Annu. Rev. Public Health 2005. 26:469–500
doi: 10.1146/annurev.publhealth.26.021304.144542

First published online as a Review in Advance on January 11, 2005

PSYCHOSOCIAL FACTORS AND CARDIOVASCULAR DISEASES

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Key Words depression, anger, hostility, stress, pathophysiological mechanisms

■ **Abstract** Rapidly accruing evidence from a diversity of disciplines supports the hypothesis that psychosocial factors are related to morbidity and mortality due to cardiovascular diseases. We review relevant literature on (*a*) negative emotional states, including depression, anger and hostility, and anxiety; (*b*) chronic and acute psychosocial stressors; and (*c*) social ties, social support, and social conflict. All three of these psychosocial domains have been significantly associated with increased risk of cardiovascular morbidity and mortality. We also discuss critical pathophysiological mechanisms and pathways that likely operate in a synergistic and integrative way to promote atherogenesis and related clinical manifestations. We conclude by discussing some of the important challenges and opportunities for future investigations.

OVERVIEW

Traditional cardiovascular risk factors, including smoking, high blood pressure, high cholesterol, and diabetes, do not fully account for or explain the excess burden of cardiovascular diseases (CVD) in the population. Most individuals who develop CVD have at least one of these risk factors (67); nevertheless, other factors contribute to the development and progression of CVD. Several psychosocial characteristics are importantly related to coronary heart disease (CHD), hypertension, stroke, and other cardiovascular disorders. Indeed, the literature on this topic is quite expansive. The purpose of this review is to provide a selected summary of key findings in this literature. We note some of the classic studies and historical developments important to the field and focus on prospective, epidemiological studies, with clinical endpoints [e.g., myocardial infarction (MI), CVD mortality, stroke] and/or subclinical cardiovascular disease (e.g., carotid atherosclerosis, coronary calcification) as the outcome. We begin with current statistics on the impact and cost of CVD, outline and review the literature on three important psychosocial domains that have received much of the research attention, discuss key pathophysiological mechanisms and pathways by which psychosocial factors may

influence CVD, and discuss some future directions likely to be critical to advancing the field.

CARDIOVASCULAR DISEASE BURDEN

Cardiovascular diseases are the leading cause of death and disability in the United States and in most countries around the world (4, 16). In 1999, an estimated 17 million persons worldwide succumbed to CVD (16). In 2001, the most recent year for which U.S. mortality data are available, more than 38% of all deaths that occurred in the United States were attributed to CVD; nearly three quarters of these deaths were due specifically to CHD and stroke. In total numbers, more women than men die from CVD each year in the United States. Indeed, while mortality due to CVD has declined steadily among men in the past 25 years, CVD mortality among women has remained relatively constant (4). This event is, at least in part, due to the fact that women typically survive to older ages, when CVD is most prevalent.

Cardiovascular diseases are the leading cause of death among nearly all race or ethnic groups in the United States. However, African American men and women experience disproportionately higher rates of hypertension, CHD, MI, and stroke than do Caucasians and a greater prevalence of these disorders occurs at younger ages (4, 144). Among females, Mexican Americans also have a greater prevalence of CVD than do Caucasians (4). The incidence of many chronic diseases, including CHD, stroke, hypertension, and heart failure, likely will increase in the coming decades as our population ages (16, 28). Moreover, the rapidly increasing prevalence of obesity and type 2 diabetes occurring in all segments of the U.S. population (149) likely will contribute to a growing epidemic of CVD in the United States in future years. The projected direct and indirect costs of CVD for 2004 are more than $386 billion (4). Clearly, the personal, economic, and population impact of cardiovascular diseases is enormous, making CVD one of the largest public health problems of the twenty-first century.

NEGATIVE EMOTIONS, PSYCHOSOCIAL STRESS, AND SOCIAL FACTORS RELATED TO CARDIOVASCULAR DISEASES

A broad range of psychological and social characteristics have been investigated in relation to CVD and related risk factors. Indeed, clinical anecdotes and historical observations have ascribed etiological importance to emotional and personality factors in the manifestation of CVD for many centuries (see 35 for a review). We have chosen to focus on three psychosocial domains in this review: (*a*) negative emotional states—here defined as depression or depressive symptoms, anger and hostility, and anxiety; (*b*) chronic psychosocial stressors, particularly occupation

or work-related stress, and acute life stress; and (*c*) social factors—specifically social ties, social support, and social conflict. Research on these domains has dominated much of the literature. Table 1 lists sample items from some of the most commonly used questionnaire measures assessing these three psychosocial domains. We do not cover research on socioeconomic position or social class and health. The impact of socioeconomic position on nearly all aspects of health is one of the most widely observed and enduring observations in all of public health (92); however, this vast literature is beyond the scope of this review.

Negative Emotional States and Cardiovascular Disease Risk

In the past 15–20 years, understanding of the contribution of negative emotional states to CVD and CVD-related health outcomes has grown exponentially. Research has typically focused on (*a*) depression or depressive symptoms, (*b*) anger and hostility, or (*c*) anxiety. Each of these areas is reviewed separately, below.

DEPRESSION AND DEPRESSIVE SYMPTOMS Major depressive disorder, current depressive symptoms, and a history of depression all have been associated with increased risk of CVD morbidity and mortality. The earliest reports of an association between depression and mortality appeared in the 1930s when it was noted that depressed psychiatric inpatients had a higher incidence of CHD-related death than did nonpsychiatric controls (64, 129). More recent studies of psychiatric patients similarly found high rates of CVD mortality in patients with unipolar or bipolar depression (213, 218). Among cardiac patients, it has long been recognized clinically that rates of depression are high among patients after suffering an MI, that depression adversely impacts the prognosis of CVD, and that there are high rates of sudden cardiovascular death in depressed patients (176). These observations have been confirmed in empirical studies with cardiac patients (9, 21, 61).

Epidemiological evidence on the cardiovascular consequences of depression or depressive symptoms comes from selected and unselected population samples that have included both male and female participants ranging in age from young adulthood to older ages. In 1993, Anda and colleagues (5) reported that depressed affect, measured by 4 items from the General Health Questionnaire, was significantly associated with a 50%–60% excess risk of fatal and nonfatal ischemic heart disease (IHD) after adjusting for traditional coronary risk factors over 12 years of follow-up of more than 2800 initially healthy men and women from the National Health Examination Follow-up Survey (NHEFS). Subsequently, a number of population- or community-based studies have reported similar findings. Results from several well-controlled studies are noted below.

Pratt and colleagues (169) reported that a diagnosis of major depression was significantly related to a 4.5-fold increased risk of self-reported MI, and a history of dysphoria predicted a 2.7-fold increased risk of self-reported MI in a sample of 1551 adults drawn from the general population and who were initially free of heart disease. Depressive symptoms, measured by the Center for Epidemiological

TABLE 1 Sample items included in commonly used scales assessing psychosocial factors

Psychosocial factor

Depressive symptoms (CES-D, Radloff 1977) (170)
- "I felt that I could not shake off the blues, even with help from my family and friends."
- "I had trouble keeping my mind on what I was doing."
- "I felt that everything I did was an effort."
- "I had crying spells."
- "I felt sad."

Hopelessness (Everson et al. 1996) (45)
- "It is impossible for me to reach the goals that I would like to strive for."
- "The future seems to me to be hopeless and I can't believe things are changing for the better."

Anxiety (*trait*) (Spielberger 1980) (202)
- "I am a steady person."
- "I feel nervous and restless."
- "I get in a state of turmoil or tension as I think over my recent concerns and interests."
- "I worry too much over something that does not matter."

Hostility/cynical distrust (Cook & Medley 1954) (27)
- "I think most people would lie to get ahead."
- "It is safer to trust nobody."
- "No one cares much what happens to you."
- "Most people make friends because friends are likely to be useful to them."
- "Most people are honest chiefly through fear of being caught."

Anger-in (Spielberger et al. 1985) (203)
- "I am irritated more than people are aware."
- "I pout or sulk."
- "I harbor grudges."
- "I am seething inside but don't show it."

Anger-out (Spielberger et al. 1985) (203)
- "I do things like slam doors."
- "I say nasty things."
- "I strike out at whatever infuriates me."
- "If someone annoys me, I'm apt to tell him or her how I feel."

Social connections (Kaplan et al. 1988) (93)
- "What is your current marital status?"
- "How often do you visit friends and relatives?"
- "How many people usually come to see your or call you per day?"
- "How often do you go to meetings of clubs, associations, or societies?"

Emotional support (Seeman & Berkman 1988) (188)
- "Can you count on someone to provide you with *emotional* support (talking over problems or helping you make a difficult decision)?"
- "Could you have used more emotional support than you needed?"

Availability of emotional support/attachment (Orth-Gomér et al. 1993) (160)
- "Someone special, whom [you] can lean on"
- "Someone to share feelings with"
- "Someone to confide in"
- "Someone to hold and comfort [you]"

(*Continued*)

TABLE 1 (*Continued*)

Psychosocial factor
Job strain (Karasek et al. 1998) (96)
"Do you have time enough to do your work?"
"Do you have to work fast?"
"Are there conflicting demands in your job?"
"Do you learn new things in your job?"
"Is your job monotonous?"
"Can you influence how your work is to be performed?"
Effort-reward imbalance (Siegrist et al. 2004) (198)
"I have constant pressure due to a heavy work load."
"I have a lot of responsibility in my job."
"People close to me say I sacrifice too much for my job."
"I experience adequate support in difficult situations."
"My job promotion prospects are poor."
"Considering all my efforts and achievements, I receive the respect and prestige I deserve at work."
"Considering all my efforts and achievements, my salary/income is adequate."

Studies Depression (CES-D) Scale, predicted greater than 70% excess risk of incident CHD in women and men and 2.34-fold greater CHD mortality in men in adjusted analyses after nearly 10 years of follow-up in the first National Health and Nutrition Examination Survey (54). Most recently, data from the Women's Health Initiative Observational Study, which followed a multi-ethnic sample of nearly 94,000 women aged 50–79 years for approximately 4 years, found that current depressive symptoms, measured by a short form of the CES-D, were associated with a significant 1.5-fold higher risk of death, after controlling for education, income, and traditional coronary risk factors (216). Depressive symptoms also have been linked to incident stroke (89, 157), stroke mortality (52), and incident hypertension (31).

Hopelessness is one symptom of depression that appears to have particularly adverse effects on health. In their report from the NHEFS, Anda et al. (5) reported that the single item on hopelessness from their measure of depressed affect predicted a more than twofold risk of fatal and nonfatal IHD and was a stronger predictor than the complete measure. In the San Antonio Heart Study, high levels of hopelessness predicted all-cause and CVD mortality in Mexican Americans and Caucasians (204). Everson and colleagues (45) found that hopelessness predicted a twofold increase in CVD mortality, MI, and all-cause mortality over six years of follow-up in a population sample of middle-aged Finnish men from the Kuopio Ischemic Heart Disease (KIHD) study, after controlling for demographic characteristics, cardiovascular risk factors, and overall depressive symptoms. Hopelessness also was related to accelerated progression of intimal-medial thickening (IMT) in

the carotid arteries and threefold greater risk of incident hypertension over four years in the KIHD study (48, 49).

Some studies have failed to support the hypothesis that depressive symptoms are associated with greater CVD morbidity or mortality (113, 146, 175). Moreover, studies have varied in the extent to which they adequately controlled for potential confounding variables such as concurrent health status and behavioral risk factors. As reviewed above, however, a number of methodologically sound studies have consistently identified a positive association between depression or depressive symptoms using a variety of assessment tools in a number of different populations.

Nonetheless, because the majority of published studies have not included racial or ethnic minorities, less is known about the impact of depressive symptoms on CVD in these populations. Available evidence suggests that depressive symptoms may confer greater CVD risk in African Americans, particularly with respect to hypertension and stroke outcomes. Data from the Coronary Artery Risk Development in Young Adults (CARDIA) study showed that high scores on the CES-D were associated with 2.8-fold increased risk of hypertension after 5 years of follow-up among African Americans but not among Caucasians (31), although more recent data from CARDIA with 15 years of follow-up did not show racial differences in psychosocial risk factors for hypertension (226). Two reports from the NHEFS found that negative affect (symptoms of anxiety and depression) predicted twice the risk of incident hypertension and a 1.73-fold greater risk of stroke over 7–22 years of follow-up, with the strongest associations observed among African Americans (88, 89). Interestingly, studies suggest that African Americans, compared with Caucasians, report higher levels of depressive symptoms (86, 215) but no difference in the prevalence of major depressive disorder (86, 104), although earlier reports suggest the prevalence of depressive disorder was lower among African Americans (105). With the documented higher rates of CVD among African Americans and other minorities, further work is needed to assess the impact of depressive symptoms and other psychosocial characteristics among racial and ethnic minority populations.

ANGER AND HOSTILITY Investigations into the effects of anger and hostility on risk for CVD have a long history. Early psychoanalytic and psychodynamic literature described episodes of anger, hostility, or other strong emotions or personality characteristics, such as aggressiveness and a need to be hard-driving and tough-minded, in patients with heart disease or hypertension (1, 7, 39). These observations, together with the need to provide a clearer definition and assessment of what was deemed "coronary-prone behavior," motivated work in the 1950s and 1960s on what came to be called the Type A behavior pattern. On the basis of observations of their own cardiac patients, Rosenman & Friedman described the Type A individual as one who was exceedingly hard-driving and ambitious, competitive, time-urgent, and unusually quick-tempered and tightly wound (62). Their initial work suggested that Type A men and women had higher cholesterol levels and greater evidence of CHD, compared with those who were "Type B" (62). This

distinction led to the Western Collaborative Group Study, a prospective study of more than 3100 middle-aged men, which established Type A as a risk factor for CHD (179). In that study, Type A men were twice as likely as Type B men to develop CHD in the subsequent 8.5 years—a level of risk equivalent to that conferred by any traditional coronary risk factors. This now classic work on the Type A behavior pattern was critical in advancing our understanding of psychosocial factors in relation to CVD risk. Indeed, Type A was the first psychosocial factor to be accepted by the medical community as a recognized coronary risk factor (28).

Shortly following the medical community's acceptance of the Type A behavior pattern, studies with negative findings began to appear in the literature (171, 193, 194). Because many of the historical observations had focused on anger, hostility, and aggressive qualities as predisposing factors in CHD and hypertension, attention then turned to identifying whether these aspects or features of Type A were the important or "toxic" components (35).

Hostility is typically characterized by a suspicious, mistrustful attitude or disposition toward interpersonal relationships and the wider environment; it is considered to be enduring, i.e., a personality trait. Anger is an emotion that is considered one component of a broader, multidimensional construct that includes hostility and aggressive behavior (201, 203). Anger usually is triggered in response to perceptions of unjust events or actions and has both trait and situational aspects.

In the past two decades, numerous studies have investigated hostility and anger, measured with various instruments, in relation to risk of hypertension, stroke, and CVD morbidity and mortality, with both positive and null findings. The literature reported and quality of studies are quite mixed, and many studies used selected samples (3, 10, 72, 73, 119). However, a meta-analytic review of 45 studies published in 1996 concluded that hostility is an independent risk factor for CHD and all-cause mortality (147). A number of studies investigating hostility and/or anger and incident CVD have been published since then; the majority reported positive associations. Selected findings from these more recent studies are noted below.

A recent case-control study from the Multiple Risk Factor Intervention Trial showed that men at high risk for CVD who scored high on a behavioral rating of hostility were more likely to die from CVD in the intervening 16 years than were men who were low in hostility, after adjustment for coronary risk factors (139). In the Normative Aging Study, each 1-point increase in hostility scores predicted a 6% increased risk of incident CHD over 3 years (155), and after 7 years of follow-up, men with high levels of anger (upper 20% of the distribution) at baseline had experienced 2.5 times more incident coronary events (nonfatal MI, fatal CHD, angina pectoris) than had men with low levels of anger (lowest 20%) (100). In the KIHD study, hostility predicted a more than twofold increased risk of MI and CV mortality over nine years (50), which was largely explained by behavioral risk factors in subsequent adjusted analyses. In contrast, anger expression style (i.e., "anger-out") was associated with twice the risk of incident stroke over eight years of follow-up (47), and both "anger-out" and "anger-in" were associated with a significantly increased four-year risk of incident hypertension in the KIHD study

(46) in adjusted analyses. Recent data from CARDIA found that individuals scoring in the upper quartile on hostility and the time urgency–impatience component of Type A behavior experienced 80% excess risk of cumulative 15-year incidence of hypertension in the total sample (226). The Atherosclerosis Risk in Communities (ARIC) study found that anger predicted incident CHD (223) and incident stroke (222), after adjusting for age, sex, and race/ethnicity.

Some studies have found that hostility and anger are associated with subclinical cardiovascular disease. High hostility scores and high trait anger and anger-in were associated with the extent and severity of carotid atherosclerosis 10 years later in a sample of 200 healthy postmenopausal women (140). Among middle-aged men in the KIHD study, high hostility scores together with high levels of anger control were associated with a twofold greater progression of carotid atherosclerosis over two years (90). Finally, Iribarren and colleagues (82) reported that higher hostility was associated with greater coronary artery calcification ten years later in a subset of participants from the CARDIA study.

Taken together, the available evidence, especially from methodologically strong population-based studies, indicates that anger and hostility do increase the risk of CVD in healthy populations. A review by Hemingway & Marmot (74), however, concluded that prospective data in patients with documented CHD indicate that anger and hostility are not strong predictors of recurrent events or mortality in coronary patients. Moreover, as noted above, the vast majority of research in this area has been limited to men, especially Caucasian men. Although the few studies that have included women have generally reported positive findings, it remains to be seen whether anger and hostility will be clearly and consistently associated with CVD risk in women as well as in ethnic minorities.

ANXIETY Studies with psychiatric and coronary patients and community-based samples suggest that anxiety disorders may be associated with greater mortality, particularly sudden cardiac death, and greater cardiovascular morbidity. Early evidence suggested that psychiatric patients with panic disorder had increased mortality rates (29). Among coronary patients, higher levels of anxiety have been associated with poorer prognosis and greater recurrence of cardiac events post-MI (60, 205); however, findings are inconsistent. Frasure-Smith & Lesperance (59) found that higher trait anxiety predicted greater cardiac-related mortality in a sample of nearly 900 MI patients, but this effect was nonsignificant following adjustment for disease severity. Two earlier studies found that high anxiety levels were protective in coronary patients (15, 76).

Several epidemiologic studies support the hypothesis that high levels of anxiety increase risk for CHD, although most of these studies are limited to men. Men with high levels of anxiety had nearly four times greater risk of fatal CHD over 10 years than did men with low levels of anxiety after adjusting for traditional CVD risk factors (69). Similarly, phobic anxiety predicted 2.45-fold greater risk of fatal CHD in a sample of nearly 34,000 male health professionals initially free of disease (98). In the Normative Aging Study, men with at least two self-reported

anxiety symptoms had increased risk of cardiac death, compared with men with no symptoms of anxiety, although only a small number of events occurred (102). In separate analyses from that study (109), men who reported high levels of worrying had a more than twofold increased risk of nonfatal MI after 20 years of follow-up.

Among women, epidemiologic evidence regarding the association between anxiety and CVD risk is weaker and more limited. Symptoms of anxiety were associated with significantly greater risk of incident MI and cardiac death after 20 years among homemakers but not among employed women in more than 700 initially healthy women from the Framingham Heart Study (41). Baseline levels of trait anxiety were not related to mean levels of carotid IMT 10 years later in a sample of 200 healthy postmenopausal women (140). More recently, a study of more than 700 French men and women without a history of MI or angina found that individuals with sustained high levels of anxiety over 2 years showed greater 4-year increases in carotid artery IMT relative to those who were not anxious, although this association was only marginally significant among women ($p = 0.07$) after multivariate adjustment, and relatively few men ($n = 29$) or women ($n = 47$) reported sustained high anxiety levels (164).

In sum, studies examining the influence of anxiety on CVD risk among men are generally positive, but the association among women is weaker, and some clinical evidence suggests anxiety may be protective. Moreover, because this work has been limited largely to Caucasian samples, it is unclear whether anxiety is related to CVD risk in minority populations.

Psychosocial Stressors and Cardiovascular Disease Risk

Research on the role of psychosocial stressors in CVD also has a long history. Early epidemiologic and sociologic observations noted the impact of stressors such as poverty, poor housing, and work conditions on the health of populations (177). In addition, Cannon and Selye, two prominent physiologists working in the early half of the twentieth century, made critical theoretical and empirical observations that have motivated much of the research on the effects of stress on health. Cannon (20) identified the fight-or-flight response, a set of physiological responses to threat or challenge, and Selye (191) was the first to recognize that severe, prolonged stress could lead to tissue damage and disease. Their observations have stimulated research in many disciplines that has helped elucidate the physiologic pathways by which psychosocial factors may increase risk of CVD.

OCCUPATIONAL/WORK-RELATED STRESSORS Epidemiological studies of stress and CVD often have focused on occupational or work-related stressors. The job strain model posits that high job demands coupled with low job control have a particularly deleterious effect on cardiovascular health (95, 110). The more recent effort-reward imbalance model suggests that high efforts (high demands and/or high involvement) in the presence of low rewards (low pay, low esteem, few career opportunities, and/or job insecurity) may have a hazardous influence on

cardiovascular health (196, 198). Although not unequivocal (78, 114), a number of large-scale, prospective studies have found positive associations between overall job strain and CVD morbidity and mortality (95, 110, 210); the low control aspect of the job strain model had the most consistent negative effects (17, 186).

Other studies have found significant associations between effort-reward imbalance and indices of CVD, including progression of atherosclerosis (51, 125) and new coronary events (196, 197). In a sample of 6895 men and 3413 women from the Whitehall II cohort, Bosma and colleagues (17) found that effort-reward imbalance and aspects of job strain (low job control) independently predicted cardiovascular outcomes, conferring a 1.56- to 2.38-fold greater risk of new coronary disease over 5 years of follow-up. Consequently, researchers have begun to combine information from the two models to improve estimation of cardiovascular outcomes (165). Recent studies have found significant associations between a more generalized measure of work stress and CVD mortality (138) as well as job insecurity (also a component of the effort-reward imbalance model) and incident CHD (117). On average, job strain, effort-reward imbalance, and other occupational stressors have consistently predicted cardiovascular outcomes for men, but less consistently for women (114, 161).

ACUTE PSYCHOSOCIAL STRESSORS Other types of psychosocial stressors also predict CVD endpoints. Historically, anecdotal observations and case studies have often noted that the development of cardiac disease follows an experience of acute stress (44, 66). For example, bereavement was associated with increased mortality from IHD and all causes in a sample of more than 95,000 men and women (94). Fairly severe acute life stressors, such as earthquakes and terrorist attacks, also are associated with increased sudden cardiac death (97, 120, 211). In 1991, following the Iraqi missile attack on Israel, Kark et al. (97) noted a 58% increase in total population mortality, largely attributable to out-of-hospital deaths due to CVD. Loer and colleagues (120) conducted a comprehensive review of county coroner records the week before, the day of, and the week following the Northridge, California, earthquake in 1994. They observed a sharp increase in the number of sudden cardiac deaths—from an average of 4.6 deaths during the week preceding the earthquake to 24 deaths on the day of the earthquake.

CHRONIC PSYCHOSOCIAL STRESSORS Relatively few studies have examined the relationship between chronic, nonoccupational daily life stressors and the onset or exacerbation of CVD. In a sample of more than 73,000 Japanese men and women initially free of CVD, women who reported high levels of (nonspecific) daily life stress had a 1.6- to 2-fold higher age-adjusted risk of death from CVD after 8 years of follow-up compared with women with low stress levels (83). Results for men were less pronounced: Men with moderate daily life stress had higher rates of MI compared with their low-stress counterparts, but no associations were observed between daily life stress and other CVD endpoints.

Two reports from the Nurses Health Study show a strong association between another chronic stressor, caregiving, and incident CHD, including mortality, in women. Women caring for an ill spouse for 9 or more hours a week had nearly twice the risk of incident CHD over 4 years (116). Women who reported high levels of caregiving for non-ill children (more than 21 hours a week) or grandchildren (more than 9 hours a week) also experienced increased CHD risk (115), compared with women without caregiving responsibilities.

In summary, a number of psychosocial stressors are prospectively associated with incidence and progression of CVD. Most studies have examined chronic stressors in the form of work stress or caregiving and produced fairly consistent results. These effects may be patterned by gender; occupational stressors appear to influence outcomes more for men, whereas other types of stressors (daily life stress, caregiving) may influence CVD risk in women. In addition, with few exceptions (83), studies examining clinical outcomes have largely focused on samples of Caucasian men and, more recently, Caucasian women. Further work is needed to determine whether associations between psychosocial stressors and CVD outcomes vary by ethnicity.

Social Ties, Social Support, Social Conflict, and Cardiovascular Disease Risk

In the 1960s and 1970s, investigations into the influence of environmental conditions, social stress, and status on chronic diseases, such as hypertension and CHD, proliferated (79, 87, 208, 209). In addition, theoretical and empirical work on the importance of social relationships to the health and well-being of individuals and communities (14, 24, 80) was rapidly expanding. We review here the literature on three related social stressors: social ties, social support, and social conflict.

SOCIAL TIES Epidemiological studies have consistently found associations between social ties and CVD (19, 93, 159). Social isolation has been defined as living alone or being unmarried (23, 225), and/or having little social contact with relatives, friends, and other social groups (19, 93). Socially isolated individuals typically have higher rates of CVD morbidity (159) and mortality (19, 43, 93). In a study of 32,624 initially healthy men, socially isolated men experienced a nearly twofold greater risk of CVD mortality over 4 years, compared with socially integrated men (99). Further analyses of the same cohort revealed similar associations after 10 years of follow-up; socially isolated men have a twofold greater risk of fatal CHD, compared with nonisolated men (43).

Kaplan and colleagues (93) found that Finnish men in the lowest two quintiles on a scale measuring social connectedness were at an increased risk of CVD mortality compared with men in the highest quintile. Similarly, coronary patients with small social networks (three or fewer individuals) were found to have a 2.4-fold higher rate of mortality over 5 years, compared with those with larger networks, after adjusting for age and disease severity (19).

Most epidemiological studies in this area have assessed objective indices of social isolation in the form of marital status and number of social contacts; subjective measures of social isolation also may be associated with CVD endpoints. A prospective study of 1290 patients undergoing coronary bypass surgery found that patients who agreed with the statement "I feel lonely" prior to surgery had a significant 2.61-fold increased mortality after 30 days and a 1.78-fold increased risk 5 years later, compared with patients who did not feel lonely (75).

SOCIAL SUPPORT Social ties measure quantitative aspects of an individual's social behavior, whereas social support captures the qualitative aspects of social interactions. Several major subtypes of social support have been described (emotional, instrumental, and informational); however, emotional support has been the most commonly assessed subtype in the CVD literature. Emotionally supportive relationships, characterized by high degrees of caring, sympathy, understanding, and esteem support (160, 188), have shown to be cardio-protective (108, 178, 214). Conversely, low levels of emotional support have been associated with a number of negative cardiovascular health outcomes (214, 225). In one study, low levels of emotional support from close friends were associated with a significant 3.1-fold increased risk of incident MI and CHD mortality over 6 years of follow-up in a sample of 736 initially healthy men, after controlling for other potential risk factors (160).

Low levels of emotional support appear to be particularly harmful in individuals who are already ill. In a sample of 194 male and female patients hospitalized for acute MI, Berkman and colleagues (13) observed a 2.9-fold increase in mortality over the course of 6 months in individuals reporting low levels of emotional support. Absence of a close confidante conferred a three-fold greater risk of mortality in a group of male and female patients with pre-existing CAD (225). More recently, Krumholz et al. (108) observed a 3-fold greater risk of fatal and non-fatal CVD in a sample of 292 male and female heart failure patients without emotional support.

SOCIAL CONFLICT Research on social relationships has focused primarily on the positive, health-enhancing effects of social networks and social support. However, there is a growing recognition that social relationships have both positive and negative aspects (56, 57). Although some investigators speculate that social conflict may be associated with poorer health outcomes, few studies have prospectively examined these issues with respect to CVD. A specific form of social conflict—marital distress—may be associated with CVD morbidity and mortality. In a study of 292 female coronary patients aged 30–62 years, women who reported severe marital stress had a 3-fold greater likelihood of recurrent coronary events (defined as cardiac death, hospitalization for recurrent AMI, and revascularization) over a 4-year follow-up, compared with women who reported low or no marital stress, after controlling for demographic, behavioral, and disease status variables (161). Matthews & Gump (138) reported that marital dissolution was associated with a significant 1.37-fold greater risk of CVD mortality over 9 years of follow-up in a sample of nearly 11,000 men.

Taken together, these findings suggest that social factors (networks, supports, and conflicts) have a relatively consistent impact on CVD; the strongest effects have been observed in populations already affected by or at risk for CVD. The majority of studies exploring the impact of social factors on CVD have included primarily samples of Caucasian men (93, 99, 138, 160) and, to a lesser extent, Caucasian women (13, 14, 161). Less is known about the role of social factors in CVD risk in minority populations.

PATHOPHYSIOLOGICAL MECHANISMS

The rapid growth of research on psychosocial factors and CVD morbidity and mortality over the past few decades has brought about a greater focus on the pathophysiological mechanisms or pathways by which psychosocial factors influence disease development and progression. A number of important and potentially interrelated physiological mechanisms may underlie the observed associations. These represent direct pathophysiological effects of negative emotions, stress, and social factors that can contribute to disease. Activation of the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS), serotonergic dysfunction, secretion of proinflammatory cytokines, and platelet activation, reviewed below, are four critical mechanisms by which psychosocial factors may contribute to atherogenesis. Figure 1 presents a proposed integrative model that illustrates some of the interrelationships among these mechanisms and the pathways through which psychosocial factors may lead to atherosclerosis and related clinical outcomes. The relationship between psychosocial factors and CVD is highly complex and multifactorial. Environmental, social, and behavioral pathways also have important influences on this relationship; however, such pathways are not depicted because the focus in this review is on putative and recognized biologic pathways.

HPA and ANS Activation

Psychosocial factors may influence cardiovascular function and promote atherogenesis through the HPA axis and/or the ANS, which are activated in response to fear, anxiety, depression, anger, and stress (142, 151, 173). Chronic dysregulation of the HPA axis, which occurs in depression (166, 173), can result in hormonal and neuroendocrine alterations, including hypercortisolemia or excess glucocorticoid secretion (190). Even small increases in glucocorticoids sustained over time can contribute to hypertension, insulin resistance, visceral obesity, coagulation changes, and increased lipid levels, all of which are precursors to CVD (25, 151). Other research has found that hostile individuals have higher circulating levels of catecholamines (206), greater cardiovascular reactivity (i.e., exaggerated blood pressure and heart rate responses) to psychological challenge (207), and higher cortisol levels (167) than do their nonhostile counterparts. Similarly, chronic stress such as job strain has been associated with higher levels of blood pressure

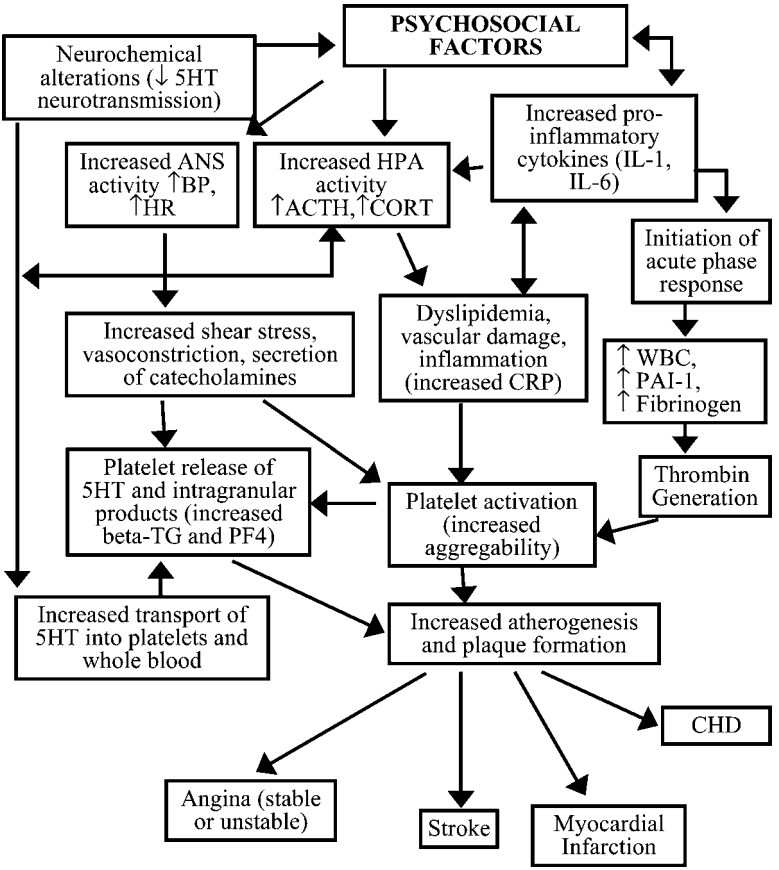

Figure 1 Proposed physiological mechanisms and pathways linking psychosocial factors and atherogenesis and related outcomes. (Adapted from Reference 133). Abbreviations: 5H, serotonin; ANS, autonomic nervous system; BP, blood pressure; HR, heart rate; ACTH, adrenocorticotropin hormone; CORT, cortisol; IL-1, interleukin-1; IL-6, interleukin-6; CRP, C-reactive protein; WBC, white blood cell count; PAI-1, plasminogen activator inhibitor; ß-TG, beta-thromboglobulin; PF4, platelet-factor 4; CHD, coronary heart disease.

(137, 185) and increased blood pressure over time (121). Social factors also may influence the HPA axis and ANS activation. The presence of social support during stressful situations attenuates blood pressure and heart rate responses to stress in women (65, 91) and reduces cortisol reactivity in men (107). Poor-quality relationships and low social support have been associated with higher levels of epinephrine (58, 189). In animal models, social isolation and chronic social stress have been associated with excess cortisol secretion, HPA dysfunction, altered autonomic activity, and endothelial damage (182, 217, 224).

Serotonergic Dysfunction

Abnormalities in serotonergic function may be another mechanism by which negative emotional states and stress influence atherogenesis. Serotonin is critical in the regulation of mood, emotions, and behavior. Preclinical investigations and clinical studies indicate that depression is associated with serotonergic dysfunction in the central nervous system (8, 30, 145) and in peripheral circulating platelets (162). Moreover, both central and peripheral serotonergic mechanisms influence thrombovascular processes. Serotonin has known vasoactive properties and is involved in thrombogenesis, platelet activation, and hypertension (33, 55, 184). Most of the circulating serotonin in the blood is contained within platelets (68). Serotonin secreted by platelets activated at the site of vascular injury contributes to smooth muscle cell proliferation, vasospasms, and thrombus formation (32). Depressed patients, especially those with high levels of anxiety, showed serotonin-stimulated increases in platelet intracellular calcium, which is involved in platelet activation and maintenance of blood pressure (34). Chronic stress also can produce alterations in serotonin levels and function (143, 144). Serotonergic dysregulation plays a critical role in aggressive behavior and impulsivity and may be associated with high levels of anger and hostility (124, 131). Current hostility and lifetime history of aggressive behavior in adults with major depression have been associated with high levels of platelet serotonin (130), and increasing levels of hopelessness have been associated with high whole blood serotonin levels in a population-based sample of older adults (53). Central and peripheral indices of serotonergic function appear to be inversely associated with one another; however, the human and animal data supporting this association are limited (141, 195), and the mechanisms by which these two systems may be related are unknown at the present time.

Secretion of Pro-Inflammatory Cytokines

Inflammatory processes play a critical, early role in atherogenesis. Indeed, the likely primary event in atherogenesis is injury to the arterial endothelium (180). Endothelial injury and damage can result from fluid mechanical forces or large shear stress gradients in the vasculature (36); traditional coronary risk factors, including cigarette smoking, high cholesterol, diabetes, and hypertension (180); as well as infectious agents (156). Endothelial injury results in the induction of cytokines, vasoactive molecules, and growth factors that stimulate the endothelium to have procoagulant rather than anticoagulant properties, which initiates an acute phase response and resultant cascade of atherogenic changes (181). Psychosocial factors, including stress and negative emotional states, can adversely affect these inflammatory processes, particularly via the action of proinflammatory cytokines. This pathway is clearly bidirectional (see Figure 1). Cytokines can induce behavioral and psychological expressions of stress, including negative emotional states. The pro-inflammatory cytokines IL-1 and IL-6 stimulate the HPA axis, initiating a classic stress response that results in elevated circulating glucocorticoids (11, 183). Cytokines also induce "sickness behavior," fatigue, anorexia, anhedonia, and

decreased psychomotor activity (103), which are recognized symptoms of depression. Increased plasma concentrations of IL-1, IL-6, and other cytokines have been observed in patients with major depression, with a concomitant increase in acute phase proteins significantly associated with IL-6 (128, 200). Human and animal models indicate that IL-6 levels are increased under conditions of psychological and social stress (106, 163, 228).

Platelet Activation

Markovitz & Matthews (133) initially proposed that enhanced platelet response to psychological stress is a key mechanism whereby psychosocial stress may trigger acute ischemic events and contribute to the development and progression of CVD. Figure 1 is an adaptation and extension of their proposed model, which incorporates additional mechanisms discussed in this review. Platelets play a central role in hemostasis, thrombosis, and the development of atherosclerosis and acute coronary syndromes (118). Depressive symptoms have been associated with increased platelet activation and exaggerated platelet reactivity in patients with major depression (152, 153). Patients with IHD and comorbid depression showed increased plasma concentrations of platelet-specific proteins, β-thromboglobulin (β-TG), and platelet factor-4 (PF4), compared with nondepressed patients with IHD or healthy control subjects (111). Hostility similarly has been associated with increased β-TG (134) and platelet activation among CHD patients but not among healthy controls (132). Anger expression has been positively correlated with platelet aggregability (219). The relation between psychosocial factors and platelet activation and/or reactivity may be mediated, at least in part, by alterations in serotonergic function (133).

Other Mechanisms

Other pathophysiological mechanisms may play a role in explaining how various psychological or social factors influence CVD risk. Altered autonomic control of the heart appears to be important, particularly concerning negative emotional states. Several studies have reported that patients who are depressed or have anxiety disorder have reduced heart rate variability and impaired or poor vagal control (22, 101). Similarly, research suggests that hostile men have diminished vagal control of cardiac function, compared with nonhostile men (199). This evidence indicates that negative emotions may promote arrhythmogenesis. Recent findings support this hypothesis. Anger triggered ventricular arrhythmias in patients with implantable defibrillators (112), and anger and hostility predicted incident atrial fibrillation in men but not women in the Framingham Offspring Study (42). Earlier studies suggested that acute psychological distress precedes arrhythmias (18, 172). Animal studies have reported that cardiac arrhythmias are more frequent in social compared with nonsocial stress (192).

Psychosocial factors also may indirectly influence CVD development and progression through nonphysiological pathways. It is well-documented that

individuals who are anxious, depressed, angry, or hostile, or who have more stressful lives or are more socially isolated, frequently have poor behavioral risk profiles or less healthy lifestyles, including higher rates of smoking, more sedentary lifestyles, excess consumption of alcohol, and poor compliance with medical regimens (6, 98, 123). However, the majority of studies published to date have found that the excess CVD risk associated with psychosocial characteristics is not adequately explained by these factors and largely persists following statistical adjustment for known cardiovascular risk factors. Thus, our focus here has been on biologically plausible physiological mechanisms by which psychosocial factors can influence CVD.

RECOMMENDATIONS FOR FUTURE STUDIES

A number of important and emerging issues provide impetus to and a framework for future investigations into the role of psychosocial factors and risk for CVD. We have identified seven areas of research that we believe are particularly promising and briefly describe each of these areas below.

Investigating the Impact of Differential Exposure to Psychological Stress on CVD Risk Among Minorities

A majority of studies to date have included only male participants and largely Caucasian populations. This is particularly true in studies of clinical cardiovascular endpoints, although a growing number of studies have included women and ethnic minority samples. African Americans may be more susceptible to the adverse cardiovascular consequences of negative emotions, especially hypertension and stroke (31, 88, 89). Minority populations also experience a disproportionate burden of CVD (4). Several researchers have argued that ethnic disparities in CVD are a result primarily of ethnic differences in exposure to psychosocial stress (e.g., poverty, chronic stress, discrimination, negative emotions) (85, 221). African Americans frequently report greater exposure to discrimination (187, 212, 221), negative life events (84, 187), higher rates of hostility (2, 81), and more depressive symptomatology (86) than do Caucasians. Hispanics also have a higher prevalence of major depressive disorder (148, 154) than do Caucasians. Differential exposure rates to psychosocial stress may confer an increased vulnerability to clinical manifestations of CVD; however, few studies have investigated these relationships.

Understanding Psychosocial Factors that May Uniquely Influence Minority and Immigrant Populations

Certain psychological or social factors may be especially relevant to the experience of minority or immigrant populations. There is growing interest in the cardiovascular consequences of chronic social status stressors in the form of discrimination

and unfair treatment, although no prospective epidemiological investigations of these associations have been reported. Available cross-sectional data suggest that reports of discrimination may be associated with higher levels of IMT (212) and, in some instances, hypertension (220), although evidence to date has been inconsistent (70). Degree of acculturation also may be particularly significant in the development of CVD among immigrant populations. Greater acculturation has been associated with greater prevalence of CHD in Japanese Americans (136) and first-generation Indian immigrants (150) and greater prevalence of stroke among Mexican Americans (158). These effects have not been examined prospectively.

Examining Multiple Psychological and Social Influences That Impact People's Lives

Numerous psychological and social influences affect individuals' lives and ultimately their health. Empirical research to date rarely reflects this; most investigations have focused on only one or perhaps two psychological characteristics or social factors and have ignored interrelationships among these factors and how they jointly affect cardiovascular health. However, available evidence is suggestive. In the KIHD study, men who reported feeling hopeless, hostile, and socially isolated experienced greater progression of carotid artery IMT over four years (127) and were nearly three times as likely to suffer an MI or CVD death over eight years of follow-up (126), compared with men with none of these characteristics. Moreover, the health outcomes of the men with all three psychosocial risk factors was significantly worse than among men with one or two characteristics. Other work found that the effects of perceived stress on cardiovascular function were pronounced among those with low social support but buffered in those with high social support (26). Among post-MI patients, a pattern of high stress, social isolation, and limited education predicted mortality in men (181), and suppressed emotions and economic disadvantage predicted mortality in women (168). Such intriguing findings emphasize the need to study reciprocal or intercorrelated relationships among individuals' psychological characteristics and their social environments.

Understanding Neighborhood Effects on CVD Risk and Health Outcomes

A burgeoning literature has documented important neighborhood effects on health. Residents in a low social environment experienced significantly higher 11-year mortality risk than did residents of a high social environment, after adjusting for individual education, income, race, health status, and behavioral risk factors (227). Living in a disadvantaged neighborhood increased the risk of incident CHD over nine years of follow-up in the ARIC study, after considering age and personal socioeconomic indicators (38). Neighborhood environments likely impact health via psychosocial and behavioral characteristics (174). These and related findings point to the potential significance of multilevel analyses of psychosocial determinants of cardiovascular health (37, 135).

Exploring Continuing Scientific Advances in the Measurement of CVD

In the past 15 years there has been a dramatic growth in studies using noninvasive assessment techniques (e.g., B-mode ultrasonography, electron beam tomography), as such technology has become available, to detect early indications of atherosclerotic changes. These technological advances have enabled investigators to examine whether and to what extent psychosocial factors are important early in the disease process. This trend will continue as advances in the measurement of CVD are made. Knowledge gleaned from such work can help inform future intervention and prevention efforts.

Investigating Pathophysiological Mechanisms that Underlie the Associations between Psychosocial Characteristics and CVD Risk

Continued refinement of pathophysiological mechanisms and pathways is needed as we achieve greater understanding of the complexity of mechanisms that link psychosocial factors and CVD. One integrative hypothesis has been put forth recently. Harris & Matthews (71) proposed that interactions between endothelial function and ANS regulation, including sympathetic and parasympathetic activity, may be one mechanism by which psychosocial factors are related to CVD. Further understanding of pathophysiological mechanisms will help identify effective interventions that may lead to a reduction in CVD mortality and morbidity.

Examining the Efficacy of Psychosocial Interventions to Reduce Disease Risk and Prevent the Development of CVD

The literature on psychosocial interventions dates back more than 25 years and is decidedly mixed. Two meta-analytic reviews recently concluded that psychosocial interventions in post-MI patients reduce cardiac morbidity and mortality (40, 122); yet relatively few large, well-controlled clinical trials have been conducted. The most promising early results were from the Recurrent Coronary Prevention Project, which found that type A behavior modification and group counseling successfully reduced type A behavior and hostility and reduced the risk of recurrent coronary events in a sample of 1013 MI patients, of whom 592 received the intervention (63). Most recently, findings from the Enhancing Recovery in Coronary Heart Disease trial, a comparison of cognitive behavioral therapy for depression and/or social isolation versus usual care in 2481 post-MI patients from 8 clinical settings, showed that although the intervention improved the psychosocial risk of participants, it had no impact on coronary outcomes (12). Further research is needed to explore the efficacy of psychosocial interventions in reducing the risk of recurrent events among patients with CVD and in preventing coronary events in at-risk individuals. Much also remains to be learned about the psychophysiological mechanisms by which psychosocial interventions may reduce cardiac events.

SUMMARY

In this review, we have summarized some of the rapidly accruing findings relating psychosocial factors to CVD morbidity and mortality. Population-based and community studies, studies of psychiatric and cardiac patients, and experimental investigations from varied scientific disciplines, including epidemiology, cardiology, psychiatry, sociology, psychology, and physiology, have contributed to this literature. Taken together, this breadth and diversity of scientific work on the role of psychological and social characteristics in the development and progression of CVD make the relative consistency of the findings all the more remarkable. Indeed, these observations highlight the temporality and strength of the relationships between psychosocial factors and CVD, coherence and consistency of the findings, and the biologic plausibility of the associations. Each of these features strengthens the hypothesis that psychosocial factors are causally related to CVD (77).

We focused on three psychosocial domains: negative emotional states (depression, anger and hostility, and anxiety); chronic and acute psychosocial stressors, especially job stress; and three related social factors (social ties, social support, social conflict). Although not unequivocal, available evidence indicates that these psychosocial domains all are associated with increased risk of CVD morbidity and mortality. Moreover, accumulating data show that these psychosocial characteristics have direct pathophysiological effects. These pathophysiological mechanisms are multifactorial and undoubtedly act in an integrative and synergistic fashion to promote atherogenesis and its clinical manifestions (Figure 1). The work reviewed here has contributed greatly to our knowledge and understanding about psychosocial factors and risk for CVD. Nonetheless, many opportunities for future research remain. Some of the most important challenges facing future work in this area include identifying the impact of psychosocial factors in ethnic minority populations, who suffer a disproportionate burden of CVD; expanding conceptual and empirical models to determine how interrelated psychological and social factors relate to CVD risk; utilizing multilevel models to explore the complexity of psychosocial determinants of cardiovascular health; keeping pace with scientific advances in CVD measurement techniques; further refining our understanding of pathophysiological mechanisms and pathways linking psychosocial factors to CVD; and exploring the efficacy and utility of interventions to reduce psychosocial risk and thereby decrease risk of CVD morbidity and mortality.

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