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Posttraumatic Stress Disorder and Cardiovascular Disease

Clinicians, researchers, and patients have long recognized the link between psychological stress and physical health. In their classic article on the physiological impact of stress, McEwen and Stellar (1993) used PTSD as an example to describe how psychological trauma and subsequent, repeated reminders of traumatic events trigger a cascade of neuronal, hormonal, and immunologic effects that damage the body over time. Though studies have found patients with psychological trauma and PTSD are at greater risk of a variety of chronic physical ailments, associations with cardiovascular disease (CVD) are particularly concerning. Despite advances in prevention and treatment, CVD remains the leading cause of death worldwide and accounts for over \$316 billion dollars annually in healthcare costs and lost productivity in the United States (Mozaffarian et al., 2016).

Though many CVD prevention efforts have focused on reducing exposure to traditional risk factors, such as smoking and diabetes, there is increasing recognition of the importance of psychological risk factors. Some of the earliest studies to focus specifically on the cardiovascular consequences of psychological trauma examined the impact of wartime stress. In 1989, Sibai, Armenian, and Alam published a case control study finding substantially increased acute and chronic war exposure in patients with versus without angiographically proven coronary artery disease seen at a hospital in Beirut. A subsequent study from Croatia found significantly increased rates of admission and in-hospital mortality for myocardial infarction during a two-week period of frequent air raid alerts (Bergovec et al., 1992). The landmark INTERHEART study expanded on the work of these and other regional studies by recruiting nearly 30,000 people from 52 countries to comprehensively examine a wide range of traditional and novel CVD risk factors. Psychosocial factors, including stressful major life events, accounted for approximately one third of the population attributable risk of heart attacks (Yusuf et al., 2004).

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Therefore, targeting PTSD and other psychological conditions could dramatically reduce the burden of CVD, improving the function, quality of life, and longevity of millions of people. In this overview, we summarize prior studies of CVD risk in patients with PTSD, discuss potential underlying mechanisms, and highlight the clinical pathways to reduce CVD risk in patients with PTSD.

Population Based Studies of PTSD and CVD

Numerous population-based studies have demonstrated that patients with PTSD are more likely to develop and die from CVD. These findings have been confirmed in diverse populations, including Veterans and active-duty military personnel, nurses, and 9/11 survivors. In 2007, Kubzansky, Koenen, Spiro, Vokonas, and Sparrow published one of the first prospective studies of PTSD and CVD. Using data from nearly 2,000 male Veterans from the VA Normative Aging Study, they found that each standard deviation increase in PTSD symptom severity was associated with an 18% increased risk of coronary heart disease (CHD), even after adjusting for known coronary risk factors. Similarly, Boscarino (2008) examined a random-sample of male Veterans who served in the Army during the Vietnam War. Patients with PTSD had double the risk of death from heart disease during a 15-year follow-up period, and each 5-point increase in PTSD symptom score corresponded with a 20% increase in risk of heart disease mortality.

Similar results have been found in women. In a study of over 1,000 women, each additional PTSD symptom increased the risk of developing incident CHD by 17% (Kubzansky, Koenen, Jones, & Eaton, 2009). Furthermore, the authors identified a threshold effect, as women with 5 or more symptoms had approximately 3 times the risk of developing CHD as compared to their counterparts without any symptoms, but women with 1-4 symptoms did not appear to be at elevated risk.

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Sumner and colleagues (2015) expanded upon these findings in an analysis of nearly 50,000 women who participated in the Nurses Health Study II. Women who had been exposed to trauma but did not have PTSD symptoms and women who were exposed to trauma and endorsed ≥ 4 PTSD symptoms were significantly more likely to have an increased risk of CVD. Importantly, adult health behaviors and medical risk factors accounted for an estimated 14% of the association in those with trauma but without PTSD symptoms, and 47% of the risk in those with trauma and ≥ 4 symptoms. In another large non-military cohort, Jordan, Miller-Archie, Cone, Morabia, and Stellman (2011) found that among 9/11 survivors recruited into the World Trade Center Health Registry both injury on 9/11 and PTSD symptoms were significantly associated with later heart disease, with associations appearing at relatively low PTSD checklist scores of 26-34.

In the majority of studies described above, PTSD and CVD were assessed at least a decade after trauma. However, an analysis of over 60,000 participants from the Millennium Cohort Study investigated the more immediate cardiovascular effects of trauma and PTSD over a mean of 5.6 years of follow-up (Crum-Cianflone et al., 2014). Patients with combat exposure were significantly more likely to have incident CHD by self-report and by diagnostic coding in medical records as compared to those deployed but without combat exposure. Adjustment for traditional CVD risk factors, PTSD, depression, and anxiety attenuated this association, but it remained significant. In contrast, PTSD was not associated with incident CHD in fully adjusted models. Crum-Cianflone et al. (2014) noted that the independent effects of chronic PTSD on CVD may take more time to manifest and that their cohort was relatively young (mean age of 34.4 years at baseline) with an expected low incidence of heart disease. Further follow-up of this important cohort will help clarify the cardiovascular effects of combat trauma and PTSD.

Despite these prospective studies that have linked trauma and PTSD to increased CVD in multiple populations, professional cardiovascular societies have not officially recognized PTSD as a cardiovascular risk factor. In their excellent recent review, Koenen and colleagues (2017) outline key steps for advancing the field and enhancing causal inference from observational studies, including designing studies with detailed, repeated measures of PTSD, CVD, and potential confounders. Another concern with prior studies is the quality of CVD outcome assessment. Due to the large samples and extended follow-up required, many studies have defined CVD by retrospective review of diagnostic codes in administrative records or by patient self-report. These methods may be subject to ascertainment bias from higher medical care utilization by patients with PTSD or to misclassification. Fortunately, several studies have expanded upon important population-based surveys by examining PTSD and CVD using objective cardiovascular testing.

Studies with Objective Cardiovascular Testing

Ahmadi and colleagues (2011) published one of the first objective studies, which included 637 Veterans without known coronary artery disease who underwent coronary artery computed tomography (CT) scanning for clinical purposes. These CT scans measure calcium deposits in atherosclerotic plaque, generating a coronary artery calcium (CAC) score that is predictive of future CVD risk. After matching for CVD risk level based on traditional factors, patients with PTSD were significantly more likely to have CAC deposits and to have a higher CAC score, indicating a greater burden of atherosclerotic heart disease.

A subsequent study by Vaccarino and colleagues (2013) used positron emission tomography scans to measure blood flow to the heart in 281 Vietnam-era Veteran twin pairs. In addition to having an increased risk of incident CHD over 13 years of follow-up, twins with PTSD had decreased myocardial perfusion after pharmacologically induced cardiovascular stress. The unique design of the study allowed the authors to conduct within group comparisons of PTSD discordant twin pairs, which control for shared genetic, sociodemographic, and early childhood environmental factors. Doing so only modestly reduced the association of PTSD and CVD outcomes. Goetz and colleagues (2014) used this same twin population to study PTSD and carotid artery intima-media thickness (CIMT), a validated measure of subclinical atherosclerosis. They found PTSD was associated with greater CIMT. However, in contrast to the study of myocardial perfusion and incident CHD, this association was not observed within twin pairs, suggesting it was largely mediated by shared genetic and childhood environmental factors. Finally, our group evaluated 663 VA patients using exercise treadmill testing (Turner, Neylan, Schiller, Li, & Cohen, 2013). This standard clinical procedure for detecting CVD involves walking on a treadmill at increasing speed and incline while a continuous electrocardiogram monitors the heart for signs of decreased blood flow, or ischemia. We found that patients with PTSD had over twice the risk of myocardial ischemia independent of traditional CVD risk factors and depression.

Taken together, these large, population-based cohorts and more in depth clinical studies provide strong evidence that patients with PTSD have a greater burden of atherosclerotic plaque and reduced myocardial blood flow that can lead to clinical CVD events. The next logical step to further evaluate causality and identify targets for intervention is to determine how PTSD increases CVD risk. Many of the studies presented above found the association of PTSD and CVD was independent of traditional risk factors, such as smoking, high blood pressure, and obesity. Therefore, it is important to evaluate the cardiovascular effects of the additional biological, behavioral, and psychosocial changes that accompany PTSD.

Mechanisms

Many potential mechanisms have been investigated, including inflammation (Brudey et al., 2015; Gill, Saligan, Woods, & Page, 2009; Spitzer et al., 2010), altered autonomic nervous system and neurochemical function (Brudey et al., 2015; Wentworth et al., 2013), genetics (Holman, 2012; Pollard et al., 2016), and health behaviors (Kronish, Lin, Cohen, Voils, & Edmondson, 2014; Wolf & Schnurr, 2016).

Numerous studies have found evidence of increased inflammatory biomarkers in patients with PTSD (for a review, see Gill et al., 2009). In one population-based study, Spitzer and colleagues (2010) found participants with PTSD had a nearly two-fold risk of increased C-reactive protein (CRP) levels compared to their counterparts without PTSD. This relationship remained even after adjusting for known factors that impact CRP levels such as age, sex, and body mass index (BMI). Other studies have confirmed elevations in basal levels of pro-inflammatory cytokines as well as higher cytokine production after antigen exposure (Gill et al., 2009).

Recently, Brudey and colleagues (2015) summarized the impacts of stress on autonomic function, the renin-angiotensin system (RAS), and the immune system, and detailed how these changes could interact to cause CVD. Traumatic stress activates the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic-adrenal-medullary system

causing increased production of catecholamines, rennin, angiotensin II, and aldosterone. These factors can directly damage the cardiovascular system through increases in blood pressure, impairment of vasodilation, formation of atherosclerotic plaques and heightened plaque instability. Though it has been hypothesized that these biological processes explain increased CVD risk in patients with PTSD, prior studies have not included simultaneous, repeated measures of PTSD, inflammation, RAS activity, sympathetic nervous system activity, and CVD. Therefore, their contribution as mediators, though likely, has not been fully established or quantified.

Other studies have explored a shared genetic vulnerability to PTSD and CVD. Pollard and colleagues (2016) used the candidate gene approach to identify genes associated with both PTSD and CVD. They found 36 genes that were common to both PTSD and CVD, with many of these genes known to impact immune function. In a sample of 527 respondents to a national survey of stress following the 9/11 attacks, an angiotensin converting enzyme genotype associated with HPA axis hyperactivity predicted both acute stress response and subsequent physician-diagnosed CVD (Holman, 2012). Further valuable information on possible shared risk will come from the Psychiatric Genomics Consortium, which is conducting the first large scale genome wide association study of PTSD.

Finally, PTSD has been linked to numerous behavioral changes that could increase CVD risk (i.e. decreased activity levels and medication adherence, increased smoking and substance use, and sleep disturbances; Kronish et al., 2014; Wolf & Schnurr, 2016). The literature review by Wolf and Schnurr (2016) summarizes important evidence regarding this interaction, including the development of a valuable conceptual model that details how health behaviors link to the biological mechanisms of increased CVD risk described above.

Implications and Future Directions

As research to identify the underlying mechanisms continues, we must evaluate ways to reduce CVD risk in patients with PTSD. Although traditional CVD risk factors do not fully explain the association of PTSD and CVD, it is still important to encourage patients to maintain a healthy diet and weight, quit smoking, and to test for and treat hypertension, dyslipidemia, and diabetes using appropriate evidence-based guidelines. As yet, there is no evidence to suggest direct CVD screening through coronary CTs, exercise testing, or nuclear screens in asymptomatic patients with PTSD will improve outcomes. Therefore, we should explore the impact of reducing PTSD symptoms on CVD risk as well as examine novel methods to improve cardiovascular health in patients with PTSD. Burg and colleagues (2017) examined electronic health records data from over 194,000 VA patients and found patients with PTSD who were receiving treatment with psychotherapy and/or medication had a lower risk of incident hypertension than those who were untreated. Though it is difficult to infer causality from these observational data, a currently recruiting randomized control trial of cognitive processing therapy in patients with PTSD will examine whether improvements in PTSD symptoms correlate with improvements in biomarkers of subclinical cardiovascular disease (Duke University, 2016). Adding cardiovascular outcomes to other ongoing trials of behavioral and pharmacologic therapies for PTSD will also be informative and help establish the cardiovascular benefits of PTSD treatment.

In addition, we can explore treatments that may have shared benefit for PTSD and cardiovascular health. For example, exercise is a cornerstone of preventive cardiology and exercise-based

cardiovascular rehabilitation programs substantially reduce mortality and recurrent CVD events after myocardial infarction. A recent meta-analysis of clinical trials found that patients who participated in physical activity interventions, including aerobic exercise and yoga, had small to moderate reductions in PTSD symptoms (Rosenbaum et al., 2015). Though there was insufficient data on cardiovascular outcomes, a VA Office of Research and Development (2016) supported trial will examine the effect of an exercise intervention on PTSD symptoms as well as surrogate markers of CVD risk. Trials of behavioral therapies targeted at general stress reduction have also demonstrated cardiovascular benefit. Gullicksson and colleagues (2011) randomized patients to cognitive behavioral therapy (CBT) for stress management versus standard care following a CVD event. Those in the CBT group had a 41% lower rate of recurrent CVD events over a mean 7.8 years of follow-up. Another trial of patients with CHD found those randomized to meditation versus an educational control had a significantly lower rate of heart attack, stroke, or all-cause mortality (Schneider et al., 2012). Finally, researchers have suggested trials of anti-inflammatory medications, omega-3 fatty acids, angiotensin converting enzyme inhibitors and angiotensin receptor blockers to provide dual benefits for PTSD and cardiovascular health.

Though much work remains to be done, our understanding of the cardiovascular consequences of PTSD has evolved rapidly. We have moved from an era of establishing an association of PTSD and CVD to elucidating the exact mechanisms and finding the best methods to prevent and control CVD. Continuing these efforts will be vitally important to preserving the health and quality of life of the many Veterans and non-Veterans living with chronic PTSD.

FEATURED ARTICLES

Ahmadi, N., Hajsadeghi, F., Mirshkarlo, H. B., Budoff, M., Yehuda, R., & Ebrahimi, R. (2011). **Post-traumatic stress disorder, coronary atherosclerosis, and mortality.** *American Journal of Cardiology*, 108, 29-33. doi:10.1016/j.amjcard.2011.02.340 PTSD is associated with increased risk of multiple medical problems including myocardial infarction. However, a direct link between PTSD and atherosclerotic coronary artery disease (CAD) has not been made. Coronary artery calcium (CAC) score is an excellent method to detect atherosclerosis. This study investigated the association of PTSD to atherosclerotic CAD and mortality. 637 veterans without known CAD (61 ± 9 years of age, 12.2% women) underwent CAC scanning for clinical indications and their psychological health status (PTSD vs non-PTSD) was evaluated. In subjects with PTSD, CAC was more prevalent than in the non-PTSD cohort (76.1% vs 59%, $p = 0.001$) and their CAC scores were significantly higher in each Framingham risk score category compared to the non-PTSD group. Multivariable generalized linear regression analysis identified PTSD as an independent predictor of presence and extent of atherosclerotic CAD ($p < 0.01$). During a mean follow-up of 42 months, the death rate was higher in the PTSD compared to the non-PTSD group (15, 17.1%, vs 57, 10.4%, $p = 0.003$). Multivariable survival regression analyses revealed a significant linkage between PTSD and mortality and between CAC and mortality. After adjustment for risk factors, relative risk (RR) of death was 1.48 (95% confidence interval [CI] 1.03 to 2.91, $p = 0.01$) in subjects with PTSD and CAC score > 0 compared to subjects without PTSD and CAC score equal to 0. With a CAC score equal to 0, risk of death was not different between subjects with and without PTSD (RR 1.04, 95% CI

0.67 to 6.82, $p = 0.4$). Risk of death in each CAC category was higher in subjects with PTSD compared to matched subjects without PTSD (RRs 1.23 for CAC scores 1 to 100, 1.51 for CAC scores 101 to 400, and 1.81 for CAC scores ≥ 400 , $p < 0.05$ for all comparisons). In conclusion, PTSD is associated with presence and severity of coronary atherosclerosis and predicts mortality independent of age, gender, and conventional risk factors.

Boscarino, J. A. (2008). **A prospective study of PTSD and early-age heart disease mortality among Vietnam veterans: Implications for surveillance and prevention.** *Psychosomatic Medicine*, 70, 668-676. doi:10.1097/PSY.0b013e31817bccaf *Objective:* To examine prospectively early-age heart disease (HD) among a national random sample of 4328 male Vietnam veterans, who did not have HD at baseline in 1985. Studies have suggested that posttraumatic stress disorder (PTSD) may result in cardiovascular disease. However, many past studies had important methodological limitations to their designs. *Method:* Using Cox regressions, we assessed PTSD, age, race, intelligence, family history, obesity, smoking, alcohol abuse, antisocial personality, and depression in predicting HD mortality at follow-up in December 31, 2000. The men were <65 years old at follow-up. *Results:* Using two PTSD measures, a Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition (DSM-III) measure (D-PTSD) and one developed by Keane (K-PTSD), we found that among Vietnam theater and era veterans combined (era veterans had no Vietnam service), having PTSD was associated with HD mortality for D-PTSD (hazard ratio (HR) = 2.25, $p = .045$) and approached significance for K-PTSD (HR = 2.16, $p = .066$). However, having higher PTSD symptoms on either scale was associated with mortality, with a 5-point increase associated with $\sim 20\%$ increase in mortality risk (all $p < .05$). Controlling for lifetime depression only slightly altered the results. The effects for theater veterans alone were stronger (D-PTSD: HR = 2.58, $p = .025$; K-PTSD: HR = 2.73, $p = .022$). Among theater veterans, controlling for lifetime depression or combat exposure made little difference. *Conclusion:* PTSD was prospectively associated with HD mortality among veterans free of HD at baseline. This study suggests that early-age HD may be an outcome after military service among PTSD-positive veterans.

Brudey, C., Park, J., Wiaderkiewicz, J., Kobayashi, I., Mellman, T. A., & Marvar, P. J. (2015). **Autonomic and inflammatory consequences of posttraumatic stress disorder and the link to cardiovascular disease.** *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*, 309, R315-R321. doi:10.1152/ajpregu.00343.2014 Stress- and anxiety-related disorders are on the rise in both military and general populations. Over the next decade, it is predicted that treatment of these conditions, in particular, posttraumatic stress disorder (PTSD), along with its associated long-term comorbidities, will challenge the health care system. Multiple organ systems are adversely affected by PTSD, and PTSD is linked to cancer, arthritis, digestive disease, and cardiovascular disease. Evidence for a strong link between PTSD and cardiovascular disease is compelling, and this review describes current clinical data linking PTSD to cardiovascular disease, via inflammation, autonomic dysfunction, and the renin-angiotensin system. Recent clinical and preclinical evidence regarding the role of the renin-angiotensin system in the extinction of fear memory and relevance in PTSD-related immune and autonomic dysfunction is also addressed.

Burg, M. M., Brandt, C., Buta, E., Schwartz, J., Bathulapalli, H., Dziura, J., . . . Haskell, S. (2017). **Risk for incident hypertension associated with posttraumatic stress disorder in military veterans and the effect of posttraumatic stress disorder treatment.** *Psychosomatic Medicine*, 79, 181-188. doi:10.1097/PSY.0000000000000376 *Objective:* Posttraumatic stress disorder (PTSD) increases cardiovascular disease and cardiovascular mortality risk. Neither the prospective relationship of PTSD to incident hypertension risk nor the effect of PTSD treatment on hypertension risk has been established. *Methods:* Data from a nationally representative sample of 194,319 veterans were drawn from the Veterans Administration (VA) roster of United States service men and women. This included veterans whose end of last deployment was from September 2001 to July 2010 and whose first VA medical visit was from October 1, 2001 to January 1, 2009. Incident hypertension was modeled as 3 events: (1) a new diagnosis of hypertension and/or (2) a new prescription for antihypertensive medication, and/or (3) a clinic blood pressure reading in the hypertensive range ($\geq 140/90$ mm Hg, systolic/diastolic). Posttraumatic stress disorder diagnosis was the main predictor. Posttraumatic stress disorder treatment was defined as (1) at least 8 individual psychotherapy sessions of 50 minutes or longer during any consecutive 6 months and/or (2) a prescription for selective serotonin reuptake inhibitor medication. *Results:* Over a median 2.4-year follow-up, the incident hypertension risk independently associated with PTSD ranged from hazard ratio (HR), 1.12 (95% confidence interval [CI], 1.08-1.17; $p < .0001$) to HR, 1.30 (95% CI, 1.26-1.34; $p < .0001$). The interaction of PTSD and treatment revealed that treatment reduced the PTSD-associated hypertension risk (e.g., from HR, 1.44 [95% CI, 1.38-1.50; $p < .0001$] for those untreated, to HR, 1.20 [95% CI, 1.15-1.25; $p < .0001$] for those treated). *Conclusions:* These results indicate that reducing the long-term health impact of PTSD and the associated costs may require very early surveillance and treatment.

Crum-Cianflone, N. F., Bagnell, M. E., Schaller, E., Boyko, E. J., Smith, B., Maynard, C., . . . Smith, T. C. (2014). **Impact of combat deployment and posttraumatic stress disorder on newly reported coronary heart disease among US active duty and reserve forces.** *Circulation*, 129, 1813-1820. doi:10.1161/CIRCULATIONAHA.113.005407 *Background:* The recent conflicts in Iraq and Afghanistan have exposed thousands of service members to intense stress, and as a result many have developed posttraumatic stress disorder (PTSD). The role of military deployment experiences and PTSD on coronary heart disease (CHD) is not well-defined, especially in young US service members with recent combat exposure. *Methods and Results:* We conducted a prospective, cohort study to investigate the relationships between war-time experiences and PTSD on CHD. Current and former US military personnel from all service branches participating in the Millennium Cohort Study during 2001-2008 ($n=60,025$) were evaluated for newly self-reported CHD. Electronic medical record review for ICD-9-CM codes for CHD was conducted among a subpopulation of active duty members ($n=23,794$). Logistic regression models examined the associations between combat experiences and PTSD with CHD while adjusting for established CHD risk factors. A total of 627 (1.0%) participants newly reported CHD over an average of 5.6 years of follow-up. Deployers with combat experiences had an increased odds of newly reporting CHD (odds ratio [OR] = 1.63; 95% confidence interval [CI], 1.11-2.40) and having a diagnosis code for new-onset CHD (OR = 1.93; 95% CI,

1.31-2.84) compared with noncombat deployers. Screening positive for PTSD symptoms was associated with self-reported CHD prior to, but not after, adjusting for depression and anxiety, and was not associated with a new diagnosis code for CHD. *Conclusions:* Combat deployments are associated with new-onset CHD among young US service members and veterans. Experiences of intense stress may increase the risk for CHD over a relatively short period among young adults.

Goetz, M., Shah, A., Goldberg, J., Cheema, F., Shallenberger, L., Murrain, N. V., . . . Vaccarino, V. (2014). **Posttraumatic stress disorder, combat exposure, and carotid intima-media thickness in male twins.** *American Journal of Epidemiology, 180*, 989-996. doi:10.1093/aje/kwu225 Posttraumatic stress disorder (PTSD) is associated with an increased risk of ischemic heart disease, though the pathophysiological mechanisms remain unclear. Carotid artery intima-media thickness (CIMT) is a measure of subclinical atherosclerosis. We examined whether PTSD and combat exposure were associated with CIMT in Vietnam War-era twins after controlling for shared genetic and childhood factors. Between 2002 and 2010, we studied 465 middle-aged twins from the Vietnam Era Twin Registry who were free from cardiovascular disease. PTSD was diagnosed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, and CIMT was measured by ultrasound. Mixed-effects regression models were used to examine individual, between-pair, and within-pair associations. Approximately 13% of participants met the criteria for PTSD, and 45% served in the Vietnam Theater. PTSD was associated with 32.7 μm higher CIMT (95% confidence interval (CI): 0.9, 64.5) after adjustment for confounders. The average CIMT for the pair increased by 59.7 μm for each additional twin with PTSD (95% CI: 15.9, 104.2). We found no significant within-pair differences in CIMT when comparing PTSD-discordant co-twins. Results for combat exposure were similar, but its association with CIMT weakened after adjustment for PTSD (95% CI: 7.0, 45.3). Among Vietnam War-era veterans, combat exposure and PTSD are associated with CIMT, though the associations are largely mediated by shared childhood factors.

Jordan, H. T., Miller-Archie, S. A., Cone, J. E., Morabia, A., & Stellman, S. D. (2011). **Heart disease among adults exposed to the September 11, 2001 World Trade Center disaster: Results from the World Trade Center Health Registry.** *Preventive Medicine, 53*, 370-376. doi:10.1016/j.ypmed.2011.10.014 *Objective:* To examine associations between 9/11-related exposures, posttraumatic stress disorder (PTSD), and subsequent development of heart disease (HD). *Methods:* We prospectively followed 39,324 WTC Health Registry participants aged ≥ 18 on 9/11 for an average of 2.9 years. HD was defined as self-reported physician-diagnosed angina, heart attack, and/or other HD reported between study enrollment (2003-2004) and a follow-up survey (2006-2008) in enrollees without previous HD. A PTSD Checklist (PCL) score ≥ 44 was considered PTSD. We calculated adjusted hazard ratios (AHR) and 95% confidence intervals (CI) to examine relationships between 9/11-related exposures and HD. *Results:* We identified 1162 HD cases (381 women, 781 men). In women, intense dust cloud exposure was significantly associated with HD (AHR 1.28, 95% CI 1.02-1.61). Injury on 9/11 was significantly associated with HD in women (AHR 1.46, 95% CI 1.19-1.79) and in men (AHR 1.33, 95% CI 1.15-1.53). Participants with PTSD at enrollment had an elevated HD risk (AHR 1.68, 95% CI 1.33-2.12 in women, AHR 1.62, 95% CI 1.34-1.96 in men). A dose-response

relationship was observed between PCL score and HD risk. *Conclusion:* This exploratory study suggests that exposure to the WTC dust cloud, injury on 9/11 and 9/11-related PTSD may be risk factors for HD.

Kubzansky, L. D., Koenen, K. C., Jones, C., & Eaton, W. W. (2009). **A prospective study of posttraumatic stress disorder symptoms and coronary heart disease in women.** *Health Psychology, 28*, 125-130. doi:10.1037/0278-6133.28.1.125 *Objective:* Posttraumatic stress disorder (PTSD) reflects a prolonged stress reaction and dysregulation of the stress response system and is hypothesized to increase risk of developing coronary heart disease (CHD). No study has tested this hypothesis in women even though PTSD is more prevalent among women than men. This study aims to examine whether higher levels of PTSD symptoms are associated with increased risk of incident CHD among women. *Design:* A prospective study using data from women participating in the Baltimore cohort of the Epidemiologic Catchment Area study ($n = 1059$). Past year trauma and associated PTSD symptoms were assessed using the NIMH Diagnostic Interview Schedule. *Main Outcome Measures:* Incident CHD occurring during the 14-year follow-up through 1996. *Results:* Women with five or more symptoms were at over three times the risk of incident CHD compared with those with no symptoms (age-adjusted OR = 3.21, 95% CI: 1.29-7.98). Findings were maintained after controlling for standard coronary risk factors as well as depression or trait anxiety. *Conclusion:* PTSD symptoms may have damaging effects on physical health for civilian community-dwelling women, with high levels of PTSD symptoms associated with increased risk of CHD-related morbidity and mortality.

Kubzansky, L. D., Koenen, K. C., Spiro, A., Vokonas, P. S., & Sparrow, D. (2007). **Prospective study of posttraumatic stress disorder symptoms and coronary heart disease in the Normative Aging Study.** *Archives of General Psychiatry, 64*, 109-116. doi:10.1001/archpsyc.64.1.109 *Context:* Various correlates of posttraumatic stress disorder (PTSD), such as high levels of sympathetic activation and hypothalamic-pituitary-adrenal axis dysregulation, have been linked to arterial damage and coronary heart disease (CHD) risk. While psychological disturbance is frequently found among patients with cardiac disease, whether psychological problems precede or occur as a result of having a potentially fatal disease is not clear. To our knowledge, no prospective studies to date have evaluated whether PTSD is associated with increased risk of CHD. *Objective:* To test the hypothesis that high levels of PTSD symptoms may increase CHD risk, using 2 different measures of PTSD. *Design:* Prospective cohort study. *Setting:* Community-dwelling men from the Greater Boston, Mass, area who served in the military. *Participants:* Data are from the Veterans Affairs Normative Aging Study. Men who completed either the Mississippi Scale for Combat-Related PTSD in 1990 ($n = 1002$) or the Keane PTSD scale in 1986 ($n = 944$) were included in the study. *Main Outcome Measure:* Incident CHD occurring during follow-up through May 2001. *Results:* Levels of PTSD symptoms in this cohort were low to moderate. Men with preexisting CHD at baseline were excluded, and PTSD was measured with the Mississippi Scale for Combat-Related PTSD. For each SD increase in symptom level, men had age-adjusted relative risks of 1.26 (95% confidence interval, 1.05-1.51) for nonfatal myocardial infarction and fatal CHD combined and 1.21 (95% confidence interval, 1.05-1.41) for all of the CHD outcomes combined (nonfatal myocardial infarction, fatal CHD, and angina).

Findings were replicated using the Keane PTSD scale and somewhat strengthened after controlling for levels of depressive symptoms. **Conclusions:** To our knowledge, this is the first study to demonstrate a prospective association between PTSD symptoms and CHD even after controlling for depressive symptoms. These results suggest that a higher level of PTSD symptoms may increase the risk of incident CHD in older men.

Pollard, H. B., Shivakumar, C., Starr, J., Eidelman, O., Jacobowitz, D. M., Dalgard, C. L., . . . Ursano, R. J. (2016). **“Soldier’s heart”: A genetic basis for elevated cardiovascular disease risk associated with post-traumatic stress disorder.** *Frontiers in Molecular Neuroscience*, 9, 87. doi:10.3389/fnmol.2016.00087 “Soldier’s Heart,” is an American Civil War term linking post-traumatic stress disorder (PTSD) with increased propensity for cardiovascular disease (CVD). We have hypothesized that there might be a quantifiable genetic basis for this linkage. To test this hypothesis we identified a comprehensive set of candidate risk genes for PTSD, and tested whether any were also independent risk genes for CVD. A functional analysis algorithm was used to identify associated signaling networks. We identified 106 PTSD studies that report one or more polymorphic variants in 87 candidate genes in 83,463 subjects and controls. The top upstream drivers for these PTSD risk genes are predicted to be the glucocorticoid receptor (NR3C1) and Tumor Necrosis Factor alpha (TNFA). We find that 37 of the PTSD candidate risk genes are also candidate independent risk genes for CVD. The association between PTSD and CVD is significant by Fisher’s Exact Test ($P = 3 \times 10^{-54}$). We also find 15 PTSD risk genes that are independently associated with Type 2 Diabetes Mellitus (T2DM; also significant by Fisher’s Exact Test ($P = 1.8 \times 10^{-16}$)). Our findings offer quantitative evidence for a genetic link between post-traumatic stress and cardiovascular disease. Computationally, the common mechanism for this linkage between PTSD and CVD is innate immunity and NF κ B-mediated inflammation.

Rosenbaum, S., Vancampfort, D., Steel, Z., Newby, J., Ward, P. B., & Stubbs, B. (2015). **Physical activity in the treatment of post-traumatic stress disorder: A systematic review and meta-analysis.** *Psychiatry Research*, 230, 130-136. doi:10.1016/j.psychres.2015.10.017 People with PTSD experience high levels of cardiovascular disease and comorbid mental health problems. Physical activity (PA) is an effective intervention in the general population. We conducted the first systematic review and meta-analysis to determine the effect of PA on PTSD. We searched major electronic databases from inception till 03/2015 for RCTs of PA interventions among people with PTSD. A random effects meta-analysis calculating hedges g was conducted. From a potential of 812 hits, four unique RCTs met the inclusion criteria ($n=200$, mean age of participants 34–52 years). The methodological quality of included trials was satisfactory, and no major adverse events were reported. PA was significantly more effective compared to control conditions at decreasing PTSD and depressive symptoms among people with PTSD. There was insufficient data to investigate the effect on anthropometric or cardiometabolic outcomes. Results suggest that PA may be a useful adjunct to usual care to improve the health of people with PTSD. Although there is a relative paucity of data, there is reason to be optimistic for including PA as an intervention for people with PTSD, particularly given the overwhelming evidence of the benefits of PA in the general population. Robust effectiveness and implementation studies are required.

Spitzer, C., Barnow, S., Völzke, H., Wallaschofski, H., John, U., Freyberger, H. J., . . . Grabe, H. J. (2010). **Association of posttraumatic stress disorder with low-grade elevation of C-reactive protein: Evidence from the general population.** *Journal of Psychiatric Research*, 44, 15-21. doi:10.1016/j.jpsychires.2009.06.002

Background: PTSD has been associated with several somatic diseases, and low-grade inflammation may be one psychobiological mechanism mediating this relationship. We assessed the association between PTSD and elevated serum levels of C-reactive protein (CRP; > 3 mg/L) in a large general population sample [Study of Health in Pomerania (SHIP)]. **Methods:** About 3,049 adults living in the community were included in the present study. CRP, lipoproteins, and triglycerides were determined. Participants were also examined with regard to blood pressure, body mass index (BMI), physical activity, comorbid somatic diseases, medication, daily alcohol intake, and depression. **Results:** PTSD was diagnosed in 55 participants (1.8%), and low-grade inflammation (i.e. CRP > 3 mg/L) was found in 701 subjects (23.0%). PTSD positive participants had significantly higher odds for elevated CRP values than those without PTSD (OR = 2.27; 95% CI: 1.32-3.93). Even after adjusting for sex, age, other sociodemographic factors, BMI, blood pressure, lipoproteins and triglycerides, physical activity, comorbid somatic diseases, daily alcohol intake, and trauma exposure, there were almost twofold higher odds for elevated CRP levels in participants with PTSD compared to those without PTSD (OR = 1.87; 95% CI: 1.05-3.35). **Conclusions:** Our findings suggest a close relationship between PTSD and low-grade inflammation possibly representing one psychobiological pathway from PTSD to poor physical health, particularly with respect to cardiovascular and pulmonary disease as well as diabetes.

Sumner, J. A., Kubzansky, L. D., Elkind, M. S. V., Roberts, A. L., Agnew-Blais, J., Chen, Q., . . . Koenen, K. C. (2015). **Trauma exposure and posttraumatic stress disorder symptoms predict onset of cardiovascular events in women.** *Circulation*, 132, 251-259. doi:10.1161/CIRCULATIONAHA.114.014492

Background: Psychological stress is a proposed risk factor for cardiovascular disease (CVD), and posttraumatic stress disorder (PTSD), the sentinel stress-related mental disorder, occurs twice as frequently in women as men. However, whether PTSD contributes to CVD risk in women is not established. **Methods and Results:** We examined trauma exposure and PTSD symptoms in relation to incident CVD over a 20-year period in 49978 women in the Nurses’ Health Study II. Proportional hazards models estimated hazard ratios and 95% confidence intervals for CVD events confirmed by additional information or medical record review ($n=548$, including myocardial infarction [$n=277$] and stroke [$n=271$]). Trauma exposure and PTSD symptoms were assessed by using the Brief Trauma Questionnaire and a PTSD screen. In comparison with no trauma exposure, endorsing ≥ 4 PTSD symptoms was associated with increased CVD risk after adjusting for age, family history, and childhood factors (hazard ratio, 1.60; 95% confidence interval, 1.20–2.13). Being trauma-exposed and endorsing no PTSD symptoms was associated with elevated CVD risk (hazard ratio, 1.45; 95% confidence interval, 1.15–1.83), although being trauma-exposed and endorsing 1 to 3 PTSD symptoms was not. After adjusting for adult health behaviors and medical risk factors, this pattern of findings was maintained. Health behaviors and medical risk factors accounted for 14% of the trauma/no symptoms–CVD association and 47% of the trauma/4+ symptoms–CVD association.

Conclusion: Trauma exposure and elevated PTSD symptoms may increase the risk of CVD in this population of women. These findings suggest that screening for CVD risk and reducing health risk behaviors in trauma-exposed women may be promising avenues for prevention and intervention.

Turner, J. H., Neylan, T. C., Schiller, N. B., Li, Y., & Cohen, B. E. (2013). **Objective evidence of myocardial ischemia in patients with posttraumatic stress disorder.** *Biological Psychiatry*, 74, 861-866. doi:10.1016/j.biopsych.2013.07.012 **Background:** Patients with posttraumatic stress disorder (PTSD) are at increased risk for cardiovascular disease (CVD), but few studies have included objective measures of CVD and how PTSD causes CVD remains unknown. We sought to determine the association between PTSD and objectively assessed CVD and examine potential underlying mechanisms. **Methods:** Outpatients from two Veterans Affairs Medical Centers were enrolled from 2008 to 2010. Posttraumatic stress disorder was identified using the Clinician Administered PTSD Scale, and standardized exercise treadmill tests were performed to detect myocardial ischemia. **Results:** Of the 663 participants with complete data, ischemia was present in 17% of patients with PTSD versus 10% of patients without PTSD ($p = .006$). The association between PTSD and ischemia remained significant after adjusting for potential confounders (age, sex, prior CVD) and mediators (traditional cardiac risk factors, C-reactive protein, obesity, alcohol use, sleep quality, social support, and depression), adjusted odds ratio (OR) 2.42, 95% confidence interval (CI) 1.39 to 4.22, $p = .002$. Findings remained significant when those with prior CVD were excluded (fully adjusted OR 2.24, 95% CI 1.20–4.18, $p = .01$) and when continuous PTSD symptom score was used as the predictor (fully adjusted OR per 10-point change in Clinician Administered PTSD Scale score 1.12, 95% CI 1.03–1.22, $p = .01$). **Conclusions:** Posttraumatic stress disorder was associated with ischemic changes on exercise treadmill tests independent of traditional cardiac risk factors, C-reactive protein, and several health behaviors and psychosocial risk factors, suggesting additional mechanisms linking PTSD and ischemia should be explored. The association of PTSD and ischemia among patients without known CVD highlights an opportunity for early interventions to prevent progression of cardiovascular disease.

Vaccarino, V., Goldberg, J., Rooks, C., Shah, A. J., Veledar, E., Faber, T. L., . . . Bremner, J. D. (2013). **Post-traumatic stress disorder and incidence of coronary heart disease: A twin study.** *Journal of the American College of Cardiology*, 62, 970-978. doi:10.1016/j.jacc.2013.04.085 **Objectives:** The aim of this study was to determine whether post-traumatic stress disorder (PTSD) is associated with coronary heart disease (CHD) using a prospective twin study design and objective measures of CHD. **Background:** It has long been hypothesized that PTSD increases the risk of CHD, but empirical evidence using objective measures is limited. **Methods:** We conducted a prospective study of middle-aged male twins from the Vietnam Era Twin Registry. Among twin pairs without self-reported CHD at baseline, we selected pairs discordant for a lifetime history of PTSD, pairs discordant for a lifetime history of major depression, and pairs without either condition. All underwent a clinic visit after a median follow-up of 13 years. Outcomes included clinical events (myocardial infarction, other hospitalizations for CHD and coronary revascularization) and quantitative measures of myocardial perfusion by [¹³N] ammonia positron emission tomography, including a stress total severity score

and coronary flow reserve. **Results:** A total of 562 twins (281 pairs) with a mean age of 42.6 years at baseline were included in this study. The incidence of CHD was more than double in twins with PTSD (22.6%) than in those without PTSD (8.9%; $p < 0.001$). The association remained robust after adjusting for lifestyle factors, other risk factors for CHD, and major depression (odds ratio: 2.2; 95% confidence interval: 1.2 to 4.1). Stress total severity score was significantly higher (+95%, $p = 0.001$) and coronary flow reserve was lower (-0.21 , $p = 0.02$) in twins with PTSD than in those without PTSD, denoting worse myocardial perfusion. Associations were only mildly attenuated in 117 twin pairs discordant for PTSD. **Conclusions:** Among Vietnam-era veterans, PTSD is a risk factor for CHD.

Wolf, E. J., & Schnurr, P. P. (2016). **Posttraumatic stress disorder-related cardiovascular disease and accelerated cellular aging.** *Psychiatric Annals*, 46, 527-532. doi:10.3928/00485713-20160729-01 We reviewed the literature from 2010 to 2016 on the relationship between posttraumatic stress disorder (PTSD) and cardiometabolic health conditions, including metabolic syndrome, coronary artery disease, stroke, and myocardial infarction, among others. Collectively, PTSD was associated with increased risk of cardiometabolic health problems, with preclinical and clinical studies offering evidence of behavioral (eg, poor sleep, cigarette use, poor diet, and insufficient exercise) and biological (eg, autonomic reactivity, inflammation) mediators of these associations. We discuss the possibility that these behavioral and biological mechanisms lead to accelerated cellular aging, as regulated in the epigenome, which contributes to premature cardiometabolic health decline. This has implications for the assessment, prevention, and treatment of cardiometabolic conditions among those with PTSD. It also highlights the need to better understand the mechanisms linking PTSD to accelerated aging and to develop interventions to attenuate or reverse this phenomenon.

Yusuf, S., Hawken, S., Ôunpuu, S., Dans, T., Avezum, A., Lanas, F., . . . Lisheng, L. (2004). **Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study.** *Lancet*, 364, 937-952. doi:10.1016/S0140-6736(04)17018-9 **Background:** Although more than 80% of the global burden of cardiovascular disease occurs in low-income and middle-income countries, knowledge of the importance of risk factors is largely derived from developed countries. Therefore, the effect of such factors on risk of coronary heart disease in most regions of the world is unknown. **Methods:** We established a standardised case-control study of acute myocardial infarction in 52 countries, representing every inhabited continent. 15152 cases and 14820 controls were enrolled. The relation of smoking, history of hypertension or diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins (Apo), and psychosocial factors to myocardial infarction are reported here. Odds ratios and their 99% CIs for the association of risk factors to myocardial infarction and their population attributable risks (PAR) were calculated. **Findings:** Smoking (odds ratio 2.87 for current vs never, PAR 35.7% for current and former vs never), raised ApoB/ApoA1 ratio (3.25 for top vs lowest quintile, PAR 49.2% for top four quintiles vs lowest quintile), history of hypertension (1.91, PAR 17.9%), diabetes (2.37, PAR 9.9%), abdominal obesity (1.12 for top vs lowest tertile and 1.62 for middle vs lowest tertile, PAR 20.1% for top two tertiles vs lowest tertile), psychosocial factors (2.67, PAR 32.5%), daily consumption of fruits and vegetables (0.70, PAR 13.7% for lack

FEATURED ARTICLES *continued*

of daily consumption), regular alcohol consumption (0.91, PAR 6.7%), and regular physical activity (0.86, PAR 12.2%), were all significantly related to acute myocardial infarction ($p < 0.0001$ for all risk factors and $p = 0.03$ for alcohol). These associations were noted in men and women, old and young, and in all regions of the world. Collectively, these nine risk factors accounted for 90% of the PAR in men and 94% in women. *Interpretation:* Abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and regular physical activity account for most of the risk of myocardial infarction worldwide in both sexes and at all ages in all regions. This finding suggests that approaches to prevention can be based on similar principles worldwide and have the potential to prevent most premature cases of myocardial infarction.

ADDITIONAL CITATIONS

Bergovec, M., Mihatov, S., Prpić, H., Rogan, S., Batarelo, V., & Sjerobabski, V. (1992). **Acute myocardial infarction among civilians in Zagreb city area.** *Lancet*, 339, 303. doi:10.1016/0140-6736(92)91370-N This early study found a significant increase in myocardial infarction among civilians in the Zagreb city area in Croatia during September of 1991 (when the first air raid sirens were sounded during the war), as compared to years previously without that additional stressor. It is one of the first studies suggesting psychological stress could have cardiovascular impacts.

Duke University. (2016). **The effect of reducing posttraumatic stress disorder symptoms on cardiovascular risk (ACCEPT)** (Clinicaltrials.gov Identifier NCT02736929). Retrieved from <https://clinicaltrials.gov/ct2/show/NCT02736929> This ongoing clinical trial is designed to explore how reducing symptoms of PTSD affects cardiovascular disease risk. Investigators at Duke University randomly assign participants to either a Cognitive Processing Therapy or control group, and then assess the impact of changes in PTSD symptoms on cardiovascular measures such as heart rate variability and blood pressure.

Gill, J. M., Saligan, L., Woods, S., & Page, G. (2009). **PTSD is associated with an excess of inflammatory immune activities.** *Perspectives in Psychiatric Care*, 45, 262-277. doi:10.1111/j.1744-6163.2009.00229.x This review details current literature linking PTSD to increased inflammation, which may be an important mechanism of increased CVD risk.

Gulliksson, M., Burell, G., Vessby, B., Lundin, L., Toss, H., & Svärdsudd, K. (2011). **Randomized controlled trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary Health Care project (SUPRIM).** *Archives of Internal Medicine*, 171, 134-140. doi:10.1001/archinternmed.2010.510 This study is a randomized controlled trial of CBT after a CHD event. Patients who received CBT had significant reductions in CVD-related events (41% lower rate of recurrent CVD events and 45% lower rate of recurrent MI), suggesting CBT may be helpful in reducing risk of recurrent CVD events.

Holman, E. A. (2012). **Acute stress and cardiovascular health: Is there an ACE gene connection?** *Journal of Traumatic Stress*, 25, 592-597. doi:10.1002/jts.21746 This study investigated the

ADDITIONAL CITATIONS *continued*

relationship between renin-angiotensin-aldosterone system activity and both CVD and acute stress in a nationally representative sample of European-Americans following the 9/11 attacks. The authors found that a single nucleotide polymorphism of the ACE gene was associated with increased CVD risk and acute stress.

Koenen, K. C., Sumner, J. A., Gilsanz, P., Glymour, M. M., Ratanatharathorn, A., Rimm, E. B., . . . Kubzansky, L. D. (2017). **Post-traumatic stress disorder and cardiometabolic disease: Improving causal inference to inform practice.** *Psychological Medicine*, 47, 209-225. doi:10.1017/S0033291716002294 This review summarizes the literature linking PTSD to CVD and type 2 diabetes and describes important pathways to better evaluate the causality of this association. It focuses on improvements in the design and analysis of observational work as well as examination of the impact of PTSD phenotypes and testing the cardiometabolic effects of PTSD treatment.

Kronish, I. M., Lin, J. J., Cohen, B. E., Voils, C. I., & Edmondson, D. (2014). **Posttraumatic stress disorder and medication nonadherence in patients with uncontrolled hypertension.** *JAMA Internal Medicine*, 174, 468-470. doi:10.1001/jamainternmed.2013.12881 This study found that patients with PTSD had significantly increased odds of medication nonadherence compared to those without PTSD in a sample of patients with uncontrolled hypertension. These findings suggest medication nonadherence may be a mechanism by which PTSD is associated with CVD risk.

McEwen, B. S., & Stellar, E. (1993). **Stress and the individual: Mechanisms leading to disease.** *Archives of Internal Medicine*, 153, 2093-2101. doi:10.1001/archinte.1993.00410180039004 This literature review is one of the first articles to systematically describe how chronic psychological stress can impact a number of different biological systems that in turn damage physical health over time.

Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., . . . Turner, M. B. (2016). **Heart disease and stroke statistics—2016 update: A report from the American Heart Association.** *Circulation*, 133, e38-e360. doi:10.1161/CIR.0000000000000350 This yearly report provides updated statistics on cardiovascular disease in the United States.

Schneider, R. H., Grim, C. E., Rainforth, M. V., Kotchen, T., Nidich, S. I., Gaylord-King, C., . . . Alexander, C. N. (2012). **Stress reduction in the secondary prevention of cardiovascular disease: Randomized, controlled trial of transcendental meditation and health education in Blacks.** *Circulation: Cardiovascular Quality and Outcomes*, 5, 750-758. doi:10.1161/CIRCOUTCOMES.112.967406 This randomized controlled trial of black men and women with CHD investigated the impact of a Transcendental Meditation program on CVD. Those in the treatment group had a significantly reduced risk of mortality, MI and stroke during follow-up.

Sibai, A. M., Armenian, H. K., & Alam, S. (1989). **War-time determinants of arteriographically confirmed coronary artery disease in Beirut.** *American Journal of Epidemiology*, 130, 623-631. This case-control study found that patients with coronary artery disease on angiography were significantly more likely to report acute wartime exposure, as well as crossing the “green-lines” that separate two opposing sides.

ADDITIONAL CITATIONS *continued*

VA Office of Research and Development. (2016). **Improving mind/body health and functioning with integrative exercise** (Clinicaltrials.gov Identifier NCT02856412). Retrieved from <https://clinicaltrials.gov/ct2/show/NCT02856412> This new clinical trial in San Francisco is designed to investigate the efficacy of an exercise rehabilitation therapy for Veterans with PTSD (compared to a health education class) and includes measures of cardiovascular fitness.

Wentworth, B. A., Stein, M. B., Redwine, L. S., Xue, Y., Taub, P. R., Clopton, P., . . . Maisel, A. S. (2013). **Post-traumatic stress disorder: A fast track to premature cardiovascular disease?** *Cardiology in Review*, 21, 1-7. doi:10.1097/CRD.0b013e318265343b

This review details potential pathways by which PTSD could increase risk for CVD. These pathways include behavioral changes, chemical pathways such as dysregulation of the HPA axis and autonomic dysfunction, and biological impacts such as increased inflammation and cardiac hyperactivity.