. Heart rate variability is widely recognized as an important index of autonomic function that is useful as a prognostic indicator of risk for both CVD and metabolic syndrome. Previous research has indicated that reduced 24-h HRV independently predicts mortality in patients with stable CVD [80] or a recent myocardial infarction [81]. More recent evidence also supports the

prognostic significance of HRV as a predictor of mortality in patients with heart failure [82]. A number of previous studies have reported reduced levels of short-term HRV in participants with anxiety disorders as well as in those with PTSD [83]. While these findings suggest that impaired HRV may contribute to risk in PTSD patients, a deeper understanding of the role of the autonomic nervous system in the increased risk of mortality in PTSD would be aided by the use of 24-h electrocardiogram (ECG) recordings, a method that can offer an improved estimation of risk over short-term ECG recordings [84]. Use of 24-h ECG recordings may be especially relevant to individuals with PTSD, as their reduced sleep duration and sleep efficiency may lead to reduced levels of ambulatory HRV [85]. Daily stressors and worry have also been associated with low HRV, during both wake and sleep [85]. Sleep and wake have profoundly different effects on HRV, with parasympathetic control of heart rate being substantially higher during sleep periods [86, 87]. Preliminary data suggest that circadian variation in HRV may be impaired in some veterans post-deployment, a group at high risk for PTSD [88]. These findings suggest that people with PTSD have alterations in HRV that would be better characterized by ecologically valid assessments that include overnight measurement of HRV.

The influence of the PNS on autonomic dysfunction has been assessed using respiratory sinus arrhythmia (RSA), the changes in heart rate rhythm associated with inspiration and expiration [83]. RSA reflects vagal tone and is one index of PNS function. One study noted that the elevated basal heart rate frequently observed in PTSD was only present in those with lower respiratory sinus arrhythmia, an indication of diminished PNS activity [83]. Further evidence of the prominent role played by the PNS in autonomic dysfunction in PTSD comes from a study that observed significantly lower RSA in participants with PTSD listening to trauma scripts than in those listening to neutral scripts, which suggests stress-induced suppression of the PNS. The heart rate increase associated with the trauma script for all participants was of longer duration in those participants with lowered RSA [89].

Cardiovascular functioning can also be assessed using power spectral analysis. The total heart variance is assessed with various outcome measures, including high frequency, which indicates vagal activity from the PNS; and low frequency, which indicates both SNS and PNS activity; and very low frequency [90]. Increased risk of CVD in PTSD could be influenced by elevated noradrenergic responsiveness. This interpretation is supported by similarities between the hyperarousal symptoms of PTSD and effects observed immediately following administration of catecholamines such as epinephrine and norepinephrine [90].

In a study comparing people with PTSD to those with panic disorder and to healthy controls, PTSD was associated with increased baseline sympathetic nervous system activation, as measured by the electrodermal activity and heart rate [31]. PTSD was also associated with diminished parasympathetic control of heart rate as measured by RSA. When participants were anticipating electric shocks, those with PTSD exhibited diminished electrodermal sensitivity relative to the other groups. These results support previous interpretations of autonomic dysregulation in PTSD that emphasized the interplay of sympathetic and parasympathetic components [78].

Although most evidence suggests that autonomic dysfunction is the result, rather than the cause, of chronic disease, some studies have documented autonomic dysfunction (as measured by RSA) among at risk individuals prior to disease onset [91]. Impaired autonomic control of heart rate is an early event in the progression of type 2 diabetes and is often present at the time of diagnosis [92–94]. Autonomic dysfunction is also present in children newly diagnosed with insulin-dependent diabetes mellitus [95]. These results raise the possibility that decreased vagal tone may play a role in the pathogenesis of certain chronic diseases, including CVD and type 2 diabetes. Recent research has provided further evidence of the role of autonomic dysfunction in the onset of chronic disease. In overnight fasting healthy volunteers, reduced autonomic function (as measured by baroreceptor sensitivity) was significantly associated with fasting plasma insulin after controlling for other predictors of baroreceptor sensitivity, such as age, blood pressure, and BMI [96]. HRV parameters were lower in diabetic patients with chronic complications compared to those without chronic complications [97].

Lipids

A number of studies provide evidence that PTSD is linked to CVD, but comparatively fewer studies have investigated the relationship between PTSD and metabolic abnormalities. However, some research on PTSD and cardiovascular/metabolic disease has included investigation of elevated lipids. In a study comparing people with PTSD to people with major depressive disorder (MDD), PTSD was associated with a number of lipid variables, including elevated cholesterol, low-density lipoproteins, and triglycerides, as well as decreased high-density lipoproteins [98]. A large medical record review of veterans enrolled in primary care split patients into the following four groups: PTSD only; MDD only; PTSD with comorbid MDD; and a comparison group with neither disorder. Using these groups, the authors found that among patients with depression, those with comorbid PTSD were 56% more likely to have cholesterol above 135 mg/dL and 38% more likely to have a low-

density lipoprotein level above 110 mg/dL [99]. The group with comorbid PTSD and depression also had significantly higher weight and BMI. However, effect sizes were generally small for either PTSD or depression alone. Karlovic and colleagues [100] conducted a similar study with male Croatian combat veterans. They split participants into PTSD, MDD, and PTSD comorbid with MDD groups to compare to a healthy male control group, comprising mostly hospital employees. In this study, veterans with PTSD had significantly higher cholesterol, low-density lipoproteins, low-density/high-density lipoprotein ratio, and triglyceride concentrations relative to not only healthy controls, but also to veterans with MDD. Veterans with comorbid PTSD and MDD had elevations similar to those seen in the PTSD only group [100]. High-density lipoproteins were lowest in both groups comprising people with PTSD [100]. An additional study of Croatian soldiers with PTSD also found elevated lipids and cholesterol values relative to a healthy control group [101]. A study of police officers found that, relative to officers without PTSD, those with PTSD had elevated total cholesterol, triglycerides, and low-density lipoproteins. The effects on total cholesterol and triglyceride elevations were independent of socio-demographics, BMI, and tobacco, alcohol, and medication use [102].

Allostatic Load Model

Friedman and McEwen [103] provided a comprehensive theory for understanding links between PTSD and physical illness by using the allostasis model. Allostasis refers to the process of adaptation to stressors to achieve stability through change [104]. While short-term adaptation to stress is characteristic of a healthy organism, allostasis can contribute to physical costs if the organism must endure challenges too frequently, fails to habituate to repeated exposure to similar stressors, fails to shut off physiological responses after the stressor is over, or can no longer mount an adequate stress response. These physical costs can result in elevated blood pressure, elevated inflammatory cytokine production due to inadequate glucocorticoid levels, or sustained exposure of body tissue to glucocorticoids [103]. The cumulative physical costs of allostasis are termed allostatic load.

Stress appraisals have consistently demonstrated activation of two specific pathways: the HPA axis, which culminates in the secretion of cortisol, and the locus coeruleus/norepinephrine-sympathetic system, which secretes epinephrine and norepinephrine. Disrupted HPA axis functioning in PTSD could play a role in the development and progression of cardiovascular [23] and metabolic disorders [105]. In addition, coeruleus/norepinephrine-sympathetic system activity is often elevated in PTSD and has been associated with cardiovascular abnormalities [103]. Con-

ceptualized within the allostatic load framework, disruption of these systems contributes to cardiovascular and metabolic disease through the cumulative effects on body systems. Continued overactivation of the HPA axis has, for example, been associated with various conditions including memory impairment, hypertension, osteoporosis, insulin resistance, and CVD [106].

Influences of Hostility and Health Behaviors on Cardiovascular/Metabolic Disease in PTSD

The clinical significance of atherosclerotic CVD and type 2 diabetes is becoming a topic of interest in individuals with PTSD. However, mechanisms underlying the relationship of PTSD to CVD and type 2 diabetes are not well understood. In non-psychiatric populations, several mechanisms have been proposed, including personality factors (e.g., hostility), behavioral and lifestyle factors, and biological pathways. As this body of evidence accumulates, a more detailed understanding of the process by which PTSD might influence cardiovascular/metabolic disease becomes increasingly valuable. Some research has provided evidence of tertiary factors that might serve to mediate or moderate the conditions under which PTSD is associated with cardiovascular/metabolic disease. Of these factors, hostility has emerged as a promising construct for contributing to a more complete understanding of this relationship.

Hostility

Meta-analytic, epidemiological, and laboratory studies have shown that individuals with PTSD have higher hostility than those without PTSD [107–109]. In addition, PTSD intensity has been positively correlated with hostility level [110]. Furthermore, in some but not all PTSD studies [111–113], hostility and anger have been negatively associated with treatment response [114]. For this reason, the variability and potential predictive role of hostility in people with PTSD are of potential clinical significance. For our purposes, hostility is defined as a broad construct [4, 115] comprising cognitive components such as negative beliefs about others; affective components such as anger, annoyance, resentment, disgust, and contempt; and behavioral components ranging from subtle interpersonal conflicts to overt physical aggression to more subtle conflicts with others.

A large body of research on hostility has noted an association with adverse health outcomes [2, 4, 8, 33, 38, 108, 115–126]. These outcomes include more severe coronary artery disease, peripheral artery disease, and hypertension; lower physician ratings of functional health; and premature mortality from all causes [121, 127, 128]. Hostility has been shown to be a risk factor for poor health, including an

association with increased rates of hypertension and higher levels of lipids in both men and women [129–142] and increased risk of coronary heart disease and myocardial infarction [118, 119, 143–148]. Even when traditional risk factors (e.g., smoking, cholesterol levels) are controlled, hostility is a significant predictor of all-cause mortality [139, 144, 149]. Angry feelings have been shown to be related to CVD risk factors [150, 151] and to predict the risk for development of metabolic syndrome in women [152].

Several recent studies have complemented previous research on hostility and increased risk of cardiovascular/metabolic disease by noting a link between hostility and altered physiological reactivity. For example, male participants in one study who were "quarrelsome" exhibited decreased PNS activity during social interactions [153], a finding that parallels studies of impaired PNS reactivity in PTSD. Previous research with police officers reporting varying levels of PTSD symptoms noted a more than twofold increase in flow-mediated dilation following occlusive pressure in officers with low levels of PTSD symptoms, relative to those with severe PTSD symptoms [154]. This finding suggests poor reactivity of the vasculature and provides a potential mechanism for links between PTSD and CVD. Some research has found that individuals with PTSD exhibit greater cardiovascular responsivity when reliving an anger-provoking event from their past [115]. However, another study observed that hostile individuals who received a good apology had quick recoveries of both heart rate and blood pressure [141]. This study is particularly interesting, because recent research suggests that it is the prolonged duration of the physiological response, rather than an exaggerated initial reactivity, that is strongly associated with elevated trait hostility [155].

The physiological reactivity associated with hostility may also be related to social environment. In a study of couple interactions, the physiological reactivity of women high in hostility varied as a function of their husbands' hostility. Women with husbands who were low in hostility exhibited low baseline heart rate and blood pressure but exaggerated reactivity to conflict. In contrast, when both the husband and wife were high in hostility, the women were elevated on baseline cardiovascular measures, but exhibited less reactivity to conflict [156]. These findings imply that environmental variables could contribute to sustained changes in physiological indices, even when trait hostility remains elevated. Modification of physiological reactions in hostile people provides encouraging evidence of the possibility of effective intervention.

As with research on medical illness in PTSD, relatively few studies have investigated relationships between hostility and medical illness in women [157]. In one study of women, hostility was related to increased intima-media thickness of the carotid artery wall, suggestive of the early stages of atherosclerosis [158]. Insulin resistance and fasting insulin level have also been significantly associated with hostility, but only in women [159].

Research into the influence of hostility on the relationship between PTSD and cardiovascular/metabolic health has yet to definitively identify the precise role of hostility. Hostility could be useful in identifying the conditions under which PTSD might be related to cardiovascular and/or metabolic disease. Research indicating that only people with PTSD who are high in hostility are at increased risk of disease would support an interpretation of hostility as a moderator, while studies observing that PTSD is associated with increased risk of cardiovascular/metabolic disease through its effects on hostility would support the conceptualization of hostility as a mediator. In addition to acting as a full mediator hostility could also partially mediate the relationship between PTSD and cardiovascular/metabolic disease. A partial mediation model is similar to the full mediation model in that PTSD would alter hostility levels, which would in turn alter risk of cardiovascular/metabolic disease. However, in a partial mediation model, hostility would only explain a portion of the increased risk of cardiovascular/metabolic disease, with the remaining effects being independent of hostility. Gottdiener and colleagues [160] assessed people without any coronary artery disease, congestive heart failure, or diabetes. A mental stress task was associated with significantly diminished flow-mediated arterial vasodilation. Those high in hostility exhibited enhanced effects of mental stress on flow-mediated dilation. In this case, higher trait hostility was a condition under which flow-mediated dilation was further diminished, though no test of moderation was conducted. There has generally been little investigation into how anger and hostility relate to health outcomes among those with PTSD; however, Ouimette and colleagues [161] found that anger/hostility was significantly associated with disease among only those with PTSD [162]. Several additional studies have found a relationship between hostility and cardiovascular activity among only people with PTSD [115]. In a recent study of women with and without PTSD, increases in hostility were associated with greater increases in heart rate suggesting that hostility may moderate the effect of PTSD on cardiovascular outcomes [163].

As reviewed above, there is evidence that both individuals high in hostility and individuals with PTSD have increased sympathetic nervous system hyperreactivity [73, 116, 128, 138–140, 149, 150, 164–169]. Indeed, hostility may account for the hyperreactivity observed in people with PTSD. The well-established links between hostility and SNS hyperreactivity and chronic illness support the relevance of hostility to the association of PTSD with cardiovascular/metabolic disease. A few studies have

examined PTSD symptom clusters to explore relationships with physical illness. In one study, symptom severity on the hyperarousal cluster, which includes irritability, was related to a higher concentration of precoagulant factors in the vasculature [162]. An analysis of data from a large sample of Vietnam veterans with PTSD found no association between dissociative symptoms and a number of physiological symptoms, including heart rate, skin conductance, electromyographic data, and blood pressure [170]. Another study comparing 20 male Croatian combat veterans to non-PTSD males matched on age and BMI found no differences in blood platelet function [171]. However, the authors cautioned that this study was designed as a pilot study with low power to detect group differences. Taken together, the research to date suggests that hostility may interact with PTSD to increase cardiovascular and metabolic risk factors and that this interaction may contribute to increased risk of poorer health outcomes and cardiovascular mortality.

Depression

Research has consistently found that symptoms of depression are common in PTSD populations. In addition, a number of studies have linked depression with CVD [172]. In fact, the research on depression and CVD serves as a valuable model for PTSD research, as initial observational studies of individuals with pre-existing CVD were followed by community studies of individuals without established CVD [172]. Because MDD is often comorbid with PTSD [173, 174], examination of this comorbidity is likely to reveal important information in the risk for adverse physical health outcomes in those with PTSD.

Several studies have observed an association between depression and biomarkers of CVD risk, such as reduced 24-h HRV [175, 176] and endothelial dysfunction [177]. These findings indicate that depression needs to be considered as a potential confounder or effect modifier in studies of PTSD. A few studies have investigated the influence of depression on the relationship between PTSD and physical disease. For example, controlling for depression, PTSD has been associated with a twofold increase in self-reported CVD in American Indians [21]. In contrast, the association of MDD with CVD was not significant after accounting for both traditional risk factors and PTSD [21]. Data from civilian women suggest that while controlling for depression attenuates the relationship between PTSD and CVD, women with PTSD still suffer from higher rates of CVD [22]. Concordant with data on CVD, available evidence links depression with elevated levels of blood glucose [159, 178, 179] and risk of diabetes [180, 181]. Therefore, it is important that research on the relationships between PTSD and cardiovascular/metabolic disease address the issue of comorbid depression.

To effectively evaluate this relationship, it will be essential to measure depression and account for its influence in studies of PTSD and cardiovascular/metabolic illness. In addition, intervention research could compare people with PTSD only to those with PTSD and comorbid depression. Finally, future research must consider the potential impact of low socioeconomic status and social isolation, which are associated with not only PTSD and depression, but also increased risk for CVD [172].

Health Risk Behaviors

A number of behaviors may contribute to the increased risk for poorer health in individuals with PTSD. For example, a number of studies have documented a tendency for PTSD patients to engage in increased alcohol use, higher BMI, and greater rates of smoking [7, 8, 182–185]. Studies of both men and women have noted an association between hostility and reports of higher BMI [186, 187] and poorer health habits including less physical exercise, less self-care, more alcohol use [188–191], more cigarette smoking [134, 191–193], and greater caloric intake [187].

Only a few studies have investigated the effects of PTSD on cardiovascular/metabolic disease separately from the effects of behavioral health habits. A study of patients with substance use disorders found that those with PTSD had significantly increased rates of CVD [194]. This effect was independent of gender and ethnicity. In a study comparing patients from a VA rehabilitation unit with PTSD to demographically matched inpatients with alcohol dependence, those with PTSD were reported to have a higher frequency of CVD and diabetes [195]. Although the alcohol dependence group had more cigarette smoking pack years, the PTSD group had higher blood cholesterol and triglyceride levels and higher rates of obesity [195]. These findings suggest that increased risk of cardiovascular/metabolic disease in PTSD may be independent of alcohol intake, but these results might be explained by other behavioral health factors. Future research would benefit from consideration of behavioral health differences when investigating physical health in PTSD.

Conclusions and Future Directions

Limitations to Current Evidence

Despite a number of important findings, the research on PTSD and cardiovascular and metabolic disorders has several important issues to address to more completely evaluate a possible link. To complement the literature with male veterans, epidemiologic studies of PTSD and physical illness must continue to establish that results are consistent

across demographic groups, such as age, race, gender, veteran status, socioeconomic status, and marital status. There is also a need for longitudinal data [22] and large, prospective epidemiologic trials with established clinical assessments of PTSD and medical disorders [3].

While the focus of this review has been on the development of cardiovascular and metabolic disease in people who already have PTSD, pre-clinical markers and disease sometimes precede the onset of PTSD. Several studies have documented the development of PTSD following life-threatening events that accompany CVD, such as myocardial infarction, as well as life-threatening events that accompany metabolic disease, such as hyperglycemic episodes. Longitudinal research can address the question of temporal precedence by following people with PTSD without pre-clinical markers of cardiovascular/metabolic disease to determine whether they are more likely to develop disease markers or the disease itself than people without PTSD. Longitudinal research might also enable investigation of the distinct influences of comorbid psychological disorders on pre-clinical disease markers, as well as provide information on associations between PTSD and pre-clinical disease markers before the onset of other disorders.

While the relative contributions of genetic factors and PTSD to the development of cardiovascular/metabolic disorders have not been established, it is possible that there may be genetic factors that predispose individuals to both conditions, and these may account for some or all of the association between PTSD and cardiovascular/metabolic disease. Furthermore, although this review has examined influences of PTSD on cardiovascular/metabolic disease, it is possible that traumatic experiences increase the risk of disease even in individuals who do not develop PTSD. Risk of medical illness could increase with injuries sustained during the trauma or infections occurring during the trauma or treatment. Much of the research into this topic has compared people with PTSD to similarly traumatized, non-PTSD individuals to consider the effects of PTSD independently. This methodology has strengthened the understanding of health effects in PTSD and will be an important part of future research.

It would be helpful to have pre-trauma physical health information to determine whether PTSD played a role in the development of a given medical illness and/or whether the illness could have resulted from shared risk factors (e.g., socioeconomic status) for PTSD and medical problems. Due to the relative lack of research available on a possible link between PTSD and metabolic disorders, there needs to be much more research to account for the influences of the many contributors to metabolic health risk in people with PTSD. Disease biomarkers of potential interest include autonomic dysregulation, endothelial dysfunction, metabolic syndrome, and insulin resistance.

Future studies could evaluate whether PTSD with or without comorbid MDD is associated with pre-clinical markers of cardiovascular risk. Promising pre-clinical markers include vascular endothelial function, 24-h heart rate variability, and baroreflex sensitivity. Considering that individuals with both PTSD and high hostility are at a higher risk for poor cardiovascular health, future research could also extend existing findings on third variables in the relationship between PTSD and risk of cardiovascular/metabolic disease in order to determine whether there is an interaction between PTSD and hostility. Analyses could evaluate whether PTSD is related to insulin resistance and whether levels of hostility moderate this relationship. Inclusion of both a PTSD without comorbid MDD and a PTSD with comorbid MDD group will allow for direct evaluation of the effect of PTSD, and the potential additive effect of MDD.

Although a number of studies have examined the relationship between traumatization and health outcomes, there are no studies to date evaluating multiple precursor measures of CVD and diabetes in a younger PTSD sample. Given that much of this evidence has been collected in older samples, the literature in this area would be strengthened by careful assessment of PTSD and biomarkers of CVD and type 2 diabetes in a younger, trauma-exposed sample.

Pre-trauma Vulnerability

The research literature has not fully established the extent to which reactivity to aversive stimuli is the result of PTSD, rather than a pre-trauma vulnerability factor. While some evidence suggests that measures such as pre-trauma eye-blink startle and skin conductance under contextual threat predict the development of PTSD symptoms, similar predictive power has not been evident with regard to pre-trauma heart rate response to contextual threat [196]. Orr and colleagues [49] have shown that individuals with PTSD have an exaggerated heart rate response to startle relative to that of their healthy monozygotic twins. Twins research offers evidence that trauma exposure and PTSD alter physiological responses to trauma cues; however, there is also evidence that genetic factors play a role in PTSD vulnerability [197, 198]. Specifically, recent twins research points to increased vulnerability in individuals with neurological abnormalities such as subtle neurological dysfunction (also known as neurological soft signs), decreased hippocampal volume, and abnormal cavum septum pellucidum [199]. While these variables probably represent pre-trauma risk factors, a substantial literature documents that cardiovascular, particularly heart rate, reactivity to trauma cues often results from the development of PTSD.

It is important to note the traits that put individuals at risk for suffering trauma could also contribute to increased risk of cardiovascular or metabolic disease. For example, there is evidence that trauma exposure rates are higher in men, younger people, and members of minority groups residing in urban areas [200]. In addition to demographic predictors, elevated trauma exposure rates have been documented in people with traits such as neuroticism and extraversion, as well as pre-existing psychiatric disorders [201]. The presence of these potential confounders in PTSD and health research underscore the importance of longitudinal designs, diverse study samples, and assessment of relevant pre-trauma characteristics in future research.

Prevention of Cardiovascular and Metabolic Disease in PTSD

Given the high prevalence of PTSD [202] and the accumulating evidence of an accompanying medical morbidity and mortality [203], there is a need for research identifying specific intervention targets for reducing the medical burden in PTSD, especially when PTSD becomes chronic. The literature on PTSD and cardiovascular disease indicates that increased monitoring of pre-clinical markers of CVD is warranted. Although the current state of research on metabolic disorders is more equivocal, patients with PTSD might also benefit from increased screening of pre-clinical markers such as lipids and blood glucose levels.

As a complement to increased preventive medical care in those with PTSD, it will be important to implement and augment screening and treatment of psychiatric disorders in medical settings. Considering the frequency with which patients with psychiatric disorders present in primary care rather than mental health facilities [204], screening in medical settings has the potential to be quite beneficial.

While PTSD treatment has clear implications for psychiatric well-being, the implications for physical health are not established. In the absence of treatment, autonomic nervous system activation by trauma cues may be particularly difficult to control for people with PTSD. Experimental findings suggest that when expecting an aversive event, people with PTSD exhibit exaggerated eyeblink responses that are not ameliorated either by cues warning of the timing of aversive stimuli or by cues indicating that the aversive event will not occur [196]. However, a number of studies suggest that physiological abnormalities in PTSD remit partially or completely during treatment sessions [205, 206] or after successful PTSD pharmacological [207, 208] or psychotherapeutic [36, 209–212] treatment, as well as combination treatment [210]. One potential clinical implication of the heart rate response to trauma cues was described in a case study detailing the use of heart rate data during psychotherapy to confirm that patients are not engaging in avoidance during exposure and as part of the measures of in-session and between-session habituation to trauma cues [213].

Mechanisms of Links between PTSD and Physical Illness

As reviewed above, the allostatic load model of PTSD and physical illness proposed by Friedman and McEwen [103] is useful in characterizing the onset and progression of cardiovascular and metabolic disease in PTSD. More broadly, the allostatic load model also includes a number of body systems and physiological processes that combine to produce physical illness in people with PTSD. Other reviews have highlighted links between PTSD and chronic inflammation [214]. In addition, disrupted HPA and SAM axis activity likely contributes to medical morbidity in PTSD [5]. Although not reviewed here, significant alterations in physical health could also result from stress-related abnormalities of the immune system, growth hormone production, or release of neuropeptide Y [103].

Although PTSD is typically conceptualized as a mediator of the relationship between trauma and physical disease, longitudinal studies are needed to determine which variables may serve as moderators or mediators in the relationship between PTSD and cardiovascular/metabolic outcomes. For example, if an effect of a predictor on an outcome variable is to be mediated by a third variable, it is conceptually reasonable that the predictor and mediator would precede the outcome temporally. Longitudinal research could provide clarity to mediation models by establishing the temporal precedence necessary to infer causality [215]. As a complement to research on mediation, moderation models suggested by research reporting associations of PTSD with cardiovascular/metabolic disease outcomes that vary at different levels of a third variable could also be valuable in identifying intervention targets and groups. In addition to overt phenotype characteristics such as gender, genetic research could prove valuable in identifying groups of individuals with PTSD who are at risk of cardiovascular/metabolic disease.

Summary

Although a relatively large literature supports a general link between PTSD and cardiovascular abnormalities, further investigation is needed in several areas. Relatively few studies have investigated metabolic disease and biomarkers as they relate to PTSD diagnosis. The extant evidence suggests a relationship between PTSD and metabolic abnormalities, but inconsistencies prevent definitive conclusions in this area. Both fields of research would benefit from longitudinal designs in diverse samples. In addition, much of the existing literature has based PTSD diagnosis

on self-report measures or medical record reviews rather than more valid interview-based PTSD assessments. Furthermore, it will continue to be important to consider the impact of comorbid disorders such as depression, substance misuse, and behavioral health problems that could influence the development of physical illness in PTSD. Finally, given the large body of research documenting associations between hostility and physical illness, both generally and in PTSD, it will be important to more fully understand the role of various mediators and moderators in explaining the association between PTSD and physical illness. Clinical implications of this research area are significant in that early detection and prevention as well as possible integrated physical and mental health treatment could substantially modify long-term trajectories in individuals with chronic PTSD. Continued research in this area is necessary to help guide prevention and treatment efforts aimed toward reducing morbidity and mortality in those with PTSD.

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