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Is posttraumatic stress disorder related to development of heart disease? An update*

ABSTRACT

It has long been hypothesized that posttraumatic stress disorder (PTSD) increases coronary heart disease (CHD) risk; however, empirical evidence is limited. In the first prospective study to date, individuals with higher PTSD symptom levels had a significantly increased risk for CHD, after controlling for known coronary risk factors. PTSD indicates a chronic stress reaction and is hypothesized to influence CHD either by causing biological alterations that lead to cardiovascular damage, or by leading to adverse health behaviors that increase CHD risk. A key issue is whether PTSD contributes to the development of CHD, if PTSD and CHD share common pathways, or if CHD causes PTSD. Research combined across different disciplines suggests that prolonged or chronic stress does influence the development of CHD. A better understanding of the relationship will increase prevention and intervention efforts. Cardiologists may be most effective when they can recognize and manage emotional distress in practice.

We recently published the first prospective test of the hypothesis that individuals with higher levels of posttraumatic stress disorder (PTSD) symptoms are at higher risk of developing coronary heart disease (CHD). With colleagues from the Normative Aging Study, we used a questionnaire-based measure to assess PTSD in a sample of men who had served in the military and did not have CHD at the start of the study. All CHD end points were confirmed by a board-certified cardiologist. Over an average of 10 years of follow-up, for each standard deviation increase in symptom level, men had age-adjusted relative risks of 1.26 (95% confidence interval [CI], 1.05–1.51) for nonfatal myocardial infarction (MI) and fatal CHD combined. Results were maintained after controlling for all known coronary risk factors and replicated when considering an alternative measure of PTSD.[1]

Several aspects of the findings were particularly interesting. Cardiotoxic effects of PTSD symptoms were evident even though PTSD symptom levels were low to moderate in this group. In fact, few of the men would have met criteria for a PTSD diagnosis. There was also a dose-response relation between levels of symptoms and CHD risk, suggesting individuals with significantly higher levels of distress would be at considerably greater risk. Moreover, effects of PTSD symptoms on angina were significantly weaker than effects on MI and fatal CHD, each an objectively verified outcome. These results suggest that individuals with PTSD do not merely appear to be ill because they report more pain. Effects were also maintained even after accounting for potentially damaging health behaviors that have often been linked with PTSD. Finally, because PTSD and depression often occur together and since depression has been identified as a risk factor for CHD, an ongoing debate has considered whether PTSD per se may have cardiotoxic effects, or if effects can be explained by its association with depression. Findings from this study indicated that PTSD symptoms were associated with CHD, independent of depression.

NATURE OF PTSD

PTSD has been identified as a marker of extreme distress in response to a potentially traumatic event and may also be indicative of a chronic stress reaction. Diagnosis of PTSD is often difficult because PTSD symptoms overlap with those of anxiety and affective disorders, both of which are generally more recognized. However, unlike depressive and anxiety disorders, PTSD is defined by the combination of exposure to a potentially

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traumatic event (eg, combat, sexual assault, or serious natural disaster) and the occurrence of three types of symptoms: reexperiencing the traumatic event, avoidance of traumatic reminders and emotional numbing, and hyperarousal.[2] The time course of PTS can follow one of several patterns, where high levels of symptoms after traumatic exposure are followed by recovery, chronic symptoms persist over time, or symptoms relapse and remit.[3] Since the disorder reflects dysregulation of the stress-response system, which is associated with potentially atherogenic processes, a link between PTSD and CHD has long been speculated.[4]

PATHWAYS BETWEEN PTSD AND CHD

Numerous studies have found that cardiovascular disease and its risk factors are more prevalent among individuals with PTSD.[5–7] PTSD is hypothesized to contribute to the development of CHD, but because these studies have examined concurrent PTSD and cardiovascular disease or risk, they cannot determine the direction of causality. The causal relationship between PTSD and CHD has been hypothesized based on a model of prolonged stress reaction that posits that stress leads to impaired adaptation and increased wear and tear on the body. These processes may ultimately lead to atherosclerosis and cardiovascular system damage.[8] Adults with PTSD exhibit neuroendocrinologic alterations characterized by enhanced negative feedback sensitivity of glucocorticoid receptors in the stress-response system and lower than normal urinary and plasma cortisol levels. Exaggerated catecholamine responses to trauma-related stimuli have also been found in adults diagnosed with PTSD.[4] Higher concentrations of circulating catecholamines and increased total body sympathetic activity may eventually lead to autonomic nervous system dysfunction, including diminished heart rate variability, baroreflex dysfunction, and increased QT variability.[9] Chronic stress and emotional arousal may also lead to or exacerbate endothelial damage and promote the development of atherosclerosis.

Another hypothesized pathway by which PTSD may influence CHD is through behavior. Studies have consistently demonstrated that individuals with PTSD are more likely to engage in adverse behaviors, which are themselves risk factors for CHD. For example, individuals with PTSD are more likely to smoke and to abuse alcohol.[10,11] Interestingly, although these behaviors are generally believed to be on the causal pathway between PTSD and CHD, epidemiologic studies generally control for them. As a result, the magnitude of the association between PTSD and CHD may well be underestimated.

COULD THE ASSOCIATION BETWEEN PTSD AND CHD BE SPURIOUS?

At the heart of the endeavor to understand the relationship between PTSD and CHD is the question of whether PTSD actually leads to CHD through behavioral or biological alterations or if PTSD and CHD simply share common pathways. Another possibility is that the development of CHD (which itself can be a traumatic event) may cause PTSD.[7] Biomedicine has generally been somewhat skeptical of the notion that feelings or psychological stress may lead to physical health outcomes, with three primary objections typically identified:

- A third underlying factor (eg, one or more genes or toxic environmental exposures) may cause both PTSD and CHD
- Most studies to date have been cross-sectional, leaving the question of causality unresolved
- Even with prospective studies, findings may be explained by either unmeasured potential confounds (ie, physical activity) or residual confounding by inadequately measured factors.

Moreover, since PTSD can develop in response to physical trauma, it may be difficult to distinguish whether effects on CHD are due to physical harm or psychological stress reactions.

CONCLUSION

Support for the theory that PTSD is causally related to CHD is provided by the recent prospective findings and the fact that they are highly consistent with findings from work in related areas. Several studies have reported that exposure to trauma and adverse events increases the risk of CHD.[12,13] Other research has suggested that trauma increases the risk of adverse health outcomes only when PTSD develops in response to the trauma.[14,15] Moreover, there is a growing body of evidence that chronic stress in various forms (eg, work stress), as well as high levels of emotional distress, may increase risk of CHD.[9] Findings from this body of work are less susceptible to the concern that physical trauma rather than psychological stress reaction is driving the effects. Other work has also linked PTSD with reduced vagal tone[16] and hypercoagulability.[17] Taken together, research to date suggests that prolonged or chronic stress does play a role in the development of CHD **(Table 1)**.

FUTURE PERSPECTIVE

PTSD is common in the general population. Approximately 7% of Americans will meet diagnostic criteria for PTSD in their lifetime.[18] Prevalence rates are much

TABLE 1
Executive summary

Does posttraumatic stress disorder increase risk of coronary heart disease?

- In the first prospective study to date, individuals with higher levels of posttraumatic stress disorder (PTSD) symptoms were at significantly increased risk for developing coronary heart disease (CHD), after controlling for all known coronary risk factors.

Nature of PTSD

- PTSD is defined by the combination of exposure to a potentially traumatic event and the occurrence of three types of symptoms: reexperiencing the traumatic event, avoidance of traumatic reminders and emotional numbing, and hyperarousal.
- Since PTSD reflects dysregulation of the stress-response system, a link between PTSD and CHD has long been speculated.

Pathways between PTSD and CHD

- A causal relationship between PTSD and CHD has been hypothesized based on a model of prolonged stress reaction, which posits that stress leads to impaired adaptation and increased wear and tear on the body. These processes may ultimately lead to atherosclerosis and cardiovascular system damage.
- Another hypothesized pathway by which PTSD may influence CHD is through behavior. Studies have consistently demonstrated that individuals with PTSD are more likely to engage in adverse behaviors (eg, smoking), which are themselves risk factors for CHD.

Could the association between PTSD and CHD be spurious?

- A key issue is whether PTSD contributes to the development of CHD through behavioral or biological alterations, or if PTSD and CHD simply share common pathways.
- Another possibility is that the development of CHD (which can be a traumatic event in and of itself) may actually cause PTSD.

Conclusion

- Overall, research combined across different disciplines suggests that prolonged or chronic stress plays a role in the development of CHD.

Future perspective

- More conclusive evidence and a better understanding of the mechanisms will increase our ability to identify effective forms of prevention and intervention.
- Cardiologists may be most effective when they can recognize and manage emotional distress in practice.

higher among war veterans; in a recent study, 13% of US military personnel who served in Iraq screened positive for PTSD.[19] If PTSD is demonstrated to have significant cardiotoxic effects, there are numerous implications for both prevention and treatment.

More conclusive evidence of the association may be obtained using a variety of approaches. A first step will be to obtain longitudinal data in more diverse samples. This will include considering other groups (ie, women), individuals with clinically significant PTSD, and individuals with non-combat-related PTSD. Additional work will further examine exactly the duration or chronicity of PTSD necessary to initiate pathophysiological processes. Moreover, it is unknown whether the cardiotoxic effects of PTSD can be reversed if PTSD is successfully treated. Future work may compare long-term cardiac outcomes between individuals with PTSD who were successfully treated and those whose PTSD was refractory to treatment. A more careful examination of biological mechanisms is also required. Numerous studies have linked other types of chronic emotional distress with altered vagal tone, increased rate of atherosclerosis, and inflammation, suggesting these as likely pathways.[9] However, the possibility of acute effects of PTSD should also be considered in light of recent work that found evidence of myocardial stunning in response to extreme emotional distress.[20]

More conclusive evidence and a better understanding of the mechanisms will increase our ability to identify effective forms of prevention and intervention. Currently, individuals who are at high risk of trauma exposure by virtue of their occupations (eg, police or firefighters) are often screened for PTSD. Work on PTSD and CHD may suggest that these individuals should also be monitored or screened for development of adverse cardiovascular outcomes. Pertinently, this adds to the evidence suggesting that cardiologists may be more effective if they can recognize and manage emotional distress in practice. Emotional distress may increase the risk of developing disease (and sometimes actually presents as cardiac disease). It can also adversely impact on a patient's prognosis by affecting treatment adherence and shaping the course of the

disease.[9] With improved prevention and more effective treatment strategies, we have the potential to significantly improve patient outcomes.

Addendum

Since the original publication of this review, several new studies have been published that uniformly provide additional empirical support for the hypothesis that individuals with higher levels of PTSD symptoms are at increased risk of developing CHD.

ADDITIONAL PROSPECTIVE STUDIES

Population-based study of military veterans

A second prospective study was conducted using a random sample of men less than 65 years of age at follow-up who served in the US Army during the Vietnam War.[21] Two measures of PTSD were obtained, one based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition* (DSM-III), and a second one using the Keane PTSD scale. After excluding any men with a history of heart disease at baseline and controlling for known coronary risk factors, the researchers found that a diagnosis of PTSD (using the DSM-III measure) more than doubled the risk for early-age heart disease mortality (hazard ratio = 2.25; 95% CI, 1.02–4.95). These results were maintained after controlling for depression and whether or not men actually served in Vietnam or elsewhere, and results were similar when the Keane PTSD measure was used. Compared with the men participating in the Normative Aging Study, this study's population had generally higher PTSD symptom levels and had a significantly younger average age. Thus, findings from this population-based study of US veterans are highly consistent with earlier findings from a more limited sample within the Normative Aging Study.

Community-based study of civilian women

To address the question of whether effects are constrained to men with military experience (and likely combat exposure) or to older individuals, we recently examined the association between PTSD and CHD in civilian women, again using a prospective study design.[22] Past-year trauma and associated PTSD symptoms were assessed using the National Institute of Mental Health Diagnostic Interview Schedule and considered in relation to incident CHD during the 14-year follow-up. After excluding individuals with heart disease at baseline and controlling for known coronary risk factors as well as depression and trait anxiety, we found that women with 5 or more PTSD symptoms had a threefold increase in the risk of incident CHD (odds ratio = 3.21; 95% CI, 1.29–7.98) compared with women with no PTSD symptoms. These findings were unchanged after women with angina were excluded and after known coronary risk factors were controlled for. Women in this study were even younger than the men in the prior prospective studies, with a mean age at baseline of 44.4 years. This study provides evidence that that damaging effects of PTSD symptoms are not limited to military men but are also evident among initially healthy community-dwelling civilian women exposed to non-combat-related trauma.

Together, these studies suggest that PTSD may be involved in the etiology of CHD, as all were meticulous in excluding individuals who might have already had heart disease at baseline.

MORE STUDIES FOCUSING ON POTENTIAL MECHANISMS

As empirical evidence emerges that consistently suggests that PTSD is involved in the etiology of CHD, more studies are focusing on potential mechanisms and biological alterations related to PTSD that may help to explain its association with CHD. It has long been observed that individuals with PTSD often exhibit hypocortisolism and corresponding alterations in hypothalamic-pituitary-adrenal axis regulation that seem to be linked with reduced responsiveness to glucocorticoids.[23] Moreover, several studies have suggested an association of PTSD with inflammatory and autoimmune diseases, leading investigators to speculate that PTSD causes chronic low-level inflammation.[21,24]

As a result, studies focusing directly on the relationship between PTSD and inflammation or consequences of inflammation are beginning to appear. For example, one recent study compared levels of both proinflammatory and anti-inflammatory activity across patients with PTSD and age- and gender-matched controls without PTSD.[25] Findings indicated the presence of a low-grade systemic proinflammatory state among patients with PTSD, and levels of proinflammatory activity were associated in a dose-response fashion with PTSD symptom levels. In another study, patients with PTSD were found to have more endothelial dysfunction, as measured by plasma concentrations of soluble tissue factor, compared with age- and gender-matched controls without PTSD.[26]

Another line of research has considered whether links between PTSD and CHD may be explained in part by alterations in vagal function.[27] Various studies in small samples have found reduced heart rate vari-

ability and increased sympathetic activity at rest,[28–30] with parasympathetic activity blunted in response to challenge or trauma reminder among PTSD patients compared with healthy individuals without PTSD.[16,29,31] A similar line of work has considered the effect of PTSD on parasympathetic nervous system functioning by examining effects on baroreflex sensitivity. Arterial baroreflex responses contribute to parasympathetic tone and have been linked with psychosocial stress, carotid atherosclerosis, and increased risk of cardiovascular disease.[32–34] Two studies have considered whether baroreflex sensitivity is reduced among individuals with PTSD relative to those without PTSD.[35,36] One study, conducted among smokers, found reduced baroreceptor sensitivity among women but not men after controlling for demographics, medications, diagnostic characteristics, and smoking variables.[36] A second study, conducted among women only, found baroreceptor sensitivity to again be reduced among women with PTSD after controlling for a range of potential confounders, including comorbid psychiatric disorders.[35] These women also appeared to have attenuated parasympathetic withdrawal response during a stressful challenge condition, similar to findings from studies of heart rate variability. Results from this small number of studies are somewhat preliminary, but given the consistency across these initial findings and other work linking related disorders (such as depression and anxiety) with reduced heart rate variability, ongoing work in this area is recommended.[27]

CAN IT BE SHOWN THAN PTSD PRECEDES CHD DEVELOPMENT?

One of the challenges for studying potential mechanisms and biological alterations that explain how PTSD might influence the development of CHD is establishing that PTSD actually precedes the biological change under study. Much of the research to date compares individuals with PTSD or high levels of PTSD symptoms to individuals without PTSD or its symptoms. As a result, these studies cannot definitively determine whether PTSD caused the biological alteration or if presence of the biological alteration preceded PTSD and in fact increased susceptibility to the disorder.[23] Convincing evidence that PTSD is involved in the etiology of CHD will include demonstrating that PTSD precedes the biological changes posited to contribute to the development of CHD.

Suggestive evidence from an animal model

One recent study in animals provides some reassurance that the posited direction of effects for the research reviewed above is plausible. Using an animal model of PTSD, rats were randomly assigned to exposure to a severe stress (a predator) for 10 minutes or to a control group.[37] Behavioral reactions were tested 7 days after the stress exposure, and measures of ACTH, prolactin, and heart rate variability were obtained. Rats exposed to extreme stress demonstrated behavioral and biological changes commensurate with disruptions expected with PTSD. For example, stressed rats exhibited increased plasma ACTH, higher heart rate, lower heart rate variability, and many more maladaptive behaviors when compared with control rats. Since the animals were randomly assigned to exposure to severe stress, it is unlikely that these effects could be attributed to biological differences between the groups at baseline. Moreover, clear biological changes were evident as a result of exposure to severe stress. Taken together, these findings provide some reassurance that PTSD may have biological sequelae that in turn influence the risk of CHD, although prospective studies of PTSD and biological alterations in human populations clearly are needed.

AS PTSD PREVALENCE RISES, URGENCY FOR INSIGHTS INCREASES

PTSD occurs commonly in the general population but is of particular concern for individuals working in high-risk service occupations and in the military. With ongoing conflicts we may expect to see significant increases in the population prevalence of PTSD. Giving due consideration to the burden of illness associated with PTSD has added urgency, as recent studies have highlighted problems with access to and quality of mental health care.[19,38] Thus, understanding the relationship between PTSD and CHD remains critical. Insights obtained from this work may increase our understanding of how biological susceptibility to heart disease develops and may aid in identifying strategies for disease prevention and intervention.

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