# **REVIEWS**

## Stress and cardiovascular disease

Andrew Steptoe and Mika Kivimäki

Abstract | The physiological reaction to psychological stress, involving the hypothalamic–pituitary—adrenocortical and sympatho–adrenomedullary axes, is well characterized, but its link to cardiovascular disease risk is not well understood. Epidemiological data show that chronic stress predicts the occurrence of coronary heart disease (CHD). Employees who experience work-related stress and individuals who are socially isolated or lonely have an increased risk of a first CHD event. In addition, short-term emotional stress can act as a trigger of cardiac events among individuals with advanced atherosclerosis. A stress-specific coronary syndrome, known as transient left ventricular apical ballooning cardiomyopathy or stress (Takotsubo) cardiomyopathy, also exists. Among patients with CHD, acute psychological stress has been shown to induce transient myocardial ischemia and long-term stress can increase the risk of recurrent CHD events and mortality. Applications of the 'stress concept' (the understanding of stress as a risk factor and the use of stress management) in the clinical settings have been relatively limited, although the importance of stress management is highlighted in European guidelines for cardiovascular disease prevention.

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#### Introduction

Psychological stress is increasingly recognized as an important issue in, and a potentially modifiable risk factor for, cardiovascular disease. Stress is relevant to cardiovascular health at several stages of the disease process; exposure to cardiovascular risk factors (such as the stress-related reduction in physical activity), the long-term development of atherosclerosis and subclinical coronary heart disease (CHD), and the acute triggering of cardiac events in people with advanced CHD. In addition, among patients who have survived an acute coronary syndrome or stroke, stress can impair recovery and affect quality of life in the long term (Figure 1). Stress management is being incorporated into cardiac rehabilitation in many centers, and work-related stress is increasingly regarded as a public-health problem.

The concept of psychological stress has evolved from early studies of 'fight-or-flight responses' by the American physiologist Walter Cannon at the beginning of the 20th century3 to more-nuanced formulations.45 Most investigators now argue that stress responses arise when demands on people exceed their psychosocial resources or adaptive capacity, and that individual differences exist in how well people cope with challenges or losses in their lives. Demands or stressors can take the form of acute life events such as the death of a loved one, long-term challenges such as chronic work-related stress or caring for someone with dementia, and daily minor harassments such as traffic problems while commuting. The psychosocial resources relevant to these stressors include social support and personality traits, such as optimism and the ability to cope flexibly with challenges. Genetic

Epidemiology and Public Health, University College London, 1–19 Torrington Place, London WC1E 6BT, UK (A. Steptoe, M. Kivimäki)

Department of

Correspondence to:
A. Steptoe
a.steptoe@ucl.ac.uk

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factors can also affect an individual's response to stress.<sup>6</sup> Both high levels of demand and poor social and psychological resources are relevant to the impact of stress on cardiovascular health. However, as will become evident, definitively establishing causal links between stress and cardiovascular disease in studies of humans is difficult.

The purpose of this Review is to summarize the evidence for an association between stress and cardio-vascular disease focusing particularly on CHD and, to a lesser extent, stroke. The primary focus is on exposure to external stressors, rather than on psychological and biological factors affecting vulnerability to adversity. The contribution of depression and anxiety to the etiology and prognosis of CHD are separate issues that are not addressed in this Review.

## Physiological stress response

Stress produces a range of physiological changes, only some of which are likely to be relevant to cardiovascular disease. The hypothalamic-pituitary-adrenocortical (HPA) and sympatho-adrenomedullary axes are the primary biological systems activated during the stress response (Figure 2).<sup>7,8</sup> Stress perception activates hypophysiotrophic neurons in the hypothalamus that secrete releasing hormones (for example, corticotropin-releasing hormone and arginine vasopressin) acting on the anterior pituitary to promote the secretion of adrenocorticotropic hormone (ACTH). In turn, ACTH acts on the adrenal cortex to initiate the synthesis and release of glucocorticoid hormones, such as cortisol, promoting the mobilization of stored energy. Stress perception also results in activation of preganglionic sympathetic neurons in the spinal cord, which project to prevertebral or paravertebral ganglia that, in turn, project to end organs, including the

heart, and to the adrenal medulla. Related physiological changes include elevations in epinephrine and norepinephrine levels, an increase in heart rate and peripheral vasoconstriction, vagal (parasympathetic) withdrawal, and increased energy mobilization. Components of the biological response to stress that plausibly contribute to CHD include raised blood pressure, reduced insulin sensitivity, increased hemostasis, and endothelial dysfunction;<sup>7</sup> however, the key pathological mechanisms of long-term stress and acute stress differ, as described below.

## Long-term stress and CHD

Research on long-term stress has identified external stressors that are likely to elicit harmful reactions in a substantial proportion of people. These include work-related factors, such as excessive work demands, and factors in private life, such as marital problems, financial difficulties, caregiver strain, and social isolation. The INTERHEART study is probably the largest study to date in which the relationship between long-term stress (over the previous 12-month period) and CHD has been examined along with other potentially modifiable risk factors. In this study, 15,152 patients with acute myocardial infarction (MI) and 14,820 control individuals free from CHD were enrolled from 52 countries worldwide. Long-term stress was included in a psychosocial composite score, which comprised stress at work and home, financial strain, lack of control, and depression. The INTERHEART investigators found that exposure to long-term stress added to the risk of acute MI even after taking into account combined exposure to conventional risk factors such as smoking, diabetes mellitus, hypertension, apolipoprotein (Apo) B:ApoA1 ratio, and obesity. The odds ratio for MI was more than double (increasing from 69 to 183) among individuals who were exposed to psychosocial adversity in addition to conventional risk factors compared with those free of stress (Figure 3). These findings were robust, as a similar pattern of associations was found in men and women, old and young individuals, and in all continents of the world.9

Given that MI is often preceded by a long subclinical phase of atherosclerosis development, a case-control study such as the INTERHEART study, despite its large size, cannot rule out the possibility that stress perception can be, in fact, a consequence of disease process rather than a cause. More specifically, people with advanced atherosclerosis might experience exhaustion more quickly and to a greater extent than others and, therefore, regard their environments as more stressful than those who are physically fit. Prospective cohort studies, in which the temporal order between long-term stress and CHD can be assessed, could provide a more-valid study design than a case-control approach. The largest amount of prospective evidence published to date relates to stressors in the work place, but a growing number of studies have focused on social isolation and loneliness.

## Stress related to work or social isolation

The most-widely tested conceptual model of workrelated stress is the 2D 'job strain model',10 in which

## **Key points**

- Psychological stress contributes to cardiovascular disease at several stages, including the long-term development of coronary heart disease and acute triggering of cardiac events
- Disturbances of inflammatory, hemostatic, and autonomic processes are likely to be the mechanisms by which short-term psychological stress triggers acute myocardial infarction
- Chronic stress at work and in private life is associated with a 40-50% increase in the occurrence of coronary heart disease in prospective observational studies
- Indicators of elevated long-term stress, such as social isolation and work-related stress, are associated with poor prognosis among patients with established coronary heart disease
- Stress-management interventions improve the quality of life of patients with advanced coronary heart disease, but effects on disease prognosis have been

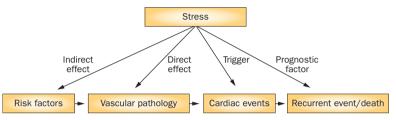
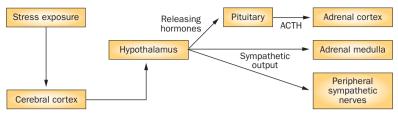


Figure 1 | Stress as a risk factor for cardiovascular disease and mortality.

employees whose work is highly demanding, but over which they have a low level of control, are proposed to be in a 'job strain' situation. If prolonged, this state increases the risk of stress-related diseases, such as CHD. The highest risk of illness is assumed to relate to isolated strain (iso-strain) jobs, which are characterized by high demands, low control, and low social support at work.<sup>10</sup> Other common sources of stress in the work place include an imbalance between effort and reward (in terms of income, respect, and status control),11 and organizational injustice characterized by unfair treatment and management procedures.<sup>12</sup>

Several reviews summarizing the evidence from prospective studies on work-related stress and CHD are available,13-17 but only one, published in 2006,14 provided quantitative estimates made on the basis of a metaanalysis. This study showed that employees exposed to stress in the work place have an average 50% excess risk of CHD compared with those who do not experience this type of stress.14 The age-adjusted and sex-adjusted summary estimate of the relative risk of CHD across 10 individual studies<sup>18-28</sup> on job strain was 1.4 (95% CI 1.2-1.8).14 The summary estimates for studies using other conceptualizations of work-related stress were of similar magnitude; 1.6 (95% CI 0.8-3.0) for imbalance between effort and reward at work, and 1.6 (95% CI 1.2-2.1) for organizational injustice.14 To take into account the latest evidence, we updated our 2006 meta-analysis14 in relation to job strain, including prospective studies published up to December 2011. With the same search strategy as used in the original meta-analysis, seven new studies were identified.<sup>29-35</sup> According to the pooled estimate, job strain was associated with a 1.4-fold (95% CI 1.2-1.6) increased risk of CHD with no significant heterogeneity between studies (I-squared <8%), suggesting



**Figure 2** | The physiological stress response. Stress perception stimulates the hypothalamus to secrete releasing hormones, which act on the anterior pituitary to promote the secretion of ACTH. This hormone then acts on the adrenal cortex to initiate the synthesis and release of glucocorticoid hormones, promoting the mobilization of stored energy. In addition, stress perception activates preganglionic sympathetic neurons in the spinal cord, which project to prevertebral or paravertebral ganglia that, in turn, project to end organs, including the heart, and to the adrenal medulla. Abbreviation: ACTH, adrenocorticotropic hormone.

that the effect size was not affected by the inclusion of new data (A. Steptoe & M. Kivimäki, unpublished work). Notably, in these studies, job strain in relation to CHD was investigated in both men and women.<sup>29–35</sup>

Other than meta-analysis, another way of summarizing evidence is to apply quality filters to the data. That is, instead of extracting summary estimates across all studies, only the best papers are selected to improve the estimation of effect size. In a systematic review published in 2009, Eller et al. assessed the quality of articles on work-related stress and ischemic heart disease published up to 2008. 17 Each study was rated in terms of the validity of exposure and outcome assessment, how well the working population was represented, coverage of full age range, sufficient follow-up period, sex-specific analysis, and adjustment for potential confounding factors. Of the 33 prospective and case-control studies identified, only four received the maximum, or almost maximum, quality scores and three of these high-quality studies reported an estimate for the association between job strain and CHD.17 To facilitate interpretation, we conducted a meta-analysis of these three studies; the age-adjusted and sex-adjusted summary estimate for relative risk between job strain and no job strain was 1.3 (A. Steptoe & M. Kivimäki, unpublished work). Thus, the evidence from these high-quality studies is consistent with the conclusions that we have drawn from the updated meta-analysis and suggests a moderate association between job strain and CHD.

In addition to long-term work-related stressors, data from prospective studies have shown associations between sources of stress not related to work—such as marital problems,<sup>36</sup> widowhood,<sup>37</sup> death of a child,<sup>38</sup> and caring for a sick spouse at home<sup>39</sup>—and increased risk of CHD. Social isolation and loneliness have been highlighted as increasingly common sources of chronic stress. For example, over the past 2 decades, a threefold increase in the number of US citizens who report having no confidant has been reported.<sup>40</sup> In the UK, according to a 2010 survey by the Mental Health Foundation, one in ten people often feels lonely, one-third have a close friend or relative whom they think is very lonely, and half of those surveyed thought that people are getting lonelier in general.<sup>41</sup>

We are not aware of any published meta-analyses on social isolation in relation to the incidence of CHD; however, analyses of the association between social isolation and disease prognosis among individuals with CHD or other chronic conditions have been published. 42 To quantify the excess risk of incident CHD associated with social isolation and loneliness, we performed a systematic literature review and meta-analysis of prospective cohort studies published up to December 2011 in CHD-free populations. 43-48 The pooled relative risk of CHD related to social isolation and loneliness across the nine studies identified was 1.51, an excess risk of broadly similar magnitude as that for work-related stress (A. Steptoe & M. Kivimäki, unpublished work). Although we did not find any clear evidence of publication bias, we cannot rule out the possibility that such bias existed because the studies were observational and publication bias is more common for observational data than for clinical trials. Our meta-analyses might, therefore, overestimate rather than underestimate the effects of work-related stress and social isolation on CHD risk. To evaluate this issue further, analyses pooling data from individual participants in published and unpublished studies are needed in the future.

## Evidence of a dose-response pattern

In epidemiological studies, demonstrating a doseresponse relationship strengthens the argument for cause and effect. In the British Whitehall II study, 49 repeated measurements have been performed to examine the importance of the duration of the exposure to stress for CHD risk.50-52 A dose-response relationship was found between exposure to work-related stress over a 14-year period and risk of the metabolic syndrome at the end of the follow-up. The odds ratios for developing the metabolic syndrome were 1.1 (95% CI 0.6–2.0), 1.5 (95% CI 0.7-2.9), and 2.3 (95% CI 1.3-3.8) times higher for employees who were exposed to work-related stress once, twice, and either three or four times, compared with those who were not exposed to work-related stress. Among participants aged ≤50 years, long-term work-related stress was also associated with a 1.7-fold (95% CI 1.2-2.4) increased risk of CHD compared with no exposure to stress. In the group of participants aged >50 years, however, no such association was observed (relative risk 1.1, 95% CI 0.7-1.8 with the highest level of work-related stress).<sup>52</sup> This finding could possibly be the result of exposure misclassification owing to retirement and the fact that, in general, relative risks associated with cardiovascular risk factors tend to decrease in elderly populations.9 Therefore, some evidence exists of a dose-response relationship between duration of workrelated stress and the incidence of CHD in younger (aged ≤50 years) employees. We are not aware of any studies in which CHD risk has been evaluated as a function of the length of the exposure to social isolation and loneliness.

## **Underlying mechanisms**

Testing causality involves the investigation of plausible mechanisms through which long-term stress might

impact CHD risk. In the Whitehall II study,<sup>52</sup> longer duration of work-related stress was associated with a greater morning rise in cortisol level and reduced heartrate variability, suggesting a direct effect of stress on the autonomic nervous system and neuroendocrine function. In the CARDIA study,<sup>53</sup> work-related stress was associated with an increase in the incidence of hypertension, a finding not replicated in the Whitehall II study.<sup>52</sup> Social isolation has also been suggested to disrupt autonomic regulation of the heart,<sup>54</sup> and is associated with elevated levels of molecular stress markers, such as cortisol and epinephrine, 55,56 although the evidence is not entirely consistent.<sup>57</sup> Long-term stress has also been linked to increased risk of depressive disorders<sup>58-62</sup> (a risk and prognostic factor for CHD),63 the metabolic syndrome,51 and reduced telomere length<sup>64</sup> (a marker of cellular ageing and a risk factor for CHD).<sup>65</sup> The evidence linking stress and the development of atherosclerosis is mixed.<sup>66–72</sup> A link between problems in social relationships and reduced immune functioning and immune-mediated inflammatory processes has been indicated in a number of studies. 73,74 Both of these outcomes contribute to CHD risk.75 A weak, bidirectional association might also exist between long-term stress and weight change, such that stress causes some individuals to gain and others to lose weight.76-78 Weight gain is a risk factor for CHD, but whether the impact of stress is mediated through weight changes is not known.

Stress can also influence CHD risk indirectly by increasing health-risk behaviors. For example, in the Finnish Public Sector study<sup>79</sup> of over 50,000 participants (one of the largest cohort studies in the field), smokers who reported work-related stress were 50% more likely to smoke over 20 cigarettes per day than those who did not experience work-related stress. In the Copenhagen City Heart Study, 80 individuals with high compared with low levels of stress were less likely to quit smoking, more likely to become physically inactive, and less likely to stop drinking alcohol above the sensible limits. Studies of long working hours show that continuously working ≥11 h per day is associated with shortened sleep duration and increased sleep disturbance,81 both of which can increase the risk of CHD, especially if combined.<sup>82,83</sup> In addition, loneliness has been linked to increased likelihood of smoking and physical inactivity.84,85

In combination, these findings suggest both direct and indirect mechanisms for the relationship between stress and CHD. Further insight might be gained from studies of biological responses to acute mental stress, in which greater cardiovascular and HPA axis responses have been associated prospectively with underlying CHD and disease progression<sup>86,87</sup> and with clinical cardiac events.88,89

## Noncausal explanations

In observational studies, such as those reviewed above, confounding by imprecise measurement of factors in statistical models, or unmeasured additional factors, is an alternative explanation for observed associations between exposure and outcome. CHD can take decades

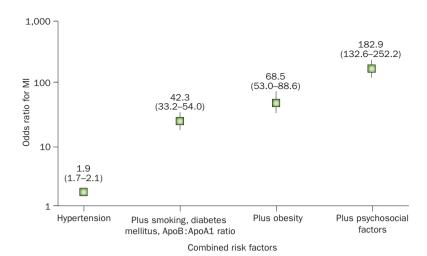


Figure 3 | Risk of acute MI associated with exposure to multiple risk factors among 29,972 individuals across 52 countries in the INTERHEART study.9 The 95% CIs are shown in brackets. Abbreviations: Apo, apolipoprotein; MI, myocardial infarction.

to develop and is associated with a wide variety of risk factors in childhood and adulthood. The possibility of confounding arises when these risk factors additionally predict long-term stress.

One potential confounder is socioeconomic disadvantage because, in many cohorts, experience of such adversity is more common among individuals with stress than in those who do not report stress.<sup>49</sup> The excess risk of CHD observed among people with stress could, therefore, in principle, be the result of factors associated with socioeconomic adversity, marking increased exposure to infectious agents and passive smoking, poor diet, and few opportunities for physical activity and high-quality health care, in addition to stress. Results from a Scottish study support this possibility.90 Psychological stress was, by contrast to most other studies, associated with socioeconomic advantage rather than socioeconomic disadvantage. Surprisingly, psychological stress was associated with lower rather than higher cardiovascular mortality, leading the investigators to conclude that socioeconomic circumstances might confound the association between psychological stress and CHD.90 However, an unusual measure of stress (the Reeder stress inventory, which is a measure of stressful feelings rather than stress exposure and can be confounded by neuroticism) was used in this study and the findings have not been replicated.

Social isolation and loneliness also mark a range of coronary risk factors other than those directly related to stress, raising the possibility of residual confounding. A twin study, published in 2010, found that loneliness is moderately heritable.91 Confounding would occur if the genetic predisposition associated with loneliness is also associated with increased CHD risk. Evidence to support this possibility is currently not available. Only data from randomized controlled trials can rule out bias from confounding, but no trials of long-term stress or loneliness and CHD risk are currently in progress. In addition, such trials could be argued to be impractical, unfeasible, and unethical.

#### Box 1 | Difficulties in studying emotional triggers of cardiac events

- Survival effects: information is typically collected retrospectively, and effects can be different for fatal and nonfatal cardiac events
- Memory problems: patients might not accurately recall the circumstances surrounding the onset of symptoms
- Timing difficulties: the exact moment of the onset of symptoms, such as severe
  chest pain, leading up to acute cardiac events might be difficult to define
- Retrospective biases: patients try to make sense of what has happened to them, so might retrospectively magnify the stress that they were under before the event
- Base rates: the fact that a patient experienced intense emotion immediately before a cardiac event needs to be assessed in the context of how frequent such emotions are for that individual

## Clinical relevance

The relevance of long-term stress in evaluating a patient's absolute risk of developing CHD (that is, in risk prediction) is unclear. In determining CHD risk, the focus must be on the 'total risk' because the presence of a single, high-level risk factor might be associated with lower overall risk than several slightly elevated risk factors in combination. To evaluate the overall risk, clinicians examine standard risk factors, such as age, sex, adverse lipid profiles, high blood pressure, diabetes, and smoking habits, and summarize these measurements by using mathematical equations, such as the Framingham risk score. 92 Data published in 2011 suggest that information on work-related stress, assessed by a questionnaire on long working hours, might slightly improve prediction of CHD made on the basis of the Framingham risk score.93 Corresponding analyses of social isolation and loneliness are not available.

Current European guidelines on cardiovascular disease prevention recommend assessment of long-term stress, including work-related stressors and social isolation, by clinical interview or standardized questionnaires. The guidelines suggest that patients who experience stress or are at high risk owing to other factors, and those who have established cardiovascular disease should receive individual or group counseling for coping with stress and illness. In the case of clinically relevant emotional distress, referral to a specialist is needed. Corresponding recommendations are not included in prevention guidelines by the AHA or the ACC. 95

## Acute stress triggers cardiac events

Triggers are defined as activities or stimuli that exacerbate the acute physiological and pathophysiological processes that initiate cardiac events such as acute MI or sudden cardiac death. <sup>96–98</sup> Triggers include physical exertion, exposure to air pollution, and respiratory infection. <sup>99,100</sup> The notion that psychological stress could trigger acute MI was first studied systematically after a major earthquake in Athens in 1981, when an excess of cardiac deaths was found over the following 3 days. <sup>101</sup> Over the past 30 years, an increase in rates of MI and sudden cardiac death has been reported after other earthquakes. Some inconsistencies in the data exist, which could be related to variations in the season of the

year or the time of day at which the disasters occurred. Earthquakes that occur early in the day over the cold winter months are more likely to be associated with risk of cardiac events. 102-104 Other disasters have also been investigated, including major industrial accidents, 105 wars, and terrorist attacks 106,107 and have been related to an increase in rates of acute MI or sudden cardiac death. Related literature exists concerning the impact of major sports matches on cardiovascular events in spectators. 108, 109 Witte et al. showed that the risk of death from MI or stroke was increased (relative risk 1.51, 95% CI 1.08–2.09) among Dutch men aged ≥45 years on the day on which the Dutch soccer team lost to the French under dramatic circumstances in the 1996 European Cup. 110 No equivalent increase was seen for women. A subsequent evaluation of cardiac emergencies in the Munich region of Germany during the 2006 soccer World Cup identified peaks on days on which the German team played (2.66-fold higher than during the control period; 95% CI 2.33-3.04, P < 0.001), particularly in the 2 h after the start of matches.111

These studies show associations between acute cardio-vascular events and emotionally important public events. However, we cannot be completely certain that psychological stress is the trigger, since the circumstances surrounding each case are difficult to reconstruct in the turmoil surrounding such occasions. Other factors such as physical exertion, heat, excessive alcohol consumption, or exposure to pollutants might also contribute. Additionally, most acute cardiovascular events do not take place in response to major events affecting entire populations, but to individuals under more personal circumstances.

To study emotional triggers in individual patients, a number of methodological difficulties must be overcome (Box 1). Stress is often mentioned when survivors of acute cardiac events are interviewed in hospital and asked about what they think caused their cardiac event,113 but these reports might not be reliable. This field of research took a major step forward in the mid 1990s with the application of case-crossover methodology by Mittleman et al. in the MI Onset Study. 114 These investigators compared the 'hazard period' (for example, the 2 h before the onset of cardiac symptoms) with comparable control periods for the same individual. The casecrossover method eliminates many confounding factors, since the hazard and control period are both assessed in the same person, and also takes the base rate of stress exposure into account. Mittleman et al. established that patients were at increased risk of acute MI in the 2 h after an episode of intense anger,114 a pattern that has been replicated by other researchers.115-117

This methodology has also be used to demonstrate that short-term work-related stress, acute sadness, and the acute effects of bereavement act as triggers of cardiac events, 118-121 Interestingly, the impact of acute emotional stress has been shown to be more pronounced among people of lower socioeconomic status, 114,117 suggesting a socioeconomic gradient in vulnerability to acute, as well as chronic, stress.

## Biological processes in acute triggering

Progress has been made in understanding the biological processes underlying stress-related triggering of cardiovascular events. Triggering takes place against a background of advanced atherosclerosis, so is rare in people with little underlying CHD. In this respect, emotional triggering of MI and stroke is different from Takotsubo or stress cardiomyopathy, 7,122,123 a stress-specific syndrome identified some 20 years ago (Box 2 and Figure 4). No evidence exists that psychological stress directly stimulates coronary or carotid artery plaque disruption through rupture or erosion. However, plaque disruption has adverse consequences when it is associated with acute inflammation, procoagulant responses such as platelet activation, and hemodynamic stress. 124 Cardiac imaging studies have revealed that a substantial proportion of patients with advanced CAD show transient myocardial ischemia in response to acute mental stress. 125,126 Some patients manifest coronary artery vasoconstriction during stress, particularly in regions of marked stenosis.127 Cardiac rhythm can also be disturbed;128 for example, a study of patients in the New York area of the USA with implanted cardioverter-defibrillators showed a marked increase in tachyarrhythmias in the month after the attacks on the World Trade Center on 11 September 2001. 129

Whether patients who have actually experienced emotional triggering of acute cardiac events have a particular susceptibility to psychological stress has not been widely studied. However, one comparison of survivors of acute coronary syndromes who did or did not report emotional triggers in the 2 h before symptom onset showed that the trigger group produced markedly greater increases in platelet activation and aggregation after experimental mental stress, as well as with slowed recovery of blood pressure responses after stress (Figure 5). 130 If these inflammatory, hemostatic, and autonomic responses coincide with plaque rupture, the result could be the development of severe coronary occlusion.

## Clinical relevance

The clinical relevance of triggering processes for patient care has still to be established. Whether cardiac medications are protective against triggering is not clear, although some evidence exists that aspirin is associated with reduced risk of triggering by emotional stress.98 Ensuring that patients with CHD avoid all intense emotions is not feasible and natural disasters, by their very nature, are difficult to predict. Tofler and Muller have argued that programs to increase awareness of triggers among clinicians and the public would be beneficial, along with ensuring that emergency equipment is readily available.<sup>131</sup> Importantly, although the relative risk associated with acute emotional stress is substantial, the absolute risk is not large. An attempt to quantify the public-health impact of triggers of MI has been made by Nawrot and colleagues. 132 They concluded that the relative risk of MI associated with negative emotions is high, but that the population-attributable risk (which takes account of the prevalence of the risk factor across

#### Box 2 | Stress cardiomyopathy

- Also known as Takotsubo cardiomyopathy or transient left ventricular apical ballooning cardiomyopathy7
- Patients typically present with chest pain, electrocardiographic abnormalities, and elevated levels of cardiac enzymes; the syndrome is, therefore, often confused with acute MI122
- Patients with stress cardiomyopathy do not have obstructive coronary heart disease and, in many cases, the coronary arteries are normal
- Unlike acute MI, myocardial dysfunction in stress cardiomyopathy is reversible
- Stress cardiomyopathy is thought to account for some 2% of suspected acute coronary syndrome admissions, and is much more common in women than men<sup>122</sup>
- Acute triggering by emotional stress or by physical stimuli is observed in the majority of cases
- Pathology can be related to increased catecholamine levels, although other physiological dysfunctions have also been reported

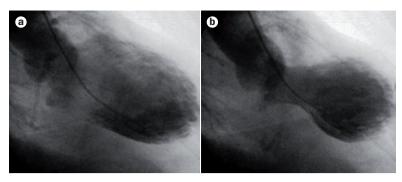
Abbreviation: MI, myocardial infarction.

the population) is smaller, with emotional stress having a role in only 3.9% of events. By comparison, 7.4% of events were related to exposure to heavy traffic, 6.2% to physical exertion, and 5.0% to heavy alcohol consumption. 131

## Stress and the prognosis of CHD

Relatively little research has been carried out into the role of stress in the prognosis of people with established CHD. Studies of the psychological predictors of recurrent cardiac events and mortality after acute coronary syndromes have been dominated by research into depression<sup>133</sup> and, to a lesser extent, social support. <sup>134</sup> However, in the Beta-Blocker Heart Attack Trial carried out in the late 1970s a composite measure of stress from work, family difficulties, and negative life events was used. The investigators found that a high level of stress, particularly when combined with social isolation, predicted a doubling of mortality risk over the 3-year period after an acute MI.135 Another early study of men who had survived an MI before the age of 45 years found that mortality over the subsequent 5-year period was greater in those who had returned to working in jobs characterized by high demands and limited opportunities to learn new things. 136

The impact of work-related stress on recurrent cardiac events has been investigated in a population of predominantly male patients from Quebec, Canada who experienced a first MI when aged <60 years and returned to work. One analysis found that high job strain, defined by high demands and low control, reported at both 6 weeks and 2 years (but not just once) after returning to work was associated with recurrent CHD.<sup>137</sup> A later analysis indicated that a high level of imbalance between effort and reward measured 2 years after returning to work predicted recurrent cardiac events, particularly in the small subgroup of female patients. 138 The effect of job strain during the 5 years before an index cardiac event was evaluated over 8.5 years of follow-up in survivors of acute MI from the Stockholm Heart Epidemiology Program. 139 High job strain predicted the combined outcome of cardiac death and nonfatal MI, with a hazard ratio of 1.7 (95% CI 1.1–2.8) relative to those with low job strain.



**Figure 4** | Left ventriculography of a patient with stress cardiomyopathy.  $\bf a$  | During diastole.  $\bf b$  | During systole. Note the typical apical ballooning pattern during systole with apical and mid-ventricular akinesis and normal contractility at the base. Image courtesy of I. S. Wittstein, MD; Johns Hopkins University School of Medicine, Baltimore, MD, USA.

A study of 202 female survivors of acute cardiac events showed that financial strain (difficulty in paying bills) was associated with fatal or nonfatal recurrent events independent of age, education, income, marital status, initial diagnosis, and stress management. Although these findings suggest that stress might have an impact on prognosis in a similar fashion to that described earlier for long-term etiology, insufficient evidence exists to draw firm conclusions.

The literature suggesting that social support is related to favorable prognosis among patients with CHD, and that social isolation relates to poor prognosis, is extensive. A 2010 review of prognostic studies of MI patients showed that low functional support (lack of aid and encouragement provided to the individual by their social network) increases cardiovascular and all-cause mortality, with pooled estimates of relative risk ranging between 1.6 and 1.7.<sup>141</sup>

## Stress management and the heart

The stress process can be modified at various stages that are potentially relevant to cardiovascular disease prevention and management. These include changes in exposure to stressful environments, for example through modifying working practices, changes in the emotional responses to stressful situations through altering cognitive appraisals or strengthening psychological coping resources, or changes in physiological responses to stress through relaxation training or pharmacological intervention. Various types of coping strategy have been associated with modified risk of MI and with potential biological mediators such as cortisol production. <sup>142,143</sup> Coping by hiding negative feelings seems to predict increased risk, whereas strategies such as problem solving are related to reduced cortisol levels. <sup>142,143</sup>

No studies of primary prevention of cardiovascular disease through stress reduction have been carried out, but extensive literature exists on the use of stress-management techniques for secondary prevention in patients with CHD. Stress-management procedures previously investigated include relaxation-based methods and cognitive behavioral techniques designed to improve skills for coping with stress and to reduce negative

emotional responses. 144-146. Often, stress management has formed part of intervention packages that also include exercise training, dietary change, or education about medication regimens, such that identifying the distinct effects of stress reduction is difficult. 144-146

Extensive research has been conducted on the management of depression in cardiac patients, although a discussion of these data falls outside the scope of this article. Varied conclusions have been drawn about the impact of stress-management on cardiac outcomes in patients with CHD. 144, 145 In a Cochrane review of randomized controlled trials of psychological interventions, in which studies with follow-up periods of <6 months were excluded, Whalley et al. concluded that modest improvements in depression and anxiety occurred, but that effects on cardiac outcomes were uncertain. 145 No significant reductions in total mortality or incidence of revascularization were reported, but a small improvement in cardiac mortality was observed. 145 In these reviews, 144,145 a variety of psychological interventions, such as those focused on depression or Type A behavior (impatience, aggressiveness, and competitiveness), were assessed rather than stress management in particular. In addition, a largescale study conducted in the 1990s demonstrated little benefit of psychological therapy, relaxation training, and stress-management training in terms of clinical sequelae or mortality. 147 Two studies published in the past 3 years indicate that extensive stress-management programs might have beneficial cardiac effects. Orth-Gomér et al. randomly assigned 237 women to stress management or usual care after acute MI, CABG surgery, or percutaneous coronary intervention (PCI).148 The stress-management program was carried out on a group basis over 20 sessions, and centered on cardiovascular health education, self-monitoring, relaxation, and cognitive restructuring. During the follow-up period (mean 7.1 years), 20% and 7% of the usual-care and stress-management groups died, respectively (HR 0.3, 95% CI 0.1-0.7).148 The second study involved 362 patients hospitalized with acute MI, CABG surgery, or PCI. 149 Again, participants were randomly assigned to 20 group sessions of stress management or usual care. Stress management in this study focused on coping with stress, time urgency, reducing daily stress, and controlling hostility. No difference in total mortality between the two groups was observed over the 7.8 year follow-up, but slightly fewer patients in the intervention group (36%) than in the control group (47%) experienced fatal or nonfatal cardiovascular events, a difference that reached statistical significance in multivariate analysis. 149 Evidence also exists that stress management can attenuate stress-induced hemodynamic and myocardial ischemic responses in patients with cardiac conditions, 150,151 supporting the notion that the effectiveness of stress management is partly the result of direct modifications in physiological regulation.

Stress-management programs of the type described here require considerable commitment both from staff and patients, and their feasibility as methods of secondary prevention in general clinical practice is uncertain. However, the benefits of such programs in terms of improved psychological well-being should not be underestimated, and can be regarded as legitimate goals in themselves.

#### **Conclusions**

Evidence is accumulating from population and clinical studies that stress might contribute to risk of cardiovascular disease at a number of stages, including the long-term development of atherosclerosis and the acute triggering of cardiac events. Most evidence concerning long-term stress comes from studies of the work place, and other sources of stress have not been studied extensively. Data come primarily from observational studies, so causality cannot be definitively established. Triggering of acute cardiac events by emotional stress has been repeatedly documented, but is likely to occur in a minority of patients. Stress management seems to have a favorable impact on cardiovascular health, but effects are difficult to disentangle from other lifestyle modifications that often occur at the same time.

Among the priorities for future research on stress and cardiovascular disease, we would highlight the following. First, the pooling of published and unpublished studies to carry out individual participant meta-analysis will allow associations between CHD and exposure to stress to be investigated with greater power and precision than is possible in separate studies. Such collaborative programs are now in progress. 152 Second, more extensive study of the role of psychological stress in other cardiovascular outcomes, including stroke and stress cardiomyopathy, is needed. Third, a better integration of studies of biological processes with population and clinical research would improve our understanding of the pathways responsible for the effects of stress, and help to identify new targets for prevention and management of cardiovascular events. Fourth, to complement observational studies and rigorously test causal relationships, natural experiments<sup>153</sup> and studies with designs that involve exogenous factors will be needed. In addition, randomized controlled trials of stress modification in relation to surrogate cardiovascular end points (such as arterial stiffness and arterialwall thickness) will be required. These studies are more feasible than large-scale trials powered for clinical outcomes, and could also provide valuable information about

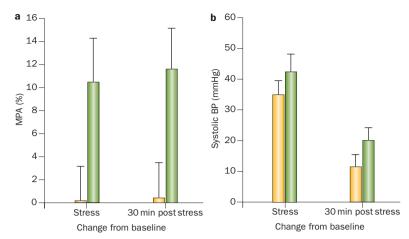


Figure 5 | The effects of stress on platelet activation and BP. Mean changes from baseline in a | platelet activation indexed by MPA% and b | systolic BP in survivors of acute coronary syndromes who experienced emotional triggers (green bars) or no emotional triggers (yellow bars). 130 Results are adjusted for age, BMI, the use of aspirin and β-blockers, and baseline values of MPA% and systolic BP. Error bars are standard errors of the mean. Abbreviations: BP, blood pressure; MPA, monocyte-platelet aggregates.

mechanisms. Research into stress and cardiovascular disease is at an exciting stage of development and has the potential to deepen our understanding of causal processes and to improve patient care.

## **Review criteria**

We searched Medline for prospective epidemiological studies on the association between stress and CHD published up to December 2011 using the terms "job strain", "social isolation", "loneliness" together with "cardiovascular". "coronary heart disease", and "prospective". In addition, we scrutinized the reference sections of all systematic review articles. We included prospective cohort studies if quantitative estimates and confidence intervals (or standard errors) of the relative risk were reported. We excluded studies with no original data, those lacking relevant measurement of the exposure or outcomes, those that were not genuine prospective cohort studies, and overlapping papers reporting duplicate data. In cases of duplicate reports, we selected the paper with most cases of CHD. We did not include studies with stroke as the outcome.

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## **Author contributions**

Both authors researched data for the article, contributed to the discussion of content, wrote the article, and reviewed/edited the manuscript before submission.