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Authors
Cohen, Beth E
Edmondson, Donald
Kronish, Ian M

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Beth E. Cohen,[1,2] Donald Edmondson,[3] and Ian M. Kronish[3]

The notion that psychological states can influence physical health is hardly new, and perhaps nowhere has the mind-body connection been better studied than in cardiovascular disease (CVD). Recently, large prospective epidemiologic studies and smaller basic science studies have firmly established a connection between CVD and several psychological conditions, including depression, chronic psychological stress, posttraumatic stress disorder (PTSD), and anxiety. In addition, numerous clinical trials have been conducted to attempt to prevent or lessen the impact of these conditions on cardiovascular health. In this article, we review studies connecting depression, stress/PTSD, and anxiety to CVD, focusing on findings from the last 5 years. For each mental health condition, we first examine the epidemiologic evidence establishing a link with CVD. We then describe studies of potential underlying mechanisms and finally discuss treatment trials and directions for future research.

Keywords: anxiety disorders; blood pressure; cardiovascular disease; coronary heart disease; depression; hypertension; PTSD; stress.

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DEPRESSION AND CVD

Epidemiology

Depression is highly prevalent in patients with cardiovascular disease (CVD) and portends adverse cardiovascular outcomes and increased health care costs. One in 5 patients with coronary artery disease or heart failure is depressed, a prevalence that is at least 3 times greater than in the general population.[1–3] An even greater proportion of stroke survivors—nearly 1 in 3—is depressed after stroke.[4] Coronary heart disease (CHD) and heart failure patients with depressive symptoms are more likely to have physical limitations and poor quality of life, even after accounting for objective measures of cardiac function.[2,5] Patients with comorbid CVD and depressive symptoms are also at increased risk for recurrent cardiovascular events and mortality.[6–8] For example, depressed patients with acute coronary syndrome have double the risk of future major adverse cardiovascular events,[6] a level similar to conventional risk factors such as reduced left ventricular ejection fraction and diabetes.[9] This is true whether depression is defined by a clinical diagnosis (i.e., major depressive disorder) or by a self-report symptom severity measure.[10] Prior studies also show a dose-response relationship between depressive symptoms and cardiac events in patients with CHD, with even mildly elevated depressive symptoms associated with poor prognosis.[11] The cardiotoxic effects of depressive symptoms have been consistently observed despite the continual improvement in cardiovascular interventions, medications, and care.[12] Based on the strength of the evidence linking depression with poor prognosis after acute coronary syndrome, the American Heart Association issued a 2014 Scientific Statement recommending that depression be elevated to the status of a risk factor in acute coronary syndrome survivors.[13] Though the majority of research has been conducted in patients with existing CVD, depression is also associated with incident CHD (pooled adjusted relative risk: 1.90 (1.49–2.42),[6] and stroke pooled adjusted hazard ratio (HR): 1.45 (95% confidence interval (CI): 1.29–1.63))[14] according to recent meta-analyses. In contrast with other types of CVD, the association between depression and hypertension has been less clear with some, but not all studies showing a modest association.[15,16]

Potential mechanisms

Both behavioral and biological mechanisms have been explored as potential pathways linking depression with CVD risk. With respect to behavioral factors, depression has been associated with poor adherence to multiple risk reducing health behaviors including physical activity, smoking, and adherence to cardiovascular medications,[17,18] and several studies suggest that these factors mediate, at least in part, the association between depression and poor prognosis.[19,20]

Correspondence: Beth E. Cohen (beth.cohen@ucsf.edu)

1Department of Medicine, University of California, San Francisco, California, USA; 2General Internal Medicine, San Francisco VA Medical Center, San Francisco, California, USA; 3Center for Behavioral Cardiovascular Health, Department of Medicine, Columbia University Medical Center, New York, New York, USA.

With respect to biological mechanisms, there is a growing body of evidence linking depression with inflammatory processes (either as a byproduct of these processes and/or by increasing them),[21] autonomic nervous system dysfunction,[22] and impaired coronary flow reserve that increases risk of myocardial ischemia.[23] There is also the potential for bidirectional influences and feedback loops linking behavioral and biological factors. For example, poor adherence to physical activity and anti-inflammatory medications may increase inflammation, which may, in turn, increase depressive symptoms. With respect to hypertension, some studies suggest that depression may increase cardiovascular risk by decreasing nighttime blood pressure dipping.[24] Despite the plausibility of these biological and behavioral mechanisms, inconsistent results have been reported for each of these mechanisms and there remains a gap in knowledge regarding which mechanisms best account for the association between depression and CVD risk.

Clinical implications and future research directions

Though many pharmacological and behavioral therapies are available to treat depression, we do not know which treatments are best to lower the risk of CVD events and mortality associated with depression. Researchers have conducted numerous randomized controlled trials to test whether enhanced treatment of depressive symptoms with conventional antidepressant therapies such as cognitive behavioral therapy,[25] medications,[26] or combination therapy[27] can decrease both depressive symptoms and CVD events. The vast majority of this work has focused on secondary prevention among patients with established CVD. Thus far, conventional depression treatments have only modestly reduced depressive symptoms in patients with a history of CHD or stroke; however, it is worth noting that the effectiveness of such treatments appears to be of the same order of magnitude as when provided to general medical patients.[28,29] One of the more promising approaches to reducing depressive symptoms in patients with CVD has involved a patient preference, stepped-care approach in which depressed patients participate in decisions over whether to initiate medications and/or psychotherapy and receive frequent follow-up assessments of symptom levels with concomitant decisions over whether to intensify, switch, or maintain therapies.[30,31] Yet, thus far, even these more potent interventions have not been proven to reduce cardiovascular risk.[28,32] These findings increase the importance of identifying alternative treatments for depressive symptoms that more directly target the disrupted pathways that increase depressive symptoms, increase cardiovascular risk, or both in patients with CVD and depressive symptoms.

In addition to preventive treatments, questions remain about whether to actively screen patients with CVD for depression. Some argue for screening given its high prevalence, profound impact on quality of life and prognosis, and the availability of brief screening instruments and effective depression treatments.[33] Others reply that screening is not without risks (e.g., potential for overtreatment and misallocation of finite health care resources) and that we do not

yet have proven treatments for patients who screen positive.[34] An ongoing trial sponsored by the National, Heart, Lung, and Blood Institute that seeks to settle this debate is currently underway.[35] Another active question is how best to disseminate enhanced depression treatments for patients with CVD into clinical practice. One innovative approach is to develop a clinical service that screens for and provides enhanced collaborative care for common mental disorders, not just depression, among all patients admitted to hospital cardiac services. This approach was tested in the MOSAIC trial and demonstrated significant reductions in depressive symptoms among patients with heart failure and CHD.[30] Whether there are sufficient resources to sustain such collaborative care models in the emerging health care system that seeks to incentivize team-based care remains to be seen. Others have sought to "blend" nurse-led collaborative care for depression with concurrent collaborative management of cardiovascular risk factors. One trial of such an intervention showed significant reductions in depressive symptoms (0.4 points on SCL-20) and CVD risk factor control (7 mg/dl difference in low-density lipoprotein cholesterol, 5 mm Hg difference in systolic blood pressure) in a cost-effective manner.[36,37] Finally, others wish to test novel approaches to treating depression using interventions that more directly target the mechanisms likely linking depression with CVD risk. For example, anti-inflammatory treatments suggest promise as an approach to reducing depressive symptoms in depressed CVD patients.[38]

PSYCHOLOGICAL STRESS, TRAUMA, AND POSTTRAUMATIC STRESS DISORDER AND CVD

Epidemiology

Evidence is accumulating that exposure to chronic, daily stressors, and/or severe psychological trauma can also increase the risk of developing and dying from CVD. In terms of common, daily stressors that may be experienced over prolonged periods, meta-analyses of prospective observational studies found that social isolation and loneliness were associated with a 50% increased risk of incident CVD events (pooled relative risk = 1.5, 95% CI: 1.2–1.9).[39] The increased risk associated with work-related stress was similar at 40% (pooled relative risk = 1.4, 95% CI: 1.2–1.8).[39] Chronic stressors have also been linked to worse prognosis in patients with existing CVD. Indeed multiple qualitative studies demonstrate that patients believe daily stressors are key underlying causes of CVD and CVD risk factors, such as poor diet and sedentary lifestyles.[40,41]

Evidence is better established for psychological trauma and posttraumatic stress disorder (PTSD) than for the chronic but perhaps less severe stressors described above. Multiple prospective cohort studies have now estimated the association of PTSD with incident CVD events and/or CVD death, with HRs ranging from 1.46 to 3.28.[42–48] However, data collection on many of these cohorts, particularly those focused on military veterans, was begun years to decades after the original traumatic event. A recently published analysis of active duty US military service members participating in the Millennium Cohort Study was able to examine the effects

of trauma over a shorter period. The study compared self-report or medical record diagnosis of new CHD events in service members deployed on combat vs. non-combat missions, with the majority of deployments occurring shortly after the baseline study assessment.[49] Combat deployment was associated with a significantly increased risk of incident CHD by self-report or medical record diagnoses. Those who screened positive for PTSD symptoms had an increased likelihood of incident self-report but not medical record CHD diagnoses.

Potential mechanisms

Despite the large number of studies described above that have found significant associations between stress, trauma, and/or PTSD and CVD risk, conclusions have been limited by the use of unsubstantiated patient self-report or diagnostic codes from administrative data to establish CVD events. Several recent studies have expanded upon prior work by examining the association of PTSD and CVD using objective methods. This has provided more convincing evidence as well as shed light on the biological changes and possible mechanisms that may be leading to CVD events. In a study of 281 Vietnam-era veteran twin pairs, Vaccarino *et al.*[48] found patients with PTSD had over twice the risk of increased incident CHD events during an average of 13 years of follow-up and that this association was independent of traditional CVD risk factors, depression, and substance abuse or dependence. Importantly, the authors also found those with PTSD had decreased myocardial blood flow on cardiac positron emission tomography scans. Another study of 637 veterans without known coronary artery disease found those with PTSD had higher levels of coronary artery calcium, a marker of atherosclerosis, on computed tomography scans.[50] Finally, a study of patients recruited from VA medical centers found that those with PTSD were significantly more likely to have evidence of myocardial ischemia on exercise treadmill testing after controlling for traditional CVD risk factors and a number of psychosocial factors.[51]

A large body of literature examining patients with existing coronary artery disease has also demonstrated that 30%–70% of patients develop acute myocardial ischemia, as measured by perfusion imaging or echocardiography, in response to psychological stressors.[52] This mental stress-induced ischemia often does not cause chest pain or other typical ischemic symptoms but is associated with increased risk of recurrent CVD events and higher mortality. The reasons for the lack of classic anginal symptoms are not known but hypotheses include distinct underlying ischemic mechanisms. For example, coronary microvascular dysfunction has been observed in mental stress-induced ischemia and leads to atypical symptoms, such as fatigue and vague discomfort.[53,54] Together with the previously described work, these studies provide objective evidence of the damaging impact of psychological stress and trauma on the cardiovascular system and suggest that CVD events may be due to a combination of chronic accumulation of atherosclerotic plaque and acute myocardial ischemia triggered by stress.

In attempting to identify the mechanisms underlying coronary atherosclerosis and myocardial ischemia, many of the observational studies described above adjusted for traditional CVD risk factors, such as smoking, hypertension, diabetes, increased cholesterol, and obesity. Typically, adjustment for these factors only modestly attenuated study findings and the association of PTSD and CVD remained independent. Several studies also adjusted for a broader array of health behaviors and psychosocial factors, such as socioeconomic status, depression, and alcohol and substance abuse, but again, these did not explain the association. In the twin study described above, analyses in the subset of twins discordant for PTSD status could further control for shared genetic and early childhood environmental factors. In these analyses, PTSD remained associated with increased risk of clinical events and decreased myocardial perfusion.

Additional biological mechanisms may be responsible, including increased hypothalamic-pituitary-adrenal axis activity, autonomic nervous system reactivity, inflammation, oxidative stress, and endothelial dysfunction. There is strong evidence that these changes occur in response to chronic, daily stressors as well as traumatic events and PTSD, but it remains to be seen whether they are responsible for the associations of stress/trauma and CVD.[55–60] In addition, research in animal models emphasizes the importance of an individual's response to stress in modulating these neurobiological pathways to cardiovascular damage. In a rodent stress model, Wood *et al.*[60,61] found that animals who responded with passive rather than active coping strategies demonstrated greater hypothalamic-pituitary-adrenal reactivity and activation of proinflammatory genes as well as cardiac hypertrophy and reduced heart rate variability. This provides encouraging evidence that it may be possible to ameliorate the effects of acute and chronic stress on the cardiovascular system.

Clinical implications and future research directions

As the number of studies finding associations between psychological stressors, PTSD, and CVD grows, the focus of research has appropriately turned to prevention. In order to identify causal mechanisms that could serve as targets for interventions, further prospective studies with repeated measures of psychological stress, biological factors, and cardiovascular outcomes or surrogate markers of CVD are needed. Ongoing data collection in some of the prospective cohort studies described above should help to establish the pathways linking stress and CVD.

However, as we work to untangle these mechanisms, clinicians are left with many questions about how to counsel patients and prevent psychological stressors from impacting their cardiovascular health. Though more psychologically oriented CVD prevention trials have focused on reducing depressive symptoms, some evidence for the protective effects of stress reduction on CVD risk is available. Previous small trials found a variety of psychosocial interventions reduced risk of recurrent CVD events when added to traditional cardiovascular rehabilitation programs.[62] More recent large trials with carefully selected control groups have provided further support. Gulliksson *et al.*[63] randomized 362

men and women with a CHD event in the last year to standard care that included control of traditional cardiovascular risk factors or to standard care plus a 20-session cognitive behavioral therapy intervention focused on stress management. Over a mean follow-up period of 7.8 years, the stress management group had significantly fewer recurrent CVD events (HR: 0.59, 95% CI: 0.42–0.83) and myocardial infarctions (HR: 0.55, 95% CI: 0.36–0.85). Another recent trial comparing transcendental meditation to health education in 201 black men and women with CHD found the meditation group had a significant reduction in a combined endpoint of all-cause mortality, myocardial infarction, or stroke over a mean of 5.4 years (HR: 0.52, 95% CI: 0.29–0.92).[64] Additional studies are needed to examine the effects of stress reduction for primary prevention of CVD as well as to explore treatments in patients with PTSD. However, these prior studies suggest that psychological stress is a reasonable target for CVD prevention.

ANXIETY AND CVD

Epidemiology

Anxiety is characterized by transient fear, uncertainty, and apprehension about the future, but individuals vary on the frequency and intensity with which they experience anxiety.[65] When an individual experiences anxiety frequently, at high intensities, and/or in inappropriate situations, they may then be diagnosed with an anxiety disorder, including generalized anxiety disorder, panic disorder, phobias, and others. Of note, DSM 5, reclassified PTSD as a "trauma and stressor-related disorder" rather than an anxiety disorder. In the United States, the lifetime prevalence of any anxiety disorder is greater than 25%.[66]

Relative to psychological stress/trauma[67] and depression,[6] less is known about the association of anxiety and anxiety disorders with cardiovascular risk. In a 2010 meta-analysis of 20 studies ($N = 249,846$) assessing the association of anxiety (i.e., anxiety, panic, phobia, posttraumatic stress, and worry) with incident CHD, Roest et al.[68] found that initially healthy individuals with high anxiety were at increased risk for incident CHD (HR: 1.26; 95% CI: 1.15–1.38; $P < 0.0001$) and cardiac death (HR: 1.48; 95% CI: 1.14–1.92; $P = 0.003$), independent of demographic variables, biological risk factors, and health behaviors. Although studies of posttraumatic stress were included, no significant differences in effect size estimates were found by anxiety type, suggesting that PTSD did not account for the significant meta-analytic estimate. However, the meta-analytic estimate for the association of anxiety with CHD was not adjusted for depression, which is highly comorbid with anxiety.

More recently, 2 large prospective national registry studies have reported on the association of anxiety with incident CHD. In a study of 49,321 men who were assessed for anxiety prior to military service, any anxiety disorder diagnosis was strongly associated with incident CHD and acute myocardial infarction (MI) over 37 years of follow-up (multivariate adjusted HR: 2.17 (95% CI: 1.28–3.67) and 2.51 (95% CI: 1.38–4.55), respectively).[69] Another prospective cohort study of 25,895 Finnish men and women reported a significant

association of anxiety with elevated risk of incident CHD over 7 years of follow-up.[70] However, after adjustment for confounders and concurrent depression, the only remaining signal of an association of anxiety with fatal and nonfatal CHD was in women, with a HR of 1.24 (95% CI: 0.91–1.70) per unit increase in anxiety symptoms. Further, the anxiety scale assessed somatic symptoms such as palpitation without exercise, irregular heartbeat, chest pain upon anger or emotion, sweating without exercise, and flushing which may themselves be symptoms of cardiovascular abnormalities that predisposed patients to cardiovascular events rather than due to anxiety, alone. The association of anxiety with adverse outcome in patients with existing CHD is similarly mixed. For example, in some studies generalized anxiety disorder is associated with increased risk for recurrent events and mortality (HRs = 1.7–1.9),[71,72] but others have found no association,[73] or even a protective effect for this anxiety disorder.[74]

Potential mechanisms

Although the true association between anxiety/anxiety disorders and CVD is unclear, a number of pathways by which anxiety may influence CVD onset or progression have been proposed. For example, anxiety is associated with poorer health behaviors, such as cigarette smoking, excess alcohol consumption, lower physical activity,[75] and poor diet,[76] which increase the risk of CVD. Interestingly, anxiety has not been clearly associated with medication nonadherence.[77]

The most commonly cited biological model proposes a cumulative effect of anxiety on autonomic nervous system activity and hemodynamics, similar to that proposed for chronic stress and other negative emotions. In that model, anxiety causes excess activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, increased release of plasma catecholamines, and endothelial damage, ultimately leading to atherosclerosis, coronary artery disease, and acute coronary events.

If that model is true, one might expect that anxiety would be consistently associated with increased blood pressure. However, the evidence for a link between anxiety and risk for incident hypertension is mixed. Although cross-sectional studies have found small to moderate associations between the 2, and a large NHANES study found a prospective association of anxiety/stress/worry/tension with incident hypertension in middle-aged adults,[78] one recent Norwegian population-based study found that anxiety symptoms were associated with lower blood pressure over 11 years of follow-up.[79] In the CARDIA study, where participants were followed for 15 years, no association of anxiety with incident hypertension was found.[80]

Another model that may explain not only inconsistent findings in epidemiological studies but also inconsistent mechanistic studies, is the emotional triggering model in which the timing of anxiety measurement is essential.[81] In line with the acute cardiac effects of mental stress described above, acute anxiety is associated with increased cardiovascular reactivity to stress and resting heart rate, decreased heart rate variability, baroreflex dysfunction, and greater variability in ventricular repolarization.[9] Taken together, the effects

of sympathetic nervous system and hypothalamic-pituitary-adrenal axis hyperactivity along with altered sympathovagal control of the heart may increase the risk of incident CVD and lower the threshold for cardiac ischemia, arrhythmias, and sudden cardiac death. Indeed, some studies have found stronger associations between anxiety and sudden cardiac death than between anxiety and incident CHD.[82] Similarly, Mittleman et al.[83] found that patients reported significantly higher levels of anxiety during the 2-hour hazard window prior to an MI than during comparison control periods. In that study, anxiety was associated with 1.6 times greater (95% CI: 1.1–2.2) risk for MI.

Clinical implications and future research directions

Anxiety appears to be one of many negative cognitive/affective states associated with CVD incidence and recurrence, although empirical evidence is mixed (see Epidemiology, above). The measurement of anxiety may contribute to the mixed findings reviewed here. Anxiety is nearly universally experienced, and fluctuates over time, so attempts to classify individuals as anxious or not with a single assessment may be unreliable. Indeed, anxiety disorder diagnosis (which explicitly takes into account a longer period than many anxiety questionnaires) and repeated measures of anxiety tend to be most strongly associated with cardiovascular events[71] and proposed mechanisms.[84] In one of the few studies to directly assess the independent contributions of the nonoverlapping symptoms of anxiety and depression, as well as general distress, Kubzansky et al.[85] found that anxiety was independently associated with incident CHD over 11 years of follow-up in 1,300 men (161 events).

Anxiety disorders are common, and should be treated with pharmacotherapy and cognitive behavioral therapy, based on the substantial quality of life burden they represent. Although anxiety disorders may contribute to cardiovascular risk, and may set the stage for emotionally triggered acute events in particular, currently no study has demonstrated whether treating anxiety disorders offsets cardiovascular risk. Thus, based on current evidence, clinicians should focus on assessing and treating anxiety disorders in cardiovascular patients as an approach to improving the quality of life of their patients.

DISCUSSION

The studies outlined in the sections above illustrate the increasing evidence base establishing mental health problems as risk factors for the development and progression of CVD. Though evidence is more consistent for depression and traumatic stress, sufficient studies demonstrate that chronic anxiety and exposure to daily stressors also have a negative impact on cardiovascular health. Guidelines from major societies also reflect the growing recognition of the connection between mental and cardiovascular health. The American Heart Association now officially recognizes depression as risk factor for poor prognosis among patients following acute coronary syndromes.[13] In addition, European guidelines identify depression, anxiety, and

psychosocial stressors, such as work-related stress or poor social support, as risk factors for incident CVD and adverse outcomes in patients with existing CVD.[86]

Both the American and European guidelines acknowledge that more work needs to be done to establish the mechanisms through which psychological factors influence CVD and to identify effective treatments to reduce their impact on CVD morbidity and mortality. Still, we can make some suggestions based on the current evidence. A large body of work demonstrates that each of the psychological risk factors described above is associated with unhealthy lifestyle behaviors that could increase CVD risk, and certainly patients should be screened for and counseled about risk factors such as smoking, poor diet, and a sedentary lifestyle. However, current evidence also demonstrates that these factors alone are not responsible for the increased CVD risk seen in depression, stress, and anxiety. Each of these conditions may promote biological changes, such as heightened inflammation or endothelial dysfunction that could contribute to CVD. In the case of stress and anxiety, autonomic dysfunction and acute cardiovascular changes may also play an important role. Further studies are needed to definitively establish these mechanisms.

Another avenue for CVD risk reduction is treatment of the primary psychological disorder. Though trials of psychological interventions have yielded conflicting results in terms of effects on CVD outcomes, they are likely to improve patients function, quality of life, and general health.[87–89] It is also well known that psychological problems are under-reported and under-treated. Data from the National Comorbidity Survey Replication study found the median time from symptom onset to first treatment contact was 8 years for major depressive disorder and 9–23 years for various types of anxiety disorders, including PTSD.[90] Recognition of the damaging impact of psychological stress and disorders on physical health, such as increased CVD risk, may help improve adoption of screening and intervention programs that can reduce delays to receiving treatment and better engage patients in mental health care. In summary, much progress has been made in understanding the contribution of stress and psychological disorders to CVD and future research is likely to provide clearer guidelines on how we can best protect and improve patients' mental and cardiovascular health.

DISCLOSURE

The authors declared no conflict of interest.

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