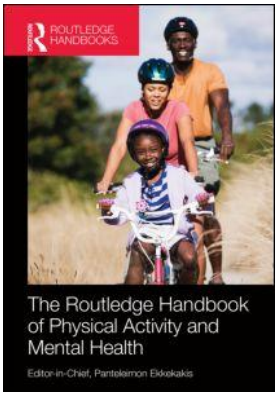

Routledge Handbook of Physical Activity and Mental Health

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Publication details
https://www.routledgehandbooks.com/doi/10.4324/9780203132678.ch8
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Published online on: 23 Apr 2013

PART 3

Depression and mood disorders

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EXERCISE AND PHYSICAL ACTIVITY IN THE PREVENTION AND TREATMENT OF DEPRESSION

Patrick J. Smith and James A. Blumenthal

Depression is a term that refers both to a transient mood state and a clinical syndrome or disorder. As a mood state, depression is characterized by feeling despondent or unhappy, while depression as a mood disorder is a persistent set of symptoms as described in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV). Specifically, major depressive disorder (MDD) is a psychiatric condition in which diagnostic criteria require five or more depressive symptoms, one of which must include either depressed mood or loss of interest or pleasure. Other depressive symptoms include significant weight loss, sleep changes (i.e., insomnia or hypersomnia), psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, diminished ability to think or concentrate, and recurrent thoughts of death. MDD is also distinguished from normal symptoms of sadness by criteria for symptom severity and duration: symptoms of depression must have been present during the same two-week period, be present all or most of the time, and represent a *change* from a previous level of functioning.

Epidemiology of major depressive disorder

Although the estimates of depression prevalence vary between samples, community surveys generally find that up to 20% of adults and 50% of children and adolescents report depressive symptoms during the past 6 months (Kessler, Avenevoli, & Ries Merikangas, 2001; Kessler, Merikangas, & Wang, 2008) and 6.6% of U.S. adults experienced MDD during the last year (Kessler et al., 2003). Estimates vary depending primarily on whether the presence of depressive symptoms or clinical depression is assessed. Of the depressive episodes experienced by adults during the last year, nearly one-third were severe (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Depression is somewhat more common among whites compared to African Americans, and is twice as common among women in comparison to men (Kessler, Berglund, et al., 2005).

In the United States there has been recent concern that the prevalence of depression is increasing, particularly among teenagers and young adults. For example, compared with adults over the age of 60, 18–29-year-olds are 70% more likely to have experienced a major depressive episode in their lifetimes (Kessler, Berglund, et al., 2005). Depression is also commonly observed to co-occur in many medical conditions (Katon, 2003), including highly prevalent and costly diseases such as obesity (Roberts, Deleger, Strawbridge, & Kaplan, 2003), diabetes (Katon et al.,

2008), cardiovascular disease (Lichtman et al., 2008), and Alzheimer's disease (Ownby, Crocco, Acevedo, John, & Loewenstein, 2006), and has been associated with negative health behaviors such as physical inactivity (Roshanaei-Moghaddam, Katon, & Russo, 2009), poor dietary patterns (Katon et al., 2008), medical nonadherence (DiMatteo, Lepper, & Croghan, 2000), and substance use (Davis, Uezato, Newell, & Frazier, 2008).

Health consequences of depression

MDD is associated with poorer quality of life and is a significant burden on the healthcare system, increasing medical expenditures and healthcare utilization. In addition, depression is one of the leading sources of disability in the United States and is associated with significantly increased missed time at work. Although depression is a treatable condition, as many as 1 in 10 individuals with chronic depression may ultimately commit suicide (Wulsin, Vaillant, & Wells, 1999). MDD is a significant source of emotional suffering and a healthcare burden and is one of the leading causes of disability in the United States and internationally (Simon, 2003). According to the World Health Organization, depression is the leading cause of years lived with disability, the fourth leading cause of disability adjusted life years (DALYs), and is associated with greater health decrements in comparison with angina, arthritis, asthma, and diabetes (Moussavi et al., 2007). Depression is also associated with an increased risk for a variety of medical conditions, including diabetes and cardiovascular disease.

Conventional treatments for depression

Pharmacotherapy

Depression is most commonly treated with antidepressant medication (Olfson et al., 2002). Many randomized clinical trials (RCTs) have examined the effectiveness of various pharmacological compounds on depression outcomes (Lieberman et al., 2005). Antidepressants generally have been shown to have efficacy in improving depression and reducing relapse rates. The current recommendations for depression treatment typically involve treatment using a selective serotonin reuptake inhibitor (SSRI) (Trivedi, Fava, et al., 2006), although treatments with tricyclic antidepressants, benzodiazepines, and combined therapies are also common (Gelenberg et al., 2010). Approximately 50% of patients will have a clinical "response" to treatment (i.e., a 50% reduction in symptoms), whereas many individuals will require augmented treatment with more than one antidepressant agent (Hollon, Thase, & Markowitz, 2002).

Recent evidence suggests that the effects of antidepressant therapy may vary by severity of depression, with patients with more severe depressive symptomatology achieving the greatest benefit. This evidence is consistent with some treatment guidelines suggesting that patients with more severe depression are the most likely to benefit from pharmacotherapy treatment. In a meta-regression of randomized, placebo-controlled trials, Fournier and colleagues (Fournier et al., 2010) found differential effects of antidepressant therapy depending on the severity of depression at study entry among depressed adults. Patients with Hamilton Depression Rating Scale (HDRS) scores above 22 (suggesting moderate to severe levels of depression) at study entry were more likely to benefit from treatment compared to placebo, whereas participants with less severe levels of depression did not differ significantly from placebo controls.

Psychotherapy for depression

Depression is one of the most common presenting problems among outpatient psychiatric clinics and is highly prevalent in inpatient psychiatric settings. Accordingly, numerous studies have examined the effects of various forms of psychotherapy as a treatment for depression, which are reviewed in detail elsewhere in a number of publications (Cuijpers, van Straten, Andersson, & van Oppen, 2008). Multiple meta-analytic studies have attempted to combine the results of these RCTs to quantify the efficacy of various forms of psychotherapy (Cuijpers et al., 2008). Therapies typically involve individual treatment over the course of several months, although several studies of longer duration have been reported. The primary types of treatment examined are cognitive behavioral therapy (CBT), psychodynamic therapy, (nondirective) supportive treatment, behavioral activation treatment, problem-solving therapy, interpersonal psychotherapy, and social skills training. Among these, the most commonly used treatments for depression include CBT, which focuses on identifying and modifying maladaptive thought patterns, and interpersonal therapy (IPT), which is a structured, time-limited psychotherapy that emphasizes the social context in which depression occurs.

Previous reviews have documented the effectiveness of psychotherapy among individuals with depression, which appears to improve depression to a similar extent as pharmacotherapy (Robinson, Berman, & Neimeyer, 1990). In an early review, Robinson and colleagues (Robinson et al., 1990) combined results from 58 studies of psychotherapy for depression among adults in trials comparing psychotherapy versus a no-treatment control. In this case, the no-treatment control condition consisted of either waitlist controls or placebo treatments, including attention conditions or placebo drugs. Comparing participants at post-treatment, the authors found that psychotherapy was associated with substantial reductions in depressive symptoms (mean effect size improvement = 0.73) and that this improvement tended to be retained during follow-ups (mean effect size improvement = 0.68). In addition, there were no significant differences in depression outcomes between types of psychotherapeutic treatment in this study.

A recent meta-analytic study by Cuijpers and colleagues (Cuijpers et al., 2008) reported similar results in a comparison of various psychotherapeutic treatments of depression. Studies were included if they used a randomized allocation strategy, included only adults, compared two psychological treatments, and were conducted among individuals with MDD or elevated depressive symptoms. In order to examine the effects of various treatments separately, the authors conducted 7 separate meta-analytic analyses, including data from 53 primary trials among 2,757 participants with mild to moderate levels of depression. The authors found that all the major types of psychotherapy treatment were associated with improvements in depressive symptoms compared to control conditions. Although there was some indication that IPT was superior to other forms of therapy, all forms of therapy appeared to be equally efficacious. In addition to the above findings among patients with MDD, similar findings have been reported for patients with subclinical depression, e.g., depressive symptoms that do not meet criteria for MDD. In a meta-analytic study of 7 "high-quality trials," participants who received psychotherapy treatment showed greater improvements in depressive symptoms compared with control conditions and these results tended to persist in 4 studies that examined depressive symptoms among 533 participants at a 1-year follow-up time point, although the findings narrowly missed statistical significance (Cuijpers, Smit, & van Straten, 2007) (d = 0.16 [95% CI: -0.02 to 0.35]).

Summary of conventional treatments

Antidepressants and psychotherapy are effective for many patients, but not everyone benefits from treatment. Moreover, results of RCTs suggest that these conventional therapies do not

always perform better than placebo controls, particularly in patients with less severe MDD. Also, these treatments are costly, time consuming, and, in the case of pharmacotherapy, are often associated with side effects. Novel approaches to treating depression are therefore needed. As described below, exercise may be one such approach.

Physical activity and exercise for depression

Epidemiological studies

Observational studies have found that higher levels of physical activity are associated with reduced incidence of depression and that more physically active individuals report lower levels of depressive symptoms compared to their sedentary counterparts (Brosse, Sheets, Lett, & Blumenthal, 2002; Camacho, Roberts, Lazarus, Kaplan, & Cohen, 1991). In one of the earliest observational studies, the first National Health and Nutritional Examination Survey (NHANES I) reported that participants who were not depressed at baseline but reported little or no physical activity were nearly twice as likely to report depressive symptoms during an 8-year follow-up examination compared to participants reporting more regular physical activity (Farmer et al., 1988). A dose-response relationship between physical activity and depression was also found in a 20-year follow-up study of 21,596 men in the Harvard alumni study (Paffenbarger, Lee, & Leung, 1994). In the Alameda County Study, Camacho and colleagues (Camacho et al., 1991) prospectively found that participants who were physically active were at lower risk for depression over an 18-year follow-up compared to less active participants. In addition, those participants who initially had higher levels of depression were at lower risk for later depression if they initiated exercise over the course of the study. Longitudinal studies suggest that exercise is associated with reduced rates of depression in non-depressed adults and also those who were initially depressed. For example, Harris and colleagues (Harris, Cronkite, & Moos, 2006) followed a cohort of 424 depressed adults for 10 years, conducting examinations of depression and physical activity at baseline, 1 year, 4 years, and 10 years. They found that greater levels of physical activity were associated with less concurrent depression. In addition, exercise appeared to be a buffer against negative life events, with physically active participants experiencing one negative life event reporting the same level of depression as sedentary participants without any negative life events.

There is preliminary evidence that the intensity of exercise may predict subsequent depressive symptoms. Lampinen and colleagues (Lampinen, Heikkinen, & Ruoppila, 2000) studied 663 Finnish older adults who were assessed in a baseline examination in 1988 and were reassessed in 1996. Results showed that approximately 50% of participants reported regular walking and approximately 20% reported participating in strenuous exercise. Participants who had decreased their intensity of exercise from baseline to follow-up examinations had significantly higher levels of depressive symptoms, whereas no increase was observed among individuals whose intensity remained unchanged. In a separate study, the authors found a similar relationship when they compared mobility-disabled and non-disabled individuals, with mobility-disabled participants having a greater likelihood of reporting depressive symptoms (Lampinen & Heikkinen, 2003). In contrast, Brown and colleagues (Brown, Ford, Burton, Marshall, & Dobson, 2005) found beneficial effects across a range of intensities in an analysis of 9,207 women participating in the Australian Longitudinal Study on Women's Health. Depressive symptoms were lower among participants who reported regular physical activity and this association remained significant even among individuals who reported "low" levels of physical activity, suggesting that any exercise is better than no exercise and that higher levels of exercise are not necessarily more beneficial compared to lower-intensity exercise.

Despite these positive findings, not all prospective studies have reported a protective effect of exercise on depressive symptoms. For example, Cooper-Patrick and colleagues (Cooper-Patrick, Ford, Mead, Chang, & Klag, 1997) did not observe a relationship between physical activity level and the development of subsequent depression in a sample of more than 700 former medical students. Participants' physical activity levels and depression status were assessed by self-report and review of medical records. Examination of follow-up data showed that the risk of depression was similar for exercisers and non-exercisers. Kritz-Silverstein and colleagues (Kritz-Silverstein, Barrett-Connor, & Corbeau, 2001) found a relationship between self-reported exercise and lower depressive symptoms among participants in the Rancho Bernardo Study in cross-sectional but not longitudinal studies. Participants were older men and women (aged 50–89 years) who were assessed at a baseline visit from 1984 to1987 and a follow-up visit from 1992 to 1995. Cross-sectionally, participants who were exercising had significantly lower depressed mood in comparison with their sedentary counterparts. However, longitudinal analyses found that participants who reported exercising during their baseline assessment did not show lower depression levels during their follow-up assessments. It is possible that these findings were influenced by sample selection causing a "floor effect," as participants who were clinically depressed at baseline were excluded and depression scores were higher among participants who failed to complete the follow-up assessment.

In sum, most, but not all, studies report an inverse association between physical activity and depressive symptoms, although it is noteworthy that observational studies cannot establish a causal relationship between higher levels of physical activity and fewer depressive symptoms. Intervention studies provide the highest level of evidence that exercise is causally related to reduced depression.

Interventional studies

The effects of exercise among individuals with clinical depression have been examined in over two dozen RCTs (Mead et al., 2009) and has been the topic of several systematic reviews (Stathopoulou, Power, Berry, & Smits, 2006), meta-analyses (Lawlor & Hopker, 2001), and one Cochrane review (Mead et al., 2009). Existing studies have varied substantially in size, type of control group, methodological rigor, length of follow-up, and even the type of exercise modality. Randomized trials have generally varied in length from 6 weeks to 4 months. At the time of this review, nearly 30 trials have examined the effects of exercise on depressive symptoms among adults with major depression. As reviewed elsewhere, there is also emerging evidence that exercise improves depression among adolescents (Larun, Nordheim, Ekeland, Hagen, & Heian, 2006), although little high-quality evidence is currently available that examines the effects of exercise in this age group. Although multiple trials have been conducted among adults with depression, few studies have utilized high-quality methodologies in which treatment allocation is concealed, intention-to-treat analyses are used, and assessment of depression is conducted by a trained psychologist instead of being based on self-report.

Several systematic reviews and meta-analytic studies have examined the effects of exercise on depression. In a quantitative and qualitative review, Stathopoulou and colleagues (Stathopoulou et al., 2006) examined the effects of randomized trials of exercise for depression in which only studies with non-active comparison conditions, such as waitlist controls, low-level exercise, and health education, were compared. In addition, only studies among individuals with elevated depressive symptoms were included in this analysis. This meta-analysis also examined the effects of exercise on other psychological disorders, including alcohol abuse, eating disorders, and anxiety disorders. Examining depression outcomes, 14 studies met their inclusion criteria and provided

sufficient data to be included in analyses. Results showed large improvements in depression with exercise in comparison with nonactive controls (mean overall effect size of g = 1.39 [95% CI: .89 to 1.88] or d = 1.42 [95% CI: .92 to 1.93]).

Rethorst and colleagues (Rethorst, Wipfli, & Landers, 2009) also conducted a meta-analysis of the antidepressant effects of exercise. The authors combined data from 58 randomized trials, incorporating data from 2,982 individuals. In contrast to the Stathopoulou (Stathopoulou et al., 2006) study, the authors included all studies examining exercise as an intervention and did not limit their sample to depressed subjects. The authors found that exercise was associated with a –0.80 effect size (95% CI: –0.67 to –0.92) improvement in depressive symptoms, leading the authors to classify these findings as a level 1, Grade A quality for the effects of exercise on depression. In sensitivity analyses, the authors found that higher-quality studies, such as those using blinding, reported greater effects than lower-quality studies. Importantly, comparison of studies among depressed versus non-depressed samples showed a much stronger effect of treatment among depressed participants, with smaller benefits among non-depressed samples. Similar to other meta-analytic studies, the authors did not find a dose-response relationship between exercise volume and improvements in depression.

Lawlor and Hopker (2001) performed a meta-regression of aerobic exercise and depression among published randomized trials conducted among adults. Their literature search yielded 14 studies for inclusion, incorporating data from approximately 850 individuals. All studies had important methodological weaknesses, including inadequate concealment of randomization, failure to use intention-to-treat analyses, and lack of blinded assessment techniques. Using the Beck Depression Inventory as their outcome measure, the authors reported that exercise reduced depressive symptoms by –7.3 points (95% confidence interval –10.0 to –4.6), and that this effect was greater in trials with shorter follow-up periods. Despite the findings of improved depressive symptoms, the authors concluded that the effectiveness of exercise in treating depression could not be determined due to a lack of good research in clinical populations and a lack of appropriate follow-up assessments.

In a subsequent review, Mead and colleagues (Mead et al., 2009) conducted a comprehensive literature search of randomized controlled trials in adults in which exercise was compared to a standard treatment, no treatment, or a placebo control. Their search yielded 28 studies that met their inclusion criteria. Methodological quality varied substantially across studies, with a minority of studies adequately concealing treatment, using intention-to-treat analyses, and using objective (i.e., not self-reported) measures of depressive symptoms. Approximately half of the studies (n = 13) included used a two-arm design, comparing exercise with controls only. Many other studies utilized a three-arm design (n = 11), comparing exercise with one other treatment modality (e.g., pharmacotherapy, cognitive therapy, or a different intensity exercise group) and a control group. Most studies used jogging/running as their treatment modality, but some used walking, aerobic training with an instructor, stationary cycling, or mixed exercise (e.g., resistance training and stretching).

This Cochrane review limited the primary analyses to those trials comparing exercise treatment with no treatment or a control intervention (n = 25) and found a large, clinically meaningful improvement associated with exercise in comparison with controls (standardized mean difference [SMD] = –0.82 (95% CI –1.12 to –0.51). However, when the analyses were further limited to those trials using intention-to-treat analyses and blinded outcome assessment, the effect was modestly attenuated, and showed only a moderate benefit associated with exercise. In addition, when analyses were conducted among the five trials that collected long-term follow-up data, the effects of treatment were again slightly attenuated for a moderate clinical improvement (SMD –0.44 [95% CI –0.71 to –0.18]). The authors concluded that "exercise did seem to improve the

symptoms of depression," which was somewhat surprising, given that only two new studies were included that were not part of their previous 2001 review (Blumenthal & Ong, 2009).

The beneficial effects of exercise have also been examined among individuals with heart failure. In the HF–ACTION (Heart Failure–A Controlled Trial Investigating Outcomes of Exercise Training) multicenter randomized trial, participants were randomized to either supervised aerobic exercise training for 1 to 3 months followed by home exercise, or to a guideline-based usual care group (O'Connor et al., 2009) and were followed for approximately 30 months. Depressive symptoms were assessed using the BDI-II every 3 months for a year (Blumenthal et al., 2012a). Depression scores were consistently lower in the aerobic exercise group compared to usual care controls at 3 months and 12 months. These improvements tended to be even greater among participants with clinically elevated depressive symptoms at baseline (BDI-II scores > 14). Volume of exercise was inversely related to depressive symptoms, such that participants reporting 90 minutes of exercise per week showed the greatest improvements in depression; there did not appear to be added benefit for exercise >90 minutes, however.

Comparative effectiveness

Several studies have compared exercise with other accepted forms of depression treatment, including psychotherapy and pharmacotherapy. The Mead meta-analysis (Mead et al., 2009) examined several of these comparative effectiveness analyses, conducting sensitivity analyses of those trials comparing these interventions directly. For example, the authors also reported the results when exercise was compared directly with CBT. Six trials examined this relationship, with data from 152 participants. Results showed no difference between exercise and cognitive therapy (SMD = –0.17 [95% CI –0.51, 0.18]).

An additional sensitivity analysis was conducted comparing the results of exercise compared with antidepressant medication. Only two studies, both from researchers at Duke University, compared the effectiveness of exercise with pharmacotherapy. No differences between exercise and antidepressant medication were noted (SMD = –0.04 [95% CI –0.31, 0.24]).

In the first Duke study, known as the SMILE study (Standard Medical Interventions and Longterm Exercise), we compared the effects of aerobic exercise to sertraline treatment among 156 older adults with MDD (Blumenthal et al., 1999). Participants were randomized to either aerobic exercise, sertraline, or a combined exercise and sertraline group. The treatment period of the trial lasted 16 weeks and participants' depression severity was assessed before and after treatment by a psychologist blinded to treatment condition. Participants in the exercise conditions exercised three times per week at 70–85% of their heart rate reserve. Importantly, participants exercised in groups, which were supervised by a study exercise physiologist. Participants in the sertraline condition were titrated for therapeutic response on sertraline by a study psychiatrist (50–200mg). Following 16 weeks of treatment, groups did not differ in their level of depressive symptoms. However, analysis of trajectory of change of depressive symptoms showed that patients receiving sertraline alone showed a faster initial response in the first 2 weeks compared with either the combination group or the exercise alone group. Interestingly, a follow-up examination of these participants conducted 10 months after the completion of the treatment period showed that participants in the exercise group showed lower rates of depression relapse in comparison with both the sertraline and combined groups (Babyak et al., 2000). The results were difficult to interpret, however, since many participants initiated exercise on their own following the completion of the 4-month trial. At the time of follow-up assessments, 48% of participants in the sertraline group began exercising, and 64% of participants in the exercise group and 66% of participants in the combination group continued to exercise following the trial intervention.

Regardless of group assignment during the active portion of the trial, participants who reported engaging in regular exercise during the follow-up period were more than 50% less likely to be depressed at their 10-month assessment.

In a second SMILE study, we extended these findings by including a placebo control group and by including a home-based exercise condition in which participants exercised at home on their own without supervision (Blumenthal et al., 2007). Participants were randomized to either home-based or supervised aerobic exercise, sertraline, or placebo pill for a 4-month period. Home-based exercisers were provided with the same exercise prescription as supervised participants and received an initial home visit to establish their exercise training routine, as well as instructions on how to monitor their heart rates accurately. Again, treatment allocation was concealed and participants' depressive symptoms were assessed by a psychologist blinded to treatment condition before and after the trial. Results revealed that participants in either exercise or sertraline groups tended to show greater improvement in comparison with placebo participants and these results became statistically significant when "early responders" (i.e., participants who experienced a self-reported improvement in depressive symptoms of >50% within the first week of treatment) were eliminated from analyses. In a recent follow-up analysis (Hoffman et al., 2011), participants' depression was reassessed one year following their completion of the active treatment phase of the intervention. Interestingly, neither group assignment nor antidepressant medication usage during the follow-up period was a significant predictor of depression at this follow-up time-point. Instead, the only significant predictor was self-reported exercise during the follow-up period. Regardless of group assignment or background characteristics, those individuals who engaged in regular exercise were less likely to be depressed at follow-up.

We also recently examined the impact of exercise or pharmacotherapy on depressive symptoms among individuals with coronary artery disease participating in the UPBEAT trial (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) (Blumenthal et al., 2012b). One hundred and one participants were randomized to receive either supervised aerobic exercise, sertraline, or placebo treatment for 4 months. Participants in the exercise and sertraline groups showed improvements in depressive symptoms compared with the placebo group. Participants in the exercise and sertraline groups also showed improvements in heart rate variability compared with placebo participants.

Adjunctive therapy

Several studies have examined the effects of exercise as an adjunctive therapy among patients already being treated with antidepressants or psychotherapy. Mather and colleagues (Mather et al., 2002) examined this question in a randomized trial of 86 outpatients with depression and free from cognitive impairment. Importantly, in order to be considered eligible for the trial, all participants had to have been in receipt of a therapeutic dose of antidepressant therapy for at least 6 weeks without evidence of sustained response. Participants were then randomized to either exercise classes or health education for 10 weeks. Participants in the exercise group exercised for 45 minutes twice per week, performing strength training exercises. Clinical improvement in depressive symptoms (i.e., "response" to treatment) was defined as a >30% reduction in clinician-rated depressive symptoms. At the end of the 10-week intervention, 55% of participants in the exercise group showed improvements, compared to 33% in the control group. However, the groups did not show significant differences in mean levels of depressive symptoms. Several other trials have examined the effects of exercise alone versus exercise combined with antidepressant therapy, with results generally showing that exercise is equally effective when compared with a combined intervention. Martinsen and colleagues (Martinsen, Medhus, & Sandvik, 1985)

examined the effects of exercise alone and combined with tricyclic antidepressants (TCAs). Specifically, 14 patients in the control group and 9 in the exercise group were given TCAs to augment treatment. Results showed that both groups exhibited similar improvements in depressive symptoms. In a second study, Martinsen and colleagues (Martinsen, Hoffart, & Solberg, 1989) compared aerobic and nonaerobic exercise in treating 99 inpatients with depression. Fourteen participants in each group were administered TCAs and results showed that exercise with TCA augmentation tended to show larger improvements in depression compared with exercise alone. As reviewed previously, Blumenthal and colleagues (Blumenthal et al., 1999) also examined the combined effects of aerobic exercise and sertraline versus either aerobic exercise or sertraline separately and found that all groups were equally effective in improving depression. Interestingly, a follow-up study 10 months after the completion of this intervention suggested that participants in the exercise alone group were the least likely to be depressed (Babyak et al., 2000).

One of the largest trials to examine exercise as an adjunctive treatment was the recently completed Treatment with Exercise Augmentation for Depression (TREAD) study (Trivedi, Greer, et al., 2006). In this randomized trial, 126 adults with unremitted depression following SSRI treatment were randomized to augmentation treatment with either 16 kcal/kg/week or 4 kcal/kg/week for 12 weeks. Although both groups showed lower remission rates with treatment, the higher-intensity exercise group showed greater rates of remission (28.3%) compared to the lower-intensity group (15.5%) (Trivedi et al., 2011).

Exercise prescriptions typically consider four critical elements: mode, frequency, duration, and intensity. Most studies have focused on aerobic exercise, but several studies have also considered resistance (strength) training alone or combined with an aerobic program. In the Mead meta-analysis both strength training and aerobic exercise interventions were effective in improving depression, but the aggregated effects of these different exercise modalities had a wide confidence interval, suggesting a large, heterogeneous effect of both types of training (Mead et al., 2009). Similarly, the Rethorst meta-analysis failed to find a relationship between exercise volume and improvement in depressive symptoms (Rethorst et al., 2009). In one of the more widely cited studies, Singh and colleagues (Singh et al., 2005) randomized 60 community-dwelling older adults with depression to either a high- or low-intensity progressive muscle training intervention, or a general practitioner control group. Following 8 weeks of intervention, depressive symptoms were most improved in the high-intensity group followed by the low-intensity group and then controls, demonstrating the value of strength training and suggesting a dose-response relationship between the intensity of strength training and the degree of improvement in depressive symptoms.

The issue of the intensity of aerobic exercise and whether greater intensity or duration of exercise is associated with dose-response improvements in depressive symptoms has also been the subject of both observational studies and RCTs. Observational studies have suggested a possible dose-response relationship between amount of physical activity and depressive symptoms (Hamer, Stamatakis, & Steptoe, 2009). Several RCTs have also examined this issue. In an early trial, DiLorenzo and colleagues (DiLorenzo et al., 1999) examined the effects of a variable intensity exercise intervention compared with a control condition on depressive symptoms among healthy adults. Exercise participants were randomized to either a 24-minute variable intensity exercise program four times per week or a 48-minute fixed intensity exercise program four times per week for a period of 12 weeks. Participants were assessed before and after the 12-week intervention and again at a 1-year follow-up. Exercise was found to have a beneficial effect on depressive symptoms in both exercise groups with no clear benefit of one exercise modality over another, and these findings persisted at one year.

In one of the more elegant RCTs that examined the optimal "dose" of exercise, Dunn and colleagues (Dunn, Trivedi, Kampert, Clark, & Chambliss, 2005) conducted a randomized, controlled trial of 80 young and middle-aged adults with mild to moderate MDD in which participants were randomized to treatment groups at varying levels of energy expenditure and frequency of exercise. Four aerobic exercise treatment groups were used, with two levels of energy expenditure (7 kcal/kg/week or 17.5 kcal/kg/week) and two levels of frequency (3 days per week or 5 days per week) for 12 weeks. 17.5 kcal/kg/week was selected because this level of energy expenditure corresponds to current public health recommendations. The authors found that participation in the 17.5 kcal/kg/week group was associated with the greatest improvements in depressive symptoms and remission rates, whereas the lower dose group was not significantly improved compared with control participants.

There is also some evidence to suggest that improvements in fitness may be associated with improvements in depressive symptoms among patients with cardiovascular disease, again suggesting a possible dose-response relationship. Among cardiac patients, for example, Milani and Lavie (Milani & Lavie, 2007) found that improvements in peak $\dot{V}O_2$ were associated with improvements in depression. In their retrospective analysis of cardiac rehabilitation participants, the authors found that those participants achieving modest (1–10%) or robust (>10%) increases in peak $\dot{V}O_2$ were likely to show reductions in depressive symptoms. Similarly, we have previously found that reductions in depression among individuals with hypertension were mediated by improvements in peak $\dot{V}O_2$ (Smith et al., 2007). However, in the Mead meta-analysis (Mead et al., 2009) only half of the trials showing improvements in fitness reported concurrent improvements in depressive symptoms.

Impact on depressive symptoms

Several studies have attempted to examine the effects of exercise on various clusters of depressive symptoms. Although depression is typified by depressed mood and anhedonia, many of the other symptoms are heterogeneous and may not present in any given depressed individual. Many previous factor analytic studies of depression inventories, for example, have identified different clusters of depressive symptoms. Although these vary somewhat between studies, they have generally clustered into three factors: affective factors (depressed mood, irritability, crying, etc.), somatic factors (sleep difficulties, fatigue, etc.), and cognitive factors (concentration difficulties, indecisiveness, etc.) (Vanheule, Desmet, Groenvynck, Rosseel, & Fontaine, 2008).

The impact of exercise on sleep has been examined in several studies, although none, to our knowledge, have examined aerobic exercise as a treatment for disturbed sleep among depressed adults. Observational studies have shown that regular physical activity is associated with better sleep (Penedo & Dahn, 2005). In addition, several intervention studies have shown that aerobic and strength training exercises improve sleep compared with a waitlist condition. King and colleagues (King, Oman, Brassington, Bliwise, & Haskell, 1997), for example, found that 16 weeks of four 30–40-minute aerobic exercise sessions improved sleep duration by 42 minutes among 48 community-dwelling adults. These findings were recently replicated using polysomnography to objectively measure sleep (King et al., 2008). Similar findings for aerobic exercise were reported among individuals with insomnia, as Reid and colleagues (Reid et al., 2010) have shown that a 16-week aerobic exercise intervention with sleep hygiene improved sleep duration by 75 minutes in the intervention group, while participants in the control condition improved by only 13 minutes. Although no studies of aerobic exercise on sleep have been conducted among depressed adults, Singh and colleagues (Singh et al., 2005) demonstrated that high-intensity weight training

was associated with improved sleep duration, efficiency, and latency, although low-intensity training and a control group also showed similar, albeit weaker improvements.

There is some evidence that exercise may also improve cognitive functioning, including memory, concentration, and executive functions, although few studies have examined this relationship. In a substudy from the SMILE study described earlier (Blumenthal et al., 1999), Khatri and colleagues (Khatri et al., 2001) found that several measures of memory and executive function were modestly improved following a 16-week exercise intervention as compared to antidepressant medication, although no improvements were observed in attention/concentration or psychomotor speed. In contrast, a more recent substudy (Blumenthal et al., 2007) by Hoffman and colleagues (Hoffman et al., 2008) failed to find cognitive benefits associated with exercise compared with placebo participants following a 16-week intervention. Although exercise may not impact cognitive function among individuals with depression directly, there is evidence that cognitive coping thoughts may be improved with exercise (Stathopoulou et al., 2006). Quasi-experimental studies have shown that women participating in exercise reported higher coping self-efficacy, greater use of distraction, and lower depression compared with control participants (Craft, 2005), and similar findings have been suggested for anxiety (Steptoe, Edwards, Moses, & Mathews, 1989). Interventions targeting self-efficacy appear to have particularly strong effects in improving positive affect (Bodin & Martinsen, 2004), which is associated with lower levels of depression.

Other populations

Although the majority of existing evidence has examined the effects of exercise among adults with depression, several trials have been conducted among other populations, including adolescents, women with post-partum depression, and older adults (Greer & Trivedi, 2009). Few studies have been conducted among adolescents and the only available quantitative review of these studies found no high-quality trials examining this question (Larun et al., 2006). Preliminary evidence, however, suggests benefits associated with exercise among depressed youth. For example, Brown and colleagues (Brown, Welsh, Labbe, Vitulli, & Kulkarni, 1992) found that supplemental aerobic exercise training improved depressive symptoms among hospitalized psychiatric patients over the course of a 9-week intervention. Most recently, Nabkasorn and colleagues (Nabkasorn et al., 2006) found that group jogging improved depressive symptoms among 49 females aged 18–20 with mild-to-moderate depressive symptoms. Participants were randomized to either five 50-minute jogging sessions or to usual daily activities for 8 weeks. Following the intervention, participants in the exercise group showed reduced depressive symptoms in comparison with control participants, as well as reduced cortisol and epinephrine levels assessed from 24-hour urinary excretions.

Another area of interest has been the effects of exercise in women following childbirth. Postpartum depression is common and associated with poorer quality of life. Although few studies have examined the effects of exercise in postpartum depression, preliminary evidence suggests improvements in depressive symptoms. Participation in physical activity following childbirth has been associated with improved mood and reduced anxiety (Koltyn & Schultes, 1997) and two randomized trials have suggested positive benefits of increased physical activity during the postnatal period (Armstrong & Edwards, 2004; Heh, Huang, Ho, Fu, & Wang, 2008). Heh and colleagues (Heh et al., 2008) alternately assigned 80 first-time mothers with depressive symptoms to an exercise support group or control group beginning 6 weeks after childbirth. Participants in the exercise group participated in 1 hour of exercise per week at the hospital and two exercise sessions at home per week using an audio-guided regimen for 3 months. Following the 3-month

intervention, participants in the exercise group were less likely to have elevated depression scores in comparison with control participants. Armstrong and colleagues (Armstrong & Edwards, 2004) conducted a similar randomized intervention of pram-walking among mothers who had given birth within the last 12 months. Participants assigned to pram-walking, who exercised twice per week for 40 minutes at 60–75% of age-predicted heart rate, showed improvements in both fitness and depressive symptoms compared to a social support control group.

Several randomized trials have been conducted among depressed older adults. In the UPLIFT trial, Sims and colleagues (Sims, Hill, Davidson, Gunn, & Huang, 2006) randomized adults aged 65 and older with depressive symptoms to progressive resistance training three times per week for 10 weeks, or to a brief advice control group. Participants in the exercise group tended to have lower Geriatric Depression Scale scores (P = .08) and a strong correlation was found between improvement in depressive status and number of exercise sessions completed in post hoc analyses (r = -0.8). In the Depression in Late Life Intervention Trial of Exercise (DeLLITE) (Kerse et al., 2008), participants aged 75 years and older with depressive symptoms were randomized to either an individualized physical activity program or to a social visit control condition. The exercise condition used moderate-intensity balance training, progressive resistance exercises, and walking, which were conducted three times a week for 30 minutes. Both groups showed improvements in psychosocial outcomes, without significant between-group differences, suggesting that both interventions were beneficial on psychosocial outcomes. As reviewed earlier, Blumenthal and colleagues (Blumenthal et al., 1999) also conducted an aerobic exercise, sertraline, or combined intervention among depressed adults. Results of this trial showed that all groups had improvement in depression severity, without significant between-group differences. In addition, a follow-up study from this trial suggested that regular physical activity was associated with significantly improved rates of remission (Babyak et al., 2000).

Proposed mechanisms

A number of potential biologic, social, and psychological mechanisms for the antidepressant effect of exercise have been proposed and are beyond the scope of this chapter. They are described in detail in the next two chapters.

Summary and future directions

In summary, available evidence suggests that exercise is an effective treatment for depression, improving depressive symptoms to a comparable degree as pharmacotherapy and psychotherapy. Observational studies generally have shown that individuals who are more physically active have lower rates of depression, although it is less clear whether greater physical activity levels protect against the subsequent development of depression. The majority of evidence supports aerobic exercise as a treatment for depression among adults, although a growing body of evidence supports its use as a treatment among adolescents as well, and also that other forms of exercise, including resistance training, may be effective. It appears that any level of exercise is better than no exercise. There have been relatively few studies that have examined the optimal dose of exercise, although available evidence suggests that 12–16 weeks of treatment may be necessary for therapeutic benefit and that the total volume of exercise may be more important than either frequency or intensity. A number of possible mechanisms have been suggested to explain how exercise may reduce depression, and examination of putative mechanisms is an important area for future research. In addition, more rigorous RCTs are needed in order to assess the beneficial effects of exercise for depression in adolescents and young adults. Other patient populations, including patients with

coronary disease, should also be the focus of further research, especially in light of the accumulating evidence that depression in cardiac patients is a risk factor for increased morbidity and mortality, as well as for reduced quality of life.

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