The Role of Exercise in Preventing and Treating Depression

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Abstract

Depression is a leading cause of global burden. The mainstay of treatment is pharmacological and psychological interventions. While effective, not all people will respond to those treatments and alternative approaches for preventing and treating depression are required. Recent literature has demonstrated that higher physical activity (PA) levels and exercise confer protective effects on incident depression. Also, exercise has demonstrated efficacy on reducing symptoms for people with depression. Despite its effectiveness, similar to other treatments, some people may benefit more from exercise and identifying these potential predictors of response is necessary to deal with patients' and professionals' expectations. Dropout from exercise interventions is comparable to dropout from other treatments for depression and similar to dropout from exercise in other clinical populations. However, some strategies to increase adherence are important. In the present article, we provide an updated overview of the use of PA and exercise for the prevention and treatment of depression.

Introduction

Major depressive disorder (MDD) is a highly prevalent disorder in most cultures across the world with a point prevalence ranging from 6% to 18% across different countries (1). When considering the prevalence of people with subsyndromal/subthreshold depression, or those that have significant depressive symptoms but do not meet the criteria for a formal diagnosis of MDD, the prevalence rate is approximately 15% to 20% (2). MDD is one of the top 10 causes of years lived with disability across the world and a leading global cause of burden (3), and the economic costs are considerable. For instance, the costs associated with the days lost of work due to depression and anxiety is estimated in US $ 1.15 trillion per year worldwide, and this amount is expected to increase twofold by 2030 (4).

The core features of depression symptoms include low mood, decreased interest or pleasure in most or all activities of the day, decreased motivation, increases or decreases in appetite and weight, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, cognitive impairments, such as memory deficit, and suicidal thoughts with or without suicidal plans or attempts (5). In addition to the profound burden on mental health and well-being, there is a growing body of evidence to suggest that people with MDD experience substantially poorer physical health (6). For example, people with depression present increased prevalence of cardiometabolic disease (7), diabetes (8), and cardiovascular disease (9), and experience premature mortality by 10 yr compared with the general population (10). While suicide accounts for a part of the premature deaths among people with depression, it is well established that the higher levels of cardiovascular and metabolic disease when compared with the general population play a significant role to the premature mortality gap (10).

The current focus of treatment for people with confirmed MDD consists of antidepressants and psychotherapies. While antidepressants are typically more efficacious than placebo (11), some evidence suggests that only about half of the people taking antidepressants achieve a clinically significant response (a decrease of 50% or more on depressive symptoms) (12). Also, dropout rates are considerable, ranging from 15% to 132% higher than placebo (11). Another factor that influences adherence is the side effects of antidepressant medication which can include weight gain, increased diabetes risk, and sexual dysfunction among others. Psychological therapies, such as cognitive behavioral therapy, have a small-to-moderate effect for people with depression (13), the impact of psychotherapies on the poor physical health and premature-associated mortality is unclear.

Given the considerable individual and societal burden of depression, there is a pressing need to identify modifiable risk factors which may be amenable to change. To this end, there is growing recognition that lifestyle behaviors, such as physical activity (PA) and exercise partially contribute to the risk of developing depression and can be useful strategies for treating depression, reducing depressive symptoms, improving quality

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of life, and improving physical health outcomes. In the present article, we provide a brief overview of the current evidence for: (1) the role of PA and exercise in the potential prevention of incident depression; and (2) the use of PA and exercise as therapeutic strategies for depression, including the use of exercise as a strategy for acute management of symptoms, the effects of exercise training, the potential predictors/moderators of response, the neurobiological mediators, prescription, adherence and dropout from exercise, and the translation of the evidence by current guidelines of depression treatment.

PA and Exercise as Protective Factors for Incident Depression

Cross-sectional studies have shown that people with higher levels of PA present decreased depressive symptoms, and these results are consistent across different countries and cultures. For example, recent evidence using data from the Brazilian National Health Survey, accounting for 59,399 individuals, demonstrated that a lack of PA for leisure was associated with depression in young males (odds ratio [OR], 1.45; 95% confidence interval [CI], 1.02–2.06), middle age (OR, 2.38; 95% CI, 1.4–4.03), and older adults (OR, 5.35; 95% CI, 2.14–13.37) (14). A similar pattern is seen in older Japanese adults, where individuals with lower PA have a higher risk of depressive symptoms (15), and in the United States, where people 20 yr and older, who engaged in only light PA, were more likely to have experienced depression than those who engaged in vigorous PA with OR of 3.18 (95% CI, 1.59–6.37) (16). Also, a study across 36 countries demonstrated that lower levels of PA (defined as less than 150 min of moderate-vigorous PA per week) were consistently associated with elevated depression (OR, 1.42; 95% CI, 1.24–1.63) (17). Clearly, this association has the potential to be bidirectional. Previous studies have shown that people with depression have lower levels of PA (17) and higher levels of sedentary behavior (18). In fact, a meta-analysis of all of the published data demonstrated that people with MDD have about 50% higher chance of not meeting the 150 min of moderate to vigorous PA (19) as recommended by general public health guidelines.

A limitation of cross-sectional studies is the inability to infer directionality. Thus, prospective cohort studies which follow nondepressed people at baseline and measure PA and future depression can provide a better indication of whether PA is truly a modifiable risk factor for depression. In this regard, a systematic review by Mammen and Faulkner (20) reviewed 30 prospective cohort studies looking at whether PA conferred protective effects on incident depression. In their narrative review, the authors reported that 25 of the 30 studies found that PA is prospectively associated with reduced incident depression. Mammen and Faulkner (20), however, did not perform a meta-analysis; they just counted the number of studies showing a protective effect and those that did not show it. Therefore, the consistency and magnitude of the protective effect were uncertain. The authors have not evaluated whether some other factors like adjustments for potential covariates, potential cultural differences, and ages could modify the effects. Trying to update the literature and fill these gaps, we performed a meta-analysis including only prospective cohorts evaluating the effects of PA and incident depression in studies of at least 1 yr follow up. For that, we compared the incident depression in people with higher levels versus lower levels of PA at baseline, including a total of 49 unique studies, and a sample of 266,939 participants, accounting for a total of 1,837,794 person-years (21). To avoid reverse causality only studies with people free from depression at baseline were included (21). We found that PA reduced the risk of depression 17% in studies adjusting the odds for potential covariates and a reduced odds of 41% in studies that did not adjust their analysis for potential covariates and calculated using only raw numbers.

We performed several subgroup analyses exploring the potential differences across different countries, ages, and the variables included for adjustments in the regression models. According to our subgroups analyses, the protective effects were significant across all ages: children and adolescents (10% decreased odds), adults (12% decreased odds), and older adults (21% decreased odds); all the countries where we have found studies: Asia (24% decreased odds), Europe (17% decreased odds), North America (14% decreased odds), and Oceania (35% decreased odds); and the potential covariates included in the models for adjustment: age and sex (17% decreased odds), body mass index (13% decreased odds), smoking (26% decreased odds), and the combination of these three factors (17% decreased odds). The odds for those completing the 150 min of moderate to vigorous PA per week were decreased by about 22% (21).

PA as a Treatment for Depression

Acute Management of Symptoms (Effects of a Single-exercise Bout)

People with MDD can benefit from a single bout of exercise. A study by Meyer and colleagues (22) compared the effects of a 20-min cycling bout at three different intensities: light (RPE, 11), moderate (RPE, 13), or hard (RPE, 15) on 24 women with MDD versus a control group (sitting quietly). The comparative analyses showed that all intensities were equally effective and better than the control in promoting well-being at 10 and 30 min after the exercise. Also, in a following analysis of the same trial, Meyer and colleagues (23) investigated the role of self-selected or preferred intensity on acute well-being. For this, the patients exercised at light (RPE, 11), moderate (RPE, 13), or hard (RPE, 15) intensities, or chose the workload themselves across a 20-min cycling session. Interestingly, no differences were found between the self-selected/preferred intensity and the closest intensity, suggesting that all intensities can equally promote acute well-being in people with MDD, regardless if it is self-selected or determined.

Effects of Exercise Training

A large body of trials has been performed over the last 40 yr, evaluating the role of exercise as a therapy for depression. These results have been summarized in several meta-analyses. Despite this enormous body of evidence, some discussion on the magnitude of the antidepressant effect, and even if the effect really occurs, are still present. A meta-analysis that we have performed in 2016 (24), including 25 studies and more than 1487 people with depression (757 randomized to exercise and 730 to control conditions) identified a very large and significant antidepressant effect favors exercise (standardized mean difference [SMD], 0.98; 95% CI, 0.68–1.28; $P < 0.001$). When adjusted for potential publication bias

according to the Duval and Tweedie trim and fill technique, the effect was equal to 1.11 (95% CI, 0.79–1.43). Also, when we restricted the analyses to the studies identified as having a lower risk of bias, the effect remained significant (SMD, 0.88; 95% CI, 0.22–1.54; $P = 0.009$). This result is consistent with the direction of a meta-analysis published some months later that corroborated our findings (25) and with the overall analysis published by Krogh et al. (26). However, in the Krogh et al. study (26), a subgroup analysis including only four trials that were considered of "low risk of bias" did not find a significant effect of exercise (SMD, –0.11; 95% CI, –0.41 to 0.18, $P = 0.45$). Of note, two of the four trials included in this analysis compared exercise versus a control group that performed "light-intensity" exercise (27,28). Comparing "exercise versus exercise" is a significant limitation of the analysis since exercise, even when it is of lower intensity, exhibits a significant reduction in depressive symptoms (29). Therefore, an effective "control" group may mask the effects of a comparison intervention. This limitation is even more important in this case since one of the included studies, the DEMO trial, found greater increases on $\dot{V}O_2$ in the control group than in the exercise group, suggesting that the physiological intensity of the control group was even greater in this group than in the exercise group (27).

Moderators of Response

Exercise can improve depressive symptoms in people with depression. However, similar to other treatments, exercise is not a panacea and may not work equally for all. A seminal study by Dunn et al. (30), the Depression Outcomes Study of Exercise, found a response rate of about 40% in depressed people free from other treatments. These results are comparable with more recent data found in the REGASSA trial, the largest study with exercise and depression, which found a response rate of about 50% (31). The remission rate (people who no longer meet criteria for MDD diagnosis) was evaluated in the Treatment with Exercise Augmentation for Depression (TREAD) study (32) using and adapting (16 kilocalories per kilogram of weight spent in exercise per week) the pioneering idea of Andrea Dunn in determining the exercise dose based on the energetic expenditure did find a remission rate of about 28%. To maximize the benefits to the patients and to deal with patients' and health professionals' expectations, matching the "right patient for the right treatment," or understanding who are the patients that are more likely to benefit the most regarding depressive symptoms reduction, is necessary. For doing that, understanding the potential predictors and moderators of the antidepressant effects of exercise is required.

A previous systematic review identified some potential 1) biological, 2) clinical, 3) psychological, 4) social factors, as well as, 5) the interaction between two or more factors (composed) that were associated with greater response/remission rates (33). Since the publication of this study, some studies have improved the state of the art in the field. We will briefly mention the findings below:

1) Biological: higher levels of brain-derived neurotrophic factor (BDNF), interleukin (IL)-1B, and of tumor necrosis factor-alpha are associated with greater response to exercise. A further study analyzing data from the REGASSA trial identified that higher levels of IL-6 predicts greater response rates (34).
2) Clinical: better global functioning, as well as more severe physical symptoms, predict response to exercise. Later, data from the TREAD study revealed that atypical depression benefits more from exercise than other subtypes (35). Also, lower cardiorespiratory fitness is linked to a greater chance of nonresponse (36).
3) Psychological: higher self-esteem and life satisfaction predict better outcomes (33).
4) Social: social support was the only moderator/predictor that was consistently associated with better outcomes (31).
5) Composed: it is reasonable to expect that a better-described group and limited group, including a greater number of identifiable traits or characteristics, may present a greater chance of response. For example, when we say that men respond more to exercise, in this group of men, there will be subgroups that may respond more while others will respond less, or some won't respond at all. Therefore, it is expected that models including more variables will have a better predictive value.

Some studies have evaluated whether two or more traits or characteristics are linked to a greater response to exercise interventions. In this regard, data from the TREAD US study revealed that people with higher BDNF levels and higher BMI present greater response rates than people with lower BDNF and BMI (37). Also, men, regardless of the family history of mental illness, and women, without family history of mental illness, are more likely to benefit from exercise (32). A reanalysis of this study data, accounting a greater number of potential of variables (BDNF, IL-1B, depressive symptom severity, postexercise positive affect, cardiorespiratory fitness, and IL-6), achieved predictive values greater than 70%, suggesting that people with higher BDNF levels, higher IL-1B levels, lower depressive symptoms, and higher positive affect to exercise are more likely to achieve positive outcomes from exercise (36).

Neurobiological Mediators of the Antidepressant Response

The neurobiological mechanisms underpinning the antidepressant effects of exercise are largely unclear. However, some hypotheses involving inflammation, oxidative stress, and neuronal regeneration are speculated (38).

Inflammation and oxidative stress markers are altered in people with depression. For example, IL-6 and IL-1B (39), inflammation markers, and thiobarbituric acid reactive species (40) are increased in people with depression. Exercise training, however, is able to promote increases in anti-inflammatory and anti-oxidant enzymes, referred to as an hormesis response (38,41), and subsequently decrease IL-6 levels (34). This effect was demonstrated in the REGASSA trial, where decreases in IL-6 serum levels were associated with reductions in depressive symptoms (34).

Substantial evidence demonstrates that people with depression have decreased levels of BDNF (42), a marker of neuronal growth and plasticity. Potentially, these reduced levels of neuronal regeneration are linked to a decreased volume and activity of certain brain regions, including hippocampus, orbitofrontal

cortex, anterior and posterior cingulate, insula, and temporal lobes observed in people with depression (43). Exercise, inversely, can promote brain plasticity, increasing hippocampus volume (44). However, there is not enough evidence on changes in brain volume due to regular exercise in people with depression (38).

Prescription, Adherence, and Dropout to Exercise Interventions

Starting and sustaining an exercise program is a challenge for any clinical population, and naturally, this also is true for people with depression. For example, the dropout rates to exercise interventions is about 20% for people with type II diabetes mellitus (45), 29% for people with HIV (46), 26% for people with schizophrenia (47), and 17% for children with attention deficit hyperactivity disorder (48). The dropout rate in exercise trials for people with depression is not greater than that for other clinical populations, being of about 18% (49). Also, it is important to note that adherence to other treatments for depression is equally challenging. For example, dropout rate from psychotherapies, in general, is about 19% (50) while the dropout rate from selective serotonin reuptake inhibitors are about 26% and tricyclics about 28% (51).

Some strategies may be useful for clinicians and exercise professionals to help people with depression to engage in PA and to prevent dropout. First, Vancampfort et al. (52) suggests that autonomous motivation may "hold the key" to keep people with mental illness active. Autonomous motivation is the motivation that leads someone to do something for its own sake, for example, finding exercise enjoyable or challenging. Therefore, adapting exercise prescription for people with depression should account for personal preferences and previous experiences in terms of making it the most enjoyable experience possible. In this line, Brand and Ekkekakis (53) have suggested that self-selected intensities or intensities above the ventilatory threshold can be used as an appropriate option for public health promotion. Self-selected intensities and intensities above the ventilatory threshold are linked to positive core affective valence, whereas higher intensities are usually linked to a negative core affective valence in sedentary and low-active groups (53), which is the case for people with depression (19). It should be noted, however, that higher intensities have demonstrated greater effects on reducing depressive symptoms (24); therefore, a progression of the exercise intensity should be considered. Second, some strategies have been shown useful in other clinical samples and can be used by physicians and health professionals to help people with depression to engage in regular PA (54). For example, Green prescriptions constituted by written exercise prescription by health professionals, defined according to patients' state of change and individual goals and supported by exercise professionals' calls and face-to-face meetings have resulted in an increase in 34 $min \cdot wk^{-1}$ of leisure exercise over 12 months in patients consulting general practitioners (54). Lastly, supervision provided by trained exercise professionals, as such as physiotherapists, exercise physiologists, physical educators, and others are a protective factor for dropout in people with depression, showing the clear relevance of these professionals in the field (49). Social support is a potential moderator for symptom improvements from exercising (33), thus encouraging patients to exercise with friends or family may increase the chance of success of treatment and the subsequent adoption and maintenance of exercise.

Exercise for Improving Physical Health of People with Depression

People with mental illness have a reduced life expectancy of about 10 yr when compared with the general population (55). Much of this reduction is attributable to an increased rate of cardiometabolic diseases in this population. For example, people with MDD have a higher risk (relative risk [RR], 1.36; 95% CI, 1.29–1.72) of having type II diabetes (56), metabolic syndrome (RR, 1.54; 95% CI, 1.21–1.97) (57), and of cardiovascular disease (OR, 2.08; 95% CI, 1.51–2.88) (9) than age and sex-matched controls.

Exercise and PA are key factors for preventing and managing cardiovascular disease and associated mortality (58) in the general population, and this is not different for people with MDD. Evidence has shown that PA and exercise should be prescribed to people with MDD to promote cardiometabolic health, as shown in improvements on cardiovascular and metabolic markers as fitness (59,60), high-density lipoprotein (60), and weight (60), epicardial and subcutaneous adipose tissue (61). For example, exercise can increase aerobic capacity of about 3.05 $mL \cdot kg^{-1} \cdot min^{-1}$ from baseline to postintervention in people with MDD. This increase is associated with significant reductions on the risk of premature mortality and can help to reduce the mortality gap (62).

Treatment Guidelines for Depression

The evidence of the use of exercise is substantial and growing fast. Despite this substantial evidence, the incorporation of exercise as a key component in treatment is inconstant. Some guidelines have incorporated PA and exercise as recommended therapeutic strategies for depression (63–66) while others have not. Despite this acknowledgement, PA still appears to not receive the deserved attention and its use in clinical practice is not of equitable value to the more dominant strategies such as pharmacotherapy and psychotherapies (67). According to Ekkekakis and Muri (67), this can be potentially attributable to the lack of awareness, incredulity, skepticism, or even a reluctance to the existent evidence. Addressing this issue and the current reliance on the two-pronged approach of talking therapies and medication is important in going forward.

Conclusions

PA can confer protection from the development of depression in children, adults, and older adults. These effects are evident in all continents. Also, among people with depression, exercise can be used for acutely managing symptoms. Also, a robust body of evidence from randomized controlled trials demonstrates that exercise is effective in treating depression.

Exercise has multiple benefits to several domains of physical and mental health and should be promoted to everyone. However, the use of moderators/predictors (*e.g.*, biological, clinical, psychological, social) and composed in response should be considered to deal with patients' and professionals' expectations and to maximize success chance. Dropouts to exercise are a challenge for all clinical populations, which is not different from people with depression. However, adherence imposes a challenge to all other treatments. To keep exercise adherence, autonomous motivation may play a central role.

Social support can be critical, and the supervision of exercise professionals can increase the chance of adherence and success to the treatment.

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