15 October 2017

# Contribution of stress to the aetiology and prognosis of cardiovascular disease

*Mika Kivimäki and Andrew Steptoe*

Department of Epidemiology and Public Health (M Kivimäki) and Research Department of Behavioural Science and Health (A Steptoe), University College London, 1–19 Torrington Place, London WC1E 6BT, UK

Brief biography:

Mika Kivimaki is Professor and Chair of Social Epidemiology at University College London, UK. He leads several cohort studies and research consortia on the risk factors of cardiovascular disease and has published more than 900 peer-reviewed papers, including state-of-the-art reviews and meta-analyses in the Lancet and Nature Reviews with particular focus on the health effects of chronic stress.

Andrew Steptoe is Head of the Department of Behavioural Science and Health in the Institute of Epidemiology and Health Care in the Faculty of Population Health Sciences, University College London, UK. He was British Heart Foundation Professor of Psychology from 2000-2016, and is well known for research on cardiovascular effects of episodic stress and depression. He has published more than 550 peer-reviewed articles and is author or editor of 19 books, including Stress and Cardiovascular Disease (London: Springer-Verlag 2012).

Manuscript statistics:

212 words in Abstract, 7239 words in text, 180 references, 2 Boxes, 2 Tables, 5 Figures.

Correspondence to:

Prof Mika Kivimäki, Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, WC1E 6BT London, UK
Email: m.kivimaki@ucl.ac.uk

**Abstract** | Cardiovascular disease remains the leading cause of disease burden globally. This underlies the continuing need to identify new complementary targets for prevention. Over the last 5-10 years, pooling of multiple datasets into mega studies has accelerated progress in research on stress as a risk factor for cardiovascular disease. Severe stressful experiences in childhood, such as physical abuse and household substance abuse, can damage health and increase the risk of multiple chronic conditions in adulthood. Compared with stress in childhood and adulthood classic risk factors, such as smoking, high blood pressure and serum cholesterol, the harmful effects of stress in adulthood are generally less marked. However, adulthood stress has an important role as a disease trigger in persons who already have a high atherosclerotic plaque burden and as a determinant of prognosis and outcome in those with preexisting cardiovascular or cerebrovascular disease. Mechanistic studies corroborate in real-life settings earlier laboratory-based observations on stress-related pathophysiological changes that underlie triggering, such as lowered arrhythmic threshold, increased sympathetic activation with related increases in blood pressure as well as proinflammatory and procoagulant responses. In some clinical guidelines, stress is already acknowledged as a target for prevention for people with high overall cardiovascular risk or established cardiovascular disease. However, few scalable evidence-based interventions are currently available.

## Introduction

Advances in understanding the risk factors of cardiovascular disease have been extraordinary given that the first cohort studies for cardiovascular disease, such as the Minnesota Business and Professional Men study[1], the Framingham Heart study,[2] and the British Doctors study,[3] were initiated only six or seven decades ago. Since that time declines in age-specific cardiovascular disease rates have been enormous, more than those for cancer and neurological disorders.[4] According to the Global Burden of Disease estimates, age-standardised years of life lived with ishaemic heart disease declined by 47% and that of cerebrovascular disease by 17% between 1990 and 2016. Reductions in recognized cardiovascular disease risk factors, such as smoking, blood pressure and serum cholesterol, have helped in preventing the disease.[5,6] In addition, the prognosis of cardiovascular disease has improved because of improved medical care, including diagnosis, treatment of acute events, and post-hospital care.[5,6]

Despite this progress, coronary heart disease and stroke remain the two leading causes of disease burden globally.[4] From 2006 to 2016, the number of people dying from cardiovascular disease actually increased by 15% reaching 17.6 million per year, because of population ageing and growth.[4] The number of years lost due to ill-health, disability or early death from cardiovascular disease is 18 times higher, 321.9 million per year.[7] This underlines the continuing need to identify new complementary targets for prevention and to evaluate future potential of therapeutic management of patients.

One emerging risk and prognostic factor for cardiovascular disease is stress, the topic of this review. A large body of prospective research links stress to increased rates of coronary heart disease, stroke and other presentations of cardiovascular disease, such as atrial fibrillation. In addition, analyses of 27,461 to 603,838 adults with prospective follow-up confirm outcome specificity, supporting the associations with cardiovascular

disease,[8-11] diabetes[12-14] and mental health[15] but not with cancer of all sites, the lung, prostate, breast, colon or rectum[16,17] or diseases in the gastrointestinal[18] and respiratory system.[19,20]

In this Review, we assess the current evidence for stress as a risk factor of cardiovascular disease. Our main focus is on reproducible findings obtained from the largest stress studies to date and most recent literature-based and individual-participant-data meta-analyses. Rather than just updating previous field synopses,[21-26] we seek to determine the clinical importance and population impact of major stressors in relation to various presentations of cardiovascular disease and provide comparisons to more established risk factors and treatments for cardiovascular disease, such as smoking, physical activity, and statin therapy.

To cover the multiple roles of stress in vascular pathology, the Review is organized according to the disease process, from the long-term development of atherosclerosis to subclinical disease and the acute triggering of cardiac or cerebrovascular events in people with advanced underlying disease. In addition to this aetiological process, stress is thought to impair recovery, accelerate the progression of the disease, and contribute to cardiovascular death among patients who have survived an acute coronary syndrome or stroke: in other words, it may act as a prognostic factor. Evidence on these factors is also included in the Review. We conclude this paper with implications for cardiovascular disease prevention and treatment.

## Measurement of stress

The most commonly studied adult stressors include stress at work and social isolation,[22] although other stressors, such as marital problems, caring for a sick spouse or child at home and the death of a close person, have also been linked to increased risk.[27-29] Further

stressors are natural and man-made disasters (e.g., earthquakes, terrorist attacks, wars, etc.) that elicit clinical events and cardiac abnormalities.[30,31] Commonly studied episodic stressors include emotional upset, sporting events and stressful changes at work, such as layoffs.[32,33] We review evidence on these stressors and also overall perceived stress whereas other reviews are available for depression,[34 35,36] anxiety,[37] common mental disorder/psychological distress,[38] vital exhaustion[39] and posttraumatic stress disorder,[40] which, although being correlates of stress, represent consequences rather than sources of stress. Various personality types or characteristics have been considered as being risk factors for both psychological distress and cardiovascular disease. These include the type A behaviour pattern[41] and type D personality[42] as well as anger-proneness and hostility.[43] We do not discuss these personality factors as they have been addressed elsewhere. [41-43]

There are at least three distinct ways to measure stress: (a) by self-report (perception), (b) by external observation, and (c) by biomarkers. The latter include measuring stress on moment-to-moment basis (e.g., via salivary cortisol) and summary measures over longer time spans (e.g., 3-month cortisol assay by analyzing hair samples)(**Box**). While self-completion questionnaire and interviews are still the most commonly used methods, new technology is increasingly providing opportunities to make progress in stress measurement. A wide range of mobile, even wearable, electrochemical sensors and biosensors has been developed for real-time non-invasive monitoring of electrolytes and metabolites in sweat or saliva as indicators of a wearer's biological status; 'mHealth' applications in mobile telephones and wearable devices for interactive communication allow more precise monitoring of specific stress exposures and their timing in relation to physiological changes.[44] For example, PTSD Coach is a smartphone application designed to help individuals who have post-traumatic stress disorder (PTSD) symptoms measure and self-manage their symptoms;[45] Surface Enhanced Raman

Spectroscopy biosensor assays have been develop to detect stress hormone cortisol from saliva;[46] and stored electrocardiograms (ECG) from implantable cardioverter defibrillators can be used as real-time data to investigate associations of stress with arrhythmia.[47]

**Scale of the problem**

Pooling of multiple individual-level prospective datasets into mega studies involving hundreds of thousands of participants has accelerated progress in research on stress and cardiovascular disease, corresponding to developments in genetics and study of classic cardiovascular risk factors. For stress research, this is a relatively recent paradigm shift as major multi-cohort consortia, such as the IPD-Work (Individual-Participant-Data Meta-analysis in Working Populations) consortium, were established less than ten years ago.[48,49] There are several advantages for combining data across studies: Pooled data increase precision for effect estimates (although not necessarily accuracy) and the power to detect "weak" signals between the risk factor and disease. Most chronic stressors probably fall into this category. Further advantages include the possibility of testing the robustness of associations across subgroups to examine whether the observed relationship is a result of a third factor. In addition, with large datasets it is possible to show and publish absence of associations convincingly.

Risk factors doubling the likelihood of developing a disease are considered to have a "large effect size" in evaluations of the evidence.[50] Meta-analyses have reported a hazard ratio of 2 or greater for the associations of classic risk factors, such as diabetes and midlife high blood pressure, with coronary heart disease and ischemic stroke.[51,52] This is also the case for high cholesterol before age 50 in relation to vascular death.[53] It is also found that severe obesity ($BMI \geq 35 kg/m^2$) doubles the risk of cardiovascular disease and

increases the risk of comorbid cardiovascular disease and diabetes by >10 times.[54] The rates of myocardial infarction in smokers are more than two times those in non-smokers.[55]

**Figure 1** summarises evidence on stress as a predictor of chronic diseases from meta-analyses of published papers and pooled analyses of individual-participant data from multiple cohort studies. While the exposure and outcome definitions were heterogeneous in published studies, predefined and harmonised exposures were used in individual-participant-data analyses, an approach that reduces bias due to multiple testing.[48,49] The findings from the two types of multi-cohort studies are consistent in showing that compared to the classic risk factors, the hazard ratios of incident coronary heart disease and ischaemic stroke for stress in adulthood are less marked in the general population.[8-11,56,57] The only exception is the excess risk associated with a history of multiple severe stress experiences in childhood.[58] This association may be indirect as individuals who have had such experiences are more than twice as likely to be smokers or heavy drinkers in adulthood and almost six times as likely to drink problematically than are those who have had no severe stress experiences in childhood.[58]

In contrast to the moderate associations of adulthood stress with cardiovascular and cerebrovascular events in the general population, strong associations between stressors and cardiovascular disease have been observed in high-risk populations,[29,32,59,60] suggesting that stress in adulthood may have a more pronounced role in triggering cardiovascular disease than as a contributor of the development of the disease (**Figure 1**). In patients of cardiovascular disease, several stressors have also been strongly related to cardiovascular endpoints, such as recurrent events and mortality.[61-64] In general, strong associations are less likely to be confounded than weak associations. For example, the 4.7-fold excess risk of cardiac event during anger outburst[60] could be explained away

only if an unmeasured confounder was associated with both stress and cardiac event by as large hazard ratio as 9.0; a weaker uncontrolled confounding could not do so (**Figure 2**). In contrast, an unmeasured confounder doubling the likelihood of long working hours and stroke could explain the entire 1.3-fold increased risk of stroke among individuals working long hours.[10]

## Stress mechanisms and pathophysiology

Acute stress response, an integrated cascade of physiological reactions in the face of challenge, has been well described.[21,26] Much less is known about how stress responses over time convert to pathological changes, contributing to the development and progression of cardiovascular disease. Similarly, while the evidence quantifying links between various stressors and disease endpoints is rapidly accumulating (Figure 1), less progress has been made in understanding which specific pathophysiological changes underlie these links. In the following section, we describe main features of acute stress response and review evidence on stress-related pathophysiological changes, both in relation to atherosclerosis and triggering of major cardiovascular events.

### *Acute stress response*

Activation of stress response produces changes in brain stress responsive neurocircuitry, affecting vigilance to sensory stimuli, producing emotional responses of fear and avoidance, and stimulating peripheral physiological responses.[21] The latter include the autonomic nervous system response, hypothalamus-pituitary-adrenal (HPA) responses, and elevation of inflammatory proteins in the absence of pathogens (known as sterile inflammation).[23,65]

Briefly, the autonomic nervous system, which innervates nearly all organs of the body, activates within seconds after exposure to a stressor, inducing both sympathetic and parasympathetic nervous system responses. Catecholamines epinephrine (released by the adrenal medulla) and norepinephrine (released the sympathetic nerve terminals) increase heart rate and decrease heart rate variability, optimise blood flow to muscle, and elevate core body temperature.[66] The sympathetic nervous system has direct cardiostimulatory effects (chronotropy and inotropy via β1-adrenergic receptors) and pressor effects (via α1-adrenergic receptors) and also affects metabolism (insulin resistance and lipolysis) and the immune system,[67,68] including inhibition of mast-cell degranulation by stimulation of interleukin 6 release. The parasympathetic nervous system releases acetylcholine to inhibit sympathetic nervous system drive to tissues. However, the stress-related regulatory process is often characterised by removal of inhibition to enhance excitation. For example, stress response may involve initial simultaneous activation of both the sympathetic and parasympathetic systems, followed by parasympathetic nervous system withdrawal to sustain stress-evoked elevated heart rate.[69]

The HPA axis activates within minutes of the exposure to a stressor. The hypothalamus releases corticotropin-releasing hormone in the anterior pituitary.[66] This stimulates the release of adrenocorticotropic hormone into the blood circulation, which stimulates the adrenal cortex to release a steroid hormone glucocorticoid cortisol, producing increases in blood glucose.[70] When circulating glucose level is high, beta cells in the pancreas release peptide hormone insulin which promote the absorption of glucose from the blood into fat, liver and skeletal muscle cells. In combination, the autonomic nervous system and HPA-axis response, affect haemostatic factors, increasing platelet activation, fibrinogen, viscosity, and coagulation factors.

Activation of the stress system, especially after severe stressors, with increasing circulating catecholamines, can stimulate exosomal damage/danger-associated molecular patterns (DAMPs) which are endogenous molecules that can stimulate increases in inflammatory proteins.[65] Stress response may also reduce exosomal mRNA cargo, a further factor contributing to stress-related sterile inflammation.[65] One of the puzzles of stress is why there are simultaneous increases in inflammation and glucocorticoids such as cortisol, given that steroid hormones are anti-inflammatory. One explanation is that chronic or repeated stressor exposure lead to stress response exhaustion contributing to chronic low-grade inflammation and antigen-specific immunosuppression.[65] Furthermore, cortisol may only limit inflammatory responses, and proinflammatory cytokine expression would be much greater in the absence of increased cortisol.[71] It also appears that glucocorticoids have proinflammatory effects under some circumstances. *In vitro* administration of glucocorticoids induces cytokine overexpression and activation of nuclear transcription factors in isolated macrophages,[72] while pre-treatment with cortisol has been found to enhance IL-6 responses to endotoxin.[73] It has been proposed that glucocorticoid responses to stress may be neuroendocrine warning signals to the innate immune system, sensitizing neuroinflammatory processes even after the corticosteroid response has dissipated.[74]

*Plausible pathophysiological changes accelerating atherosclerosis*

Stress-related changes in sympathetic-parasympathetic balance and the tone of the HPA-axis might adversely affect the cardiovascular system both by accelerating the atherosclerotic process and by precipitating the occurrence of a cardiac or cerebrovascular event.[26] While pathophysiological effects on atherosclerosis are likely to involve repeated or chronic exposure to stress, stress-related triggering of events among people with

already a high atherosclerotic plaque burden is also contributed by the acute stress response.

In the general population, combined long-term effects of both the autonomic nervous system and HPA-axis dysfunction can, in principle, contribute to factors accelerating atherosclerosis, such a increases in blood pressure, reduced balance between vasodilating and vasoconstricting substances produced by, or acting on, the endothelium.[21] In accordance, stress has been linked to an increased risk of developing diabetes,[14] a major risk factor for coronary heart disease, ischaemic stroke, and haemorrhagic stroke.[51] This association was observed both among individuals with a healthy lifestyle and those with unhealthy lifestyle factors.[12,14] In contrast, there is no consistent evidence to demonstrate an association of stress with such major atherosclerosis risk factors as hypertension and LDL-cholesterol.[75-78]

The mechanisms underlying the increased risk of developing cardiovascular disease among individuals with stress can also be indirect via lifestyle changes that accelerate atherosclerosis. For example, there is evidence to suggest that work-related stress is associated with reduced leisure-time physical activity.[79] A marginal increase in smoking intensity has been observed in smokers under stress,[80] and meta-analyses show that individuals with long working hours are more likely to increase their alcohol use to levels that pose a health risk.[81] In the British Whitehall II study, participants with long-term stress taking part in the Whitehall II study were more likely to have an unhealthy diet than those free of stress.[82] Furthermore, at least two meta-analyses, one based on published studies[83] and the other combining published and unpublished individual-level data[84] confirmed an association between stress and obesity, although the association with weight change appears to be complex as some individuals tend to lose weight under stress, others gain weight and still others experience no change.[85]

*Pathophysiological changes contributing to triggering*

The potential of psychological stress to trigger myocardial ischaemia in people with underlying coronary arterial disease was recognised several hundred years ago.[86] The first detailed description of angina pectoris in the medical literature in 1772 noted "it is increased by disturbance of the mind".[87] Numerous independent studies have subsequently confirmed this in experimental and real-life settings.[88-94]

Among individuals who already have a high atherosclerotic plaque burden, multiple stress-related mechanisms may act as triggers that precipitate the occurrence of a cardiac or cerebrovascular event (**Figure 3**).[95] The common pathology in acute cardiac or cerebrovascular events is rupture or disruption of the fibrous cap of the plaque, coupled with active inflammation and hypercoagulability, which are the result of multiple processes.[96-98] Relevant physiological changes, in addition stress-induced ischaemia, include expression of proinflammatory cytokines and adhesion molecules that contribute to atherosclerotic plaque destabilization and monocyte chemotaxis; tissue-factor release; increased blood viscosity, platelet activation and increases in coagulation and fibrinolytic factors and in the hepatic production of fibrinogen (an acute-phase protein important in both coagulation and whole blood viscosity); systemic vasoconstriction and an increase in arterial blood pressure; increases in sinus node firing rates and atrioventricular conduction velocity, thereby increasing the heart rate; changes in the balance between sympathetic and parasympathetic cardiac control in favour of the former; and increases in myocardial oxygen consumption and myocardial work.[99]

These physiological responses interact with one another; for example, reduced parasympathetic activity is correlated with systemic inflammation, catecholamine release promotes cardiac repolarisation abnormalities, while heightened haemodynamic

responses are associated with increased plasma viscosity.[100-102] These responses, in turn, stimulate pathophysiological effects including electrical instability of the heart and transient myocardial ischaemia as well as plaque disruption and thrombus formation. The result may be acute clinical events such as ventricular fibrillation or myocardial infarction (Figure 2).

As shown in **Figure 4**, the findings from large-scale population studies are consistent with the above described process and show that stress is linked to both increased systemic inflammation and coagulation/viscosity as indicated by higher platelet levels[77] and excess risk of pulmonary embolism.[29] Stress is also related to cardiac arrhythmia,[78] elevated ambulatory blood pressure[103] --a measure that is more sensitive to temporary elevations in blood pressure than clinic-assessed blood pressure -- and increased alcohol use in men,[77,81,104] three further factors which may precipitate the rupture of vulnerable atherosclerotic plaque or the formation of blood clots. Studies that have used online diary (eDiary) assessments of emotions combined with portable devices that continuously monitor electrical activity of the heart have confirmed that stress often precedes arrhythmia episodes.[47,105]

In atrial fibrillation, the irregular rhythm may cause blood to pool in left atrium and form clots which may travel to the brain causing a stroke. A recent individual-participant meta-analysis of nearly 85,500 men and women found that people who work long hours have an increased risk of developing atrial fibrillation.[78] This association was evident in individuals with no history of coronary heart disease or stroke suggesting that the adverse effects may not be attributable to preexisting cardiovascular disease.

Other advances in the study of stress mechanisms have focused on the central nervous system rather than the heart and vessels. An association between resting metabolic activity within the amygdala (a region of the brain implicated in emotional

experience) and the risk of developing cardiovascular disease was found in a 4-year follow-up of 300 participants with a median age of 55 years: the higher the amygdala activity, the higher was the risk.[106] Amygdala hyperactivity was related to conventional stress mechanisms, such as arterial inflammation measured by arterial $^{18}$F-FDG uptake, in line with findings from experimental studies.[107] These observations are preliminary but give rise to the hypothesis that the amygdala could be critical structure in the mechanism linking stress to cardiovascular-disease events. Additionally, the dorsal anterior cingulate cortex is particularly involved with the regulation of cardiovascular responses to acute challenge,[108] and inflammatory cytokine expression links this neural region with preclinical atherosclerosis.[109] Conversely, greater levels of social support that may be cardioprotective are associated with diminished activity in the dorsal anterior cingulate cortex and reduced cortisol responses to stress.[110]

Finally, it has been suggested that stressed individuals with cardiovascular disease may have poorer self-care, being more likely to ignore symptoms of disease and having longer pre-hospital delays in relation to acute cardiovascular events than those who are free of stress.[111] Patients with heart failure and coronary heart disease who become depressed show poor self-care and reduced adherence to medication.[112,113] In addition, stress has been linked to reduced chances of successful modification of risk factors (such as smoking cessation)[114] and high stress may also adversely affect participation in rehabilitation among patients.[62]

**Long-term development of cardiovascular disease**

Multiple severe stressful experiences in childhood, such as physical abuse, household substance abuse and mental illness, childhood sexual abuse and domestic violence, can damage health and increase the risk of multiple chronic conditions in adulthood. In a

meta-analysis of over 120,000 participants from 8 studies, individuals with at least four adverse childhood experiences were at 2.1 (95% confidence interval 1.7 to 2.6) times higher risk of future cardiovascular disease compared to those with no such experience.[58] The risk ratios for adverse behavioural and mental health outcomes in adulthood, such as sexual risk taking, psychiatric disorders, drug use, and problematic alcohol use were higher, varying between 3 and 6.

In adult general populations, the associations between chronic stress and cardiovascular risk have been weaker (**Figure 1**).[8,22,115] A recent meta-analysis of first cardiac events in the general population showed a 1.5-fold (95% confidence intervals 1.2 to 1.9) pooled relative risk related to social isolation or loneliness, compared with other stressors, across nine cohort studies.[23] The risk ratio for coronary heart disease was 1.4-fold (1.1 to 1.8) for people experiencing multiple work stressors (high workload combined with low control over work, plus high efforts relative to income, job security or recognition) compared with low work stress.[9] These associations remained robust after exclusion of the first three or five years of follow-up, suggesting that the association is not attributable to bias arising from the effects of pre-existing cardiovascular disease on stress levels.[9,48]

Research on other presentations of cardiovascular disease includes stroke and atrial fibrillation. A pooled analysis of unpublished and published data on over 500,000 men and women found that those working long hours, in other words 55 hours or more per week, had a 1.3 times (95% confidence intervals 1.1 to 1.6) higher risk of incident stroke compared with individuals working the standard 35-40 hours per week.[10] A similar association between isolation or loneliness and stroke incidence was reported in another meta-analysis, with a 1.3-fold (1.0 to 1.7) relative risk that was unchanged when studies at risk of information bias were excluded.[56] Job strain was associated with a 1.2-fold

(95% confidence interval 1.1 to 1.5) risk of ischaemic stroke, but there was no association with haemorrhagic stroke.[57] Atrial fibrillation is the most common form of clinical cardiac arrhythmia and it has been found that individuals with long working hours and job strain are more likely to develop this disorder.[78,116,117]

**Stress and disease triggering**

In investigating episodic stress and triggering, researchers have exploited 'natural experiment' designs that include a change in stress level due to an adverse life event. This design does not rely on randomisation and is therefore subject to confounding and bias, but probably to a lesser extent than traditional prospective studies with a single baseline assessment and follow-up of the outcome.

Natural disasters, such as earthquakes and hurricanes, as well as unnatural events (e.g. in civilian communities under threat of imminent missile attack) have been associated with increases in cardiovascular events immediately after the event.[118-121] Excess cardiovascular event rates have been observed even in major sporting competitions.[122,123] In a German study, for example, the incidence of acute cardiac events was 2.0 times higher on match days involving the German national team during the 2006 FIFA World Cup (**Figure 1**).[63]

Other commonly studied triggers, such as the death of a close person, exceptionally stressful work changes and emotional upset, have also been associated with considerable increases in the risk of both cardiovascular events and death (**Figure 1**).[29,32,33,60,124-126] For example, it was found in a matched cohort study using the UK primary-care database, which included over 30,000 elderly people with experience of partner bereavement and more than 83,000 matched non-bereavement controls that within a month of the partner's death the risk of cardiovascular disease in the bereaved

compared with the non-bereavement group was 2.1-fold for myocardial infarction and 2.4-fold for stroke.[29] Moreover, the bereaved group had a 2.2-fold increased risk of acute coronary syndromes other than myocardial infarction, and a 2.4-fold risk of pulmonary embolism in the first 90 days.

The large INTERHEART study conducted in 52 countries relied on a case-control design and found that anger or emotional upset in the case period immediately preceding symptom onset was associated with 2.4-times increased odds of acute myocardial infarction (99% confidence interval 2.1 to 2.9), with no effect modification by geographical region, prior cardiovascular disease, cardiovascular risk-factor burden, cardiovascular-prevention medications, or time of day or day of onset of the infarction.[32]

A more advanced approach, known as case-crossover design, is based on within-person comparisons between a hazard period before symptom onset and a control period in the same individual, thereby taking account of base-rate issues and individual differences between cases and controls.[127] A recent meta-analysis identified five studies that used a comparable time period of 24 hours before the hazard period as a control.[23] In this analysis, the pooled relative risk of symptom onset for acute coronary syndrome in periods of stress, anger or depressed mood was 2.5 (95% confidence interval 1.7 to 3.5). Single studies have reported even larger effects. Mostofsky and others,[60] for example, found an incidence of acute cardiac event as high as 21-fold in the 24 hours following the death of a significant person. It was further reported in a larger cohort study from Sweden that the relative risk of death attributable to cardiovascular disease was 5.6-fold (95% CI 5.2 to 5.9) after having been given a cancer diagnosis.[128] This is in agreement with a previous case-crossover study reporting an odds ratio of 14.0 (95% CI 4.4 to 89.7) for negative emotions in the two hours before stroke onset.[129] The increased risk is lower at

3-fold (2.2 to 4.0) but still substantial when major stressful events in the month before ischaemic stroke are considered.[130]

Major downsizing in workplaces that have traditionally provided stable employment, such as public-sector organisations in Finland prior to the major economic recession in the 1990s, is a potential stressor not only for those who lose their jobs, but also for employees who continue working in heavily downsized units with increasing workloads.[131] According to one analysis, 22,400 Finnish public-sector employees remaining in their organisations post-downsizing in the 1990s had a 2.0 (95% confidence interval 1.0 to 3.9) times higher risk of cardiovascular death than those who worked where there had been no downsizing.[33] Splitting the follow-up period into two halves produced a 5.1 (95% confidence interval 1.4 to 19.3) times increase in cardiovascular mortality following major downsizing during the first years, but no excess risk was observed during the second half of the follow-up. Given the long preclinical phase in cardiovascular disease, this finding suggests that the affected employees were those who already had underlying disease.

Besides the above reviewed common presentations of cardiovascular disease, stress has been linked to stress cardiomyopathy, a transient systolic and diastolic left ventricular dysfunction with wall-motion abnormalities often accompanied with emotional or physical stress.[132-134] Stress cardiomyopathy is considered an acute heart failure syndrome[134] and one hypothesis is that an overstimulation of the sympathetic nervous system resulting in a cardiotoxic discharge of circulating catecholamines plays a role in this acute coronary syndrome.[133,135] Data from cohort studies and registries suggest more than half of patients with stress cardiomyopathy have a history of psychiatric or neurologic disorder, supporting a neurogenic origin for this disorder.[134]

**Progression of cardiovascular disease**

In aetiological research the aim is to examine whether development of a disease can reliably be attributed to a particular risk factor. However, both episodic and chronic stress may also affect the outcomes of the disease, and its course and progression. This type of research is prognostic as the aim is to examine factors that affect the risk of future adverse outcomes in individuals who already have cardiovascular disease.

Arrhythmias, particularly ventricular tachycardia and ventricular fibrillation, are common causes of sudden cardiac death. Implantable cardioverter defibrillators are used in the management of ventricular arrhythmia and stored electrocardiograms from these devices have been used to investigate associations of stress with arrhythmia. It was reported in a case-crossover study that approximately 15% of atrial arrhythmias leading to discharge of the implantable cardioverter defibrillator were preceded by negative emotion, compared with 3% of the control periods, a 5-fold difference.[47] Another study of patients with implantable cardioverter defibrillators showed that ventricular tachyarrhythmias increased significantly in the 30 days following the 9/11 attack in the US, compared with the control months.[136]

Work stress has been linked to an increased risk of recurrent cardiac events in patients with coronary heart disease, but the sample size in these studies has typically been small and the findings are not entirely consistent.[27,137-141] A more holistic assessment of perceived life stress, irrespective of the source, has yielded clearer findings. A measure combining work, family and life-event stress predicted increased 3-year mortality in the Beta-Blocker Heart Attack Trial, and the effect was accentuated when coupled with social isolation.[142] In a more recent cohort study of 4,200 patients with acute myocardial infarction, those who were stressed had an elevated 2-year death risk compared with those who were not stressed, the mortality being 12.9% and 8.6%, respectively.[62] This

association was not attributable to socio-demographic differences, clinical factors, revascularization status, or discharge risk as indicated by the confounder-adjusted hazard ratio of 1.4 (95% confidence interval 1.2 to 1.8) for mortality under stress compared to no stress.

As shown in summary **Figure 1**, comparatively few studies have examined the association between stress and disease progression to date. Given the promising findings, this field would merit more high-quality research.

**Prevention and treatment**

Preventive recommendations need to be justified by strong evidence, because non-evidence-based interventions may expose the target population to potentially harmful or ineffective strategies and the use of such interventions may also divert attention and resources from strategies that may be more effective.[143]

The two major approaches to prevention are universal (population-wide) strategy and targeted strategy, the first involving the general population and the latter being focused on those at the highest risk of adverse endpoints.[144] The number needed to treat (NNT) is a simple statistics to evaluate cost-effectiveness and is defined as the number who one should intervene to prevent one extra event. In **Table 3**, we provide the NNT to prevent 1 additional cardiovascular event for various interventions and risk factors to illustrate that the unit cost should be lower for population-wide interventions than for targeted interventions in order to achieve the same cost-effectiveness.[48,145-149] Accordingly, in the general working population, 550 employees without coronary heart disease and with job strain should become free of job strain to prevent 1 myocardial infarction or cardiac death within 5 years.[48] The NNT in the general population for increase in physical activity to a level recommended by WHO(≥150 minutes per week of

moderate intensity of physical activity) is 310 to prevent 1 myocardial infarction and 195 to prevent 1 major cardiovascular event within 5 years.[146] For statin and antihypertensive pharmacotherapy the NNT to prevent 1 major cardiovascular event is 80 for a targeted groups of individuals at intermediate risk of cardiovascular disease.[147] The corresponding NNT for antihypertensive medication alone is 70 for people with hypertension[145] and that for statin treatment alone is 18 for patients with established cardiovascular disease.[149]

The relevance of stress as a target for cardiovascular disease prevention, universal or targeted, remains under debate. There are at least four alternative scenarios for such prevention:

(1) 'Stress as a universal risk factor' – this is the most far-reaching option involving the entire population to reduce stress or its adverse effects.

(2) 'Stress treated as a risk factor in high-risk groups only' – this option assumes the association between stress and cardiovascular disease is causal, but only targeted anti-stress interventions are clinically meaningful and cost-effective.

(3) 'Stress is only a risk marker' – under this scenario, stress is treated as a risk marker to identify at-risk groups for targeted prevention which focusses on the management of standard stroke risk factors in this group. Alternatively, this option is applied to population-wide approaches where people with stress represent only one of the groups that benefit from the intervention.

(4) 'Wait for more definite evidence' - This option is to defer the inclusion of stressors in universal or targeted cardiovascular disease prevention programmes until better evidence is forthcoming.[150]

*Universal strategies*

Data from randomised general-population trials on stress and cardiovascular disease are limited; the few intervention studies available are small in scale and based on case-specific tailor-made solutions rather than scalable interventions.[151,152] A major barrier for large intervention studies is the practical challenge in modifying stressors in healthy individuals as methods of stress interventions are often difficult and time-consuming to implement at the population level. Adherence is poor even for treatments as simple as taking a pill once a day to lower blood pressure or cholesterol levels; in stress management interventions, which may require study participants to modify long-held habits, the adherence problem is orders of magnitude greater. A further barrier is funding. Large drug trials are expensive but often also profitable investments for the pharmaceutical industry. For stress intervention studies, however, the financial incentives for industrial partners are less clear.

Natural (non-randomised) experiments might be informative. A far-reaching population-wide option against stress in the general population is to legislate against common stressors in the same way as other health hazards are dealt with, for example exposure to chemical toxins. This approach has been adopted at least in relation to work stress. One example comes from the European Union and Canada where legislation that provides workers with the right to cap their working at 48 hours per average week has been implemented.[153] Another example is a French law for employees' "right to disconnect". It requires companies to establish hours when staff should not send or answer emails, with a view to ensuring rest periods and preventing burnout by protecting private time. Neither of these laws was enacted with cardiovascular disease prevention in mind. Nonetheless, analyses of cardiovascular disease risk before and after the implementation of the legislation with comparisons to countries with no such policy

could provide an opportunity to evaluate the effects of stress-related interventions in the general population. We are not aware of such analyses.

There may also be population-strategies for reducing the risk of acute triggering of cardiac events by stress.[154] One possibility is increasing precautions in high risk situations, such as major sporting events and natural disasters. Improved access to defibrillators, public health awareness programmes, and education of emergency and health professional staff in the dangers of these settings would ensure more rapid responses to potentially fatal symptoms. Mobile technologies and mHealth interventions may also offer ways of delivering mental health support to mitigate stress of people experiencing war, ethnic conflict, and human-caused and natural disasters. The platforms include social media, video teleconferencing, text messaging, and smartphone-based applications (e.g., PTSD Coach has been downloaded over 243,000 times in 96 countries).[155] To date, systematic research on the potential benefits in terms of cardiovascular prevention is not available.

For stressors that are difficult to manipulate, a way forward is to intervene on the intermediary factors that are downstream on the causal pathway and target them by proven evidence-based prevention strategies. As cardiovascular disease is a multifactorial disease, removal of any of the standard risk factors would reduce overall risk. Accordingly, physical activity has been suggested as an intervention to mitigate adverse stress effects.[156] There is indirect evidence to support this because meta-analyses of trial findings have shown that physical activity may alleviate distress feelings, such as depression and anxiety,[157] and extensive observational evidence supports a protective effect on cardiovascular disease.[146] Workplace wellness programs, such as those promoted by the American Heart Association, have been designed to be implemented in all workplaces to support healthy lifestyles, including routine health screenings, the

facilitation of healthy eating, weight management, and physical activity.[158,159] They could also be beneficial for people under stress, although again systematic research on benefits and harms is lacking.

*Targeted strategies*

In **Figure 5**, we illustrate that, in terms of reducing absolute risk, prevention and treatment focusing on individuals at high overall cardiovascular disease risk[32] and patients with pre-existing disease[62] may appear a more attractive target group than the general population.[10] The rationale is that for example a 1.5-fold increase in relative risk of disease due to stress would mean that a person with a high >10% overall risk of a cardiovascular disease event in the next 10 years based on the established risk factors would actually have a 15% overall risk after also accounting stress. In contrast, taking into account a similar 1.5-fold excess risk due to stress for a person with a low 1% overall cardiovascular disease risk would increase the overall risk only to 1.5%, a relatively trivial clinical difference.

The greatest stress effects relate to triggering of cardiovascular events among individuals with high cardiovascular risk or establish disease and stressful events, such as emotional upset, adverse changes at work, major life events, and natural and unnatural catastrophes. These are difficult to address by interventions as such events are typically stochastic events which are difficult to predict. For this reason, a more typical approach in targeted interventions involves strengthening stress management skills and psychosocial support more generally.

A systematic review and meta-analysis of psychological treatment among cardiac patients, published in 2007, identified 43 relevant randomised trials, of which 23 reported mortality data for almost 10,000 patients.[160] A benefit of the treatment was observed

among men in terms of reduced all-cause mortality at follow-ups of 2 years or less. The odds ratio comparing the intervention group of psychological treatment and usual care with the comparison group receiving only usual care was 0.7 (95% confidence interval 0.6 to 1.0) for men but 1.0 (95% confidence interval 0.9 to 1.7) for women. A longer follow-up attenuated this effect. Although some individual trials have shown impressive results,[161,162] summary evidence from a Cochrane review, published in 2017 of 35 studies which randomized 10,703 people with coronary heart disease, showed little change in the strength of the evidence in general.[163] The review suggests that psychological treatment might reduce the rate of cardiac mortality, but the trials available were of low quality and there was no robust data to suggest an effect on total mortality, the risk of revascularisation procedures, or the rate of non-fatal myocardial infarction.

In addition, comprehensive cardiac rehabilitation for cardiovascular disease patients often includes a psychological component related to life-style behaviour change, risk factor modification, and psychosocial well-being.[164] While exercise training remains the cornerstone of cardiac rehabilitation, an additional goal is to identify patients with psychosocial risk factors and to offer stress-management interventions for those in need.[165] Meta-analyses suggest that exercise-based cardiac rehabilitation is effective at reducing cardiovascular risk,[164,166] although there are notable exceptions with null findings (e.g., the large UK RAMIT trial).[167] Exercise training in patients with chronic disease may additionally have stress mitigating effects.[168] No specific cardiovascular benefits have been shown for including stress management as part of rehabilitation.[164,166]

*Current clinical guidelines*

While findings from randomized controlled trials represent the gold standard evidence, such evidence is lacking for much of modern medical practice and in many cases no

randomized controlled trial is even being planned to provide evidence for action.[169] An argument that has been used to justify this is that waiting for more data represents an implicit decision not to act or to act on the basis of past practice rather than best available evidence.[169]

The 2016 European clinical guidelines for the prevention of cardiovascular disease include family history of premature cardiovascular disease, familial hyperlipidaemia, smoking, high blood pressure, diabetes and raised lipid levels as key risk factors.[170] Stress is acknowledged as a potential contributing factor to both the development and progression of the disease and targeted rather than universal strategy for stress management is recommended.

More specifically, the guideline ranks the strength of evidence and recommendations into four classes. Class I evidence (referring to evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective and "is recommended") relates to risk factors, such as hypertension and high cholesterol. The evidence on the status of stress as a cardiovascular disease risk factor is rated as Class IIa indicating that weight of evidence is in favour of usefulness/efficacy and that addressing the risk factor "should be considered". The guideline recommends assessment and management of stress and other psychosocial factors (socio-economic adversity, lack of social support, stress at work and in family life, hostility, depression, anxiety and other mental disorders) in individuals at high risk of cardiovascular disease or with established cardiovascular disease, but not in the general population.

The Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation of the European Society of Cardiology additionally emphasises that "the success of cardiac rehabilitation may critically depend on the interdependence of the body and mind and this interaction needs to be reflected through

the assessment and management of psychosocial risk factors in line with robust scientific evidence, by trained staff, integrated within the core cardiac rehabilitation team" (p. 1290).[165]

The recommendations of other prevention guidelines are more indirect in terms of stress prevention or they identify insufficient evidence to provide a recommendation. The Canadian 2016 guidelines, for example, note that health care providers can explore stress management techniques for patients with myocardial infarction and depression to optimize quality of life; the importance of moderate sleep duration is also emphasised.[171] In contrast, the most recent WHO report on cardiovascular disease management in primary health care, the American Heart Association (AHA) and American College of Cardiologists risk assessment tool and the AHA/ American Stroke Association secondary prevention guideline do not list stress as a specific prevention target.[172-174] Nonetheless, most clinical guidelines make recommendations regarding the composition of a multi-disciplinary cardiac rehabilitation team and acknowledge that core components should include components, such as initial assessment, structured exercise training, nutrition counselling, patient education, risk factor management and psychosocial support.[175]

**Conclusions and future research directions**

Recent individual-level meta-analyses suggest that stress in adulthood has a relatively modest role in cardiovascular disease aetiology among healthy individuals, as compared with severe childhood stress or adult classic risk factors, such as hypertension, high cholesterol, diabetes, smoking, and obesity. In contrast, adulthood stress may be an important disease trigger in susceptible persons and a determinant of prognosis and outcome in those with preexisting cardiovascular or cerebrovascular disease. Understanding the cardiovascular implications of stress pathophysiology, including

disturbance in autonomic, metabolic, inflammatory and hemostatic processes is accumulating and new discoveries have involved functional changes in the central nervous system. While the main emphasis in stress studies has traditionally been on cardiovascular disease aetiology, the emerging evidence is increasingly shifting weight into the role of stress in disease progression among individuals at high risk or with cardiovascular disease.

To complement research on disease causation and mechanisms, there is a need for studies aimed at developing cost-effective scalable stress interventions which could deliver substantial health gain; in other words, science of delivery. The first steps towards clinical application have already been made in the European guidelines acknowledging stress as a contributing factor to cardiovascular disease. 'Precision medicine' is an emerging overall approach in medical sciences which seeks to predict more accurately which prevention and treatment strategies for a disease will work in a specific group of individuals.[176] In the future, it is important to examine whether information on stress could contribute to precision medicine approaches by characterising distinct groups of individuals in need of special attention or as part of targeted prevention and treatment strategies.

Although clinical guidelines have favoured, if anything, targeted rather than universal strategies for stress prevention, this may need reconsidering when more evidence accumulates. Population-wide policies and strategies have been shown to be cost-effective in reducing classic risk factors, such as smoking by means of clean indoor air legislation, cigarette price increases, and reductions in license for tobacco outlets.[177-179] Modelling studies suggest universal diet interventions, such as the UK 'sugar tax', might also benefit population health.[180] Given the much higher numbers of people with stress in the general population than among individuals with advanced disease, the

population-attributable risk (a measure of preventive potential) is broadly similar for heart disease in these groups, at 3-7% for chronic stressors in the general population and approximately 4% for stress triggers in high-risk individuals.[9,48,62,124] This suggests there might be scope for multiple stress intervention strategies, including targeted interventions for people with high overall risk and a general plan for everyone, a public health approach.

**References**


1 Keys, A. *et al.* Coronary Heart Disease among Minnesota Business and Professional Men Followed Fifteen Years. *Circulation* **28**, 381-395 (1963).

2 Mahmood, S. S., Levy, D., Vasan, R. S. & Wang, T. J. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. *Lancet* **383**, 999-1008, doi:10.1016/S0140-6736(13)61752-3 (2014).

3 Doll, R. & Hill, A. B. The mortality of doctors in relation to their smoking habits; a preliminary report. *Br Med J* **1**, 1451-1455 (1954).

4 Collaborators, G. B. D. C. o. D. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* **390**, 1151-1210, doi:10.1016/S0140-6736(17)32152-9 (2017).

5 Tzoulaki, I., Elliott, P., Kontis, V. & Ezzati, M. Worldwide Exposures to Cardiovascular Risk Factors and Associated Health Effects: Current Knowledge and Data Gaps. *Circulation* **133**, 2314-2333, doi:10.1161/CIRCULATIONAHA.115.008718 (2016).

6 Ezzati, M. *et al.* Contributions of risk factors and medical care to cardiovascular mortality trends. *Nature reviews. Cardiology*, doi:10.1038/nrcardio.2015.82 (2015).

7 DALYs, G. B. D. & Collaborators, H. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* **390**, 1260-1344, doi:10.1016/S0140-6736(17)32130-X (2017).

8 Kivimaki, M. & Kawachi, I. Work Stress as a Risk Factor for Cardiovascular Disease. *Curr Cardiol Rep* **17**, 630, doi:10.1007/s11886-015-0630-8 (2015).

9 Dragano, N. *et al.* Effort-reward imbalance at work and incident coronary heart disease: a multi-cohort study of 90,164 individuals. *Epidemiology* **28**, 619-626, doi:10.1097/EDE.0000000000000666 (2017).

10 Kivimaki, M. *et al.* Long working hours and risk of coronary heart disease and stroke: a systematic review and meta-analysis of published and unpublished data for 603 838 individuals. *Lancet* **386**, 1739-1746, doi:10.1016/S0140-6736(15)60295-1 (2015).

11 Huang, Y. *et al.* Association between job strain and risk of incident stroke: A meta-analysis. *Neurology* **85**, 1648-1654, doi:10.1212/WNL.0000000000002098 (2015).

12 Nyberg, S. T. *et al.* Job strain as a risk factor for type 2 diabetes: A pooled analysis of 124 808 men and women. *Diabetes care* (2014).

13 Ferrie, J. E. *et al.* Job insecurity and risk of diabetes: a meta-analysis of individual participant data. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* **188**, E447-E455, doi:10.1503/cmaj.150942 (2016).

14 Hackett, R. A. & Steptoe, A. Type 2 diabetes mellitus and psychological stress - a modifiable risk factor. *Nat Rev Endocrinol* **13**, 547-560, doi:10.1038/nrendo.2017.64 (2017).

15 Madsen, I. E. H. *et al.* Job strain as a risk factor for clinical depression: systematic review and meta-analysis with additional individual participant data. *Psychological medicine* **47**, 1342-1356, doi:10.1017/S003329171600355X (2017).
16 Heikkila, K. *et al.* Work stress and risk of cancer: meta-analysis of 5700 incident cancer events in 116,000 European men and women. *Bmj* **346**, f165 (2013).
17 Heikkila, K. *et al.* Long working hours and cancer risk: a multi-cohort study. *British journal of cancer* **114**, 813-818, doi:10.1038/bjc.2016.9 (2016).
18 Heikkila, K. *et al.* Job strain and the risk of inflammatory bowel diseases: individual-participant meta-analysis of 95,000 men and women. *PloS one* **9**, e88711 (2014).
19 Heikkila, K. *et al.* Job strain and COPD exacerbations: an individual-participant meta-analysis. *The European respiratory journal* **44**, 247-251 (2014).
20 Heikkila, K. *et al.* Job strain and the risk of severe asthma exacerbations: a meta-analysis of individual-participant data from 100 000 European men and women. *Allergy* **69**, 775-783, doi:10.1111/all.12381 (2014).
21 Brotman, D. J., Golden, S. H. & Wittstein, I. S. The cardiovascular toll of stress. *Lancet* **370**, 1089-1100 (2007).
22 Steptoe, A. & Kivimaki, M. Stress and cardiovascular disease. *Nature reviews. Cardiology* **9**, 360-370 (2012).
23 Steptoe, A. & Kivimaki, M. Stress and cardiovascular disease: an update on current knowledge. *Annual review of public health* **34**, 337-354 (2013).
24 Rozanski, A., Blumenthal, J. A., Davidson, K. W., Saab, P. G. & Kubzansky, L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: The emerging field of behavioral cardiology. *Journal of the American College of Cardiology* **45**, 637-651 (2005).
25 Rozanski, A., Blumenthal, J. A. & Kaplan, J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* **99**, 2192-2217 (1999).
26 McEwen, B. S. Protective and damaging effects of stress mediators. *The New England journal of medicine* **338**, 171-179 (1998).
27 Orth-Gomer, K. *et al.* Marital stress worsens prognosis in women with coronary heart disease: The Stockholm Female Coronary Risk Study. *Jama* **284**, 3008-3014 (2000).
28 Lee, S., Colditz, G. A., Berkman, L. F. & Kawachi, I. Caregiving and risk of coronary heart disease in U.S. women: a prospective study. *American journal of preventive medicine* **24**, 113-119, doi:S0749379702005822 [pii] (2003).
29 Carey, I. M. *et al.* Increased risk of acute cardiovascular events after partner bereavement: a matched cohort study. *JAMA Intern Med* **174**, 598-605, doi:10.1001/jamainternmed.2013.14558 (2014).
30 Kario, K., McEwen, B. S. & Pickering, T. G. Disasters and the heart: a review of the effects of earthquake-induced stress on cardiovascular disease. *Hypertens Res* **26**, 355-367 (2003).
31 Qureshi, E. A., Merla, V., Steinberg, J. & Rozanski, A. Terrorism and the heart: implications for arrhythmogenesis and coronary artery disease. *Card Electrophysiol Rev* **7**, 80-84 (2003).

32 Smyth, A. *et al.* Physical Activity and Anger or Emotional Upset as Triggers of Acute Myocardial Infarction: The INTERHEART Study. *Circulation* **134**, 1059-1067, doi:10.1161/CIRCULATIONAHA.116.023142 (2016).

33 Vahtera, J. *et al.* Organisational downsizing, sickness absence, and mortality: 10-town prospective cohort study. *Bmj* **328**, 555 (2004).

34 Correll, C. U. *et al.* Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry* **16**, 163-180, doi:10.1002/wps.20420 (2017).

35 Gan, Y. *et al.* Depression and the risk of coronary heart disease: a meta-analysis of prospective cohort studies. *BMC psychiatry* **14**, 371, doi:10.1186/s12888-014-0371-z (2014).

36 Gathright, E. C., Goldstein, C. M., Josephson, R. A. & Hughes, J. W. Depression increases the risk of mortality in patients with heart failure: A meta-analysis. *J Psychosom Res* **94**, 82-89, doi:10.1016/j.jpsychores.2017.01.010 (2017).

37 Celano, C. M. *et al.* Association between anxiety and mortality in patients with coronary artery disease: A meta-analysis. *Am Heart J* **170**, 1105-1115, doi:10.1016/j.ahj.2015.09.013 (2015).

38 Russ, T. C. *et al.* Association between psychological distress and mortality: individual participant pooled analysis of 10 prospective cohort studies. *Bmj* **345**, e4933, doi:10.1136/bmj.e4933 (2012).

39 Cohen, R., Bavishi, C., Haider, S., Thankachen, J. & Rozanski, A. Meta-Analysis of Relation of Vital Exhaustion to Cardiovascular Disease Events. *The American journal of cardiology* **119**, 1211-1216, doi:10.1016/j.amjcard.2017.01.009 (2017).

40 Edmondson, D., Kronish, I. M., Shaffer, J. A., Falzon, L. & Burg, M. M. Posttraumatic stress disorder and risk for coronary heart disease: a meta-analytic review. *Am Heart J* **166**, 806-814, doi:10.1016/j.ahj.2013.07.031 (2013).

41 Hemingway, H. & Marmot, M. Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. *Bmj* **318**, 1460-1467 (1999).

42 Grande, G., Romppel, M. & Barth, J. Association between type D personality and prognosis in patients with cardiovascular diseases: a systematic review and meta-analysis. *Ann Behav Med* **43**, 299-310, doi:10.1007/s12160-011-9339-0 (2012).

43 Chida, Y. & Steptoe, A. The association of anger and hostility with future coronary heart disease: a meta-analytic review of prospective evidence. *Journal of the American College of Cardiology* **53**, 936-946, doi:10.1016/j.jacc.2008.11.044 (2009).

44 Bandodkar, A. J. & Wang, J. Non-invasive wearable electrochemical sensors: a review. *Trends Biotechnol* **32**, 363-371, doi:10.1016/j.tibtech.2014.04.005 (2014).

45 Kuhn, E. *et al.* Preliminary evaluation of PTSD Coach, a smartphone app for post-traumatic stress symptoms. *Mil Med* **179**, 12-18, doi:10.7205/MILMED-D-13-00271 (2014).

46 Mitchell, J. S., Lowe, T. E. & Ingram, J. R. Rapid ultrasensitive measurement of salivary cortisol using nano-linker chemistry coupled with surface plasmon resonance detection. *Analyst* **134**, 380-386, doi:10.1039/b817083p (2009).

47 Lampert, R. *et al.* Triggering of symptomatic atrial fibrillation by negative emotion. *Journal of the American College of Cardiology* **64**, 1533-1534, doi:10.1016/j.jacc.2014.07.959 (2014).

48 Kivimaki, M. *et al.* Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data. *Lancet* **380**, 1491-1497 (2012).

49 Kivimaki, M., Singh-Manoux, A., Ferrie, J. E. & Batty, G. D. Post hoc decision-making in observational epidemiology--is there need for better research standards? *International journal of epidemiology* **42**, 367-370 (2013).

50 Balshem, H. *et al.* GRADE guidelines: 3. Rating the quality of evidence. *Journal of clinical epidemiology* **64**, 401-406, doi:10.1016/j.jclinepi.2010.07.015 (2011).

51 Sarwar, N. *et al.* Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* **375**, 2215-2222 (2010).

52 Lewington, S. *et al.* Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* **360**, 1903-1913 (2002).

53 Lewington, S. *et al.* Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* **370**, 1829-1839 (2007).

54 Kivimaki, M. *et al.* Overweight, obesity, and risk of cardiometabolic multimorbidity: pooled analysis of individual-level data for 120 813 adults from 16 cohort studies from the USA and Europe. *Lancet Public Health* **2**, e277-e285, doi:10.1016/S2468-2667(17)30074-9 (2017).

55 Parish, S. *et al.* Cigarette smoking, tar yields, and non-fatal myocardial infarction: 14,000 cases and 32,000 controls in the United Kingdom. The International Studies of Infarct Survival (ISIS) Collaborators. *Bmj* **311**, 471-477 (1995).

56 Valtorta, N. K., Kanaan, M., Gilbody, S., Ronzi, S. & Hanratty, B. Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies. *Heart* **102**, 1009-1016, doi:10.1136/heartjnl-2015-308790 (2016).

57 Fransson, E. I. *et al.* Job strain and the risk of stroke: an individual-participant data meta-analysis. *Stroke* **46**, 557-559, doi:10.1161/STROKEAHA.114.008019 (2015).

58 Hughes, K. *et al.* The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *Lancet Public Health* **2**, e356–366 (2017).

59 O'Donnell, M. J. *et al.* Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet* **388**, 761-775, doi:10.1016/S0140-6736(16)30506-2 (2016).

60 Mostofsky, E., Penner, E. A. & Mittleman, M. A. Outbursts of anger as a trigger of acute cardiovascular events: a systematic review and meta-analysis. *European heart journal* **35**, 1404-1410, doi:10.1093/eurheartj/ehu033 (2014).

61 Li, J., Zhang, M., Loerbroks, A., Angerer, P. & Siegrist, J. Work stress and the risk of recurrent coronary heart disease events: A systematic review and

meta-analysis. *International journal of occupational medicine and environmental health* **28**, 8-19, doi:10.2478/s13382-014-0303-7 (2015).

62 Arnold, S. V., Smolderen, K. G., Buchanan, D. M., Li, Y. & Spertus, J. A. Perceived stress in myocardial infarction: long-term mortality and health status outcomes. *Journal of the American College of Cardiology* **60**, 1756-1763, doi:10.1016/j.jacc.2012.06.044 (2012).

63 Wilbert-Lampen, U. *et al.* Cardiovascular events during World Cup soccer. *The New England journal of medicine* **358**, 475-483, doi:10.1056/NEJMoa0707427 (2008).

64 Stewart, R. A. H. *et al.* Persistent psychological distress and mortality in patients with stable coronary artery disease. *Heart*, doi:10.1136/heartjnl-2016-311097 (2017).

65 Fleshner, M. & Crane, C. R. Exosomes, DAMPs and miRNA: Features of Stress Physiology and Immune Homeostasis. *Trends Immunol* **38**, 768-776, doi:10.1016/j.it.2017.08.002 (2017).

66 Chrousos, G. P. & Gold, P. W. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *Jama* **267**, 1244-1252 (1992).

67 Huang, Q. H., Takaki, A. & Arimura, A. Central noradrenergic system modulates plasma interleukin-6 production by peripheral interleukin-1. *Am J Physiol* **273**, R731-738 (1997).

68 Goebel, M. U., Mills, P. J., Irwin, M. R. & Ziegler, M. G. Interleukin-6 and tumor necrosis factor-alpha production after acute psychological stress, exercise, and infused isoproterenol: differential effects and pathways. *Psychosomatic medicine* **62**, 591-598 (2000).

69 Carrive, P. Dual activation of cardiac sympathetic and parasympathetic components during conditioned fear to context in the rat. *Clin Exp Pharmacol Physiol* **33**, 1251-1254, doi:10.1111/j.1440-1681.2006.04519.x (2006).

70 Tsigos, C. & Chrousos, G. P. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *J Psychosom Res* **53**, 865-871 (2002).

71 Munck, A., Guyre, P. M. & Holbrook, N. J. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocr Rev* **5**, 25-44, doi:10.1210/edrv-5-1-25 (1984).

72 Smyth, G. P. *et al.* Glucocorticoid pretreatment induces cytokine overexpression and nuclear factor-kappaB activation in macrophages. *The Journal of surgical research* **116**, 253-261, doi:10.1016/S0022-4804(03)00300-7 (2004).

73 Yeager, M. P., Pioli, P. A. & Guyre, P. M. Cortisol exerts bi-phasic regulation of inflammation in humans. *Dose Response* **9**, 332-347, doi:10.2203/dose-response.10-013.Yeager (2011).

74 Frank, M. G., Watkins, L. R. & Maier, S. F. Stress-induced glucocorticoids as a neuroendocrine alarm signal of danger. *Brain, behavior, and immunity* **33**, 1-6, doi:10.1016/j.bbi.2013.02.004 (2013).

75 Babu, G. R. *et al.* Is hypertension associated with job strain? A meta-analysis of observational studies. *Occupational and environmental medicine* **71**, 220-227, doi:10.1136/oemed-2013-101396 (2014).

76 Nyberg, S. *et al.* Job strain and cardiovascular disease risk factors: An individual-participant data meta-analysis of 47,000 men and women. *PLoS ONE* (2013).

77 Magnusson-Hanson, L. *et al.* Work stress, anthropometry, lung function, blood pressure, and blood-based biomarkers: a cross-sectional study of 43,593 French men and women. *Scientific Reports* **ePub ahead of print** (2017).
78 Kivimäki, M. *et al.* Long working hours as a risk factor for atrial fibrillation: a multi-cohort study. *European Heart Journal (ePub ahead of print)*, doi:ehx324, https://doi.org/10.1093/eurheartj/ehx324 (2017).
79 Fransson, E. I. *et al.* Job strain as a risk factor for leisure-time physical inactivity: An individual-participant meta-analysis of up to 170 000 men and women - The IPD-Work Consortium. *American journal of epidemiology* (2012).
80 Heikkila, K. *et al.* Job strain and tobacco smoking: an individual-participant data meta-analysis of 166,130 adults in 15 European studies. *PloS one* **7**, e35463 (2012).
81 Virtanen, M. *et al.* Long working hours and alcohol use: systematic review and meta-analysis of published studies and unpublished individual participant data. *Bmj* **350**, g7772, doi:10.1136/bmj.g7772 (2015).
82 Chandola, T. *et al.* Work stress and coronary heart disease: what are the mechanisms? *European heart journal* **29**, 640-648 (2008).
83 Wardle, J., Chida, Y., Gibson, E. L., Whitaker, K. L. & Steptoe, A. Stress and adiposity: a meta-analysis of longitudinal studies. *Obesity* **19**, 771-778 (2011).
84 Nyberg, S. T. *et al.* Job strain in relation to body mass index: pooled analysis of 160 000 adults from 13 cohort studies. *Journal of internal medicine* **272**, 65-73, doi:10.1111/j.1365-2796.2011.02482.x (2012).
85 Kivimäki, M., Singh-Manoux, A., Nyberg, S. N., Jokela, M. & Virtanen, M. Job strain and risk of obesity: Systematic review and meta-analysis of cohort studies. *Int J Obesity* (2015).
86 Arri, S. S., Ryan, M., Redwood, S. R. & Marber, M. S. Mental stress-induced myocardial ischaemia. *Heart* **102**, 472-480, doi:10.1136/heartjnl-2014-307306 (2016).
87 Heberden, W. *Commentaries on the history and cure of diseases.*, (Payne, 1818).
88 Rozanski, A. *et al.* Mental stress and the induction of silent myocardial ischemia in patients with coronary artery disease. *The New England journal of medicine* **318**, 1005-1012 (1988).
89 Blumenthal, J. A. *et al.* Mental stress-induced ischemia in the laboratory and ambulatory ischemia during daily life. Association and hemodynamic features. *Circulation* **92**, 2102-2108 (1995).
90 Deanfield, J. E. *et al.* Silent myocardial ischaemia due to mental stress. *Lancet* **2**, 1001-1005 (1984).
91 Krantz, D. S., Sheps, D. S., Carney, R. M. & Natelson, B. H. Effects of mental stress in patients with coronary artery disease: evidence and clinical implications. *Jama* **283**, 1800-1802 (2000).
92 Gottdiener, J. S. *et al.* Induction of silent myocardial ischemia with mental stress testing: relation to the triggers of ischemia during daily life activities and to ischemic functional severity. *Journal of the American College of Cardiology* **24**, 1645-1651 (1994).

93 Gullette, E. C. *et al.* Effects of mental stress on myocardial ischemia during daily life. *Jama* **277**, 1521-1526 (1997).
94 Strike, P. C. & Steptoe, A. Systematic review of mental stress-induced myocardial ischaemia. *European heart journal* **24**, 690-703 (2003).
95 Strike, P. C. *et al.* Pathophysiological processes underlying emotional triggering of acute cardiac events. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 4322-4327 (2006).
96 Arbab-Zadeh, A., Nakano, M., Virmani, R. & Fuster, V. Acute coronary events. *Circulation* **125**, 1147-1156, doi:10.1161/CIRCULATIONAHA.111.047431 (2012).
97 Anderson, J. L. & Morrow, D. A. Acute Myocardial Infarction. *The New England journal of medicine* **376**, 2053-2064, doi:10.1056/NEJMra1606915 (2017).
98 Naghavi, M. *et al.* From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. *Circulation* **108**, 1772-1778, doi:10.1161/01.CIR.0000087481.55887.C9 (2003).
99 Edmondson, D., Newman, J. D., Whang, W. & Davidson, K. W. Emotional triggers in myocardial infarction: do they matter? *European heart journal* **34**, 300-306, doi:10.1093/eurheartj/ehs398 (2013).
100 Ackland, G. L. *et al.* Autonomic regulation of systemic inflammation in humans: A multi-center, blinded observational cohort study. *Brain, behavior, and immunity*, doi:10.1016/j.bbi.2017.08.010 (2017).
101 Lampert, R. Mental Stress and Ventricular Arrhythmias. *Curr Cardiol Rep* **18**, 118, doi:10.1007/s11886-016-0798-6 (2016).
102 Steptoe, A. & Marmot, M. Psychosocial, hemostatic, and inflammatory correlates of delayed poststress blood pressure recovery. *Psychosomatic medicine* **68**, 531-537, doi:68/4/531 [pii]10.1097/01.psy.0000227751.82103.65 (2006).
103 Landsbergis, P. A., Dobson, M., Koutsouras, G. & Schnall, P. Job strain and ambulatory blood pressure: a meta-analysis and systematic review. *American journal of public health* **103**, e61-71, doi:10.2105/AJPH.2012.301153 (2013).
104 Heikkila, K. *et al.* Job strain and alcohol intake: a collaborative meta-analysis of individual-participant data from 140,000 men and women. *PloS one* **7**, e40101 (2012).
105 Park, H. W. *et al.* Neural mechanisms of atrial fibrillation. *Curr Opin Cardiol* **27**, 24-28, doi:10.1097/HCO.0b013e32834dc4e8 (2012).
106 Tawakol, A. *et al.* Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. *Lancet* **389**, 834-845, doi:10.1016/S0140-6736(16)31714-7 (2017).
107 Muscatell, K. A. *et al.* Greater amygdala activity and dorsomedial prefrontal-amygdala coupling are associated with enhanced inflammatory responses to stress. *Brain, behavior, and immunity* **43**, 46-53, doi:10.1016/j.bbi.2014.06.201 (2015).
108 Silvestrini, N. Psychological and neural mechanisms associated with effort-related cardiovascular reactivity and cognitive control: An integrative approach. *Int J Psychophysiol* **119**, 11-18, doi:10.1016/j.ijpsycho.2016.12.009 (2017).
109 Gianaros, P. J. *et al.* An inflammatory pathway links atherosclerotic cardiovascular disease risk to neural activity evoked by the cognitive

regulation of emotion. *Biological psychiatry* **75**, 738-745, doi:10.1016/j.biopsych.2013.10.012 (2014).

110 Eisenberger, N. I., Taylor, S. E., Gable, S. L., Hilmert, C. J. & Lieberman, M. D. Neural pathways link social support to attenuated neuroendocrine stress responses. *NeuroImage* **35**, 1601-1612, doi:10.1016/j.neuroimage.2007.01.038 (2007).

111 Meschia, J. F. *et al.* Guidelines for the Primary Prevention of Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*, doi:10.1161/STR.0000000000000046 (2014).

112 Kessing, D., Denollet, J., Widdershoven, J. & Kupper, N. Psychological Determinants of Heart Failure Self-Care: Systematic Review and Meta-Analysis. *Psychosomatic medicine* **78**, 412-431, doi:10.1097/PSY.0000000000000270 (2016).

113 Rieckmann, N. *et al.* Course of depressive symptoms and medication adherence after acute coronary syndromes: an electronic medication monitoring study. *Journal of the American College of Cardiology* **48**, 2218-2222, doi:10.1016/j.jacc.2006.07.063 (2006).

114 Doyle, F. *et al.* Systematic review and meta-analysis of the impact of depression on subsequent smoking cessation in patients with coronary heart disease: 1990 to 2013. *Psychosomatic medicine* **76**, 44-57, doi:10.1097/PSY.0000000000000020 (2014).

115 Richardson, S. *et al.* Meta-analysis of perceived stress and its association with incident coronary heart disease. *The American journal of cardiology* **110**, 1711-1716, doi:10.1016/j.amjcard.2012.08.004 (2012).

116 Toren, K., Schioler, L., Soderberg, M., Giang, K. W. & Rosengren, A. The association between job strain and atrial fibrillation in Swedish men. *Occupational and environmental medicine* **72**, 177-180, doi:10.1136/oemed-2014-102256 (2015).

117 Fransson, E. I. *et al.* The Association between Job Strain and Atrial Fibrillation: Results from the Swedish WOLF Study. *BioMed Research International* (2015 (in press)).

118 Leor, J., Poole, W. K. & Kloner, R. A. Sudden cardiac death triggered by an earthquake. *The New England journal of medicine* **334**, 413-419, doi:10.1056/NEJM199602153340701 (1996).

119 Trichopoulos, D., Katsouyanni, K., Zavitsanos, X., Tzonou, A. & Dalla-Vorgia, P. Psychological stress and fatal heart attack: the Athens (1981) earthquake natural experiment. *Lancet* **1**, 441-444 (1983).

120 Jiao, Z. *et al.* Effect of Hurricane Katrina on incidence of acute myocardial infarction in New Orleans three years after the storm. *The American journal of cardiology* **109**, 502-505, doi:10.1016/j.amjcard.2011.09.045 (2012).

121 Meisel, S. R. *et al.* Effect of Iraqi missile war on incidence of acute myocardial infarction and sudden death in Israeli civilians. *Lancet* **338**, 660-661 (1991).

122 Witte, D. R., Bots, M. L., Hoes, A. W. & Grobbee, D. E. Cardiovascular mortality in Dutch men during 1996 European football championship: longitudinal population study. *Bmj* **321**, 1552-1554 (2000).

123 Carroll, D. *et al.* Blood pressure reactions to acute psychological stress and future blood pressure status: a 10-year follow-up of men in the Whitehall II study. *Psychosomatic medicine* **63**, 737-743 (2001).

124 Nawrot, T. S., Perez, L., Kunzli, N., Munters, E. & Nemery, B. Public health importance of triggers of myocardial infarction: a comparative risk assessment. *Lancet* **377**, 732-740, doi:10.1016/S0140-6736(10)62296-9 (2011).
125 Tofler, G. H. *et al.* Triggers and Timing of Acute Coronary Syndromes. *The American journal of cardiology* **119**, 1560-1565, doi:10.1016/j.amjcard.2017.02.022 (2017).
126 Mittleman, M. A. & Mostofsky, E. Physical, psychological and chemical triggers of acute cardiovascular events: preventive strategies. *Circulation* **124**, 346-354, doi:10.1161/CIRCULATIONAHA.110.968776 (2011).
127 Maclure, M. & Mittleman, M. A. Should we use a case-crossover design? *Annual review of public health* **21**, 193-221, doi:10.1146/annurev.publhealth.21.1.193 (2000).
128 Fang, F. *et al.* Suicide and cardiovascular death after a cancer diagnosis. *The New England journal of medicine* **366**, 1310-1318, doi:10.1056/NEJMoa1110307 (2012).
129 Koton, S., Tanne, D., Bornstein, N. M. & Green, M. S. Triggering risk factors for ischemic stroke: a case-crossover study. *Neurology* **63**, 2006-2010 (2004).
130 Guiraud, V., Touze, E., Rouillon, F., Godefroy, O. & Mas, J. L. Stressful life events as triggers of ischemic stroke: a case-crossover study. *Int J Stroke* **8**, 300-307, doi:10.1111/j.1747-4949.2012.00810.x (2013).
131 Kivimäki, M., Vahtera, J., Pentti, J. & Ferrie, J. E. Factors underlying the effect of organisational downsizing on health of employees: longitudinal cohort study. *Bmj* **320**, 971-975 (2000).
132 Ghadri, J. R. *et al.* Happy heart syndrome: role of positive emotional stress in takotsubo syndrome. *European heart journal* **37**, 2823-2829, doi:10.1093/eurheartj/ehv757 (2016).
133 Dawson, D. K. Acute stress-induced (takotsubo) cardiomyopathy. *Heart*, doi:10.1136/heartjnl-2017-311579 (2017).
134 Templin, C. *et al.* Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. *The New England journal of medicine* **373**, 929-938, doi:10.1056/NEJMoa1406761 (2015).
135 Wittstein, I. S. *et al.* Neurohumoral features of myocardial stunning due to sudden emotional stress. *The New England journal of medicine* **352**, 539-548 (2005).
136 Steinberg, J. S. *et al.* Increased incidence of life-threatening ventricular arrhythmias in implantable defibrillator patients after the World Trade Center attack. *Journal of the American College of Cardiology* **44**, 1261-1264, doi:10.1016/j.jacc.2004.06.032 (2004).
137 Aboa-Eboule, C. *et al.* Job strain and risk of acute recurrent coronary heart disease events. *Jama* **298**, 1652-1660 (2007).
138 Laszlo, K. D., Ahnve, S., Hallqvist, J., Ahlbom, A. & Janszky, I. Job strain predicts recurrent events after a first acute myocardial infarction: the Stockholm Heart Epidemiology Program. *Journal of internal medicine* **267**, 599-611 (2010).
139 Biering, K., Andersen, J. H., Lund, T. & Hjollund, N. H. Psychosocial Working Environment and Risk of Adverse Cardiac Events in Patients Treated for Coronary Heart Disease. *J Occup Rehabil* **25**, 770-775, doi:10.1007/s10926-015-9585-2 (2015).

140 Aboa-Eboule, C. *et al.* Effort-reward imbalance at work and recurrent coronary heart disease events: a 4-year prospective study of post-myocardial infarction patients. *Psychosomatic medicine* **73**, 436-447, doi:10.1097/PSY.0b013e318222b2d8 (2011).

141 Georgiades, A., Janszky, I., Blom, M., Laszlo, K. D. & Ahnve, S. Financial strain predicts recurrent events among women with coronary artery disease. *Int J Cardiol* **135**, 175-183, doi:10.1016/j.ijcard.2008.03.093 (2009).

142 Ruberman, W., Weinblatt, E., Goldberg, J. D. & Chaudhary, B. S. Psychosocial influences on mortality after myocardial infarction. *The New England journal of medicine* **311**, 552-559, doi:10.1056/NEJM198408303110902 (1984).

143 Nieuwlaat, R., Schwalm, J. D., Khatib, R. & Yusuf, S. Why are we failing to implement effective therapies in cardiovascular disease? *European heart journal* **34**, 1262-1269, doi:10.1093/eurheartj/ehs481 (2013).

144 Rose, G. Sick individuals and sick populations. *International journal of epidemiology* **14**, 32-38 (1985).

145 Brugts, J. J. *et al.* Impact of renin-angiotensin system inhibitors on mortality and major cardiovascular endpoints in hypertension: A number-needed-to-treat analysis. *Int J Cardiol* **181**, 425-429, doi:10.1016/j.ijcard.2014.11.179 (2015).

146 Lear, S. A. *et al.* The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. *Lancet*, doi:10.1016/S0140-6736(17)31634-3 (2017).

147 Yusuf, S. *et al.* Blood-Pressure and Cholesterol Lowering in Persons without Cardiovascular Disease. *The New England journal of medicine* **374**, 2032-2043, doi:10.1056/NEJMoa1600177 (2016).

148 Collins, R. *et al.* Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* **388**, 2532-2561, doi:10.1016/S0140-6736(16)31357-5 (2016).

149 Cholesterol Treatment Trialists, C. *et al.* The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* **380**, 581-590, doi:10.1016/S0140-6736(12)60367-5 (2012).

150 Macleod, J. & Davey Smith, G. Psychosocial factors and public health: a suitable case for treatment? *Journal of epidemiology and community health* **57**, 565-570 (2003).

151 Masi, C. M., Chen, H. Y., Hawkley, L. C. & Cacioppo, J. T. A meta-analysis of interventions to reduce loneliness. *Pers Soc Psychol Rev* **15**, 219-266, doi:10.1177/1088868310377394 (2011).

152 Lucini, D. & Pagani, M. From stress to functional syndromes: an internist's point of view. *Eur J Intern Med* **23**, 295-301, doi:10.1016/j.ejim.2011.11.016 (2012).

153 Buchholz, L. Working Late, Courting Stroke. *Jama*, Oct 9:1-2. doi: 10.1001/jama.2015.12245. [Epub ahead of print], doi:10.1001/jama.2015.12245 (2015).

154 Tofler, G. H. & Muller, J. E. Triggering of acute cardiovascular disease and potential preventive strategies. *Circulation* **114**, 1863-1872, doi:10.1161/CIRCULATIONAHA.105.596189 (2006).

155 Ruzek, J. I., Kuhn, E., Jaworski, B. K., Owen, J. E. & Ramsey, K. M. Mobile mental health interventions following war and disaster. *Mhealth* **2**, 37, doi:10.21037/mhealth.2016.08.06 (2016).
156 Rozanski, A. Exercise as medical treatment for depression. *Journal of the American College of Cardiology* **60**, 1064-1066, doi:10.1016/j.jacc.2012.05.015 (2012).
157 Rebar, A. L. *et al.* A meta-meta-analysis of the effect of physical activity on depression and anxiety in non-clinical adult populations. *Health Psychol Rev* **9**, 366-378, doi:10.1080/17437199.2015.1022901 (2015).
158 Fonarow, G. C. *et al.* Workplace wellness recognition for optimizing workplace health: a presidential advisory from the American Heart Association. *Circulation* **131**, e480-497, doi:10.1161/CIR.0000000000000206 (2015).
159 Kornitzer, M. *et al.* Belgian heart disease prevention project: incidence and mortality results. *Lancet* **1**, 1066-1070 (1983).
160 Linden, W., Phillips, M. J. & Leclerc, J. Psychological treatment of cardiac patients: a meta-analysis. *European heart journal* **28**, 2972-2984, doi:10.1093/eurheartj/ehm504 (2007).
161 Gulliksson, M. *et al.* Randomized controlled trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary Health Care project (SUPRIM). *Archives of internal medicine* **171**, 134-140, doi:10.1001/archinternmed.2010.510 (2011).
162 Blumenthal, J. A. *et al.* Enhancing Cardiac Rehabilitation With Stress Management Training: A Randomized, Clinical Efficacy Trial. *Circulation* **133**, 1341-1350, doi:10.1161/CIRCULATIONAHA.115.018926 (2016).
163 Richards, S. H. *et al.* Psychological interventions for coronary heart disease. *The Cochrane database of systematic reviews* **4**, CD002902, doi:10.1002/14651858.CD002902.pub4 (2017).
164 Anderson, L. *et al.* Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-Analysis. *Journal of the American College of Cardiology* **67**, 1-12, doi:10.1016/j.jacc.2015.10.044 (2016).
165 Pogosova, N. *et al.* Psychosocial aspects in cardiac rehabilitation: From theory to practice. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation of the European Society of Cardiology. *European journal of preventive cardiology* **22**, 1290-1306, doi:10.1177/2047487314543075 (2015).
166 van Halewijn, G. *et al.* Lessons from contemporary trials of cardiovascular prevention and rehabilitation: A systematic review and meta-analysis. *Int J Cardiol* **232**, 294-303, doi:10.1016/j.ijcard.2016.12.125 (2017).
167 West, R. R., Jones, D. A. & Henderson, A. H. Rehabilitation after myocardial infarction trial (RAMIT): multi-centre randomised controlled trial of comprehensive cardiac rehabilitation in patients following acute myocardial infarction. *Heart* **98**, 637-644, doi:10.1136/heartjnl-2011-300302 (2012).
168 Herring, M. P., Puetz, T. W., O'Connor, P. J. & Dishman, R. K. Effect of exercise training on depressive symptoms among patients with a chronic illness: a systematic review and meta-analysis of randomized controlled trials.

*Archives of internal medicine* **172**, 101-111, doi:10.1001/archinternmed.2011.696 (2012).

169 Frieden, T. R. Evidence for Health Decision Making - Beyond Randomized, Controlled Trials. *The New England journal of medicine* **377**, 465-475, doi:10.1056/NEJMra1614394 (2017).

170 Piepoli, M. F. *et al.* 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *European heart journal* **37**, 2315-2381, doi:10.1093/eurheartj/ehw106 (2016).

171 Anderson, T. J. *et al.* 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Can J Cardiol* **32**, 1263-1282, doi:10.1016/j.cjca.2016.07.510 (2016).

172 Goff, D. C., Jr. *et al.* 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology* **63**, 2935-2959, doi:10.1016/j.jacc.2013.11.005 (2014).

173 Technical package for cardiovascular disease management in primary health care Report No. http://www.who.int/cardiovascular_diseases/hearts/Hearts_package.pdf (accessed in Aug 17, 2017), (World Health Organization, Geneva, Switzerland, 2016).

174 Kernan, W. N. *et al.* Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* **45**, 2160-2236, doi:10.1161/STR.0000000000000024 (2014).

175 Pesah, E., Supervia, M., Turk-Adawi, K. & Grace, S. L. A Review of Cardiac Rehabilitation Delivery Around the World. *Prog Cardiovasc Dis*, doi:10.1016/j.pcad.2017.08.007 (2017).

176 Collins, F. S. & Varmus, H. A new initiative on precision medicine. *The New England journal of medicine* **372**, 793-795, doi:10.1056/NEJMp1500523 (2015).

177 Becker, C. M., Lee, J. G. L., Hudson, S., Hoover, J. & Civils, D. A 14-year longitudinal study of the impact of clean indoor air legislation on state smoking prevalence, USA, 1997-2010. *Preventive medicine* **99**, 63-66, doi:10.1016/j.ypmed.2017.01.016 (2017).

178 White, V. M. *et al.* What impact have tobacco control policies, cigarette price and tobacco control programme funding had on Australian adolescents' smoking? Findings over a 15-year period. *Addiction* **106**, 1493-1502, doi:10.1111/j.1360-0443.2011.03429.x (2011).

179 Pulakka, A. *et al.* Association Between Distance From Home to Tobacco Outlet and Smoking Cessation and Relapse. *JAMA Intern Med*, doi:10.1001/jamainternmed.2016.4535 (2016).

180 Briggs, A. D. M. *et al.* Health impact assessment of the UK soft drinks industry levy: a comparative risk assessment modelling study. *Lancet Public Health* **2**, e15-e22, doi:10.1016/S2468-2667(16)30037-8 (2017).

**Acknowledgements**

M Kivimäki's work was supported by the UK Medical Research Council (K013351), NordForsk (75021), the Academy of Finland (311492), and a Helsinki Institute of Life Science Fellowship.

**Key points**

Pooling of individual-level and published data from multiple cohorts into mega studies has allowed more precise assessment of the association between stress and cardiovascular disease.

In the general population, adults with stress at work or private life have a 1.1 to 1.6-fold increased risk of incident coronary heart disease and stroke.

This excess cardiovascular disease risk is less marked compared with those for smoking, high blood pressure, high serum cholesterol, obesity or a history of multiple severe stressful experiences in childhood, such as sexual abuse, domestic violence and household substance abuse.

However, stress in adulthood has an important role as a disease trigger in persons with high atherosclerotic plaque burden and as a determinant of outcome in those with preexisting cardiovascular or cerebrovascular disease. In these specific groups of people, summary hazard ratios for stress typically exceed 2.

Pathophysiological effects of stress as a disease trigger in vulnerable people involve increased cardiac electrical instability, myocardial ischaemia, plaque distribution, and thrombus formation, contributing to clinical events, such as dysrhythmia, myocardial infarction, cardiomyopathy, and stroke.

European guidelines for cardiovascular disease prevention acknowledge stress as a clinically meaningful risk factor among persons with high overall cardiovascular risk or established cardiovascular disease.

Other clinical guidelines do not identify stress as a target for prevention or treatment of cardiovascular disease.

**BOX | Stress assessment**

**Focus of stress measurements**
*Chronic stressors*
*Major life events*
*Daily events*
*Perceived stress*
*Stress biomarkers*

**Mode of measurement**
*Observation*
*Interview*
*Self-completion questionnaires & checklists*
*eDiaries, smartphone applications*
*Biosamples (blood, saliva, urine, hair)*
*Wearable biomonitoring techniques*

## TABLE AND FIGURE LEGENDS

**Table 1** | Meta-analyses and large-scale studies on the cross-sectional association of stress at work with atherosclerosis and metabolic risk factors. Stress is more consistently related to metabolic factors than major atherosclerosis factors.

**Table 2** | Number needed to treat to prevent one cardiovascular event within 5 years by eliminating job strain and physical inactivity in the general population and by statin and antihypertensive drug treatment in targeted populations.

**Figure 1** | Meta-analyses and large cohort studies on stress as a risk factor for cardiovascular disease in the general population, individuals at high cardiovascular disease risk, and patients with established cardiovascular disease. Except for extreme childhood stress, the associations between stress and cardiovascular endpoints are weak or moderate in the general population (hazard ratio less than 2, shown with blue plots). In contrast, the associations with clinical endpoints are strong in high-risk populations (hazard ratio higher than 2, red plots). In individuals with preexisting cardiovascular disease, the associations of stress with recurrent events and death are moderate or strong. Statistically non-significant associations are shown with white plots.

**Figure 2** | Evaluation of unmeasured confounding that could explain the observed stress-cardiovascular disease associations in the general population and a subgroup of individuals with high overall cardiovascular disease risk. Although studies have

adjusted analyses for a number of classic cardiovascular disease risk factors, residual confounding by unmeasured or imprecisely measured cardiovascular risk factors that are associated with both the stressor and the risk of cardiovascular disease remains possible. Such an unmeasured confounder should be associated with a doubling of the likelihood of stress and cardiovascular disease to explain the observed association in the general population and be associated with 9-fold increased risk of stress and cardiovascular disease to explain the observed association in individuals with high overall cardiovascular disease risk.

**Figure 3** | Schematic model of physiological responses and pathophysiological effects of stress that contribute to triggering of cardiovascular event. The figure shows that response to emotional stress involves changes in the hypothalamus-pituitary-adrenal cortex (HPA) axis function and the autonomic nervous system. Among individuals who already have a high atherosclerotic plaque burden, stress may be the trigger that precipitates the occurrence of a cardiac or cerebrovascular event. The common pathology in acute cardiac and cerebrovascular events is rupture or disruption of the fibrous cap of the plaque, coupled with active inflammation and hypercoagulability. Cardiac electrical instability, myocardial ischaemia and possibly excessive levels of circulating catecholamines are also contributing factors. Stress-related clinical events include ventricular tachycardia/fibrillation, atrial fibrillation, myocardial infarction and other forms of acute coronary syndromes (e.g., instable angina and stress cardiomyopathy), and stroke.

**Figure 4** | Meta-analyses and large-scale studies on cross-sectional associations between adulthood stress and factors increasing the risk of rupture or disruption of the

fibrous cap of the plaque and thrombus formation leading to cardiac or cerebrovascular event. The associations with high work-time ambulatory blood pressure, increased risk of atrial fibrillation and pulmonary embolisms, high platelet and white cell counts, and increased alcohol consumption (indicated by elevated gamma GT levels and self-reported increasing alcohol use) support the notion that stress contributes to triggering of cardiac and cerebrovascular events. Statistically significant associations are shown with blue plots and non-significant with white plots.

**Figure 5** | Estimated five year risk of incident disease or death by status of stress in stroke-free population,[10] coronary heart disease-free population,[48] high-risk population[32] and patients with a history of myocardial infarction.[62] The bars illustrate that due to low overall incidence rates, the difference in absolute disease risk between disease-free individuals with and without stress is small. In contrast, high-risk populations and cardiovascular disease patients have high overall rates of morbidity and mortality and in these groups the moderately and strongly increased relative risk associated with stress translates to large differences in absolute risk between those exposed versus not exposed to stress.

Table 1| **Meta-analyses and large-scale studies on the cross-sectional association of stress in adulthood with atherosclerosis and metabolic risk factors. Stress is more consistently related to metabolic factors than major atherosclerosis factors.**

| | Stressor | Estimate (95% CI) | N (total) | N (studies) | Reference* | P <0.05 |
|---|---|---|---|---|---|---|
| **Atherosclerosis Factors** | | | | | | |
| **Hypertension** | Job strain | Odds ratio 1.24 (1.09 to 1.41) | 24,711 | 6 | [75] (P) | Yes |
| **Hypertension** | Job strain | Odds ratio 0.99 (0.93 to 1.04) | 47,045 | 8 | [76] (I) | |
| **Systolic blood pressure** | Job strain | Mean difference -0.01 (-0.38 to 0.36) mmHg | 44,106 | 8 | [76] (I) | |
| **Systolic blood pressure** | Effort-reward imbalance | Mean difference 0.01(-0.01 to 0.03) SD | 20,899 (m) | 1 | [77] (I) | |
| **Systolic blood pressure** | Effort-reward imbalance | Mean difference 0.01(-0.01 to 0.03) SD | 22,432 (f) | 1 | [77] (I) | |
| **Diastolic blood pressure** | Job strain | Mean difference 0.01 (-0.24, 0.26) mmHg | 44,104 | 8 | [76] (I) | |
| **Diastolic blood pressure** | Effort-reward imbalance | Mean difference 0.06 (0.03 to 0.09) SD | 20,899 (m) | 1 | [77] (I) | Yes |
| **Diastolic blood pressure** | Effort-reward imbalance | Mean difference 0.02 (0.00 to 0.05) SD | 22,432 (f) | 1 | [77] (I) | |
| **LDL cholesterol** | Effort-reward imbalance | Mean difference 0.04 (0.01 to 0.07) SD | 20,899 (m) | 1 | [77] (I) | Yes |
| **LDL cholesterol** | Effort-reward imbalance | Mean difference 0.03 (0.00 to 0.06) SD | 22,432 (f) | 1 | [77] (I) | |
| **Smoking** | Job strain | Odds ratio 1.14 (1.08 to 1.20) | 46,553 | 8 | [76] (I) | Yes |
| **Smoking** | Long working hours | Odds ratio 1.15 (1.02 to 1.31) | 85.494 | 8 | [78] (I) | Yes |
| | | | | | | |
| **Metabolic Factors** | | | | | | |
| **Obesity, class I** | Job strain | Odds ratio 1.07 (1.02 to 1.12) | 161,746 | 13 | [84] (I) | Yes |
| **Obesity, classes II & III** | Job strain | Odds ratio 1.14 (1.01 to 1.28) | 161,746 | 13 | [84] (I) | Yes |
| **Obesity** | Long working hours | Odds ratio 1.34 (1.17 to 1.54) | 85.494 | 8 | [78] (I) | Yes |
| **BMI** | Effort-reward imbalance | Mean difference 0.07 (0.05 to 0.10) SD | 20,899 (m) | 1 | [77] (I) | Yes |
| **BMI** | Effort-reward imbalance | Mean difference 0.09 (0.06 to 0.12) SD | 22,432 (f) | 1 | [77] (I) | Yes |
| **Diabetes** | Job strain | Odds ratio 1.29 (1.11 to 1.51) | 46,510 | 8 | [76] (I) | Yes |
| **Fasting glucose** | Effort-reward imbalance | Mean difference 0.03 (0.01 to 0.06) SD | 20,899 (m) | 1 | [77] (I) | Yes |
| **Fasting glucose** | Effort-reward imbalance | Mean difference 0.01 (-0.01 to 0.03) SD | 22,432 (f) | 1 | [77] (I) | |
| **HDL cholesterol** | Job strain | Mean difference -0.001 (-0.01, 0.01) mmol/l | 45,728 | 8 | [76] (I) | |
| **HDL cholesterol** | Effort-reward imbalance | Mean difference -0.06 (-0.09 to -0.03) SD | 20,899 (m) | 1 | [77] (I) | |
| **HDL cholesterol** | Effort-reward imbalance | Mean difference -0.06 (-0.09 to -0.03) SD | 22,432 (f) | 1 | [77] (I) | |
| **Triglycerides** | Job strain | Mean difference -0.001 (-0.02 to 0.02 mmol/l) | 18,858 | 4 | [76] (I) | |
| **Triglycerides** | Effort-reward imbalance | Mean difference 0.08 (0.05 to 0.12) SD | 20,899 (m) | 1 | [77] (I) | Yes |
| **Triglycerides** | Effort-reward imbalance | Mean difference 0.05 (0.02 to 0.07) SD | 22,432 (f) | 1 | [77] (I) | Yes |
| **Physical inactivity** | Job strain | Odds ratio 1.26 (1.15 to 1.38) | 170,162 | 14 | [79] (I) | Yes |
| **Physical inactivity** | Long working hours | Odds ratio 1.18 (1.07 to 1.30) | 85.494 | 8 | [78] (I) | Yes |

* P = data from published studies; I = individual-participant data.
M, male; F, female.

Table 2 | **Number needed to treat to prevent one cardiovascular event within 5 years by eliminating job strain and physical inactivity in the general population and by statin and antihypertensive drug treatment in targeted populations.**

| Intervention/elimination of risk factor | Population | Outcome | NNT | Reference |
|---|---|---|---|---|
| **Change from job strain to no job strain*** | General population without CHD | Coronary heart disease | 550 | [48] |
| **Change from physically inactive to physically active*** | General population without CVD | Myocardial infarction | 310 | [146] |
| **Change from physically inactive to physically active*** | General population without CVD | Major CVD event | 195 | [146] |
| **Statin and antihypertensive medication versus neither†** | People at intermediate risk of CVD | Major CVD event | 80 | [147] |
| **ACE inhibitor treatment versus not†** | People with hypertension | Myocardial infarction | 70 | [145] |
| **Statin therapy reducing LDL-C by 1mmol/L†** | People with established CVD | Major CVD event | 18 | [149] |

*NNT estimated from observational data by comparing risks between exposed and unexposed groups with 5-year follow-up.
†NNT estimated from results from randomised controlled trials for 5-year follow-up.
CVD, cardiovascular disease; NNT, number needed to treat to prevent 1 cardiovascular event