The Relationship Between Psychological Distress and Bio-behavioral Processes in Cardiovascular Disease

Stefania Balzarotti, Barbara Colombo, and Amanda Christensen

Contents

Abstract

Cardiovascular disease (CVD) has been proven to be the largest contributor to morbidity and mortality in the developed world. By considering the psychosocial factors that have been linked to CVD, this chapter will focus on the role of psychological *distress*. Existing empirical evidence shows that stress can be considered as a risk factor starting from the early years, while in adulthood the risk associated with distress derives mainly from either social isolation or workplace-related chronic stressors. Both behavioral and neurobiological mechanisms have been proposed to underlie this association, including sustained activation of the sympathetic nervous system and reduced heart rate variability. Finally, we report research emphasizing the potential protective

S. Balzarotti
Department of Psychology, Catholic University of the Sacred Heart, Milan, Italy
e-mail: stefania.balzarotti@unicatt.it

B. Colombo (✉) · A. Christensen
Neuroscience Lab, Champlain College, Burlington, VT, USA
e-mail: bcolombo@champlain.edu; amanda613@me.com

S. Govoni et al. (eds.), *Brain and Heart Dynamics*,
https://doi.org/10.1007/978-3-319-90305-7_14-1

role of positive psychological constructs such as well-being, optimism, and positive affect.

Keywords
Stress · Distress · Cardiovascular disease · Well-being · Risk factors

Introduction

Cardiovascular disease (CVD) has been proven to be the largest contributor to morbidity and mortality in the developed world [1]. Extensive literature has so far targeted the identification of risk factors for CVD as well as the assessment of their predictive ability, as these factors are critical for disease prevention and treatment. Risk factors can be defined as the measurable characteristics that have been shown to increase a person's probability of heart disease based on epidemiological evidence [2]. Risk for heart disease is determined based on the "total risk," that is, a summation of all possible risk factors, because one single high-level risk variable may contribute to a lower overall risk than a number of low-level risk variables [3, 4].

A great deal of research has been conducted on the impact of the so-called traditional risk factors on CVD [1], which include physical inactivity, diabetes, cigarette smoking, hypertension, dyslipidemia, and family history of premature coronary disease [5]. By contrast, the body of research on nontraditional risk factors – comprising biomarkers such as oxidative stress, inflammation, and insulin resistance [6] – is smaller [7]. Among nontraditional risk factors, several authors have emphasized the role of the *psychosocial* factors [8], which include stress/distress [9], emotional disorders such as anxiety and depression [10], and personality traits [11].

By considering the psychosocial factors that have been linked to CVD, this chapter will focus on the role of psychological *distress*. First, we will examine the definitions of distress, and of *stress* more broadly, provided by psychological literature in the attempt to disentangle related constructs. We will then address existing empirical evidence linking psychological stress and distress to CVD. Third, the main behavioral and neurobiological mechanisms that have been proposed to underlie this association will be briefly considered. Finally, we will conclude by highlighting the potential protective role of psychological variables such as well-being, optimism, and positive emotions. Although the chapter is meant to provide an overview of the link between CVD and distress, it is important to bear in mind that psychosocial factors are likely to occur and cluster together, raising in this way the risk ratios for cardiac events [12].

Stress and Distress: Definitions

Stress: A Challenging Definition

Stress can be defined as a perturbation to the organism, which can derive from changes to the physiological homeostasis or psychological well-being.

The first definition of stress was suggested in the 1950s by Selye [13] who, starting from his medical training, measured stress in terms of physiological responses, focusing mainly on the sympathetic adrenal-medullary activity and the pituitary-adrenal-cortical activity. Selye also discussed what he called the general adaptation syndrome (GAS), suggesting that being overexposed to stressful situation would lead the individual's body to overproduce chemicals that would lead to ulcers and high blood pressure. In his view, though, stress was mainly conceived as a non-specific response of the body to any noxious stimulus. For this reason, this initial definition has long proven to be only partially correct. Yet, it is important because it was the first attempt to explain how disease can be caused not by a purely physiological cause but how stress can affect the immune system as well as the adrenal glands.

The second step was introducing some more specific elements, by distinguishing between stressors and stress responses. Internal or external changes that can trigger a stress response are defined as stressors. A stressor has been commonly intended as a stimulus that threatens homeostasis, and the stress response is the

reaction of the organism aimed to regain homeostasis [14]. When the body perceives the change triggered by the stressor, it activates different coping mechanisms or adaptive changes, including behavioral reactions, activation of the sympathetic nervous system and adrenal medulla, secretion of stress hormones (e.g., glucocorticoids and prolactin), and mobilization of the immune system.

There at least two problematic aspects about these definitions. The first one is linked to the term homeostasis, which was originally introduced by Cannon [15], and is commonly used when referring both to stress and to stressors. Since homeostasis is a virtual baseline, it is easy to understand how almost any activity of the organism itself concerns, more or less directly, a form of defense of the homeostasis. For these reasons, several authors [16, 17] pointed out how defining of stress as a threat to homeostasis is not exhaustive and how more critical consideration to get to a better understanding of stress and stressors is needed.

The second problematic aspect is linked to the fact that many times authors do not consider if a stimulus is indeed perceived as a stressor in the sense that it is considered as an actual threat to homeostasis and thus to physical and psychological health, but they either only focus on detecting the presence of a stress response, which is read as an indicator of stress exposure [18], or focus on a stimulus that they classify as aversive and consequently interpret the response to that stimulus as a stress response [19].

Stress and Distress

The individual's perception and evaluation of a stressor have been accounted by Lazarus' theory of stress [20], which focused on the wide range of cognitive and behavioral responses people commonly use to cope with stress and face everyday problems. Lazarus' theory stressed the role of cognitive appraisal in the individual's response to a stressful situation and focused attention to the ways in which the individual copes with such a situation. According to Lazarus' model, three different kinds of evaluation take place: (a) the primary appraisal, which consists of how the situation is evaluated; (b) the secondary appraisal, which deals with how the organism views its own capabilities and resources to respond; (c) and finally the coping process, which is how the organisms attempt to manage the relation with the environment that caused stress [21]. In this perspective, it is not stress itself that constitutes a threat to a person's overall well-being but how the individual copes with it: "stress is a natural and expectable feature of living, but it also makes the coping process necessary" [22]. If coping is effective, stress is likely to remain under control, whereas if coping is ineffective, stress may have damaging consequences for physical and psychological health. Although extensive research has examined the strategies through which people cope with stressors and their impact on psychological health outcomes (under the hypothesis that coping strategies moderate the harmful effects of stress on health), far less research has addressed the association between coping and biological health indicators, including indicators of CVD [23].

Along with this line of reasoning, *distress* is thought to occur when the individual cannot cope against the assault of one or more stressors. Distress has been defined as an aversive, negative state in which coping and adaptation processes fail; it can include a variety of negative affective responses such as anxiety and sadness, together with a sense of helplessness [24]. The transition of stress to distress may depend on several factors. Existing research suggests that unpredictability and uncontrollability (the absence of an anticipatory response and loss of control) are central features of stressful experiences that can qualify as distress and end up having negative consequences on the organism [19]. For this reason, negative stress, or distress, should be used as a construct when predictability and controllability are at stake [19]. Especially when focusing on clinical or preclinical samples, it is also important to highlight how evidence from the human literature on stress and distress supports the fact that it is not the actual control that counts but the perceived control [25], with data supporting increased stress and

perceived pain in response to unpredictable stimuli [26, 27].

Both acute (deriving from demands and pressures of the recent past or the near future) and chronic stress (ongoing environmental condition or as a stressor with enduring impact) can be linked to distress [28], but chronic stress appears to have a strong link to distress, as we just defined it, because of the fact that the longer a stressor lasts, the more likely it is to be perceived as out of control from the individual experiencing it. This line of reasoning is confirmed by the fact that chronic stress, both at early life and adulthood, has been associated with increased risk of CVD (up to 60%) [29] and individuals who report "permanent stress" at work or at home are more than two times more likely to suffer from a myocardial infarction [30].

Finally, a relevant distinction concerns the concept of stress/distress (i.e., the response to a current stressor) and an individual's general, stable propensity to experience distress, which has been captured by different personality traits and mood dispositions. In other terms, people may differ in their tendency to chronically experience distress. For instance, Costa and McCrae [31] have defined *neuroticism* as the tendency to experience and report negative emotional states. Similarly, Watson and Clark [32] have proposed *negative affectivity* to correspond to a general dimension of subjective distress, reflecting stable individual differences in negative mood. Other research has examined the so-called Type D (Distressed) personality defined as the tendency toward negative affectivity and social inhibition, finding that it is linked to adverse cardiovascular outcomes (for a review, see [11]).

In the next paragraph, we will discuss more specifically the role of stress as a risk factor for cardiovascular diseases.

Stress as a Risk Factor for Cardiovascular Disease

The different levels of risks for CVD that are associated with distress have been widely explored in literature [29], supporting the hypothesis of stress as a predictor of CVD. A recent review [29] reports how stress can be considered as a risk factor starting from the early years: childhood abuse and early socioeconomic adversity are positively correlated with higher risk of CVD in adulthood. A meta-analysis [4] also highlights the risk associated with distress derived either from social isolation or workplace-related chronic stressors.

Early Life Experiences

Recent literature reporting clinical studies on different population has been increasingly stressing how being exposed to early life stress can be seen as an independent risk factor for the development of chronic diseases. Among the most frequently reported, we can find several CVD like ischemic heart disease, cardiovascular disease, and stroke [33–36].

Childhood abuse has been proved [37] to be a predictor of specific CVD, such as heart attack and stroke. Self-report data support the notion that even less traumatic childhood adversities can double the risk of CVD, when individuals reported three or more [38]. Focusing specifically on a sample of women, a 45-year follow-up study allowed to add the role of early experienced chronic stress (linked to low childhood socioeconomic status) as a risk factor, which appeared to increase the chances of mortality by CVD by 1.4 times [39].

Evidence from meta-analysis and reviews highlights how it is not always the distress experienced early in life the source of the problem per se: Traumatic events can not only be harmful but also have some partially positive effects on the development of successful coping mechanism, depending on their duration, intensity, and timing [40]. This line of reasoning is supported by the evidence that can be found in literature, supporting the fact that the intensity, length, and number of adverse factors seem to have an additive effect in the physiological outcomes analyzed and certainly predict an enhanced risk to develop cardiovascular disease during the adult life [41].

Work-Related Distress

Work-related stress is the most widely studied form of chronic stress, and in line with what we have been discussing, at a general level, low job control predicts future cardiac problems [42]. Being more specific, both chronic and subacute work-related distress (i.e., the accumulation of stressful life events over several months) have been widely investigated as a possible risk factor for CVD, and several interesting correlations have been reported in literature. For example, higher level of distress appears to be positively correlated with elevation of arterial blood pressure [43] and neurohumoral arousal [44]. This symptom has also been frequently reported in association with subacute distress [45]. The level of subacute stress has been proved to be positively correlated with sudden cardiac death in different samples, like healthy middle-aged men [46] as well as patients presenting with acute myocardial infarction [47]. A more specific example relates to the number of hours per week an individual tends to work: long hours (>55 h on the average week) increase the risk of CVD of 40% [48].

The relevance of stress as a risk factor for CVD appears to be also linked to whether stress is the only risk factor or if it happens to be associated with other potential risks. For example, when studying the risk ratios for myocardial infarction, both distress and social isolation appear to be valid predictors [49]. Yet, when these two factors happen together, the risk of a myocardial infarction to happen doubled [49]. The same trend has also been reported when studying risks factors in healthy individuals [46].

Social Isolation

Chronic stress derived from social isolation and loneliness experienced by adults [50], especially when older, is another significant risk factor for CVD. To be more precise, according to meta-analytic evidence, social isolation does not appear to trigger CVD but is significantly linked to a worse prognosis [51].

Many studies report a strong positive correlation between perceived lack of social/emotional support and subsequent incidence of CVD [51]. Other studies assessing directly the magnitude of actual social support experienced by different samples reported a negative correlation between the level of social support and future incidence of CVD [51–53]. Interestingly enough, those adults who report the need for seeking social support in response to distress, because they feel like they are lacking a supportive social network in their life [54], tended to be readmitted more often for coronary heart disease [55].

Mechanisms Underlying the Link Between Psychological Stress and CVD

Several researchers have focused their attention on the bio-behavioral processes that mediate the relationship between psychological stress and CVD (for reviews, see, for instance, [8, 56]). The understanding of these underlying processes may in fact contribute to the prevention and treatment of stress-related cardiovascular pathologies. A first type of processes concerns behavioral mechanisms, in which stress is thought to lead to higher risk of CVD by means of its association with adverse health and lifestyle behavior [12]. In other words, stressful experiences increase the likelihood that individuals engage in unhealthy behaviors such as smoking and substance abuse [57–60], which in turn have been shown to represent risk factors for CVD.

A second class of mediators includes pathophysiological mechanisms, which are thought to act at many points along the pathophysiological steps leading to cardiac events (for a discussion, see, for instance, [56]). Within this class, research has examined the role of the autonomic nervous system (ANS) – which comprises the sympathetic (SNS) and parasympathetic nervous system (PNS) – and of the hypothalamic-pituitary-adrenocortical (HPA) axis, as they represent major components of the physiological response to stress [61].

The HPA Axis

The HPA axis is one of the primary biological systems activated during a stress response [29, 61]. A recent review [62] has examined the effects of the hormones produced by the HPA axis on the cardiovascular systems showing that the prolonged dysregulation of the HPA axis and glucocorticoid production may lead to various types of pathologies, including hypertension and vascular damage. It is still unclear, however, whether risk for CVD is directly linked to the activation of the HPA due to stress or heart disease may develop as a consequence of the metabolic strain generated by extreme levels of glucocorticoids.

Autonomic Imbalance

Autonomic imbalance between the sympathetic and parasympathetic regulation of the heart – characterized by heightened activity of the SNS and suppressed activity of the PNS – has been proposed as a key component in stress-related cardiovascular disease [63, 64].

Autonomic responses prepare the body to cope with stressors: The general response to stress involves the activation of the SNS, which is in charge of defensive behavior (e.g., the so-called "fight or flight" response), together with the inhibition of the PNS [65]. Sympathetic activation increases myocardial oxygen demand by increasing heart rate, blood pressure, and cardiac contractility. Although this acute mobilization most often represents an adaptive bodily response to stressors and threats, persistent activation of SNS (e.g., due to prolonged or repeated stress exposure) can have adverse health effects, including cardiovascular problems [24]. Sustained stimulation of cardiac sympathetic outflow has been identified as a contributor to cardiac events such as myocardial infarction, ventricular arrhythmias, and sudden death [8]. It is thought that sympathetic activation triggered by acute physical or mental stressors may contribute to the development of CVD through various pathways, such as increased platelet aggregation, potential atherosclerotic plaque rupture, reduced blood flow to the myocardium, and electrical instability of the heart [8]. Likewise, excessive activation of the SNS has been proposed as a mediator between chronic distress (e.g., work stress) and adverse cardiovascular consequences, such as the development of hypertension and atherosclerosis [12].

A second (smaller) group of studies has considered the mediating role of impaired cardiac vagal control in the association of CVD with stress (for a review, see [63, 66, 67]) – notably, several risk factors for CVD such as hypertension, diabetes, and cholesterol have been related to decreased vagal function [67, 68]. For instance, it has been shown that work stress predicts coronary heart disease and that this association may be partly mediated by lowered heart rate variability [57, 64]. Other studies have found impaired control of parasympathetic regulation of the heart to be associated with cardiovascular mortality in patients with coronary artery disease and in elderly people [69, 70]. Finally, cardiac vagal control was found to mediate cardiovascular responses (e.g., diastolic blood pressure, peripheral resistance, myocardial oxygen demand) to a mental stress task in patients with coronary artery disease [71].

Cardiovascular Reactivity

Cardiovascular reactivity (CR) has been defined as a dispositional, stable tendency to exhibit SNS hyper-reactivity (i.e., pronounced heart rate and blood pressure responses) in front of stressors [72, 73]. Researchers have advanced the hypothesis (called the *reactivity hypothesis*) that people with the largest physiological response to stressors are at a higher risk for CVD [74, 75]. So far, studies have found some empirical evidence of an association of CR with hypertension [76] and atherosclerosis [77, 78].

To explain how cardiac reactivity may lead to CVD, Lovallo and Gerin [73] have proposed a three-level bio-behavioral model linking the

brain and the heart under the hypothesis that both the central and the peripheral nervous systems may contribute to heightened CR. More in detail, this model assumes that individual differences in CR may be accounted for by considering (1) cognitive-emotional responses to stressors, (2) heightened hypothalamic and brainstem responsivity, and (3) peripherally altered tissue function.

At the top level, cognitive (e.g., threat appraisals) and emotional responses to stressors can shape autonomic and endocrine activation patterns [79]. These responses depend on the activity of the frontal cortex and the limbic system, which have been shown to underlie the organism's ability to detect external challenges/threats and to coordinate both behavioral and physiological reactions to them [80]. Notably, individuals differ with respect to their habitual emotional response styles in terms of temperament and personality traits (e.g., neuroticism, hostility) [81], so that biases at this level may result in altered reactivity to stress and contribute to CVD [82].

The next level includes the hypothalamus and brainstem activity, as these brain structures regulate autonomic and endocrine pathways by means of which emotional responses are translated into physiological outputs. At this level, CR is thought to result from altered hypothalamic and brainstem functions: For instance, some studies have found that greater physiological activation in response to anticipation of physical stress was related to negative cardiovascular consequences [83], while other studies have shown that individuals with borderline hypertension tended to exhibit higher activation to mental stress tasks than control healthy individuals, even though no difference emerged in self-reported emotional evaluations [84].

Finally, peripherally altered tissue functions (e.g., vascular wall thickening, coronary artery plaque) may cause excessive responses to stimuli even when emotional and brainstem outputs are normal [85]. A person may thus show exaggerated reactions to stressors without any malfunction in cognitive appraisals or emotions or alteration in endocrine or autonomic outflow.

Psychological Protective Factors: Positive Psychological Functioning

While risk factors are associated with increased likelihood to develop CVD, protective factors can be defined as those characteristics or variables associated with lower probability of adverse cardiac outcomes, or able to reduce the impact of a risk factor.

In recent years, positive psychology has complemented the traditional focus of psychological literature on pathology with the scientific study of the individual's well-being and positive or "optimal" functioning [86]. Well-being and ill-being have been shown to represent independent dimensions of mental health, so that well-being is not simply an absence of pathology but implies that the individual feels good about his/her life and functions well [87].

Notably, positive psychological functioning has been shown to have a beneficial impact on cardiovascular health and a protective role against CVD [for a review see [88]]. For instance, some studies have found higher optimism (defined as the cognitive disposition to expect positive, favorable outcomes in one's life [89]) to be associated with lower risk of CVD [90], stroke [91], hospitalization after bypass surgery [92], and heart failure [93] in middle-aged and elderly adults. Also, highly optimistic individuals are more likely to engage in healthy behaviors such as physical activity and refrain from smoking [94]. Likewise, other studies have found significant associations between reduced risk of coronary heart disease and positive constructs such as emotional vitality [95, 96] and displays of positive affect [97].

Finally, a recent meta-analytic review [98] has focused on the effects of positive psychological constructs such as optimism, positive affect, and well-being on health-related outcomes (i.e., self-reported health status, mortality, and re-hospitalization) in patients with established heart disease (e.g., coronary artery disease, ventricular arrhythmia). The results showed that most of the studies considered in the review (though not all) found prospective significant associations between positive psychological constructs and health outcomes within multiple forms of heart

disease: Positive psychological characteristics predicted reduced rates of re-hospitalization and mortality.

Conclusions

This chapter aimed to provide an overview of the specific role that psychological distress plays as a risk factor for CVD.

We have seen how different categories of distress might predict the chances for individuals to develop CVD at various stages of their life.

Distress might start playing a role if experienced early in life [33–36], and it can mainly trigger chronic CVD. Yet experiencing distress per se does not automatically lead to a higher chance of developing CVD. The evidence discussed in the chapter highlights how the intensity, length, and number of adverse factors seem to predict better the level of risk to develop cardiovascular disease during adult life [41]. The same can be said for the other main categories of distress that are linked to CVD: work-related distress and social isolation.

If it is true that low job control predicts future cardiac problems [42] and lack of social support is related to the incidence of CVD [52, 53] and to the positive vs. negative prognosis of the disease [99], it is also true that the way people perceive the stressors and the coping mechanism that they adopt can moderate if not resolve the adverse effects of the distress per se.

This means that the reported effects on the HPA axis (one of the primary biological systems activated during a stress response [29, 61]), the autonomic imbalance between the sympathetic and parasympathetic regulation of the heart, and cardiovascular reactivity are moderated by the psychological responses of the individuals to the different life-related stressors.

This line of reasoning leads us to focus on what can constitute protective factors against developing CVD as a response to specific factors. Literature reports how positive psychological constructs such as optimism, positive affect, and well-being can influence health-related outcomes in patients with established heart disease [98] – possibly because they lead to a different evaluation and consequently bio-behavioral responses to different sources of distress.

References

1. Kelly BB, Fuster V. Promoting cardiovascular health in the developing world: a critical challenge to achieve global health. Washington, DC: National Academies Press; 2010.
2. Rosmond R, Bjorntorp P. The hypothalamic-pituitary-adrenal axis activity as a predictor of cardiovascular disease, type 2 diabetes and stroke. J Intern Med. 2000;247(2):188–97.
3. Ofori SN, Odia OJ. Risk assessment in the prevention of cardiovascular disease in low-resource settings. Indian Heart J. 2016;68(3):391–8.
4. Steptoe A, Kivimäki M. Stress and cardiovascular disease. Nat Rev Cardiol. 2012;9(6):360–70.
5. de Goma EM, Knowles JW, Angeli F, Budoff MJ, Rader DJ. The evolution and refinement of traditional risk factors for cardiovascular disease. Cardiol Rev. 2012;20(3):118–29.
6. Balagopal P, de Ferranti SD, Cook S, Daniels SR, Gidding SS, Hayman LL, et al. Nontraditional risk factors and biomarkers for cardiovascular disease: mechanistic, research, and clinical considerations for youth: a scientific statement from the American Heart Association. Circulation. 2011;123(23):2749–69.
7. Shaima C, Moorthi P, Shaheen N. Cardiovascular diseases: traditional and non-traditional risk factors. J Med Allied Sci. 2016;6(2):46.
8. Hering D, Lachowska K, Schlaich M. Role of the sympathetic nervous system in stress-mediated cardiovascular disease. Curr Hypertens Rep. 2015;17(10):80.
9. Ferketich AK, Binkley PF. Psychological distress and cardiovascular disease: results from the 2002 National Health Interview Survey. Eur Heart J. 2005;26(18):1923–9.
10. Chauvet-Gelinier J-C, Bonin B. Stress, anxiety and depression in heart disease patients: a major challenge for cardiac rehabilitation. Ann Phys Rehabil Med. 2017;60(1):6–12.
11. Denollet J, Schiffer AA, Spek V. A general propensity to psychological distress affects cardiovascular outcomes: evidence from research on the type D (distressed) personality profile. Circ Cardiovasc Qual Outcomes. 2010;3(5):546–57.
12. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation. 1999;99(16):2192–217.
13. Selye H. Endocrine reactions during stress.∗. Anesth Analg. 1956;35(3):182–93.
14. Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol. 2009;5(7):374–81.

15. Cannon WB. The wisdom of the body. New York: WW Norton and Company; 1939.
16. Day TA. Defining stress as a prelude to mapping its neurocircuitry: no help from allostasis. Prog Neuro-Psychopharmacol Biol Psychiatry. 2005;29(8): 1195–200.
17. Levine S. Developmental determinants of sensitivity and resistance to stress. Psychoneuroendocrinology. 2005;30(10):939–46.
18. Armario A. The hypothalamic-pituitary-adrenal axis: what can it tell us about stressors? CNS Neurol Disord Drug Targets. 2006;5(5):485–501.
19. Koolhaas JM, Bartolomucci A, Buwalda B, de Boer SF, Flügge G, Korte SM, et al. Stress revisited: a critical evaluation of the stress concept. Neurosci Biobehav Rev. 2011;35(5):1291–301.
20. Lazarus RS. Psychological stress and the coping process. New York: McGraw-Hill; 1966.
21. Somerfield MR, McCrae RR. Stress and coping research: methodological challenges, theoretical advances, and clinical applications. Am Psychol. 2000;55(6):620–5.
22. Lazarus RS. Emotions and interpersonal relationships: toward a person-centered conceptualization of emotions and coping. J Pers. 2006;74(1):9–46.
23. von Känel R, Mausbach BT, Dimsdale JE, Mills PJ, Patterson TL, Ancoli-Israel S, et al. Ways of coping and biomarkers of an increased Atherothrombotic cardiovascular disease risk in elderly individuals. Cardiovasc Psychiatry Neurol. 2012;2012:1–9.
24. Kemeny ME. The psychobiology of stress. Curr Dir Psychol Sci. 2003;12(4):124–9.
25. Salvador A. Coping with competitive situations in humans. Neurosci Biobehav Rev. 2005;29(1): 195–205.
26. Seidel E-M, Pfabigan DM, Hahn A, Sladky R, Grahl A, Paul K, et al. Uncertainty during pain anticipation: the adaptive value of preparatory processes: uncertainty during pain anticipation. Hum Brain Mapp. 2015; 36(2):744–55.
27. Yoshida W, Seymour B, Koltzenburg M, Dolan RJ. Uncertainty increases pain: evidence for a novel mechanism of pain modulation involving the periaqueductal gray. J Neurosci. 2013;33(13):5638–46.
28. Rojo-Moreno L, Livianos-Aldana L, Cervera-Martínez G, Dominguez-Carabantes JA, Reig-Cebrian MJ. The role of stress in the onset of depressive disorders. Soc Psychiatry Psychiatr Epidemiol. 2002; 37(12):592–8.
29. Steptoe A, Kivimäki M. Stress and cardiovascular disease: an update on current knowledge. Annu Rev Public Health. 2013;34(1):337–54.
30. Rosengren A, Hawken S, Ôunpuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):953–62.
31. Costa PT, McCrae RR. The revised neo personality inventory (neo-pi-r). The SAGE handbook of personality theory and assessment. 2008;2(2):179–198.
32. Watson D, Clark LA. Negative affectivity: the disposition to experience aversive emotional states. Psychol Bull. 1984;96(3):465–90.
33. Alastalo H, Räikkönen K, Pesonen A-K, Osmond C, Barker DJP, Heinonen K, et al. Early life stress and blood pressure levels in late adulthood. J Hum Hypertens. 2013;27(2):90–4.
34. Low CA, Salomon K, Matthews KA. Chronic life stress, cardiovascular reactivity, and subclinical cardiovascular disease in adolescents. Psychosom Med. 2009;71(9):927–31.
35. Parrish C, Surkan PJ, Martins SS, Gattaz WF, Andrade LH, Viana MC. Childhood adversity and adult onset of hypertension and heart disease in São Paulo, Brazil. Prev Chronic Dis. 2013;10:130193.
36. Su S, Wang X, Pollock JS, Treiber FA, Xu X, Snieder H, et al. Adverse childhood experiences and blood pressure trajectories from childhood to young adulthood: the Georgia stress and heart study. Circulation. 2015;131(19):1674–81.
37. Wegman HL, Stetler C. A meta-analytic review of the effects of childhood abuse on medical outcomes in adulthood. Psychosom Med. 2009;71(8):805–12.
38. Scott KM. Association of childhood adversities and early-onset mental disorders with adult-onset chronic physical conditions. Arch Gen Psychiatry. 2011;68 (8):838.
39. Power C, Hyppönen E, Davey Smith G. Socioeconomic position in childhood and early adult life and risk of mortality: a prospective study of the mothers of the 1958 British birth cohort. Am J Public Health. 2005;95(8):1396–402.
40. Garner AS, Shonkoff JP, Siegel BS, Dobbins MI, Earls MF, McGuinn L, et al. Early childhood adversity, toxic stress, and the role of the pediatrician: translating developmental science into lifelong health. Pediatrics. 2012;129(1):e224–e31.
41. Dong M, Giles WH, Felitti VJ, Dube SR, Williams JE, Chapman DP, et al. Insights into causal pathways for ischemic heart disease: adverse childhood experiences study. Circulation. 2004;110(13):1761–6.
42. Kivimäki M, Virtanen M, Elovainio M, Kouvonen A, Väänänen A, Vahtera J. Work stress in the etiology of coronary heart disease—a meta-analysis. Scand J Work Environ Health. 2006;32(6):431–42.
43. Schnall PL, Schwartz JE, Landsbergis PA, Warren K, Pickering TG. A longitudinal study of job strain and ambulatory blood pressure: results from a three-year follow-up. Psychosom Med. 1998;60(6):697–706.
44. Theorell T, Perski A, Akerstedt T, Sigala F, Ahlberg-Hulten G, Svensson J, et al. Changes in job strain in relation to changes in physiological state. A longitudinal study. Scand J Work Environ Health. 1988;14(3): 189–96.

45. Freeman LJ, Nixon PGF, Sallabank P, Reaveley D. Psychological stress and silent myocardial ischemia. Am Heart J. 1987;114(3):477–82.
46. Rosengren A, Orth-Gomer K, Wedel H, Wilhelmsen L. Stressful life events, social support, and mortality in men born in 1933. BMJ. 1993;307(6912):1102–5.
47. Pignalberi C, Patti G, Chimenti C, Pasceri V, Maseri A. Role of different determinants of psychological distress in acute coronary syndromes. J Am Coll Cardiol. 1998;32(3):613–9.
48. Virtanen M, Heikkila K, Jokela M, Ferrie JE, Batty GD, Vahtera J, et al. Long working hours and coronary heart disease: a systematic review and meta-analysis. Am J Epidemiol. 2012;176(7):586–96.
49. Ruberman W, Weinblatt E, Goldberg JD, Chaudhary BS. Psychosocial influences on mortality after myocardial infarction. N Engl J Med. 1984;311(9):552–9.
50. McPherson M, Smith-Lovin L, Brashears ME. Social isolation in America: changes in core discussion networks over two decades. Am Sociol Rev. 2006;71(3): 353–75.
51. Berkman LF. Emotional support and survival after myocardial infarction: a prospective, population-based study of the elderly. Ann Intern Med. 1992; 117(12):1003.
52. House JS, Robbins C, Metzner HL. The association of social relationships and activities with mortality: prospective evidence from the Tecumseh Community health study. Am J Epidemiol. 1982;116(1):123–40.
53. Welin L, Larsson B, Svardsudd K, Tibblin B, Tibblin G. Social network and activities in relation to mortality from cardiovascular diseases, cancer and other causes: a 12 year follow up of the study of men born in 1913 and 1923. J Epidemiol Community Health. 1992; 46(2):127–32.
54. Penley JA, Tomaka J, Wiebe JS. The association of coping to physical and psychological health outcomes: a meta-analytic review. J Behav Med. 2002;25(6): 551–603.
55. Stewart MJ, Hirth AM, Klassen G, Makrides L, Wolf H. Stress, coping, and social support as psychosocial factors in readmissions for ischaemic heart disease. Int J Nurs Stud. 1997;34(2):151–63.
56. Merz CNB, Dwyer J, Nordstrom CK, Walton KG, Salerno JW, Schneider RH. Psychosocial stress and cardiovascular disease: pathophysiological links. Behav Med. 2002;27(4):141–7.
57. Chandola T, Britton A, Brunner E, Hemingway H, Malik M, Kumari M, et al. Work stress and coronary heart disease: what are the mechanisms? Eur Heart J. 2008;29(5):640–8.
58. Kassel JD, Stroud LR, Paronis CA. Smoking, stress, and negative affect: correlation, causation, and context across stages of smoking. Psychol Bull. 2003;129(2): 270–304.
59. Sinha R. Chronic stress, drug use, and vulnerability to addiction. Ann N Y Acad Sci. 2008;1141(1):105–30.
60. Torres SJ, Nowson CA. Relationship between stress, eating behavior, and obesity. Nutrition. 2007;23 (11–12):887–94.
61. Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. Nat Rev Neurosci. 2009;10(6):397–409.
62. Burford N, Webster N, Cruz-Topete D. Hypothalamic-pituitary-adrenal Axis modulation of glucocorticoids in the cardiovascular system. Int J Mol Sci. 2017;18(10): 2150.
63. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. Biol Psychol. 2007;74(2):224–42.
64. Vrijkotte TGM, van Doornen LJP, de Geus EJC. Effects of work stress on ambulatory blood pressure, heart rate, and heart rate variability. Hypertension. 2000;35(4):880–6.
65. Porges SW. The polyvagal perspective. Biol Psychol. 2007;74(2):116–43.
66. Sharpley CF. Heart rate reactivity and variability as psychophysiological links between stress, anxiety, depression, and cardiovascular disease: implications for health psychology interventions. Aust Psychol. 2002;37(1):56–62.
67. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol. 2010;141(2):122–31.
68. Masi CM, Hawkley LC, Rickett EM, Cacioppo JT. Respiratory sinus arrhythmia and diseases of aging: obesity, diabetes mellitus, and hypertension. Biol Psychol. 2007;74(2):212–23.
69. Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. Circulation. 1993;88(3):927–34.
70. Tsuji H, Venditti FJ, Manders ES, Evans JC, Larson MG, Feldman CL, et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham heart study. Circulation. 1994;90(2):878–83.
71. Grossman P, Watkins LL, Wilhelm FH, Manolakis D, Lown B. Cardiac vagal control and dynamic responses to psychological stress among patients with coronary artery disease. Am J Cardiol. 1996;78(12):1424–7.
72. Lovallo WR. Cardiovascular reactivity: mechanisms and pathways to cardiovascular disease. Int J Psychophysiol. 2005;58(2–3):119–32.
73. Lovallo WR, Gerin W. Psychophysiological reactivity: mechanisms and pathways to cardiovascular disease. Psychosom Med. 2003;65(1):36–45.
74. Schwartz AR, Gerin W, Davidson KW, Pickering TG, Brosschot JF, Thayer JF, et al. Toward a causal model of cardiovascular responses to stress and the development of cardiovascular disease. Psychosom Med. 2003;65(1):22–35.
75. Treiber FA, Kamarck T, Schneiderman N, Sheffield D, Kapuku G, Taylor T. Cardiovascular reactivity and development of preclinical and clinical disease states. Psychosom Med. 2003;65(1):46–62.

76. Menkes MS, Matthews KA, Krantz DS, Lundberg U, Mead LA, Qaqish B, et al. Cardiovascular reactivity to the cold pressor test as a predictor of hypertension. Hypertension. 1989;14(5):524–30.
77. Kamarck TW, Everson SA, Kaplan GA, Manuck SB, Jennings JR, Salonen R, et al. Exaggerated blood pressure responses during mental stress are associated with enhanced carotid atherosclerosis in middle-aged Finnish men: findings from the Kuopio ischemic heart disease study. Circulation. 1997;96(11):3842–8.
78. Lynch JW, Everson SA, Kaplan GA, Salonen R, Salonen JT. Does low socioeconomic status potentiate the effects of heightened cardiovascular responses to stress on the progression of carotid atherosclerosis? Am J Public Health. 1998;88(3):389–94.
79. Scherer KR, Schorr A, Johnstone T. Appraisal processes in emotion: theory, methods, research. New York: Oxford University Press; 2001.
80. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: the neural basis of normal emotion perception. Biol Psychiatry. 2003;54(5):504–14.
81. Bates JE. Temperament as an emotion construct: theoretical and practical issues. In: Handbook of emotions, vol. 2. New York: Guilford Press; 2000. p. 382–96.
82. Eysenck HJ. Prediction of Cancer and coronary heart disease mortality by means of a personality inventory: results of a 15-year follow-up study. Psychol Rep. 1993;72(2):499–516.
83. Everson SA, Kaplan GA, Goldberg DE, Salonen JT. Anticipatory blood pressure response to exercise predicts future high blood pressure in middle-aged men. Hypertension. 1996;27(5):1059–64.
84. al'Absi M, Lovallo WR, McKey BS, Pincomb GA. Borderline hypertensives produce exaggerated adrenocortical responses to mental stress. Psychosom Med. 1994;56(3):245–50.
85. Mills PJ, Dimsdale JE, Ziegler MG, Berry CC, Bain RD. Beta-adrenergic receptors predict heart rate reactivity to a psychosocial stressor. Psychosom Med. 1990;52(6):621–3.
86. Seligman MEP, Csikszentmihalyi M. Positive psychology: an introduction. Am Psychol. 2000;55(1):5–14.
87. Ryff CD, Dienberg Love G, Urry HL, Muller D, Rosenkranz MA, Friedman EM, et al. Psychological well-being and ill-being: do they have distinct or mirrored biological correlates? Psychother Psychosom. 2006;75(2):85–95.
88. Boehm JK, Kubzansky LD. The heart's content: the association between positive psychological well-being and cardiovascular health. Psychol Bull. 2012;138(4):655–91.
89. Scheier MF, Carver CS. Optimism, coping, and health: assessment and implications of generalized outcome expectancies. Health Psychol. 1985;4(3):219–47.
90. Giltay EJ, Geleijnse JM, Zitman FG, Hoekstra T, Schouten EG. Dispositional optimism and all-cause and cardiovascular mortality in a prospective cohort of elderly Dutch men and women. Arch Gen Psychiatry. 2004;61(11):1126.
91. Kim ES, Park N, Peterson C. Dispositional optimism protects older adults from stroke: the health and retirement study. Stroke. 2011;42(10):2855–9.
92. Scheier MF, Matthews KA, Owens JF, Magovern GJ, Lefebvre RC, Abbott RA, et al. Dispositional optimism and recovery from coronary artery bypass surgery: the beneficial effects on physical and psychological well-being. J Pers Soc Psychol. 1989;57(6):1024–40.
93. Kim ES, Smith J, Kubzansky LD. Prospective study of the association between dispositional optimism and incident heart failure. Circ Heart Fail. 2014;7(3):394–400.
94. Boehm JK, Williams DR, Rimm EB, Ryff C, Kubzansky LD. Association between optimism and serum antioxidants in the midlife in the United States study. Psychosom Med. 2013;75(1):2–10.
95. Boehm JK, Peterson C, Kivimaki M, Kubzansky L. A prospective study of positive psychological well-being and coronary heart disease. Health Psychol. 2011;30(3):259–67.
96. Kubzansky LD, Thurston RC. Emotional vitality and incident coronary heart disease: benefits of healthy psychological functioning. Arch Gen Psychiatry. 2007;64(12):1393.
97. Davidson KW, Mostofsky E, Whang W. Don't worry, be happy: positive affect and reduced 10-year incident coronary heart disease: the Canadian Nova Scotia health survey. Eur Heart J. 2010;31(9):1065–70.
98. DuBois CM, Lopez OV, Beale EE, Healy BC, Boehm JK, Huffman JC. Relationships between positive psychological constructs and health outcomes in patients with cardiovascular disease: a systematic review. Int J Cardiol. 2015;195:265–80.
99. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. PLoS Med. 2010;7(7):e1000316.