Review Article

Exercise and Stress Reactivity in Humans and Animals: Two Meta-Analyses

ERNESTO RAMIREZ†[1], and BRAD WIPFLI‡[2]

[1]Joint Doctoral Program in Public Health (Health Behavior), San Diego State University and University of California, San Diego, CA, USA; [2]Center for Research on Occupational and Environmental Toxicology, Oregon Health & Science University, Portland, OR, USA

†Denotes graduate student author, ‡Denotes professional author

ABSTRACT

International Journal of Exercise Science 6(2) : 144-156, 2013. Previous meta-analyses examining the effects of exercise on stress reactivity have included methodologically weak studies; we therefore conducted a meta-analysis utilizing more stringent inclusion criteria. An analysis of 33 randomized controlled trials involving humans (*N* = 1,252) revealed a moderate effect (*ES* = -0.31; 95% CI = -.43, -.20) for exercise as a method to reduce stress reactivity. An additional analysis with 27 randomized controlled trials of physical activity in animals (*N* = 462) also revealed a moderate reduction (*ES* = -0.33; 95% CI = -0.15, -0.52) in stress reactivity. The combined results of these analyses indicate that exercise diminishes the negative effects of increased reactivity to stressors.

KEY WORDS: Physical activity, hormones, neurochemicals

INTRODUCTION

Most adults in the U.S. believe that they experience unhealthy amounts of stress (5), and stress is the second leading cause of workplace health problems in the EU (60). Some sources of stress are unavoidable; however, it is an individual's reaction to stress (e.g., increases in blood pressure, heart rate, stroke volume; 14) that can lead to negative health outcomes. Human and animal studies indicate that chronic stress and elevated stress reactivity are related to negative health outcomes such as hypertension, increased left ventricular mass, arthrosclerosis, suppressed immune function, and the risk of having a heart attack (29, 34, 48, 54, 57, 65, 74).

Decades of research have examined the use of exercise as a method to protect against elevated stress reactivity. The theory that the body's response to exercise will lead to positive stress reactivity adaptations has been termed the cross-stressor adaptation hypothesis (78). The theory posits that exercise helps the body regulate the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), in particular the locus ceruleus-sympathetic-adrenomedulary system (LCSA or LC-NE), all of which play significant roles in the physiological stress response (16, 47, 87).

Narrative reviews of the effects of exercise on stress reactivity have found conflicting results (21, 85). Several meta-analyses have also examined this relationship, and most have found significant improvements in stress reactivity after exercise (3, 19; *ES*s 0.37 and 0.48, respectively). A recent meta-regression (45), however, reported that increased cardiorespiratory fitness is associated with a small increase in stress reactivity ($ES = 0.08$, $p < .001$) and a quicker recovery ($ES = -0.27$, $p < .001$). These quantitative studies have been plagued by the inclusion of a large number of correlational studies. Furthermore, Jackson and Dishman (45) suggest the need for a greater number of randomized controlled trials examining exercise and stress reactivity, which can be accomplished by incorporating human and animal studies into one review.

The purpose of this study is to provide a comprehensive review of the effects of exercise on stress reactivity. We conducted two separate meta-analyses, using only randomized, controlled trials with human participants (Meta I) and animal subjects (Meta II). This study represents the first meta-analysis on the effects of stress reactivity in animals, which removes potential sources of bias in human research such as volunteerism and experimenter expectancy effects, and allows the examination of stress related hormones and neurochemicals after exercise.

Hypothesis 1: Human exercise treatment groups have significantly greater reductions in stress reactivity compared to no-treatment- or placebo-control groups.

Hypothesis 2: Animal exercise groups have significantly greater reductions in stress reactivity compared to no-treatment- or placebo-control groups.

METHODS

Meta-Analysis I: Human Literature

Literature Search: We conducted a literature search using the following electronic databases: PsycInfo, SPORTDiscus, PubMed, Medline, and Dissertations & Theses (formerly Dissertation Abstracts International) to find studies related to exercise and stress reactivity. We conducted searches using combinations of the following key words: randomized controlled trial, exercise, cardiovascular, training, physical activity, stress, recovery, reactivity, laboratory stress, and psychological stress. We then supplemented electronic searches by cross-referencing narrative reviews, meta-analyses, and included articles by hand. The search was not restricted by year of publication.

Inclusion criteria: The analysis was limited to English language studies that used a randomized, controlled design to assess the effects of either a chronic or acute exercise intervention on stress reactivity. Because of the aforementioned importance of cardiovascular and immune system responses to stressful stimuli, only studies using psychophysiological outcomes of reactivity (e.g., heart rate, blood pressure, cortisol) that used an acute psychological stressor (e.g., cognitive tasks, public speaking) were included. Studies involving the use of physical stressors or pharmacological challenges were not included because of the potential confounding effects of non-stress related changes on cardiovascular or immune system reactivity.

Coding: We coded studies that met the inclusion criteria for potential moderating variables a priori. Potential moderator variables were primarily derived from previous meta-analyses (19, 33, 39, 45), and included participant characteristics, intervention design characteristics, stressor characteristics, and dependent measures of stress reactivity.

Participant characteristics: Genetic and environmental differences between individuals are important when analyzing the stress response (56, 77). Therefore, we coded studies for: mean age; race (white, black, not reported); gender (male, female, mixed); health status (healthy, hypertensive, clinical condition); and fitness at baseline (fit, unfit, not reported).

Design characteristics: Characteristics related to the design of the intervention were coded to best inform recommendations for using exercise to reduce stress reactivity. Studies were coded based on whether they used a chronic exercise intervention or an acute bout of exercise. Other coded variables related to the intervention design were type of activity (aerobic, anaerobic), duration of activity, and intensity of activity. Intensity of activity for aerobic exercise was based on the percentage of maximum heart rate or percentage of VO2 peak and then categorized by American College of Sports Medicine guidelines (≤ 39% = low, 40-59% = moderate, 60-95% = high; 4). If intensity was published as absolute heart rate, we calculated average intensity based on the mean age of the subjects using a method to determine maximal heart rate in adults ([208 – 0.7 × age]; 83). Guidelines from the National Strength and Conditioning Association were used to classify resistance exercises in a similar manner (7). For chronic interventions, additional variables relating to the length of participation (in weeks), percent improvement in cardiorespiratory fitness, and the method of fitness assessment (VO2 max, submax, other) were also coded.

Stressor characteristics: The type and duration of the stressor were coded to determine if variation in the applied stressor had an effect on the cardiovascular or immune system response. Type of stressor was divided into active tasks, multiple active tasks, passive tasks, and a combination of active and passive tasks. Active tasks included the Stroop color-word conflict task, mental arithmetic (continuous subtraction/addition), tracing tasks, reaction time tasks, and various puzzles and processing tasks. Speaking tasks are also considered active tasks, defined as tasks involving a prepared speech during which the participant was told that he or she would be graded based on various criteria. Studies were coded as multiple active tasks if they used any of the previously mentioned tasks in succession. Passive tasks included application of a cold pressor to the hand, foot, or forehead. While the cold pressor task has been classified as both a psychological and physical stressor in the literature, we include it here because of the inhibitory mental processes involved with coping with the pain induced during the task (89). Finally, many studies combined different types of stressors to either elicit the greatest stress response or assure that a combination of passive and active stressors were present. The duration of the stressor was coded as 0-3 min, 3-6 min, 6-9 min, 9-12 min, greater than 12 min, or not reported.

Dependent measures: Dependent measures of stress reactivity included heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (SBP), mean arterial pressure (MAP), rate pressure product, artery diameter, skin conductance, pulse transit time, rescaled pulse amplitude, rescaled R-wave amplitude, rescaled T-Wave amplitude, respiration rate, respiration amplitude, norepinephrine (NE), epinephrine (E), cluster of differentiation-4 cells (Cd4), and cluster of differentiation-56 cells (Cd56).

Effect size calculation: Effect sizes were independently calculated for each study that met inclusion criteria. A single, average *ES* was calculated for each study that used multiple dependent measures and/or multiple treatment groups to assure that each *ES* remains independent and has equal weight in the analysis. Hedges' g was used to calculate *ES*s in the current analysis, in which $g = \frac{M_E - M_C}{SD_{Pooled}}$, where ME = the mean of the experimental group, Mc = the mean of the control, and $SD_{Pooled} = \sqrt{\frac{(N_E-1)SD_E^2+(N_C-1)SD_{EC}^2}{N_E+N_C-2}}$. Alternate equations were used to calculate *ES*s for studies that did not report means or standard deviations (55, 69). All *ES* calculations used post-test data. A correction factor was used to account for the more precise estimate of population parameters from studies with larger sample sizes: $Corrected\ ES = ES\left(1 - \frac{3}{4N-9}\right)$ (40). All *ES*s were then weighted by the inverse of the variance. Finally, for studies that reported pre and post-intervention data, gains *ES*s were calculated according to the formula: $g = \frac{M_{Post} - M_{Pre}}{SD_{Pooled}}$, and $SD_{Pooled} = \sqrt{\frac{(N_{Pre}-1)SD_{Pre}^2+(N_{Post}-1)SD_{Post}^2}{N_{Pre}+N_{Post}-2}}$ (40). Each *ES* was coded so that a negative value is indicative of a reduction in stress reactivity. Effect sizes were then classified according to the following criteria: small (> 0.0, but ≤ 0.20), moderate (> 0.20, but ≤ 0.50), or large (> 0.50, but ≤ 0.80; 18).

An overall Q value was calculated to test for homogeneity among *ES*s. The overall Q statistic represents the total amount of variance among all *ES*s used in the analysis and is distributed as a $\chi 2$, in which $df = k - 1$, where k = number of *ES*s. If the *ES*s included in the analysis produce a significant Q value they are considered heterogeneous and a random effects model is applied (40, 44; 73). As suggested by Higgins, Thompson, Deeks, and Altman (41), *I2* was calculated to examine percent of variation across the included studies where $I^2 = \frac{Qb-df}{Qb}$. Many researchers use a significant Q value as an indication of population differences and justification to examine moderator variables (40). However, Hall and Rosenthal (38) argue that a significant test of heterogeneity is not required to examine moderator variables. Rosenthal and DiMatteo (66) elaborate, explaining that an analysis of moderator variables can be fundamental to understanding the details of the applicable theories and a clearer picture of the relevant literature regardless of significant heterogeneity among *ES*s. Therefore, all moderator variables were examined by portioning the variance for each variable into *Qwithin* and *Qbetween*. These values were tested for significance against a $\chi 2$ distribution, in which $df = k - 1$, where k = number of categories of the moderator variable. A significant *Qbetween* value indicates that the moderator variable it

describes is a significant contributor to the variance among the *ES*s. For each category, weighted *ES*s, standard errors, and 95% confidence intervals were then calculated. For all moderator variables with a significant *Qbetween* value, pairwise comparisons were conducted between all *ES*s to identify significant differences among levels of the moderator variable (40).

Meta-Analysis II: Animal Literature

Literature search: We conducted a second literature search to locate articles with animal subjects, using the same methods employed in the previous meta-analysis. Key words from Meta I were used, along with the following terms: animal, rat, mouse, wheel running, and activity. Over 100 potential articles were located and reference lists of the included studies were crosschecked by hand.

Inclusion Criteria: The inclusion criteria for Meta II mimic those of Meta I and include additional criteria based on training methodology. Only studies that employed voluntary or freewheel running or unforced treadmill training as the mode of exercise were included in the analysis because forced treadmill running in Sprague-Dawley rats has been shown to affect markers of chronic stress, such as decreased circulating corticosteroid binding globulin and decreased lymphocyte production (58), and increases in activated CRH neurons (92).

Coding: Studies that met inclusion criteria were coded for potential moderating variables a priori based on subject characteristics, intervention design characteristics, stressor characteristics, and dependent measures of stress reactivity.

Subject characteristics: As in the analysis of the human literature, it is important to understand the potential role of genetic influence on treatment effects. Studies were coded for animal type (C57BL/6N Mice, Sprague-Dawley rat, Fisher rat, Wistar rat) and gender.

Design characteristics: The included studies were coded based on the length of the intervention (1 to 3, 4 to 6, 7 to 10, and >10 weeks). Because studies involving animal subjects typically do not account for exercise intensity, only distance (<1 km/week, 1-3 km/week, 3.01-5 km/week, 5.01-7 km/week, 7+km/week) of freewheel running was coded. Change in aerobic fitness was coded as yes, no, or not reported because the majority of the included studies did not assess changes in fitness. Finally, time of measurement or time of dissection after stressor cessation were coded concurrent, immediate, 30 min, 90-120 min, or 24 hrs.

Stressor characteristics: The type and duration of the stressor were coded to determine if variation in the applied stressor had an effect on cardiovascular or immune system response. Type of stressor was divided into controllable footshock, uncontrollable footshock, restraint, novel environment, and mixed stressors. While these stressors include a physical component, we include them here because inducing psychological stress without physical manipulation is difficult, if not impossible, in animal studies (89).

Dependent measures: Dependent measures were coded to examine changes in cardiovascular and immune system response to stress. Cardiovascular reactivity

measures included HR, SBP, DBP, and MAP. Neuroendocrine and neurochemical reactivity measures included adrenocorticotropic hormone (ACTH), NE, E, corticosterone, prolactin, brain-derived neurotophic factor, serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), dopamine (DA), 3,4-dihydroxy-phenylacetic acid (DOPAC), and L-trytophan. Additionally, measures of cellular changes such as the number of c-fos reactive cells and 5-HT positive cells were included.

RESULTS

Meta-Analysis I: Human Literature

Overall effect: A total of 150 studies were located for possible inclusion in the analysis, 47 of which met inclusion criteria. Of the 47 articles, 30 had sufficient information to calculate *ES*s. Three articles reported multiple studies involving different control groups, which led to 33 studies in the final analysis. The 33 studies had a combined total of 1,252 participants (average N = 39.13). The overall weighted *ES* was -0.31 (95% *CI* = -.43, -.20)1, which is significantly different from zero. This moderate effect indicates that individuals randomly assigned to an exercise program experienced a one third of a standard deviation greater reduction in reactivity to psychological stressors than individuals randomly assigned to a control group.

Gains: Of the 33 studies included in the analysis, 18 contained sufficient information for the calculation of gains *ES*s. The overall weighted gains *ES* for the exercise group was -0.42 (95% *CI* = -0.26, -0.58). The overall weighted gains *ES* for the control group was -0.07 (95% *CI* = 0.09, -0.23).

Homogeneity: The standard test for homogeneity of variance was nonsignificant, Q = 34.76, p = .38. For the 33 included studies $I2$ = .08, indicating a very small amount of variability across studies. Due to the observed homogeneity among *ES*s, a random effects model was not fit. As explained by Hall and Rosenthal (38), a set of homogenous *ES*s may have significant moderators that account for the small amount of variance in the overall effect and we therefore conducted analyses of potential moderating variables.

Moderator variables and dependent measures: Moderator variables (see Table 1) did not account for a significant amount of the overall variance as evidenced by non-significant *Qb* values for all variables. The most common dependent measures (see Table 2) used to quantifyreactivity to psychological stressors were SBP (k = 46), DBP (k = 45), HR (k = 45), and MAP (k = 21). Based on data from pre-intervention exposure to psychological stressors across control and experimental group participants, the moderate effect represents a reduction of 3.56 mmHg for SBP, 3.42 mmHg for DBP, 2.09 beats per min for HR, and 4.41 mmHg for MAP for individuals in exercise groups compared to control group participants.

File Drawer Test: The file drawer problem is a potential threat to the validity of a systematic review as there may be a lack of published studies with non-significant results (67). Using the methods outlined by Rosenberg (64), 189 additional RCTs with non-significant results would have to be included in the current analysis to create a

non-significant overall effect. This is considered to be a robust number when Rosenthal's criterion (5*n* +10, where *n* is equal to the number of studies included in the analysis; 68) is applied.

Meta-Analysis II: Animal Literature

Overall effect: A total of 50 studies were located for possible inclusion in this analysis, 34 of which met inclusion criteria. Of the 34 articles, 19 had information sufficient to calculate *ES*s. The final analysis resulted in 27 studies as five studies reported data on multiple studies involving different control groups. The 27 studies had 462 subjects (average N = 17.11). The overall weighted *ES* was -0.33 (95% *CI* = -0.15, -0.52; $p < .05$). This moderate effect indicates that animals randomly allowed to participate in chronic wheel running experienced one third of a standard deviation greater reduction in reactivity to psychological stress than animals randomly assigned to a sedentary control group.

Homogeneity: This weighted overall effect is a result of using a fixed effects model, which is appropriate when there is a lack of heterogeneity in the analysis. The test for homogeneity of variance was non-significant, Q = 33.70, p = 0.14. For the 27 included studies there was a moderate amount of variability across studies (*I2* = 0.22).

Moderator variables and dependent measures: As indicated by non-significant *Qb* statistics for each category, no moderator variable accounted for a significant amount of the overall variance (see Table 3). No pairwise comparisons of moderator variable categories were conducted. The most commonly assessed neuroendocrine markers of stress reactivity assessed in the included studies were ACTH, Corticosterone, NE, 5-HT, and c-Fos (see Table 4).

File drawer test: Using the methods outlined by Rosenberg (64), it was found that 50 additional studies with non-significant results would have to be included in the current analysis to create a non-significant effect. Although this does not meet the criterion for robustness (68), it does represent a large number of unpublished, non-significant, RCTs when compared to the amount of literature discovered in our search.

DISCUSSION

Meta-Analysis I: Human Literature

The *ES* of -.31 resulting from the analysis of randomized controlled trials with a large sample of participants (N = 1,252) represents evidence for the use of exercise to reduce reactivity to psychological stressors. The overall *ES* is similar in magnitude to *ES*s in previous meta-analyses, but is more reliable due to the exclusive use of RCTs in this meta-analysis.

The reduction in blood pressure reactivity to psychological stressors closely mimics the findings of a previous meta-analysis on the effects of exercise on blood pressure, which found that aerobic exercise was associated with a significant decrease in both SBP and DBP (-3.84 and-2.58 mm Hg, respectively; 91). Although the reductions found in the current study may seem minimal (3.56 mm Hg for SBP and 3.42 mm Hg for DBP), one must consider the accumulation of stressful stimuli experienced over time. As evidenced by research linking increased cardiovascular reactivity to disease states ranging from

sub-clinical to life-threatening diseases states (46, 48), even small reductions in cardiovascular reactivity can be clinically beneficial over time.

The homogeneity of the overall *ES* indicates that exercise-induced reductions in stress reactivity are applicable to the general population; however, one limitation of this meta-analysis is that participant and design characteristics were similar across included studies. Many studies examined reactivity to an active stressor in a population of healthy, mixed gender individuals who were engaged in a chronic aerobic exercise intervention. Future research should focus on addressing issues of variability in sample populations, including research to understand how exercise may affect those who are at greater risk from negative effects of stress reactivity.

Meta-Analysis II: Animal Literature

The overall weighted *ES* of = -0.33 indicates that animals allowed to engage in aerobic training had moderate reductions in stress reactivity. This finding has the dual purpose of offering an insight into the stress mechanisms that might be affected by chronic exercise, as well as providing support for the results found in Meta I. The main finding of this analysis indicates that participation in chronic activity has moderate positive effects on hormone and catecholamine reactivity to stressors.

The animal studies in the current analysis are unique because the subjects were not placed in a training program per se, but allowed to exercise freely in regards to duration and intensity. Interestingly, two moderator variables that approached significance indicated a trend between longer running distance (> 5 km/week), and greater intervention length (> 10 weeks) and stronger effects (*ES*s = -0.46, p = .08 and -1.19, p = .06, respectively).

As in Meta I, many of the animal studies used similar design and subject characteristics, and future animal studies should address this lack of variability. While it would be preferable to use animal models to further examine differences in training intensities, training methods, and stress protocols, these variables prove to be problematic because changes in design characteristics such as animal handling time may mask the true effects of exercise on stress reactivity. Future studies should employ voluntary physical activities that are likely to induce changes in cardiovascular fitness (e.g., gradual addition of resistance to wheel running equipment). Additionally, the inclusion of stressors that mimic those experienced by humans or the introduction of highly populated, novel environments may be enlightening.

The results of the current analyses indicate that exercise is associated with moderate reductions in stress reactivity. Over time, such reductions have the potential to reduce the burden of serious medical conditions associated with stress, such as CVD and immune system dysfunction. The consistency of the findings provides strong support for the effects of exercise on stress reactivity, and the use of only RCTs limits the potential bias and error inflation that results from quantitative reviews of less rigorously designed studies. Based on the homogeneity of study characteristics (healthy individuals and chronic, moderate-intensity exercise), future research should examine the effects of exercise on stress reactivity in clinical populations, such as people with diagnosed stress disorders or

elevated cardiac risk factors. Finally, the analysis of animal research confirms results from research with humans, and shows that exercise is associated with beneficial stress reactivity adaptations at the hormonal and neurochemical levels.

REFERENCES

*Included in Meta I (Humans)
**Included in Meta II (Animals)

1. **Adlard PA, Cotman CW. Voluntary exercise protects against stress-induced decreases in brain-derived neurotrophic factor protein expression. Neuroscience 124(4): 985-992, 2004.

2. *Albright CL, King AC, Barr Taylor C, Haskell WL. Effect of a six-month aerobic exercise training program on cardiovascular responsivity in healthy middle-aged adults. J Psychosom Res 36(1): 25-36, 1992.

3. Alderman BL, Rogers TJ, Landers DM, Arent SM. The effects of exercise and fitness on stress reactivity: a meta-analytic review. Unpublished manuscript, 2004.

4. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006. 368 p.

5. Stress in America [Internet].Washington, DC: American Psychological Association; 2007, October 24. Available from from http://www.apa.org/pubs/info/reports/2007-stress.doc.

6. *Anshel MH. Effect of chronic aerobic exercise and progressive relaxation on motor performance and affect. Behav Med 21(4):186-196, 1996.

7. Baechle TR, Earle RW. Essentials of strength and conditioning. 2nd ed. Champaign, IL: Human Kinetics; 2000. 672 p.

8. *Ballinger DA. Changes in stress response following physical conditioning. Unpublished doctoral dissertation: Arizona State University; 1987.

9. *Bartholomew JB. Stress reactivity after maximal exercise: the effect of manipulated performance feedback in endurance athletes. J Sports Sci 18(11):893-899, 2000.

10. *Blumenthal JA, Fredrikson M, Kuhn CM, Ulmer RL, Walsh-Riddle M, Appelbaum M. Aerobic exercise reduces levels of cardiovascular and sympathoadrenal responses to mental stress in subjects without prior evidence of myocardial ischemia. Am J Cardiol 65:93-98, 1990.

11. *Blumenthal JA, Fredrikson M, Matthews KA, et al. Stress reactivity and exercise training in premenopausal and postmenopausal women. Health Psychol 10(6):384-391, 1991.

12. *Blumenthal JA, Emery C, Walsh M, et al. Exercise training in healthy type A middle-aged men: effects on behavioral and cardiovascular responses. Psychosom Med 50(4):418-433, 1988.

13. *Bond V, Mills RM, Caprarola M, et al. Aerobic exercise attenuates blood pressure reactivity to cold pressor test in normotensive, young adult African American women. Ethn Dis 9(1):104-110, 1999.

14. Boutcher SH, Hamer M. Psychobiology of physical activity. Champaign, IL: Human Kinetics; 2006. Psychobiological reactivity, physical activity, and cardiovascular health; p. 161-172.

15. **Campisi J, Leem TH, Greenwood BH, et al. Habitual physical activity facilitates stress-induced HSP72 induction in brain, peripheral, and immune tissues. Am J Physiol Regul Integr Comp Physiol 284:R520-R530, 2002.

16. Carrasco GA, Van de Kar LD. Neuroendocrine pharmacology of stress. Eur J Pharmacol 463:235-272, 2003.

17. *Chafin S. Reducing cardiovascular arousal to psychological stress with brief physical exercise. Unpublished doctoral dissertation: University of California, San Diego; 2007.

18. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Earlbaum Associates; 567 p., 1988.

19. Crews D, Landers DM. A meta-analytic review of aerobic fitness and reactivity to psychosocial stressors. Med Sci Sports Exerc 19:S121-S129, 1987.

20. de Geus E, van Doornen L. The effects of fitness training on the physiological stress response. Work Stress 7:141-159, 1993.

21. *de Geus JC, Van Doornen LJP, De Visser DC, Orlebeke JF. Existing and training induced differences in aerobic fitness: their relationship to physiological response patterns during different types of stress. Psychophysiology 27:457-478, 1990.

22. **Dishman, RK, Bunnell BN, Youngstedt SD, Yoo HS, Mougey EH, Meyerhoff JL. Activity wheel running blunts increased plasma adrenocorticotropin (ACTH) after footshock and cage-switch stress. Physiol Behav 63, 911-917, 1998.

23. **Dishman RK, Renner KJ, Youngstedt SD, et al. Activity wheel running reduces escape latency and alters brain monoamine levels after footshock. Brain Res Bull 42:399-406, 1997.

24. **Dishman RK, Warren JM, Youngstedt SD, et al. Activity wheel running attenuates suppression of natural killer cell activity after footshock. J Appl Physiol 78:1547-1554, 1995.

25. *Don BW. The effects of strength training on cardiovascular reactivity to stress and psychological well-being in college women. Unpublished doctoral dissertation: Boston University; 1996.

26. **Droste SK, Gesing A, Ulbricht S, Muller MB, Linthorst ACE, Reul JM. Effects of longterm voluntary exercise on the mouse hypothalamic-pituitary-adrenocortical axis. Endocrinology 144:3012-3023, 2003.

27. **Droste SK, Chandramohan Y, Hill LE, Linthorst A, Reul JM. Voluntary exercise impacts on the rat hypothalamic-pituitary-adrenocortical axis mainly at the adrenal level. Neuoroendocrinology 86:26-37, 2007.

28. **Droste SK, Schweizer MC, Ulbricht S, Ruel, JM. Long-term voluntary exercise and the mouse hypothalamic-pituitary-adrenocortical axis: impact of concurrent treatment with the antidepressant drug tianeptine. J Neuroendocrinology 18:915-925, 2006.

29. Fauvel JP, Quelin P, Ducher M, Rakotomalala H, Laville M. Perceived job stress but not individual cardiovascular reactivity to stress is related to higher blood pressure at work. Hypertension 38:71-75, 2001.

30. **Fediuc S, Campbell JE, Riddell MC. Effect of voluntary wheel running on circadian corticosterone release and on HPA axis responsiveness to restraint stress in Sprague-Dawley rats. J Appl Physiol 100:1867-1875, 2006.

31. **Fleshner M. Exercise and neuroendocrine regulation of antibody production: protective effect of physical activity on stress-induced suppression of the specific antibody response. Int J Sports Med 21(S1):S14-S19, 2000.

32. **Fleshner M, Campisi J, Deak T, et al. Acute stressor exposure facilitates innate immunity more in physically active than in sedentary rats. Am J Physiol Regul Integr Comp Physiol 282:R1680-R1686, 2002.

33. Forcier K, Stroud LR, Papandonatos GD, et al. Links between physical fitness and cardiovascular reactivity and recovery to psychological stressors: a meta-analysis. Health Psychol 25:723-739, 2006.

34. Glaser R, Kiecolt-Glaser JK, Bonneau R, Malarkey W, Hughes J. Stress-induced modulation of the immune response to recombinant hepatitis B vaccine. Psychosom Med 54:22-29, 1992.

35. **Greenwood BN, Foley TE, Burhans D, Maier SF, Fleshner M. The consequences of uncontrollable stress are sensitive to duration of prior wheel running. Brain Res 1033:164- 178, 2005.

36. **Greenwood BN, Kennedy S, Smith TP, Campeau S, Day HEW, Fleshner M. Voluntary freewheel running selectively modulates catecholamine content in peripheral tissue and c-fos expression in the central sympathetic circuit following exposure to uncontrollable stress in rats. Neuroscience 120:269-281, 2003a.

37. **Greenwood BN, Foley TE, Campisi J, Hammack SH, Campeau S, Maier S, Fleshner M. Freewheel running prevents learned helplessness/behavioral depression: role of dorsal

raphe serotonergic neurons. Journal Neurosci 23:2889-2898, 2003b.

38. Hall JA, Rosenthal R. Testing for moderator variables in meta-analysis: issues and methods. Commun Monogr 58:437-448. 1991.

39. Hamer M, Taylor A, Steptoe A. The effect of acute aerobic exercise on stress related blood pressure responses: a systematic review and meta-analysis. Bio Psychol 71:183-190, 2006.

40. Hedges LV, Olkin I. Statistical methods for meta-analysis. Orlando, FL: Academic Press; 369 p., 1985

41. Higgins PT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in metaanalysis. BMJ 327:557-560, 2003.

42. *Hobson ML, Rejeski WJ. Does the dose of acute exercise mediate psychophysiological responses to mental stress? J Sport Exerc Psychol 15:77-87, 1993.

43. *Holmes DS, Roth DL. Effects of exercise training and relaxation training on cardiovascular activity during psychological stress. J Psychosom Res 32:469-474, 1988.

44. Hunter JE, Schmidt FE. Methods of meta-analyses: correcting error and bias in research findings. Thousand Oaks, CA: Sage; 616 p., 2004

45. Jackson EM, Dishman RK. Cardiorespiratory fitness and laboratory stress: a meta-regression analysis. Psychophysiology 43:57-72, 2006.

46. Jennings JR, Kamarck TW, Everson-Rose SA, Kaplan GA, Manuck SB, Salonen JT. Exaggerated blood pressure responses during mental stress are prospectively related to enhanced carotid atherosclerosis in middle-aged Finnish men. Circulation 110:2198-2203, 2004.

47. Johnson EO, Kamilaris TC, Chrousos GP, Gold PW. Mechanisms of stress: a dynamic overview of hormonal and behavioral homeostasis. Neurosci Biobehav Rev 16:115-130, 1992.

48. Keys A, Taylor HL, Blackburn H, Brozeki J, Anderson JT, Simonson E. Mortality and coronary heart disease among men studied for 23 years. Arch Intern Med 128:201-214, 1971.

49. *King AC, Bouman 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 57:M26–M36, 2002.

50. *Kubitz KA, Landers DM. The effects of aerobic training on cardiovascular responses to mental stress: an examination of underlying mechanisms. J Sport Exerc Psychol 15(3):326- 337, 1993.

51. **Lancel M, Droste SK, Sommer S, Reul JM. Influence of regular voluntary exercise on spontaneous and social stress-affected sleep in mice. Eur J Neurosci 17:2171-2179, 2003.

52. *LaPerriere AR, Antoni MH, Schneiderman GI, et al. Exercise intervention attenuates emotional distress and natural killer cell decrements following notification of positive serologic status for HIV-1. Biofeedback Self Regul 15:229-242, 1990.

53. **Levenson CW, Moore JB. Response of rat adrenal neuropeptide Y and tyrosine hydroxylase mRNA to acute stress is enhanced by long-term voluntary exercise. Neurosci Lett 242(3):177-179, 1998.

54. Lindquist TL, Beilin LJ, Knuiman MW. Influence of lifestyle, coping, and job stress on blood pressure in men and women. Hypertension 29:1-7, 1997.

55. Lipsey MW, Wilson DB. Practical meta-analysis. Thousand Oaks, CA: Sage; 264 p., 2000

56. Lovallo WR. Stress and health: biological and psychological interactions. 2nd ed. Thousand Oaks, CA: Sage; 296 p., 2005

57. Manuck SB, Kaplan JR, Adams MR, Clarkson TB. Effects of stress and the sympathetic nervous system on coronary artery atherosclerosis in the cynomolgus macaque. Am Heart J 116:328-333, 1988.

58. Moraska A, Deak T, Spencer RL, Roth D, Fleshner M. Treadmill running produces both positive and negative physiological adaptations in Sprague-Dawley rats. Am J Physiol Regul Integr Comp Physiol 279:R1321-R1329, 2000.

59. **Morimoto K, Tan N, Nishiyasu T, Sone R, Murakami N. Spontaneous wheel running

attenuates cardiovascular responses to stress in rats. Eur J Physiol 440(2):216-222, 2000.

60. Oortwijn W, Nelissen E, Adamini S, van den Heuvel S, Geuskens G, Burdof L. Social determinants state of the art reviews - gealth of people of working age - full report. European Commission Directorate General for Health and Consumers: Luxembourg, 2011.

61. **Rakhshani, N. Effects of short- and long-term voluntary exercise training on diurnal rhythm, the acute stress response and adrenal sensitivity in male Sprague-Dawley rats. Unpublished doctoral dissertation: York University, Canada; 2006.

62. *Rendeiro, T. The effects of aerobic training on physiological reactivity to active and passive psychological stressors. Unpublished master's thesis: Pennsylvania State University; 1987.

63. *Rogers MW, Probst MM, Gruber JJ. Differential effects of exercise training intensity on blood pressure and cardiovascular responses to stress in borderline hypertensive humans. J Hypertens 14:1369-1375, 1996.

64. Rosenberg M. The file-drawer problem revisited: a general weighted method for calculating fail-safe numbers in meta-analysis. Evolution 59(2):464–468, 2005.

65. Rosengren A, Hawken S, Ôunpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 364:953-962, 2004.

66. Rosenthal R, Dimatteo MR. Meta-analysis: recent developments in quantitative methods for literature reviews. Annu Rev Psychol 52(1):59-82, 2001.

67. Rosenthal R. The ''file drawer problem'' and tolerance for null results. Psychol Bull 86:638– 641, 1979.

68. Rosenthal R. Meta-analytic procedures for social research. Newbury Park, CA: Sage; 168 p., 1991

69. Rosenthal R. The handbook of research synthesis. New York, NY: Russell Sage Foundation; Parametric measures of effect size; p. 231-244., 1994

70. *Roth DL. Acute emotional and psychophysiological effects of aerobic exercise. Psychophysiology 26:593-602, 1989.

71. *Roth DL. An experimental comparison of cardiovascular and self-reported health effects of aerobic exercise and progressive relaxation. Unpublished doctoral dissertation: University of Kansas; 1985.

72. *Roy M, Steptoe A. The inhibition of cardiovascular responses to mental stress following aerobic exercise. Psychophysiology 28(6):689-700, 1991.

73. Shadish WR, Haddock CK. The handbook of research synthesis. New York, NY: Russell Sage Foundation; 1994. Combining estimates of effect size; p. 261-284.

74. Sheridan JF, Dobbs CM. Handbook of human stress and immunity. San Diego, CA: Academic Press; 1994. Stress, viral pathogenesis, and immunity; p 101-123.

75. *Sherwood A, Light KC, Blumenthal JA. Effects of aerobic exercise training on hemodynamic responses during psychosocial stress in normotensive and borderline hypertensive type A men: a preliminary report. Psychosom Med 51(2):123-136, 1989.

76. **Soares J, Holmes PV, Renner KJ, Edwards GL, Bunnell BN, Dishman RK. Brain noradrenergic responses to footshock after chronic activity-wheel running. Behav Neurosci 113(3):558-566, 1999.

77. Sothman MS. Psychobiology of physical activity. Champaign, IL: Human Kinetics; The cross-stressor adaptation hypothesis and exercise training; p. 149-158., 2006

78. Sothman MS, Buckworth J, Claytor R, Cox RH, White-Welkley JE, Dishman RK. Exercise training and the cross-stressor adaptation hypothesis. Exerc Sport Sci Rev 24:267-287, 1996.

79. *Sothman MS, Hart BA, Horn TS. Sympathetic nervous system and behavioral responses to stress following exercise training. Physiol Beh 51(6):1097-1103, 1992.

80. *Spalding TW, Lyon LA, Steel DH, Hatfield BD. Aerobic exercise training and cardiovascular reactivity to psychological stress in sedentary young normotensive men and women. Psychophysiology 41(4):552-562, 2004.

81. *Stein PK. The effect of moderate intensity aerobic exercise training on cardiovascular reactivity in sedentary middle-aged men. Unpublished doctoral dissertation: University of Virginia; 1990.

82. *Steptoe A, Moses J, Edwards A, Mathews A. Exercise and responsivity to mental stress: discrepancies between subjective and physiological effects of aerobic training. Int J Sport Psychol 24:110-129, 1993.

83. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. J Am Coll Cardiol 37:153-156, 2001.

84. *Taylor A, Katomeri M. Effects of a brisk walk on blood pressure responses to the stroop, a speech task and a smoking cue among temporarily abstinent smokers. Psychopharmacology 184(2):247-253, 2006.

85. Taylor AH. Physical activity and psychological well-being. New York, NY: Routledge; Physical activity, anxiety, and stress; p. 10-45., 2000

86. *Thorne LC, Bartholomew JB, Craig J, Farrar RP. Stress reactivity in fire fighters: an exercise intervention. Int J Stress Manag 7:235-246, 2000.

87. Toates F. Stress: conceptual and biological aspects. New York, NY: John Wiley & Sons; 352 p., 1995

88. *Tsutsumi T. The effects of strength training on mood, self-efficacy, cardiovascular reactivity and quality of life in older adults. Unpublished doctoral dissertation: Boston University; 1997.

89. Turner R. Cardiovascular reactivity and stress: patterns of physiological response. New York, NY: Plenum Press; 260 p., 1994

90. *Vona M, Rossi A, Capodaglio P, et al. Impact of physical training and detraining on endothelium-dependent vasodilatation in patients with recent acute myocardial infarction. Am Heart J 147(6):1039-1046, 2004.

91. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. Ann Intern Med 136(7):493-503, 2002.

92. Yanagita S, Amemiya S, Suzuki S, Kita I. Effects of spontaneous and forced running on activation of hypothalamic corticotropin-releasing hormone neurons in rats. Life Sci 80(4):356-363, 2007.