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TITLE PAGE:

Defining the Importance of Stress and Stress Reduction in Preventing and Managing Cardiovascular Disease - The role of exercise

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Abstract:

Traditional risk factors for cardiovascular disease (CVD) have long been the focus of preventive strategies. Stress conditions, both acute and chronic, appear to be strong risks for CVD

development, however they are underappreciated in clinical practice guidelines. The purpose of this article is to review the impact of stress on CVD risk, how stress is currently appreciated and how it may be re-positioned in existing clinical practice guidelines, and approaches for stress reduction with emphasis on the role of physical activity. The response to stress includes the activation of the autonomic nervous system and hypothalamo-pituitary-adrenal axis which adversely affect the cardiovascular system by both accelerating the atherosclerotic process/endothelial dysfunction and precipitating cardiovascular events. The impact of family stress, depression, anxiety, outbursts of anger, hostility, pessimism, job strain and insecurity, purpose in life, social support, early life stress and social isolation are well recognized in the pathophysiology of stress disorders. Due to the broad risk posed to global health systems and the increasing economic costs, innovative approaches to offset and combat the broad challenges that CVD pose, which are augmented by sustained exposure to stress, are desperately needed. Approaches to reducing sedentary behaviors and the promotion of sustained physical activity profiles as part of a healthy lifestyle are well documented but hindered by a lack of successful population-level interventions that promote lasting change. A substantial body of evidence supports the stress-buffering effects of regular exercise, both aerobic and resistance, however excessive doses of exercise can be counterproductive and cause unintended harm by chronically exposing the body to stress hormones. It is evident that programmed exposure to physical stress (i.e., regular exercise) leads to better adaptiveness to other types of stress, however, it remains unknown whether the total amount of stress one can receive before negative health effects is unlimited.

Introduction

Stress is defined as a state of homeostasis being challenged [1,2]. While acute stress is known as short-term stress, chronic stress is defined as "long-term" stress, characterized by an ongoing specific environmental condition or stressor with enduring impact [3]. Stress effects are biological consequences resulting from the struggle with stressors [4–6]. It might include reestablishing homeostasis to promote health (good stress - eustress) [1,2]. Conversely, sustress (inadequate stress) or distress (bad stress) can cause damage to the body or even disease [1,2].

Stress conditions, both acute and chronic, appear to be strong risks for cardiovascular disease (CVD) development, however they are hugely under-considered and under-appreciated in clinical practice [1-3]. The impact of family stress, depression, anxiety, outbursts of anger, hostility, pessimism, job strain and insecurity, purpose in life, social support, early life stress and social isolation are well recognized in the pathophysiology of stress disorders [1-3]. On the other hand, physical activity has long been used to reduce stress, but it's direct link to stress and CVD is still insufficiently emphasized.

In this review, we will analyze the impact of stress on cardiovascular health, stress related mechanisms that promote atherosclerosis and risk factors for unwanted stress reaction. Also, we will address the current place of stress as a risk factor in clinical practice guidelines and its reclassification potential, as well as approaches for stress reduction with emphasis on the role of physical activity in the context of CVD development.

Mechanisms of stress reaction

Responses to stressful situations are generally regarded as reactions of the organism to accommodate or compensate for stress [1,2]. This reaction is previously described as an activation of the sympathoadrenal system (SAM) and the hypothalamic-pituitary-adrenocortical (HPA) axis [2,7–

[10]. This response occurs during both exercise as well as in psychological stress [1,2,7–10]. Interestingly, there is a delayed response of the HPA axis observed during exercise in comparison to psychological stress and points to involvement of different neurobiological and cognitive emotional mechanisms [8,10,11]. However, the activation of the stress system also exhibits marked variability, influenced by gender, age, race, genetic factors, body composition, type of stress and physical activity [6,8,12–14].

Previous reports have shown the relationship between physical stress and HPA axis activation, which deals mostly with the influence of physical activity on stress hormones levels [6,8,10]. Furthermore it was shown that higher levels of physical activity are associated with lower HPA axis reactivity to psychological stressors [15,16]. As a result, physical activity has beneficial effects on both physical and mental health, affording protection against the detrimental consequences of chronic stress and stress-related diseases, such are CVD and depression [10,17]. For example, it was previously shown that elite athletes demonstrated markedly reduced physiological and psychological stress responsiveness compared to untrained subjects [10]. Highly trained individuals have reduced salivary free cortisol and heart rate responses to a psychosocial stressor compared to untrained individuals [10]. Moreover, trained individuals were generally calmer and exhibited better mood and lower anxiety throughout stress exposure compared to untrained individuals who showed an increase in anxiety and a decrease in mood and calmness during stress [10]. Since chronic exposure to physical stressors affords redundant activation of the HPA axis and the sympathetic nervous system, the authors posited that stress reactivity of elite athletes might be explained by an exercise-induced modulation of the hormonal stress-responsive and autonomic nervous systems [10]. These findings are in line with other studies which report that aerobic training leads to lower cardiovascular reactivity to psychological stressors [17,18]. Furthermore, exercise-

induced adaptations may also mitigate the responsiveness to other stressors, such as psychosocial stressors [10]. It has also been shown that children and adolescents who are more physically active not only had more optimal physical health but also enjoyed better mental health [19]. In this context, a better understanding of stress-responsive physiological systems can lead to the development of multidimensional prevention programs against stress-related disorders, which combine physical and cognitive coping strategies.

Impact of stress on cardiovascular health and stress mechanisms that promote atherosclerosis

Stress conditions increase the risk for atherosclerosis and related diseases, including stroke and heart attack [20]. The effect of stress on atherosclerosis involves multiple complex mechanisms that remain to be fully elucidated [21].

The response to stress involves the activation of the autonomic nervous system and HPA which adversely affect the cardiovascular system both by accelerating the atherosclerotic process and by precipitating the occurrence of a cardiovascular or cerebrovascular event [22,23]. Whereas the pathophysiological effects on the progression of atherosclerosis are likely to involve repeated or chronic exposure to stress, stress-related triggering of events among people with an already high atherosclerotic plaque burden might also be a consequence of acute stress responses [22,23]. In acute cardiac events, excessive levels of circulating catecholamines are known to be a contributing factor to disruption of the fibrous cap of atherosclerotic plaque, coupled with active inflammation and hypercoagulability and followed by electric instability [24]. Stress-related clinical events include ventricular tachycardia and ventricular fibrillation, atrial fibrillation, stroke, myocardial infarction and other forms of acute coronary syndromes (i.e., unstable angina and stress cardiomyopathy).

Relevant pathophysiological changes, in addition to stress-induced ischemia, include: 1) an increase in the levels of pro-inflammatory cytokines and adhesion molecules that contribute to atherosclerotic plaque destabilization and monocyte chemotaxis; 2) release of tissue factor; 3) increased blood viscosity; 4) platelet and coagulation activation; 5) systemic vasoconstriction and an increase in arterial blood-pressure levels; 6) increase in sinus node firing rate and atrioventricular conduction velocity; 7) change in the balance between sympathetic and parasympathetic cardiac control; and 7) increase in myocardial oxygen consumption [22,23].

Previous studies implicate chronic stress as an important driver of metabolic syndrome, diabetes, and cardiovascular disease (CVD) development [25]. The INTERHEART 128 study (29,972 participants from 52 countries) and the INTERSTROKE study (26,919 participants from 32 countries) both identified psychosocial stress as one of ten modifiable risk factors for CVD onset. Namely, the activation of the HPA and the sympatho-adrenal-medullary (SAM) axis, provokes the release of hormones such as adrenocorticotropic hormone, cortisol, growth hormone, prolactin, epinephrine and norepinephrine [25]. Increased cortisol has many somatic effects, including the precipitation of insulin resistance, increased blood pressure, central redistribution of adiposity and an impaired immune response [26]. Increased circulating levels of catecholamines additionally promote insulin resistance, increased blood pressure and heart rate, and systemic inflammation by elevating production of inflammatory cytokines (intercellular adhesion molecule-1 – (ICAM-1), acute phase reactant C-reactive protein (CRP) and proinflammatory cytokine interleukin-6 (IL-6)), which are significantly heightened in chronic stress. Chronic stress can suppress or dysregulate innate and adaptive immune responses by altering the type 1/type 2 cytokine balance, thereby inducing low-grade inflammation and suppressing the function of immuno-protective cells[27]. The increase of inflammatory cytokines and the expression of adhesion

molecules via certain pathways can induce mononuclear cell aggregation and lymphocyte adhesion. [27] Furthermore, chronic stress changes the homeostasis of the sympathetic and vagal nervous systems. Autonomic disorders caused by chronic stress may be a common mechanism that increases risk. [27,28] The sympathetic nervous system activation triggers increased vascular tone, myocardial oxygen consumption, platelets activation, as well as activation of renin-angiotensin system, which results in endothelial dysfunction, and hence, the development of CVD [27,28].

Recent studies suggest that psychological stress triggers endothelial dysfunction [29]. As previously stated, psychological stress activates the sympathetic nervous system, renin-angiotensin system and the HPA axis, triggering increased levels of catecholamines, glucocorticoids and Ang II and pro-inflammatory cytokines, respectively. All these mediators can promote endothelial dysfunction due to the increase in oxidative stress and circulating inflammatory mediators, as well as reduced nitrogen-monoxide production or bioavailability. These alterations lead to vascular inflammation and, consequently, the development of atherosclerosis. Furthermore, TNF-alpha and MAP kinases (mitogen activated protein) signaling pathway play a potential role in the inflammatory process, as well as the adrenergic receptors and CXCL12 chemokine that are involved with hematopoietic activation and the development of atherosclerotic lesions [29].

Several neural centers in the brain's salience network play a critical role in an organism's response to its environment [20,21]. The amygdala is one important component of this network that is involved in the emotional perception and physiological response to stressors. As such, the amygdala could be a critical structure in the central nervous system mechanisms linking stress to CVD [20,21].

As an impressive example, stress has been linked to stress-induced cardiomyopathy (SIC), a transient systolic and diastolic left ventricular dysfunction with wall-motion abnormalities considered an acute heart failure syndrome[30]. SIC is a self-resolving syndrome that may present as a mimic to ischemic heart disease or as a complication during critical illness, particularly those diseases involving the neurohumoral axis [31,32]. This syndrome has gone by many names in the literature, including "cardiac syndrome X", "broken heart syndrome", "ampulla cardiomyopathy", "tako-tsubo cardiomyopathy", "transient LV apical ballooning syndrome", "neurogenic stunned myocardium", and "neurogenic stress cardiomyopathy"[32,33]. It was initially described in the Japanese population in the early 1990s, as a transient cardiomyopathy frequently following stressful events, with the absence of coronary artery disease[31,33]. Perhaps the best definition presently available is the absence of any established cause of reversible myocardial dysfunction. The majority of patients (80–90%) are women, predominantly postmenopausal women. Many cases (14–70%) are preceded by a stressor, either emotional or physical. In patients without another identifiable cause, a recent acute emotional stress frequently precedes the syndrome. SIC is relatively common in patients with severe neurologic injury, as well as in other situations where catecholamines are clearly elevated, such as in the setting of a pheochromocytoma, status epilepticus, tetanus, sepsis, systemic lupus erythematosus, anorexia nervosa, thyrotoxicosis and diabetic ketoacidosis [34–43]. The presumed etiology of SIC is excessive sympathetic stimulation of the myocardium, likely mediated by the brain. Catecholamines may lead to cardiac dysfunction via microvascular dysfunction or direct toxicity [44]. Hormones also may play a role in the pathogenesis of SIC. Estrogen may attenuate the cardiac response to catecholamines, explaining the higher frequency of SIC in postmenopausal women [35,45]. Patients present with chest pain and dyspnea. Pathologic electrocardiogram and cardiac enzyme changes are present [31,35].

Echocardiography and contrast ventriculography detect a dyskinesia with a ballooning of the left ventricular apex [46]. The classic pattern of wall motion abnormalities seen on echocardiogram in SIC is one of apical ballooning or hypokinesia of the apex of the heart with hypercontractility of the basal segments. In one-third of all patients, a subtle dyskinesia of the right ventricular apex is also observed[46]. However, coronary angiography shows no evidence of a relevant epicardial obstructive disease[31]. The natural course of SIC syndrome is near-complete resolution over several days to weeks. A large study of patients presenting with acute coronary syndrome and a pattern of apical ballooning on echocardiogram with normal coronary angiography found no increase in 4-year mortality compared with matched controls and a 1–2% annual recurrence rate [47,48].

Types of stress and cardiovascular health: the impact of family stress, depression, posttraumatic stress disorder, anxiety, outbursts of anger, hostility, pessimism, job strain and insecurity, long working hours, purpose in life, social support, early life stress and social isolation

Numerous factors, such as lifestyle behaviors, psychosocial variables, personality types, and mental illnesses, can have a direct impact on the etiology of CVD. Importantly, these factors can also precipitate or worsen pre-existing CVD conditions [49–52].

A growing body of evidence indicates an inverse relationship between marital quality and coronary heart disease morbidity and mortality [53]. There is a link between marital quality and carotid artery intima-media thickness and coronary artery calcification burden – common indicators of atherosclerosis [54,55]. In addition, recent reports indicate both affiliation and control related elements of marital interaction can influence individual cardiovascular reactivity and

subsequent manifestations of unwanted blood pressure patterns [56]. Similarly, associations between depression/depressive symptoms, post-traumatic stress disorder (PTSD), anxiety, and anger/hostility are well documented [57–59]. An individual with depression without prior heart disease is 2.7 times more likely to die from ischemic heart disease over a median follow-up of 8.5 years [60], and 20–30% of cardiovascular patients generally have depression [61]. Mechanistically, excessive sympathetic and/or reduced parasympathetic modulation [62], blunted inhibitory feedback in the HPA axis [63], elevated levels of platelet factor 4 and β-thromboglobulin [64], endothelial dysfunction [65] and increased CRP, tumor necrosis factor-α and interleukins [66] in depression, are considered the main causes of cardiovascular anomalies. The latter includes high blood pressure, reduced heart rate variability (HRV), and worsening of atherosclerosis.

Similarly, the association between characteristics of PTSD, including reliving the traumatic event, avoidance of reminders, hyperarousal, anhedonia, detachment, restricted affect, sleep difficulty, intense negative emotions, and potential CVD is incontrovertible [58,67]. Physiologically, it is likely that a combination of changes in brain activity, somatic nervous system, endothelial dysfunction and inflammatory reaction are involved in a plausible link between PTSD and CVD [68]. For instance, autonomic imbalance manifested as low HRV [69] and high resting heart rate [70], HPA axis dysfunction reflected as low diurnal cortisol levels [71], increased platelet activation [72], endothelial dysfunction manifested as significant reduction in flow mediated dilatation [73] and inflammatory perturbations with significantly high levels of IL-1β, IL-6, and interferon γ [74], can be directly associated and/or lead to exacerbation of existing CVD. In addition, behavioral changes that may accompany traumatic events including, but not limited to smoking, inactivity, obesity, and nonadherence to medications, can also increase the potential for development of CVD [75,76].

Anger and hostility, typically associated with Type A personality traits, and comprising numerous constructs such as physiological, cognitive, phenomenological, and behavioral variables, have been linked with ill-health since antiquity [77]. A substantial body of evidence indicates a positive relationship between anger and hostility with increased CVD events in healthy populations, as well as in patients with existing CVD [78,79]. Excessive (and in some instances, paradoxical) vasoconstriction mediated by endothelial dysfunction[80], pronounced adrenocorticotropic responses to socially salient stress 81, and increased intima media thickness [82], are some of the mechanisms linking anger and hostility with potential CVD.

Although pessimism and optimism do not anchor the two ends of one spectrum [83], empirical evidence suggests that the former is associated with increases in coronary heart disease, stroke, all-cause mortality [84–86], and the latter with increased protection against CVD [87,88]. Many of the protective effects of optimism can be attributed to indirect, positive behavioral changes including increased physical activity levels, better diet quality, and reductions in smoking [87]. A substantial evidence base support associations between pessimism and pathophysiologic dysfunction, mediated via neuro-endocrine (i.e., HPA axis), nervous system (i.e., blood pressure), immune system, genetic, endothelial, and metabolic function modulations [89–92].

Demand for increased productivity and efficiency has increased, leading to increased pressure upon employees and workforces globally [93]. Whilst high levels of mental and physical wellbeing are closely associated with increased performance [94], sustained pressures, contractual requirements and incentivized employment opportunities relating to performance have an adverse effect upon work-life balance, absenteeism, and physical and mental wellbeing [93]. Prolonged sedentary profiles are a well-defined risk factor and the product of increased working hours, a reduction in active job roles, increased technological innovation and more recently remote working

[95]. Stress associated with work has also been identified as a major risk factor for CVD, in a review of 600,000 workers from 27 cohort studies, Kivimäki & Kawachi suggest that stressors from employment such as pressure relating to success, job strain and long working hours (>50 hours per week) increase the incidence of developing coronary heart disease and stroke by up to ~40%[96] compared with those free of such stressors. Poor work-life balance caused by job strain and long working hours is detrimental to mental and physical wellbeing, it also associated with broad social impacts that are linked to a 1.5 increased risk of experiencing social isolation [97] and cardiovascular events.

A rapidly growing literature base has also identified and increased the understanding that positive psychological wellbeing can protect against adverse physical health outcomes, including CVD [98]. A meta-analysis of 10 prospective studies by Cohen et al demonstrated that having an increased sense of purpose (directed and motivated by valued life goals) is associated with reduced CVD risk [99]. Whilst more work is needed to determine the associated mechanisms, the continued presence of stress and the associated biological functions are associated with negative implications for healthy ageing and pre-disposing individuals and increased CVD risk factors [100]. The concept of healthy ageing is affected by exposure to 'early life stress' which influences the biological responsiveness to future stress and is associated with increased incidence of developing a broad range of chronic conditions such as CVD later in life [101]. Whilst the exact mechanistic details are not understood in their entirety, broad associations have been determined in both central and peripheral systems. Exposure to stress in early life alters the biological programming of the cardiovascular system inducing lasting effects on the responsiveness to stress stimuli, pre-disposing stress during early life as an independent risk factor [102].

Due to the broad risk posed to global health systems and the increasing economic costs, currently estimated at $351.2 billion per annum [103], innovative approaches to offset and combat the broad challenges that CVD, which are augmented by sustained exposure to stress, are desperately needed. Approaches to reducing sedentary behaviors and the promotion of sustained activity profiles and healthy lifestyles are well documented but hindered by a lack of successful population-level interventions that promote lasting change. Laughter and enjoyment have been shown to reduce stress and by consequence CVD risk [104] and must be considered in the development of innovative lifestyle interventions that seek to reduce stress, instill work-life balance, and promote increased mental and physical health and wellbeing.

The place of stress as a risk factor in current guidelines and risk estimation systems - reclassification potential?

Traditional risk factors for CVD have long been the focus of preventive strategies. However, they interplay with psychological factors which additionally strongly impact outcomes. A recent population study identified the impact of various psychological disorders on the incidence of CVD[105]. They identified that stress related disorders were strongly associated with early onset CVD in those below and above the ages of 50 years [hazard ratio 1.40 (1.32 to 1.49) and 1.24 (1.18 to 1.30), respectively]. The INTERHEART study, demonstrated exposure to long-term stress added to the risk of acute myocardial infarction even after considering combined exposure to conventional risk factors, with odds ratios increasing from 69-183, when participants were exposed to psychosocial adversity [106]. The INTERHEART study also found that psychosocial factors were one among the top three factors contributing to presentation of acute coronary syndrome. More recently, the Young Finns study, in which the authors found favorable childhood experiences to be associated with lower coronary artery calcium scores when assessed 28 years later [107]. In

adulthood, workplace stress has also been seen to contribute to the risk of incident CVD, by an increase of 40% [108]. All these population studies strengthen the physiological basis that the heart and mind are greatly interlinked with one another and can have a tremendous impact on cardiovascular health. [109]

Based on evidence, it is apparent that stress is a major contributor to CVD, however, given attention in the current guidelines hugely underestimates its role. Many years ago, the World Health Organization recommended the need for clinical history related to psychosocial factors, however, did not provide any evidence-based recommendations on its management [110]. The European guidelines provide a class IIa, Level B recommendation for the assessment of psychosocial risk factors along with class I, level A recommendation for multimodal behavioral interventions in those with CVD[111]. However, treatment of these conditions with the aim of preventing CVD was a class IIa, level B recommendation. The more recent ACC/AHA guidelines did consider the social determinants of health and did recommend the need for regular assessment of psychosocial stressors and their treatment through counselling [112]. However, no further details were provided.

Contrary to the CVD prevention guidelines, cardiac rehabilitation statements, however, have emphasized the need for addressing psychosocial components and have made it a core component [113,114]. Even guidelines focusing on low-resource settings have emphasized echoed this need [115]. Despite this being a core component, the number of programs around the world delivering this component remains low [116,117]. This could be due to the limited number of mental health professionals around the world available to provide such care (~ 57.8%) [116].

There are three aspects of the stress experience that complicate its inclusion as a routine consideration in clinical practice. First, as discussed before, stress is a ubiquitous aspect of the human experience, ranging from benign daily stress (e.g., being stuck in traffic) to stress which manifests from lifelong discrimination. Second, the mechanisms by which excessive stress exposure increases CVD risk are multi-factorial and have not been full elucidated. Using the examples above, regular but acute stress in the workplace may partially increase CVD risk through autonomic nervous system dysregulation. Whereas stress resulting from lifelong discrimination may lead to chronic low-grade inflammation and advanced cellular aging. [118] Third, both the magnitude of stress and the physiological effects of stressors are likely dependent on resiliency and coping strategies. Using the workplace example, one individual may internalize negative criticism from a line manager and 'cope' by engaging in other harmful behaviors (e.g., smoking or binge eating), whereas as second worker may, for example, have learned to better communicate with the line manager, go for a walk, or practice mindfulness. In this way, one can consider that it is not just the stressor that is the CVD risk factor, but rather the collective perception of, reaction to, and subsequent physiological reactivity from the stressor.

While stress is a complex CVD risk factor, it does not mean we are unable to help a given individuals. But the operative word is 'individual'. There is no one scale that can represent the stress by all individuals. Similarly, there is unlikely to be one physiological biomarker to encapsulate the effects of stress on cardiovascular health. However, stress as a general entity can be subjectively measured, with an example scale being the Perceived Stress Scale (PSS). [119] The 10-item PSS is one of the most widely administrated scales for measuring perceptions of stress over the past month, and has been associated with poor health outcomes, including depression and CVD [120,121]. As such, this scale can be used to monitor perceptions of stress and to track reductions

that may occur through changing in lifestyle or the incorporation of other stress management strategies.

Strategies that have been used to enhance stress management have traditionally focused on mind-body interventions in which there is often both a physical activity as well as a cognitive-behavioral/mental component. [122–124] Yoga and tai chi are examples of a mind-body therapies which incorporate both physical and mental components[125–127]. Both physical activity and mental (e.g., cognitive-behavioral) approaches such as mindfulness meditation have been independently linked to reduced stress, or more precisely – reduced perceptions and negative reactivity from stress[128–130]. Further work is needed to determine if there is a synergistic effect from combining physical and mental/cognitive stress-reduction strategies, and whether certain strategies should be focused on specific subsets of the population.

Hormonal background of psychological and physical stress – is it the same?

Both physical and psychological stress are primarily mediated via co-activity of the autonomic nervous system and a constellation of HPA axis [131]. While responsiveness (i.e., magnitude and time course) of both systems is highly stressor specific, the outcomes of the former are realized through a multitude of autonomic pathways (e.g., SAM system, dopamine system, etc.) whereas outputs of the latter are modified by input from intricate brain regions such as locus coeruleus, amygdala, anterior cingulate cortex, paraventricular nucleus and the hippocampus [131,132]. Amongst the effector hormonal milieu that determines the overall stress response, epinephrine/norepinephrine (SAM) and cortisol (HPA) can be considered the ‘major players’, at least in the peripheral tissues [133].

The stress response is both natural and adaptive with optimally reacting systems, and by activating various feedback loops, can return the body to a steady state once the initial threat has subsided [134]. The magnitude of the stress response is a key component in one's progression to ill-health, and existing evidence indicates that a "Goldilocks" response (i.e., intermediate, not too high or low) is the most adaptive and resilient [135]. In contrast, both exaggerated and blunted reactivity of the autonomic and hypothalamic pathways are associated with some of the most pervasive cardiovascular conditions such as hypertension, coronary artery calcification and increases in carotid intima media thickness [136–141]. These responses are suggestive of an inverted-U shaped association between stress reactivity and disease.

Additionally, duration of exposure is also a key factor that determines adaptiveness or deleterious stress [133]. Bouts of short-term stress (i.e., stress that lasts from minutes to hours) interspersed with adequate time for system recovery is thought to be associated with salubrious adaptive effects [142]. In contrast, chronic stress (e.g., stress that persists for several hours a day for weeks/months) can lead to maladaptation such as dysregulation of circadian cortisol rhythm [143,144]. Depression – which is strongly linked with CVD – is a classic example of 'stress pathway overdrive' leading to deleterious health outcomes[145]. For instance, existing literature is replete with examples of laboratory stressors such as the Trier Social Stress Test – which activates the same corticolimbic circuitry implicated in depression [146] – simulating the hyperactivity of corticotropin releasing hormone-adrenocorticotropin-cortisol (i.e., HPA axis) system, that is commonplace in major depression etiology [145,147].

Exercise, as a form of physical stress, shares several characteristics of an acute stressor, and challenges both nervous and endocrine arms of the stress machinery [148]. For instance, exercise

of sufficient dose (i.e., volume and intensity) can increase circulating levels of many stress-related factors including cortisol, epinephrine/norepinephrine and inflammatory cytokines [149,150].

The role of exercise in managing and mitigating stress

Particularly noteworthy, as postulated in the cross-stressor adaptation hypothesis, regular exercise can result in adaptations that lead to reduced sensitivity to subsequent heterotypic (other than exercise) stressors [151]. A substantial body of evidence indicate stress-buffering effects (both autonomic and hypothalamic pathways) of regular exercise [152,153].

The 2018 Federal Physical Activity Guidelines Advisory Committee's Scientific Report determined that there was a strong body of evidence supporting the anxiolytic effects of acute and regular physical activity in adults and older adults[154]. This was an update to the 2008 report which had concluded that there was insufficient evidence available to make such an observation. Although there is still a relatively small pool of studies in this area compared to more prominent topics (i.e., cardiovascular and skeletal muscle health/function), a growing body of work consistently supports the beneficial effects of both aerobic and resistance exercise in lowering symptoms of stress [155,156]. Most randomized controlled studies investigating the effects of aerobic exercise on stress have employed moderate continuous aerobic exercise at volumes comparable to the Federal Physical Activity guidelines (i.e., 70% of peak VO_2, ~30 minutes per session, 3-5 days per week) [157–159] and therefore, little is known about the potential graded effects of higher intensities and/or volumes of aerobic exercise on stress. However, a previous meta-analysis found a dose-response relation between cardiorespiratory fitness and the risk of common mental health disorders [160]. With higher intensities and volumes of exercise leading to greater improvements in cardiorespiratory fitness [161], it is feasible that chronic high-volume exercise may promote more

favorable decreases in stress symptoms over time. Future studies are needed to determine whether this holds true.

Regular resistance exercise training (i.e., at least two days of muscle strengthening activity per week) is a vital component of the physical activity guidelines as it slows the loss of muscle mass with aging, reduces risk of serious falls and helps individuals maintain their physical independence [154]. Moreover, a meta-analysis by Gordon and colleagues concluded resistance exercise may lead to similar improvements in markers of stress as aerobic exercise in chronically ill patients and those with anxiety related disorders [155]. Furthermore, initial evidence suggests that resistance exercise intensity may modulate the degree of improvement in stress related disorders in older adults [162]. A 12-week resistance exercise training intervention conducted by Tsutsumi and colleagues [162] found greater strength gains in those completing vigorous resistance exercise training (75 to 85% of one repetition maximum, 8-10 repetitions) than those randomized to moderate intensity (55 to 65% of one repetition maximum, 14 to 16 repetitions), but found that the moderate intensity group had a significantly greater decrease in anxiety. Suggesting that moderate intensity resistance exercise training may be more beneficial in improving psychological health. Additional studies will be needed to confirm this.

To date, much uncertainty remains about the mechanism that explain the anxiolytic effects of aerobic and resistance exercise, though certain neurobiological and psychological mechanisms have been proposed. Perhaps the most recognized response is the increase in serum brain-derived neurotrophic factor after acute exercise (i.e., 70% of peak VO_2 for 30 min), but whether this factor remain chronically elevated in those with anxiety disorders is not known [163,164]. Improvements in self-efficacy and negative affect may play a key role in decreasing symptoms associated with stress disorders with exercise [165]. It is important to note that many exercise interventions have been

conducted in group settings which may provide an inadvertent support group atmosphere and facilitate coping stress [166]. Nevertheless, with previous studies [167] showing that a single session of aerobic exercise can lower stress levels may suggest that this occurs independent of the potential effects of exercising in a group. Certainly, an individual's exercise preferences and response to group settings may modify stress levels. Accordingly, additional work in this area is needed to establish individualized recommendations on exercise settings relative to individual preferences and responses. There is however sufficient evidence to support the promotion of aerobic and resistance exercise as a method of lowering stress.

Of note, despite the 'stress-busting' effects, excessive doses of exercise can be counterproductive and cause unintended harm by chronically exposing the body to stress hormones [150,168,169]. However, given the widespread availability of labor-saving technologies and unprecedented levels of sedentarism spanning most physical activity domains, it is unlikely that significant numbers of individuals will engage in excessive amounts of exercise [170,171].

Conclusion

In summary, stress is a complex and highly subjective construct. Acute and chronic stress are hugely underestimated as risk factors for CVD in clinical practice, and as such there is a lack of recommended coping strategies that may reduce stress-related diseases burden. There is not a one-size fits all approach to managing stress, and any management strategies should be mindful of individual traits and lived experiences. More attention is needed to better understand mechanisms of stress-related negative health outcomes, through research, as evidence is needed to confirm the obvious role of stress in overall health and disease. Nonetheless, there are means by which to monitor stress and strategies which are reported to be effective in managing stress. Regular

exercise, both aerobic and anaerobic, leads to better adaptiveness to stress. However, questions remain regarding the total amount of stress one can receive before negative health effects are experienced.

Central illustration. Stress and exercise

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