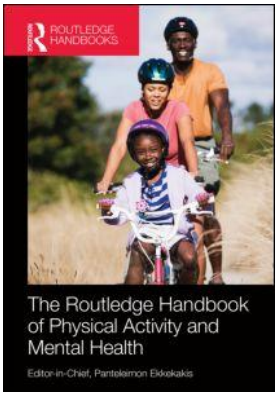

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Psychosocial stress

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PHYSICAL ACTIVITY, STRESS REACTIVITY, AND STRESS-MEDIATED PATHOPHYSIOLOGY

Mark Hamer and Andrew Steptoe

Stress refers to the consequences of the failure of a human or animal to respond appropriately to emotional or physical threats to the organism, whether actual or imagined (Seyle, 1965), resulting in disruption of homeostasis. In particular, the causes or consequences of stress in modern-day life include interpersonal, social, familial, societal, and social psychological factors. Evidence from population cohort studies suggests that psychosocial stress is a risk factor for cardiovascular diseases (CVD) (Kivimaki et al., 2012; Brotman, Golden, & Wittstein, 2007; Rosengren et al., 2004). An important way of investigating the mechanisms underlying these associations is acute psychophysiological stress testing, involving measurement of cardiovascular and biological responses to laboratory-induced behavioural stressors (Steptoe, 2007). Psychophysiological stress testing allows individual differences in responses to standardised stress tasks to be evaluated and related to psychosocial factors (Chida & Hamer, 2008) and future risk of CVD (Chida & Steptoe, 2010). Behaviourally evoked psychophysiological responses are relatively stable individual characteristics, consistent across time and stressor type. The magnitude or pattern of an individual's stress response is largely mediated by the immediate actions of the autonomic nervous system and delayed response of the hypothalamic pituitary adrenal (HPA) axis, which releases various hormones (i.e., catecholamines, cortisol, etc.) into the circulation. These systems drive specific responses that include an increase in blood pressure (BP) and heart rate, changes in cardiac sympatho-vagal balance, skeletal muscle vasodilatation, the stimulation of haemostatic and inflammatory responses, and activation of various immune cells, all of which might be relevant to CVD risk. Individual differences in patterns of stress responding are accounted for by factors such as race and ethnicity, genetics, background stress, and lifestyle habits. In particular, exercise has been studied for its stress buffering effects. Physical exercise and mental stress have similar acute physiological effects in that both result in cardiovascular activation and release of catecholamines and cortisol, although paradoxically they have different chronic effects on health – regular exercise is associated with protective effects whilst chronic mental stress has been linked with health risks, in particular CVD. This paradox is poorly understood, and might prevent some health professionals from acknowledging the true importance of physical activity in treating stress-related illnesses. The goal of this chapter is to focus on the effects of exercise on psycho-physiological stress responses, with reference to pathophysiological mechanisms in health and disease.

Stress mediated pathophysiology

Much of the evidence linking psychosocial stress with disease risk has come from epidemiological studies that follow cohorts of individuals over time and are able to assess the association between chronic stress exposure and long-term health outcomes such as death and clinical CVD events. Some examples of epidemiological findings include the association between work stress and an increased risk of CVD (Kivimaki et al., 2012) and a body of evidence showing higher risks of premature death in caregivers under emotional strain (Schulz & Beach, 1999). Further epidemiological evidence suggests that factors such as depression, hostility, loneliness, and social networks are related to a greater risk of future CVD and mortality in initially healthy individuals (Van der Kooy et al., 2007; Chida & Steptoe, 2009; Heffner, Waring, Roberts, Eaton, & Gramling, 2011). It is problematic to experimentally induce chronic stress in humans although some studies have assessed the effects of stress reduction interventions on health outcomes. Results from recent intervention trials that have examined the effects of various stress reduction and anti-depressant treatments on future risk of CVD events and mortality have been inconsistent (Blumenthal et al., 2005; Burg et al., 2005; Glassman, Bigger, & Gaffney, 2009), even when psychological symptoms are resolved, which has therefore raised some doubts about the direct role of stress in CVD. Nevertheless, none of this work has been performed in the context of primary prevention since the aforementioned studies have all been undertaken in patient groups.

The pathways linking stress and CVD are poorly understood but both behavioural pathways and direct pathophysiological processes appear to be involved. Behavioural pathways might include reduced physical activity, smoking, alcohol, and diet. In particular, physical activity levels are lower in participants that report depression or psychological distress, which has been shown to partly explain their increased risk of CVD (Hamer, Molloy, & Stamatakis, 2008; Whooley et al., 2008). Similarly, acute life events, social networks, and various types of chronic adversity such as work stress are associated with unhealthy diets and with smoking (Heikkilä et al., 2012; Christakis & Fowler, 2008; Steptoe et al., 1998). Pathophysiological processes might include sympathetic nervous system hyperactivity, inflammation, haemostasis, and altered metabolic and cardiac autonomic control. The existing evidence suggests that these pathways explain a modest amount of the association between stress and CVD. For example, in a recent study adiposity appeared to partly mediate the association between depression and coronary atherosclerosis in women (Greco et al., 2009). Disturbed sympathetic activity is a plausible mechanism in explaining the stress–CVD association, and the increased prevalence of carotid plaque found in chronically stressed spousal caregivers of people with Alzheimers disease was partly explained by prolonged sympathoadrenal arousal to acute stress (Roepke et al., 2011). Inflammatory markers [C-reactive protein (CRP) and interleukin-6] and the metabolic syndrome explained approximately 17% and 7%, respectively, of the association between depression and CVD events in women with suspected coronary ischemia (Vaccarino et al., 2007). Autonomic dysfunction and inflammation contributed 12.7% to the increased cardiovascular mortality risk associated with depression in the Cardiovascular Health Study (Kop et al., 2010). In other studies, various inflammatory markers did not, however, explain any of the association between depressive symptoms/stress and risk of CVD (Surtees et al., 2008; Nabi et al., 2008); thus there is clearly a need for further research in this area.

A clear limitation of the existing work in this area is that most studies are unable to provide a robust test of mediation because the potential mediating variables are usually measured at the same point in time as the markers of stress exposure, thus making it difficult to determine the temporal nature of the association. Indeed, the association of stress with intermediate risk factors for CVD might be bi-directional in that stress not only causes disturbances in behaviour and

pathophysiological markers but also vice versa. For example, there appears to be a bi-directional association between depressive symptoms and inflammatory markers (Gimeno et al., 2009). As discussed elsewhere in this *Handbook*, physical activity appears to be protective against the development of depression and stress-related illness, although individuals with mental illness are less likely to undertake any activity.

Psychophysiological stress testing can also be used to better understand the mechanisms underlying the association between stress and CVD. Although acute psychophysiological responses are not clinically meaningful in themselves, they represent the way in which individuals respond to daily stressors in their normal lives, and if elicited regularly might have clinical relevance. A body of work has examined the association between psychophysiological stress reactivity and cardiovascular risk (Chida & Steptoe, 2010). Much of the work in humans has been based upon seminal work in primates, which demonstrated significantly greater coronary artery atherosclerosis in monkeys with exaggerated heart rate responses to behaviourally induced stressors (Manuck, Kaplan, Adams, & Clarkson, 1989). The research in humans to date has largely focused on the associations between cardiovascular (BP, heart rate) stress responses and future risk using various markers of sub-clinical CVD, such as carotid intima-media thickness (IMT) and coronary artery calcification (CAC). These measures are important since they are associated with risk of future CVD events. Additionally, assessment of sub-clinical atherosclerosis before clinical events occur helps delineate the temporal relationship between stress and CVD. In studies that have included healthy participants at baseline, BP reactivity to standardised stressors has been most consistently related to risk of sub-clinical atherosclerosis. For example, in 756 men from the Kuopio Ischemic Heart Disease study, systolic BP reactivity at the baseline assessment was related to carotid IMT after 7 years' follow-up and also to the progression of IMT, independently of established risk factors including smoking, cholesterol, fasting glucose, and resting BP (Jennings et al., 2004). Two separate studies in healthy women showed that greater pulse pressure and systolic BP reactivity were respectively associated with greater carotid IMT (Matthews et al., 1998) and the presence of CAC (Matthews, Zhu, Tucker, & Whooley, 2006). In both of these studies, however, measures of atherosclerosis were not available at baseline, thus the possibility of reverse causality cannot be ruled out. A recent study of cardiovascular risk in young Finns showed that higher heart rate, respiratory sinus arrhythmia, and pre-ejection period reactivity were associated with lower IMT values (Heponiemi et al., 2007), which is in contrast to data in US women that showed a greater response in heart rate variability was related to higher CAC (Gianaros et al., 2005).

The existing evidence therefore suggests that vascular stress reactivity (indexed by BP responses) more consistently predicts the progression of atherosclerosis than do cardiac autonomic responses. From a mechanistic standpoint, stress-induced BP surges that contribute to increased shear stress in the arteries could promote endothelial damage and inflammatory responses that are thought to play a role in atherogenesis (Kher & Marsh, 2004). Endothelial dysfunction plays a key role in the initiation of atherosclerosis because nitric oxide production from healthy endothelial cells has an anti-atherogenic effect by inhibiting cellular adhesion, migration, and proliferation responses (Ross, 1999). Heightened cardiovascular stress reactions have also been shown to predict future hypertension (Flaa, Eide, Kjeldsen, & Rostrup, 2008), increases in lipid levels and adiposity (Steptoe & Brydon, 2005; Steptoe & Wardle, 2005), and development of insulin resistance (Flaa, Aksnes, Kjeldsen, Eide, & Rostrup, 2008), which may represent key mechanisms in relation to stress and CVD risk. Chida and Steptoe's (2010) meta-analysis concluded that the strength of the association between stress reactivity and CVD risk is modest but consistent. Rate of recovery following stress exposure may also be important, although the evidence is limited at present. For example, prolonged recovery of systolic BP after stressors was

associated with carotid IMT in various studies after accounting for conventional risk factors (Chida & Steptoe, 2010).

Exercise and cardiovascular stress buffering effects

Similarities between central and peripheral responses to exercise and psychological stressors have led to the theory of "cross-stressor adaptation", where adaptations resulting from regular exercise lead to both improved physiological control during exercise, and also lower cardiovascular responses to psychological stressors. Since exaggerated responses to mental stress can have detrimental effects on health, the potential stress buffering effects of exercise are of importance. Much of the existing psychophysiological work relating to physical activity has focused on cardiovascular responses, and several types of study have been carried out. These include experiments testing the impact of single bouts of exercise, the aim of which is to test whether stress reactivity or rate of recovery is modified after physical activity; comparisons of stress responses in physically fit and unfit individuals; and training studies in which psychophysiological stress responses are compared before and after exercise training.

The most consistent evidence is from the acute studies, where a single bout of acute exercise has been repeatedly associated with buffering BP and cardiac responses to standardised behavioural challenges in the laboratory (Hamer, Taylor, & Steptoe, 2006). Studies that have examined psychophysiological responses in relation to physical fitness (an indicator of training status) and exercise training have produced more mixed results. In an early meta-analytic review of 34 studies, aerobic fitness was associated with nearly half a standard deviation reduction in BP stress reactivity (Crews & Landers, 1987), but more recent updated reviews suggested both positive and inverse associations between fitness and heart rate reactivity (Dishman & Jackson, 2006; Forcier et al., 2006). Dishman and Jackson (2006) reported that fitness was related to greater heart rate reactivity but better recovery from mental challenge in 73 studies, although these effects were diminished when only randomised controlled exercise training studies were included and when fitness was measured as peak oxygen uptake. In contrast, Forcier and colleagues (2006) demonstrated an inverse association between fitness and heart rate reactivity in an analysis containing only studies with evidence of an exercise training effect. One of the difficulties in interpreting data from short-term (often 8–12 weeks) exercise trials is that individual changes in fitness are usually modest, which suggests a short period of exercise training may not be sufficient to induce the types of chronic adaptations required to observe stress buffering effects. Another common problem in this area is limited sample size, which can often lead to studies with insufficient statistical power. This issue was, however, addressed in a recent large randomised trial consisting of 149 healthy, young sedentary participants who were randomised to a 12-week exercise programme followed by a further 4 weeks of sedentary de-conditioning (Sloan et al., 2011). Participants performed various stressors before and after the intervention, including a public speaking task, mental arithmetic, and the Stroop Color-Word task, although there was no indication of any stress buffering effects following exercise training. In addition, a recent trial that examined the effects of 8 weeks' exercise training on muscle sympathetic nervous activity measured directly from the peroneal nerve found no evidence of sympatho-inhibition (Ray & Carter, 2010). Another study examined exercise training in the context of weight loss in obese children, and found that weight loss through 4 months of exercise training and diet, but not diet alone, improved vasodilatation responses to the Stroop mental challenge. This suggests that exercise in combination with weight loss might be important (Ribeiro et al., 2005).

From the present evidence it is difficult to conclude whether physical fitness per se or habitual physical activity underlies possible stress buffering effects. Much of the research in this field has

relied on self-report measures of physical activity, and the problems with these are well known. We therefore conducted a study to examine the association between objectively measured habitual physical activity levels and psychophysiological responses in women (Poole et al., 2011). Participants wore an accelerometer device during waking hours for 1 week, and in addition recorded their daily moods and took part in psychophysiological testing. We observed robust associations between objectively assessed physical activity and daily mood, which is displayed in Figure 20.1, where physical activity groups reflect tertile of average daily minutes active recorded by accelerometry. However, we found no associations with cardiovascular reactivity to behavioural stressors administered in the laboratory. Further work is required to examine whether habitual physical activity is more closely linked with physiological reactivity to naturalistic stressors. Taken together, inconsistencies in this area may be due, in part, to small sample sizes, insufficient exercise training effects, inconsistencies in methodology (i.e., design, types of stressors, types of stress response measures), failure to account for the after-effects of a recent bout of acute exercise, and other confounding factors. Furthermore, based on the law of initial values, it is likely that exercise will have the greatest effects in those individuals with heightened responses from the outset or some degree of underlying disease pathology. For example, exercise has been strongly associated with stress buffering effects in participants with parental history of hypertension (Hamer, Boutcher, & Boutcher, 2002) and chronically stressed individuals, such as caregivers (King, Baumann, O'Sullivan, Wilcox, & Castro, 2002) compared with healthy low-risk individuals. It should also be noted that previous studies have generally tended to measure BP intermittently with conventional arm cuffs, which may not capture the full contour of the response that can be obtained using beat-to-beat devices such as the Finometer.

The potential stress buffering benefits of regular exercise may be largely accounted for by the fact that exercisers are more often in the post-exercise window when they encounter daily stressors. The attenuation in BP reactivity immediately following a single bout of acute exercise is thought to be best explained by a reduction in regional vascular resistance mediated by sympathetic nervous inhibition (Halliwill, 2001). West, Brownley, and Light (1998) observed a significant reduction in vascular resistance during mental challenge following acute exercise. Brownley et al. (2003) also showed that reduced noradrenaline response to a behavioural stress task was the best single predictor of the attenuation in post-exercise BP stress responses. Furthermore, significant increases in post-exercise β1- and β2-receptor responsiveness were

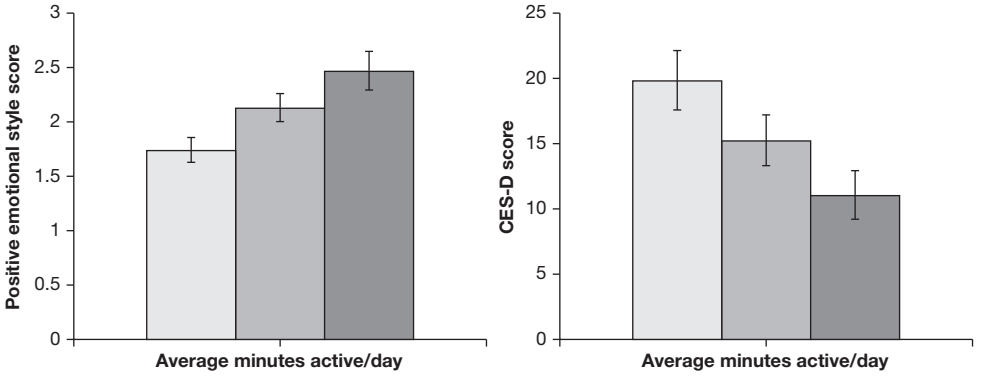

Figure 20.1 The association between physical activity and (a) daily positive mood and (b) depressive mood measured from the Centre Epidemiological Studies Depression (CES-D) scale. Physical activity groups reflect tertile of average daily minutes active recorded by accelerometry (≤213.88 minutes/day, 213.89–262.33 minutes/day and ≥262.34 minutes/day).

observed, indicating that the BP response was primarily blunted by enhancing β2-mediated vasodilatation (Brownley et al., 2003). Taken together, improvements in haemodynamic function during mental stress may be an important mechanism contributing to the stress buffering effects of acute exercise in relation to CVD risk. Consistent with this, studies in cardiac patients have demonstrated that exercise training reduces mental stress-induced ischaemia and results in fewer adverse cardiac events compared with controls over 5 years of follow-up (Blumenthal et al., 2002).

Exercise and psychobiology

A number of biological processes may explain the association between mental stress and physical disease, although far less work has focused upon neuroendocrine, inflammatory, and haemostatic processes. The HPA axis, for example, plays an important role in the stress response by releasing cortisol into the circulation. Abnormalities in HPA function have been described in several chronic inflammatory disorders, and it is thought to be one of the possible mechanisms through which psychosocial stress may influence the risk of CVD (Nijm & Jonasson, 2009). Several population studies have demonstrated associations between disturbances in diurnal cortisol profiles and sub-clinical atherosclerosis (Dekker et al., 2008; Matthews, Schwartz, Cohen, & Seeman, 2006). In a sample of 514 healthy British civil servants taken from the Whitehall II cohort we recently demonstrated an association between cortisol responses to laboratory-induced mental stress and sub-clinical coronary disease (Hamer, O'Donnell, Lahiri, & Steptoe, 2010). Those participants with a notable (>1nmol/l) rise in cortisol following two mental stress tasks were over two times more likely to have clinically relevant levels of coronary artery calcium after accounting for conventional risk factors such as cholesterol, smoking, and blood pressure.

Recent studies have consistently demonstrated blunted HPA responses to mental stressors in physically trained individuals (Traustadottir, Bosch, & Matt, 2005; Rimmele et al., 2009). For example, in a sample of elderly women, those defined as physically fit demonstrated plasma cortisol stress responses that were comparable with those of younger sedentary participants, but were blunted in comparison to elderly unfit counterparts (Traustadottir et al., 2005). Interestingly, physical fitness levels were not associated with cardiovascular responses to mental stress in these elderly women. In young men a blunted HPA stress response was only apparent in highly trained sportsmen, but amateur sportsmen had similar responses to the untrained men (Rimmele et al., 2009). This suggests that a certain threshold of exercise training is required to achieve adaptations in HPA stress responses. Paradoxically, recent data have demonstrated higher levels of cortisol in the hair of trained athletes compared with controls, suggesting greater chronic exposure to cortisol in trained individuals (Skoluda, Dettenborn, Stalder, & Kirschbaum, 2012).

There has been a large amount of interest in studying inflammatory responses to stress, since these mechanisms might be important in CVD (Steptoe, Hamer, & Chida, 2007). The specific nature of inflammatory responses to different types of stressors is, however, poorly understood. There is strong animal and in vitro evidence that the autonomic nervous system and neuroendocrine pathways are involved in the stimulation of interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α production (Sanders & Kavelaars, 2007). Since these pathways are activated during acute mental stress and exercise, they could be responsible for increased circulating levels of inflammatory factors. Bierhaus and colleagues (2003) elegantly demonstrated that nuclear factor-κB (NF-κB) in peripheral blood mononuclear cells (PBMC) is rapidly induced during acute mental stress exposure in parallel with catecholamine and cortisol responses. This might represent a key mechanism given that NF-κB is a redox-sensitive and oxidant-activated transcription factor that regulates inflammation-related gene expression. In animal models, the

activation of NF-κB is stimulated by norepinephrine-dependent pathways. Parasympathetic stimulation has the reverse effect, inhibiting NF-κB activation (Pavlov & Tracey 2005). However, direct evidence for sympathoadrenal processes in acute inflammatory stress responses in humans is limited at present. In a randomised controlled trial, von Känel et al. (2008) showed that 5 days' administration of aspirin but not propranolol attenuated the stress-induced increase in plasma IL-6 levels. In contrast, intravenous infusion of epinephrine rapidly increased plasma IL-6 in rats and this response could be blocked by propranolol (DeRijk, Boelen, Tilders, & Berkenbosch, 1994), but prolonged β-adrenergic stimulation at physiologic levels in humans induces local IL-1β, IL-6, and TNF-α expression in the myocardium without altering circulating levels (Murray, Prabhu, & Chandrasekar, 2000). Other data indicate that sympathoadrenal pathways play only a limited role in IL-6 responses to physical exercise (Febbraio & Pedersen, 2002), and intramuscular IL-6 expression appears to be regulated instead by a network of signalling cascades that are likely to involve the CA^{2+}/NFAT and glycogen/p38 MAPK pathways (Pedersen, 2011).

The precise mechanisms through which cytokine release is stimulated acutely therefore remain unclear. Controversially, it has been argued that the increases in circulating IL-6 that are observed after exercise promote an anti-inflammatory environment by increasing IL-1 receptor antagonist and IL-10 synthesis, while inhibiting pro-inflammatory markers such as TNF-α (Febbraio & Pedersen 2002). Indeed, the cytokines released during exercise are thought to originate from exercising skeletal muscle, and work in a hormone-like fashion exerting specific endocrine effects on various organs and signalling pathways. This hypothesis might explain why a large number of observational studies have demonstrated an inverse association between regular physical activity and various pro-inflammatory markers in humans (Hamer, 2007). In contrast, the release in IL-6 that is consistently observed following acute mental stress probably originates from a different source and is thought to be pro-inflammatory, which has been linked with indicators of CVD risk (Ellins et al., 2008). In addition, data from epidemiological studies also demonstrate positive associations between chronic psychosocial stress (indicated by low social economic status, chronic work stress, caregiver strain, early life adversity, hostility, and social isolation) and circulating levels of C-reactive protein, IL-6, and TNF-α. In one of the only studies to date, Hamer and Steptoe (2007) examined the association between physical fitness and inflammatory cytokine (IL-6 and TNF-α) responses to mental stress in a sample of 207 healthy, older adults. Physical fitness was assessed using a sub-maximal exercise test, and participants in the lowest tertile of fitness demonstrated the highest inflammatory responses to mental stress, independently of age, gender, social position, smoking, alcohol consumption, and basal levels of inflammatory markers, which is shown in Figure 20.2. Thus, there appears to be a unique cross-over effect of exercise in terms of stress-induced inflammatory responses.

In a further study we experimentally manipulated physical activity levels by asking a group of habitual exercisers to withdraw from their regular training for 2 weeks (Endrighi, Steptoe, & Hamer, 2011). The adherence to exercise withdrawal was mixed, as indicated by objective physical activity records, but in participants with greater mood disturbances (assessed using the 28-item General Health Questionnaire) following 2 weeks' withdrawal we observed significantly higher inflammatory responses to mental stress compared to those with low or no mood disturbance. These findings are presented in Figure 20.3, which shows that participants in the highest tertile of mood disturbance demonstrated the greatest inflammatory responses to mental stress after statistical adjustments for age, gender, body mass index, and pre-intervention inflammatory stress response. These results largely support our previous cross-sectional findings showing an inverse association between fitness and inflammatory stress responses, although it is difficult to conclude whether exercise withdrawal or mood disturbance per se is mainly driving the observed disturbances in inflammatory responses. One important aspect might be the ability

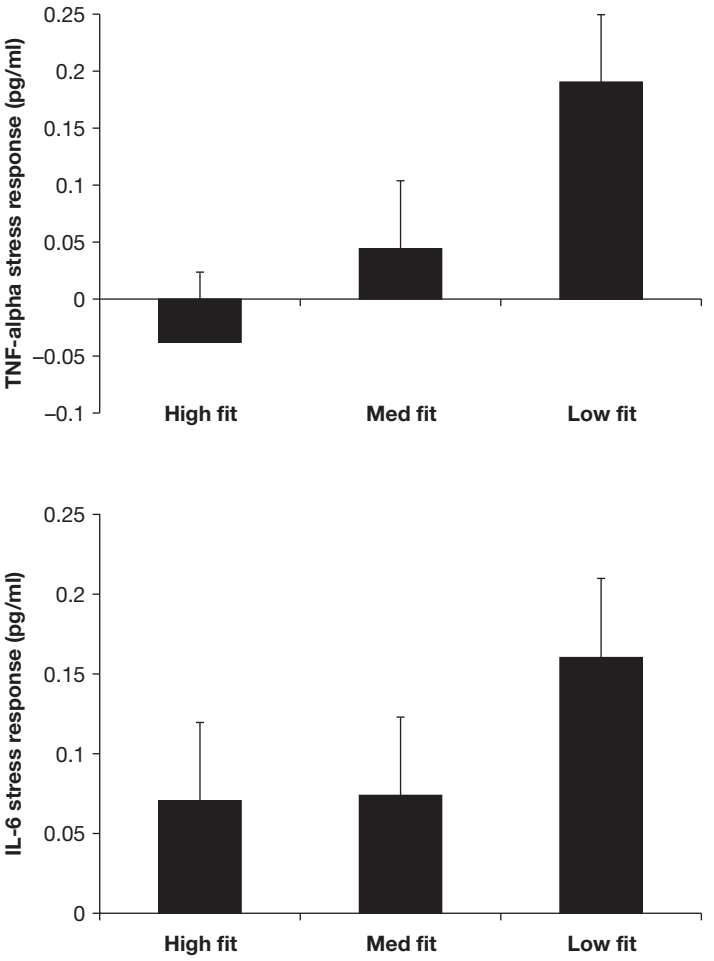

Figure 20.2 The association between physical fitness and the inflammatory response to mental stress [TNF-α (upper panel) and IL-6 (lower panel)]. Participants were 207 men and women drawn from the Whitehall II epidemiological cohort. Data are presented as mean ± SEM, adjusted for age, gender, body mass index, employment grade, smoking, alcohol, and basal levels of inflammatory cytokines. Physical fitness tertiles are based on heart rate response to cycling ergometry exercise at a standardised workload.

of the neuroendocrine system to suppress inflammatory responses. Following stress, the sensitivity of the immune system to dexamethasone (a synthetic version of the hormone cortisol that has potent anti-inflammatory properties) inhibition is reduced, as manifest by a reduction in this hormone's capacity to suppress the production of inflammatory cytokines (Rohleder, Schommer, Hellhammer, Engel, & Kirschbaum, 2001). In endurance-trained individuals, however, an acute bout of exercise has been shown to increase tissue sensitivity to glucocorticoids, which is thought to act as a mechanism to prevent an excessive muscle inflammatory reaction (Duclos, Gouarne, & Bonnemaison, 2003).

It is likely that the immune system interacts with the HPA axis and sympathetic nervous system in orchestrating an overall stress response. Previous research has indicated an intriguing link between efferent cholinergic activity of the vagus nerve (the parasympathetic arm of the

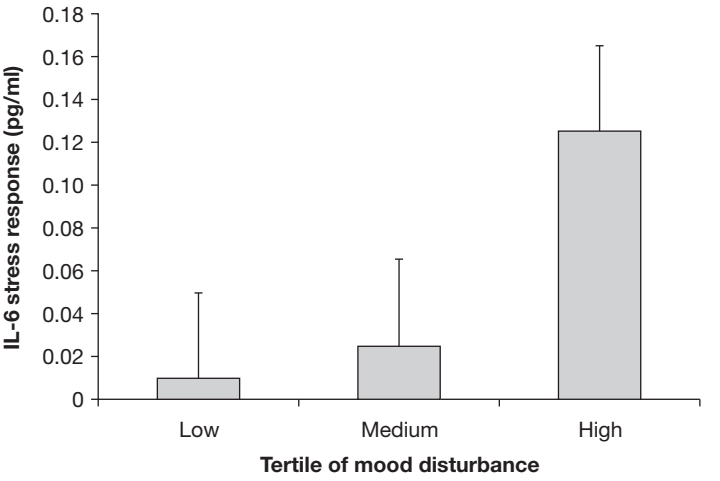

Figure 20.3 The association between mood disturbance following 2 weeks' exercise withdrawal and IL-6 responses to mental stress. Participants were 41 healthy men and women regularly engaged in exercise. Mood disturbance was assessed using the 28-item General Health questionnaire. Data are presented as mean ± SEM, adjusted for age, gender, body mass index, and pre-intervention inflammatory stress response.

autonomic nervous system) and inhibition of inflammatory processes (Tracy, 2002). Our findings indicated that fitter individuals maintained greater parasympathetic control during mental stress and also demonstrated the lowest inflammatory stress responses (Hamer & Steptoe 2007). The decline in parasympathetic control with ageing is attenuated with regular exercise training (Carter, Banister, & Blaber, 2003). Thus it is feasible that fitness-related improvements in parasympathetic activity may play a role in mediating the inhibition of stress-induced inflammatory processes. Other mechanisms are also likely to be important. For example, exercise has a favourable impact on insulin sensitivity and recent research has shown that the highest inflammatory cytokine responses to stress were in participants with the greatest levels of insulin resistance (Suarez, Boyle, Lewis, Hall, & Young, 2006). Other potential mediating effects may involve high-density lipoprotein cholesterol, adiponectin, and reduced reactive oxygen species—all of which demonstrate anti-inflammatory actions and are influenced by exercise training (Greenburg & Obin, 2006).

Conclusion

Interventions that reduce the magnitude of psychophysiological responses are justified, at least in part, by the notion that exaggerated responses to mental stress can have detrimental effects on health. Regular exercise is known to be an effective lifestyle intervention in the primary prevention of CVD, and this could be partly mediated through the buffering of haemodynamic, neuroendocrine, inflammatory, and haemostatic responses to daily mental stressors. There is reasonably strong evidence to suggest that a single bout of acute exercise can blunt cardiovascular stress responses although data from chronic training intervention studies are less consistent. Inconsistencies in this area may be due, in part, to small sample sizes, insufficient exercise training effects, inconsistencies in methodology (i.e., design, types of stressors, types of stress response measures), failure to account for the after-effects of a recent bout of acute exercise, and other confounding factors. At present there is some limited evidence to suggest that exercise might

also modify biological stress responses (cortisol, inflammatory markers), although further experimental work is needed to extend the current findings.

Acknowledgements

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