Psychosocial Stress and Cardiovascular Disease Risk: The Role of Physical Activity

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ABSTRACT

Chronic stress and depression are associated with increased risk of cardiovascular disease and poorer prognosis, and physical (in)activity may be a key underlying biobehavioral mechanism. Physical activity has antidepressant effects and physically fitter, more active individuals appear to be more biologically resilient to psychosocial stressors. This paper will present data from a series of population cohort studies and laboratory based psychophysiological studies to explore the role of physical activity as a protective factor against the effects of psychosocial stress on cardiovascular disease. These mechanisms may improve treatment and prevention of stress-related illnesses, and thus has important implications for public health and clinical care of high-risk patients.

Key words: cardiovascular disease, depression, epidemiology, physical activity, psychophysiology, stress.

CVD = cardiovascular disease; **MI** = myocardial infarction; **IL** = interleukin; **TNF-α** = tumor necrosis factor-alpha; **CRP** = C-reactive protein; **BDNF** = brain derived neurotrophic factor; **HPA** = hypothalamic pituitary adrenal

INTRODUCTION

Psychosocial risk factors involve a wide range of different variables, including mental stress, depression, anxiety, hostility, loneliness, and social circumstances and networks. Evidence from prospective cohort studies in humans that has emerged over the last several decades consistently demonstrates an association between various psychosocial risk factors and future risk of cardiovascular disease (CVD) in both initially healthy samples and cardiac patients (1-4), with effect sizes that are comparable to conventional risk factors such as hypertension, obesity and smoking (5).

The issue of how to tackle factors such as chronic stress and depression for disease prevention has been an area of considerable interest and intense debate in clinical and research work. In order for treatment to be successful it is essential to understand the pathways that might explain the associations between psychosocial stress and disease. Our understanding of the mechanisms is evolving (see Figure 1), and this knowledge base continues to develop. The reasons that the underlying pathways linking stress and CVD are incompletely understood can be partly attributed to methodological limitations and lack of controlled trial data. At present, the evidence base is largely limited to findings from observational population studies and psychophysiological experiments. Population studies enable large numbers of participants to be followed over time for hard clinical endpoints although causal inferences cannot be established. Acute psychophysiological stress testing involves the assessment of individual differences in biological responses to standardized stressors that can be related to psychosocial risk factors, thus is a useful technique to investigate underlying mechanisms (6,7).

Physical activity is a potentially important mediator of the link between stress and CVD. The last 50 years of epidemiological research in physical activity have provided strong evidence for the beneficial effects of physical activity on both cardiovascular (8,9) and mental health outcomes (10,11) although the causality of the former cardiovascular effects is much better established than that on mental health outcomes (12,13). The aim of this paper is to provide a selective review of the evidence for physical activity as a key intermediate pathway in the association between psychosocial factors and CVD.

EPIDEMIOLOGICAL EVIDENCE

In recent years epidemiological approaches to modelling the relationship between stress and CVD have been refined; traditionally researchers have aimed to test if the association between exposure (stress) and outcome (CVD) is maintained after adjustments for numerous covariates. However, more contemporary studies have started to treat covariates such as physical activity as mediators, thus examining the extent to which effect estimates are changed when a potential mediator is added to the model. Such an approach is grounded in theory and must conform to the main criteria for mediation, that is: the exposure should be associated with the potential mediator(s); the potential mediator should predict the outcome; the exposure variable should be associated with the outcome and this association should be significantly attenuated after adjustment for the mediator. Evidence from contemporary studies (14-18) has clearly demonstrated that participants categorised as stressed/depressed report lower physical activity levels, which can explain up to 30% of the association between stress/depression and CVD (see Table 1). For

example, among 6576 healthy community dwelling participants, those reporting psychological distress at baseline were at 50% increased risk of a CVD event during 7 years of follow up (14). Subsequent adjustment for physical inactivity in the models was associated with a 22% reduction in the strength of association between distress and CVD events, despite accounting for other covariates such as, age, sex, socioeconomic status, smoking status, and other conventional CVD risk factors. Similar findings were observed among 1017 outpatients with stable coronary disease from the Heart and Soul study (15). In a small cohort of 909 healthy, elderly European men, physical inactivity explained a negligible amount of the association between depression and CVD mortality during 10 years of follow up (18), although depression and inactivity combined to produce an additive risk increase of 33%. In one of the largest behavioural intervention trials to date, consisting of 2481 myocardial infarction (MI) patients suffering from depression and low perceived social support, treatment with cognitive behaviour therapy had no effect on event free survival after 29 months follow up despite significant improvement in depression and perceived social support (19). However, in a secondary analysis of the ENRICHD cohort, self- reported exercise in the 6 months following MI was associated with more than a 50% reduction in the risk of subsequent death (20). Physical inactivity not only carries cardiovascular health risks but is also important in predicting the onset of physical decline in older adults (21) and partly explains the link between depression and disability (22). Thus, physical decline, together with perceived barriers towards physical activity, such as fear and negative experiences, low self-efficacy, and lack of knowledge, may partly explain the increased risk of physical inactivity among participants with depressive symptoms. In addition, cognitive factors such as impaired executive function, with

reduced ability to handle, process, and retain new information may also partly explain why depressed patients are less likely to adhere to treatments and lifestyle modification.

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 vice versa. For example, 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 (23). These types of issues might be resolved in the future by the use of contemporary statistical approaches that reveal individual heterogeneity in the direction of the effect (24). Another weakness of this area is the reliance on self-reported physical activity. One of the most significant developments in field over the last decade has been the introduction of small solid-state accelerometer devices that now permits physical activity to be assessed objectively over several days at low cost, thus making it is feasible to incorporate such measures in large scale population studies such as the National Health and Nutrition Examination Survey. Physical activity epidemiologists have traditionally employed self-report measures, which have the possibility of introducing reporting biases and making it more difficult to precisely define the dose-response association between physical activity and health. Objective measures are not only able to assess intensity and duration of activity more effectively, but can also better delineate the duration of continuous bouts of activity

and periods of prolonged inactivity (sitting) (Figure 2). Very few studies have examined associations between objectively assessed physical activity and mental health, and those that have reveal inconsistent findings (25-29). Some of these limitations inherent to epidemiological studies can be reduced by investigations that use experimental manipulations of physical activity levels and those using stress reactivity paradigms.

EXERCISE AND CARDIOVASCULAR STRESS REACTVITY

Psychophysiological stress testing can be used to establish the mechanisms and time-trajectories 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 (6), which on balance suggests that the effect sizes are modest but consistent after accounting for established risk factors. Paradoxically, both exercise and mental stress elicit substantial cardiovascular reactivity although these responses are considered healthy in the context of exercise whereas the same reactivity measures are purportedly 'bad' when examined in the context of mental stress. In fact similarities between central and peripheral responses to exercise and mental stressors have led to the theory of "cross-stressor adaptation" (30), where adaptations resulting from regular exercise lead not only to improved physiological control during exercise, but also in response 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. Several experiments have tested the impact of single bouts of exercise, the aim of which is to examine whether stress reactivity or rate of recovery is modified after physical activity; others have made 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.

Studies examining the effects of acute exercise have resulted in relatively consistent evidence, such that a single bout of exercise is associated with buffering of blood pressure and cardiac responses to standardised behavioural challenges in the laboratory (31). 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 blood pressure stress reactivity (32), but more recent updated reviews suggested both positive and inverse associations between fitness and heart rate reactivity (33,34). Dishman and Jackson (33) 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 randomized controlled exercise training studies were included and when fitness was measured as peak oxygen uptake. In contrast, Forcier and colleagues (34) demonstrated an inverse association between fitness and heart rate reactivity in an analysis containing only studies with evidence of an exercise training effect. A common problem in this area is limited sample size that can often lead to studies with insufficient statistical power. This issue was, however, addressed in a recent controlled trial consisting of 149 healthy, young sedentary

participants who were randomised to a 12 week exercise program followed by a further 4 weeks of sedentary de-conditioning (35). 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 eight weeks exercise training on muscle sympathetic nervous activity measured directly from the peroneal nerve found no evidence of sympatho-inhibition (36). Another study examined exercise training in the context of weight loss in obese children, and found that weight loss through four months of exercise training and diet, but not diet alone, improved vasodilatation responses to the Stroop mental challenge (37). This suggests that exercise in combination with weight loss might be important in attenuating cardiovascular reactivity in response to mental challenges.

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 type of chronic adaptations required to observe stress buffering effects. Here, a comparison of persons with a longer history of low and high levels of habitual physical activity may be helpful. 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 (29). Participants wore an accelerometer device during waking hours for one 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, (Figure 3) although no associations were found with cardiovascular reactivity to behavioural stressors administered in the laboratory. Further work is required to examine if habitual physical activity is more closely linked with physiological reactivity to naturalistic stressors. In addition, sedentary behaviour may play an important role (38), although no work has examined if sedentary behaviour (prolonged sitting) is related to psychophysiological responses independently of physical activity. 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 (39) and chronically stressed individuals, such as caregivers (40) compared with healthy low-risk individuals. It should also be noted that previous studies have generally tended to measure blood pressure intermittently with conventional arm cuffs, which may not capture the full contour of the response that can be obtained using beat-to-beat devices.

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 blood pressure 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 (41). Indeed studies have shown that reduced noradrenaline response to a behavioural stress task was the best single predictor of the attenuation in post-exercise blood pressure stress responses (42). Furthermore, significant increases in post-exercise β1- and β2-receptor responsiveness were observed, indicating that the blood pressure response was primarily blunted by enhancing β2-mediated vasodilatation (42). 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.

PHYSICAL ACTIVITY, STRESS AND INFLAMMATION

The immune system may play an important role in psychobiological processes that link psychosocial stress with CVD and other health outcomes (43). Acute mental stress has been shown to induce increases in circulating inflammatory markers such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α) (44) and these responses are more pronounced in participants with enduring chronic stress and depressive symptoms (45,46), although less pronounced in physically fit participants (47). Numerous studies have also demonstrated elevated concentrations of various inflammatory markers at rest in differing populations reporting depressive symptoms (48). A large amount of interest has focused on the potential anti-inflammatory effects of exercise. It has been argued that the increases in circulating IL-6 that are observed after an acute bout of 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 (49). The cytokines released during exercise are thought to originate from exercising skeletal muscle, which work in a hormone-like fashion exerting specific endocrine effects on various organs and signalling

pathways. Unlike IL-6 release during acute mental stress, which appears to be dependent on activation of the Nuclear Factor κB signalling pathway (50), intramuscular IL-6 expression is regulated by a network of signalling cascades that are likely to involve the CA^{2+}/NFAT and glycogen/p38 MAPK pathways. This might partly explain why exercise-induced IL-6 release is not acting as a strong pro-inflammatory agent. This hypothesis is also consistent with data from numerous observational studies demonstrating an inverse association between regular physical activity and various pro-inflammatory markers (51). Results from controlled exercise trials have not always consistently found reductions in inflammatory markers following intervention, although given that the majority of health benefits from exercise are established through chronic training adaptations, it is difficult to draw firm conclusions from short-term exercise trials often only lasting for 3 months. In the Whitehall II cohort we recently demonstrated that maintenance of habitual physical activity over 10 years was associated with lower levels of C-reactive protein (CRP) and IL-6 at follow-up and the differences in inflammatory markers between active and inactive remained stable over time (52).

Given the described link between both psychological stress and exercise with inflammatory pathways, it can be hypothesized that better mental wellbeing experienced by regular exercisers might be partly explained by an underlying inflammatory mechanism. We conducted a study in a sample of 3609 older adults from the English Longitudinal Study of Ageing, to examine if the association between persistent depressive symptoms and inflammatory markers over 2 years follow up could be partly explained by physical activity behaviour. Participants with recurrent elevated depressive symptomatology at both time points displayed significantly elevated levels of CRP and fibrinogen at follow-up compared to non-depressed, and

this relationship was partly explained through lower levels of physical activity in participants with depressive symptoms (53). The anti-inflammatory effects of exercise might also be relevant at a neurobiological level, since alterations in neurotransmitter function involving serotonin, norepinephrine and dopamine are known to induce depression and are targets for currently available psychopharmacological treatments. Exercise is thought to alter serotonin metabolism, release endogenous opioids, and increase central noradrenergic neurotransmission which may all contribute to antidepressant and anxiolytic effects. The dopaminergic system is thought to play a key role in depression, and polymorphisms of the dopamine D2 receptor gene have also been implicated in physical activity behaviour (54). Further research has focused on the hippocampus, where exercise induced neurogenesis and growth factor expression has been proposed as potential mediators (55). An emerging theory is that exercise enhances several growth factors, such as brain derived neurotrophic factor (BDNF) and insulin like growth factor, which mediate the protective and therapeutic effects of exercise on depression. It has been shown that an acute bout of exercise increases peripheral levels of serum BDNF in an exercise intensity dependent fashion, but resting levels of BDNF does not seem to be affected by long term exercise training (56) suggesting that other compensatory mechanisms might be at play. In connection to the effects of exercise on neurotrophins the endocannabinoid system might represent an important mediating signalling pathway (57).

Another important aspect may be the interaction of the immune system with the hypothalamic pituitary adrenal (HPA) axis and autonomic nervous system. Following mental stress, the sensitivity of the immune system to dexamethasone inhibition (a synthetic version of the hormone cortisol that has potent anti-

inflammatory properties) is reduced, as manifest by a reduction in this hormone's capacity to suppress the production of inflammatory cytokines (58). In endurance trained individuals, however, an acute bout of exercise has been shown to increase tissue sensitivity to glucocorticoids (59). HPA axis dysregulation and cortisol hyper-secretion has been implicated in adverse mental health and cardiovascular outcomes. For example, in a healthy sub-sample of participants from the Whitehall ll cohort we showed that exaggerated cortisol responses to two behavioral stress tasks were predictive of coronary artery calcium progression over 3 years follow up and incident hypertension (60,61). Exercise may have beneficial effects on HPA functioning as some studies have shown lower stress-induced cortisol responses in physically trained individuals compared to the untrained (62,63). However, we failed to replicate previous findings in our work that examined associations between objectively assessed physical activity levels and cortisol responses to acute mental stress (29). In addition, recent data demonstrated higher levels of cortisol in the hair of trained athletes compared with controls, suggesting greater chronic exposure to cortisol in trained individuals (64). Some of these inconsistencies might be attributed to differences in measures, as cortisol from hair is a reflection of chronic exposure but does not necessarily provide information about glucocorticoid sensitivity or acute variations which are better assessed through psychophysiological studies and diurnal sampling. Thus, teasing apart chronic effects from acute variations in daily diurnal patterns will be an interesting avenue of future research.

In summary, the link between physical activity and stress could be explained through several biological processes, including the inflammatory, dopaminergic and neuroendocrine systems, which might have relevance to CVD pathology and other diseases in which inflammatory processes play a contributing role. However, there is

a lack of experimental and longitudinal evidence to show the long-term health consequences of physical activity on these biological pathways.

THE EXERCISE WITHDRAWAL PARADIGM

Exercise training trials are costly and require a large amount of manpower in administering supervised exercise sessions. Additionally, 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 and some participants are non-adherent, which suggests a short period of exercise training may not be sufficient to induce the type of chronic adaptations required to observe stress buffering effects. The exercise withdrawal paradigm therefore represents a useful, more practical alternative since mood disturbances can be elicited in habitual exercisers after 1-2 weeks withdrawal from their regular training activities, which provides a model to investigate the links between exercise, stress, and the underlying biology. We and others have hypothesized that mood disturbances caused by withdrawal from regular exercise might act as a mild inflammatory stimulus. However, recent studies have been unable to confirm this hypothesis. Several studies, including one of our own that have successfully induced an increased negative mood following several weeks of exercise withdrawal, did not find any robust changes in a range of inflammatory markers, such as IL-6, CRP, TNF-α, fibrinogen and soluble intracellular adhesion molecule-1 (65,66). Similarly, one week withdrawal from exercise in highly active men did not elicit any substantial changes in CRP, IL-6, TNF-α, and circulating leukocyte concentration (67). In the same study, no changes in inflammatory markers were observed among sedentary participants who undertook 30 min of brisk walking each day for one week. Healthy men that reduced their daily step count by

85% for two weeks developed impaired glucose tolerance, attenuation of postprandial lipid metabolism, and a 7% increase in intra-abdominal fat mass, although plasma cytokines and muscular expression of TNF was not altered (68). However, another study reported that reduced parasympathetic nervous activity as measured by heart rate variability was predictive of negative mood following exercise withdrawal (69). These findings are consistent with emerging data on underlying molecular mechanisms. For example, the expression of exercise-regulated muscle genes, such as the transcriptional co-activator PGC1α, that is thought to promote anti-inflammatory effects (70), is known to be rapidly induced after a single bout of acute exercise although quickly reverts back to basal levels. In contrast to the transient changes following acute exercise, greater levels of PGC1α are present in chronically trained exercised muscle than in untrained. Thus, there is a clear difference between short-term and long term adaptations, which might explain why a short two week exercise withdrawal period in trained participants is insufficient to see changes. Furthermore, adherence to exercise withdrawal in regular, fit exercisers may be problematic because habitually active individuals are less likely to agree to stop their training regime and perhaps compensate in other ways to maintain a physically active lifestyle (e.g., taking up active commuting for the period of exercise withdrawal). This creates other inherent limitations as removing self-chosen leisure time behaviors may in itself induce psychological distress regardless of exercise cessation.

In a further study we investigated the impact of exercise withdrawal on psychophysiological responses to mental stress because this method can sometimes detect differences that might not otherwise be seen under resting conditions. Although the effects of cytokines are often thought to be transient, they

may provoke a time-dependent sensitisation so that the response to a later cytokine or stressor stimulus is enhanced, resulting in an increased vulnerability to depressed mood (71). We experimentally manipulated physical activity levels by asking a group of habitual exercisers to withdraw from their regular training for two weeks (72). The adherence to exercise withdrawal was mixed, as indicated by objective accelerometry physical activity records, but in participants with greater mood disturbances (assessed using the 28 item General Health Questionnaire) following two weeks withdrawal we observed significantly higher inflammatory responses to mental stress compared to those with low or no mood disturbance. In the same study, cortisol responses to mental stress were higher in the exercise withdrawal phase compared to control period with a significant difference emerging at 20 minutes post-stress. These results, although preliminary, suggest that inflammatory and neuroendocrine factors may in part mediate the protective or buffering effect of physical activity on stress-related physiological activation.

To summarise, the exercise withdrawal paradigm offers a promising way in which to elucidate some of the mechanistic pathways linking physical activity to stress and CVD risk. Future work is needed to better understand the temporal relationship between exercise-induced mood disturbances and changes in inflammatory and neuroendocrine factors.

CONCLUSIONS AND FURTHER WORK

Numerous intermediate mechanisms might explain the link between psychosocial factors and CVD and other diseases, including behavioural and biological processes. Increasing our knowledge about these mechanisms will contribute to more effective prevention and treatment strategies and help establish priorities for the allocation of

health care and research resources. Taken together, the currently available data from epidemiological studies suggest physical activity plays an important role in explaining the association between psychosocial factors and CVD. Interventions that reduce the magnitude of psychophysiological responses are also of interest as 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 hemodynamic, neuroendocrine, inflammatory, and hemostatic responses to daily mental stressors. There is reasonably strong evidence to suggest that a single bout of acute exercise can blunt cardiovascular stress responses and as these effects last for 2 to 4 hours a person that exercises three times a week may be in a stress-buffered state up to 12 hours a week. Data from chronic training intervention studies on the effects beyond the after-effects of a recent bout of acute exercise 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), and other confounding factors. At present there is 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

REFERENCES

1. Steptoe A, Kivimäki M. Stress and cardiovascular disease. Nat Rev Cardiol. 2012;9:360-70.

2. Brotman DJ, Golden SH, Wittstein IS. The cardiovascular toll of stress. Lancet. 2007;370:1089-100.

3. Hamer M, Kivimäki M, Stamatakis E, Batty GD. Psychological distress as a risk factor for cerebrovascular disease mortality: A population study in 68,652 adults. CMAJ [epub ahead of print]. First published June 18, 2012, doi: 10.1503/cmaj.111719.

4. Kivimaki M, Nyberg ST, Batty GD, Fransson EI, Heikkilä K, Alfredsson L et al.; IPD Work Consortium. Job strain as a risk factor for future coronary heart disease: Collaborative meta-analysis of 2358 events in 197,473 men and women. Lancet 2012 (in press).

5. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937-52.

6. Chida Y, Steptoe A. Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status: a meta-analysis of prospective evidence. Hypertension. 2010;55:1026-32

7. Chida Y, Hamer M. Chronic psychosocial factors and acute physiological responses to laboratory-induced stress in healthy populations: a quantitative review of 30 years of investigations. Psychol Bull. 2008;134:829-85.

8. Hamer M, Chida Y. Walking and primary prevention: a meta-analysis of prospective cohort studies. Br J Sports Med. 2008;42:238-43.

9. Sattelmair J, Pertman J, Ding EL, Kohl HW 3rd, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. Circulation. 2011;124:789-95.

10. Rethorst CD, Wipfli BM, Landers DM. The antidepressive effects of exercise: a meta-analysis of randomized trials. Sports Med. 2009;39:491-511.

11. Herring MP, O'Connor PJ, Dishman RK. The effect of exercise training on anxiety symptoms among patients: a systematic review. Arch Intern Med. 2010;170: 321-331.

12. De Moor MH, Boomsma DI, Stubbe JH, Willemsen G, de Geus EJ. Testing causality in the association between regular exercise and symptoms of anxiety and depression. Arch Gen Psychiatry. 2008;65:897-905.

13. Chalder M, Wiles NJ, Campbell J, Hollinghurst SP, Haase AM, Taylor AH, Fox KR, Costelloe C, Searle A, Baxter H, Winder R, Wright C, Turner KM, Calnan M, Lawlor DA, Peters TJ, Sharp DJ, Montgomery AA, Lewis G. Facilitated physical activity as a treatment for depressed adults: randomised controlled trial. BMJ. 2012;344:e2758.

14. Hamer M, Molloy GJ, Stamatakis E. Psychological distress as a risk factor for CVD events: pathophysiological and behavioural mechanisms. J Am Coll Cardiol 2008;52:2156-62.

15. Whooley MA, de Jonge P, Vittinghoff E, Otte C, Moos R, Carney RM. Depressive symptoms, health behaviours, and risk of cardiovascular events in patients with coronary heart disease. JAMA. 2008;300: 2379-88.

16. Hamer M, Bates CJ, Mishra GD. Depression, physical function, and risk of mortality: National Diet and Nutrition Survey in adults older than 65 years. Am J Geriatr Psychiatry. 2011;19:72-8.

17. Win S, Parakh K, Eze-Nliam CM, Gottdiener JS, Kop WJ, Ziegelstein RC. Depressive symptoms, physical inactivity and risk of cardiovascular mortality in older adults: the Cardiovascular Health Study. Heart. 2011;97:500-5.

18. Kamphuis MH, Geerlings MI, Tijhuis MA, Giampaoli S, Nissinen A, Grobbee DE, Kromhout D. Physical inactivity, depression, and risk of cardiovascular mortality. Med Sci Sports Exerc. 2007;39:1693-9.

19. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ et al. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. JAMA 2003;289:3106-16.

20. Blumenthal JA, Babyak MA, Carney RM, Huber M, Saab PG, Burg MM, et al. Exercise, depression, and mortality after myocardial infarction in the ENRICHD trial. Med Sci Sports Exerc. 2004;36:746-55.

21. Lang IA, Guralnik JM, Melzer D. Physical activity in middle-aged adults reduces risks of functional impairment independent of its effect on weight. J Am Geriatr Soc 2007;55:1836-41.

22. Lee Y, Park K. Does physical activity moderate the association between depressive symptoms and disability in older adults? Int J Geriatr Psychiatry. 2008;23:249-56.

23. Azevedo Da Silva M, Singh-Manoux A, Brunner EJ, Kaffashian S, Shipley MJ, Kivimäki M, Nabi H. Bidirectional association between physical activity and symptoms of anxiety and depression: the Whitehall II study. Eur J Epidemiol. 2012;27:537-46.

24. Rosmalen JG, Wenting AM, Roest AM, de Jonge P, Bos EH. Revealing causal heterogeneity using time series analysis of ambulatory assessments:

application to the association between depression and physical activity after myocardial infarction. Psychosom Med. 2012;74:377-86.

25. Yoshiuchi K, Nakahara R, Kumano H, Kuboki T, Togo F, Watanabe E, Yasunaga A, et al. Year-long physical activity and depressive symptoms in older Japanese adults: cross-sectional data from the Nakanojo study. Am J Ger Psych 2006;14: 621-624.

26. Mendlowicz MV, Jean-Louis G, von Gizycki H, Zizi F, Nunes J. Actigraphic predictors of depressed mood in a cohort of non-psychiatric adults. Austr NZ J Psych 1999;33: 553-558.

27. Janney CA, Richardson CR, Holleman RG, Glasheen C, Strath SJ, Conroy MB, Kriska AM. Gender, mental health service use and objectively measured physical activity: Data from the National Health and Nutrition Examination Survey (NHANES 2003-2004). Mental Health Physical Activity 2008;1: 9-16.

28. Hamer M, Stamatakis E. Objectively assessed physical activity, fitness and subjective wellbeing. Mental Health Physical Activity 2010;3: 67-71.

29. Poole L, Steptoe A, Wawrzyniak AJ, Bostock S, Mitchell ES, Hamer M. Associations of objectively measured physical activity with daily mood ratings and psychophysiological stress responses in women. Psychophysiology. 2011;48:1165-72.

30. Sothmann MS, Buckworth J, Claytor RP, Cox RH, White-Welkley JE, Dishman RK. Exercise training and the cross-stressor adaptation hypothesis. Exerc Sport Sci Rev 1996;24:267-87.

31. Hamer M, Taylor A, Steptoe A. The effect of acute aerobic exercise on stress related blood pressure responses: a systematic review and meta-analysis. Biol Psychol 2006;71: 183-90.

32. Crews DJ, Landers DM. A meta-analytic review of aerobic fitness and reactivity to psychosocial stressors. Med Sci Sports Exerc 1987;19: S114-20.

33. Dishman RK, Jackson EM. Cardiorespiratory fitness and laboratory stress: A meta-regression analysis. Psychophysiol 2006;43: 57-72.

34. Forcier K, Stroud LR, Papandonatos GD, Hitsman B, Reiches M, Krishnamoorthy J, Niaura R. Links between physical fitness and cardiovascular reactivity and recovery to psychological stressors: A meta-analysis. Health Psychol 2006;25: 723-39.

35. Sloan RP, Shapiro PA, Demeersman RE, Bagiella E, Brondolo EN, McKinley PS, Crowley O, Zhao Y, Schwartz JE, Myers MM. Impact of aerobic training on cardiovascular reactivity to and recovery from challenge. Psychosom Med 2011;73: 134-41.

36. Ray CA, Carter JR. Effects of aerobic exercise training on sympathetic and renal responses to mental stress in humans. Am J Physiol Heart Circ Physiol. 2010;298:H229-34.

37. Ribeiro MM, Silva AG, Santos NS, Guazzelle I, Matos LN, Trombetta IC, Halpern A, Negrao CE, Villares SM. Diet and exercise training restore blood pressure and vasodilatory responses during physiological maneuvers in obese children. Circulation 2005;111: 1915-23.

38. Hamer M, Stamatakis E, Mishra G. Television- and screen-based activity and mental well-being in adults. Am J Prev Med. 2010;38:375-80.

39. Hamer M, Jones J, Boutcher SH. Acute exercise reduces vascular reactivity to mental challenge in offspring of hypertensive families. J Hypertens. 2006;24:315-20.

40. King AC, Baumann K, O'Sullivan P, Wilcox S, Castro C. Effects of moderate-intensity exercise on physiological, behavioral, and emotional responses to family caregiving: a randomized controlled trial. J Gerontol A: Biol Sci Med Sci 2002;57: M26-36.

41. Halliwill JR. Mechanisms and clinical implications of post-exercise hypotension in humans. Exerc Sport Sci Rev 2001;29: 65-70.

42. Brownley KA, Hinderlitter AL, West SG, Girdler SS, Sherwood A, Light KA. Sympathoadrenergic mechanisms in reduced hemodynamic stress responses after exercise. Med Sci Sports Exerc 2003;35: 978-986.

43. Vaccarino V, Johnson BD, Sheps DS, Reis SE, Kelsey SF, Bittner V, Rutledge T, Shaw LJ, Sopko G, Bairey Merz CN; National Heart, Lung, and Blood Institute. Depression, inflammation, and incident cardiovascular disease in women with suspected coronary ischemia: the National Heart, Lung, and Blood Institute-sponsored WISE study. J Am Coll Cardiol 2007;50:2044-50.

44. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. Brain Behav Immun. 2007;21:901-12.

45. Hamer M, Williams E, Vuonovirta R, Giacobazzi P, Gibson EL, Steptoe A. The effects of effort-reward imbalance on inflammatory and cardiovascular responses to mental stress. Psychosom Med. 2006;68: 408-13.

46. Pace TW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, Heim CM. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. Am J Psychiatry. 2006;163: 1630-3.

47. Hamer M, Steptoe A. The association between physical fitness, parasympathetic control, and pro-inflammatory responses to mental stress. Psychosom Med. 2007; 69: 660-66.

48. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med. 2009;71:171-86.

49. Pedersen BK. Exercise-induced myokines and their role in chronic diseases. Brain Behav Immun 2011;25: 811-6.

50. Bierhaus A, Wolf J, Andrassy M, Rohleder N, Humpert PM, Petrov D, Ferstl R, von Eynatten M, Wendt T, Rudofsky G, Joswig M, Morcos M, Schwaninger M, McEwen, B, Kirschbaum C, Nawroth PP. A mechanism converting psychosocial stress into mononuclear cell activation. PNAS. 2003;100:1920-1925.

51. Hamer M. The relative influences of fitness and fatness on inflammatory factors. Prev Med. 2007; 44: 3-11.

52. Hamer M, Sabia S, Batty GD, Shipley MJ, Tabák AJ, Singh-Manoux A, Kivimaki M. Physical activity and inflammatory markers over 10 years follow up in men and women from the Whitehall II cohort study. Circulation 2012 (in press).

53. Hamer M, Molloy GJ, de Oliveira C, Demakakos P. Persistent depressive symptomatology and inflammation: to what extent do health behaviours and weight control mediate this relationship? Brain Behav Immun. 2009;23:413-8.

54. Simonen RL, Rankinen T, Perusse L, Leon AS, Skinner JS, Wilmore JH, Rao DC, Bouchard C. A dopamine D2 receptor gene polymorphism and physical activity in two family studies. Physiol Behav. 2003;78:751-7.

55. Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci. 2007;30: 464-72.

56. Knaepen K, Goekint M, Heyman EM, Meeusen R. Neuroplasticity - exercise-induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. Sports Med. 2010;40: 765-801.

57. Heyman E, Gamelin FX, Goekint M, Piscitelli F, Roelands B, Leclair E, Di Marzo V, Meeusen R. Intense exercise increases circulating endocannabinoid and BDNF levels in humans--possible implications for reward and depression. Psychoneuroendocrinology. 2012;37:844-51.

58. Rohleder N, Schommer NC, Hellhammer DH, Engel R, Kirschbaum C. Sex differences in glucocorticoid sensitivity of proinflammatory cytokine production after psychosocial stress. Psychosom Med 2001;63: 966-72.

59. Duclos M, Gouarne C, Bonnemaison D. Acute and chronic effects of exercise on tissue sensitivity to glucocorticoids. J Appl Physiol 2003;94:869-75.

60. Hamer M, Endrighi R, Venuraju SM, Lahiri A, Steptoe A. Cortisol responses to mental stress and the progression of coronary artery calcification in healthy men and women. PLoS One. 2012;7:e31356.

61. Hamer M, Steptoe A. Cortisol responses to mental stress and incident hypertension in healthy men and women. J Clin Endocrinol Metab. 2012;97:E29-34.

62. Rimmele U, Seiler R, Marti B, Wirtz PH, Ehlert U, Heinrichs M. The level of physical activity affects adrenal and cardiovascular reactivity to psychosocial stress. Psychoneuroendocrinology 2009;34:190-8.

63. Traustadóttir T, Bosch PR, Matt KS. The HPA axis response to stress in women: effects of aging and fitness. Psychoneuroendocrinology 2005;30:392-402.

64. Skoluda N, Dettenborn L, Stalder T, Kirschbaum C. Elevated hair cortisol concentrations in endurance athletes. Psychoneuroendocrinology. 2012;37:611-7.

65. Poole L, Hamer M, Wawrzyniak AJ, Steptoe A. The effects of exercise withdrawal on mood and inflammatory cytokine responses in humans. Stress. 2011;14:439-47.

66. Kop WJ, Weinstein AA, Deuster PA, Whittaker KS, Tracy RP. Inflammatory markers and negative mood symptoms following exercise withdrawal. Brain Behav Immun. 2008;22:1190-6.

67. Lund AJ, Hurst TL, Tyrrell RM, Thompson D. Markers of chronic inflammation with short-term changes in physical activity. Med Sci Sports Exerc. 2011;43: 578-83.

68. Krogh-Madsen R, Thyfault JP, Broholm C, Mortensen OH, Olsen RH, Mounier R, Plomgaard P, van Hall G, Booth FW, Pedersen BK. A 2-wk reduction of ambulatory activity attenuates peripheral insulin sensitivity. J Appl Physiol. 2010;108:1034-40.

69. Weinstein AA, Deuster PA, Kop WJ. Heart rate variability as a predictor of negative mood symptoms induced by exercise withdrawal. Med Sci Sports Exerc. 2007;39:735-741.

70. Handschin C, Spiegelman BM. The role of exercise and PGC1alpha in inflammation and chronic disease. Nature 2008;454:463-9.

71. Anisman H, Merali Z. Cytokines, stress and depressive illness: brain-immune interactions. Ann. Med. 2003;35:2-11.

72. Endrighi R, Steptoe A, Hamer M. Mood disturbance following exercise withdrawal is associated with greater inflammatory responses to stress. Psychosom Med. 2011;73:A110.

Table 1. A summary of the results from epidemiological studies exploring the extent to which physical activity behaviour explains the association between stress/depression and CVD.

Study	Sample	Exposure & outcome	% explained by physical activity
Hamer et al. (14)	Healthy general UK population (n=6576)	GHQ-12; CVD events, 7.2 y follow-up	22%
Whooley et al. (15)	Cardiac patients (n=1017)	PHQ-9; Recurrent CVD, 4.8 y follow-up	31%
Hamer et al. (16)	UK elderly population (n=1007)	GDS-15; CVD death, 9.2 y follow-up	25% *(12.5% activity; 12.5% function)*
Win et al. (17)	Healthy general US population (n=5888)	CES-D; CVD death, 10.3 y follow-up	26%
Kamphuis et al. (18)	Healthy European elderly men (n=909)	Zung Self-Rating Depression Scale; CVD death, 10 y follow-up	9%

Abbreviations; GHQ-12, General Health Questionnaire; PHQ-9, Patient Health Questionnaire; GDS-15, Geriatric Depression Scale; CES-D, Centre for Epidemiological Studies Depression scale.

Figure captions

Figure 1. A conceptual framework for the possible mechanisms that explain the association between psychosocial risk factors and cardiovascular disease.

Figure 2. Data from an accelerometry device that was worn by a healthy male participant over a 24 hour period. The data emphasizes the complex patterns of activity that can be captured by an objective measure.

Figure 3. The association between physical activity and (a) daily positive mood; (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).

Midnight ⟷ Midnight

- - - - Sedentary to light cut off .... Light to moderate cut off - · - · - Moderate to vigorous cut off

Light **Activity**

Tuesday (2011-11-08)

Activity Summary

- Sedentary 0.10 - Light
- Moderate - Vigorous

3%
11%
5%
81%