Stress and Cardiovascular Disease: An Update on Current Knowledge

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Abstract

Considerable progress has been made during the past decade in research on cardiovascular effects of stress. Early-life stressors, such as childhood abuse and early socioeconomic adversity, are linked to increased cardiovascular morbidity in adulthood. Our updated meta-analyses of prospective studies published until 2011 show a 1.5-fold (95% confidence interval 1.2–1.9) increased risk of coronary heart disease among adults experiencing social isolation and a 1.3-fold (1.2–1.5) excess risk for workplace stress; adverse metabolic changes are one of the underlying plausible mechanisms. Stress, anger, and depressed mood can act as acute triggers of major cardiac events; the pooled relative risk of acute coronary syndrome onset being preceded by stress is 2.5 (1.8–3.5) in case-crossover studies. Stress is also implicated in the prognosis of cardiovascular disease and in the development of stress (takotsubo) cardiomyopathy. A major challenge over the next decade is to incorporate stress processes into the mainstream of cardiovascular pathophysiological research and understanding.

INTRODUCTION

CVD: cardiovascular disease

CHD: coronary heart disease

ACS: acute coronary syndrome

MI: myocardial infarction

The cardiovascular diseases (CVDs) discussed in this review include coronary heart disease (CHD), hypertension, and stroke. In 2008, CVDs accounted for 33% of deaths in the United States, about half of which were attributable to CHD (89). Fortunately, the number of CVD deaths has substantially declined over the past 40 years; in the United States, the annual rate of deaths attributable to CVD declined by 31% between 1998 and 2008 alone, with similar patterns in European Union countries. Ford et al. (27) estimate that around half of the decrease resulted from improvements in the treatment of people with advanced disease, whereas much of the remainder has been due to changes in risk factors, such as smoking, and treatments for high cholesterol and hypertension, though these benefits have been offset in part by increasing obesity and diabetes.

The disease process underlying clinical CHD and many strokes is atherosclerosis, a condition starting early in life and developing progressively as people age. The disease typically comes to clinical attention in one of three forms: angina pectoris, an acute coronary syndrome (ACS) including myocardial infarction (MI) and unstable angina, or sudden cardiac death. Sudden cardiac death is usually defined as a natural death resulting from an abrupt loss of heart function (cardiac arrest) occurring within a short time of symptom onset. The mechanism involves disturbance in the electrical stability of the heart leading to a fatal arrhythmia such as ventricular fibrillation.

The recognized risk factors for CHD include hypertension, dyslipidemia, smoking, diabetes, and family history. Other behaviors are linked to risk such as physical activity, diet and energy intake, and alcohol consumption. The notion that stress is involved dates back more than 100 years (11) and has been investigated using the complementary approaches of epidemiology, mechanistic psychophysiological experiments, and clinical studies.

This update of current knowledge is organized around the different phases of CVD evolution. First, we discuss stress as a contributor to the long-term development of CHD, outlining the epidemiological evidence for associations between stress exposure and CHD development and detailing the biobehavioral mechanisms that may be responsible. Hypertension has been a major focus of stress research, so it is described separately. Next, we review the evidence for stress as a trigger of acute cardiac events, in people both with and without advanced underlying CHD. Finally, we consider the role played by stress following an acute coronary event and its significance for prognosis and future health. Although the focus is primarily on the development of CVD, we also outline implications for public health interventions.

LONG-TERM DEVELOPMENT OF CORONARY HEART DISEASE

Stress may influence the development of CHD across the life course, affecting risk factors and the progression of coronary atherosclerosis. Understanding these processes involves an integration of longitudinal epidemiologic studies and mechanistic research on biobehavioral processes.

A 1.5-Fold Excess Risk

Chronic stress, both at early life and adulthood, has been associated with ~40–60% excess risk of CHD (103). The association with stroke is less certain (111). Much of the evidence on early-life stress discusses childhood adversities, such as sexual abuse, parental substance use, parental disease, and chronic stressors, such as poor socioeconomic circumstances. The most commonly studied adult stressors have been social isolation and stress at work; however, marital problems (81), death of a child (63), and care for a sick spouse at home (62) have also been linked to increased CHD risk.

A recent meta-analysis showed childhood abuse to be associated with various physical diseases, the strongest links being seen for neurological and musculoskeletal problems

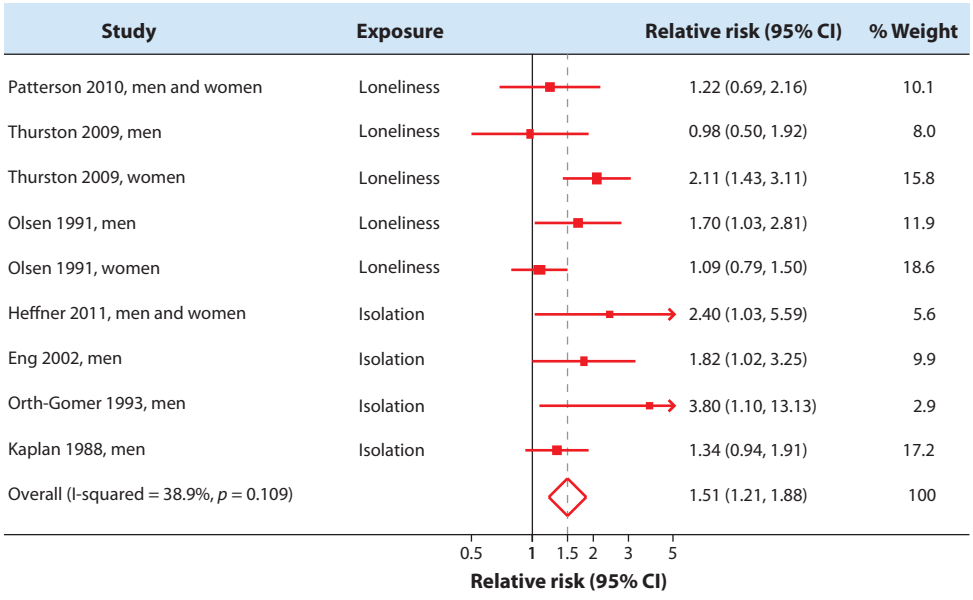

Figure 1

Meta-analysis of prospective studies on loneliness and social isolation: Age- and sex-adjusted relative risk of incident coronary heart disease for presence versus absence of loneliness/isolation by study and its summary estimate [relative risk estimates and confidence intervals (CIs) >1 favor increased risk]. References to cited studies can be found in the **Supplemental Studies** list online (follow the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org**).

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followed by respiratory diseases and vascular diseases, such as heart attack and stroke (116). In a pooled analysis of data from community surveys in 10 countries, there was a more than twofold increased risk of heart disease among those who reported 3 or more childhood adversities compared with those reporting none (93). These results may overestimate the strength of the association because data were retrospective and based on self-reports. In a 45-year prospective follow-up of British women (86), early adversity indicated by low childhood socioeconomic position was associated with a 1.4 times higher mortality from CHD compared with high childhood socioeconomic position, after adjustment for potentially important confounding factors, such as adulthood socioeconomic position and smoking.

In adults, social isolation and loneliness are common sources of chronic stress (72). Meta-analytic reviews show that patients with CHD or other chronic conditions have significantly worse prognosis if they experience social isolation (47). **Figure 1** shows results from our meta-analysis of prospective cohort studies in CHD-free populations, published up until December 2011. The pooled relative risk for social isolation, loneliness, and first CHD event across the 9 studies identified was 1.5 [95% confidence intervals (CI) 1.2 to 1.9].

Estimates for the association of CHD with exposure to stress at work or "job strain" (i.e., high job demands combined with low control) are of similar magnitude. According to a meta-analysis of prospective cohort studies published by 2006, an age- and sex-adjusted summary estimate of the relative risk for job strain is 1.4 (95% CI 1.2 to 1.8) (56). **Figure 2** shows forest plots from our updated meta-analysis. The pooled age- and sex-adjusted hazard ratio after inclusion of the 7 new studies published between 2006 and December 2011 and 10 new studies from the Individual Participant Data Meta-Analysis in Working Populations

CI: confidence interval

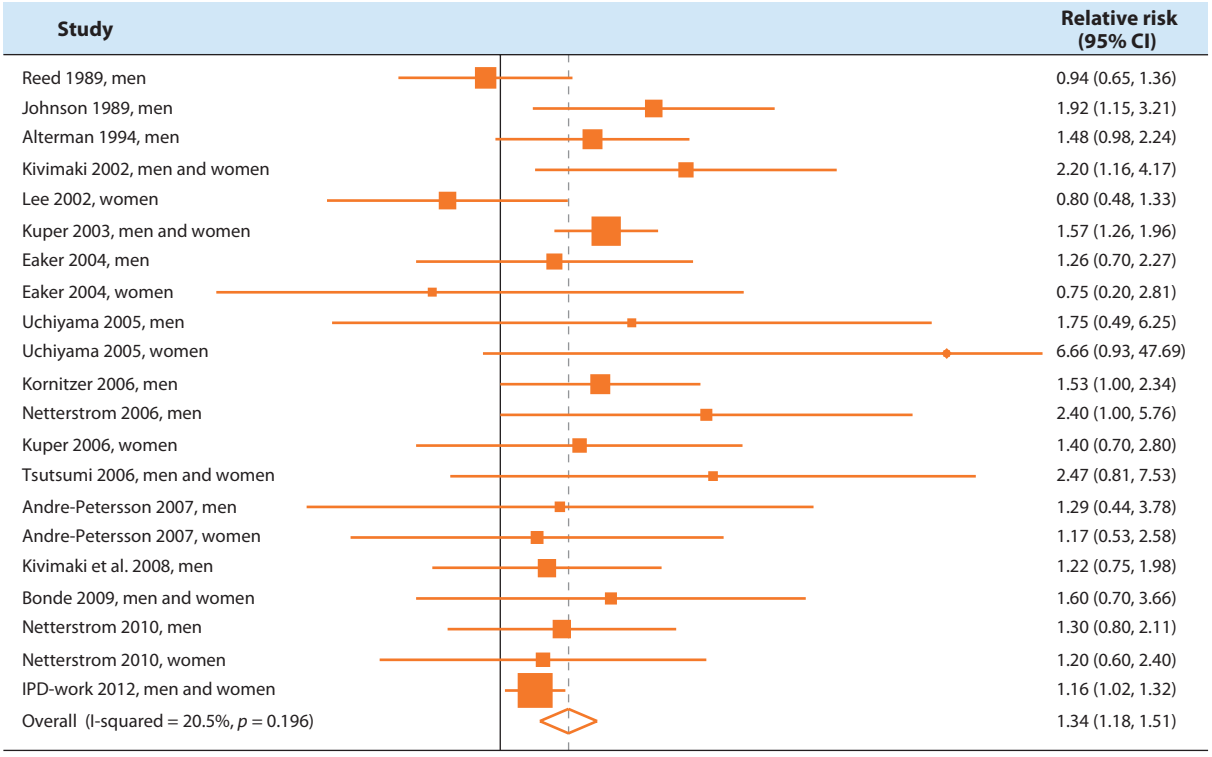

Figure 2

Meta-analysis of prospective studies on job strain: Age- and sex-adjusted relative risk of incident coronary heart disease for job strain versus no job strain by study and its summary estimate [relative risk estimates and confidence intervals (CIs) > 1 favor increased risk]. References to cited studies can be found in the **Supplemental Studies** list online (follow the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org**).

(IPD-Work) Consortium (55) is 1.34 (95% CI 1.2 to 1.5). Working long hours (>55 hours on the average week) is also related to a ~40% excess risk of incident CHD (113). Evidence on the association of workplace stress with stroke is scarce and inconsistent (51).

These findings support the status of stress as a causal risk factor for CHD. However, the evidence is also compatible with a "common soil" hypothesis, which posits that stress and CHD share common pathophysiological, behavioral, or environmental antecedents (56). The studies described here tried to rule out this explanation by adjustments for various coronary risk factors, such as risk behaviors and education, but residual confounding by unmeasured common causes remains a possible explanation in observational research. Furthermore, underlying subclinical CHD might increase the likelihood of participants reporting stress or changing their willingness to take up stressful commitments, introducing reverse causation bias (67). However, our observation in the IPD-Work consortium analysis that the association between job strain and clinical CHD remains the same after excluding events in the first five years after baseline argues against reverse causation (55).

These observations about social isolation and stress at work could form the basis for public health intervention. However, the estimated population attributable risk is relatively modest (<4%) compared with factors such as smoking, physical inactivity, and adiposity (55, 124). Interventions could be warranted by the impact of isolation and work stress on well-being and

other health outcomes, but resources specifically to reduce CHD might be better deployed in promoting healthier behavioral profiles.

Stress Mechanisms: Laboratory Studies and Animal Models

Animal research can document the links between stress and CVD using experimental designs that establish causality in a way that is rarely possible in humans. The program of research by Kaplan and colleagues (49, 50) has shown that social stress in monkeys stimulates accelerated coronary atherogenesis, albeit with complex interactions with gender and social position, and has highlighted mechanisms such as sympathetic nervous system activation and increased abdominal fat deposition. The atherosclerotic process is characterized by inflammation of the arterial vessel walls, promoting endothelial dysfunction and the infiltration of low-density lipoprotein (LDL) particles and immune cells into the intimal layer. Cytokines and other inflammatory proteins help orchestrate these processes (40). At later stages, hemostatic factors are implicated in thrombus formation following plaque disruption through rupture or erosion. Experimental research in humans is limited to studying short-term responses to acute mental stress. Stress leads to transient impairment of endothelial function (30), increases in circulating levels of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (102), platelet activation, and prothrombotic changes in molecules involved in coagulation (46).

The challenge is to prove the clinical significance of acute responses to stress. The magnitude of individuals' responses and poststress recovery back to baseline levels varies widely, and we assume that highly responsive people will be at higher risk for future CVDs. A meta-analysis of longitudinal studies found no association between blood pressure (BP) or heart rate stress reactivity and subsequent CVD events ($r = 0.27$, 95% CI −0.06 to 0.54) but showed a positive relationship between impaired poststress recovery and progression of carotid intima-media thickness (IMT) ($r = 0.14$, 95% CI 0.05 to 0.23) (16). More recently, Hamer et al. (37) showed that cortisol responsivity to acute stress predicts progression of coronary artery calcification independent of other risk factors.

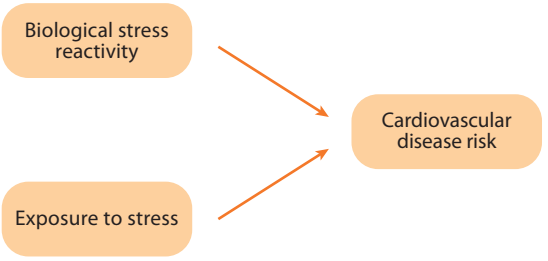

Figure 3

Schematic association between biological stress responsivity, stress exposure in everyday life, and vulnerability to cardiovascular disease.

One reason for the weak relationship between physiological stress responses and future disease is that mental stress testing measures a propensity to high- or low-stress responsivity. This propensity is determined by several factors, including genetic processes, early-life experience, the characteristics of the behavioral challenge, and psychological coping resources (100). But whether it increases CVD risk will depend on exposure in everyday life to the conditions that elicit these responses, and it is the combination of high responsivity and exposure that is likely to be pathogenic (**Figure 3**). Longitudinal investigations that measure both stress responsivity and stress exposure are rare (25) but may identify more robust associations with future CHD.

Population-Level Mechanistic Studies

Understanding of the biological mechanisms linking life stress to CHD at a population level remains an ongoing challenge. Several studies have linked stress to increased levels of

BP: blood pressure

IMT: intima-media thickness

catecholamines and cortisol, i.e., biomarkers of catabolic processes, and lower levels of testosterone, a marker of reduced anabolic processes. As yet, few population-based studies have investigated inflammatory processes or endothelial dysfunction as mediators of associations between stress exposure and CHD. However, the plausible underlying mechanisms for a causal stress-CHD relationship should also involve major coronary risk factors because they explain ~90% of CHD at a population level (125). Below, we therefore review research on structural markers of atherosclerosis and standard biological risk factors as potential stress mediators (71, 103).

Carotid intima-media thickness. Measurement of IMT is feasible in population studies because it can be carried out noninvasively using external ultrasound. In a study of adolescents, trajectory of increasing life stress over approximately three years was accompanied by increases in cardiovascular reactivity to standardized laboratory stressors. Increased cardiovascular reactivity, in turn, was associated with faster progression of IMT, but life stress was not; this finding led the authors to speculate that the effects of chronic stress on IMT may emerge only later in life, after individuals have more time to accumulate atherosclerotic plaque (66). In a subsequent investigation of young adults, job strain was cross-sectionally associated with increased IMT in men but not women (45), but other investigations focusing on middle-aged adults found no consistent association between workplace or perceived stress and carotid IMT in men or in women (90, 124). Thus, the stress-related atherosclerotic effects seen in animal models seem not to be reliably replicated in human data.

The metabolic syndrome. There is promising stress research on the metabolic syndrome, which is commonly defined as having at least three risk factors among central obesity, hypertension, hyperglycemia, elevated triglycerides, and low levels of high-density lipoprotein (HDL) cholesterol, although other definitions are also available (2, 34, 78). Early studies of chronic exposure to stress, operationalized as socioeconomic status (SES), showed lower SES to be associated with increased risk of the metabolic syndrome (9); this finding has been replicated in a variety of different populations (65, 69, 82, 87) with the temporal order between exposure and outcome confirmed by cross-lagged analyses (22). Analyses of other stressors, such as loneliness (118), marital stress (in women but not men) (119), and workplace stress (14), have also found a longitudinal association with the onset of the metabolic syndrome, even after controlling for SES. These findings have motivated studies to test statistically the extent to which the metabolic syndrome is likely to explain the stress-CHD association at a population level. In the British Whitehall II study, a greater number of times participants reported stress over time was associated with a greater risk of the metabolic syndrome at the end of follow-up (14), which explained ~16% of the effect of stress on CHD (13). Efforts to modify stress processes to reduce the CVD risk associated with intermediate phenotypes, such as the metabolic syndrome, may well prove fruitful.

Obesity, dyslipidemia, and hyperglycemia. In the Whitehall II study, chronic stress and psychological distress were also associated with the components of metabolic syndrome, such as higher waist (central obesity), high body mass index (general obesity), and dyslipidemia, indicated by higher triglycerides and lower HDL cholesterol (13, 53). Two recent meta-analyses, one based on published studies (115) and the other on published and unpublished individual-level data (80), confirmed an association between stress and obesity. The latter meta-analysis revealed that stress may also be associated with underweight, suggesting that stress may be related to weight gain in some individuals but weight loss in others. Because all the observed associations were relatively weak, weight change alone seems to account for only a modest part of the excess CHD risk among stressed individuals.

Dyslipidemia is a major risk factor for CHD and is an important target for preventive treatments by drug therapy. Despite some studies linking stress to dyslipidemia (39), statistical tests based on multivariable adjustments indicate that total LDL and HDL cholesterol and triglycerides explain little of the association between stress and CHD (13, 54). Although stress is not currently considered to be a major risk factor for adult-onset diabetes (97, 107), some evidence does relate diabetes onset with depression (74).

HYPERTENSION

Transient elevations in BP occur as part of the acute response to stress. The hypothesis that exposure to extended periods of stress may contribute to the development of persistent hypertension seems therefore plausible (98). A greater number of occasions on which the participant was lonely in childhood, adolescence, and early adulthood was associated with a greater number of adult coronary risk factors, such as high BP, obesity, dyslipidemia, and high glycated hemoglobin concentration in the Dunedin, New Zealand, cohort study (12). In middle-aged and older adults, the association between loneliness and BP follows a dose-response pattern (42, 94) and strengthens with age (41).

Despite these promising findings, epidemiologic evidence from various other stressors provides limited support for a conversion of temporary BP elevations to chronic high BP in relation to long-term stress (18, 48, 52, 110) or for the idea that this mechanism would mediate between stress and CHD. Whereas in the U.S. Nurses' Health Study, retrospective reports of childhood abuse were associated with self-reported hypertension (88), findings from the Whitehall II study provide little support for hypertension as the link between stress and CHD (52).

Mechanistic Studies

Mechanistic studies provide somewhat more compelling evidence for a role of stress in hypertension than do population studies of stress exposure. Four types of investigation are relevant. First are studies demonstrating that hypertension is characterized by heightened sympathetic nervous system activity in many cases. Individuals with mildly elevated BP commonly show enhanced cardiac sympathetic activity (33), whereas increased norepinephrine spillover into blood draining from the brain, heart, and other tissues is observed in hypertension (23). In a randomized controlled trial, Esler et al. (24) demonstrated that renal sympathetic denervation in patients with treatment-resistant hypertension led to substantial drops in BP. Stress plausibly contributes to these signs of raised sympathetic nervous activity.

Second, accumulating evidence indicates that BP measured either at home or using ambulatory techniques is more strongly predictive of CVD outcomes than is standard office or clinic BP (17, 114). These findings may be due in part to the greater number of BP readings obtained, leading to more reliable estimates of true BP. But part of the explanation may be that BP recorded under real-life conditions is influenced by daily stress and other factors that are masked during office assessments.

Third, animal models have established that psychological stress can induce hypertension. The early evidence from Henry's group emphasized that hypertension following social stress in mice was associated with increased norepinephrine turnover (43). Other animal models of stress have explored the role of inflammatory responses (70) and renal mechanisms (44). Finally, a substantial literature has described physiological responses to acute mental stress in relation to hypertension. People with hypertension or borderline elevated BP show enhanced cardiovascular responses to stress, particularly when exposed to challenges eliciting active coping responses with uncertain outcomes (28). Longitudinal studies testing the prognostic significance of heightened BP and heart rate stress reactivity have shown positive but limited associations with incident hypertension and increased clinic BP (16). However, other components of the stress response such as

inflammatory or cortisol reactions may be significant for future hypertension but correlate only moderately with BP reactivity (10, 38).

The reason why evidence from mechanistic studies of hypertension more strongly supports stress than do population studies is not clear. It may reflect the heterogeneity of the condition and the possibility that stress contributes to subtypes of pathophysiology that are difficult to identify at the population level. Alternatively, population studies seldom account for both stress exposure and individual differences in physiological stress responsivity (**Figure 3**), which may limit their ability to demonstrate stress-related effects. Until these discrepancies are resolved, it is difficult to recommend specific public health strategies to mitigate the effects of stress on hypertension.

ACUTE CARDIAC EVENTS

Acute cardiac events typically occur in people with advanced coronary atherosclerosis. The most common pathology is coronary plaque rupture accompanied by thrombosis, when the fibrous cap of the plaque is mechanically disrupted (3). Pathological and intravascular ultrasound studies have shown that plaque rupture and thrombosis formation are relatively common occurrences that often do not lead to acute cardiac events (15). Cardiac events are most likely to occur in people who have a high atherosclerotic plaque burden and when plaque disruption is accompanied by inflammation and procoagulant blood, specifically platelet aggregation and other markers of hypercoagulability (77). Acute triggers, stimuli that provoke these physiological and pathophysiological processes in the hours preceding the coronary event, may contribute to this process. The best established acute trigger is physical exertion (19), though other factors such as air pollution and upper respiratory infection also contribute (79).

Acute emotional stress can also act as a trigger. There are obvious difficulties in studying emotional triggers in victims of sudden cardiac death, but investigations of survivors of ACS are also challenging. Problems include retrospective and memory biases in recollecting and evaluating experiences in the hours before the acute event and ignoring the base rate of exposure. Case-crossover methods are now commonly used to analyze emotional triggering (68). These involve comparisons between a hazard period before symptom onset and a control period in the same individual, thereby accounting for base rate issues and individual differences between cases and controls.

Figure 4 summarizes a meta-analysis of 5 studies that used the comparable time period 24 h before the hazard period as the control. The pooled relative risk of ACS symptom onset being preceded by a period of anger, stress, or depressed mood was 2.48 (95% CI 1.75–3.51). Studies that employed more distant control periods show similar but more varied effects, possibly because it is more difficult for patients to recollect their emotions reliably over an extended period (75). The findings are remarkably consistent, despite variation in the nature and intensity of the emotional states assessed, though it is possible that very intense distress has stronger effects. Mostofsky et al. (76) reported that the incidence of acute MI increased 21-fold in the 24 h following the death of a significant person, whereas a large cohort study in Sweden found that the relative risk of death due to CVD was 5.6 (95% C.I. 5.2 to 5.9) in people within one week of a diagnosis of cancer (26). There may be interplay between the intensity of the trigger and the severity of the underlying cardiac disease substrate (61). An analysis of population attributable risk estimated that emotional stress had a role in 3.9% of acute cardiac events (79). The use of case-crossover methods for stroke has been limited, but one study reported an odds ratio as high as 14.0 (95% CI 4.4–89.7) for negative emotion in the two hours before stroke onset (58).

Triggering has also been investigated in the context of population-level stressors. Several studies have focused on earthquakes, with elevated levels of sudden cardiac death or acute MI immediately following some, though not all, earthquakes (101). Differences may be due to the times of year and day on which quakes

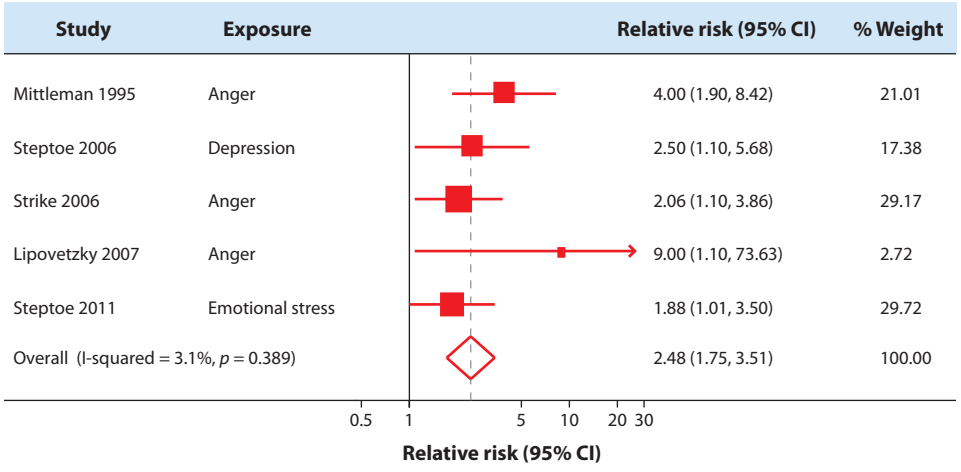

Figure 4

Meta-analysis of case-crossover studies of emotional stress as an acute trigger of acute coronary syndrome: age- and sex-adjusted relative risk of acute coronary syndrome for anger, depressive mood, or emotional stress versus absence of these states, by study and as a summary estimate [relative risk estimates and confidence intervals (CIs) >1 favor increased risk]. The meta-analysis is limited to studies that compared the hazard period with the same time period 24 h earlier. References to cited studies can be found in the **Supplemental Studies** list online (follow the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org**).

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occurred; events early in the morning on cold winter days were particularly dangerous (8). Studies have also been carried out during major sporting events such as international soccer games and the Super Bowl; evidence shows elevated rates of cardiac events in the cities or regions of the teams involved, particularly when their team lost (57, 120). Results of these sporting event studies have been inconsistent (109), and it is not clear that effects can be attributed to stress. Other factors such as heat and excessive alcohol consumption may play a part, and it is seldom known whether the people who suffered cardiac events had been watching the matches.

The implications of emotional triggering for public health have yet to be explored in detail. It is clearly impractical to advise patients with established CHD to avoid all intense negative emotions, and natural disasters are difficult to predict. But Tofler & Muller (108) have suggested that efforts to increase awareness of triggers among health care workers and the general public would be beneficial and that locations that host major sporting events should ensure that emergency health staff are familiar with these issues. However, such methods have yet to be systematically evaluated.

Stress-Induced Myocardial Ischemia

Insight into the mechanisms underlying acute triggering may come from studies of stress-induced transient myocardial ischemia (106). Myocardial imaging techniques such as radionuclide ventriculography demonstrate that mental stress stimulates transient reversible ischemia indexed by ventricular wall motion abnormalities, whereas coronary artery vasoconstriction during mental stress has been observed using angiography (123). These responses are rare in healthy individuals and are typically secondary to advanced coronary artery disease. Ambulatory studies indicate that episodes of myocardial ischemia in everyday life are associated with anger, stress, and other emotions (35). Prospective associations between transient ischemia during mental stress and cardiovascular morbidity and mortality

ICD: implantable cardioverter defibrillator

have also been described, independent of clinical cardiac disease severity (5, 96). A study of patients who survived a stress-triggered ACS found that these individuals responded to acute experimental stress with heightened platelet activation compared with nontrigger patients, confirming the importance of coagulation pathways in this pathology (105). Together, these mechanistic observations suggest that hemodynamic, hemostatic, and inflammatory processes underlie acute triggering by stress.

Stress and Cardiac Arrhythmia

A substantial proportion of sudden cardiac deaths are due to arrhythmias, particularly ventricular tachycardia and ventricular fibrillation. Coronary atherosclerosis is an important determinant of ventricular arrhythmia because decreased myocardial perfusion promotes ventricular instability, though heightened sympathetic nervous system activity also contributes. Implantable cardioverter defibrillators (ICDs) are commonly used to manage ventricular arrhythmia, and the stored electrocardiograms from these devices can be used to investigate associations of arrhythmia with psychological stress. For example, Lampert et al. (59) showed in a case-crossover study that some 15% of ventricular arrhythmias leading to ICD discharge were preceded by heightened anger, compared with 3% of control periods. Indicators of repolarization such as T wave alternans can be stimulated by acute negative events and predict future ventricular arrhythmia (60). Exposure to stress in real life also activates this mechanism: A study of patients in the New York area with ICDs showed that tachyarrhythmias increased significantly in the 30 days following the 9/11 attacks, compared with control months (99).

Stress Cardiomyopathy

Although acute cardiac events are usually a product of advanced coronary atherosclerosis, a new syndrome of transient left ventricular systolic dysfunction and heart failure has been described over recent years (121). Variously called transient left ventricular apical ballooning syndrome and takotsubo cardiomyopathy, stress cardiomyopathy is characterized by chest pain and shortness of breath, moderately elevated cardiac enzymes, and electrocardiographic abnormalities, including ST segment elevation in many cases (122). These are also typical of acute MI, so recognizing the syndrome has been difficult. However, it has distinct features; the cardiac dysfunction is short term and reversible and occurs in people with little or no structural coronary artery disease. The large majority of cases are women, and stress cardiomyopathy is thought to account for ~2% of suspected ACS.

The other striking feature of this syndrome is that it is frequently preceded by acute emotional or physical stress. For example, one series of 136 consecutive cases identified intense emotional stress in 47% of cases and physical stress (including comorbid illness) in 42% (95), whereas a study of 324 cases in Germany reported emotional stress in 47% of female and 28% of male patients (92). Elevated catecholamines stimulated by stress (e.g., high norepinephrine levels) have been postulated as a cause of this cardiomyopathy, and many of the cardiac features of the syndrome can be mimicked by intravenous catecholamines or beta-receptor agonists; however, other mechanisms may also be involved (121).

STRESS AND PROGNOSIS FOLLOWING MYOCARDIAL INFARCTION

Psychosocial research on patients who have survived an MI or other ACS has been dominated by investigations of depression. Clinical depression is present in ~1 in 5 patients in the weeks following acute MI, and a further 25% report significant depressive symptoms. Depression following MI is an adverse prognostic indicator, being associated with increased all-cause and cardiac mortality and with recurrent nonfatal cardiac events (73). The impact of stress on the development of depression

after MI has not been studied extensively. One study of 314 MI patients found that stressful life events over the 12 months before MI was not associated with post-MI depression (20), whereas another showed that acute stress during the 2-hour trigger period before cardiac symptom onset predicted greater depression 1-12 months later, particularly among patients of lower socioeconomic status (104).

Stress may also be a prognostic indicator in its own right. In the 1970s, a measure combining work, family, and life event stress predicted increased three-year mortality in the Beta-Blocker Heart Attack Trial, and the effect was accentuated when coupled with social isolation (91). Limited evidence indicates that persistent work stress predicts recurrent cardiac events following MI in younger patients (1), and Georgiades et al. (29) have described associations between financial strain and recurrent events. The largest study to date assessed perceived stress in more than 4,000 MI survivors. Thirteen percent of patients who reported moderate or high stress died over the next two years compared with 9% of patients with low stress, an effect that was independent of clinical factors, revascularization, sociodemographic variables, and depression (4). There is a pressing need for further systematic data on the impact of ongoing stress on prognosis in patients with advanced CHD.

STRESS AND THE MANAGEMENT OF CVD

The role of psychosocial interventions in CVD management is not the primary focus of this review. Research in this field has been dominated over the past decade by studies of depression management. However, the failure of depression-management trials based on cognitive-behavior therapy (6) and pharmacotherapy (31, 112) to document beneficial effects on cardiac outcomes has led to questioning of the nature of depression in patients with CHD (85). Stress management has also been applied both to improve emotional adaptation and to positively impact physical health. Reviews of this literature have come to divergent conclusions about the benefits of psychological interventions, with little consistent evidence of effects on cardiovascular outcomes (64, 117). A new generation of stress-management interventions both for CHD in general (36) and for specific issues such as ICD discharge (21) are emerging, which may allow investigators to draw more definitive conclusions.

CONCLUSIONS

The study of stress and CVD requires the integration of epidemiological research with focused clinical and experimental mechanistic studies. The predominance of observational designs means that causal conclusions are difficult to draw. Nevertheless, the weight of existing evidence suggests that work stress, social isolation, and loneliness play a role in the long-term etiology of CHD and that effects may be mediated in part by metabolic dysfunction. Evidence for the role of stress in hypertension is stronger in mechanistic than in population-level longitudinal studies, possibly because mechanistic studies focus on the interaction between stress exposure and individual differences in stress responsivity rather than on the stress exposure alone. Acute emotional stress also appears to play a part in triggering some acute MIs and other cardiac events such as tachyarrhythmia and stress cardiomyopathy. There is as yet limited evidence for the role of stress in prognosis following MI.

We have previously recommended that future work needs to involve more extensive pooling of studies to carry out individual participant meta-analysis; that there needs to be more extensive study of the role of psychological stress in other cardiovascular outcomes, such as stroke, apart from CHD; and that natural experiments and designs involving exogenous factors should be used to help test causality more rigorously (103). Additionally, a literature on the protective effect of positive psychological well-being in relation to CVD is emerging that may provide a counterpoint to research on stress (7). The major challenge over the next

decade is to incorporate stress processes into the mainstream of cardiovascular pathophysiological research and understanding.

Interventions to reduce the impact of stress-related processes on CVD have concentrated primarily on patients with advanced cardiac disease, and primary prevention at the public health level has received little attention. The 2012 European Guidelines on CVD prevention in clinical practice recommend that psychosocial factors such as work and family stress, social isolation, depression, and anxiety be assessed by clinical interview or questionnaire (84). Tailored clinical management is recommended for those at high CVD risk, coupled with education about cardiac risk and support for healthy lifestyles such as smoking-cessation programs and exercise training. Recommendations about stress are not included in the American Heart Association (AHA) guidelines for primary prevention of CHD (83) or in the AHA/American Stroke Association guidelines for the primary prevention of stroke (32).

Finally, direct evidence of the benefits of stress-reduction interventions in terms of cardiovascular health are lacking, but current preventive guidelines emphasize the importance of focusing on the total risk rather than on single risk factors. It is likely that healthy lifestyle changes (eating a balanced diet, taking regular exercise, and quitting smoking) as well as treatment of elevated blood pressure, dyslipidemia, and high glucose levels will largely offset the excess risk associated with stress. These trial-proven interventions are therefore particularly relevant for individuals under stress and, along with stress management, should be routinely recommended.

SUMMARY POINTS

1. In population-based studies, long-term stress has been related to ~1.5-fold excess risk of developing CHD.
2. A causal effect is likely to explain only part of this association; the remainder has been attributed to shared physiological, behavioral, and environmental antecedents.
3. Adverse metabolic change is one of the plausible mediating mechanisms for long-term stress effects.
4. Emotional stress may act acutely to trigger major cardiac events in people with advanced CHD.
5. Investigators have observed an adverse effect of stress on prognosis following MI.
6. Strategies to prevent CVD and manage patients with CHD will be enhanced by the integration of stress into the broader context of cardiovascular pathophysiology.

DISCLOSURE STATEMENT

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