

Comorbid PTSD 1



Post-traumatic stress disorder and cardiovascular disease

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In this paper, a first in a Series of two, we look at the evidence for an association of post-traumatic stress disorder with incident cardiovascular disease risk and the mechanisms that might cause this association, as well as the prevalence of post-traumatic stress disorder due to cardiovascular disease events and its associated prognostic risk. We discuss research done after the publication of previous relevant systematic reviews, and survey currently funded research from the two most active funders in the field: the National Institutes of Health and the US Veterans Administration. We conclude that post-traumatic stress disorder is a risk factor for incident cardiovascular disease, and a common psychiatric consequence of cardiovascular disease events that might worsen the prognosis of the cardiovascular disease. There are many candidate mechanisms for the link between post-traumatic stress disorder and cardiovascular disease, and several ongoing studies could soon point to the most important behavioural and physiological mechanisms to target in early phase intervention development. Similarly, targets are emerging for individual and environmental interventions that might offset the risk of post-traumatic stress disorder after cardiovascular disease events.

Introduction

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that occurs in 7–8% of civilians^{1,2} and as many as 20% of military veterans,³ although changes in diagnostic criteria might alter these estimates slightly.⁴ PTSD symptoms include re-experiencing symptoms, avoidance of trauma reminders, physiological hyperarousal, and persistent negative alterations in cognition and mood.⁵ Investigation of the association of PTSD symptoms with the development and prognosis of cardiovascular disease began less than 20 years ago,⁶ but it has progressed rapidly thanks to the more established literature describing the effect of stress on cardiovascular risk.

The current understanding of the link between PTSD and cardiovascular disease is that PTSD is probably an independent risk factor for acute cardiac events including acute coronary syndromes (ie, myocardial infarction or unstable angina) and possibly stroke.⁷ The association of PTSD with cardiovascular disease risk is probably due to interacting behavioural and physiological mechanisms that relate to PTSD symptoms and, in turn, influence cardiovascular disease risk. Additionally, acute and potentially life-threatening cardiovascular disease events can themselves cause PTSD, and PTSD secondary to cardiovascular disease events might be associated with increased risk for subsequent cardiovascular disease events and mortality.⁸

In this paper we describe the emerging epidemiological, mechanistic, and intervention literature on the association of PTSD with incident cardiovascular disease risk in individuals exposed to potentially traumatic events such as combat and sexual assault, and with recurrent cardiovascular disease risk in patients with cardiovascular disease who develop PTSD secondary to an acute cardiovascular disease event. Where possible, we include estimates from the most recent systematic review and meta-analyses (table), and report on research

identified in systematic searches. We also highlight important unanswered questions and active funded research in each area.

Epidemiological evidence

PTSD and risk for incident acute cardiac events

Several epidemiological studies of the link between PTSD and cardiovascular disease have focused on risk for acute cardiac events specifically, and most have estimated the association in samples of veterans. Importantly, until recently, most studies were done with US samples.

A systematic review and meta-analysis of the prospective association of PTSD with incident acute cardiac events and cardiac-specific mortality included five published studies (n=401712) that followed up participants between 1 year and 30 years. These studies found that PTSD was associated with a 53% increased risk for incident cardiac events or cardiac-specific mortality after adjustment for demographical, clinical, and psychosocial factors. After further adjustment for depression, the association was attenuated to 27%, but remained significant. Most of the reviewed studies included samples comprising predominantly male veterans with PTSD from the USA, with more recent studies corroborating the increased cardiovascular disease risk associated with PTSD in this population,²¹ but also for non-veteran populations from Europe and women.^{22,23} Since that meta-analysis was published, a retrospective cohort study that would have met its inclusion criteria was published. Beristianos and colleagues²⁴ found a larger effect size than the estimate from that meta-analysis in 138000 US military veterans aged 55 years and older who were initially free of cardiovascular disease, with an unadjusted 82% increased risk of incident myocardial infarction events associated with PTSD diagnosis (3% of sample), which was attenuated to a 49% increased risk after adjustment for standard demographical, clinical, and psychiatric

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This is the first in a Series of two papers about comorbid PTSD

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Meta-analyses support	
Cardiovascular disease events	
Incident coronary heart disease	With no adjustment for depression HR 1.55 (95% CI 1.34–1.79); with adjustment for depression HR 1.27 (95% CI 1.08–1.49) ⁷
Incident stroke or transient ischaemic attack	RR 2.36 (95% CI 2.11–2.65) ⁹
Incident venous thromboembolism	None
Recurrent myocardial infarction, unstable angina, or mortality	RR 2.0 (95% CI 1.69–2.37) ¹⁰
Recurrent stroke or transient ischaemic attack	None
Mechanisms	
Type 2 diabetes	RR 1.49 (95% CI 1.17–1.89) ¹¹
Metabolic syndrome	RR 1.82 (95% CI 1.72–1.92) ¹²
Blood pressure	Systolic unweighted Cohen's <i>d</i> 0.13 (SE 0.07); diastolic unweighted <i>d</i> 0.39 (0.21) ¹³
Inflammation	Increased concentrations of interleukin 1 β , interleukin 6, and interferon γ in PTSD ¹⁴
Cortisol	Unclear ^{15,16}
Endothelial dysfunction	None
Obesity	OR 1.35 (95% CI 1.05–1.74) ¹⁷
Smoking	Six or seven studies showed positive associations; ORs ranged from 2.04 to 4.52 ¹⁸
Sleep	None
Medication non-adherence	None
Acute coronary syndrome	
PTSD	12% of participants screened positive (95% CI 9–16) ¹⁹
Stroke or transient ischaemic attack	
PTSD	23% of participants screened positive (95% CI 16–33%) ²⁰
Venous thromboembolism	
PTSD	None
PTSD=post-traumatic stress disorder.	
Table: Associations between PTSD and various cardiovascular factors and mechanisms supported by meta-analyses evidence	

comorbidities. The size of the study and its effect size would probably increase the meta-analysis effect size estimate, suggesting that PTSD might be more strongly associated with incident coronary heart disease than previously thought, at least for older veterans.

PTSD and risk for incident stroke events

Given the overlapping risk factors and pathogenesis of acute coronary and cerebrovascular events, it is highly plausible that PTSD might also increase the risk for stroke. Data from a 2016 meta-analysis, including two cohort studies, revealed that PTSD was associated with an increased risk of incident stroke (relative risk [RR] 2.36, 95% CI 2.11–2.65).⁹ Furthermore, in the largest study (n=26000), which was a national study of

administrative records in Taiwan, established cardiovascular risk factors did not account for this relationship. Using the Danish National Patient Registry, investigators from a study found the association between PTSD and incident cases of ischaemic stroke to be stronger in men (standardised incident rate [SIR] 2.4) than women (SIR 13) after a median follow-up of 7 years.²²

New directions in epidemiological research

PTSD is at least as common in women as it is in men. One of the limitations of the existing literature on PTSD and incident cardiovascular disease events has been the reliance on secondary data analysis of overwhelmingly male samples of military veterans, with a few exceptions. Sumner and colleagues²³ found that high frequencies of PTSD symptoms were associated with increased cardiovascular disease risk (myocardial infarction or stroke; with each comprising about half of the events in the combined outcome) in 50000 women in the Nurses' Health Study II (hazard ratio [HR] 1.60, 95% CI 1.20–2.13). Furthermore, they found that health behaviours and medical risk factors explained nearly half of the association of PTSD with incident cardiovascular disease. Because PTSD and cardiovascular disease risk and symptom presentation differ between men and women, more research in women is warranted.

Another important development has been the investigation of the association of PTSD with new-onset venous thromboembolism (ie, deep vein thrombosis and pulmonary embolism), because many of the risk factors for cardiovascular disease events are also contributors to venous thromboembolism risk, and the biological mechanisms that are possibly responsible for the link between PTSD and cardiovascular disease are implicated in the development of venous thromboembolism as well. In another analysis of the Nurses' Health Study II data, Sumner and colleagues²⁵ found a graded association of PTSD symptoms with increased venous thromboembolism risk after adjustment for demographics, family history, and childhood adiposity. Women with the most severe PTSD symptoms had greater than double the venous thromboembolism risk of women who had never been exposed to trauma (HR 2.42, 95% CI 1.83–3.20). However, unlike the association of PTSD with acute cardiovascular disease events, PTSD's association with venous thromboembolism was not explained by health behaviours or comorbidities. A nationwide study from Denmark also found the risk of incident venous thromboembolism to be higher in individuals with PTSD than those without PTSD after a median follow-up of 7 years (SIR 2.1, 95% CI 1.7–2.7), although smoking was not taken into account as a confounding variable.²²

More studies are needed from non-US and non-veteran populations. Epidemiological studies should improve estimates through rigorous adjustment for depression and lifestyle, and established cardiovascular disease risk factors. Furthermore, substantial progress in risk

assessment research has shown that in addition to relative risks, which are the most commonly reported effect sizes for PTSD's relationship with cardiovascular disease risk, absolute risk assessment and population-based risks are warranted.

Open questions

In 2015, Koenen and Galea²⁶ called on the field to address rigorously the question of causality in the link between PTSD and cardiovascular disease, and Koenen and colleagues²⁷ have offered a compelling roadmap for researchers. They and others have argued that many of the studies that support the association relied on lengthy follow-up periods and measured PTSD and cardiovascular disease risk factors only once at the outset, and that PTSD is strongly related to other psychiatric risk factors as well as poor health behaviours, all of which vary over time and influence cardiovascular disease risk. These issues, and the fact that few studies have estimated the effect of PTSD onset on health behaviours or cardiovascular disease risk markers, make it impossible to determine whether PTSD causes cardiovascular disease on the basis of existing evidence.

One approach to the open causality question has been to examine potential shared genetic risk factors for PTSD and cardiovascular disease. Several carefully designed studies, using data from the Vietnam Era Twin Registry, applied a co-twin design to control for unmeasured genetic and familial confounders that could be shared between PTSD and cardiovascular disease risk. There was little evidence that the association between PTSD and the increased risk for incident coronary heart disease, confirmed by quantitative measures of reduced myocardial perfusion, was confounded by genetic or other familial or shared environmental factors; the association was also not explained by adverse health behaviours and depression, thereby suggesting PTSD is a causal risk factor for coronary heart disease.²⁸ A similarly independent association of PTSD with low heart rate variability that was reversible after PTSD symptom resolution, supports the notion that alterations in autonomic nervous system function could be a causal underlying mechanism linking PTSD with cardiovascular disease risk in male veterans.²⁹ By contrast, the authors found that PTSD is not causally linked to subclinical atherosclerosis (ie, carotid intima-media thickness and a proinflammatory state, as measured by elevated C-reactive protein serum concentrations), but that familial or shared environmental factors better account for that relationship.³⁰

Several ongoing studies might shed light on the causal association of PTSD with cardiovascular disease risk. First, Koenen and colleagues (R01 MH101269) are using state-of-the-science approaches for inferring causality by determining whether new-onset PTSD in women without cardiovascular disease produces changes in cardiovascular disease risk biomarkers, and whether

such changes are reversible when PTSD remits. Second, Watkins and colleagues (R01 HL130322) will examine how changes in PTSD symptoms after military veterans receive cognitive processing therapy affect autonomic nervous system dysregulation, chronic systemic inflammation, and vascular endothelial dysfunction. Third, Scherrer and colleagues (R01 HL125424) will analyse the US Veterans Administration (VA) clinic data to determine whether PTSD treatment reduces cardiovascular disease risk. They will also assess the influence of PTSD treatment on health behaviours. Together, these studies might yield important insights into the causal nature and reversibility of the link between PTSD and cardiovascular disease, and provide treatment targets for early phase intervention research.

Mechanisms

Trauma

A simplified model of the link between PTSD and cardiovascular disease begins with the cardiovascular consequences that accompany the experience of a traumatic event. Exaggerated activity in many physiological mechanisms of this link can be observed in the acute post-trauma phase, because they are the natural psychological, behavioural, and physiological responses to stressful, threatening events (figure).³¹ In many studies, the magnitude of these responses is predictive of the development of PTSD.^{32,33} For most individuals, this exaggerated activity will return to near pre-trauma levels relatively quickly and, by 1 month after trauma, will have normalised. For those who develop PTSD, the cognitive, behavioural, and physiological dysregulation continues.³⁴

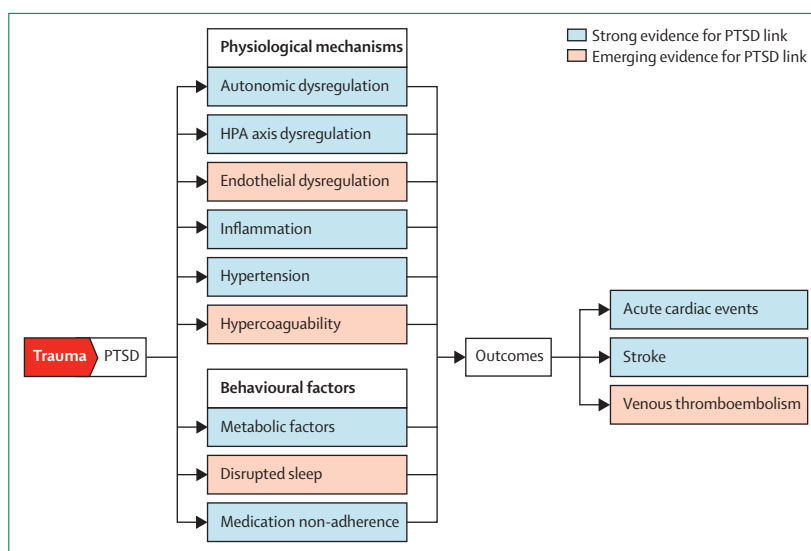


Figure: Mechanistic model of the PTSD-CVD association

The current state of evidence linking PTSD with risk for CVD events. Although most research on PTSD and mechanisms of CVD risk has been cross-sectional, the associations in this model present a logical causal chain that shows known temporal associations among physiological and behavioural mechanisms. The temporal order and causal relations in these variables should be tested in future research. PTSD=post-traumatic stress disorder. CVD=cardiovascular disease. HPA=hypothalamic-pituitary-adrenal.

At the cognitive level, alterations in perceptions of general safety or vulnerability of the self, and the sources and predictability of threat in the world, set the stage for increasing the network of associations that cause internal or external stimuli to activate the individual's fear network.^{35,36} This activation initiates the physiological cascade that defines the fight or flight response to threat.³⁴ Simultaneously, the baseline physiological readiness to respond to threat cues is heightened, with observable differences in resting indicators of autonomic and hypothalamic–pituitary–adrenal (HPA) activation.³⁷ When threat cues are perceived, physiological reactivity to these cues is exaggerated, mimicking the initial adaptive response to the traumatic event.^{38,39}

Physiological mechanisms

Autonomic balance—ie, the balance of sympathetic and parasympathetic activity—can be disrupted in PTSD, resulting in increased basal activity and intermittently exaggerated demand on the cardiovascular system. Sympathetic nervous system activity appears exaggerated in PTSD. Patients with PTSD show higher catecholamine concentrations and heart rate than do those without PTSD,¹³ particularly after exposure to reminders of their index traumatic event.^{40,41} Decades of research point to heightened activation of the sympathetic nervous system in PTSD,⁴² but most of the evidence comes from laboratory studies^{39,43,44} showing that trauma reminders cause sympathetic nervous system activation, and large increases in heart rate in particular—eg, data from a meta-analysis of laboratory studies suggest the median heart rate increase associated with trauma reminders is 10 beats per minute.⁴² Short-term increases in heart rate magnify shear stress on the endothelium that, through the rupturing of a vulnerable atherosclerotic plaque, might trigger cardiovascular disease events. High heart rate is a major risk factor for recurrent cardiac events and mortality in patients with cardiovascular disease.⁴⁵

The parasympathetic nervous system serves to reduce sympathetic reactions to stress and to promote calm behavioural states, and parasympathetic nervous system activation appears hampered in PTSD. Heart rate variability is the most commonly assessed indicator of parasympathetic nervous system activity, and PTSD has been associated with low mean heart rate variability (an index of parasympathetic nervous system withdrawal) with use of 24-hour Holter monitoring.⁴⁶ Furthermore, patients with PTSD have shown a substantial acute decrease in heart rate variability when exposed to trauma cues in the laboratory, suggesting parasympathetic nervous system withdrawal. More evidence for autonomic dysregulation in PTSD includes baroreflex dysfunction and increased QT-intervals on electrocardiogram (ECG).⁴⁷ These maladaptive alterations in threat responding might become chronic, and have direct links to cardiovascular disease risk. Low heart rate variability and reduced baroreflex sensitivity have been linked with carotid

atherosclerosis, inflammation, and hypercoagulability,^{48–50} and increased risk of incident and recurrent cardiovascular disease.^{51,52} Additionally, increased QT-variability is a predictor of sudden cardiac death.⁵³

Similarly, alterations in the activity of the HPA axis in patients with PTSD have been documented, including reduced basal cortisol concentrations and daily cortisol secretions,^{15,54} but exaggerated cortisol response to stress. HPA dysregulation has been implicated in the development of heart failure and cardiac ischaemia, and has been associated with cardiovascular disease mortality. HPA dysregulation influences blood pressure and coagulation, in part due to hormone secretions that directly affect the heart, blood vessels, and platelet activation.⁵⁵ Over time, HPA dysregulation can result in increased negative feedback sensitivity of glucocorticoid receptors in the stress–response system, decreased glucocorticoid responsiveness,⁵⁶ and decreased urinary and plasma cortisol concentrations.

Chronic increases in cardiovascular demand degrade the capacity of the cardiovascular system to support that increased demand. The accumulation of time spent in a state of physiological hyperarousal and intermittent periods of exaggerated physiological reactivity to threat cues is thought to contribute to cardiovascular disease risk through the development of a systemic proinflammatory state, and therefore more rapid progression of atherosclerosis, endothelial dysfunction, hypertension, and more pronounced coronary ischaemia under stress.

One of the earliest markers of degraded capacity to support increased cardiovascular demand is endothelial dysfunction. Endothelial cells form the inner lining of blood vessels and are responsible for vasodilation and vasoconstriction in response to stimuli that determine cardiovascular demand. Endothelial dysfunction is a key early contributor to cardiovascular disease risk through promotion of atherosclerosis, because insufficient vasodilation in conditions of high cardiovascular demand results in increased shear stress on the arterial wall, inflammatory response, and activation of prothrombotic processes. Two studies have assessed the association of PTSD with endothelial dysfunction,^{57,58} and have found a clinically significant reduction in flow-mediated dilation of the brachial artery in participants with PTSD.

Two important studies are investigating the role of endothelial dysfunction in the link between PTSD and cardiovascular disease. Vaccarino and colleagues (R01 HL125246) are doing a follow-up study of 281 male twin pairs (562 individuals) from the Vietnam Era Twin Registry 10 years after their baseline visit to determine whether PTSD is related to worsening of ischaemic heart disease with use of PET myocardial perfusion imaging, and to determine its association with vascular and immune responses to traumatic memory tasks (ie, peripheral vasoconstriction and biomarkers of endothelial injury and inflammation). Soufer and colleagues are doing a VA-funded study (101 CX000935) to determine whether

PTSD diagnosis is associated with endothelial dysfunction during standard hyperaemic probe and during emotional stress in military veterans, and whether change in PTSD symptom severity over 1 year is associated with change in the endothelial response to these challenges. They will also test the association of sympathetic, parasympathetic, and HPA axis activity with endothelial response.

PTSD symptom severity has been associated with a proinflammatory state.^{59–61} Increased inflammation is a key contributor to atherosclerosis, the process underlying atherothrombotic cardiovascular disease, and some of the inflammatory markers that are elevated in PTSD have been linked to cardiovascular disease events.⁶² In agreement with this association, Ahmadi and colleagues⁶³ found a dose–response relationship between PTSD and coronary artery calcium, and that the association of PTSD with mortality was strongest at high concentrations of coronary artery calcium.

Several cross-sectional studies exist on the associations of PTSD symptoms with a variety of inflammatory biomarkers.^{64–66} In a meta-analysis, significantly higher concentrations of interleukin 1 β , interleukin 6, and interferon γ were found in patients with PTSD than in controls, whereas interleukin 2, interleukin 4, interleukin 8, interleukin 10, soluble interleukin 2R, soluble interleukin 6R, C-reactive protein, and TNF α concentrations did not differ by PTSD status.¹⁴ Although this meta-analysis suggested no significant association between PTSD and C-reactive protein concentration in peripheral blood, Michopoulos and colleagues⁶⁷ reported that genetic variability in the *CRP* gene is associated with serum C-reactive protein concentration and PTSD symptom severity ($n=2698$), because one single nucleotide polymorphism within the *CRP* gene (rs1130864) was significantly associated with increased PTSD symptoms, particularly hyperarousal. This finding suggests that there could be a genotype effect in the association of PTSD and C-reactive protein.

A 2014 prospective study of PTSD and inflammation further complicates the picture. Concentrations of C-reactive protein and PTSD symptoms were assessed before and after deployment in 2600 US marines.⁶⁸ Each 10-point increment in pre-deployment concentrations of C-reactive protein predicted a 51% greater likelihood of having any PTSD symptoms 3 months after deployment. Related research suggests that dysregulations of the glucocorticoid signalling cascade, which influences inflammatory cytokines, might represent a vulnerability factor for the development of PTSD.⁶⁹

Regarding putative cellular and molecular mechanisms underlying inflammatory processes in PTSD, chronically elevated catecholamine concentrations and a redistribution of catecholamine receptors can increase cytokine production via stimulation of β -adrenergic receptors on immune cells and increase activity of the transcription factor NF- κ B; this activity is also modulated by cortisol function.⁷⁰ In agreement with this observation, higher

NF- κ B DNA binding activity of immune cells correlated positively with PTSD symptoms in women with early life abuse, but inversely with glucocorticoid sensitivity of pro-inflammatory cytokine production in an in-vitro system, compatible with enhanced inflammatory system activity.⁷¹

Given the autonomic, HPA axis, endothelial, and inflammatory correlates of PTSD, it is not surprising that PTSD has been associated with increased clinic and ambulatory blood pressure, because the increased cardiovascular demand and decreased arterial capacity that define these correlates are the primary determinants of blood pressure. Most of the research on PTSD and risk for incident hypertension has been done in US veterans,⁶³ with some studies finding resting systolic and diastolic blood pressure as much as 11 mm Hg and 9 mm Hg, respectively, higher among those with PTSD than those without.⁷² These studies were mostly cross-sectional, but Burg and colleagues⁷³ have found that PTSD was prospectively associated with at least a 20% increased risk for new-onset hypertension in 250 000 veterans in the VA health records data. Most importantly, they found that veterans with PTSD who received PTSD treatment were at no greater risk than those without PTSD for new-onset hypertension.

A hypercoagulable state (ie, too much coagulation activity or too little fibrinolytic activity, or both) along with hyperactive (ie, so-called sticky) platelets might facilitate acute atherothrombotic cardiovascular disease events in conjunction with endothelial dysfunction and inflammatory processes in PTSD.⁷⁴ In one study, patients with PTSD had significantly higher concentrations of soluble tissue factor than age-matched, gender-matched, and trauma-matched controls (median 163 pg/mL [IQR 142–256] vs 128 pg/mL [111–145]; $p=0.04$).⁷⁵ By contrast, there were no significant group differences in terms of fibrinogen, D-dimer, or activity levels of clotting factors VII, VIII, and XII; however, fibrinogen and clotting factor VIII activity were linked to PTSD symptom severity and degree of hyperarousal in patients with PTSD.⁷⁶ In civilians with war-related chronic PTSD, von Willebrand factor antigen concentrations were significantly higher than in controls without PTSD and, moreover, the most severe cases of PTSD had higher von Willebrand factor antigen and clotting factor VIII activity concentrations than those with less severe PTSD symptoms and controls.⁷⁷ Baseline platelet activity did not differ between combat veterans with and without PTSD,⁷⁸ but platelets from patients with PTSD showed exaggerated reactivity to in-vitro epinephrine and adenosine diphosphate stimulation mediated by the α_2 -adrenergic receptor.⁷⁹

Hypercoagulability might be particularly important in cardiovascular disease patients. In a study of patients being assessed for acute coronary syndromes in the emergency department, pre-existing PTSD symptoms were associated with activated partial thromboplastin time.⁸⁰ Procoagulant

reactivity has also been observed under stress in response to a trauma-specific interview in patients with PTSD related to an acute coronary syndrome.⁸¹

Behavioural factors

There are several plausible behavioural mechanisms linking PTSD with risk of cardiovascular disease events, many of which possibly interact with physiological mechanisms in a vicious cycle. PTSD has been associated with health risk behaviours, including smoking, physical inactivity, and obesity,^{82–84} as well as non-adherence to cardiovascular disease risk-reducing medications.^{85–87}

Metabolic syndrome is an important risk factor for cardiovascular disease. It is defined by central obesity, high blood pressure, low concentrations of HDL cholesterol, elevated concentrations of triglycerides, and hyperglycaemia. Investigators of a recent meta-analysis of nine studies ($n=16\,500$) found that the prevalence of metabolic syndrome was significantly greater in individuals with PTSD than in population-based controls (RR 1.82, 95% CI 1.72–1.92; $p<0.001$).¹² Likewise, type 2 diabetes mellitus is a powerful predictor of cardiovascular disease risk. In a recent meta-analysis of five studies ($n=150\,000$), PTSD was associated with a 50% increased risk for type 2 diabetes (RR 1.49, 95% CI 1.17–1.89).¹¹

Sleep difficulties are common in PTSD, and might be associated with cardiovascular disease risk. In a meta-analysis of 15 studies (24 cohorts; $n=475\,000$), short duration of sleep was associated with incident coronary heart disease (RR 1.48, 95% CI 1.22–1.80) and stroke (1.15, 1.00–1.31).⁸⁸ The role of short or disrupted sleep in the link between PTSD and cardiovascular disease is an active area of mechanistic research. Burg and colleagues (R01 HL125587) will test whether objectively measured poor sleep might explain differential ambulatory blood pressure progression over 2 years, and whether successful PTSD treatment could improve sleep and blood pressure progression.

An important behavioural pathway by which PTSD might influence cardiovascular disease risk is through non-adherence to medications. PTSD has been associated with medication non-adherence in patients with acute coronary syndromes,^{89,90} transplant,⁹¹ stroke or transient ischaemic attack,⁹² established cardiovascular disease,⁸³ and hypertension.⁹³ Researchers have hypothesised that cognitive deficits and avoidance of medications as reminders of risk for cardiovascular disease events might underlie this association.

For those with PTSD induced by acute cardiovascular disease events, the very medications intended to be protective might serve as aversive reminders of the traumatic index stroke event, thereby prompting non-adherence.^{94,95} Participants with stroke-induced PTSD were 2.7 times (95% CI 1.7–4.2) more likely to report non-adherence to medications than those without stroke-induced PTSD. Similarly, patients who screened

positive for acute coronary syndrome-induced PTSD had poor aspirin adherence at 1-year follow-up.⁸⁷

Link between PTSD secondary to cardiovascular disease events and prognosis

Although the lay community, or cardiologist or neurologist, might not judge cardiovascular disease events to be sufficiently traumatic to cause PTSD, the DSM-IV and available data from meta-analyses suggest that clinically relevant PTSD symptoms are common sequelae of cardiovascular disease events. Several studies have focused on PTSD due to cardiovascular disease events and its association with recurrent cardiovascular disease risk. PTSD rates and short-term cardiovascular disease risk are higher in this population than in the general population, but there are conceptual and diagnostic issues—first raised in research on PTSD secondary to cancer diagnosis and treatment—that complicate the study of PTSD secondary to an acute life-threatening illness. These issues and their implications have been elaborated since 2014 for both cancer⁹⁶ and cardiovascular disease.⁹⁴

Epidemiological evidence

In a meta-analysis of 24 studies ($n=2383$), Edmondson and colleagues¹⁰ found a 12% prevalence of PTSD secondary to acute coronary syndromes. Furthermore, across the three studies that estimated the association, PTSD was associated with a doubling of risk for acute coronary syndromes recurrence or mortality (95% CI 1.69–2.37) after adjustment for demographical, clinical, and psychosocial risk factors, including depression. Edmondson (R01 HL117832), Whang (R01 HL128310), and Kronish and colleagues (R01 HL123368) are currently doing a series of studies in a large cohort ($n=1700$) of patients with acute coronary syndromes to determine the prevalence and predictors of PTSD in patients with acute coronary syndromes, and to test mechanisms of the link between PTSD and acute coronary syndromes recurrence risk association. In particular, they will focus on objectively measured adherence to medications, and the interaction of non-adherence to β blockers and the experience of intrusive thoughts (measured by electronic momentary assessment) on ambulatory ECG markers of autonomic imbalance in the first month after an acute coronary syndrome event. They will also test the roles of physical activity and sleep.

Results from a meta-analysis of seven studies ($n=1014$) found that 23% (95% CI 15–34) of mild to moderate stroke or transient ischaemic attack survivors developed PTSD in the first year after stroke.^{85,97–102} Investigators from the first study, which assessed PTSD in a sample comprising exclusively patients with transient ischaemic attack, found that 29% of patients screened positive for PTSD at 3 months after transient ischaemic attack.¹⁰³ It is not clear whether stroke-induced PTSD is associated with

secondary cardiovascular disease risk, but Edmondson and Kronish (R01 HL132347) will test this association in a large cohort of patients with stroke or transient ischaemic attack (n=1000) followed up for 1 year, and will determine whether medication non-adherence explains any association.

Other acute cardiovascular events might also induce PTSD symptoms. Indeed, emerging qualitative research suggests that pulmonary embolism might provoke symptoms of PTSD.¹⁰⁴

Open questions

Research into PTSD secondary to cardiovascular disease events is less advanced than research into the link between PTSD and incident cardiovascular disease, but the two are strongly related. It is important to determine whether mechanisms for the possible associations are the same. The excess recurrence risk associated with PTSD after cardiovascular disease events appears to be conferred in the first year after the index cardiovascular disease event, which is a much shorter timeframe than many of the putative mechanisms of PTSD and incident cardiovascular disease require.

Offsetting the cardiovascular disease recurrence risk possibly associated with PTSD is important,¹⁰⁵ but offsetting risk for PTSD itself is preferable, and some interventions have shown promise.¹⁰⁶ Led by von Kanel, Meister and colleagues¹⁰⁷ are currently doing a study to test whether a single 45 min counselling session, targeting acute coronary syndrome-triggered traumatic reactions, delivered from the bedside in the coronary care unit within 48 h reduces post-traumatic symptoms at 3 months' and 12 months' follow-up. Hospital environment factors can also be targets for decreasing cardiovascular disease-induced PTSD risk, because objectively measured overcrowding in the emergency department and the perception of the hospital environment as hectic have been shown to increase risk for the development of PTSD.^{108,109}

Conclusion

In this Series paper, we offer an overview of the existing evidence for the association between PTSD and cardiovascular disease risk, the mechanisms that might carry that association, and the risk of PTSD due to cardiovascular disease events. We also highlight several innovative studies on target mechanisms currently being done with support from the National Institutes of Health (NIH) and the VA. Neither our review of the literature nor our survey of ongoing research were comprehensive, but together they provide a reasonable framework for understanding the state of the field and the most fruitful directions forward.

Existing epidemiological data suggest that PTSD is a risk factor for incident cardiovascular disease, and that the association is due to mechanisms that characterise

Panel: Key questions

- Is PTSD a cause of incident or recurrent cardiovascular disease?
- Can cardiovascular disease surveillance in PTSD improve outcomes?
- What are the most important behavioural or biological mechanisms to target for cardiovascular disease risk reduction in PTSD?
- Does PTSD treatment offset cardiovascular disease risk?
- Can individual or environmental interventions reduce PTSD risk in survivors of acute cardiovascular disease events?

PTSD=post-traumatic stress disorder.

the human stress response along with disrupted behavioural and lifestyle factors. Furthermore, acute cardiovascular disease events often cause PTSD, which in turn increases the risk for recurrent cardiovascular disease events. The immediate period after the cardiovascular disease event might be a particularly fertile area for intervention, because preventing PTSD development might be more efficient than treating PTSD for improving cardiovascular disease and psychiatric prognoses simultaneously. Many targets are emerging for both individual and environmental interventions that could offset PTSD risk after cardiovascular disease events.

PTSD is a relatively unusual psychiatric disorder, in that it has a clear onset after a traumatic event. Therefore, if PTSD is a causal risk factor for cardiovascular disease, interventions to offset PTSD risk or disrupt its behavioural and physiological sequelae should be prioritised. We do not know whether the association of PTSD with the risk of incident cardiovascular disease is causal, and no randomised controlled trial has been done to determine whether PTSD treatment can offset cardiovascular disease risk. Furthermore, although many candidate mechanisms for the association between PTSD and cardiovascular disease have been identified, it is uncertain which mechanisms are the most important targets for offsetting cardiovascular disease risk when PTSD is present. Innovative research on the dynamics of PTSD symptoms and cardiovascular dysfunction might yield these targets soon.

These unanswered questions are important to address (panel), because the field of behavioural medicine has previously experienced the consequences of identifying depression as a psychiatric risk factor for cardiovascular disease, observing potential mechanisms by which depression increases cardiovascular disease risk, and unfortunately, not yet being able to translate those findings into effective therapies to reduce cardiovascular disease risk. Therefore, the field must determine whether PTSD is a cause of cardiovascular disease, do systematic investigations into the interactions of behavioural and biological mechanisms of the link

Search strategy and selection criteria

We identified records by updating the searches of three previous systematic reviews on stress and post-traumatic stress disorder (PTSD) and coronary heart disease from 2011 to 2016, PTSD and acute coronary syndrome from 2012 to 2016, and PTSD and stroke from 2013 to 2016. In all cases, we searched the databases Ovid, MEDLINE, PsycINFO, PILOTS, and Scopus, and we used the updated searches from the end of the previous reviews' search to July 7, 2016. For each search, all relevant subject headings and free text terms were used to represent "PTSD" OR "stress", AND "coronary heart disease", OR "acute coronary syndrome" OR "stroke". The total number of references retrieved was 2204 and 1589 after duplicates had been removed. We identified currently funded research from two of the most active funders of the field, the National Institutes of Health and the US Veterans Administration, with use of NIH Reporter.

between PTSD and cardiovascular disease, and, most importantly, do early phase intervention trials powered to influence these mechanisms and ultimately offset cardiovascular disease risk.

Contributors

DE did the literature search and initial manuscript draft. Both authors wrote the manuscript and are responsible for the final product.

Declaration of interests

RvK has received honoraria from Vifor AG for services that are unrelated to the content of this article. DE declares no competing interests.

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