

Psychobiological Mechanisms of Exercise Dependence

Mark Hamer¹ and Costas I. Karageorghis²

1 Department of Epidemiology and Public Health, Psychobiology Group, University College London, London, UK

2 School of Sport and Education, Brunel University, London, UK

Abstract

Exercise dependence (ED) is characterised by an obsessive and unhealthy preoccupation with exercise. Previous research has focused largely on identifying behavioural aspects of ED, although the biological mechanisms remain unknown and are under researched. We review various ED hypotheses including affect regulation, anorexia analogue, sympathetic arousal and β -endorphin. We also present a novel hypothesis pertaining to ED and interleukin (IL)-6, which combines previous hypotheses with literature from the field of psycho-neuroimmunology. We explore the notion that IL-6 provides a link from the periphery to the brain, which may mediate the underlying features of ED. We propose a conceptual model indicating that, in individuals prone to ED, exercise results in a transient reduction in negative affect, but concurrently results in excessive production of IL-6 and the activation of neuroendocrine pathways, which are associated with behavioural and psychological disturbances of exercise withdrawal. Our intention is for this model to serve as a basis for further research in the area of ED, which may eventually lead to the development of successful treatment strategies. Recent developments in methods to reliably assess these biological markers from blood and saliva samples should encourage such research to be undertaken in exercise settings.

Conceptually, dependence or addiction to sport and exercise may be viewed as a process that compels an individual to continue with the activity in spite of obstacles, such as work, family commitments or medical contraindications. This may result in both physical and psychological symptoms when an individual is withdrawn from exercise participation.^[1] A number of terms have been used to describe this phenomenon, including 'addiction', 'dependence', 'obligatory', 'compulsive', 'abusive' and 'morbid',^[2] although the present review will adopt the term 'exercise dependence' (ED). As such, ED has clinical implications that relate to chronic physical injuries, psychological dysfunction and disruption of social relationships that may indirectly impact upon health.^[3] ED has been characterised as

either primary or secondary.^[4] For primary ED, the physical activity is an end in itself. In contrast, for secondary ED, which is often evident in populations with eating disorders, people are extrinsically motivated to exercise in an attempt to control or alter their body size/shape. Nevertheless, there is disagreement as to whether the categorisation of primary and secondary ED truly exists,^[5] as there are no animal models of excessive exercise, unless food restriction is present (see section 2). Estimates of the prevalence of ED from a variety of exercising populations range from 2 to 3%^[6,7] up to 20–30%.^[8–11] This variation in estimates of prevalence is mainly due to discrepancies in the identification of primary and secondary ED and also the wide variety of psychometric scales^[1,6–8,12–14] that have been devel-

Table 1. Psychometric tools^a for the measurement of exercise dependence (ED)

Inventory	Structure		Test sample (n) [exercise characteristics]	Psychometric properties		Classification of ED
	items	sub-scales		concurrent validity (r)	internal reliability (α)	
Exercise addiction inventory ^[7]	6		200ex	0.85	0.84	>24
Exercise dependence criteria ^[8]	14		NR	NR	NR	≥3 DSM-IV criteria ^b
Exercise dependence scale: revised ^[6]	21	7	1263ex [>3x/wk]	0.41–0.78	0.78–0.92	≥3 DSM-IV criteria ^b
Exercise beliefs questionnaire ^[14]	21	4	126ex [>3x/wk]	0.67–0.77	0.67–0.89	NR
Exercise dependence questionnaire ^[13]	29	8	449ex [>4h/wk]	NR	0.52–0.84	≥116
Running addiction scale ^[1]	11		47r [4 runs/wk]	0.75	0.82	NR
Obligatory exercise questionnaire ^[12]	20		30r; 30wl; 30sc	0.96	0.96	≥50

a Measures that have not demonstrated psychometric integrity or have no practical application for present research purposes have been excluded.

b Based on DSM-IV criteria for substance dependence.

DSM-IV = diagnostic and statistical manual of mental disorder IV; **ex** = exercisers; **NR** = not reported; **r** = runners; **sc** = sedentary controls; **wl** = weight lifters.

oped to quantify ED (see table 1). Nevertheless, there is strong evidence for the existence of ED despite ongoing debate regarding whether or not it warrants recognition as a clinical disorder in its own right. Specific diagnostic criteria include impaired functioning (e.g. psychological, social, physical, behavioural), exercise withdrawal symptoms and the presence of an eating disorder in the case of secondary ED.^[15] Further associated features may include tolerance (manifested as a progressive increase in exercise volume or daily stereotyped exercise that is not necessarily of high volume), solitary exercising and lying about exercising.^[15]

Whilst previous research in ED has focused on the development of valid tools for the assessment of ED and identifying the psychopathological characteristics (a summary of the literature is provided in recent reviews^[2,15]), the underlying mechanisms have received little attention and remain largely unknown. Therefore, although health practitioners may have validated tools and diagnostic criteria to identify ED, further knowledge regarding the underlying biological mechanisms may aid in the treatment of ED. Here, we discuss plausible mechanisms of ED, focusing particularly on psychobiological processes.

1. Affect Regulation Hypothesis

Tomkins^[16] presented the affect regulation model, which postulates that running serves as a “positive affect enhancer” and a “negative affect reducer.” Tomkins identified the following two types of runners: (i) the “negative runner” who runs to reduce their distress; and (ii) the “positive runner” who runs to increase their positive feeling. It was proposed that the development of compulsive running occurred when running became an end rather than a means to an end. This notion is, of course, in contrast with the view of positive psychologists who contend that optimal experiential states occur when running becomes an end in itself or an “autotelic experience.”^[17] Nonetheless, Tomkins argued that abstinence from running increased negative affect (e.g. depressed mood, anxiety), which could only be reduced by exercise.

Research to support the affect regulation hypothesis is provided by studies that have examined individual motivation to participate in exercise^[18,19] and also psychological responses to acute exercise.^[19,20] Johnsguard^[18] identified anxiety and depression reduction as one of the primary running motives in a group of older, habitual runners. Similarly, Anshel^[19] demonstrated that stress reduction was one

of the main motives for exercise in a sample of 30 addicted exercisers, in contrast to 30 normal exercisers who exercised for health, well-being and social enjoyment. Anshel^[19] also reported that ED individuals were more restless and stressed prior to exercise, but experienced a higher degree of post-exercise affect that was assessed by measuring levels of happiness and mental stress. Moreover, the addicted exercisers felt far more depressed, anxious and angry after missing a workout. Similar findings, in relation to the effects of acute exercise on the alleviation of negative affect, were recently reported^[20] with a longer lasting reduction 'profile of mood states' tension-anxiety scores among ED individuals following a maximal exercise test, when compared with non-ED individuals.

Our recent work examining the motives for exercise participation as predictors of ED suggested that the strongest predictor variable of ED was introjected regulation (a non self-determined form of extrinsic motivation), which does not support the tenets of the affect regulation model.^[21] However, our findings may have been confounded by the fact that we did not differentiate between primary and secondary ED because introjected regulation is closely comparable with the type of behaviour described in the anorexia analogue hypothesis.^[22]

Additional evidence to support the affect regulation model is offered by studies of exercise deprivation among habitual exercisers.^[23-29] For example, when unable to run, habitual runners have been observed to suffer withdrawal symptoms, including anxiety, irritability,^[24,26] guilt,^[26] depression,^[24,27] fatigue and pain-like symptoms.^[28] Thaxton^[29] also reported increased galvanic skin resistance responses among habitual runners following 1 day of abstinence. In more recent studies, a controlled experimental design has been applied to examine the incidence of withdrawal symptoms following cessation from exercise. Morris et al.^[25] observed comparatively greater somatic symptoms, insomnia, increased depression and anxiety among habitual runners who were deprived of exercise. In another deprivation study,^[27] fatigue and somatic depressive symptoms emerged 1 week after exercise withdrawal and subsequently predicted the development of cognitive-affective depressive symptoms at 2 weeks. This study also demonstrated that increased

fatigue during exercise withdrawal was partially mediated by reduced levels of fitness.^[27]

Mondin et al.^[23] performed a similar study but attempted to address some of the limitations that had blighted previous work by requiring participants to withdraw from exercise on a voluntary basis rather than offering remuneration or through cessation caused by injury, which may introduce additional confounds. Following a 3-day exercise deprivation period, participants demonstrated significant increases in total mood disturbance, anxiety, tension, depression and confusion. Collectively, these studies demonstrate that habitual exercisers experience mood disturbances on withdrawal from exercise, although, to date, little attention has been given to the biological processes that underlie such disturbances. A particular weakness in previous work has been the excessive focus on samples of habitual runners without objective measures of ED; it is likely that exercise deprivation sensations may be experienced by both non-dependent and dependent exercisers, with the former group experiencing less profound effects.

2. Anorexia Analogue Hypothesis

Yates et al.^[22] proposed that compulsive running is a male analogue of anorexia nervosa. A comparison of 60 male obligatory runners with patients suffering from anorexia nervosa indicated that both groups exhibited similar personality profiles, such as inhibition of anger, extraordinarily high self-expectations, tolerance of physical discomfort, denial of potentially serious debility and a tendency towards depression.^[22] Women are likely to attempt a resolution of identity issues through an overemphasis on physical attractiveness and dieting in order to achieve their perceived image. Men with an uncertain identity and low self-esteem may experience exaggerated anxiety about physical ineffectiveness and thus demonstrate a fanatic devotion to physical prowess. However, this hypothesis has received limited support^[30-34] and a number of studies have disputed the findings.^[35,36] Data showing that obligatory runners displayed higher levels of perfectionism and trait anxiety in comparison with non-obligatory runners provided partial support, although the two groups displayed no significant differences for sense of identity and trait anger.^[32] Others have suggested

ED is widely reported to coexist with eating disorders.^[33] Indeed, a well established animal model^[34] demonstrates that running-wheel activity is induced when rats are restricted to food once a day. The level of activity becomes excessive with dramatically reduced food intake. Recent animal research^[34] suggests an association between hypothalamic-pituitary-adrenal (HPA) axis activity and food restriction-induced increases in physical activity, mediated through body fat levels. This creates a vicious cycle by reinforcing self-starvation via reward mechanisms, which has relevance in relation to human anorexia. However, in humans no evidence of psychopathology was reported in a sample of obligatory runners compared with anorexic patients, using the Minnesota Multiphasic Personality Inventory.^[35] Furthermore, it was acknowledged that previously reported case studies^[22] were, in fact, factitious and that there were no objective data to support these assertions. In addition, no significant evidence of anorexia nervosa was demonstrated comparing habitual runners with controls using the Jackson Personality Inventory and the Eating Attitudes Questionnaire.^[36]

3. Sympathetic Arousal Hypothesis

Thompson and Blanton^[37] suggested that repeated exercise is maintained by hormonal changes resulting from exercise training. Evidence suggests that there is a decreased sympathetic nervous system output (catecholamines) as a result of exercise training.^[38] While this adaptation results in an increased efficiency of energy utilisation, the decreased output results in lethargy, fatigue and decreased arousal. Therefore, the habitually exercising individual is motivated to engage in increasing levels of exercise in order to achieve the same level of arousal, thus demonstrating a habituation effect commonly observed in ED. There has been little work to substantiate this hypothesis, although a recent study^[28] reported that individuals who develop symptoms of pain, fatigue and mood changes following 1 week of exercise deprivation have lower baseline (prior to exercise withdrawal) measures of HPA axis, immune and autonomic function. This would indeed support the notion that a subset of individuals who have hypoactive function of biological stress re-

sponse systems exercise regularly to maintain arousal and suppress symptoms.

4. β -Endorphin Hypothesis

Dopamine and opioid networks form part of the neurocircuitry reward system in the brain and are thought to be responsible for a host of addictive behaviours in humans.^[39] Aerobic exercise is known to stimulate the release of β -endorphin and other endogenous opioid peptides that appear to exert analgesic effects^[40] and may also produce addictive behaviours. In a recent animal study,^[41] chronic exercise was shown to lead to opioid tolerance and physical dependence, suggesting that regular exercise reduces the sensitivity to opioids thereby requiring higher doses of exercise to achieve the same effects. However, in the only study that has examined the relationship between β -endorphin responses to exercise and ED in humans, the authors failed to find any association.^[42] Nevertheless, this was a vastly underpowered cross-sectional study of eight female participants who all appeared to demonstrate ED scores in the normal range, albeit using a poorly validated measure of ED. Therefore, further studies are needed in humans, using larger samples and employing more sophisticated methodological designs, such as the use of opioid antagonists. A final point relates to the finding that ED may be apparent in individuals performing low volume exercise,^[5] which refutes the concept of habituation whereby individuals must continually increase exercise volume to maintain satisfaction.

5. Cytokine Hypothesis

5.1 Cytokines, Exercise and Behaviour

Until recently, little attention has been given to the pathway from the periphery of the body to the brain. Cytokines have been proposed as “immunotransmitters” that act as messengers between the immune system and the brain.^[43-45] Current knowledge indicates that cytokine signals modulate complex human central nervous system functions (including serotonergic, noradrenergic and HPA axis systems), which promote changes in brain neuronal activity and hence influence behaviour. Numerous findings corroborate the hypothesis that non-spezif-

ic immune activation and cytokines are involved in the etiology or symptomology of major depression.^[44,46] The infusion of interleukin (IL)-6 in humans has also been shown to result in changes in mood and behaviour. For example, in healthy human participants, infusion of recombinant IL-6, which induces increases in plasma IL-6 concentrations comparable with those observed after infection, resulted in increased fatigue, poorer concentration and altered sleep architecture.^[47] Also, significant increases in anxiety and depressed mood state were demonstrated in 20 healthy volunteers after injection of an endotoxin that induced increases in IL-6 and cortisol.^[48] Furthermore, IL-6 increases following infection with influenza were correlated with psychological stress.^[49] These profound behavioural disturbances, known as 'sickness behaviour' are comparable with the symptoms that are associated with exercise withdrawal in ED.

Exercise is known to have a profound influence on cytokines. The cytokine response to exercise is unique, in that the classic pro-inflammatory cytokines (tumor necrosis factor [TNF]- α and IL-1 β) do not, in general, increase with exercise, but typically IL-6 is the first cytokine present in the circulation. IL-6 has been classified as both a pro- and an anti-inflammatory cytokine,^[50] although in the case of exercise, recent data suggest that IL-6 is anti-inflammatory.^[51] Increases in circulating IL-6 are consistently observed after exercise without muscle damage.^[51] It has been suggested that exercise-induced IL-6 release causes an anti-inflammatory environment by promoting IL-1 receptor antagonist and IL-10 synthesis, but inhibiting TNF- α release.^[52] This mechanism may explain why lower baseline levels of inflammatory markers, such as C-reactive protein and TNF- α , are found in individuals who are most physically active^[53,54] and why chronic exercise training interventions also result in reduced circulating concentrations of these markers.^[55,56] Given the impact of exercise on IL-6 release and the concurrent effect of IL-6 on complex brain function, it is reasonable to speculate that the underlying features of ED may, in part, be mediated by this cytokine. Excessive production and/or intolerance of IL-6 during exercise have also been implicated as a possible mechanism prompting the overtraining syndrome in athletes.^[57-59] Overtraining

syndrome, defined as a persistent decrement in athletic performance capacity despite 2 weeks relative rest,^[60] differs markedly from the definition of ED. However, over-trained athletes and ED individuals who are withdrawn from exercise both display similar symptoms that are reminiscent of sickness behaviour. Thus, we hypothesise that IL-6 may also be an underlying mechanism of ED.

5.2 Exercise Dependence and Interleukin-6 Model

Figure 1 illustrates the proposed role of IL-6 in ED. Acute and chronic exercise have been associated with a reduction in negative affect that may be due to a number of physiological (e.g. catecholamines, endorphins, visceral feedback, hyperthermic change) and psychological (e.g. mastery, self-confidence, exercise environment, self-esteem, social support, stress management) mechanisms.^[61] In the proposed conceptual model, an initial trigger may cause an over production of IL-6 and promote cytokine-induced sickness behaviour with the associated increases in negative affect. This trigger may be caused by a number of factors, including an inability to cope with an excessive exercise load,^[62] an episode of acute psychological stress^[63] or an

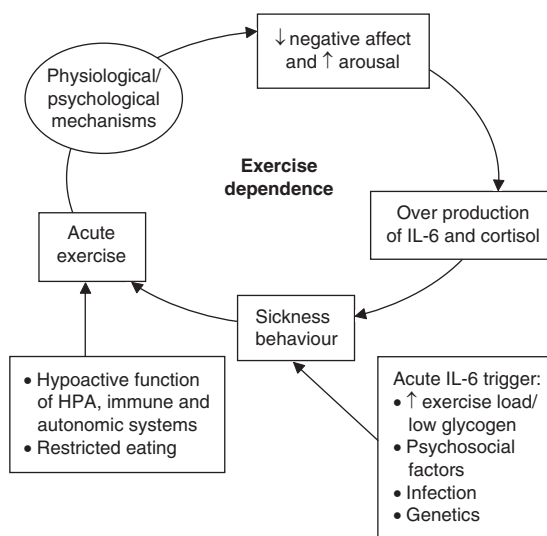


Fig. 1. A conceptual model for the psychobiological mechanisms of exercise dependence. **HPA** = hypothalamic-pituitary-adrenal axis; **IL-6** = interleukin 6; ↑ indicates increase; ↓ indicates decrease.

acute infection. Given that low muscle glycogen concentration has been shown to further enhance IL-6 production during exercise^[64,65] and ED is widely reported to coexist with eating disorders,^[4,8,33] the combination of exercise and restricted eating may also be a key trigger and re-enforce the over production of exercise-induced IL-6. Infusion of recombinant IL-6, which induces increases in IL-6 levels corresponding to the levels obtained during strenuous exercise, also results in production of cortisol.^[52] Given that cortisol levels appear to play a potentially important role in other addictions, such as being associated with cravings for alcohol during withdrawal and the prediction of relapse in alcoholics,^[66] cortisol responses to, and recovery from, exercise may also play an important role in ED. Indeed, lower HPA axis function at baseline was also predictive of exercise withdrawal symptoms of pain, fatigue and mood disturbances in healthy exercisers.^[28]

Interestingly, despite strong links between IL-6 and depressed mood, ED only affects a relatively small proportion of individuals who engage in habitual exercise. This may be due to the fact that endurance-trained individuals develop adaptive mechanisms that may protect skeletal muscle and the immune system from the potentially harmful effects of excessive exercise-induced cortisol production.^[67] Duclos et al.^[67] showed that when compared with untrained controls, trained individuals demonstrated acute exercise-induced increases in glucocorticoid (GC) sensitivity, followed 24 hours later by increases in baseline IL-6 levels and reduced GC sensitivity that was evidenced by a lower inhibition of IL-6 production with dexamethasone. Therefore, the inability to adapt to exercise training and regulate the production of cortisol and IL-6 may lead to the associated psychological and behavioural disturbances of ED. Thus, although exercise may alleviate negative affect, it is, in fact, the exercise that is an underlying cause of ongoing behavioural disturbances in ED, which is mediated by IL-6 pathways. Expectancy beliefs regarding the effects of exercise on the affective state of an individual may also play a central role in re-enforcing the ED cycle; this is apparent in models of cognitive and social learning.^[68]

The IL-6 response to stressors may, in part, be mediated by genetic factors given that there is now evidence to show an association between IL-6 genotype and baseline C-reactive protein.^[69] However, genetic factors did not account for exercise training-induced changes in C-reactive protein in a recent study.^[70]

6. Future Research and Potential Confounds

There is an incredible lack of research examining the hypothesis that biological markers may predict symptoms of exercise withdrawal^[28] and play a role in ED. Future studies should examine whether cytokine and neuroendocrine responses to stressors, and deprivation from exercise are associated with psychological and behavioural disturbances in individuals meeting criteria for ED. Recent developments in methods to reliably assess these biological markers from blood and saliva samples (e.g. using enzyme-linked immunoassay) should improve the feasibility of such studies to be undertaken in exercise laboratories. One of the most challenging aspects of this research is to accurately identify ED using universally agreed measures and diagnostic criteria. Another difficult aspect of this research is selecting suitable control groups, which have previously consisted of non-exercisers, non-ED exercisers or individuals with (or without) eating disorders.

A potential confound in the conceptual model is the amount of psychosocial stress an individual is exposed to and their susceptibility to the effects of stress on psychological functioning. For example, it may be that individuals affected by ED permanently seek exercise as a relief from negative affect because they are exposed to a greater amount of stress in their lives or are less able to cope with stress. This results in greater behavioural disturbances. Indeed, psychosocial factors may also contribute to elevated levels of IL-6 and magnify IL-6 responses to standard stressors.^[63] These psychosocial factors should be explored further in relation to ED.

Another potential confound is the mental state of individuals upon initiation of an exercise programme. Morgan^[71] noted that exercise would not reduce depression in those who do not exhibit significant symptoms of depression. This implies that individuals who exercise in order to relieve negative

affect may have psychological and behavioural disturbances prior to initiating an exercise programme. Thus, longitudinal data on the mental state of individuals who initiate exercise and subsequently become ED are required to explore this phenomenon further.

7. Conclusions

The cytokine IL-6 is associated with behavioural and psychological disturbances, and is also produced during exercise. We have proposed a conceptual model in which a trigger for the over production of IL-6 forms the basis for the development of ED. A state of chronic IL-6 over production, exacerbated by continued bouts of exercise in order to gain transient relief from cytokine-induced symptoms, may be implicated as an underlying mechanism of ED. The present model also incorporates previously proposed concepts that include the anorexia analogue and sympathetic arousal hypotheses. This should be a focus of future investigation with the overall goal to develop treatment strategies for ED.

Acknowledgements

No sources of funding were used to assist in the preparation of this article. The authors have no conflicts of interest that are directly relevant to the content of this article.

References

- Chapman CL, DeCastro JM. Running addiction: measurement and associated psychological characteristics. *J Sports Med Phys Fitness* 1990; 30: 283-90
- Hausenblas HA, Symons Downs D. Exercise dependence: a systematic review. *Psych Sports Exerc* 2002; 3: 89-123
- Uchino BN. Social support and health: a review of physiological processes potentially underlying links to disease outcomes. *J Behav Med* 2006 Aug; 29 (4): 377-87
- Veale D. Exercise addiction. In Annett J, Cripps B, Steinberg H, editors. *Motivation for participation in sport and exercise*. Leicester: British Psychological Society, 1995: 1-5
- Bamber DJ, Cockerill IM, Rodgers S, et al. Diagnostic criteria for exercise dependence in women. *Br J Sports Med* 2003; 37: 393-400
- Symons Downs D, Hausenblas HA, Nigg CR. Factorial validity and psychometric examination of the exercise dependence scale: revised. *Meas Phys Ed Exerc Sci* 2004; 8: 183-201
- Griffiths MD, Szabo A, Terry A. The exercise addiction inventory: a quick and easy screening tool for health practitioners. *Br J Sports Med* 2005; 39 (6): e30
- Zmijewski CF, Howard MO. Exercise dependence and attitudes toward eating among young adults. *Eat Behav* 2003; 4: 181-95
- Anderson SJ, Basson CJ, Geils C. Personality style and mood states associated with a negative addiction to running. *Sports Med* 1997; 27: 6-11
- Slay HA, Hayaki J, Napolitano MA, et al. Motivations for running and eating attitudes in obligatory versus non-obligatory runners. *Int J Eat Disord* 1998; 23: 267-75
- Thornton EW, Scott SE. Motivation in the committed runner: correlations between self report scales and behaviour. *Health Promot Int* 1995; 10: 177-84
- Pasman L, Thompson JK. Body image and eating disturbances in obligatory runners, obligatory weightlifters, and sedentary individuals. *Int J Eat Disord* 1988; 7: 759-69
- Ogden J, Veale D, Summers Z. The development and validation of the exercise dependence questionnaire. *Addiction Res* 1997; 5: 343-56
- Loumidis KS, Wells A. Assessment of beliefs in excessive exercise: the development and preliminary validation of the exercise beliefs questionnaire. *Pers Individ Dif* 1998; 25: 553-67
- Szabo A. Physical activity as a source of psychological dysfunction. In Biddle S, Fox K, Boutcher SH, editors. *Physical activity and psychological well-being*. London: Routledge, 2000: 130-54
- Tomkins S. A modified model of smoking behavior. In Borgatta EF, Evans RR, editors. *Smoking, health and behavior*. Chicago (IO): Aldine, 1968: 165-86
- Csikszentmihalyi M. *Flow*. New York: Harper and Row, 1990
- Johnsguard K. The motivation of the long distance runner. *J Sports Med* 1985; 25: 135-9
- Anshel MH. A psycho-behavioral analysis of addicted versus non-addicted male and female exercisers. *J Sport Behav* 1991; 14: 145-58
- Rosa DA, de Mello MT, Negrao AB, et al. Mood changes after maximal exercise testing in subjects with symptoms of exercise dependence. *Percept Mot Skills* 2004; 99: 341-53
- Hamer M, Karageorghis CI, Vlachopoulos SP. Motives for exercise participation as predictors of exercise dependence among endurance athletes. *J Sports Med Phys Fitness* 2002; 42: 233-8
- Yates A, Leehey K, Shisslak CM. Running: an analogue of anorexia? *New Engl J Med* 1983; 308: 251-5
- Mondin GW, Morgan WP, Piering PN, et al. Psychological consequences of exercise deprivation in habitual exercisers. *Med Sci Sports Exerc* 1996; 28: 1199-203
- Morgan WP. Negative addiction in runners. *Phys Sports Med* 1979; 7: 57-70
- Morris M, Steinburg H, Sykes EA, et al. Effects of temporary withdrawal from regular running. *J Psychosom Res* 1990; 34: 493-500
- Sachs ML, Pargman D. Running addiction: a depth interview examination. *J Sports Behav* 1979; 2: 143-55
- Berlin AA, Kop WJ, Deuster PA. Depressive mood symptoms and fatigue after exercise withdrawal: the potential role of decreased fitness. *Psychosom Med* 2006; 68: 224-30
- Glass JM, Lyden AK, Petzke F, et al. The effect of brief exercise cessation on pain, fatigue, and mood symptom development in healthy, fit individuals. *J Psychosom Res* 2004; 57: 391-8
- Thaxton L. Physiological and psychological effects of short-term exercise addiction on habitual runners. *J Sports Psych* 1982; 4: 73-80
- Katz JL. Long distance running, anorexia nervosa and bulimia: a report of two cases. *Compr Psychiatry* 1986; 27: 74-8
- Roberts WO, Elliot D. Malnutrition in a compulsive runner: a case conference. *Med Sci Sports Exerc* 1991; 23: 513-6
- Coen SP, Ogles BM. Psychological characteristics of the obligatory runner: a critical examination of the anorexia analogue hypothesis. *J Sport Exerc Psychol* 1993; 15: 338-54
- Davis C, Kennedy SH, Ralevski E, et al. Obsessive compulsiveness and physical activity in anorexia nervosa and high-level exercising. *J Psychosom Res* 1995; 39: 967-76

34. Duclos M, Bouchet M, Vettier A, et al. Genetic differences in hypothalamic-pituitary-adrenal axis activity and food restriction-induced hyperactivity in three inbred strains of rats. *J Neuroendocrinol* 2005; 17: 740-52
35. Blumenthal JA, O'Toole LC, Chang JL. Is running an analogue of anorexia nervosa? An empirical study of obligatory running and anorexia nervosa. *JAMA* 1984; 252: 520-3
36. Wheeler GD, Wall SR, Belcastro AN, et al. Are anorexic tendencies present in habitual runners? *Br J Sports Med* 1986; 20: 77-81
37. Thompson JK, Blanton P. Energy conservation and exercise dependence: a sympathetic arousal hypothesis. *Med Sci Sports Exerc* 1987; 19: 91-9 & 767-70
38. Koivisto VR, Hender R, Nadel E. Influence of physical training on the fuel hormone response to prolonged low-intensity exercise. *Metabolism* 1982; 31: 192-7
39. Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacol* 2001; 24: 97-129
40. Janal MN, Colt EW, Clark WC, et al. Pain sensitivity, mood and plasma endocrine levels in man following long distance running: effects of naloxone. *Pain* 1984; 19: 13-25
41. Smith MA, Yancey DL. Sensitivity to the effects of opioids in rats with free access to exercise wheels: μ -opioid tolerance and physical dependence. *Psychopharmacol* 2003; 168: 426-34
42. Pierce EF, Eastman NW, Tripathi HL, et al. β -Endorphin response to endurance exercise: relationship to exercise dependence. *Percept Mot Skills* 1993; 77: 767-70
43. Hayley S, Merali Z, Anisman H. Stress and cytokine-elicited neuroendocrine and neurotransmitter sensitization: implications for depressive illness. *Stress* 2003; 6: 19-32
44. Maier SF, Watkins LR. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychol Rev* 1998; 105: 83-107
45. Tracey KJ. The inflammatory reflex. *Nature* 2002; 420: 853-9
46. Anisman H, Merali Z. Cytokines, stress and depressive illness: brain-immune interactions. *Ann Med* 2003; 35: 2-11
47. Spath-Schwalbe E, Hansen K, Schmidt F, et al. Acute effects of recombinant human interleukin-6 on endocrine and central nervous sleep functions in healthy men. *J Clin Endocrinol Metab* 1998; 83: 1573-9
48. Reichenberg A, Yirmiya R, Schuld A, et al. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psych* 2001; 58: 445-52
49. Cohen S, Doyle WJ, Skoner DP. Psychological stress, cytokine production, and severity of upper respiratory illness. *Psychosom Med* 1999; 61: 175-80
50. Tilg H, Dinarello CA, Mier JW. IL-6 and APPs: anti-inflammatory and immunosuppressive mediators. *Immunol Today* 1997; 18: 428-32
51. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol* 2005; 98: 1154-62
52. Steensberg A, Fischer CP, Keller C, et al. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *Am J Physiol Endocrinol Metab* 2003; 285: E433-7
53. Abramson JL, Vaccarino V. Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. *Arch Intern Med* 2002; 162: 1286-92
54. Tomaszewski M, Charchar FJ, Crawford L, et al. Serum C-reactive protein and lipids in ultra-marathon runners. *Am J Cardiol* 2004; 94: 125-6
55. Mattusch F, Dufaux B, Heine O, et al. Reduction of the plasma concentration of C-reactive protein following nine months of endurance training. *Int J Sports Med* 2000; 21: 21-4
56. Tsukui S, Kanda T, Nara M, et al. Moderate-intensity regular exercise decreases serum tumor necrosis factor- α and HbA1c levels in healthy women. *Int J Obes Relat Metab Disord* 2000; 24: 1207-11
57. Robson PJ. Elucidating the unexplained underperformance syndrome in endurance athletes: the interleukin-6 hypothesis. *Sports Med* 2003; 33: 771-81
58. Armstrong LE, VanHeest JL. The unknown mechanism of the overtraining syndrome: clues from depression and psychoneuroimmunology. *Sports Med* 2002; 32: 185-209
59. Smith LL. Cytokine hypothesis of overtraining: a physiological adaptation to excessive stress? *Med Sci Sports Exerc* 2000; 32: 317-31
60. Budgett R, Newsholme E, Lehmann M, et al. Redefining the overtraining syndrome as the unexplained underperformance syndrome. *Br J Sports Med* 2000; 34: 67-8
61. Biddle SJH, Fox KR, Boutcher SH, et al. The way forward for physical activity and the promotion of psychological well-being. In: Biddle SJH, Fox K, Boutcher SH, editors. *Physical activity and psychological well-being*. London: Routledge, 2000: 154-69
62. Suzuki K, Nakaji S, Yamada M, et al. Systemic inflammatory response to exhaustive exercise: cytokine kinetics. *Exerc Immunol Rev* 2002; 8: 6-48
63. Steptoe A, Willemsen G, Owen N, et al. Acute mental stress elicits delayed increases in circulating inflammatory cytokine levels. *Clin Sci* 2001; 101: 185-92
64. Keller C, Steensberg A, Pilegaard H, et al. Transcriptional activation of the IL-6 gene in human contracting skeletal muscle: influence of muscle glycogen content. *FASEB J* 2001; 15: 2748-50
65. Steensberg A, Febbraio MA, Osada T, et al. Interleukin-6 production in contracting human skeletal muscle is influenced by pre-exercise muscle glycogen content. *J Physiol* 2001; 537: 633-9
66. Kiefer F, Wiedemann K. Neuroendocrine pathways of addictive behaviour. *Addict Biol* 2004; 9: 205-12
67. Duclos M, Gouarne C, Bonnemaïson D. Acute and chronic effects of exercise on tissue sensitivity to glucocorticoids. *J Appl Physiol* 2003; 94: 869-75
68. Brandon TH, Herzog TA, Irvin JE, et al. Cognitive and social learning models of drug dependence: implications for the assessment of tobacco dependence in adolescents. *Addiction* 2004; 99: 51-77
69. Vickers MA, Green FR, Terry C, et al. Genotype at a promoter polymorphism of the interleukin-6 gene is associated with baseline levels of plasma C-reactive protein. *Cardiovasc Res* 2002; 53: 1029-34
70. Obisesan TO, Leeuwenburgh C, Phillips T, et al. C-reactive protein genotypes affect baseline, but not exercise training-induced changes, in C-reactive protein levels. *Arterioscler Thromb Vasc Biol* 2004; 24: 1874-9
71. Morgan WP. Physical activity, fitness, and depression. In: Bouchard C, Shepard RJ, Stephens T, editors. *Physical activity, fitness, and health*. Champaign (IL): Human Kinetics, 1994: 851-67

Correspondence: Dr Mark Hamer, Department of Epidemiology and Public Health, Psychobiology Group, University College London, 1-19 Torrington Place, London, WC1E 6BT, UK.

E-mail: m.hamer@ucl.ac.uk

Copyright of *Sports Medicine* is the property of ADIS International Limited and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.