

Chapter 15

Exercise and Physical Activity for Depression

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Chapter Overview

Depression is a leading cause of global disease burden. Standard treatments include pharmacologics and psychotherapy; however, these treatments are not effective for everyone and are associated with several barriers and a substantial side effect profile. There is a need to identify alternative approaches that can be used to treat, or even prevent depression. Exercise and physical activity are two lifestyle behaviors that have been touted for decades as strategies used in the prevention and treatment of depression. The purpose of this chapter is to provide an overview of the scientific evidence supporting the role of these two lifestyle behaviors used in the prevention and treatment of depression. This chapter is organized by first providing insight into the burden of depression, how it is defined and diagnosed, and main treatment approaches. We then outline the scientific evidence for the role of exercise and physical activity in the prevention and treatment of depression. We also discuss plausible neurobiological mechanisms of the exercise-depression relationship and challenges associated with establishing such mechanisms. An overall summary is then provided and outstanding areas of inquiry for future research are highlighted throughout the chapter.

Depression

Prevalence and Burden

Major depressive disorder (MDD) is one of the most common mental illnesses, with point estimates from the Global Burden of Disease Study indicating a mean global prevalence of 3.6% each year between the years 1990 and 2019 (Global Burden of Disease Collaborative Network, 2020). MDD is a leading cause of disability around the world (Friedrich, 2017) that results in a loss of work productivity and increased morbidity (Cuijpers et al., 2014; Walker et al., 2015). MDD is also highly recurrent, with about 35% of individuals experiencing an additional MDD episode within the first year of recovery (Hardeveld et al., 2010). Even after 15 years following recovery, up to 85% of individuals experience another MDD episode. Therefore, it is unsurprising that MDD often exacts profound suffering and places a staggering burden on individuals, families, and society. Indeed, the total estimated economic burden (i.e., indirect and direct costs attributed to depression) of people with MDD was US\$210.5 billion in 2010, with ~US\$27.7 billion in direct costs due to medical and pharmaceutical services directly related to MDD treatment (Greenberg et al., 2015).

How is Depression Diagnosed?

Current diagnostic practices rely on the *Diagnostic and Statistical Manual, Fifth Edition* (DSM-5; American Psychiatric Association, 2013) and use specific symptoms as indicators of depression to reach a diagnostic threshold. To constitute a DSM-5 MDD diagnosis, an individual must endorse five of nine symptoms that are present for a minimum of 2 weeks and persist for most of the day, nearly every day (American Psychiatric Association, 2013). In terms of symptoms, individuals must endorse at least one of two core criterion symptoms: depressed or low mood (e.g., feelings of sadness) and/or loss of interest or pleasure in almost all typically or previously enjoyable activities (i.e., anhedonia). An individual must also endorse at least four other symptoms: (a) significant unintentional change in weight or appetite; (b) sleep disturbances (defined as insomnia or hypersomnia); (c) severe psychomotor agitation (e.g., restlessness) or retardation observable by others (e.g., slowed speech or movement patterns); (d) fatigue or low energy; (e) a sense of worthlessness or excessive guilt; (f) impaired ability to think or concentrate and make decisions; or (g) recurrent thoughts of death that include suicidal ideation and/or attempts. Any symptom combination including at least one core criterion symptom and four additional symptoms constitutes a MDD diagnosis. Importantly, these above-mentioned criteria are also used to inform and issue a MDD diagnosis in the United Kingdom (National Collaborating Centre for Mental Health and National Institute for Health and Clinical Excellence, 2010).

Treatments for Depression

Clinical practice guidelines recommend the use of pharmacotherapy (i.e., antidepressant drugs), psychotherapeutic approaches (e.g., cognitive-behavioral therapy [CBT]), or a combination of the two as first-line treatments for MDD (American Psychiatric Association, 2010; American Psychological Association-Depression Guideline Development Panel, 2019; National Collaborating Centre for Mental Health and National Institute for Health and Clinical Excellence, 2010). In terms of pharmacotherapy, antidepressant drugs, namely selective serotonin reuptake inhibitors (SSRIs), are among the most prescribed medications and work by blocking the reuptake of serotonin. Other classes of antidepressant drugs are also prescribed, including serotonin and norepinephrine reuptake inhibitors (SNRIs), and norepinephrine and dopamine reuptake inhibitors (NDRIs); all of which work by inhibiting the reuptake of their targeted neurotransmitter(s), thereby increasing its availability, and altering their levels in the brain.

Despite antidepressant drugs being among the most widely prescribed drugs globally, they are not consistently beneficial. For example, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which is the largest depression treatment trial ever conducted and funded by the U.S. National Institute of Mental Health, the effectiveness of antidepressant drug treatments was examined among 4,041 patients with a MDD diagnosis (age range = 18–75 years). In both specialty and primary medical care settings, patients were exposed to a tiered approach consisting of four separate treatment levels. The trial was structured such that patients who were unable to achieve remission—defined as becoming symptom-free following treatment—at one level would then move onto the next treatment level, which could consist of either a switch to a different antidepressant drug or a combination of antidepressant drug with add-on psychotherapy.

STAR*D study results indicated that between 28% and 33% of the patients achieved remission following an initial 14-week treatment with citalopram (Trivedi et al., 2006). After multiple treatment steps, Rush et al. (2006) reported a cumulative remission rate of 67%, which was computed by summing remission rates achieved across all trial stages. As highlighted by Ekkekakis (2021), it is important to note, however, that the actual remission rate is a bit unclear given that a re-analysis of the available data from the trial resulted in a remission rate of 2.7% when appropriately accounting for patients who dropped out or relapsed and remained in the trial at the end of the original trial duration (see Pigott, 2011, 2015). Regardless of the “true” remission rate, many patients were left symptomatic or clinically depressed following the STAR*D trial, which highlights the variable and limited effectiveness of antidepressant drugs in depression treatment. Furthermore, research has shown that even among patients who achieve remission using antidepressant drug treatment, long-term outcomes are uncertain, as estimates indicate that approximately 40% of remitted patients are likely to relapse within a two-year period (Boland & Keller, 2008).

The efficacy of antidepressant drugs to treat depression was also examined in a meta-analysis of six studies that evaluated the impact of antidepressant drugs in randomized placebo-controlled depression treatment trials approved by the U.S. Food and Drug Administration. After aggregating individual patient-level data from 434 patients receiving antidepressant drugs and 284 patients in placebo groups across six separate trials, Fournier et al. (2010) found that antidepressant drug efficacy varied as a function of depressive symptom severity. Only patients exhibiting severe symptoms of depression before enrolling in the trial experienced significant pre-to-post treatment reductions in depressive symptoms compared to those in placebo control groups. Antidepressant drugs were no more efficacious in reducing depressive symptoms compared to placebo control for patients experiencing mild-to-moderate symptom severity before treatment.¹ Despite their limited efficacy, there are also several barriers associated with antidepressant drugs, such as costs and a vast side effect profile, including but not limited to nausea, vomiting, diarrhea, dry mouth, constipation, and sexual dysfunction. These side effects are intolerable (Corponi et al., 2020) and a primary contributor for treatment discontinuation and poor patient compliance (Lader et al., 2004).

Various forms of psychotherapy, including CBT and behavioral activation, are broadly used to treat MDD and have shown effectiveness in reducing depression (e.g., Cuijpers et al., 2013). In the largest quantitative review conducted on the topic, Cuijpers et al. (2020) assessed whether psychotherapeutic approaches were effective in reducing depression and whether effects differed across the lifespan. The authors compiled data from 366 randomized controlled trials (RCTs) and found that psychotherapy was generally effective, resulting in moderate-to-large depressive symptom reductions among individuals with clinically diagnosed depression of all ages, with moderate-to-large

¹ Those interested in learning more about research regarding the use of antidepressant drugs in the treatment of depression should refer to review articles and commentaries by Kirsch et al. (2008), Kirsch (2014), Kirsch (2019), Möller (2008), and Turner et al. (2008).

effect sizes. As with antidepressant drugs, psychotherapy is associated with variable success rates, with many individuals often failing to adequately respond or derive antidepressant benefits to psychological treatments (DeRubeis et al., 2005). Moreover, there are several barriers to accessing psychotherapy for many individuals. Psychotherapy is costly and its effectiveness depends on some of the following: (a) availability and accessibility of mental health professionals (Olfson & Marcus, 2010); (b) characteristics of the mental health professional (Olfson et al., 2009); (c) the delivery of intervention (e.g., internet-delivered versus face-to-face versus group-based); and (d) individual preferences.

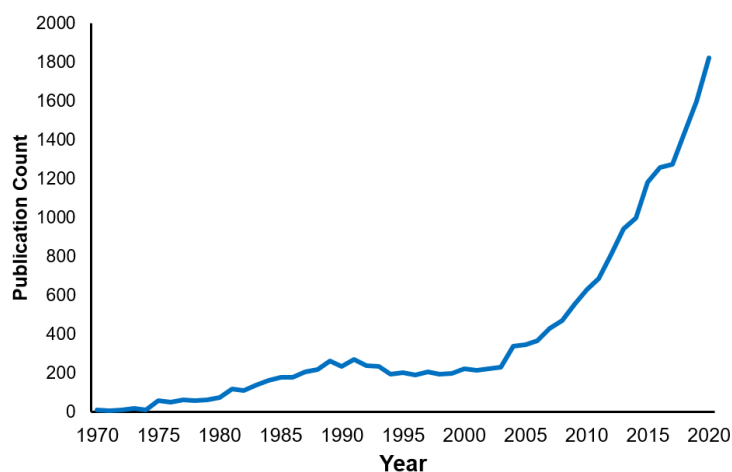
Purpose of the Chapter

Given the variable effectiveness and barriers associated with first-line treatments, there is an urgent need to identify alternative strategies or interventions that can be used to treat depression or prevent the occurrence of the disorder altogether. Exercise and physical activity are two lifestyle behaviors that have been touted for decades and even centuries in the management and treatment of depression. For example, ancient physicians and philosophers including Hippocrates (460 BCE–370 BCE), Suśruta (or Sushruta; 600 BCE) and Hua T'o from the Eastern Han Dynasty (25 CE–220 CE) recognized the importance of engaging in regular physical activity to maintain health. In particular, Hippocrates, considered by many to have been the first physician to prescribe exercise for a patient suffering from a mental health condition, believed that “eating alone will not keep a man well; he must also take exercise” (Jones, 1923; p. 229).

In the context of depression, exercise and physical activity did not gain significant traction in the scientific literature until seminal studies by William P. Morgan were published in the late 1960s to early 1970s. For example, Morgan conducted the first observational studies to indicate that patients with depression tended to have lower cardiovascular fitness levels compared to non-depressed healthy counterparts (Morgan, 1968, 1969; Morgan et al., 1970). These early efforts laid the foundation for decades of work to follow and since then, there has been burgeoning research interest in this area (see Figure 15.1), which has resulted in substantial progress toward establishing these two lifestyle behaviors as important strategies to ward off depression.

Figure 15.1

Annual Number of Research Publications on the Exercise and Physical Activity–Depression Relationship from 1970–2020



Note. The data used to create this figure were adapted from PubMed by using the search terms “exercise” OR “physical activity” AND “depression” between the years of 1970 and 2020.

In this chapter, we examine the research evidence related to exercise and physical activity² as prevention and treatment strategies used for depression. We will first summarize the evidence base of exercise and physical activity in the prevention of depression. Then, we will summarize the current evidence on the influence of exercise as a treatment for depression before offering insight into possible neurobiological mechanisms associated with the exercise-depression relationship. We highlight open questions that need to be explored in future research to help elucidate on the exercise, physical activity, and depression relationship throughout the chapter. Before presenting the evidence base, it is important to gain insight into how MDD and depressive symptoms are measured to understand conclusions that can be drawn from the evidence.



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Measurement of Major Depressive Disorder and Depressive Symptoms

Depression is characterized by substantial symptom heterogeneity, which makes its assessment difficult. For example, combinations of the nine DSM-5 criteria required for a MDD diagnosis results in 227 unique depressive symptom profiles (Fried & Nesse, 2015). Furthermore, Fried (2017) assessed content overlap of the seven most commonly used depression scales in scientific research and found 52 disparate symptoms, with little symptom overlap across instruments. Therefore, it is important to note that measurement of depression is a challenging endeavor because there is no single measure that can account for its complexity. MDD diagnoses are made using well-validated clinical interviewing instruments, while depression symptom severity is measured using self-report rating scales. Researchers often combine clinical interviews with rating scales to provide insight into the presence and nature of an individual's depression. For the purposes of this chapter, we provide a brief overview of some of the most prevalent diagnostic interviews and rating scales used in research to measure MDD and depressive symptoms.

² Physical activity is broadly defined as any bodily movement resulting in energy expenditure, while exercise is a subset of physical activity that is performed for the intention of improving or maintaining one or more aspects of physical fitness (Caspersen et al., 1985).

Diagnostic Interviews

Structured Clinical Interview for DSM-5 (SCID-5)

The SCID-5 is the most widely used structured diagnostic interview for assessing the DSM-5 disorders (First et al., 2015). Clinical psychologists and psychiatrists and other trained mental health professionals use the SCID-5 to assess for the presence of lifetime and current depressive disorders and other psychiatric disorders such as anxiety disorders (see Chapter 16; Schuch et al., 2021), psychotic disorders (see Chapter 17; Fibbins et al., 2021), substance use disorders, somatic symptom disorders, externalizing disorders and trauma-and stressor-related disorders. Research suggests that the SCID-5 has excellent reliability, sensitivity, and specificity for most of the psychological disorders with high prevalence, even when the clinical interview is conducted over the telephone (Osório et al., 2019). Due to its popularity, the SCID-5 has been translated into other languages and has been used in a variety of cultures.

Mini International Neuropsychiatric Interview (MINI)

The MINI is a short, structured diagnostic interview developed jointly by clinicians in the U.S. and Europe that follows diagnostic criteria outlined in the International Classifications of Disease and DSM-5 (Sheehan et al., 1997). The MINI is typically used in research to reduce the amount of time it takes to assess and diagnose depression. Research suggests that the reliability and validity of the MINI is on par with the SCID (Sheehan et al., 1997). The MINI can be conducted within 15 minutes and can serve as a short and accurate assessment of psychopathology.

Dimensional Measures of Depressive Symptoms

Depressive symptoms have been measured using a variety of self-report rating scales. Three commonly used rating scales of depressive symptoms are described below. These rating scales assess current depressive symptoms severity over a specified time interval and aid in determining whether treatments are effective in reducing depressive symptoms.

Beck Depression Inventory, Second Edition (BDI-II)

The BDI-II assesses the presence of depressive symptoms during a two-week period using 21 items scored on a 4-point Likert scale ranging from 0-3. Higher scores indicate greater severity of depressive symptoms (Beck et al., 1996). A score of 13 or higher on the BDI-II is generally an indication of the presence of a depressive disorder and the BDI-II has shown high sensitivity and specificity when utilized as a screening tool (Lasa et al., 2000). The BDI-II has shown good internal consistency and validity across different settings and populations (Steer et al., 1999, 2000).

Hamilton Rating Scale for Depression (HRSD)

The HRSD is a reliable assessment of the severity of depressive symptoms using 17 items scored from 0-4 (Trajković et al., 2011). A total score is obtained by summing all the items together. The HRSD provides categories that indicate the severity of depressive symptoms based on the total score. For example, a total score from 0-7 indicates normal levels of depressive symptoms, 8-16 suggests mild depression, 17-23 suggests moderate depression, and a score ≥ 24 indicates severe depression (Sharp, 2015).

Center for Epidemiologic Studies Depression Scale (CES-D)

The CES-D was originally developed to assess the number and frequency of depressive symptoms in the general population (Radloff, 1977). The CES-D exhibits strong psychometric properties, including high internal consistency and good divergent and convergent validity (Van Dam & Earleywine, 2011). The CES-D has also been validated for use in a variety of age groups, including adolescents and

young adults (Roberts et al., 1990). The CES-D has 20 items scored from 0-3. A total score is computed by summing all the items together, with possible scores ranging from 0-60. Higher scores indicate more symptoms and are weighted by frequency of occurrence during the past week. CES-D scores that are at least 16 or greater have been shown to identify individuals at risk for clinical depression (Lewinsohn et al., 1997).

In 2004, the original CES-D was revised by Eaton et al. to reflect depressive symptoms more accurately as indicated by the DSM. The CESD-R (i.e., Center for Epidemiologic Depression Scale Revised; Eaton et al., 2004) is also 20 items, with each item scored on a scale of 0-3. Higher scores reflect greater severity of depressive symptoms. Based on scoring, participants can be categorized into one of five possible depressive categories: meets criteria for major depressive episode, probable major depressive episode, possible major depressive episode, subthreshold depression symptoms, or no clinical significance. An advantage of using the CESD-R compared to other instruments is that it is free and accessible as a part of the public domain (see <https://cesd-r.com/>).

Exercise and Physical Activity in the Prevention of Depression

The potential for exercise and physical activity to prevent depression has been studied across a number of cross-sectional and prospective epidemiological studies. One of the earliest epidemiological studies to examine the relationship between physical activity levels and depression was conducted when Farmer and colleagues (1988) analyzed data from the Epidemiologic Follow-Up Study (1982–1984). Farmer et al. (1988) looked at the association between depressive symptomatology, as measured by the CES-D, and self-reported recreational and nonrecreational physical activity levels. Among 1,900 healthy adults between the ages of 25 and 77 included in analyses, increased depressive symptoms were related to lower levels of recreational physical activity. Interestingly, individuals engaging in little-to-no recreational physical activity were at almost a two-fold elevation in odds of experiencing increased depressive symptoms compared to those engaging in regular recreational physical activity. To determine whether recreational physical activity levels were a unique risk factor for increased depressive symptoms, the authors examined the influence of age, race, education, employment status, self-reported chronic health conditions, and household income on the relationship. After accounting for these variables, lower recreational physical activity levels still significantly related to increased depressive symptoms.

Goodwin (2003) extended this work by examining the relationship between regular physical activity levels and rates of MDD diagnoses among 5,877 Americans (~57% female) between the ages of 15 and 54 years who participated in the National Comorbidity Survey (1990–1992). Physical activity levels were assessed using a self-report item that asked participants, “How often do you get physical exercise—either in your job or in a recreational activity?”; MDD diagnoses were confirmed using a structured interview (i.e., the World Health Organization Composite International Diagnostic Interview). Goodwin found that regularly active individuals had a 25–38% reduced likelihood of having a MDD diagnosis compared to those who engaged in lower levels of physical activity. Importantly, this relationship remained significant even after accounting for important sociodemographic variables, such as age, gender, race, marital status, education, and income, suggesting that lower physical activity levels independently confer risk for MDD. There was also a significant dose-response³ relationship between frequency of physical activity and current prevalence of MDD in the sample, such that MDD was least prevalent among individuals who regularly engaged in physical activity (8.2%) compared to those who occasionally engaged in physical activity (11.6%), those who rarely engaged in physical activity (15.6%), and those who never engaged in physical activity (16.8%).

³ Dose-response refers to the amount of exercise or physical activity (duration, intensity, and frequency) that results in graded effects.

Gudmundsson and colleagues (2015) examined the relationship between physical activity and depression in a large-scale, prospective study of 676 Swedish women (M_{age} at baseline in 1974 = 53.4 years; $SD = 0.2$) followed over 32 years (1974–2005). Depression was measured using semi-structured interviews and the Montgomery-Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979), which assesses the presence of symptoms and signs of depression over the past month. Physical activity levels were self-reported and measured using the Saltin-Grimby Physical Activity Level Scale (Saltin & Grimby, 1968), which indexes an individual's physical activity frequency and intensity. Four separate assessments occurred across the 32-year study in 1974, 1992, 2000, and 2005, which allowed the authors to test several hypotheses. First, the authors examined cross-sectional associations and showed that lower physical activity levels were associated with increased depressive symptoms at the baseline assessment in 1974. Next, the authors were interested in determining whether changes in physical activity levels coincided with changes in depressive symptoms over time. There was a significant relationship between physical activity levels and depressive symptoms, such that decreasing physical activity levels were associated with increased depressive symptoms over time. Lastly, the authors tested whether the relationship between physical activity and depressive symptoms was bidirectional and wanted to determine whether initial depressive symptoms could predict subsequent physical activity levels. Women reporting increased depressive symptoms at the 1974 baseline assessment reported less engagement in subsequent physical activity at later time points in 1992 and 2000, but not in 2005. This study provides evidence for a potential bidirectional relationship between physical activity and depression from a large and well-characterized sample of women followed over the span of three decades and suggests that physical activity may not only be a risk factor for depression but may also be a long-term consequence of depression.

There may be specific aspects of depression that could explain the prediction of lower subsequent physical activity from depressive symptoms. For example, one of the core criterion symptoms of depression is the loss of interest or pleasure in almost all typically or previously enjoyable activities (i.e., anhedonia). In a study by Leventhal (2012), the author examined whether anhedonia was related to physical activity participation levels in a sample of 157 undergraduate students ($M_{\text{age}} = 19.9$ years; $SD = 1.8$). Increased anhedonia was associated with lower physical activity levels, providing preliminary support for the notion that anhedonia, rather than other symptoms of depression, may be associated with lower physical activity participation. It is important to be cautious in interpreting these preliminary data. Leventhal used a normative sample of undergraduate students to examine the relationship between concurrent levels of anhedonia and physical activity. The sample was relatively homogenous in terms of physical and mental health status and was more physically active compared to the general population. Further, the causative nature of the relationship cannot be established since the study employed a cross-sectional design. Therefore, these findings are only suggestive, but provide a template for examining specific symptoms of depression (e.g., anhedonia) and whether they can explain physical activity participation in clinically depressed samples.

Other prospective studies have shown significant relationships between physical activity levels and depression. A ten-year cohort study of 424 patients with depression (M_{age} at baseline = 39.9 years; $SD = 14.1$; 54% female) found that higher physical activity levels were associated with lower concurrent depressive symptoms at four separate assessment points spanning 10 years (Harris et al., 2006). This evidence corroborates previous findings demonstrating that increased physical activity is associated with a reduced incidence of depression diagnoses and symptoms.

The preventive effects of physical activity on depression (i.e., symptoms and diagnoses) have also been summarized in reviews (Mammen & Faulkner, 2013; Teychenne et al., 2008). Teychenne and colleagues (2008) performed a literature review of observational and interventional research on the relationship between physical activity and depression in adults. The authors were interested in identifying the influence of physical activity characteristics (i.e., dose, domain, and physical activity

setting) on depression outcomes. There were inverse associations between physical activity and the likelihood of developing depression. Even lower doses of physical activity (i.e., 1.5 hours of moderate-intensity leisure time physical activity per week) demonstrated a protective effect against developing depression. Leisure-time physical activity was associated with a decreased likelihood of depression, while there was insufficient evidence regarding the role of other physical activity characteristics on depression.

In 2013, the Mammen and Faulkner review aimed to update the findings from Teychenne et al. by reviewing high quality research, which was determined using criteria from the Critical Appraisal Skills Programme (CASP; see <https://casp-uk.net/>) for prospective studies. Mammen and Faulkner aimed to address three important questions: (a) do baseline physical activity levels prevent follow-up depression?; (b) is there a specific dose of physical activity that protects against depression?; and (c) do physical activity levels over time impact risk for subsequent depression?. To address their first question, Mammen and Faulkner (2013) examined studies including assessments spanning at least two separate time intervals (range of follow-up period = 1–40 years) among nonclinical community samples of women/girls and/or men/boys between the ages of 11 and 100 years. Twenty-five of 30 reviewed studies supported the notion that baseline physical activity levels protect against the incidence or onset of subsequent depression. To address their second question, the authors found that engaging in as little as 10–29 min of daily physical activity could reduce subsequent risk for depression by 10% (e.g., Lucas et al., 2011), while other research showed that being physically active just one-to-two or more times per week was associated with a 40% reduced risk for depression (Bernaards et al., 2006; Hamer et al., 2009). To address their third question, the authors found that engaging in less physical activity over time was associated with an increased risk of developing depression compared to those who either maintained or increased their activity levels over the same time frame. These findings led Mammen and Faulkner to conclude that there was sufficient support for the preventive effects of physical activity on depression, even when physical activity is performed at low levels.

A few years later, Schuch et al. (2018) conducted a meta-analysis of 49 prospective studies that included 266,939 individuals (median proportion of males = 47%) with physical activity and depression measurements at baseline and a follow-up assessments (mean follow-up period = 7.4 years; range of follow-up period = 2–15 years) across studies. The authors found that individuals of all ages (youths, working-age adults, elderly persons) who engaged in more physical activity had 16.3% decreased odds of developing future depression. These findings were observed across geographical regions around the world (Asia, Europe, North America, and Oceania) and across genders.

Exercise programs may also have preventive effects. In 2020, Hu and colleagues performed a systematic review of eight meta-analyses that comprised a total of 134 individual studies examining the role of exercise interventions in the prevention of depression. In their review, Hu et al. (2020) examined the impact of exercise on depression across the lifespan among the general population and found moderate depressive symptom reductions among children, adolescents, adults, and the elderly. Although exercise interventions decreased depressive symptoms among the general population, the authors were unable to examine whether the incidence of MDD could be prevented, as no research has specifically investigated this relationship. A notable finding was that low-intensity exercise was comparable to higher intensities of exercise in reducing depressive symptoms; however, the authors noted that this evidence is of low-quality and needs to be investigated further.

The above-mentioned evidence highlights the preventive effects of physical activity and exercise on depression and symptoms of depression; however, the following questions remain: (a) does physical activity *causally* protect against—or decrease risk for—depression; or (b) does depression *causally* reduce physical activity? These two questions formed the basis for an investigation by Choi and colleagues (2019). To answer these questions, the authors used bidirectional Mendelian Randomization

(MR),⁴ a genetically informed method for establishing causality in large-scale observational studies by testing whether genetic variants in a potential underlying trait (or risk factor) are associated with an outcome of interest. In bidirectional MR, researchers can evaluate whether the underlying trait causes the outcome and vice versa. In the Choi et al. (2019) study, the authors performed MR analysis in one direction (i.e., physical activity to depression), and then performed the analysis in the opposing direction (i.e., depression to physical activity) using genetic variants associated with each trait.

Choi et al. (2019) extracted physical activity and depression data from the U.K. Biobank Study (Klimentidis et al., 2018; Wray et al., 2018) to examine relationships between physical activity and depression. Physical activity was assessed using device-based (accelerometry) and subjective (self-report) assessments and MDD was assessed using structured clinical interviews to make a lifetime MDD diagnosis, clinician-administered checklists, or medical record reviews (see Wray et al., 2018 for details). When testing the causal pathway of physical activity to depression, the authors found that each 1SD unit increase in accelerometer-assessed physical activity was associated with a 26% reduction in risk for developing MDD. This 1SD increase in accelerometer-assessed physical activity was reported as being equivalent to replacing time spent engaging in sedentary behaviors (e.g., sitting) with 15 min of vigorous physical activity, 60 min of moderate physical activity, or a combination of light and more vigorous activities. Notably, this relationship was only evident for the accelerometer-assessed measurements of physical activity, not self-reported physical activity, suggesting that measurement artifacts associated with different self-report instruments (e.g., cognitive biases, memory recall bias) could influence inferences drawn from studies examining the physical activity-depression relationship. When testing the causal pathway of depression to physical activity, the authors found no associations, regardless of how physical activity was measured. Thus, there seems to be more evidence supporting the causal pathway of physical activity to depression rather than the reverse. That is, physical activity may offer protection against the development of depression and symptoms of depression.

Overall, the available evidence indicates that physical activity and exercise are effective strategies for preventing depression. Although some research suggests that the relationship may be bidirectional (e.g., Gudmundsson et al., 2015), the study by Choi and colleagues (2019) indicates that there may be more robust evidence supporting the preventive role of physical activity on depression.

Exercise and Physical Activity in the Treatment of Depression

Initial research on exercise as a treatment for depression was conducted in the 1980s and 1990s. These findings were first summarized in a quantitative review by North and colleagues (1990) who found that exercise alleviated depressive symptoms and demonstrated comparable effectiveness—and at times increased effectiveness—to traditional treatments (e.g., antidepressant drugs and psychotherapy). A major limitation of their review was the heterogeneous composition of the patient samples. That is, the review included both nonclinical and clinical samples. Nonetheless, this meta-analysis was the first to quantitatively demonstrate the potential benefits of exercise for reducing depressive symptoms and laid the foundation for growing interest in exercise as a treatment for depression.

In the following sections, we outline the evidence examining exercise as a treatment for depression and document the potential utility for exercise to be used either as a stand-alone or complementary intervention to existing depression treatments. To date, research has examined the effects of exercise on depression using short- (acute) and long-term (chronic) interventions. Acute

⁴ For additional reading on MR and how it can be used in physical activity studies to strengthen causal inferences, refer to the research by Byrne et al. (2017) and Choi et al. (2019), respectively. Zheng et al. (2017) also provide an overview of the different types of MR studies that can be used to evaluate causality in observational epidemiological studies.

interventions have focused primarily on providing short-term relief of specific symptoms, such as elevating low mood. Chronic interventions have assessed whether exercise can be used to effectively treat or resolve depression (i.e., the disorder) and reduce total depressive symptom severity. Below, we discuss the evidence related to both types of exercise interventions and their role in the treatment of depression.



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The Role of Acute Exercise in the Treatment of Depression

Acute (single bouts) exercise will not necessarily resolve an individual's depressive symptoms, but it has well-characterized effects on regulating mood and has the potential to manage symptoms associated with depression. For example, Yeung (1996) reviewed the effects of acute exercise on mood from studies conducted between the years of 1976 and 1995 and found support for acute exercise-induced mood benefits among normative, healthy samples. In 2005, Bartholomew et al. were interested in determining whether these acute exercise-induced mood benefits could generalize to clinical samples. Using a mixed within-between subjects experimental design, the authors examined the impact of a single bout of aerobic exercise on mood and psychological well-being among 40 adults diagnosed with MDD ($M_{\text{age}} = 38.1$ years; range = 18–55; 25 female). Twenty participants completed a 30-min bout of moderate-intensity brisk walking, while the other 20 participants completed a seated rest control condition. Mood and well-being measures were assessed at four separate time points: before the condition (i.e., baseline), 10-min post, 30-min post, and 60-min post. Compared to the control condition, moderate-intensity exercise improved psychological well-being and the mood state of vigor at all postcondition assessments.

Meyer, Koltyn, and colleagues (2016a) examined the impact of acute exercise on mood in a sample of 24 females diagnosed with MDD ($M_{\text{age}} = 38.6$ years; $SD = 14.0$). The authors were interested in determining whether postexercise mood improvements were influenced by exercise intensity prescription. In a within-subjects crossover design, participants performed three different exercise intensities and a seated rest control condition on separate days. Exercise intensities consisted of light,

moderate, or hard and were performed at a rating of perceived exertion [RPE] of 11, 13, and 15, based on the original 6–20 RPE scale (Borg, 1998), respectively, while the control condition consisted of quiet rest on a stationary bicycle. Compared to the control condition, a single, 20-min bout of cycling, regardless of intensity, significantly improved depressed mood at 10- and 30-min following exercise cessation.

Meyer, Ellingson, et al. (2016) examined whether other exercise characteristics, such as a self-selected, preferred versus prescribed exercise intensity, would influence the postexercise mood effects. Using the same study sample as above, the authors had 24 females perform an additional 20-min bout of aerobic exercise at a self-selected, preferred intensity. Mood outcomes following the preferred exercise intensity were compared to the light, moderate, or hard intensity session that was closest in terms of RPE to the exercise they did during their preferred session (i.e., if the participants exercise at a low intensity during the preferred session, then their response to that session was compared with the response to the low-intensity during the prescribed session). Although the prescribed exercise session resulted in slightly favorable effects relative to the self-selected, preferred exercise bout, these effects were small and nonsignificant, highlighting that single bouts of aerobic exercise at any intensity may benefit depressed mood for up to 30- and 60-min postexercise.

Taken together, these findings support the idea that acute exercise can influence specific mood states (e.g., depressed mood and vigor),⁵ at least in the short-term, among individuals with MDD. Given that one of the core criterion symptoms of MDD is low or depressed mood, acute exercise may be particularly effective for managing these core symptoms. Additional research has shown that acute exercise impacts other disrupted psychological processes in depression. Acute aerobic exercise can attenuate self-reported negative affect among individuals who recovered from MDD (Mata et al., 2013). Separate studies have shown that acute aerobic exercise can diminish reactivity to sad stimuli (Brush, Olson, et al., 2020) and enhance positive emotional reactivity processes (Brush, Foti, et al., 2020) among adults at risk for developing MDD (i.e., those high in depressive symptoms), respectively. Therefore, the utility of acute exercise in the treatment of depression may be most evident in the management of symptoms and psychological processes commonly disrupted in depression. Acute exercise may be most effective in managing symptoms of depression while other treatments and their effects can manifest, which can take weeks to months (e.g., Knubben et al., 2007; Legrand & Neff, 2016).

Several questions remain in the acute exercise-depression relationship. The time-course of the postexercise mood benefits are not clear. The Bartholomew et al. and the Meyer et al. studies documented benefits anywhere from 30-60 min postexercise, however, whether the effects are sustained beyond 1 hr is unknown. Studies have primarily assessed aerobic forms of exercise performed for approximately 20-30 min. Research is needed to determine how long the postexercise benefits last, whether they relate to clinical outcomes (e.g., depressive symptom reduction), and whether other exercise characteristics (e.g., modality and dose) impact the effects of acute exercise on mood among individuals with clinical depression. Further, it is unknown how acute exercise compares to other brief interventions (e.g., brief behavioral activation treatment for depression [BATD]; Gawrysiak et al., 2009; Lejuez et al., 2001, 2011) in managing symptoms of depression. Research that addresses these items can

⁵ In acute exercise studies, the Profile of Mood States (McNair et al., 1971) has been the primary instrument used to assess mood in the context of depression, which has its limitations. As highlighted by Ekkekakis and Zenko (2016), the POMS was not designed to capture the global construct of “mood”. Instead, it decomposes mood into six distinct states: (a) tension; (b) depression; (c) anger; (d) vigor; (e) fatigue; and (f) confusion. There are conceivably other mood states that are not being measured by the POMS; therefore, when interpreting studies that use the POMS, it is important to note which specific mood states are altered through exercise to draw valid and accurate inferences. Refer to Ekkekakis (2013) and Ekkekakis and Zenko (2016) for a discussion on problems associated with using the POMS in exercise psychology research.

help “push the envelope” for the role of acute exercise in the treatment and management of depression.

The Role of Chronic Exercise in the Treatment of Depression

There is a long history of research examining the effects of chronic (longer-term) exercise on depression. Numerous RCTs have examined the effects of exercise for individuals with elevated depressive symptoms. There has also been an accompanying rise in the number of meta-analyses and systematic reviews on this topic (e.g., Cooney et al., 2013; Ekkekakis, 2015; Schuch, Vancampfort, et al., 2016).

In one of the most widely cited and influential RCTs, James Blumenthal and colleagues (1999) randomized 156 men and women with MDD (aged 50 years and older) to one of three conditions: (a) an aerobic exercise training program, (b) standard antidepressant treatment with sertraline (i.e., SSRI drug), or (c) combined exercise plus sertraline treatment. For the aerobic exercise training program, three, supervised sessions per week were performed over a span of 16 consecutive weeks in a group setting. Participants were prescribed walking or jogging at a vigorous exercise intensity that ranged from 70–85% of an individual’s heart rate reserve (HRR).⁶ Although participants assigned to the sertraline treatment alone experienced a more rapid initial antidepressant response, there were no significant differences in depressive symptom reduction between groups by the end of the 16-week trial, indicating that each treatment resulted in similar-sized reductions in depressive symptoms. Of the 156 patients who entered the trial, 60.4% of patients in the aerobic exercise training program, 68.8% of patients in the sertraline treatment condition, and 65.5% of patients in the combined exercise and sertraline treatment no longer met criteria for a DSM-IV⁷-defined diagnosis of MDD post-treatment.

The authors examined long-term outcomes following each of the three treatments in a subsequent study that followed these same patients six months post-intervention. At the follow-up visit, participants assigned to the aerobic exercise group displayed significantly lower rates of depression (~30%) compared to the other two treatment groups (sertraline: 52%; combined exercise plus sertraline: 55%; Babyak et al., 2000). At the time that this study was published and to the present day, this finding has been critically important in providing some of the strongest evidence for aerobic exercise as both a stand-alone and complementary treatment to standard antidepressant drugs. Notably, the aerobic exercise treatment group experienced lower relapse compared to participants in the other two treatment groups that included antidepressant drugs, providing the first evidence for the use of aerobic exercise to resolve depression over the long-term (6 months following the end of treatment). A limitation of this study was the lack of a placebo control group, which does not permit conclusions about the specific effects of each treatment arm. Therefore, Blumenthal and colleagues (2007) performed a follow-up investigation that added a placebo group to their previous study design. In this study, 202 participants (~76% female) diagnosed with MDD were randomized to the following groups for 16 consecutive weeks: (a) home-based aerobic exercise, (b) supervised exercise in a group setting, (c) sertraline, or (d) a placebo pill. After treatment, 41% of the participants achieved remission and all active treatment groups tended to have greater remission rates compared to the placebo pill group (home-based aerobic exercise: 40%; supervised exercise in a group setting: 45%; sertraline: 47%; and placebo pill: 31%). These studies have helped establish preliminary support for the efficacy of exercise treatment for MDD.

⁶ HRR is computed as the difference between an individual’s maximal and resting HR.

⁷ The American Psychiatric Association periodically updates the DSM to reflect the most current and cutting-edge research literature on psychopathology. The most recent addition (i.e., DSM-5) was released in 2013. The first version of the DSM-IV was released in 1994.

There has been a longstanding interest in determining the presence of a dose-response relationship between exercise and reductions in depressive symptoms (Rethorst & Trivedi, 2013). In 2000, a scientific symposium sponsored by Health Canada and the U.S. Centers for Disease Control and Prevention was held to determine whether a dose-response relationship exists between physical activity and multiple health-related outcomes, including depression. At the time, experts indicated that aerobic exercise programs lasting at least 6–12 weeks were consistently associated with depressive symptom reductions comparable in magnitude to those observed following antidepressant drug treatment; however, they noted that there was insufficient evidence to make definitive conclusions regarding a dose-response relationship between exercise and depression.

Dunn et al. (2005) conducted the first RCT designed specifically to assess the dose-response relationship of exercise for depression. Dunn et al. randomized 80 patients with mild-to-moderate depression severity to two different doses of aerobic exercise (7 kcal/kg/week, low dose [LD] or 17.5 kcal/kg/week, public health dose [PHD]) performed at two different frequencies (three or five days per week) or to an attention-controlled placebo group of flexibility training. Exercise intensity was self-selected by participants assigned to the exercise conditions. There was a significant dose-response effect. A greater depressive symptom reduction (47% decrease in HRSD score) was observed in patients in the PHD group compared to the LD (30% decrease in HRSD score) and stretching control groups (29% decrease in HRSD score). Further, the treatment response following the PHD prescription was comparable to depressive symptom reductions that are typically observed following other depression treatments, including antidepressant drugs and CBT.

Additional evidence supporting a dose-response relationship was examined in a study examining the effects of a long-term exercise training program on depression among women (Chu et al., 2009). The authors randomized women with high levels of depressive symptoms to a low- or high-intensity aerobic exercise condition or to a stretching program for 10 weeks. Participants in the aerobic exercise groups met for one 30–40 min supervised session and then were asked to complete three-to-four additional unsupervised exercise sessions during the week. During the unsupervised sessions, participants in the exercise groups were permitted to choose their preferred mode of aerobic exercise, such as aerobic dancing, walking, or biking. This approach may have served to enhance motivation and adherence to exercise, since participants were afforded greater autonomy in their own exercise. All three groups demonstrated a significant reduction in depressive symptoms at the end of the 10-week intervention. After controlling for pre-treatment depressive symptoms (as measured by the BDI-II), depressive symptoms were significantly lower following the intervention for the high-intensity aerobic exercise group compared to the low-intensity and stretching groups, suggesting a potential dose-response effect that favors higher aerobic exercise intensity prescriptions for depressive symptom reduction.

Trivedi and colleagues (2011) extended these findings by showing that aerobic exercise training can also be effective as an augmentation or complementary treatment for patients with treatment-resistant depression. The authors enrolled patients who failed to achieve remission following at least six weeks of treatment with SSRIs and prescribed one of two 12-week exercise doses: to patients: a low dose (4 kcal/kg/week) or high dose (16 kcal/kg/week).⁸ Among 126 men and women, those assigned to the higher dose of exercise showed a trend for increased remission rates compared to participants who were assigned to the lower dose of exercise (28.3% for the high-dose group compared to 15.5% for the low-dose group). Higher doses of aerobic exercise may more effectively treat depression and be a viable augmentation strategy for patients with depression who have failed to respond to antidepressant drugs.

⁸ The low dose prescription of 4 kcal/kg/week is equivalent to approximately 45 min of moderate-to-vigorous intensity exercise per week, while the high dose prescription is equivalent to approximately 180 min of moderate-to-vigorous intensity exercise per week.

It is important to note that the authors found that those assigned to the lower exercise exhibited better adherence rates compared to those assigned to the higher dose. This suggests that lower doses of moderate-to-vigorous intensity aerobic exercise may be more tolerable and acceptable for individuals with depression aiming to begin an aerobic exercise program.

Most of the work on the effects of exercise as a treatment for depression has focused on the effectiveness of aerobic exercise. Indeed, a meta-analysis that aggregated findings across 25 RCTs ($M_{\text{length}} = 10.29$ weeks; range of RCT length = 3–32 weeks)⁹ indicated large reductions in depressive symptoms following exercise compared to nonactive interventions (Schuch, Vancampfort, et al., 2016). The extent to which other exercise modalities have utility in the treatment of depression has received less attention.

Resistance exercise training is known for its many health benefits, especially for increasing muscular strength, muscle mass, endurance, and/or power (U.S. Department of Health and Human Services, 2008). Research has also examined the potential antidepressant effects of resistance exercise training. Singh et al. (1997) assessed whether 10 weeks of resistance exercise training significantly reduced depression among 32 older adults over the age of 60 years ($M_{\text{age}} = 71.3$ years; $SD = 1.2$) with diagnosed major/minor depression or dysthymia.¹⁰ Intervention groups consisted of a supervised, high-intensity resistance exercise training program performed three times per week or an attention-control group. Participants in the resistance exercise group performed upper and lower body exercises for three sets of eight repetitions at 80% of an individual's one-repetition maximum (1-RM).¹¹ Following the intervention, participants in the resistance exercise group reported a 59% reduction in depressive symptoms compared to a 26% reduction in the attention-control group. Participants were encouraged to continue their resistance exercise regimen at least twice weekly for another ten weeks upon completing the intervention. After this follow-up period, ~73% of the participants in the resistance exercise group achieved remission, while only ~36% of the attention-control participants achieved remission (Singh et al., 2001). This evidence served as preliminary support for the antidepressant effects of resistance exercise in both shorter and longer periods of time.

Similar to the aerobic exercise literature, Singh and colleagues were interested in examining potential dose-response effects of resistance exercise training on depressive symptoms. In a subsequent study, the authors randomly assigned 60 older adults between the ages of 60 and 85 to a high (80% of 1-RM), low (20% of 1-RM), or treatment-as-usual comparator condition for eight weeks (Singh et al., 2005). High-intensity resistance exercise training resulted in larger antidepressant effects compared to the low-intensity and treatment-as-usual comparator groups. Interestingly, the authors examined the proportion of individuals who adequately responded to treatment, which was defined as a 50% reduction in the HRSD score from pre-to-posttreatment. The results revealed a 61% response rate in the high-intensity group compared to 29% and 21% in the low-intensity and treatment-as-usual groups, respectively. This evidence suggests that resistance exercise training may not only reduce depression, but higher intensities may be more effective.

Noting that the majority of meta-analyses conducted on the exercise and depression relationship has focused on aerobic forms of exercise, Gordon and colleagues (2018) aimed to address

⁹ One RCT included in the Schuch, Vancampfort, et al. (2016) meta-analysis did not report the trial length. Therefore, the mean and range of trial lengths reported include 24/25 RCTs that were included in the authors' meta-analysis.

¹⁰ Dysthymia is no longer considered a diagnosis in the DSM-5. It was removed from the DSM-Fourth Edition (IV) and replaced by persistent depressive disorder. Minor depression was considered a Depressive Disorder Not Otherwise Specified in the DSM-IV.

¹¹ Resistance exercise training intensity is often based off an individual's 1-RM, which is defined as the maximal amount of weight an individual can lift in a single repetition (Garber et al., 2011).

this gap in the literature by performing the first quantitative review of the effects of resistance exercise training on depression. Gordon et al.'s meta-analysis combined effects from 33 RCTs, which included a total of 1,877 participants, and found that resistance exercise training resulted in a moderately-sized reduction in depressive symptoms, regardless of sociodemographic characteristics. It is important to note that this meta-analysis combined findings from studies that included both normative and clinical samples. When examining only those with clinical levels of depression (i.e., at least mild-to-moderate depressive symptoms), the resistance exercise training had even larger antidepressant effects compared to those with subclinical depression. There was no specific impact of type of resistance exercise training protocol on depression outcomes.

Collectively, the evidence generally supports the notion that both aerobic and resistance forms of exercise are effective treatments for depression. This has been shown in studies examining exercise training as a monotherapy or complementary treatment to other treatments, namely antidepressant drugs. The antidepressant effects of exercise are at least as comparable to antidepressant drug treatments and over the long run, there is evidence to suggest that exercise may result in more favorable reductions in depressive symptoms and disorders compared to antidepressant drugs (Babyak et al., 2000). It is important, however, for future studies to continue to examine the long-term impact of exercise on depression to fully understand how long effects are sustained. Most of the research to date has been conducted in adults with depression, while the impact of exercise training in other populations that are substantially impacted by depression, including children and adolescents, is less clear. Future studies are needed in other vulnerable populations to determine whether effects are generalizable. Overall, exercise should play an important role in the treatment of depression as a stand-alone and/or complementary treatment.

Plausible Neurobiological Mechanisms of the Antidepressant Effect

Establishing neurobiological mechanisms of the antidepressant effects of exercise has historically been challenging. Depression is characterized by substantial heterogeneity; estimates indicate that anywhere from 119 (Park et al., 2017) to 681 (Akil et al., 2018) to even 1,000 (Fried & Nesse, 2015) unique combinations of depressive symptoms could meet MDD diagnostic criteria. Research attempting to explain the mechanistic effects of exercise on depression often struggle to accommodate for the diverse symptom profiles and presentations across individuals, which makes it difficult to design studies aimed at establishing the mechanisms implicated in the antidepressant effects of exercise. In addition to the heterogeneity, exercise is associated with a wide range of neurobiological effects (see Dishman et al., 2006 for an extensive overview). When considering these factors, it is unsurprising that our general understanding of the mechanisms underlying the antidepressant effects of exercise is unclear. It is likely that exercise improves mood and other specific symptoms in the short-term and reduces depression in the long-term through numerous mechanisms because of its wide range of effects. Indeed, experts have proposed several neurobiological mechanisms (Kandola et al., 2019; Schuch, Deslandes, et al., 2016). In this section, we provide a very brief overview of some of the neurobiological mechanisms that have been assessed in acute and chronic exercise studies. We only focus on neurobiological mechanisms that are hypothesized to be implicated in the pathophysiology of depression and have been studied in relation to changes in depressed mood or depressive symptoms.

Neurobiological Mechanisms Studied in the Context of Acute Exercise

In a series of secondary data analyses, Meyer and colleagues were interested in exploring potential neurobiological mechanisms implicated in the mood-enhancing benefits of acute exercise. In three separate reports, Meyer and colleagues examined whether serum concentrations of brain-derived neurotrophic factor (BDNF; Meyer, Koltyn, et al., 2016b), endocannabinoids and related lipids (Meyer et

al., 2019), and cytokines (Perez et al., 2020) could be altered by acute bouts of aerobic exercise and whether alterations were associated with acute changes in mood states. In each of these studies, blood was drawn before and within 10 min after each condition to determine changes in BDNF, endocannabinoids and related lipids, and cytokines. Specific descriptions related to each analysis are outlined below.

In Meyer, Koltyn, et al. (2016b), 24 women with MDD performed 20 min of aerobic exercise at light, moderate, and hard exercise intensities; participants also completed a quiet rest condition. While acute exercise significantly improved depressed mood and increased BDNF levels regardless of exercise intensity, these findings do not explain the mechanism, as authors failed to observe a relation between changes in depressed mood and BDNF levels. In Meyer et al. (2019), 17 women with MDD exercised for 20-min at a moderate- (prescribed exercise intensity equivalent to a RPE of 13) or self-selected, preferred-intensity of aerobic exercise (chosen exercise intensity: $M_{RPE} = 12.5$; range = 8.5–16). Moderate-intensity aerobic exercise significantly increased endocannabinoid levels (i.e., anandamide) and a related lipid (i.e., oleoylethanolamine). Most notably, changes in anandamide and oleoylethanolamine were associated with changes in mood states, suggesting that endocannabinoids and related lipids may contribute to the mood-enhancing effects of acute exercise in MDD. No such relationships were observed following the self-selected, preferred intensity of aerobic exercise. Differences in findings may be attributed to the substantial variability in how participants selected and performed their preferred exercise intensity, with some individuals exercising at lower intensities than others (see wide range of self-selected intensities above). This suggests that lower intensities of exercise may not be sufficient to induce changes in the endocannabinoid system, or alternatively, other mechanisms might be at play. In 2020, Perez et al. examined whether serum concentrations of interleukins (ILs) 6 and 8 and tumor necrosis factor- α (TNF- α) could be altered by a 20-min bout of aerobic exercise. Participants completed the same experimental conditions as the Meyer, Koltyn, et al. (2016a) study. Perez and colleagues found that hard exercise increased IL-6, IL-8, and TNF- α among 19 women with MDD, while the light and moderate exercise intensities failed to modulate these inflammatory markers. The authors also examined whether changes in each of these inflammatory markers related to changes in depressed mood but failed to find any significant relationships. The authors hypothesized that there is a possibility that acute increases in inflammatory markers following hard exercise could have potential for prompting chronic inflammatory adaptations; however, limited conclusions can be drawn from these studies with longer-term studies needed to test this possibility. Other limitations of these data include the secondary nature of the analyses, as well as the relatively small samples including only women.

In addition to this empirical evidence, Schuch, Deslandes, and colleagues (2016) propose other plausible neurobiological mechanisms that may be modulated by acute exercise, including increased levels of atrial natriuretic peptide, brain natriuretic peptide, copeptin, and growth hormone; however, currently, there is a dearth of evidence to make strong conclusions about neurobiological mechanisms sensitive to change through acute exercise in depression.

Neurobiological Mechanisms Studied in the Context of Chronic Exercise

Chronic exercise studies have examined potential neurobiological mechanisms associated with the antidepressant effects of exercise. These studies have focused on assessing whether changes in specific neurobiological mechanisms are associated with depressive symptom change in response to exercise treatment. To date, chronic exercise studies have focused mostly on oxidative stress markers, BDNF, and inflammatory markers.

In Schuch et al. (2014), the authors conducted a RCT evaluating the effects of exercise as an add-on treatment to treatment-as-usual on thiobarbituric acid-reactive substances (TBARS) and BDNF among 26 severely depressed inpatients. Fifteen individuals were randomized to an exercise plus treatment-as-

usual condition, while the other 11 participants were allocated to a treatment-as-usual comparator condition. Participants performing the add-on exercise completed a 16.5 kcal/kg/week dose three times per week throughout their hospitalization stay. Across the hospitalization stay (exercise participants: $M_{\text{duration}} = 21.63$ days; $SD = 4.5$; control participants: $M_{\text{duration}} = 23.82$ days; $SD = 5.7$), participants in the exercise group performed ~9 total sessions. Serum TBARS levels increased for the exercise group, while no effects were found for serum BDNF levels, indicating that TBARS may be a potential neurobiological mechanism implicated in the antidepressant effects of exercise for participants with depression. It was unclear from this study whether change in TBARS was associated with changes in depressive symptom improvements. Importantly, these patients were also receiving treatment-as-usual which consisted of antidepressant drugs and/or electroconvulsive therapy. It is possible that exercise may impact serum TBARS levels when combined with other forms of treatment. Future studies specifically designed to test whether TBARS is a neurobiological mechanism of the effects of exercise for depression are needed.

Lavebratt and colleagues (2017) examined whether serum IL-6 levels could be altered by 12 weeks of exercise and whether changes corresponded to changes in depressive symptoms. In their study, 116 patients (age range = 18–64 years) completed light ($n = 48$), moderate ($n = 36$), and vigorous ($n = 32$) exercise conditions for three 60-min exercise sessions over 12 weeks. Reductions in IL-6 levels were associated with depressive symptom reductions, indicating that IL-6 may be a potential mechanism of the antidepressant effects of a chronic exercise training program. The authors did not examine other inflammatory markers or mechanisms. It remains unknown whether other mechanisms could also account for the effects.

These studies suggest that there may be a role of specific oxidative stress and inflammatory markers in the antidepressant effects of exercise training. Overall, the available data for neurobiological mechanisms of the antidepressant effects are too premature to make any definitive conclusions.

Conclusion

MDD is a prevalent and burdensome mental illness that significantly impacts individuals of all age groups across the globe. Antidepressant drugs and psychotherapeutic approaches are first-line treatments for MDD; however, these treatments are associated with several barriers, have variable effectiveness, and have vast side effect profiles. Exercise and physical activity are two lifestyle behaviors that can be used to effectively prevent and treat depression. Cross-sectional and longitudinal research indicates that engaging in regular physical activity is associated with a diminished risk of current and future depression. Even engaging in small amounts of physical activity can reduce an individual's risk for depression. A large body of evidence has examined exercise programs in the treatment of depression. Acute exercise has shown to exert powerful effects on mood and other disrupted psychological processes in depression, which may have implications for using exercise as a strategy to help alleviate or manage symptoms (e.g., low mood or deficits in positive or negative affect) in the short run. In the long-term, treatment studies have shown that aerobic and resistance forms of exercise training result in moderate-to-large effect sizes in depressive symptom reduction (Gordon et al., 2018; Schuch, Vancampfort, et al., 2016). Establishing neurobiological mechanisms of the antidepressant effects of exercise has been challenging due to the heterogeneous nature of depression and the wide range of neurobiological effects of exercise, but several mechanisms have been proposed and tested. In conclusion, research suggests that consistent physical activity can reduce the risk of developing depression and acute and chronic exercise treatment programs are efficacious in improving mood and symptoms of depression.

Learning Exercises

1. Clinicians issue a diagnosis of MDD based on the presence of at least five symptoms that are present over the same two-week time period. According to the Diagnostic and Statistical Manual, Fifth Edition (DSM-5) of the American Psychiatric Association (2013), which two symptoms are required for a diagnosis? Do both symptoms need to be present in order to be issued a diagnosis? Identify the remaining symptoms that may also be present to constitute a MDD diagnosis.
2. Can physical activity be useful in protecting against the development of depression or does depression reduce physical activity levels? What evidence is there to support your answer?
3. Can exercise be used to treat depression? What evidence is there to support your answer?
4. How does exercise compare with antidepressant drugs in the treatment of depression? What are the long-term depression outcomes of either treatment?
5. Does a specific dose of exercise elicit larger antidepressant effects compared to other doses of exercise? Use the available evidence to support your answer.
6. Most treatment studies examining the effects of exercise on depression have focused on aerobic forms of exercise. Does resistance exercise have utility in the treatment of depression? Use evidence to support your answer.
7. Several neurobiological mechanisms have been proposed to underlie the antidepressant effects of exercise. Identify at least two mechanisms that change in response to exercise. Indicate the dosage of exercise that was used in terms of type, frequency, intensity, and duration.
8. A friend of yours knows that you are taking a class in sport and exercise psychology. They have recently been issued a MDD diagnosis and are currently considering different treatment options. Your friend wants you to share your insights on how to manage and alleviate their depression. Based on the evidence outlined in this chapter, provide insight into different treatment options in terms of treatment outcomes and efficacy in reducing depression over the long-term. Which treatment would you recommend?
9. What type of exercise can individuals do in the short-term versus long-term to manage and reduce their depression? Use scientific evidence to support your answer.

Further Reading

For practical recommendations and advice for using exercise and physical activity in the treatment of depression, readers are encouraged to refer to primers by Rethorst and Trivedi (2013) and Fortier et al. (2020). Readers interested in understanding the wide range of potential neurobiological mechanisms implicated in the antidepressant effects of exercise and physical activity in the prevention and treatment of depression should refer to the Schuch, Deslandes, et al. (2016) and Kandola et al. (2019) reviews.

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