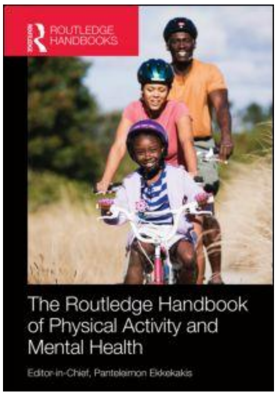

Routledge Handbook of Physical Activity and Mental Health

Panteleimon Ekkekakis, Dane B. Cook, Lynette L. Craft, S. Nicole Culos-Reed, Panteleimon Ekkekakis, Jennifer L. Etnier, Mark Hamer, Kathleen A. Martin Ginis, Justy Reed, Jasper A.J. Smits, Michael Ussher

Physical Activity and Feelings of Fatigue

Publication details
https://www.routledgehandbooks.com/doi/10.4324/9780203132678.ch29
Timothy W. Puetz, Matthew P. Herring
Published online on: 23 Apr 2013

29
PHYSICAL ACTIVITY AND FEELINGS OF FATIGUE

Timothy W. Puetz and Matthew P. Herring

Early investigators of fatigue despaired at the development of an acceptable definition and measure of fatigue and ultimately declared "that the term fatigue be absolutely banished from precise scientific discussion and consequently that attempts to obtain a fatigue test be abandoned" (Muscio, 1921, p. 45). In more recent years, fatigue has been acknowledged as a pervasive public health problem, well deserving of serious scientific query, in part because feelings of fatigue have a significant negative impact on quality of life and work productivity (Ricci, Chee, Lorandeau, & Berger, 2007). A better understanding of feelings of fatigue ultimately could contribute to enhancing quality of life as well as improving the diagnosis and treatment of a variety of fatigue-related health problems.

Physical activity is a healthful behavior that has promise for combating feelings of fatigue (O'Connor & Puetz, 2005; Puetz, 2006; Puetz, O'Connor, & Dishman, 2006a). However, there is surprisingly little empirical research on the relation of exercise to feelings of fatigue despite the routine anecdotal reports of reduced fatigue after periods of physical activity. This chapter provides a foundation for understanding the relationship between physical activity and feelings of fatigue by (a) discussing the prevalence and social impact of fatigue, (b) providing a brief history of physical activity and feelings of fatigue, (c) outlining the conceptualization, operationalization, and measurement of physical activity and fatigue, (d) examining the quality of the evidence investigating the impact of physical activity on feelings of fatigue, (e) addressing the impact of physical activity on feelings of fatigue in patient populations, and (f) examining future research needs in this area of study. This information will provide a background for understanding and rationale for examining the relationship between physical activity and feelings of fatigue.

Prevalence and social impact of fatigue

Approximately 20 percent of adults worldwide report persistent fatigue (Wessely, Hotopf, & Sharpe, 1998). This statistic is slightly higher in the United States where fatigue is reported by 24 percent of the population, with women having 1.5 times the risk of males for reporting fatigue (Chen, 1986; Kroenke & Price, 1993). The lifetime prevalence of unexplained fatigue lasting 2 weeks or more is estimated at about 14 percent (Addington, Gallo, Ford, & Eaton, 2001), and approximately 9 percent of adults at any point in time are experiencing fatigue of more than a 6-month duration (Darbishir, Ridsdale, & Seed, 2003). Among individuals experiencing unexplained fatigue during their lifetime, approximately 20 percent will likely have persistent fatigue over many years (Addington et al., 2001). Adolescents have similar trends in feelings of fatigue in that the 6-month incidence of fatigue is about 30 percent in 11- to 15-year-olds (Rimes et al., 2007).

Considering the prevalence of fatigue in the general population, it is not surprising that fatigue is a frequent complaint in primary (i.e., medical care provided by a physician who is the patient's first contact within the health care system) and secondary care (i.e., medical care provided by a specialist upon referral by a primary care physician), with prevalence rates ranging from 10 to 40 percent depending on the definition, duration, and setting (Wessely, Chalder, Hirsch, Wallace, & Wright, 1997). Each year fatigue is the primary reason for about 7 percent of all physician visits, resulting in approximately seven million visits annually (Ruffin & Cohen, 1994). However, only about 8 to16 percent of people who experience fatigue will actually consult their primary physician and only 32 percent of fatigued individuals in primary care will show improvement by 1 year (de Rijk, Schreurs, & Bensing, 2000; Joyce, Hotopt, & Wessely, 1997). This prognosis is worse in secondary care, where fewer than 10 percent return to pre-morbidity functioning (Joyce et al., 1997). Lost productivity in the United States workforce due to fatigue has amounted to a loss of approximately US$136 billion per year. This is an excess of US$101 billion in health-related lost productivity time when workers with fatigue are compared with workers without fatigue (Ricci et al., 2007).

A brief history of physical activity and feelings of fatigue

Based on a steadily growing body of literature during the past 10 to 15 years, the relationship between physical activity and feelings of fatigue has emerged as a serious area of research. The ideas underlying this area of research, however, have been around much longer. The physiology of fatigue, as opposed to the psychology of fatigue, was well studied during the nineteenth century. Italian physiologist Angelo Mosso (1846–1910) began to shift the focus of research from fatigue of the body to fatigue of the mind, which culminated in his book *La Fatica* (1891), the first text to recognize feelings of fatigue in a psychological context. Mosso, generally recognized as the father of fatigue research, acknowledged the multidimensional nature of the construct and integrated physiological, psychological, and psychosocial concepts into the study of fatigue (Di Giulio, Daniele, & Tipton, 2006). This biopsychosocial conceptualization would significantly impact multidisciplinary fatigue research on an international scale for years to come.

Early physicians recognized that fatigue could manifest as an acute or chronic generalized state. These feelings of fatigue were described as a reduced capacity to perform either mental or physical work and such disability was associated with the brain and nervous system (Poore, 1875). Influenced by the work of Mosso, clinicians began to make a sharp distinction between objective and subjective fatigue (Dearborn, 1902). The concept of subjective fatigue raised measurement issues related to the indirect measure of central nervous system activity. Despite these diagnostic limitations, treatment prescriptions for such feelings of fatigue became rest, proper diet, and light to moderate exercise (Cowles, 1893; MacDougall, 1899; Waterman, 1909).

By the mid-1940s, many physicians had adopted the holistic approach to fatigue in which both the physiological and psychological correlates of disease were considered. For example, Bartley and Chute (1947) recommended chronic fatigue research should examine the relative importance of multiple physical and psychological contributions to feelings of fatigue. These recommendations were supported by clinical reports in which fatigue was identified as being a chief complaint in most disease states such that physical and psychological disorders accounted for 20 and 80 percent of fatigue cases, respectively (Allen, 1944; Muncie, 1941). Such clinical observations in chronic disease populations blurred the line between physical and psychological etiologies, suggesting that several biopsychosocial factors contributed to feelings of fatigue. As the conceptualization of feelings of fatigue continued to evolve, the clinical management of fatigue remained a continuous dose of light to moderate exercise (Allen, 1945).

Today, feelings of fatigue remain a serious symptom that can severely impact quality of life in the general population and patient groups. Contemporary theories on physical activity and feelings of fatigue have changed little over the last century. Physical activity is still positively associated with decreased physical and mental fatigue and the mechanism for these psychological effects is likely an interaction among biopsychosocial variables (O'Connor & Puetz, 2005; Puetz, 2006; Puetz et al. 2006a). Unfortunately, the consistent recommendation of physical activity in the clinical treatment of fatigue has done little to move the research area of physical activity and feelings of fatigue forward. Against this historical background, scientific interest in the effects of physical activity on feelings of fatigue remains in its infancy.

Conceptualization, operationalization, and measurement of physical activity and fatigue

The relationship between physical activity and feelings of fatigue remains poorly understood partly because fatigue and physical activity are difficult to define. The following section outlines the conceptualization and operationalization of both physical activity and fatigue and then discusses measurement issues related to this area of research.

Definition: what is physical activity?

The field of exercise science has distinctly conceptualized physical activity. Physical activity refers to any skeletal muscle activation resulting in energy expenditure beyond that of a resting level (Caspersen, Powell, & Christenson, 1985). This is operationalized through kilocalories (kcal) per unit of time. The term exercise is often used synonymously with physical activity; however, exercise is a subcategory of physical activity. Exercise refers to planned, structured, repetitive bodily movements conducted for the purpose of improving or maintaining one or more components of health or physical fitness (Caspersen et al., 1985). Exercise can be acute or chronic. Acute exercise refers to a single, relatively short bout of exercise. Chronic exercise refers to cumulative, acute bouts of exercise carried out repeatedly over time. Chronic exercise is often quantified in terms of frequency, intensity, duration, and mode (Buckworth & Dishman, 2002).

Definition: what is fatigue?

Unlike physical activity, an accepted and sufficiently accurate definition of fatigue remains elusive. Feelings of fatigue have been described as an aversive, non-specific, subjective experience that cannot currently be measured by objective methods (Ream & Richardson, 1996). However, a number of conceptualizations of fatigue have developed along dualistic (i.e., bidirectional) lines, including acute and chronic fatigue, physiological and psychological fatigue, and central and peripheral fatigue. While dualistic approaches have proven to be popular, such definitions fail to capture the multidimensional aspects of fatigue (Shen, Barbera, & Shapiro, 2006). With no known biological markers and numerous proposed causes, the operationalization of fatigue through concrete indicators has failed to reflect the empirical reality of the construct.

Feelings of fatigue likely are multidimensional with emotional, behavioral, and cognitive components. However, for the purposes of this discussion, the focus is on fatigue conceptualized as a mood state. A mood is a transient feeling people report experiencing ranging in duration from minutes to weeks and ultimately has an influence on thoughts and behaviors (Buckworth & Dishman, 2002). The mood of fatigue specifically refers to feelings of having a reduced capacity to complete mental or physical activities (O'Connor, 2004). This reduced capacity to complete mental or physical activities is distinct from, but also often accompanies, other related moods, including depression, for example.

Some contend biological systems that regulate mood evolved through natural selection to facilitate the transfer of genes (Watson, 2000). Feelings of fatigue likely evolved to promote rest, thereby enhancing recovery from injury or illness. From this evolutionary perspective, fatigue mood states have been vital to the propagation and survival of the human species.

Measuring physical activity and feelings of fatigue

Measurement is a two-fold issue in research examining the relationship between physical activity and feelings of fatigue. There is no single standard for measuring physical activity (Montoye, Kemper, Saris, & Washburn, 1996; Paffenbarger, Blair, Lee, & Hyde, 1993) or feelings of fatigue (Aaronson et al., 1999; O'Connor, 2004). Thus, both the exposure and outcome variables must be assessed with imperfect measures. Establishing the validity of physical activity instruments has been a recognized, yet still unresolved, problem in exercise science research (LaPorte, Montoye, & Caspersen, 1985). However, the problem of establishing the validity of fatigue measures has only recently gained greater attention in the areas of medicine and mental health (Whitehead, 2009).

It is important to accurately measure physical activity because such measurement can help quantify the physiological responses that may directly or indirectly influence psychological variables (Buckworth & Dishman, 2002). There are at least 30 methods for measuring physical activity, including direct and indirect calorimetry, physiologic markers (e.g., doubly labeled water), monitors (e.g., accelerometers), surveys (e.g., exercise recall), and direct observation. The selection of methods depends on the target population and level of sensitivity and specificity necessary to answer the research question (Casperson, 1989). Thus, it is important to address the difficulty of comparing results across studies with non-uniform assessment methods when discussing physical activity.

Fatigue is a universal symptom not only associated with most acute and chronic illnesses, but also with normal, healthy function and everyday life. Over 30 fatigue scales have proliferated in the clinical and scientific community and no two scales have operationalized the construct of fatigue exactly the same (Dittner, Wessely, & Brown, 2004; O'Connor, 2004). While some measure phenomenology, fatigue severity, or impact, many assess a mixture of all of these. There is no consensus about whether fatigue is best conceptualized as a symptom, a mood, an aspect of quality of life, or in some other way (O'Connor, 2004; Ream & Richardson, 1996). The choice of scale ultimately depends on the conceptualization of fatigue, the clinical or research application, and the psychometric evidence to support interpretation of scores. Thus, fatigue research has been inundated with measures ranging widely in their ability to offer valid interpretation of the construct.

Eidelman (1979) stated, "The absence of an overall definition of fatigue preempts any scientific basis for measuring the condition, because logically that which cannot be defined cannot be measured, and is not understood" (p. 340). Although a rather bold statement, it is also quite honest. In an area of study in which exposure and outcome variables must be assessed with imperfect measures, one must be cognizant of the limitations of the research.

Research on physical activity and feelings of fatigue

The body of research on physical activity and feelings of fatigue is not as extensive as that addressing the relationship between physical activity and other psychological variables such as anxiety, depression, or quality of life. Although there are some limitations in the research related to study design and instrumentation, the overall evidence for the effects of physical activity on feelings of fatigue generally is both positive and consistent (Puetz, 2006; Puetz et al., 2006a). Epidemiological and experimental research that has addressed the relationship between physical activity and feelings of fatigue is described in the following sections.

Epidemiological evidence

Epidemiological evidence can help researchers examine the distribution and determinants of physical activity in the general population and how this health-related behavior is associated with fatigue outcomes. The application of such knowledge is vital in the prevention and control of disease and the promotion of health.

A meta-analysis was conducted to synthesize the available evidence of the effect of physical activity on feelings of energy and fatigue in the population. Twelve population-based studies examining the association between physical activity and feelings of fatigue, published between 1945 and 2005, were identified by searches of Current Contents, Google Scholar, PsycInfo, Web of Science, and PubMed databases using the following search terms: energy, fatigue, quality of life, SF-36, and vitality, combined with exercise, physical activity, epidemiology, population study, prevalence, or incidence (Puetz, 2006). Odds ratios (OR) and relative risks (RR) were calculated from studies such that scores were interpreted relative to a sedentary sample and increases in feelings of energy and decreases in feelings of fatigue resulted in positive effect sizes (ES).

Results showed that people who are physically active in their leisure time have about a 40 percent reduced risk of experiencing fatigue compared with sedentary individuals (Puetz, 2006). Figure 29.1 illustrates the ORs and 95 percent confidence intervals (lower limit, upper limit) for the seven cross-sectional studies, the RRs and 95 percent confidence intervals (lower limit, upper limit) for the five longitudinal studies, and the overall 40 percent lower risk of fatigue in physically active persons. All studies found a positive relationship between physical activity and reduced feelings of fatigue; however, these effects were moderated by the study design and fatigue measure. The magnitude of the effect was attenuated in the stronger design of longitudinal studies compared to cross-sectional studies and increased in studies that used the well-validated Medical Outcome Study Short Form 36 Vitality Scale (SF-36; Ware, 2000) compared to studies that used other less-accepted energy and fatigue measures. These results highlight the design and measurement issues that continue to limit physical activity and fatigue research.

Because epidemiological comparisons cannot establish direction of causality, such evidence should be interpreted with caution. However, the strength of epidemiological evidence can be evaluated with standard criteria (i.e., strength of association, temporal sequence, consistency, dose response, biological plausibility) in order to judge whether the observed association suggests causality in the absence of adequate experimental evidence (Hill, 1965). There was agreement among the aforementioned studies suggesting a strong, consistent, temporally appropriate, dose-response relationship between physical activity and feelings of fatigue. However, there was a lack of compelling evidence to confirm any plausible biological mechanisms to explain the apparent protective effect of physical activity against feelings of fatigue. This paucity of evidence regarding biological plausibility is another issue limiting physical activity and fatigue research.

Not all criteria must be met in order to establish direction of causality in epidemiological research. A longitudinal study by Lee and Russell (2003) of nearly 6,500 older women (aged

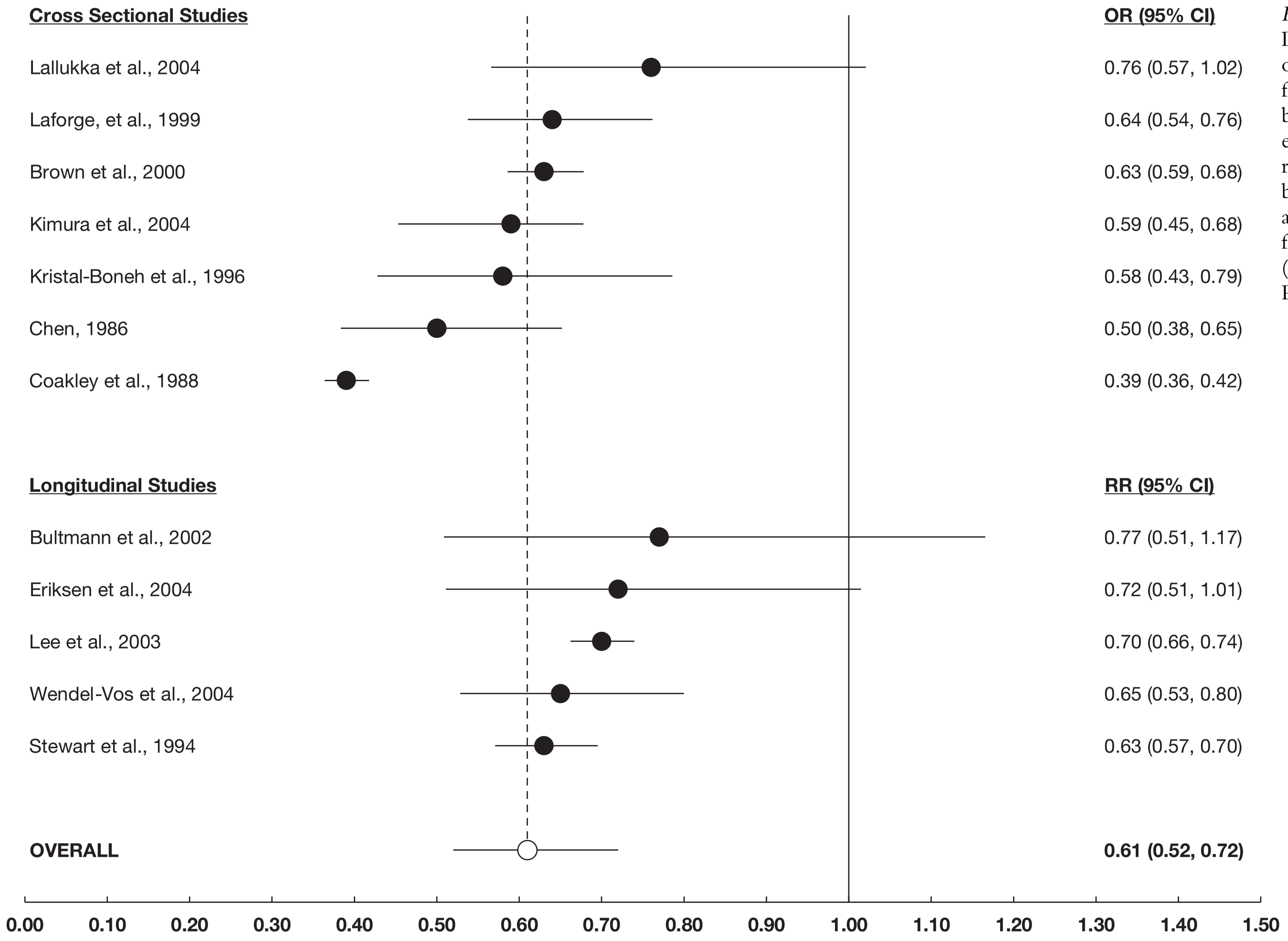

Figure 29.1 Distribution of the odds and risk ratios for population-based studies examining the relationship between physical activity and feelings of fatigue (adapted from Puetz, 2006).

70–75 years) particularly bolstered the argument for suggesting causality by examining the alterability of feelings of fatigue with the adoption or cessation of exercise. Women who reported exercise cessation during a 3-year observation period had greater decreases in SF-36 vitality scores than those who remained sedentary, those who remained physically active, or those who reported exercise adoption during that same period. The greatest increase in SF-36 vitality scores occurred among those who reported exercise adoption during the 3-year period. These changes were similar to those who remained physically active. These results not only provide evidence of temporal sequence, but also that these effects are alterable with increases or decreases in physical activity. Such epidemiological evidence is sufficiently strong to justify better-controlled prospective cohort studies and randomized controlled trials.

Experimental evidence

While experimental designs are often considered the most rigorous of all research designs, this is only the case if such a design is implemented well. Unfortunately, poor measurement and study design have limited experimental research in the area of physical activity and fatigue. This is often due to knowledge gaps as psychologists with limited background in exercise science, or physiologists with limited background in psychology, attempt to conduct physical activity and fatigue research (Buckworth & Dishman, 2002). Such issues regarding research design have been identified and discussed in a quantitative review (meta-analysis) of randomized controlled trials.

A meta-analysis of 70 randomized controlled trials examining the effects of chronic exercise on feelings of fatigue showed that exercise programs reduced fatigue in both healthy individuals and patient groups (Puetz et al., 2006a). Articles published from 1945 to November 2004 were located from searches of PsycInfo, PubMed, and Web of Science databases using the following keywords: energy, exercise, fatigue, mood, physical activity, Profile of Mood States (POMS), quality of life, resistance training, SF-36, and vitality. Articles included randomized allocation to either a chronic exercise condition or a non-exercise comparison condition and an energy or fatigue outcome measure assessed before and following the intervention. Effect sizes (ES) were computed by subtracting the mean change in fatigue for a non-exercise control group from the mean change in fatigue for an exercise group and dividing the difference by the pooled standard deviation of baseline scores (Hedges & Olkin, 1985).

The magnitude of the overall mean ES and 95 percent confidence interval (lower limit, upper limit) was moderate at 0.37 (0.29, 0.45), indicating that, on average, participants in exercise conditions reported approximately four-tenths of a standard deviation (*SD*) greater reduction in fatigue compared to participants in control conditions. The overall effect, however, was heterogeneous and moderated by a variety of study design issues. The effect varied according to the presence or absence of a usual care or placebo control (e.g., stretching or health education) and whether exercise training was completed alone or in combination with additional therapy. Investigations that used a placebo control and examined chronic exercise alone found no effect of chronic exercise on feelings of fatigue. This finding suggests that certain placebo controls may act as treatments in physical activity and fatigue studies, especially in populations of older adults and individuals with psychological distress. This could be attributed to the relative intensity of exercise in older adults who participate in stretching control interventions or placebo effects in individuals with psychological distress. Nonetheless, these results highlight the need for investigators to pursue more rigorous design methodology in physical activity and fatigue research.

Few exercise-training studies have been conducted with healthy adults characterized by feelings of fatigue (O'Connor & Puetz, 2005). Despite the lack of research specifically designed to examine changes in feelings of fatigue after exercise training in healthy, but fatigued individuals, available randomized controlled trials have shown reduced feelings of fatigue (Puetz, 2006). These experimental studies support the epidemiological evidence, suggesting a positive association between physical activity and reductions in fatigue. However, research design issues limit the strength of this evidence and preclude confirmation of the cause–effect nature of this relationship. These issues include confounded treatments in which exercise is combined with other treatments (e.g., behavior modification therapy), failure to match groups based on pre-treatment fatigue levels, inadequate description of the exercise stimulus, and failure to include no-treatment controls or placebo controls in the research design.

Such weaknesses in research design have made the effect of chronic exercise on feelings of fatigue difficult to interpret in terms of examining healthy, but fatigued, adult samples. Puetz, Flowers, and O'Connor (2008) addressed previous research limitations in a randomized controlled trial examining the effects of 6 weeks of exercise training on feelings of energy and fatigue in sedentary, healthy young adults reporting persistent fatigue. Thirty-six healthy young adults (mean age 23 years) who reported persistent feelings of fatigue were randomly assigned to a moderate-intensity, low-intensity, or no-treatment control group. Exercise conditions consisted of individually supervised cycling, 3 days per week for 30 minutes at the prescribed exercise intensity. The control condition consisted of sitting quietly on a cycle ergometer for the same frequency and duration as the exercise conditions. Results of the 6-week intervention showed significant benefits in energy and fatigue for both exercise conditions compared to the control condition. However, changes in feelings of fatigue were dependent on exercise intensity, whereas the effect on feelings of energy was similar for both the low-intensity and moderate-intensity conditions. More favorable outcomes for fatigue were seen in the low-intensity exercise group. It is noteworthy that changes in both energy and fatigue were unrelated to changes in aerobic fitness. Physical activity appears to be effective in healthy, sedentary populations. However, what is its efficacy in patient groups with chronic disease?

Physical activity and feelings of fatigue in patient populations

Physical activity may be especially beneficial in reducing feelings of fatigue in certain patient groups with chronic disease (Puetz, 2006). Three patient groups that have received significant examination of the effects of physical activity and feelings of fatigue in the scientific literature include fibromyalgia (Hauser, Bernardy, Arnold, Offenbächer, & Schiltenwolf, 2009a; Hauser et al., 2010), cardiovascular disease (Puetz, Beasman, & O'Connor, 2006b), and cancer patients (Brown et al., 2011; Cramp & Daniel, 2008; Velthuis, Agasi-Idenburg, Aufdemkampe, & Wittink, 2010). Research that has addressed the relationship between physical activity and feelings of fatigue is briefly described in the next section for each of these patient populations.

Fibromyalgia

Fibromyalgia is a disorder characterized by widespread musculoskeletal pain accompanied by fatigue, and sleep, memory, and mood dysfunction (Wolfe et al., 2010). While there is no cure for fibromyalgia, medications, cognitive behavior therapy, and exercise have consistently been recommended as a means to control symptoms (Clauw, 2009). A meta-analysis of 28 randomized controlled trials examining the effect of aerobic exercise treatment on feelings of fatigue in patients with fibromyalgia showed that aerobic exercise significantly reduced feelings of fatigue in this patient population (Hauser et al., 2010). The mean ES and 95 percent confidence interval (lower limit, upper limit) was –0.22 (–0.38, –0.05), supporting the positive effects of exercise on feelings of fatigue. The effect is slightly larger than the effect of cognitive behavior therapy (–0.09;

Bernardy, Fuber, Kollner, & Hauser, 2010) and antidepressants (–0.13; Hauser, Bernardy, Uceyler, & Sommer, 2009b) on feelings of the fatigue. This raises the question of whether a multidisciplinary therapy that combines exercise, cognitive behavioral therapy, and medical management is superior to exercise treatment alone.

The potential additive effect of a second treatment to an exercise intervention was addressed in another meta-analysis (Hauser et al., 2009a) that examined the magnitude of multicomponent treatments on feelings of fatigue in patients with fibromyalgia. Multicomponent treatments were defined as an intervention in which at least one educational or other psychological therapy was combined with exercise treatment. The mean effect for the nine randomized controlled trials included in the analysis was –0.85 (–1.50, –0.20), indicating an average of nearly nine-tenths of a *SD* greater reduction in fatigue among participants in exercise groups compared to participants in control groups. The cumulative meta-analytic evidence suggests that combination therapies incorporating exercise and behavioral therapies may provide an additive effect in the reduction of fatigue in patients with fibromyalgia. These results should be interpreted with caution because medication was not controlled in most studies. Therefore, there remains some uncertainty whether the effects reported are due only to the multicomponent treatment applied or to concomitant medications.

Lera et al. (2009) directly addressed the additional efficacy of cognitive behavioral therapy in multicomponent treatments in a randomized controlled trial analyzing the effect of two multicomponent treatments on functional capability and symptom severity in patients with fibromyalgia. Eighty-three women (mean age 50 years) with fibromyalgia were randomly assigned to a 15-week multicomponent treatment or a multicomponent treatment combined with cognitive behavioral therapy. The multicomponent treatment included medical management, exercise training, and education classes. The exercise training consisted of 40 minutes of stretching and light aerobic exercise once a week for 10 of the 15 therapy sessions. The cognitive behavioral therapy focused on coping with stress, modifying lifestyles, and changing pain behaviors. After the 15-week program both multicomponent treatments exhibited similar improvements in functional capability and symptom severity. However, a sub-analysis of fibromyalgia patients with fatigue at baseline showed that the addition of cognitive behavioral therapy leads to a greater improvement in daily functioning and health status than is achieved through a multicomponent treatment alone. The significant improvements in functional capability and symptom severity were maintained at the 6-month follow-up.

Cardiovascular disease

Compared to the literature dealing with cardiac rehabilitation exercise programs in relation to other mental health areas such as anxiety, depression, and quality of life, there have been few reviews of research on exercise-based cardiac rehabilitation and feelings of fatigue. A meta-analysis of 36 cardiac rehabilitation studies showed that cardiac rehabilitation exercise programs were consistently associated with decreases in feelings of fatigue (Puetz et al., 2006b). The magnitude of the effect was 0.51 (0.42, 0.61) showing that participants in exercise programs reported on average one half a *SD* greater reduction in fatigue compared to control groups. However, features of the research design modified this effect. Non-controlled trials had a larger effect (ES = 0.58; 0.47, 0.68) than controlled trials (ES = 0.32; 0.14, 0.50). Nineteen cardiac rehabilitation studies concurrently measured anxiety, depression, and fatigue. Comparison of ESs in cardiac rehabilitation studies concurrently measuring anxiety, depression, and fatigue suggested that exercise-based cardiac rehabilitation programs have significantly larger effects on feelings of fatigue (ES = 0.59; 0.47, 0.71) compared with anxiety (ES = 0.40; 0.28, 0.52) and depression (ES =

0.35; 0.22, 0.48). These findings suggest that cardiac rehabilitation researchers and practitioners may benefit from examining, and perhaps even focusing on, feelings of fatigue as a salient outcome.

Stern, Gorman, and Kaslow (1983) have also provided convincing evidence to support the effect of cardiac rehabilitation exercise programs on reducing feelings of fatigue. One hundred and six post-myocardial infarction patients (mean age 54 years) meeting criteria for anxiety or depression were randomly assigned to a 12-week exercise therapy, group counseling, or usual care control. Exercise therapy consisted of supervised sessions of moderate aerobic exercise 3 days per week. Participants in the group counseling and usual care conditions were requested not to begin any formal exercise programs. Anxiety, depression, and fatigue were assessed before and after these treatments and during a 6-month and 12-month follow-up, during which time no formal exercise or group therapy occurred. Whereas exercise therapy initially reduced anxiety, depression, and fatigue, after the 12-week intervention, group counseling was only effective for depression and anxiety. Fatigue actually increased for those individuals in the counseling group. However, the most interesting result of this study was that fatigue actually increased in the exercise therapy condition at the 6-month and 12-month follow-up, while depression and anxiety reductions were maintained over the same time period. In addition, fatigue rates were reduced in the group counseling and usual care conditions at 6 and 12 months (Figure 29.2). Compliance rates following the intervention likely account for these trends in that 50 percent of exercise condition patients stopped exercising following the 12-week intervention whereas approximately 30 percent of group therapy and usual care patients began some form of exercise.

Cancer

Cancer-related fatigue is a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning and has been described as a nearly universal symptom among cancer patients (Mock et al., 2000). Exercise has been proposed as an effective intervention to improve feelings of fatigue in cancer patients both during and following treatment. Of four meta-analyses that have directly examined exercise effects on cancer-related fatigue, one examined cancer patients only during treatment (Velthuis et al., 2010) and another examined cancer patients only following treatment (Brown et al., 2011), precluding direct examination of differences between these two populations. The other two quantitative reviews allowed for comparisons of cancer patients both during and following treatment (Cramp & Daniel, 2008; Puetz & Herring, 2012).

Cramp and Daniel (2008) conducted a meta-analysis of 28 studies to examine differences in the magnitude of the effect of exercise on fatigue in cancer patients during and following treatment. There was a significant effect such that cancer patients following treatment (ES = –0.37; –0.55, –0.18) had a larger reduction in fatigue than cancer patients during treatment (ES = –0.18; –0.32, –0.05). The effect following treatment was similar to that of Brown et al. (2011), ES = 0.31, but the effect during treatment was significantly smaller than Velthuis et al. (2010), ES = 0.30 (note: positive ESs in Brown et al. and Velthuis et al. indicated greater fatigue reduction in cancer patients). The limitation of the Cramp and Daniel (2008) meta-analysis was that a moderator analysis was not conducted. This limited the understanding of how characteristics of study design, exercise interventions, and patient populations may influence exercise efficacy in cancer patients during and following treatment.

These limitations were addressed in a meta-analysis of 70 randomized controlled trials examining the differential effects of exercise treatment on cancer-related fatigue in cancer patients during and following treatment (Puetz & Herring, 2012). Compared with comparison conditions,

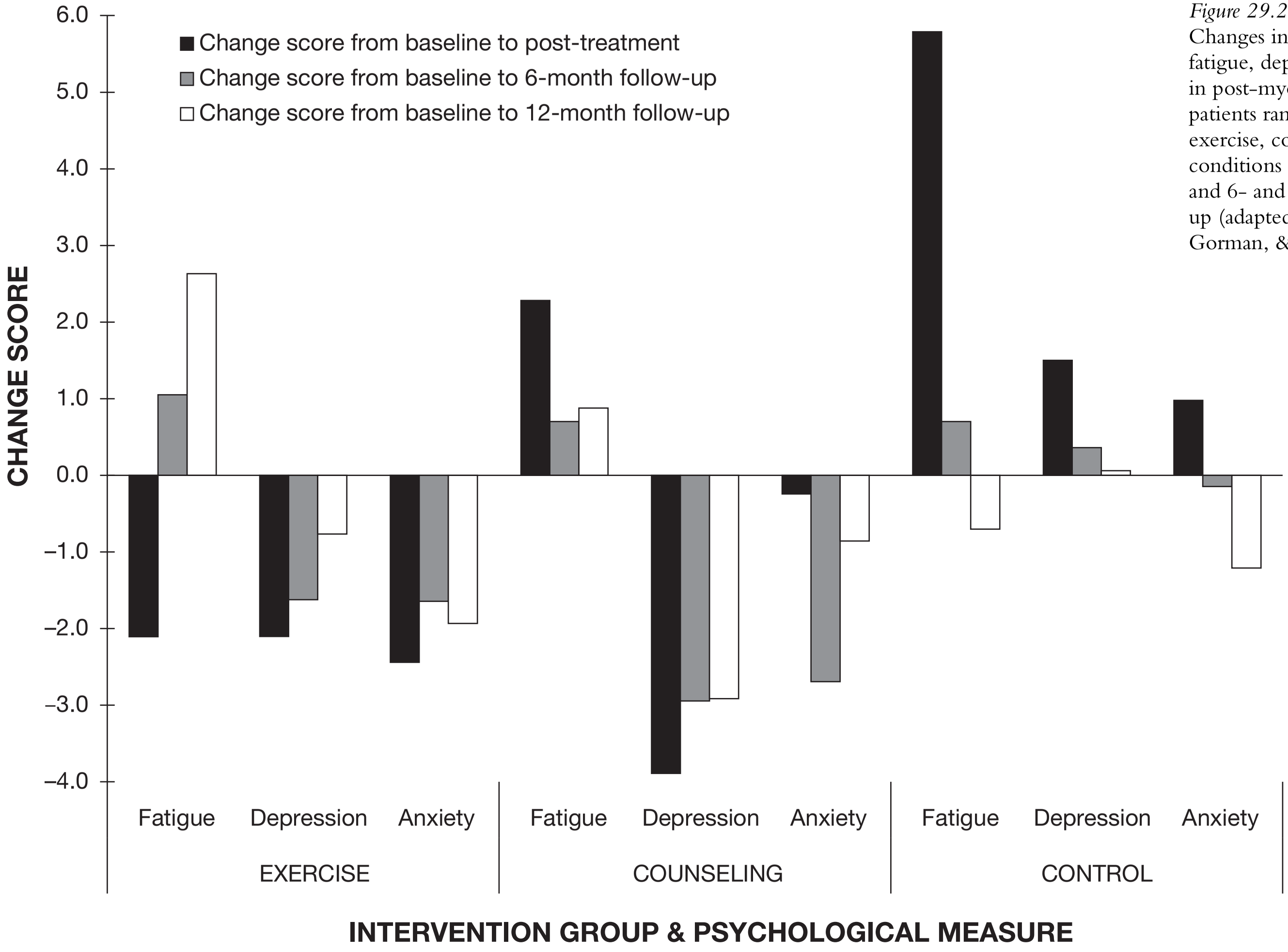

Figure 29.2
Changes in T-scores for fatigue, depression, and anxiety in post-myocardial infarction patients randomized to exercise, counseling, or control conditions at post-treatment and 6- and 12-month follow-up (adapted from Stern, Gorman, & Kaslow, 1983).

exercise treatment significantly reduced fatigue for cancer patients during (ES = 0.32; 0.21, 0.43) and following (ES = 0.38; 0.21, 0.54) treatment. Improvements for cancer patients during treatment varied according to the patient's baseline fatigue scores and exercise adherence rates such that patients with lower baseline fatigue scores and higher intervention adherence rates realized the largest improvements. Among cancer patients following treatment, improvements were largest for those trials with longer durations between treatment completion and exercise initiation, trials with shorter exercise program lengths, and trials using waitlist comparisons. Perhaps the most interesting finding was related to the differential effects exercise treatment had on fatigue between exercise and control conditions in cancer patients during and following treatment. Fatigue symptoms were mitigated in cancer patients participating in an exercise intervention (4.2 percent decrease) compared to comparison interventions (29.1 percent increase) during treatment, while fatigue symptoms were reduced in cancer patients participating in exercise programs (20.5 percent decrease) compared to comparison interventions (1.3 percent decrease) following treatment. These findings suggest exercise has a palliative effect in patients during treatment and a recuperative effect in patients following treatment.

Evidence to support the positive effects of exercise on feelings of fatigue across the time course of cancer treatment and recovery were presented in a randomized controlled trial examining the effect of a self-administered exercise intervention before, during, and after allogeneic hematopoietic stem cell transplantation (Wiskermann et al., 2011). One hundred and five cancer patients were randomly assigned to a partly self-administered exercise or social contact control condition. The exercise intervention consisted of three 20- to 40-minute light aerobic sessions and two full-body resistance training (i.e., 8–20 repetitions, 2–3 sets) sessions per week. Participants in the exercise group started exercising on an outpatient basis 1 to 4 weeks before hospital admission, continued during the inpatient period, and sustained the program until 6 to 8 weeks after discharge from the hospital. The outpatient exercise period was self-directed at home, whereas the inpatient exercise period was supervised twice weekly. The control group wore pedometers during the outpatient period to measure physical activity and received the same frequency of social contact as the exercise intervention during the inpatient period. Over the entire time course of cancer treatment and recovery from the initial medical checkup to the 6- to 8-week follow-up, the exercise condition showed a 15 percent improvement in fatigue scores and the control condition showed 28 percent deterioration in fatigue during the same time period. Several important results from this study were (a) fatigue was reduced in the 1- to 4-week period following the medical checkup prior to hospital admission for the exercise condition compared to the control condition, (b) fatigue was significantly mitigated at discharge from the hospital following cancer treatment in the exercise group compared to the control group in which fatigue actually increased, and (c) fatigue was significantly reduced at the 6- to 8-week follow-up in the exercise group compared to the control group to the extent that the exercise condition participants had scores significantly lower than baseline (Figure 29.3). These results support the conclusion that exercise has a palliative effect in patients undergoing cancer treatment and a recuperative effect in patients following treatment, and that clinicians should consider prescribing exercise at cancer diagnosis.

Directions for future investigation

Although experimental evidence in patient and non-patient populations is largely supportive of the positive effects of physical activity on feelings of fatigue, the area of research is still in its formative years. One important next step in the evolution toward strong science-based practice is the need to better understand which biological, psychological, and psychosocial aspects of

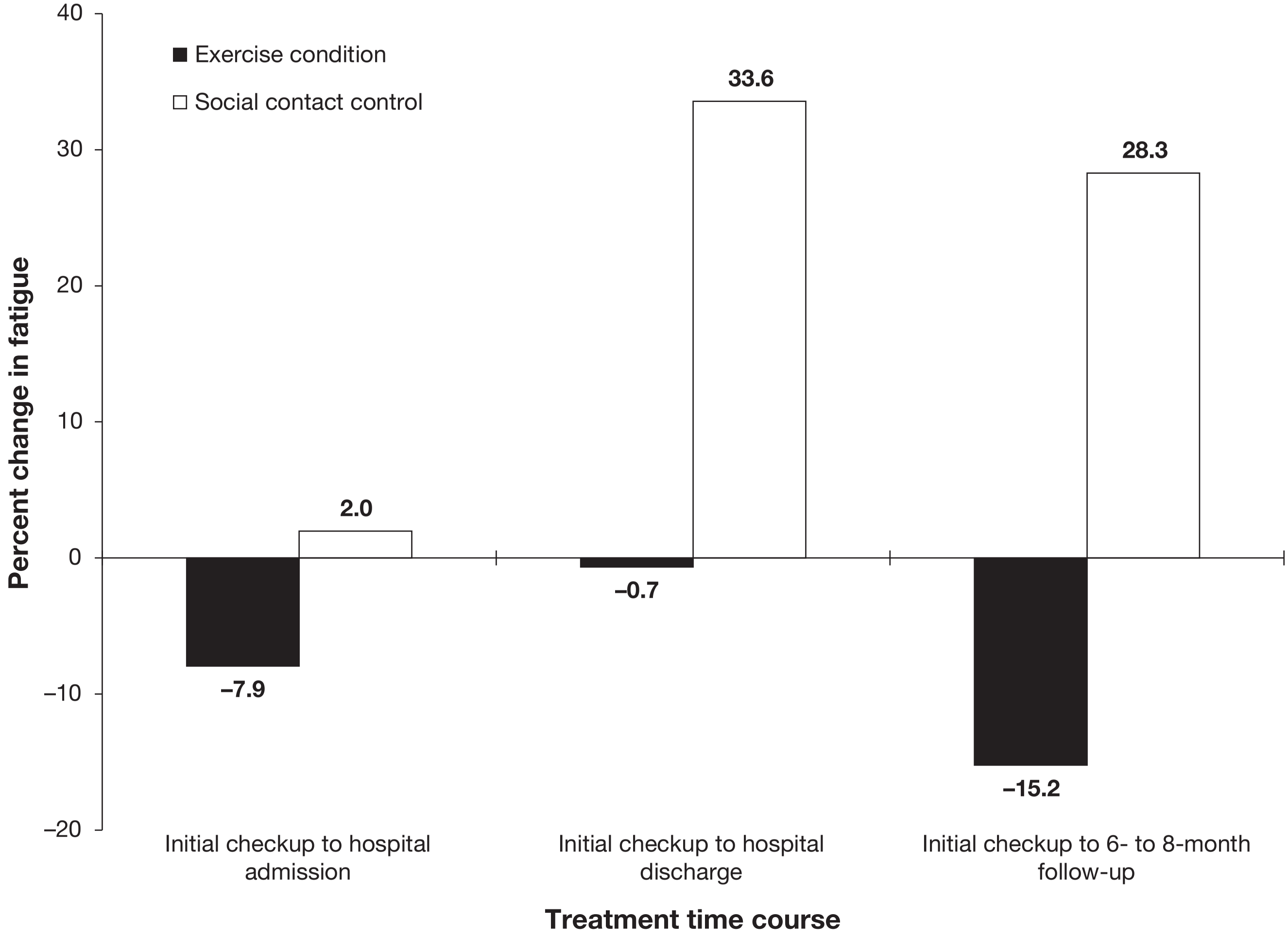

Figure 29.3 Percentage change in fatigue scores for cancer patients randomized to exercise or social control conditions at hospital admission, hospital discharge, and 6 to 8 months' follow-up (adapted from Wiskermann et al., 2011).

physical activity contribute to improved feelings of fatigue. The following section will discuss two major directions for future investigations, namely identifying biological mechanisms behind the physical activity and fatigue relationship and recognizing the importance of interdisciplinary research in further developing this area of study.

Mechanisms

The brain has long been suspected as the primary driver of feelings of fatigue. It is now generally accepted that the brain controls mental, physiological, and behavioral processes. Although genes control brain functioning, social, developmental, and environmental factors can alter gene expression. These alterations in gene expression can induce changes in brain functioning and behavior (Dishman et al., 2006). It is unclear whether the origin of fatigue is in a particular brain structure, is the result of an integrative process involving a number of different brain regions, or is the result of electrophysiological synchronization of entire brain activity (St Clair Gibson et al., 2003). However, metabolic and neurochemical pathways within the central nervous system offer testable mechanisms that might help explain the effects of physical activity on feelings of fatigue.

The specific brain mechanisms that generate the moods of energy and fatigue are unknown, but monoamine-, histamine-, acetylcholine-, glutamate-, and gamma-aminobutyric acid (GABA)-mediated neurotransmission have been implicated (Demyttenaere, De Fruyt, & Stahl, 2005; Stahl, 2002; Stahl, Zhang, Damatarca, & Grady, 2003). There is evidence that physical activity can alter these neurotransmitters and neuromodulators (Dishman et al., 2006). Understanding the neurotransmitters and neuromodulators involved in generating feelings of fatigue is important, but perhaps more important is examining how these chemical messengers regulate potentially malfunctioning neurological circuits or brain areas associated with mental and physical fatigue. For example, brain cortical areas (e.g., dorsolateral prefrontal cortex) and central nervous system components regulating motor functioning (e.g., striatum, cerebellum, spinal cord) could be reasonable candidates in mediating moods of mental and physical fatigue, respectively (Demyttenaere et al., 2005; Stahl et al., 2003).

Unfortunately, there has been very little use of the traditions and methods of biology, psychology, and neuroscience in the study of physical activity and feelings of fatigue. Future research needs to incorporate the basics of neuroanatomy, neurophysiology, and psychopharmacology along with techniques of neuroscience to facilitate sound research on physical activity and fatigue. The best strategy to employ in this course of research development is effective transdisciplinary collaboration.

Interdisciplinary research

Most research is conducted within the established boundaries of a given scientific discipline. Interdisciplinary research involves bringing together people and ideas from different disciplines to jointly frame a problem, agree on a methodological approach, and analyze data (Golde & Gallagher, 1999). As envisioned by Mosso over 120 years ago, this integration of traditional disciplines is vital in uncovering the multidimensional nature of fatigue (Mosso, 1891). The paucity of such research in the area of physical activity and fatigue is disheartening, but the few studies examining psychosocial pathways (e.g., McAuley, White, Rogers, Motl, & Courneya, 2010), immunological response (e.g., Kop, Weinstein, Deuster, Wittaker, & Tracy, 2008; Robson-Ansley et al., 2009), and neuroimaging (e.g., Dishman, Thom, Puetz, O'Connor, & Clementz, 2010) show the promise such interdisciplinary research can offer in advancing our understanding of the biopsychosocial aspects of fatigue. It is imperative that future investigators continue collaboration across scientific disciplines.

Although knowledge about physical activity and feelings of fatigue has significantly increased in the last decade, further investigation is important for the realization of increased public health and well-being. The following are some key critical objectives for future research:

- To more fully characterize the features of the physical activity or exercise stimulus (i.e., frequency, intensity, session duration, program length, and mode) on specific neurobiological and psychological outcome measures of feelings of fatigue.
- To examine the degree of overlap or independence of the effect of physical activity on feelings of fatigue with other mood states including anxiety and depression, and quality of life.
- To better understand the biological correlates and mechanisms for changes in feelings of fatigue that occur with regular exercise.
- To more closely examine the impact of physical activity on fatigue and various disease states and how sociodemographic factors such as age, sex, and socioeconomic status modify the effects of physical activity on feelings of fatigue.
- To investigate the similarities, interactions, and differences among different exercise training paradigms, psychosocial interventions, and pharmacological treatments employed to reduce feelings of fatigue.

Conclusions

Physical activity is a healthy behavior that has promise for combating feelings of fatigue (O'Connor & Puetz, 2005). Approximately 20 percent of adults worldwide report persistent fatigue (Wessely et al., 1998). Historically clinicians have recognized the physiological and psychological aspects of fatigue and have consistently recommended exercise as a treatment. The subjective nature of fatigue has made conceptualizing, operationalizing, and measuring the construct difficult. This, in conjunction with the imperfect measure of physical activity, has created some limitations in the area of physical activity and fatigue research. Despite such limitations, epidemiological evidence suggests that people who are physically active in their leisure time have about a 40 percent reduced risk of experiencing feelings of fatigue compared with sedentary comparison groups (Puetz, 2006). This population-based research has been substantiated with experimental evidence that shows physical activity does reduce feelings of fatigue across both healthy groups and patient populations. However, the quality of methodological rigor must continue to improve and evolve in a manner that integrates biological, psychological, and psychosocial factors into fatigue research. Future investigation can best meet these standards by incorporating interdisciplinary research into uncovering the biological mechanisms behind the effects of physical activity on feelings of fatigue.

References

Aaronson, L. S., Teel, C. S., Cassmeyer, V., Neuberger, G. B., Pallikkathayil, L., Pierce, J., . . . Wingate, A. (1999). Defining and measuring fatigue. *Journal of Nursing Scholarship*, *31*, 45–50.

Addington, A. M., Gallo, J. J., Ford, D. E., & Eaton, W. W. (2001). Epidemiology of unexplained fatigue and major depression in the community: The Baltimore ECA Follow-up, 1981–1994. *Psychological Medicine, 31,* 1037–44.

Allen, F. N. (1944). The differential diagnosis of weakness and fatigue. *New England Journal of Medicine*, *231*, 414–18.

Allen, F. N. (1945). The clinical management of weakness and fatigue. *Journal of the American Medical Association*, *127*, 957–60.

Bartley, S. H., & Chute, E. (1947). *Fatigue and impairment in man*. New York: McGraw-Hill.

Bernardy, K., Fuber, N., Kollner, V., & Hauser, W. (2010). Efficacy of cognitive-behavioral therapies in fibromyalgia syndrome: A systematic review and meta-analysis of randomized controlled trials. *Journal of Rheumatology*, *37*, 1991–2005.

Brown, J. C., Huedo-Medina, T. B., Pescatello, L. S., Pescatello, S. M., Ferrer, R. A., & Johnson, B. T. (2011). Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: A meta-analysis. *Cancer Epidemiology, Biomarkers, and Prevention*, *20*, 123–33.

Buckworth, J., & Dishman, R. K. (2002). *Exercise psychology*. Champaign, IL: Human Kinetics.

Caspersen, C. J. (1989). Physical activity epidemiology: Concepts, methods and applications to exercise science. *Exercise and Sport Sciences Reviews*, *17*, 423–73.

Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and physical fitness: Definitions and distinctions for health-related research. *Public Health Reports*, *100*, 126–31.

Chen, M. K. (1986). The epidemiology of self-perceived fatigue among adults. *Preventive Medicine*, *15*, 74–81.

Clauw, D. J. (2009). Fibromyalgia: An overview. *American Journal of Medicine*, *122*, S3–S13.

Cowles, E. (1893). *The mental symptoms of fatigue*. New York: Fless & Ridge.

Cramp, F., & Daniel, J. (2008). Exercise for the management of cancer-related fatigue in adults. *Cochrane Database of Systematic Reviews*, *2*, CD006145.

Darbishire, L., Ridsdale, L., & Seed, P. T. (2003). Distinguishing patients with chronic fatigue from those with chronic fatigue syndrome: A diagnostic study in UK primary care. *British Journal of General Practice*, *53*, 441–5.

Dearborn, G. V. N. (1902). On the "fatigue" of nerve centers. *Psychological Review*, *9*, 180–3.

Demyttenaere, K., De Fruyt, J., & Stahl, S. M. (2005). The many faces of fatigue in major depressive disorder. *International Journal of Neuropsychopharmacology*, *8*, 93–105.

de Rijk, A. E., Schreurs, K. M. G., & Bensing, J. M. (2000). Patient factors related to the presentation of fatigue complaints: Results from a women's general health care practice. *Women and Health*, *30*, 121–36.

Di Giulio, C., Daniele, F., & Tipton, C. M. (2006). Angelo Mosso and muscular fatigue: 116 years after the first congress of physiologists: IUPS commemoration. *Advances in Physiology Education*, *30*, 51–7.

Dishman, R. K., Thom, N. J., Puetz, T. W., O'Connor, P. J., & Clementz, B. A. (2010). Effects of cycling exercise on vigor, fatigue, and electroenphalographic activity among young adults who report persistent fatigue. *Psychophysiology*, *47*, 1066–74.

Dishman, R. K., Berthoud, H., Booth, F. W., Cotman, C. W., Edgerton, V. R., Fleshner, M. R., . . . Zigmond, M. J. (2006). The neurobiology of exercise. *Obesity*, *14*(3), 345–56.

Dittner, A., Wessely, S., & Brown, R. (2004). The assessment of fatigue: A practical guide for clinicians and researchers. *Journal of Psychosomatic Research*, *56*, 157–70.

Eidelman, D. (1979). "Fatigue on rest" and associated symptoms (headache, vertigo, blurred vision, nausea, tension, and irritability) due to locally asymptomatic, unerupted, impacted teeth. *Medical Hypotheses*, *5*, 339–46.

Golde, C. M., & Gallagher, H. A. (1999). The challenges of conducting interdisciplinary research in traditional doctoral programs. *Ecosystems*, *2*, 281–5.

Hauser, W., Bernardy, K., Arnold, B., Offenbächer, M., & Schiltenwolf, M. (2009a). Efficacy of multicomponent treatment in fibromyalgia syndrome: A meta-analysis of randomized controlled trials. *Arthritis and Rheumatism*, *15*, 216–24.

Hauser, W., Bernardy, K., Uceyler, N., & Sommer, C. (2009b). Treatment of fibromyalgia syndrome with antidepressants: A meta-analysis. *Journal of the American Medical Association*, *301*, 198–209.

Hauser, W., Klose, P., Langhorst, J., Moradi, B., Steinbach, M., Schiltenwolf, M., & Busch, A. (2010). Efficacy of different types of aerobic exercise in fibromyalgia syndrome: A systematic review and meta-analysis of randomized controlled trials. *Arthritis Research and Therapy*, *12*, R79.

Hedges, L. V., & Olkin, I. (1985). *Statistical methods for meta-analysis*. New York: Academic Press.

Hill, A. B. (1965). The environment and disease: Association or causation. *Proceedings of the Royal Society of Medicine*, *58*, 295–300.

Joyce, J., Hotopt, M., & Wessely, S. (1997). The prognosis of chronic fatigue and chronic fatigue syndrome: A systematic review. *Quarterly Journal of Medicine*, *90*, 223–33.

Kop, W. J., Weinstein, A. A., Deuster, P. A., Wittaker, K. S., & Tracy, R. P. (2008). Inflammatory markers and negative mood symptoms following exercise withdrawal. *Brain, Behavior, and Immunity*, *22*, 1190–96.

Kroenke, K., & Price, R. (1993). Symptoms in the community: Prevalence, classification, and psychiatric comorbidity. *Archives of Internal Medicine*, *153*, 2474–80.

LaPorte, R. E., Montoye, H. L., & Caspersen, C. J. (1985). Assessment of physical activity in epidemiological research: Problems and prospects. *Public Health Reports*, *100*, 131–46.

Lee, C., & Russell, A. (2003). Effects of physical activity on emotional well-being among older Australian women: Cross-sectional and longitudinal analyses. *Journal of Psychosomatic Research*, *54*, 155–60.

Lera, S., Gelman, S. M., Lopez, M. J., Abenoza, M., Zorrilla, J. G., Castro-Fornieles, J., & Salamero, M. (2009). Multidisciplinary treatment of fibromyalgia: Does cognitive behavior therapy increase the response to treatment? *Journal of Psychosomatic Research*, *67*, 433–41.

MacDougall, R. (1899). Fatigue. *Psychological Review*, *6*, 203–8.

McAuley, E., White, S. M., Rogers, L. Q., Motl, R. W., & Courneya, K. S. (2010). Physical activity and fatigue in breast cancer and multiple sclerosis: Psychosocial mechanisms. *Psychosomatic Medicine*, *72*, 88–96.

Mock, V., Atkinson, A., Barsevick, A., Cella, D., Cimprich, B., Cleeland, C., . . . Stahl, C. (2000). NCCN practice guidelines for cancer-related fatigue. *Oncology (Williston Park)*, *14*, 151–61.

Montoye, H. J., Kemper, H. C. G., Saris, W. H. M., & Washburn, R. A. (1996). *Measuring physical activity and energy expenditure*. Champaign, IL: Human Kinetics.

Mosso A. (1891). *La Fatica*. Milano, IT: Treves.

Muncie, W. (1941). Chronic fatigue. *Psychosomatic Medicine*, *3*, 277–85.

Muscio, B. (1921). Is a fatigue test possible? *British Journal of Psychology*, *12*, 31–46.

O'Connor, P. J. (2004). Evaluation of four highly cited energy and fatigue mood measures. *Journal of Psychosomatic Research*, *57*, 435–41.

O'Connor, P. J. & Puetz, T. W. (2005). Chronic physical activity and feelings of energy and fatigue. *Medicine and Science in Sports and Exercise*, *37*, 299–305.

Paffenbarger, R. S., Blair, S. N., Lee, I. M., & Hyde, R. T. (1993). Measurement of physical activity to assess health effects in free-living populations. *Medicine and Science in Sports and Exercise*, *25*, 60–70.

Poore, G. V. (1875). On fatigue. *Lancet*, *106*, 163–4.

Puetz, T. W. (2006). Physical activity and feelings of energy and fatigue: Epidemiological evidence. *Sports Medicine*, *36*, 767–80.

Puetz, T. W., Beasman, K. M., & O'Connor, P. J. (2006b). The effect of cardiac rehabilitation exercise programs on feelings of energy and fatigue: A meta-analysis of research from 1945 to 2005. *European Journal of Cardiovascular Prevention and Rehabilitation*, *13*, 886–93.

Puetz, T. W., Flowers, S. S., & O'Connor, P. J. (2008). A randomized controlled trial of the effect of aerobic exercise training on feelings of energy and fatigue in sedentary young adults with persistent fatigue. *Psychotherapy and Psychosomatics*, 77, 167–74.

Puetz, T. W., & Herring, M. P. (2012). Differential effects of exercise on cancer-related fatigue during and following treatment: A meta-analysis. *American Journal of Preventive Medicine*, *43*, e1–e24.

Puetz, T. W., O'Connor, P. J., & Dishman, R. K. (2006a). Effects of chronic exercise on feelings of energy and fatigue: A quantitative synthesis. *Psychological Bulletin*, *132*, 866–76.

Ream, E., & Richardson, A. (1996). Fatigue: A concept analysis. *International Journal of Nursing Studies*, *33*, 519–29.

Ricci, J. A., Chee, E., Lorandeau, A. L., & Berger, J. (2007). Fatigue in the U.S. workforce: Prevalence and implications for lost productive work time. *Journal of Occupational and Environmental Medicine*, *49*, 1–10.

Rimes, K. A., Goodman, R., Hotopf, M., Wessely, S., Meltzer, H., & Chalder, T. (2007). Incidence, prognosis, and risk factors for fatigue and chronic fatigue syndrome in adolescents: A prospective community study. *Pediatrics*, *119*, 603–9.

Robson-Ansley, P., Barwood, M., Canavan, J., Hack, S., Eglin, C., Davey, S., . . . Ansley, L. (2009). The effect of repeated endurance exercise on IL-6 and sIL-6R and their relationship with sensations of fatigue at rest. *Cytokine*, *45*, 111–16.

Ruffin, M., & Cohen, M. (1994). Evaluation and management of fatigue. *American Family Physician*, *50*, 625–34.

Shen, J., Barbera, J., & Shapiro, C. M. (2006). Distinguishing sleepiness and fatigue: Focus on definition and measurement. *Sleep Medicine Review*, *10*, 63–76.

Stahl, S. M. (2002). The psychopharmacology of energy and fatigue. *Journal of Clinical Psychiatry*, *63*, 7–8.

Stahl, S. M., Zhang, L. S., Damatarca, C., & Grady, M. (2003). Brain-circuits determine destiny in depression: A novel approach to the psychopharmacology of wakefulness, fatigue, and executive dysfunction in major depressive disorder. *Journal of Clinical Psychiatry*, *64*, 6–17.

St Clair Gibson, A., Baden, D. A., Lambert, M. I., Lambert, E. V., Harley, Y., & Hampson, D. (2003). The conscious perception of the sensation of fatigue. *Sports Medicine*, *33*, 167–76.

Stern, M. J., Gorman, P. A., & Kaslow, L. (1983). The group counseling vs. exercise therapy study: A controlled intervention with subjects following myocardial infarction. *Archives of Internal Medicine*, *143*, 1719–25.

Velthuis, M. J., Agasi-Idenburg, S. C., Aufdemkampe, G., & Wittink, H. M. (2010). The effect of physical exercise on cancer-related fatigue during cancer treatment: A meta-analysis of randomized controlled trials. *Clinical Oncology (Royal College of Radiologists)*, *22*, 208–21.

Ware, J. (2000). *SF-36 health survey manual and interpretation guide*. Lincoln, NE: Quality Metric.

Waterman, G. (1909). The treatment of fatigue states. *Journal of Abnormal Psychology*, *4*, 128–39.

Watson, D. (2000). *Mood and temperament*. New York: Guilford Press.

Wessely, S., Chalder, T., Hirsch, S., Wallace, P., & Wright, D. (1997). The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: A prospective primary care study. *American Journal of Public Health*, *87*, 1449–55.

Wessely, S., Hotopf, M., & Sharpe, M. (1998). *Chronic fatigue and its syndromes*. Oxford: Oxford University Press.

Whitehead, L. (2009). The measurement of fatigue in chronic illness: A systematic review of unidimensional and multidimensional fatigue measures. *Journal of Pain and Symptom Management*, *37*, 107–28.

Wiskermann, J., Dreger, P., Schwerdtfeger, R., Bondong, A., Huber, G., Kleindienst, N., . . . Bohus, M. (2011). Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. *Blood*, *117*(9), 2604–13.

Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Katz, R. S., Mease, P., . . . Yunus, M. B. (2010). The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care and Research*, *62*, 600–10.