Association Between Physical Fitness, Parasympathetic Control, and Proinflammatory Responses to Mental Stress

MARK HAMER, PHD, AND ANDREW STEPTOE, DPHIL

Objectives: To examine the association between physical fitness, cardiac parasympathetic control, and inflammatory cytokine responses to mental stress. Exercise and physical fitness may act as a buffer to the detrimental effects of psychosocial stress exposure. **Methods:** Participants were 207 men and women (52 ± 3 years) drawn from the Whitehall II epidemiological cohort. Participants completed two mental stressors consisting of a 5-minute Stroop task and a 5-minute mirror tracing task. Blood samples were obtained during baseline and 45 minutes post stress. Heart rate variability (HRV) was measured during baseline, stress, and recovery. Physical fitness was assessed from a submaximal exercise test. **Results:** Interleukin (IL)-6 and IL-1 receptor antagonist were increased significantly at 45 minutes post stress. Multiple linear regression analysis, adjusted for age, body mass index, gender, smoking, alcohol, grade of employment, and basal levels of inflammatory markers demonstrated that exercise heart rate (a fitness indicator) was related to IL-6 ($\beta = 0.24$; $p = .005$) and tumor necrosis factor (TNF)-α responses to stress ($\beta = 0.27$; $p = .002$). Exercise heart rate was also related to the HRV response to stress ($\beta = -0.23$; $p = .02$). A higher systolic blood pressure response to exercise was a predictor of TNF-α responses to stress ($\beta = 0.18$; $p = .03$). **Conclusions:** Physical fitness (as indexed by lower exercise heart rate) is associated with smaller inflammatory cytokine responses to acute mental stress, an effect that may be partly mediated through parasympathetic pathways. This may be one of the mechanisms by which physical fitness confers protection against cardiovascular risk. **Key words:** exercise, cardiorespiratory fitness, psychosocial stress, inflammatory cytokines, parasympathetic control, cardiovascular risk.

IL = interleukin; **TNF** = tumor necrosis factor; **HRV** = heart rate variability; **CHD** = coronary heart disease; **BMI** = body mass index.

INTRODUCTION

The biological processes underlying the association between psychosocial stress and coronary heart disease (CHD) are thought to involve hemodynamic, neuroendocrine, inflammatory, and hemostatic pathways. Various parameters including health behaviors and genetics may interact with psychosocial factors to modify CHD risk. In particular, acute exercise and cardiorespiratory fitness have been associated with buffering cardiovascular responses to standardized behavioral challenges in the laboratory (1,2) although there are inconsistencies reported in the literature (3,4). 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 not only to adaptations to exercise but also in response to psychological stressors (5). These cross-stressor adaptations seem to be associated with changes in autonomic control, which may influence other important pathways such as inflammatory processes. Observational studies have generally shown that physically active and fitter participants demonstrate lower levels of baseline inflammatory markers, but randomized controlled trials show less consistent results (6). It is possible that a reduction in stress-induced inflammatory responses may be one of the mechanisms by which physical fitness confers protection against cardiovascular risk (7), although the association between fitness and proinflammatory responses to mental stress has not been previously examined.

Previous research has demonstrated that inflammatory cytokine responses to mental stress are delayed post stress (8) and are highly reproducible (9). Prolonged increases in inflammatory cytokines post stress are more pronounced in lower social class groups (10) and different patterns of response have been demonstrated in men and women (11,12). Stress-induced inflammatory responses may have clinical relevance, as indicated in data showing that a higher interleukin (IL)-6 response is associated with an increase in ambulatory blood pressure over a 3-year follow up (13). Links with atherosclerotic processes, obesity, and insulin resistance have also been hypothesized (14,15). Paradoxically, the increases in circulating IL-6 that are consistently observed after exercise have been suggested to promote an anti-inflammatory environment by increasing IL-1 receptor antagonist (Ra) and IL-10 synthesis, but inhibiting tumor necrosis factor (TNF)-α release (16). Thus, it is feasible that cross-stressor adaptations may involve interaction between the pro- and anti-inflammatory effects of IL-6 (17).

The aim of the present study was therefore to examine the association between physical fitness and proinflammatory responses to mental stress. We hypothesized that higher fitness would be related to lower stress-induced inflammatory cytokine responses. All analyses were adjusted for confounding factors such as adiposity, gender, social class, smoking, and alcohol intake, which have previously been associated with inflammatory processes and are interrelated with exercise behavior. The cardiovascular and cytokine responses from this study have been published elsewhere (12) but have not been related previously to physical fitness.

METHODS

Participants

Participants were drawn from the Whitehall II epidemiological cohort (18) for a psychobiology substudy in which the laboratory stress testing was performed in 1999 to 2000. The criteria for entry into the study included no

From the Department of Epidemiology and Public Health, University College London, London, UK.

Address correspondence and reprint requests to Mark Hamer, Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London WC1E 6BT, UK. E-mail: m.hamer@ucl.ac.uk

Dr. Hamer received funding from The British Academy to present this work, in part, at the American Psychosomatic Society 65th Annual Scientific Meeting, March 8, 2007, Budapest, Hungary.

Received for publication November 15, 2006; revision received April 30, 2007.

DOI: 10.1097/PSY.0b013e318148c4c0

0033-3174/07/6907-0660

history or objective signs of CHD, no previous diagnosis or treatment for hypertension, inflammatory diseases, or allergies. Selection was stratified by grade of employment to include higher, intermediate, and lower status participants. In addition, participants were prohibited from using any antihistamine or anti-inflammatory medication 24 hours before testing and were rescheduled if they reported colds or other infections on the day of testing. The 207 volunteers (112 men, 95 women) were of white European origin, aged 45 to 59 years, lived in the London area, and were employed full time. The participants gave informed consent to participate in the study and ethical approval was obtained from the University College London Hospital Committee on the Ethics of Human Research.

Psychobiological Testing

Testing was performed in either the morning or afternoon in a light temperature-controlled laboratory (12). Participants were instructed to refrain from drinking caffeinated beverages or smoking for at least 2 hours before the study and not to have performed vigorous physical activity or consumed alcohol the previous evening. Blood pressure was measured continuously using a Portapres-2 device (Finapres Medical Systems, Amsterdam, Netherlands) and heart rate variability (HRV) was assessed as square root of the mean of the sum of squared successive differences using the impedance based Ambulatory Monitoring System (VU-AMS, Free University, Amsterdam, Netherlands). Additional cardiovascular variables including cardiac output, stroke volume, and total peripheral resistance were derived from the Portapres device using the aortic flow waveform method developed by Wesseling and colleagues (19). Data were transformed into cardiac index by correcting for body surface area. After inserting a venous cannula for obtaining periodic blood samples, participants rested for 30 minutes. Baseline cardiovascular measures were recorded during the last 5 minutes of this period and a blood sample was obtained to assess baseline inflammatory cytokines. Two behavioral tasks, designed to induce mental stress, were then administered in a random order. The tasks were a computerized version of the Stroop task and mirror tracing, both of which have been used extensively in psychobiological research. The tasks each lasted for 5 minutes, during which cardiovascular measurements were continuously assessed. Participants then rested for 45 minutes when a second blood sample was taken to assess poststress inflammatory cytokines. A 45-minute poststress sample was used because previous data suggest that acute inflammatory responses to mental stress follow a delayed time course (8).

Physical Fitness Assessment

After psychobiological testing, the participants were required to undergo a submaximal exercise test. Participants exercised on a cycle ergometer (Model 864, Monark, Sweden) for 8 minutes at a constant workload of 50 watts. Heart rate and blood pressure were measured during exercise and the average heart rate during the last 2 minutes was used as a measure of physical fitness, which is widely regarded as a reliable indicator (20). Cycle ergometry testing is one of the most popular methods to assess physical fitness because there are relatively small individual variations in mechanical efficiency. A submaximal test with a light workload was adopted in the present study because the sample consisted of older, mostly sedentary individuals.

Psychosocial, Subjective, and Adiposity Measures

Psychological well being was assessed from the 30-item General Health Questionnaire (21), a measure of psychological distress devised for population studies. Participants were asked to report the number of times a week they engaged in vigorous physical activity, their alcohol intake (units/wk), smoking habits, and level of education. Height and weight were recorded in light clothing for the calculation of body mass index (BMI). Waist circumference was measured with a metal anthropometric tape midway between the lower rib margin and the iliac crest and hip circumference was measured at the level of the great trochanters. Waist to hip ratio was calculated as a measure of central adiposity.

Cytokine Assays

Peripheral blood was collected in ethylenediaminetetraacetic acid-coated tubes and spun at room temperature. All blood samples were frozen at −20°C until assay. The analysis of plasma IL-6 and TNF-α levels was performed using high-sensitivity ELISA (R & D Systems, Oxford, UK). For the TNF-α assay, the limit of detection was 0.10 pg/ml, with intra- and interassay coefficients of variation (CVs) of 6.9 and 8.4%, respectively. For IL-6, the limit of detection was 0.09 pg/ml with intra- and interassay CVs of 5.3 and 9.2%, respectively. The determination of IL-1Ra was performed using a commercial ELISA. The limit of detection was 15 pg/ml with intra- and interassay CVs of <10%.

Statistical Analysis

Complete fitness and blood pressure data were available for 207 participants, complete cardiac index and total peripheral resistance data for 178 participants, HRV data for 140 participants, and 186 participants with inflammatory cytokine data. The reasons for missing data included problems with blood sampling and technical failure. The analysis of cardiovascular data were split into four trials, which included a 5-minute baseline, aggregated average task, post stress 1 (15–20 minutes), and post stress 2 (40–45 minutes). Inflammatory cytokine data were analyzed over two trials, which were baseline and 45 minutes post stress. These data were analyzed (repeated-measures analysis of variance) using the general linear model, with Greenhouse Geisser adjustments employed where appropriate. Task and recovery responses were calculated by subtracting baseline values from task and recovery values. Linear regression analyses were used to examine the relationship between fitness (heart rate during exercise) and stress reactivity and recovery, adjusting for a number of covariates including age, gender, BMI, employment grade (as a measure of social class), smoking, and alcohol intake. The sample was split into gender-specific fitness tertiles based on heart rate during exercise (a lower exercise heart rate is indicative of greater physical fitness) for illustrative purposes. Comparisons between groups in demographic variables were assessed using pairwise t tests with Bonferroni correction.

RESULTS

Participants' Characteristics

Descriptive characteristics of the participants in relationship to fitness level are presented in Table 1. Men in the medium fitness tertile had a significantly higher alcohol intake ($p = .04$) compared with men in the higher and lower tertiles. The men ranked with medium fitness were also marginally older ($p = .06$) with slightly higher resting diastolic blood pressure ($p = .06$). The only notable difference among females was a higher proportion of low-grade women in the least fit group ($p = .01$).

There was, on average, a significant heart rate (64.9 ± 0.6 to 82.3 ± 1.2 beat/minute; $p < .05$ from baseline to exercise) and blood pressure response (115.6 ± 0.9 to 147.3 ± 1.4 mm Hg; $p < .05$) to the submaximal exercise test (Table 1). There was also a moderate inverse association between the exercise heart rate and weekly participation in vigorous physical activity ($r = -.24$; $p = .001$), indicating that less fit individuals were more sedentary.

Responses to Mental Stress and Exercise Testing

Cardiovascular responses to stress and recovery are shown in Table 2. There were significant main effects of trial for all cardiovascular variables—systolic blood pressure ($F(3,609) = 319.2$; $p < .001$); diastolic blood pressure ($F(3,609) = 299.6$; $p < .001$); heart rate ($F(3,600) = 334.9$; $p < .001$); HRV

TABLE 1. Descriptive Characteristics of Participants in Relationship to Fitness Tertiles (mean ± standard deviation)

Variable	Men			Women		
	High Fit (n = 37)	Medium Fit (n = 37)	Low Fit (n = 37)	High Fit (n = 31)	Medium Fit (n = 32)	Low Fit (n = 32)
Age (years)	51.8 ± 2.7	53.3 ± 2.5	52.6 ± 2.7	51.8 ± 2.8	52.1 ± 2.8	51.6 ± 2.8
Body mass index (kg/m^2)	25.0 ± 3.5	26.4 ± 4.0	25.8 ± 2.9	24.5 ± 3.4	26.4 ± 4.6	25.5 ± 4.3
Waist/hip ratio	0.90 ± 0.08	0.91 ± 0.06	0.91 ± 0.07	0.77 ± 0.05	0.79 ± 0.06	0.80 ± 0.07
% Low-grade employees	24.3	21.1	35.1	12.9	28.1	48.4[a]
% Lower-education level	16.0	17.0	16.0	25.0	48.1	48.4
Current smoking (%)	5.4	13.5	2.7	3.2	12.9	9.7
Alcohol (units/wk)	10.4 ± 11.0	17.4 ± 14.6[b,c]	7.8 ± 8.5	8.5 ± 7.3	8.5 ± 8.0	6.7 ± 6.4
GHQ	3.3 ± 6.0	3.0 ± 5.8	3.9 ± 4.6	2.5 ± 3.6	2.5 ± 4.4	3.7 ± 6.6
Baseline SBP (mm Hg)	118.8 ± 11.5	120.5 ± 14.1	117.3 ± 10.5	108.3 ± 12.5	115.4 ± 11.7	109.5 ± 14.3
Baseline DBP (mm Hg)	69.8 ± 9.1	74.8 ± 9.4	71.0 ± 8.8	68.5 ± 10.3	71.6 ± 9.9	65.8 ± 9.5
Baseline HR (bpm)	62.8 ± 11.7	63.3 ± 9.5	65.1 ± 9.3	68.5 ± 7.6	65.3 ± 7.3	65.4 ± 7.3
HR response to exercise	0.3 ± 4.9[a]	10.1 ± 2.7[b,c]	24.9 ± 10.0	7.2 ± 6.4[a]	25.1 ± 4.0[b,c]	40.0 ± 6.8
SBP response to exercise	22.9 ± 11.6[a]	25.8 ± 14.8	32.5 ± 19.4	28.1 ± 17.6[a]	36.4 ± 19.7	47.6 ± 19.5
Vigorous exercise (freq/wk)	1.6 ± 1.6	1.6 ± 1.8	1.4 ± 2.1	1.6 ± 1.8	1.6 ± 1.7	0.8 ± 1.5

GHQ = general health questionnaire; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.
[a] Significant difference between high and low fit.
[b] Significant difference between medium and low fit.
[c] Significant difference between high and medium fit.

TABLE 2. Cardiovascular and Biological Responses to Mental Stress (mean ± standard error of the mean)

Variable	Baseline	Task Mean	Post Stress 1	Post Stress 2
SBP (mm Hg)	115.5 ± 0.9	138.6 ± 1.4[a]	121.0 ± 1.1[b]	121.3 ± 1.1[b]
DBP (mm Hg)	70.5 ± 0.7	84.2 ± 0.8[a]	74.9 ± 0.7[b]	75.5 ± 0.7[b]
HR (bpm)	64.9 ± 0.6	71.8 ± 0.7[a]	62.4 ± 0.6[b]	62.9 ± 0.6[b]
HRV (ms^2)	29.4 ± 1.2	26.9 ± 1.2[a]	36.0 ± 1.3[b]	36.0 ± 1.3[b]
CI (L/min/m^2)	3.4 ± 0.04	3.7 ± 0.05[a]	3.1 ± 0.04[b]	3.1 ± 0.04[b]
TPR (dyne·s/cm^5)	719.7 ± 13.3	860.0 ± 15.2[a]	871.7 ± 16.5[b]	890.3 ± 16.7[b]
IL-6 (pg/ml)	1.25 ± 0.06			1.35 ± 0.06[b]
IL-1ra (pg/ml)	229.3 ± 7.3			235.9 ± 7.4[b]
TNF-α (pg/ml)	2.37 ± 0.08			2.42 ± 0.08
Stress rating	1.4 ± 0.05	4.0 ± 0.1[a]		1.4 ± 0.05

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; HRV = heart rate variability; CI = cardiac index; TPR = total peripheral resistance; IL-6 = interleukin 6; IL-1ra = interleukin 1 receptor antagonist; TNF = tumor necrosis factor.
[a] Task mean significantly different compared with baseline ($p < .05$).
[b] Post task significantly different compared with baseline ($p < .05$).

($F(3,417) = 51.6$; $p < .001$); cardiac index ($F(3,531) = 233.5$; $p < .001$); and total peripheral resistance ($F(3,531) = 153.2$; $p < .001$). Blood pressure and peripheral resistance were significantly increased during the stress tasks and remained elevated during post stress. Heart rate increased during the tasks returning to below baseline during post stress and HRV was reduced during tasks but increased above baseline during post stress. Cardiac index increased during tasks and returned below baseline during post stress. The inflammatory cytokine responses to mental stress are also shown in Table 2. There was no significant change in TNF-α over time ($F(1,187) = 2.3$; $p = .13$), although both IL-6 and IL-1Ra were increased 45 minutes post stress (Fs(1,187) = 12.7, 4.6; $p < .05$). There were marked individual differences in responses in all three cytokines, ranging from −1.03 to 2.01 pg/ml in IL-6, −81.02 to 258.95 pg/ml in IL-1Ra, and −1.76 to 1.41 pg/ml in TNF-α. Subjective ratings of stress were significantly increased during the tasks returning to baseline during post stress ($p < .001$).

Association Between Fitness and Stress Responses

After adjustment for age, BMI, gender, smoking, alcohol, grade of employment, and basal levels of inflammatory markers, a greater heart rate during exercise (lower fitness) was related to higher IL-6 ($\beta = 0.24$; $p = .005$) and TNF-α responses to stress ($\beta = 0.27$; $p = .002$). Figure 1 shows that TNF-α responses in the low fitness group were approximately five-fold greater than those in the high fitness group. When self-reported level of vigorous physical activity was included as a covariate, this did not change any of the associations (Table 3). In addition, the systolic blood pressure response to exercise was a predictor of TNF-α responses to stress after adjustment for covariates ($\beta = 0.18$; $p = .03$). IL-1Ra stress

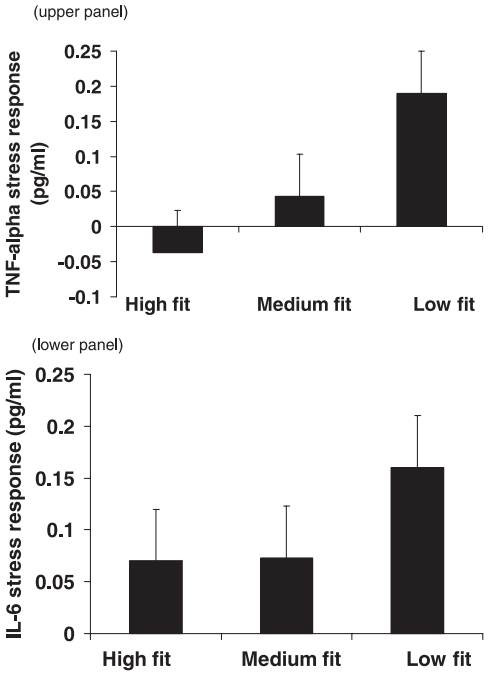

Figure 1. Association between physical fitness and the change in tumor necrosis factor (TNF)-α (upper panel) and interleukin (IL)-6 (lower panel) between baseline and poststress samples. Data are presented as mean ± standard error of the mean values, adjusted for age, gender, body mass index, employment grade, smoking, alcohol, and basal levels of inflammatory cytokines. Physical fitness tertiles based on heart rate response to cycling ergometry exercise at a standardized workload.

responses were not related to physical fitness or physical activity. In relation to the possible diurnal variation in cytokine levels, we repeated the analyses including time of testing (AM or PM) as an additional covariate. This did not, however, alter the pattern of results.

Exercise heart rate response was related to the heart rate response to stress ($r = .23$; $p = .001$), although the association did not persist after adjustment for covariates. However, exercise heart rate was also associated with the HRV response to stress, which remained significant after adjusting for covariates ($\beta = -0.23$; $p = .02$). This association is displayed in Figure 2, demonstrating that fitter participants (with lower exercise heart rate) had less pronounced reductions in HRV during stress. There was a significant correlation between the HRV response and TNF-α response to stress ($r = -0.20$; $p = .01$), indicating that participants with a greater reduction in HRV showed greater increases in TNF-α. We did not, however, observe any associations between HRV reactivity and the IL-6 stress response. We tested whether parasympathetic responses mediate the association between fitness and TNF-α stress response by introducing HRV reactivity as an additional covariate in the regression model. In this model, the association between exercise heart rate and TNF-α stress response was attenuated but remained significant ($\beta = 0.23$; $p = .03$), although HRV reactivity was no longer a predictor ($\beta = -0.15$; $p = .09$). Thus, HRV reactivity seemed to explain only a small amount of the association between fitness and TNF-α stress responses.

TABLE 3. Regression of Exercise Heart Rate on TNF-α Stress Response and IL-6 Stress Response

Variable	Standardized β	B (95% CI)	p
TNF-α stress response[a]			
Gender	−0.20	−0.19 (−0.331–−0.039)	.01
Age	0.05	0.009 (−0.016–0.034)	.48
Body mass index	0.10	0.01 (−0.006–0.031)	.17
Employment grade	−0.01	0.008 (−0.095–0.080)	.86
Smoking	−0.05	0.07 (−0.305–0.164)	.55
Alcohol	0.06	0.003 (−0.004–0.010)	.42
Vigorous exercise	0.10	0.02 (−0.011–0.061)	.17
Baseline TNF-α	−0.20	−0.08 (−0.141–−0.025)	.005
Exercise heart rate	0.27	0.007 (0.003–0.012)	.002
IL-6 stress response[b]			
Gender	−0.05	−0.04 (−0.162–0.084)	.53
Age	−0.14	−0.02 (−0.041–0.001)	.07
Body mass index	0.13	0.01 (−0.002–0.030)	.01
Employment grade	−0.04	−0.02 (−0.092–0.052)	.58
Smoking	−0.07	−0.08 (−0.278–0.109)	.39
Alcohol	−0.03	−0.001 (−0.007–0.005)	.72
Vigorous exercise	0.10	0.02 (−0.010–0.051)	.18
Baseline IL-6	−0.03	−0.01 (−0.090–0.062)	.71
Exercise heart rate	0.24	0.005 (0.002–0.009)	.005

TNF = tumor necrosis factor; IL = interleukin; CI = confidence interval.
[a] $R^2 = 0.13$; adjusted $R^2 = 0.08$.
[b] $R^2 = 0.12$; adjusted $R^2 = 0.07$.

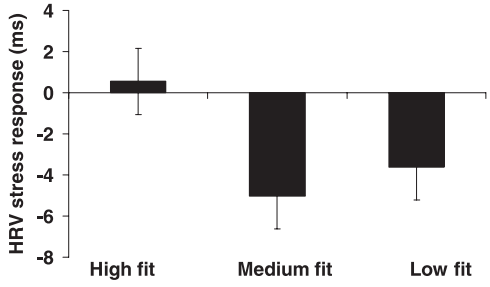

Figure 2. Association between physical fitness and heart rate variability (HRV) responses to mental stress. Data are presented as mean ± standard error of the mean values, adjusted for age, gender, body mass index, employment grade, smoking, alcohol, and baseline HRV. Physical fitness tertiles based on heart rate response to cycling ergometry exercise at a standardized workload.

There were no associations between fitness and any other cardiovascular responses to stress or during the poststress recovery phase, or with subjective stress responses. However, there were significant correlations of exercise heart rate with baseline IL-6 ($r = .19$; $p = .008$) and HRV ($r = -.26$; $p = .002$), indicating greater inflammatory status and lower parasympathetic influence in less fit participants, although the association with IL-6 did not persist after adjustment for covariates.

DISCUSSION

The aim of the present study was to examine the association between physical fitness and cardiovascular and inflammatory cytokine responses to mental stress in a sample of healthy men and women. In comparison with previous research, we used a large sample to examine the fitness-stress reactivity relationship with an objective measure of physical fitness. We found that cardiovascular reactivity and recovery from two behavioral laboratory stress tasks was generally not associated with fitness, and there were also no associations between fitness and psychological well-being. However, higher physical fitness (but not self-reported vigorous physical activity) was associated with lower inflammatory cytokine stress responses and a less pronounced reduction in HRV after controlling for confounding factors. There was also an inverse association between fitness and baseline IL-6, although this was confounded by BMI and age. We did not include a no stress comparison condition in this study because we have previously shown that cytokine levels do not change with repeated blood sampling over comparable time periods (8,10).

This is the first study, to our knowledge, that has examined the association between fitness and inflammatory cytokine responses to mental stress. Previous work has shown that regular exercisers had attenuated leukocyte trafficking and adhesion molecule expression in response to a speech task stressor compared with sedentary participants (22). The present findings are also consistent with the observation that fitter and physically active participants generally demonstrate lower levels of inflammatory markers at rest although it is unclear if these effects are mediated by adiposity (6). We found that adiposity confounded the inverse association between physical fitness and proinflammatory markers at rest, and this finding is consistent with some but not all studies (6). However, during stress, the effects were not confounded by adiposity, which may indicate that the inflammatory stress response is an independent risk factor that operates through different pathways. Our findings relating to cardiovascular stress responses are not entirely consistent with previous research. In a meta-analytic review of 34 studies, aerobic fitness was associated with nearly half a standard deviation reduction in blood pressure stress reactivity (2), although recently updated reviews suggested both positive and inverse associations between fitness and heart rate reactivity (3,4). Nevertheless, reactivity effects were not different from zero in randomized, controlled exercise training studies and when fitness was measured as peak oxygen uptake (3). Also, the inverse association between fitness and heart rate reactivity was observed from an arguably stronger analysis that only selected studies demonstrated evidence of an exercise training effect (4). These inconsistencies may also be due, in part, to small sample sizes, 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. It should also be noted that previous studies have generally measured blood pressure intermittently with conventional arm cuffs, in contrast with the continuous measure used in this study. In the present study, we can discount the confounding impact of acute exercise because participants were instructed not to exercise the day before testing. We also controlled for a number of other potentially confounding factors in the analyses, including age, gender, BMI, social class, smoking, and alcohol intake. The inverse association between fitness and heart rate reactivity was confounded by social class and BMI in the present study. Interestingly, the self-reported level of vigorous physical activity was unrelated to any psychobiological measures, which suggests that objective measures of physical fitness are more robust predictors of these responses and may reflect inaccuracy of self-report measures. Furthermore, we used two highly standardized behavioral stress tasks that elicited relatively large and robust physiological stress responses that added to the strengths of the present study.

Previous research has indicated an intriguing link between efferent cholinergic activity of the vagus nerve (the parasympathetic arm of the autonomic nervous system) and inhibition of inflammatory processes (23). The present findings indicated that the fitter individuals who maintained greater parasympathetic control during mental stress also demonstrated the lowest TNF-α stress responses. This association between HRV reactivity to mental stress and TNF-α levels at 45 minutes post stress most likely reflects the delayed time course of the stress-induced inflammatory response. The decline in parasympathetic control with ageing is attenuated with regular exercise training (24). However, given the small amount of variance explained and that we did not observe any associations between HRV reactivity and the IL-6 stress response, fitness-related improvements in parasympathetic activity may only play a small role in mediating the inhibition of stress-induced inflammatory processes. Thus, other mechanisms are also likely to be important. For example, exercise has a favorable impact on insulin sensitivity (25) and recent research has shown that the highest inflammatory cytokine responses to stress were in participants with the greatest levels of insulin resistance (26). Another important modulator of the immune system during stress is the hypothalamic-pituitary adrenal axis, with suppressive effects on proinflammatory cytokine production (27). In comparison with sedentary controls, trained individuals demonstrate acute exercise-induced increases in glucocorticoid sensitivity (28), which may play an important role in the anti-inflammatory effects. Other potential mediating effects may involve high-density lipoprotein cholesterol, adiponectin, and reduced reactive oxygen species—all of which demonstrate anti-inflammatory actions (29–31) and are influenced by exercise training.

In addition to the associations between exercising heart rate and stress-induced inflammatory responses, we also observed associations using the systolic blood pressure response to exercise as a predictor. An exaggerated systolic blood pressure response to exercise is a strong independent predictor of carotid atherosclerosis (32), hypertension (33), cardiovascular disease mortality (34), and impaired arterial function (35). Jae

et al. (36) have also shown that there is an association between the exercise blood pressure response and white blood cell count although not with C-reactive protein levels. Thus, our findings add to previous literature and suggest that inflammatory processes may be one of the underlying mechanisms mediating the associations between exaggerated exercise blood pressure responses and cardiovascular risk.

The limitations of this study should be recognized. We used a submaximal exercise test with a light workload and therefore did not obtain an indication of maximal aerobic capacity. The heart rate response to exercise is strongly predictive of physical fitness and it was not feasible to perform tests of maximal capacity in the present sample of older sedentary participants. We used time rather than frequency domain measures of HRV, and different results might have emerged if spectral analysis had been carried out. Additionally, we did not measure breathing patterns, and respiratory rate and depth are known to influence HRV. However, measures of parasympathetic modulation of heart rate that are uncorrected for respiration seem to be acceptable to index within subject changes in most stress studies (37).

The strengths of this study are that we examined a relatively large sample of men and women, controlling for a number of potentially confounding factors, which had been areas of weakness in previous research. The inverse association between physical fitness and stress induced inflammatory responses may highlight one of the mechanisms through which physical fitness confers protection against cardiovascular risk.

This research was supported by the Medical Research Council, UK, and the British Heart Foundation. We acknowledge the contributions of Prof. Sir Michael Marmot for the study design; Dr. Sabine Kunz-Ebrecht, Dr. Pamela Feldman, Dr. Gonneke Willemsen, Dr. Natalie Owen, and Bev Murray for data collection; and Dr. Vidya Mohamed-Ali for the cytokine analyses.

REFERENCES

1. 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.
2. Crews DJ, Landers DM. A meta-analytic review of aerobic fitness and reactivity to psychosocial stressors. Med Sci Sports Exerc 1987;19: S114–20.
3. Dishman RK, Jackson EM. Cardiorespiratory fitness and laboratory stress: a meta-regression analysis. Psychophysiology 2006;43:57–72.
4. 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.
5. 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.
6. Hamer M. The relative influences of fitness and fatness on inflammatory factors. Prev Med 2007;44:3–11.
7. Hamer M. Exercise and psychobiological processes: implications for the primary prevention of coronary heart disease. Sports Med 2006;36: 829–38.
8. Steptoe A, Willemsen G, Owen N, Flower L, Mohamed-Ali V. Acute mental stress elicits delayed increases in circulating inflammatory cytokine levels. Clin Sci 2001;101:185–92.
9. von Känel R, Kudielka BM, Preckel D, Hanebuth D, Fischer, JE. Delayed response and lack of habituation in plasma interleukin-6 to acute mental stress in men. Brain Behav Immun 2006;20:40–8.
10. Brydon L, Edwards S, Mohamed-Ali V, Steptoe A. Socioeconomic status and stress-induced increases in interleukin-6. Brain Behav Immun 2004; 18:281–90.
11. Edwards KM, Burns VE, Ring C, Carroll D. Sex differences in the interleukin-6 response to acute psychological stress. Biol Psychol 2006; 71:236–9.
12. Steptoe A, Owen N, Kunz-Ebrecht S, Mohamed-Ali V. Inflammatory cytokines, socioeconomic status, and acute stress responsivity. Brain Behav Immun 2002;16:774–84.
13. Brydon L, Steptoe A. Stress-induced increases in interleukin-6 and fibrinogen predict ambulatory blood pressure at 3 year follow-up. J Hypertens 2005;23:1001–7.
14. Black PH. The inflammatory consequences of psychologic stress: relationship to insulin resistance, obesity, atherosclerosis and diabetes mellitus, type II. Med Hypoth 2006;67:879–91.
15. Steptoe A, Brydon L. Psychosocial factors and coronary heart disease: the contribution of psychoneuroimmunological processes. In: Ader R, editor. Psychoneuroimmunology, 4th ed. San Diego: Academic Press; 2006.
16. Steensberg A, Fischer CP, Keller C, Moller K, Pedersen BK. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. Am J Physiol: Endocrinol Metab 2003;285:E433–7.
17. Tilg H, Dinarello CA, Mier JW. IL-6 and APPs: anti-inflammatory and immuno-suppressive mediators. Immunol Today 1997;18:428–32.
18. Marmot MG, Smith GD, Stansfeld S, Patel C, North F, Head J, White I, Brunner E, Feeney A. Health inequalities among British civil servants: the Whitehall II study. Lancet 1991;337:1387–93.
19. Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. J Appl Physiol 1993;74:2566–7.
20. Åstrand P-O, Rodahl K. Evaluation of physical performance on the basis of tests. In: Åstrand P-O, Rodahl K, editors. Textbook of work physiology—physiological bases of exercise. 3rd ed. Singapore: McGraw-Hill Book Company; 1986.
21. Goldberg D, Williams P. A user's guide to the general health questionnaire. Windsor, Berkshire, UK: NFER-NELSON Publishing Company Ltd.; 1988.
22. Hong S, Farag NH, Nelesen RA, Ziegler MG, Mills PJ. Effects of regular exercise on lymphocyte subsets and CD62L after psychological vs. physical stress. J Psychosom Res 2004;56:363–70.
23. Tracey KJ. The inflammatory reflex. Nature 2002;420:853–9.
24. Carter JB, Banister EW, Blaber AP. Effect of endurance exercise on autonomic control of heart rate. Sports Med 2003;33:33–46.
25. Mayer-Davis EJ, D'Agostino R Jr, Karter AJ, Haffner SM, Rewers MJ, Saad M, Bergman RN. Intensity and amount of physical activity in relation to insulin sensitivity: the insulin resistance atherosclerosis study. JAMA 1998;279:669–74.
26. Suarez EC, Boyle SH, Lewis JG, Hall RP, Young KH. Increases in stimulated secretion of proinflammatory cytokines by blood monocytes following arousal of negative affect: the role of insulin resistance as moderator. Brain Behav Immun 2006;20:331–8.
27. McEwen BS, Biron CA, Brunson KW, Bulloch K, Chambers WH, Dhabhar FS, Goldfarb RH, Kitson RP, Miller AH, Spencer RL, Weiss JM. The role of adrenocorticoids as modulators of immune function in health and disease: neural, endocrine and immune interactions. Brain Res Rev 1997;23:79–133.
28. Duclos M, Gouarne C, Bonnemaison D. Acute and chronic effects of exercise on tissue sensitivity to glucocorticoids. J Appl Physiol 2003;94: 869–75.
29. Navab M, Anantharamaiah GM, Fogelman AM. The role of high-density lipoprotein in inflammation. Trends Cardiovasc Med 2005;15:158–61.
30. Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. Am J Clin Nutr 2006;83:461S–5S.
31. Elosua R, Molina L, Fito M, Arquer A, Sanchez-Quesada JL, Covas MI, Ordonez-Llanos J, Marrugat J. Response of oxidative stress biomarkers to a 16-week aerobic physical activity program, and to acute physical activity, in healthy young men and women. Atherosclerosis 2003;167: 327–34.
32. Jae SY, Fernhall B, Heffernan KS, Kang M, Lee MK, Choi YH, Hong KP, Ahn ES, Park WH. Exaggerated blood pressure response to exercise

is associated with carotid atherosclerosis in apparently healthy men. J Hypertens 2006;24:881–7.
33. Singh JP, Larson MG, Manolio TA, O'Donnell CJ, Lauer M, Evans JC, Levy D. Blood pressure response during treadmill testing as a risk factor for new-onset hypertension. The Framingham heart study. Circulation 1999;99:1831–6.
34. Mundal R, Kjeldsen SE, Sandvik L, Erikssen G, Thaulow E, Erikssen J. Exercise blood pressure predicts cardiovascular mortality in middle-aged men. Hypertension 1994;24:56–62.
35. Stewart KJ, Sung J, Silber HA, Fleg JL, Kelemen MD, Turner KL, Bacher AC, Dobrosielski DA, DeRegis JR, Shapiro EP, Ouyang P. Exaggerated exercise blood pressure is related to impaired endothelial vasodilator function. Am J Hypertens 2004;17:314–20.
36. Jae SY, Fernhall B, Lee M, Heffernan KS, Lee MK, Choi YH, Hong KP, Park WH. Exaggerated blood pressure response to exercise is associated with inflammatory markers. J Cardiopulm Rehabil 2006;26:145–9.
37. Houtveen JH, Rietveld S, de Geus EJ. Contribution of tonic vagal modulation of heart rate, central respiratory drive, respiratory depth, and respiratory frequency to respiratory sinus arrhythmia during mental stress and physical exercise. Psychophysiology 2002;39:427–36.