

Update: Systemic Diseases and the Cardiovascular System (IX)

Psychiatric and Behavioral Aspects of Cardiovascular Disease: Epidemiology, Mechanisms, and Treatment

Patrick J. Smith and James A. Blumenthal*

Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina, United States

Article history:

Available online 1 September 2011

Keywords:

Stress
Cardiovascular disease
Depression
Social support

Palabras clave:

Estrés
Enfermedad cardiovascular
Depresión
Apoyo social

ABSTRACT

Psychosocial and behavioral factors, including mood (depression, anxiety, anger, and stress), personality (Type A, Type D, and hostility), and social support, are associated with both the development and progression of cardiovascular disease. "Negative" emotions have been associated with increased rates of cardiovascular death and recurrent cardiac events, although the mechanisms responsible for this association remain unclear. A number of pathophysiological mechanisms have been proposed to explain these relationships, including hypothalamic-pituitary-adrenal axis dysregulation, platelet activation, and inflammation. Behavioral factors also have been implicated, such as nonadherence to prescribed medical therapies and physical inactivity. Several randomized trials of patients with cardiovascular disease have examined the impact of pharmacologic and behavioral treatments on hard cardiovascular disease events as well as on cardiovascular disease biomarkers of risk. Although psychological treatments generally have been shown to improve quality of life and psychological functioning among cardiac patients, the benefit of psychological interventions with respect to improving clinical outcomes has not been conclusively demonstrated.

© 2011 Sociedad Española de Cardiología. Published by Elsevier España, S.L. All rights reserved.

Aspectos psiquiátricos y conductuales de la enfermedad cardiovascular: epidemiología, mecanismos y tratamiento

RESUMEN

Los factores psicosociales y conductuales, incluido el estado de ánimo (depresión, ansiedad, enojo y estrés), la personalidad (Tipo A, Tipo D y hostilidad) y el apoyo social se asocian tanto al desarrollo como a la progresión de enfermedad cardiovascular. Las emociones «negativas» se han asociado a un aumento de las tasas de muerte cardiovascular y a eventos cardíacos recurrentes, aunque continúan sin estar claros los mecanismos que explican esta asociación. Se han propuesto diversos mecanismos fisiopatológicos para explicar estas relaciones, como la alteración de la regulación del eje hipotálamo-hipófiso-suprarrenal, la activación plaquetaria y la inflamación. Se han involucrado también factores conductuales, como la falta de adherencia a los tratamientos médicos prescritos y la inactividad física. En varios ensayos aleatorizados llevados a cabo en pacientes con enfermedad cardiovascular, se ha examinado el impacto de los tratamientos farmacológicos y conductuales en las variables «duras» de eventos cardiovasculares y en los biomarcadores del riesgo de enfermedad cardiovascular. Aunque en general se ha observado que los tratamientos psicológicos mejoran la calidad de vida y la función psicológica en los pacientes cardíacos, el efecto beneficioso de las intervenciones psicológicas en cuanto a la mejora de los resultados clínicos no se ha demostrado de manera concluyente.

© 2011 Sociedad Española de Cardiología. Publicado por Elsevier España, S.L. Todos los derechos reservados.

EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) is a major public health burden in the industrialized countries, including the United States and Europe.¹ For decades CVD has been the leading cause of mortality and disability in the Western world and only recently, with

improvements in non-surgical treatments such as angioplasty and advances in medical management, has the impact of CVD begun to fall behind cancer in terms of its associated mortality.² However, it remains one of the most common and costly ailments in the Western world. The most recent estimates from the American Heart Association suggest that one third of American adults, nearly 80 million individuals, have some form of CVD, the most common forms including hypertension, coronary heart disease (CHD), chest pain, heart failure, and stroke.² Mortality data suggest that CVD was the underlying cause in 36.3% of

* Corresponding author: Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Box 3119, DUMC South, Trent Drive, Durham, NC 27710, United States.

E-mail address: james.blumenthal@duke.edu (J.A. Blumenthal).

Abbreviations

CABG: coronary artery bypass graft
 CHD: coronary heart disease
 CRP: C-reactive protein
 CVD: cardiovascular disease
 MDD: major depressive disorder
 MI: myocardial infarction
 SES: socioeconomic status
 SSRI: selective serotonin reuptake inhibitors

deaths in 2004, with current estimates that a death occurs from CVD every 36 s.³ In 2007, the estimated direct and indirect cost of CVD was \$431.8 billion. Although the impact of CVD has been relatively less in Spain, it remains a major public health burden¹ and there is evidence to suggest that CVD may be increasing in recent years.⁴

It has been estimated that 700 000 Americans would have a new myocardial infarction (MI) in 2007 and about 500 000 would experience a recurrent attack. In addition, silent MIs are common, with an estimated annual incidence of 175 000. More than half of the CVD events in adults under age 75 are due to CHD, and after age 40 lifetime risk of CHD is 49% for men and 32% for women.³ Estimates from the American Heart Association suggest that 38% of people who experience an MI in a given year will die from it. Data from prospective cohort studies have found that CVD risk factors (eg, hypertension, diabetes, physical inactivity, etc.) play a major role in the development of CHD. Case-control studies from 52 countries report that modifiable risk factors account for more than 90% of the risk of initial CHD. These factors include cigarette smoking, abnormal blood lipid levels, hypertension, diabetes, abdominal obesity, physical inactivity, low daily fruit and vegetable consumption, alcohol overconsumption, and psychological factors.^{3,5} The direct and indirect cost of CHD alone, ignoring other CVD factors, was estimated in 2007 to be \$151.6 billion.

PSYCHOSOCIAL FACTORS AND CARDIOVASCULAR DISEASE

Although traditional risk factors explain a substantial amount of CVD risk, psychological factors have also been shown to predict adverse CVD outcomes.⁶ In addition, it is very likely that psychological factors are associated with the level of CVD risk: for example, it is well known that they are associated with cigarette smoking and physical activity levels.⁷ Multiple psychological factors, each reviewed elsewhere,^{6–10} have been examined as potential risk factors for CVD and generally fall into one of 3 broad domains: *a*) negative affective states including depression, anxiety, anger, and distress, *b*) personality factors such as Type A behavior pattern, hostility, and Type D personality, and *c*) social factors including socioeconomic status (SES) and low social support.

THE RELATIONSHIP OF NEGATIVE AFFECT AND CARDIOVASCULAR DISEASE

Depression

Of all the psychological factors, depression has received the most research attention during the past decade. Indeed, due to

the overwhelming number of studies associating depression and CVD, recent clinical recommendations include depression screening and treatment among cardiac patients as a standard of care.¹¹ Depression has been variously defined in CVD research, and may vary from subclinical depressive symptoms to a full major depressive disorder (MDD), as defined in the Diagnostic and Statistical Manual of Mental Disorders – 4th edition.¹² MDD is characterized by depressed mood and/or loss of interest or pleasure in activities that represent a change from baseline function, as well as sleep disturbance, psychomotor retardation/agitation, feelings of guilt or worthlessness, significant weight loss or weight gain, fatigue or loss of energy, difficulty concentrating or making decisions, and recurrent thoughts of death. In order for these symptoms to be considered MDD, they must also have some functional impact: in other words, they must be of sufficient severity to interfere with regular activities.

Depression is common among individuals with heart disease, particularly following MI, with more than 1 in 5 patients meeting diagnostic criteria.¹³ Depression is also 3 times more common in patients after an acute MI than in the general community.^{11,14} Initial research into the relationship between depression and CVD was spurred by observational data showing that depression diagnosed during hospitalization for CHD was associated with significantly increased risk of death within the following year. Frasure-Smith et al.¹⁵ first demonstrated this in a small sample of patients hospitalized for CHD, finding that depression during the hospitalization significantly increased the risk of death within the following 6 months. These findings were soon amplified, as the authors extended their study to find that depression during hospitalization was associated with a more than 3-fold increased risk of CHD within 18 months of the hospitalization.¹⁶

One of the most interesting findings is that the association between depression and CHD events appears to be dose-response: as levels increase, so too does the risk of CHD. In a study of 5-year CHD survival among cardiac patients, Lesperance et al.¹⁷ found that incremental increases in depression, measured by the Beck Depression Inventory (BDI), were associated with dose-response increases in CHD risk. In this study, depressive symptoms were assessed both during hospitalization and again at a 1-year follow-up. Interestingly, improvements in depression were associated with a modestly reduced CHD risk, but only among those individuals with mild depression at baseline. Those participants with moderate-to-severe depressive symptoms did not experience a reduced risk of CHD with decreasing levels of depressive symptoms. Compared with participants having minimal levels of depression, participants with moderate-to-severe depression had a 3-fold increased risk of cardiac death.

The CHD risk associated with depressive symptoms has also been examined in several research syntheses. Rugulies¹⁸ conducted a meta-analysis of all prospective studies examining depression and risk of CHD. Eleven studies were eventually found to meet inclusion criteria. Across all studies, depression was either assessed by self-report through questionnaires or by clinician-diagnosed depression. The authors examined their findings using both categories of depression. When CHD risk estimates were combined across studies, depression was associated with a significantly increased risk of CHD with a combined risk ratio (RR) of 1.64 (95% confidence interval [CI] = 1.29–2.08, $P < .001$), with significant heterogeneity between studies. In sensitivity analyses, the authors found that clinician-diagnosed depression was a stronger predictor of depression (RR = 2.69) compared with depressive symptoms (RR = 1.49). These results have generally been replicated by subsequent

meta-analyses. Wulsin et al.¹⁹ reported an identical risk associated with depression in prospective studies (RR = 1.64). Barth et al.²⁰ found that depression not only increased the risk of cardiac mortality, but that the reported risk was greater in studies using longer follow-ups (odds ratio [OR] = 2.61 vs OR = 2.07 in those with shorter follow-ups). Van der Kooy et al.,²¹ in an examination of the effect of depression on CVD, found that although depression was associated with greater risk of CVD (RR = 2.54), higher quality studies found that this effect was most prominent for cerebrovascular disease (RR = 1.76). Finally, Nicholson et al.²² examined the effects of depression on cardiac outcomes in prospective studies examining post-MI patients, as well as following coronary artery bypass graft (CABG) and angioplasty. They reported similar findings, with post-MI depression doubling the risk of cardiac mortality (RR = 2.05), whereas a similar but weaker effect was observed following revascularization (RR = 1.67).

Although most of the research on depression and cardiac outcomes has focused on post-MI patients, several important studies have linked depression to adverse cardiac outcomes in other samples. At Duke University, for example, Blumenthal et al.²³ found that among patients undergoing CABG, moderate to severe depression before surgery and persistent depression following surgery are associated with increased risk of death for up to 10 years following CABG. Similar findings have been reported in heart failure patients, with greater levels of depression predicting increased risk of mortality and rehospitalization.²⁴ Similarly, Sherwood et al. at Duke University demonstrated that depression was predictive of mortality and hospitalizations, and that persistent depression was a marker for increased mortality in heart failure patients.²⁵

Several studies have reported that individual differences in background and depression characteristics may be important determinants of the relationship between CVD and depression. Recent evidence, for example, suggests that individuals with treatment-resistant depression may be at increased risk for CHD. Although definitions vary, treatment-resistant depression typically includes individuals who have failed to respond to a single trial of monotherapy, although more stringent criteria have also been applied. In a recent review, Carney et al.²⁶ present evidence from several clinical trials showing that individuals with treatment-resistant depression have a higher risk of mortality following MI.

Anxiety

Anxiety has also been associated with increased cardiac mortality, although the findings are much less consistent and appear to depend, in part, on the severity of CVD. Anxiety disorders as a category are also much more heterogeneous than MDD, encompassing diverse diagnoses such as generalized anxiety disorder, social phobia, phobic anxiety, obsessive compulsive disorder, and post-traumatic stress disorder.¹² Several prospective studies have suggested that clinically diagnosed anxiety disorders, as well as increasing symptoms of anxiety, may be predictive of CHD events. For example, Jansky et al.²⁷ recently examined the relationship between any diagnosis of anxiety and subsequent CHD events in a sample of 49 321 Swedish men ages 18 to 20, followed prospectively over a 37-year period. Participants were initially diagnosed by a psychologist using a structured interview and the International Classification of Diseases – 8th revision. Over the 37-year follow-up, the presence of anxiety was associated with more than twice the risk of CHD (hazard ratio [HR] = 2.17) and of acute MI (HR = 2.51). Interestingly, the authors did not find a significant

association between depression and CVD outcomes in this study. In a meta-analysis of 20 studies, including 249 846 individuals followed for more than 11 years, Roest et al.²⁸ also found a relationship between anxiety and CHD. Anxious individuals had higher rates of CHD (HR = 1.26) and cardiac death (HR = 1.48) after controlling for other background factors and health behaviors.

There also is evidence that phobic anxiety may be associated with increased CHD risk, and that this risk may be primarily for cardiac outputs resulting from arrhythmias. Watkins et al.²⁹ found that the presence of phobic anxiety was associated with increased risk of CHD and sudden cardiac death, but only among women. Albert et al.³⁰ reported similar findings among women participating in the Nurses' Health Study. The authors prospectively followed 72 359 women for 12 years. They found that the presence of phobic anxiety, determined by self-reported symptoms on the Crisp-Crowne Index, was associated with an increased risk of sudden cardiac death and fatal MI, but not with nonfatal MI.

Although anxiety appears to be associated with increased risk of CHD, it is also often comorbid with depression. Negative affect, which is a more general trait typified by negative emotional experiences, may be said to encompass both anxiety and depression. Several studies have therefore attempted to examine the unique and combined effects of these two psychosocial factors as they relate to CHD outcomes. In a study of 5073 middle-aged, healthy Dutch women, Denollet et al.³¹ examined the relationship between anxiety and health outcomes while controlling for depression. At a 10-year follow-up assessment, they found that anxiety was associated with a 77% increased risk of mortality, a nearly 3-fold increased risk of CHD (HR = 2.77), and a tendency to be associated with an increased risk of breast cancer. Depression was not associated with increased risk of mortality or health outcomes in this study. Several studies have examined the combined risk associated with depression and comorbid anxiety. Phillips et al.³² found that individuals with generalized anxiety disorder and depression were at greater risk for CHD than individuals with either condition alone, although it appeared that cardiovascular comorbidities were the strongest predictor of CHD outcomes in this study. In contrast, data from the Women's Ischemia Syndrome Evaluation suggested that depression and anxiety interact in predicting CHD events in a different manner: women with depression and lower levels of anxiety were at increased risk of CHD, while women with depression and higher anxiety were not.³³ It should be noted that several studies have found that anxiety may actually lower the risk of CHD. Data from the HUNT study, a population-based study of >60 000 individuals, found that higher anxiety was associated with reduced rates of CHD and all-cause mortality.³⁴ Similar results have been reported from samples without CHD at baseline.³⁵

Anger and Hostility

In a meta-analysis of prospective studies associating anger and hostility with future CHD, Chida et al.³⁶ found that higher levels of anger and hostility were associated with poorer outcomes in both healthy and cardiac populations. Among individuals healthy at study entry, higher levels of anger and hostility were associated with 19% greater risk of developing CHD (HR = 1.19). Cardiac patients with higher anger and hostility were also at greater risk, with greater anger and hostility associated with poor cardiac prognosis (HR = 1.24). Interestingly, the authors found the risk associated with anger and hostility among healthy individuals was

stronger in men than women, and the longer the duration of study follow-up, the greater the strength of the association. Another more recent study of women reported similar results. Tindle et al.³⁷ analyzed this relationship in a prospective study of 97 253 women participating in the Women's Health Initiative who were free of CVD and cancer at study entry. They found that the most cynical, hostile women had higher rates of CHD, CHD mortality, and all-cause mortality. The relationship of anger and CVD may be affected by social and other moderating factors such as physical fitness. For example, Lampert et al.³⁸ found that greater physical activity and anger were associated with increased incidence of implantable cardioverter-defibrillator discharge among cardiac patients.

Stress

The relationship of psychosocial stress and CVD can be considered in two broad categories: acute stressors, or triggers, and chronic stress. These kinds of stress have important distinctions because of how they affect the cardiovascular system and what potential mechanisms may contribute to the development and clinical manifestations of CVD. Acute mental stress impacts CVD physiology by increasing the risk for arrhythmias, myocardial ischemia, and MI,^{39,40} which may be proximally measured by physiological reactivity to mental stress in a laboratory and in real life situations. Acute stressors may include situations such as catastrophic events (war, earthquakes, etc.), intense sporting events (eg, World Cup soccer), and acute physical activity (eg, exercise or sexual activity). Chronic factors, in contrast, may be associated with CVD through chronic physiologic changes, such as persistently elevated blood pressure, coagulation factors, etc. Chronic stressors may include work-related stress, marital dissatisfaction, neighborhood factors (crowding, etc.), and lower SES.

Acute Stress

Evidence from naturalistic and animal models⁴¹ suggests that acute elevations in stress are associated with increased arrhythmic activity. In a K-9 model of stress reactivity, Lown et al.⁴¹ and Matta et al.⁴² have shown that stress induction reduces the threshold for arrhythmias and increases the frequency of ventricular arrhythmias. Acute MI, sudden cardiac death, and cardiac deaths have all been shown to increase following natural disasters, such as earthquakes⁴³ and blizzards,⁴⁴ as well as societal stressors such as military strikes like the 1991 Israeli war and the week following the events of September 11, 2001. Following the collapse of the World Trade Center buildings, arrhythmic events increased more than 2-fold over the following several weeks in comparison to the weeks preceding September 11th and during the same time in the preceding year.⁴⁵ Numerous studies using similar case-control methodologies have found that acute stressors like these, such as the San Francisco earthquake of 1989, the Athens earthquake of 1981, and the 1995 Hanshin-Awaji earthquake in Japan, increase the risk of cardiac death among individuals with CVD.⁴⁶

Chronic Stress

Various forms of chronic stress appear to increase the risk of CVD. Work-related stress has been studied extensively, and several previous meta-analyses have attempted to quantify this relationship. One of the most often cited theories explaining

this relationship is the Karasek job strain model,⁴⁷ which proposes that the combination of low decision latitude and heavy job demands is the most predictive of CVD, whereas either in isolation is not. Although this specific pattern of job strain has not always predicted CVD outcomes, other correlates of work stress have been associated with greater cardiac risk.⁴⁸ Eller et al.⁴⁹ conducted a meta-analysis to examine this question, quantifying the relationship between multiple work-related psychosocial factors and ischemic heart disease. They found that high psychological demands, lack of social support, and iso-strain were associated with increased risk of ischemic heart disease, whereas effort-reward imbalance, job insecurity, and long working hours were not related. However, it must be noted that in this study these effects could only be generalized to men, as few studies have examined these effects among women.

One of the most comprehensive studies to examine the association between stress and CVD outcomes was INTERHEART. In this case-control study, 11 119 cases and 13 648 controls from 52 countries were compared on psychosocial and behavioral risk factors, incorporating patient data from 262 medical centers from diverse geographic regions. After controlling for demographic and medical factors, individuals experiencing a first MI had greater work stress, stress at home, general stress, and permanent stress in comparison with age- and sex-matched controls.⁵⁰ In addition, a composite measure of psychosocial function, which included a measure of perceived stress, was associated with more than 2.5-fold increased chances of having an MI, comparable to the association observed with diabetes.⁵

Relationship stress also appears to increase the risk of CHD among women who are married or cohabitating. Orth-Gomer et al.⁵¹ studied this relationship in a prospective study of women with a history of CHD participating in the Stockholm Female Coronary Risk Study, finding that higher levels of relationship stress were associated with a nearly 3-fold increase in the risk of recurrent CHD during a 5-year follow-up, after accounting for background and health-related factors. Interestingly, work-related stress was not associated with increased events in this study.

Cardiovascular Stress Reactivity

Stress reactivity, which examines physiological responses to standardized laboratory stressors such as public speaking or mental arithmetic tasks, has also been examined. Cardiovascular variables examined have been diverse, but have typically included blood pressure, heart rate, heart rate variability, or changes in ejection fraction. Several studies have also examined physiological changes with mental stress as a predictor of subsequent cardiovascular outcomes, such as intima medial thickness, the development of clinical hypertension, and atherosclerotic disease. In a meta-analysis of physiological responses to mental stress, Chida et al.⁵² found that greater reactivity and slower recovery from stress was associated with poorer cardiovascular outcomes, and that these findings were strongest for the development of hypertension and higher levels of intima medial thickness.

Stress also appears to be an important predictor of myocardial ischemia during daily life among cardiac patients. Gabbay et al.⁵³ found that strenuous physical activity and stressful mental activities were predictive of myocardial ischemia. Similarly, Gullete et al.⁵⁴ found that the relative risk of ischemia increased 2-fold among cardiac patients during periods when they reported feeling tension, sadness, or frustration. Our group also has

demonstrated that, among post-MI patients, diary-reported stressful events were associated with increased irregular heart rates.⁵⁵

Laboratory paradigms have been used to study the relationship between stress and ischemia among cardiac patients.⁵⁶ Studies typically use a standardized mental stress induction procedure, like a difficult mental task (eg, mental arithmetic, maze trace, etc.) or public speaking. Multiple studies are available showing that mental stress induction increases ischemia in anywhere from 20%-55% of participants with CHD. Although it is clear that mental stress increases ischemia among CHD patients, it is less clear how well this acute induction is predictive of coronary events. Several studies have shown that stress-induced ischemia provides important information about cardiac prognosis, as several reports have shown that the presence of mental-stress-induced ischemia is predictive of clinical events in patients with CHD. Jiang et al.⁵⁷ found that mental-stress-induced ischemia was associated with a nearly 3-fold increased risk of recurrent cardiac events among patients with CHD, and that the change in ejection fraction during mental stress was an important predictor of event-free survival.

PERSONALITY AND CARDIOVASCULAR DISEASE

Type A Behavior Pattern

Several personality factors have been related to increased risk of CVD, particularly Type A and Type D personality types. Type A behavior is characterized by intense ambition, competitiveness, time urgency, and hostility.³⁶ Initial studies showed that individuals with Type A personalities were at greater risk for CVD,⁵⁸ but subsequent studies have failed to support these findings and meta-analyses of prospective studies have reported a nonsignificant association between Type A personality and subsequent CVD events.⁵⁹ Although the overall relationship between the Type A personality profile and CVD events has not been predictive of subsequent CVD events, it appears that the hostility component of this personality structure is an important predictor of CVD risk.⁵⁹

Type D Personality

In recent years, Dutch researchers shifted focus on personality characteristics to a combination of negative affect and social inhibition, which they have termed "Type D personality." Type D individuals are thought to experience more chronic levels of general distress which are not easily recognized because they are not expressed. Among patients with ischemic heart disease, the combination of high emotional negativity and high social inhibition have been associated with a nearly 2-fold increased risk of adverse cardiac outcomes,⁶⁰ and the association between Type D personality and CVD appears to be independent of CVD risk factors.⁶¹ In a review of prospective studies examining Type D personality and CVD outcomes, Denollet et al.⁶² found a >2.5-fold increased risk of CVD events among individuals with a Type D personality, and these effects were relatively consistent across studies, suggesting a stable association. In addition to Type A and Type D, there is preliminary evidence that cluster-B personality disorders, including histrionic, borderline, narcissistic, and antisocial personality disorders, are also associated with increased CVD risk, although few studies have examined this association.⁶³

SOCIAL FACTORS AND CARDIOVASCULAR DISEASE

Social Support

Social factors, including social support and SES, have also been linked with CVD outcomes. Social support may act as a buffer against negative life events, serving a protective function. Several forms of social support have been identified in the existing literature: *structural support* refers to the size, type, and density of one's social network, and the frequency of contact one has with this network. *Functional support*, sometimes referred to as tangible support, refers to the support provided by one's social structure. This includes elements of instrumental, financial, informational, appraisal, and emotional support. In one of the most comprehensive reviews of social support and heart disease to date, Lett et al.⁶⁴ conducted a comprehensive review of published studies examining the social support and heart disease relationship. The authors found that low social support was associated with a 1.5- to 2-fold increased risk of CVD in both healthy and cardiac populations, and it appeared that perceived functional support was a more important predictor of outcomes than structural support in cardiac populations.

Socioeconomic Status

A number of studies have demonstrated that SES is inversely related to the risk of CVD. The Whitehall study was one of the first to demonstrate that social gradients were associated with variations in cardiac outcomes. The authors found that gradients of SES within the British Civil Service were associated with variations in cardiac outcomes, showing that graded increases in SES were associated with a protective effect on CVD outcomes.⁶⁵ What was most striking about this study was that none of the SES groups included would be considered to be in poverty. Interestingly, there is some evidence that social factors interact with other psychosocial factors in predicting CHD. For example, Merjonen et al.⁶⁶ found that higher hostility was associated with CHD among men with lower SES levels only.

MECHANISMS

Hypothalamic Pituitary Adrenal Axis Dysregulation

Dysregulation of the hypothalamic pituitary adrenal (HPA) axis is closely tied to sympathetic activity and has been shown to occur among individuals with depression and other psychosocial risk factors. Chronic stimulation from this central output induces multiple pathophysiologic responses, including increase sympathetic nervous system activity causing heightened autonomic activity, insulin resistance, hypertension, exaggerated inflammatory response, platelet activation, endothelial dysfunction, and somatic effects, among others.⁶ Depression in particular has been shown to result in hypercortisolemia, blunted HPA activity, and diminished feedback control,⁶⁷ which may in turn increase the progression of atherosclerosis.⁶⁸ There is preliminary data to suggest that HPA dysregulation may be associated with increased risk of CVD death. In a study of psychiatric inpatients with mood disorders, Jokinen et al.⁶⁹ found that men with HPA axis dysregulation, determined by dexamethasone suppression test, were more likely to die from CHD than those without it.

Platelet Activation

Increased platelet activation has been shown to play an important role in the pathogenesis of CVD, increasing its progression⁷⁰ and predicting incident CVD among apparently healthy men.⁷¹ Accruing evidence over the past decade has suggested that psychosocial factors may also be associated with platelet activation. Although platelet activation has been most closely related to depression,^{72,73} recent evidence suggests that other 'negative' psychosocial factors, such as anxiety and mental stress,⁷⁴ are also associated with higher platelet levels. Zafar et al.⁷⁵ found that depressed adults with comorbid anxiety had the highest platelet levels compared with either condition alone. Aschbacher et al.⁷⁶ have found that elevated platelet activity following acute speech tasks about emotional interpersonal issues and these responses remained robust over 3 years of follow-up.

Interestingly, increased platelet activity has been associated with higher levels of depression among both healthy populations⁷³ and individuals with CVD,⁷⁷ leading some investigators to hypothesize that an exaggerated platelet response may be responsible for the relationship between depression and CVD.⁷⁴ One of the primary reasons to hypothesize that platelet activation might partially explain psychosocial factors and CVD is their interrelationship with serotonin, which has potent antiplatelet activities. In addition, severity of depression has been shown to correlate with platelet levels, and improvement in depressive symptoms, either treated with selective serotonin reuptake inhibitors (SSRIs) or psychotherapy, has been shown to reduce platelet levels.⁷⁸ The SSRIs also produce dose-related inhibition of serotonin uptake of platelets and may lower the risk of CVD events,⁷⁹ although evidence for this protective effect remains inconclusive.⁸⁰

Inflammation

Inflammatory factors, such as C-reactive protein (CRP), have been shown to play an important role in the pathogenesis and progression of CVD.⁸¹ The amount of circulating inflammatory markers provides important prognostic information regarding cardiac risk, as higher levels have been associated with increased incidence of adverse cardiac events⁸² as well as increased mortality after controlling for conventional risk factors.⁸³

The relationship between psychosocial factors and altered inflammatory function has long been recognized. The macrophage⁸⁴ and cytokine theories⁸⁵ of depression were early hypotheses that depressive symptoms may be in part mediated by altered endocrine function. Higher levels of inflammation, including interleukin (IL)-6, tumor necrosis factor α , and CRP, have been associated with various psychosocial factors including lower SES, chronic work stress, caregiver strain, early life adversity, hostility, and social isolation.⁸⁶ There is also mixed evidence suggesting that depression is associated with elevated levels of inflammation⁸¹ and administration of inflammatory markers has been shown to induce symptoms of fatigue, malaise, lethargy, psychomotor retardation, irritability, and anorexia.⁸⁷ In an analysis of data describing 6914 men and women between the ages of 18 and 39 years from the National Health and Nutrition Examination Survey (NHANES) III, a history of MDD was strongly associated with elevated CRP.⁸¹ Elevated inflammatory markers have also been observed among older individuals in the Health, Aging, and Body Composition study. In this study of healthy older adults aged 70 to 79 years, IL-6,

tumor necrosis factor α , and CRP were higher in depressed subjects.⁸⁸

In a recent meta-analysis, Steptoe et al. examined the relationship between acute psychological stress and inflammatory markers.⁸⁶ The authors' literature search yielded 30 studies for analysis. Their findings were that acute psychological stress was associated with increased IL-6, IL-1 β , and a trend for an association with higher CRP. However, it is also possible that increased inflammatory levels are associated with cardiac outcomes only after persistent elevations, so the findings following acute stress may not be the same as in longer-term studies. Howren et al.⁸⁹ examined this question by studying the relationship between depression and several inflammatory markers, including CRP, IL-1, and IL-6 in a meta-analysis. The authors found a dose-response relationship between depression and greater levels of inflammation across both clinical and community samples, and these relationships persisted after controlling for background factors and medications. In addition, the authors found evidence for several causal relationships between depressive symptoms and inflammation by examining prospective studies. They found evidence to suggest that depression may predispose to greater inflammation, that inflammation may increase depressive symptoms, and that there may be a bidirectional relationship, although the number of prospective studies available was not enough to draw conclusive results.

Lifestyle Factors

Although multiple psychophysiological mechanisms have been suggested as explanations for the relationship between psychosocial factors and CVD, it is also possible that behavioral factors may explain a substantial part of this relationship. Various psychosocial factors have been associated with behavioral factors such as physical activity and medication adherence. In addition, numerous studies have shown that negative psychosocial factors are related to increased substance use, such as greater frequency of cigarette smoking, alcohol consumption, and illicit drug use. Depression, for example, has been associated with lesser participation in cardiac rehabilitation,⁹ and with dose-response increases in nonadherence, as data from the Heart and Soul study found that 5% of nondepressed, 7% of mildly depressed, and 14% of depressed participants reported some nonadherence with their medication regimen.⁹⁰ It is also possible that depression may increase the delay between symptom onset and treatment among individuals with CHD.^{10,91}

IMPACT OF PSYCHOSOCIAL INTERVENTIONS ON CARDIOVASCULAR DISEASE

As described above, the association between psychosocial factors and CVD is now well established. To a lesser extent, the benefits of altering these psychosocial risk factors also have been studied. Multiple intervention studies have attempted to examine whether improving psychosocial function improves cardiac outcomes and have been the subject of several previous reviews and one Cochrane analysis.^{92–96} As noted in previous reviews,⁹² the effects of psychological interventions have varied substantially across studies, with some reporting no benefit of therapy and others reporting up to a 70% reduction in rates of mortality with treatment. Linden et al.⁹³ examined the CVD effects of psychotherapy among cardiac patients in a meta-analysis of therapy trials. Trials were included in their meta-analysis if they were predominantly a psychological or

behavioral intervention and had at least one control condition for comparison. The authors found that psychotherapy was associated with a 28% reduction in mortality in comparison with controls, using a 2-year follow-up. They also found that studies initiating treatment within 2 months of a cardiac event tended to report greater benefits, and that treatment benefits were observed only among men.

Despite these positive findings, large, controlled trials and the only available Cochrane analysis examining the effects of therapy on “hard” cardiac outcomes have generally reported equivocal results. One of the largest trials to examine this relationship was the Enhancing Recovery in Coronary Heart Disease Patients (ENRICH) randomized trial.^{97,98} In this study, post-MI patients who were depressed or who had low social support were randomized to receive either usual care or a cognitive behavioral therapy (CBT) intervention. The CBT was initiated within several weeks following MI and patients participated in a median of 11 individual sessions over a 6-month period. In addition, CBT participants underwent group therapy when feasible and participants with Hamilton Rating Scale for Depression scores >24 or with persistently elevated BDI scores were also prescribed SSRIs. The trial showed greater improvements in psychosocial outcomes, such as reduced depression and increased social support, in the treatment group compared to controls, but no greater reductions in event-free survival.⁹⁸ Interestingly, there also was evidence that treated participants with refractory depression were at greater risk for cardiac mortality in comparison with participants in whom depression was improved.⁹⁹

The Cochrane meta-analysis also reported equivocal findings, with only modest benefits of psychotherapy on CVD outcomes among depressed adults, as well as low quality in the existing body of literature. Rees et al.⁹² examined the effects of randomized controlled trials of nonpharmacological psychological interventions for cardiac disease. The authors included 36 trials in their meta-analysis, incorporating data from 12 841 patients. Approximately half of these studies were stress management interventions and the quality of studies was generally poor, with few concealing treatment allocation and few collecting data on modifiable cardiac risk factors. Results showed no differences between groups in cardiac mortality or revascularization, and only a small reduction in nonfatal reinfarctions. Notably, the improvement in reinfarction was not observed in the 2 largest trials examining this endpoint and there was evidence of publication bias.

Stress management interventions among cardiac patients have shown somewhat better results. In the Stockholm Women’s Intervention Trial for Coronary Heart Disease (SWITCHD),¹⁰⁰ 257 women were randomized to a group-based psychosocial intervention or usual care following a CVD event (MI, CABG, or percutaneous coronary intervention). The intervention was initiated 4 months after hospitalization. Results showed that women in the treatment group were nearly 3 times less likely to die during the follow-up than usual care participants. Although few studies have assessed surrogate CVD endpoints, Blumenthal et al.^{101,102} conducted several randomized trials of stress management and aerobic exercise in patients with CVD and evidence of stress-induced myocardial ischemia. In their first study, which was only partially randomized (ie, patients were randomized to exercise or stress management, while a third nonrandom group received the usual medical care without exercise or stress management), results revealed that a 4-month stress management intervention reduced myocardial ischemia during mental stress testing among cardiac patients, and that participants in the stress management group were less likely to have a cardiac event

during follow-up than the usual-care participants.¹⁰¹ Stress management was associated with a 75% reduction in risk; interestingly, exercise training reduced exercise-induced ischemia and was associated with about a 30% reduction in risk.

In a second fully randomized trial of stress management or exercise for cardiac patients, known as the Smart-Heart study, myocardial ischemia was assessed during mental stress testing, and measures of autonomic nervous system function and endothelial function also were obtained. Participants in the exercise and stress management groups showed improvements in quality of life as measured by the BDI and the General Health Questionnaire. Treatment groups showed lower reductions in ejection fraction during mental stress, fewer wall motion abnormalities, and improvements in flow-mediated dilation in comparison with participants in the control group. Stress management also showed greater improvements in heart rate variability.

Several trials have examined the effects of antidepressant pharmacotherapy on CVD outcomes among individuals with depression.¹⁰³ The SADHART trial was a randomized, double-blind, placebo-controlled, 24-week trial of sertraline for MDD among patients hospitalized for acute MI.¹⁰⁴ Results showed improvement in depressive symptoms among participants treated with sertraline, but only in patients with more severe depression. There was no difference in the full sample. The study was a safety trial, and was not powered to examine clinical outcomes. A second study replicated the safety of sertraline among patients with chronic heart failure in the SADHART-CHF trial, although sertraline did not reduce depressive symptoms any better than placebo. Moreover, the study found that participants treated with sertraline had no better clinical outcomes compared to those receiving placebo.¹⁰⁵

The MIND-IT study of antidepressant therapy for MI¹⁰⁶ showed similar results. In this multicenter randomized trial, 320 post-MI patients were randomized to either antidepressant treatment with mirtazapine or placebo, or received treatment as usual. If participants refused or did not respond to initial treatment, citalopram was offered as a second-line intervention. Results showed no differences between intervention and control participants in either depressive symptoms or cardiac outcomes.¹⁰⁶ At least one study has compared the effects of antidepressant therapy with psychotherapy in cardiac patients. In a study known as the CREATE trial, Lesperance et al.¹⁰³ examined changes in depressive symptoms in patients with MDD and CHD. In a two-by-two design, participants were randomized to receive Citalopram plus clinical management, interpersonal therapy plus clinical management, clinical management only, or placebo plus clinical management for 12 weeks. Results showed that depressive symptoms and remission rates were significantly improved in the Citalopram group, whereas no differences in depression were observed between the interpersonal therapy (plus clinical management) and clinical management alone groups.

Although individual trials have generally reported small or equivocal benefits of antidepressant therapy on CVD outcomes, at least one meta-analytic study combining trial results has reported benefits associated with treatment. As reviewed elsewhere,¹⁰⁷ trials have varied in terms of their effectiveness in improving depressive symptoms, as well as their impact on CVD events. Mazza et al.¹⁰⁷ recently conducted a meta-analysis of SSRI trials among acute CVD patients. The authors found that SSRIs tended to improve depressive symptoms, although this relationship did not achieve significance. However, they found that treatment was associated with lower rates of re-hospitalization in comparison with usual care.

CONCLUSION

In conclusion, it is apparent from the present review that psychosocial factors are related to CVD outcomes. Negative emotions, personality factors, and low social support have been shown to predict increased incidence of CVD and greater risk of recurrent CVD among cardiac patients. Several pathophysiological mechanisms have been proposed to explain this relationship. Despite the association of psychosocial factors and adverse CVD events, at this time there are limited data to indicate that changes in psychosocial risk factors improve CVD outcomes.

CONFLICTS OF INTEREST

None declared.

REFERENCES

- World Health Organization. Global status report on noncommunicable diseases 2010. Geneva: World Health Organization; 2011. Available at: http://www.who.int/nmh/publications/ncd_report2010/en/
- Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics–2011 update: a report from the American Heart Association. *Circulation*. 2011;123:e18–209.
- Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, et al. Heart disease and stroke statistics–2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2007;115:e69–171.
- Sans S, Puigdefabregas A, Paluzie G, Monterde D, Balaguer-Vintro I. Increasing trends of acute myocardial infarction in Spain: the MONICA-Catalonia Study. *Eur Heart J*. 2005;26:505–15.
- Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–52.
- Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. *J Am Coll Cardiol*. 2005;45:637–51.
- Lett HS, Blumenthal JA, Babyak MA, Sherwood A, Strauman T, Robins C, et al. Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. *Psychosom Med*. 2004;66:305–15.
- Everson-Rose SA, Lewis TT. Psychosocial factors and cardiovascular diseases. *Annu Rev Public Health*. 2005;26:469–500.
- Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. *J Psychosom Res*. 2002;53:897–902.
- Skala JA, Freedland KE, Carney RM. Coronary heart disease and depression: a review of recent mechanistic research. *Can J Psychiatry*. 2006;51:738–45.
- Lichtman JH, Bigger JT, Blumenthal JA, Frasure-Smith N, Kaufmann PG, Lesperance F, et al. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. *Circulation*. 2008;118:1768–75.
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-IV). 4th ed. Washington, DC: American Psychiatric Association; 2000.
- Thombs BD, De Jonge P, Coyne JC, Whooley MA, Frasure-Smith N, Mitchell AJ, et al. Depression screening and patient outcomes in cardiovascular care: a systematic review. *JAMA*. 2008;300:2161–71.
- Thombs BD, Bass EB, Ford DE, Stewart KJ, Tsilidis KK, Patel U, et al. Prevalence of depression in survivors of acute myocardial infarction. *J Gen Intern Med*. 2006;21:30–8.
- Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. *JAMA*. 1993;270:1819–25.
- Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. *Circulation*. 1995;91:999–1005.
- Lesperance F, Frasure-Smith N, Talajic M, Bourassa MG. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation*. 2002;105:1049–53.
- Rugulies R. Depression as a predictor for coronary heart disease. a review and meta-analysis. *Am J Prev Med*. 2002;23:51–61.
- Wulsin LR. Is depression a major risk factor for coronary disease? A systematic review of the epidemiologic evidence. *Harv Rev Psychiatry*. 2004;12:79–93.
- Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med*. 2004;66:802–13.
- Van der Kooy K, Van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry*. 2007;22:613–26.
- Nicholson A, Kuper H, Hemingway H. Depression as an aetiological and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J*. 2006;27:2763–74.
- Blumenthal JA, Lett HS, Babyak MA, White W, Smith PK, Mark DB, et al. Depression as a risk factor for mortality after coronary artery bypass surgery. *Lancet*. 2003;362:604–9.
- Lesman-Leegte I, Van Veldhuisen DJ, Hillege HL, Moser D, Sanderman R, Jaarsma T. Depressive symptoms and outcomes in patients with heart failure: data from the COACH study. *Eur J Heart Fail*. 2009;11:1202–7.
- Sherwood A, Blumenthal JA, Trivedi R, Johnson KS, O'Connor CM, Adams Jr KF, et al. Relationship of depression to death or hospitalization in patients with heart failure. *Arch Intern Med*. 2007;167:367–73.
- Carney RM, Freedland KE. Treatment-resistant depression and mortality after acute coronary syndrome. *Am J Psychiatry*. 2009;166:410–7.
- Janszky I, Ahnve S, Lundberg I, Hemmingsson T. Early-onset depression, anxiety, and risk of subsequent coronary heart disease: 37-year follow-up of 49,321 young Swedish men. *J Am Coll Cardiol*. 2010;56:31–7.
- Roest AM, Martens EJ, De Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. *J Am Coll Cardiol*. 2010;56:38–46.
- Watkins LL, Blumenthal JA, Babyak MA, Davidson JR, McCants Jr CB, O'Connor C, et al. Phobic anxiety and increased risk of mortality in coronary heart disease. *Psychosom Med*. 2010;72:664–71.
- Albert CM, Chae CU, Rexrode KM, Manson JE, Kawachi I. Phobic anxiety and risk of coronary heart disease and sudden cardiac death among women. *Circulation*. 2005;111:480–7.
- Denollet J, Maas K, Knottnerus A, Keyzer JJ, Pop VJ. Anxiety predicted premature all-cause and cardiovascular death in a 10-year follow-up of middle-aged women. *J Clin Epidemiol*. 2009;62:452–6.
- Phillips AC, Batty GD, Gale CR, Deary IJ, Osborn D, MacIntyre K, et al. Generalized anxiety disorder, major depressive disorder, and their comorbidity as predictors of all-cause and cardiovascular mortality: the Vietnam experience study. *Psychosom Med*. 2009;71:395–403.
- Rutledge T, Linke SE, Krantz DS, Johnson BD, Bittner V, Eastwood JA, et al. Comorbid depression and anxiety symptoms as predictors of cardiovascular events: results from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. *Psychosom Med*. 2009;71:958–64.
- Mykletun A, Bjerkeset O, Dewey M, Prince M, Overland S, Stewart R. Anxiety, depression, and cause-specific mortality: the HUNT study. *Psychosom Med*. 2007;69:323–31.
- Meyer T, Buss U, Herrmann-Lingen C. Role of cardiac disease severity in the predictive value of anxiety for all-cause mortality. *Psychosom Med*. 2010;72:9–15.
- Chida Y, Steptoe A. The association of anger and hostility with future coronary heart disease: a meta-analytic review of prospective evidence. *J Am Coll Cardiol*. 2009;53:936–46.
- Tindle HA, Chang YF, Kuller LH, Manson JE, Robinson JG, Rosal MC, et al. Optimism, cynical hostility, and incident coronary heart disease and mortality in the Women's Health Initiative. *Circulation*. 2009;120:656–62.
- Lampert R, Joska T, Burg MM, Batsford WP, McPherson CA, Jain D. Emotional and physical precipitants of ventricular arrhythmia. *Circulation*. 2002;106:1800–5.
- Krantz DS, Kop WJ, Santiago HT, Gottdiener JS. Mental stress as a trigger of myocardial ischemia and infarction. *Cardiol Clin*. 1996;14:271–87.
- Krantz DS, McCeney MK. Effects of psychological and social factors on organic disease: a critical assessment of research on coronary heart disease. *Annu Rev Psychol*. 2002;53:341–69.
- Lown B, DeSilva RA. Roles of psychologic stress and autonomic nervous system changes in provocation of ventricular premature complexes. *Am J Cardiol*. 1978;41:979–85.
- Matta RJ, Lawler JE, Lown B. Ventricular electrical instability in the conscious dog: effects of psychologic stress and beta adrenergic blockade. *Am J Cardiol*. 1976;38:594–8.
- Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. *N Engl J Med*. 1996;334:413–9.
- Glass RI, Zack MM. Increase in deaths from ischaemic heart-disease after blizzards. *Lancet*. 1979;1:485–7.
- Steinberg JS, Arshad A, Kowalski M, Kukar A, Suma V, Vloka M, et al. Increased incidence of life-threatening ventricular arrhythmias in implantable defibrillator patients after the World Trade Center attack. *J Am Coll Cardiol*. 2004;44:1261–4.
- Stalnikowicz R, Tsafir A. Acute psychosocial stress and cardiovascular events. *Am J Emerg Med*. 2002;20:488–91.
- Karasek R, Baker D, Marxer F, Ahlbom A, Theorell T. Job decision latitude, job demands, and cardiovascular disease: a prospective study of Swedish men. *Am J Public Health*. 1981;71:694–705.

102. Blumenthal JA, Sherwood A, Babyak MA, Watkins LL, Waugh R, Georgiades A, et al. Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease: a randomized controlled trial. *JAMA.* 2005;293:1626–34.
103. Lesperance F, Frasure-Smith N, Koszycki D, Laliberté MA, Van Zyl LT, Baker B, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *JAMA.* 2007;297:367–79.
104. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger Jr JT, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA.* 2002;288:701–9.
105. O'Connor CM, Jiang W, Kuchibhatla M, Silva SG, Cuffe MS, Callwood DD, et al. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. *J Am Coll Cardiol.* 2010;56:692–9.
106. Van Melle JP, De Jonge P, Honig A, Schene AH, Kuyper AM, Crijns HJ, et al. Effects of antidepressant treatment following myocardial infarction. *Br J Psychiatry.* 2007;190:460–6.
107. Mazza M, Lotrionte M, Biondi-Zoccai G, Abbate A, Sheiban I, Romagnoli E. Selective serotonin reuptake inhibitors provide significant lower re-hospitalization rates in patients recovering from acute coronary syndromes: evidence from a meta-analysis. *J Psychopharmacol.* 2010;24:1785–92.