



Physical Exercise in Major Depression: Reducing the Mortality Gap While Improving Clinical Outcomes

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Major depression shortens life while the effectiveness of frontline treatments remains modest. Exercise has been shown to be effective both in reducing mortality and in treating symptoms of major depression, but it is still underutilized in clinical practice, possibly due to prevalent misperceptions. For instance, a common misperception is that exercise is beneficial for depression mostly because of its positive effects on the body ("from the neck down"), whereas its effectiveness in treating core features of depression ("from the neck up") is underappreciated. Other long-held misperceptions are that patients suffering from depression will not engage in exercise even if physicians prescribe it, and that only vigorous exercise is effective. Lastly, a false assumption is that exercise may be more harmful than beneficial in old age, and therefore should only be recommended to younger patients. This narrative review summarizes relevant literature to address the aforementioned misperceptions and to provide practical recommendations for prescribing exercise to individuals with major depression.

Keywords: depression, mortality, exercise, physical activity, efficacy, cardiovascular disease

INTRODUCTION

Depression exerts an enormous impact on different domains of individual functioning, as well as physical health (1, 2). Physical exercise is increasingly recognized as an effective intervention to improve these outcomes.

Patients with major depression seldom receive adequate treatment. When they do, there is a high likelihood they remain depressed or relapse after first-line treatment (3, 4). Whereas, a substantial proportion of patients go on to receive intensive pharmacological care (5, 6).

Besides mental health outcomes, recent studies cast great concern on the physical health of depressed individuals. Depression is, in fact, accompanied by behavioral and biological features that are deleterious for physical health, particularly in the cardiovascular system (7). Moreover, when depression arises as a consequence of pre-existing physical problems, it may amplify disability, anticipate recurrences, and increase disease-related mortality (8, 9). Recently it was estimated that individuals with major depression die, on average, about 10 years earlier than those who are not depressed, even when excluding deaths by suicide (10–12).

There is wide agreement that current research and clinical efforts to address these issues are arguably not proportional to their gravity. There is an urgent need to develop and implement novel treatments that are effective to treat symptoms of depression and, at the same time, are beneficial for physical health (13). One such intervention is physical exercise, which is increasingly recognized as both an antidepressant agent (14) and a potent tool to delay mortality (15). The aim of this perspective article is to provide a concise update on the effectiveness of exercise for depression and cardiovascular mortality reduction. A specific section is dedicated to treatment of elderly patients, in consideration of their increasing demographic relevance (2). English-language reviews and meta-analyses published in the last 10 years were considered, identified with the following search string in the Pubmed database: (exercis*[ti] OR "physical activity"[ti]) AND depress*[ti] AND (review*[pt] OR review*[tiab]).

DEPRESSION IS ASSOCIATED WITH A SHORTER LIFESPAN

Even if a direct causal role is still debated (16), depression could increase mortality through several mechanisms (10). First, it negatively impacts lifestyle choices. Individuals with depression tend to be sedentary (17, 18) and less physically fit than their non-depressed counterparts (19). Moreover, they exhibit higher rates of cigarette smoking (20–22), consume more alcohol (23), adopt low-quality dietary regimens (24), and become overweight (25, 26). Of note, some of these associations seem underlined by bi-directional causal links.

Second, depression is accompanied by dysregulation of several homeostatic systems (27). Depressed individuals commonly display dysregulation of the hypothalamic–pituitary–adrenocortical (HPA) axis (28–30), immune (31, 32), and autonomic nervous system (33), as well as metabolic imbalances (34).

Third, depression can raise mortality risk by increasing the incidence of physical illnesses or worsening the outcomes of existing ones. For instance, the presence of clinically significant depression has been found to increase the incidence and mortality of cardiovascular diseases (35, 36), as well as the mortality due to diabetes (37) and stroke (38). This phenomenon could stem, among other reasons, from placing additional stress on disorder-specific pathophysiologic mechanisms, but may also reflect poor adherence to medications or problematic health behaviors (39–41). In this regard, **Table 1** reports an overview of the relationship between depression, cardiovascular risk factors, and mortality.

EXERCISE IS EFFECTIVE FOR THE PHYSICAL HEALTH OF DEPRESSED PATIENTS

Physical activity and exercise have a wide range of beneficial effects (72) that involve both “body” and “mind.” Bearing in mind this is an artifactual and anachronistic convention, here

we provide an overview of exercise effects on the body “from the neck down” that could be relevant to individuals with depression. **Table 1** reports recent literature addressing this issue.

Together with dietary caloric restriction, exercise is the main component of interventions that are effective at reducing and managing weight (73–75). The positive effect of exercise is likely mediated by enhanced regulation of appetite hormones (76) and by increased metabolic rate (47, 77, 78). Moreover, exercise improves sleep quality and duration (79).

Exercise also causes beneficial adaptations in homeostatic systems involved in the response to stress, including the HPA axis (80–82). Moreover, it dampens inflammatory processes while delaying the aging of the immune system (51–53). Exercise also improves the autonomic visceral control by restoring sympathovagal balance (57, 83, 84). Finally, it improves cardiorespiratory fitness both in healthy individuals (47) and individuals with depression (85).

While the formal acknowledgment of the salutary effects of exercise in the medical sciences has been a lengthy process, regular exercise is now recognized as an important lifestyle behavior that can ameliorate the negative impact of chronic diseases (86). Overall, it is estimated that exercise can reduce mortality to a similar extent as medications in individuals with coronary heart disease, stroke, heart failure, and diabetes (15). It would be urgent to verify if such findings can be translated to depressed subjects.

Among the many salutary effects of exercise, arguably the least researched—and probably the most controversial—are its effects on other lifestyle and health behaviors. Both the number of randomized controlled trials and the methodological quality of the trials in this area are rising. While concepts and methods continue to evolve, some early results related to smoking cessation and reducing problem drinking among individuals with mental health disorders show promise (87–89). However, at this stage, systematic reviews of the evidence on the effectiveness of exercise in promoting abstinence from smoking (60) or alcohol (58) indicate no beneficial effect. On the other hand, the effect of exercise on reducing the use of illegal substances is significant (90). In addition, whether a structured exercise intervention can reduce sedentary behavior or encourage engagement in subsequent physical activity remains hotly debated (64).

EXERCISE IS EFFECTIVE AGAINST SYMPTOMS OF MAJOR DEPRESSION

Physical exercise has been shown to be an effective treatment for major depression in adults (14, 91) in several randomized controlled trials comparing it to a wide range of other treatments, including usual care, psychological interventions, and antidepressant medications (14, 92). Although there have been contrarian meta-analytic findings [e.g., (93)], closer inspection of methodological details reveals a pattern of debatable choices (91).

Exercise interventions consisting of three sessions per week for 12–24 weeks typically result in a medium to large reduction in the severity of depression, measured by symptom

TABLE 1 | Literature examining the relationship between depression, cardiovascular risk factors, cardiovascular mortality, and physical exercise in adults.

Cardiovascular risk factor	Association between depression and risk factor	Effect of exercise on risk factor among non-depressed populations
Obesity—overweight	Depression had a 37% increased risk of becoming obese (RR: 1.37, 95%CI: 1.17–1.48); risk was highest for young and middle aged women. Nineteen prospective studies (26, 42)	Exercise was effective to reduce body weight (although less effective than hypocaloric diet) and visceral adipose tissue (more effective than hypocaloric diet). 117 trials (43)
Type 2 Diabetes	Depression was associated with an increased risk of having T2DM (RR: 1.49; 95%CI: 1.29–1.72). Ten studies, only one prospective (44)	Exercise improved Hb1AC levels and insulin resistance. 27 trials (45)
Unbalanced diet	Two out of three studies supported an association between depression and unbalanced diet. Three studies, all cross sectional (24)	na
Blood metabolic parameters	Depression was associated with a higher prevalence of Metabolic Syndrome (OR: 1.54, 95% CI 1.21–1.97), hyperglycemia (OR: 1.33, 95%CI: 1.03–1.73), hypertriglyceridemia (OR: 1.17, 95% CI 1.04–1.30). Eighteen studies, all cross-sectional (34). Depression was associated with lower serum LDL levels (mean difference: 3.15 mg/dL, 95%CI: 6.05–0.24). Eighteen cohort studies (46)	Exercise lowered fasting insulin, HOMA-IR, and Hb1AC levels. TG and APOA1 levels, increased HDL levels; trend-level effects for reductions of LDL and fasting glucose. 160 RCTs (47)
Hypertension	Depression was associated with an increased risk of incident hypertension (RR: 1.42, 95% CI: 1.09–1.86). Nine prospective studies (48)	Exercise reduced blood pressure. The magnitude of the effect changed according to exercise type and was greater for hypertensive subjects. 93 RCTs (49)
Inflammation	Depression was associated with abnormal levels of peripheral cytokines and chemokines compared to HCs. IL-6, TNF- α , IL-10, sIL-2R, CCL-2, IL-13, IL-18, IL-12, and sTNFR2 were significantly elevated, IFN-gamma was slightly reduced. Eighty-two case-control studies (50)	Exercise reduced IL6 and CRP levels in T2DM. Fourteen RCTs (51). Similar results in CAD. Twenty-six trials (52). Possible effect enhancing immune competence and delaying the aging of the immune system (53)
Autonomic dysfunction	Untreated depression was associated with reduced Heart Rate Variability (g: -0.349 , 95%CI: -0.51 to -0.19). Twenty-nine case-control studies (54)	Exercise increased HRV in 9 out of 15 trials on T2DM (55). Exercise improved HRV in CAD. Sixteen RCTs (56). Exercise improved HRV in HF. 19 trials (57)
Alcohol use	Depression was associated with increased risk of Alcohol Use Disorders (aOR: 2.09, 95%CI: 1.29–3.38). Seven studies, two of which prospective (23)	Exercise did not reduce daily alcohol consumption or AUDIT total scores. 21 trials (58)
Cigarette smoking	Among adolescents, depression increased the risk of beginning smoking (RR: 1.41, 95% CI: 1.21–1.63). Twelve prospective studies (20). Depressed smokers had lower odds of short-term (OR: 0.83, 95%CI: 0.72–0.95) and long-term abstinence (OR: 0.81, 95%CI: 0.67–0.97). Forty-two clinical trials on smoking cessation (59)	No effect of exercise on smoking cessation. 19 RCTs (60)
Adherence to medications	Depression was associated with an increased likelihood of non-adherence to medications (OR: 1.76, 95%CI: 1.33–2.57). Thirty-one U.S. based cross-sectional studies on chronic diseases (61)	na
Physical inactivity/sedentary behavior	Depression was associated with less time spent for total Physical Activity (SMD: -0.25 , 95%CI: -0.03 – 0.15), higher levels of Sedentary Behavior (SMD: 0.09, 95%CI: 0.01–0.18) and lower likelihood to meet physical activity levels recommended by guidelines (OR: -1.50 , 95%CI: -1.10 to -2.10). Twenty-four cross sectional studies (17). A recent large study confirmed the association between mental health and physical activity levels (62)	Exercise interventions yielded uncertain and/or small effects increasing subsequent physical activity (63–65)
Cardiovascular mortality	Association between depression and mortality	Effect of exercise on mortality among non-depressed populations
Coronary heart disease	Depression was associated with an increased risk of myocardial infarction-related death (HR: 1.31, 95%CI: 1.09–1.57) and coronary death (HR: 1.36; 95%CI: 1.14–1.63). Nineteen prospective studies (66). Quality of evidences appraised as “highly suggestive” (16)	Exercise reduced mortality in coronary heart disease (OR: 0.89, 95% Credible Interval: 0.76–1.04) with no difference in magnitude from ACEi, beta-blockers, ARBs and diuretics. Thirty-four RCTs (15). Exercise-based Cardiac Rehabilitation reduced cardiovascular, but not overall mortality (RR: 0.74, 95%CI 0.64–0.86). 27 RCTs (67)
Arrhythmias related mortality	Depression was associated with an increased risk of Sudden Cardiac Death (HR: 1.62; 95%CI: 1.37–1.92), ventricular arrhythmias (HR: 1.47; 95%CI: 1.23–1.76) recurrence of Atrial Fibrillation (HR: 1.88; 95%CI: 1.54–2.30). Seventeen studies, of which 15 prospective (36)	No clear effect of exercise on mortality in Atrial Fibrillation (RR: 1.00; 95%CI: 0.06–15.78). 6 RCTs (68)

(Continued)

TABLE 1 | Continued

Cardiovascular mortality	Association between depression and risk factor	Effect of exercise on risk factor among non-depressed populations
Mortality in Heart Failure	Depression was associated with an increased risk of all-cause mortality (HR: 1.20; 95%CI: 1.10–1.31). Increased risk was driven by studies on participants older than 65. 14 prospective studies (35). Quality of evidences was appraised as “highly suggestive” (16)	Exercise reduced mortality in heart failure (OR: 0.79; 95% Credible Interval: 0.59–1.00) to a greater extent than ACEI, beta-blockers, ARBs, but less than diuretics. 18 RCTs (15)
Mortality after Cardiac Surgery	Perioperative depression was associated with an increased risk of early (RR: 1.44; 95%CI: 1.01–2.05) and late postoperative mortality (RR: 1.44; 95%CI: 1.24–1.67). Sixteen prospective studies (69)	Insufficient evidence to establish a significant effect of exercise on mortality after heart valve surgery. 2 RCTs (70)
Overall mortality	Depression was associated with an increased risk of mortality relative to non-depressed participants (RR: 1.52, 95%CI: 1.45–1.59). Excess mortality risk was of similar magnitude in patients from the community vs. those with specific diseases. Two hundred and ninety-three prospective studies (10). Quality of evidence was however appraised as inadequate to support a direct causal association (16, 71)	The network meta-analysis estimated that exercise can reduce mortality to a similar extent to medications among individuals with coronary heart disease, stroke, heart failure, and diabetes. 305 RCTs (15).

This table summarizes recent literature on: (a) the relationship between depression, cardiovascular risk factors and mortality due to cardiovascular diseases; (b) the effectiveness of exercise modifying such risk factors and mortality. The latest reviews for each topic were identified through multiple searches of the Pubmed database. Quantitative reviews or meta-reviews were preferred over qualitative or narrative ones. The number and type of primary studies is specified (cross-sectional vs. longitudinal; RCTs vs. controlled trials).

Na, not available; RCTs, Randomized Controlled Trials; T2DM, Type 2 Diabetes Mellitus, CAD, Coronary Artery Disease; HF, Heart Failure; ACEI, Angiotensin Converting Enzyme Inhibitors; ARBs, Angiotensin II Receptor Blockers; OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; SMD, Standardized Mean Difference; CI, Confidence Intervals.

rating scales (91). Moreover, exercise interventions have been found to result in 22% higher likelihood of remission from depression than treatment as usual (93), the latter in turn being associated with the remission of about a third of patients (3, 4). Generally, exercise is well-tolerated and leads to about 18% of dropout rates (94). Based on the available data, the efficacy of exercise seems greater if it is aerobic, delivered in groups, and supervised by an instructor (95). Although there are relatively few head-to-head comparisons and duration of treatment may be different, the efficacy of exercise may be comparable in terms of magnitude to that of psychotherapies (3, 94–97) or antidepressant medications (98).

Some authors claim the psychological effects of exercise largely depend on “placebo,” or “non-specific” psychosocial effects, such as attention by staff (99, 100). Consistently, exercise is still listed among “alternative and complementary” therapies in some guidelines [e.g., (101)]. Skepticism has been fueled, among other reasons, by difficulties to demonstrate a clear dose-response relationship, such as would be expected in drug trials. Recent studies, however, have started to detect significant associations between the intensity and length of exercise interventions, and their antidepressant efficacy (102, 103); of note, such relationship is likely to follow non-linear patterns (104). Another long-held belief among clinicians is that exercise does only ameliorate non-specific somatic symptoms, such as sleep and appetite changes. Whereas, extant results suggest that exercise indeed reduces core symptoms of depression, such as depressed mood, anhedonia, and suicidal ideation (105, 106). On the other hand, studies examining the effects of exercise interventions on cognitive function among individuals with depression [e.g., (107)] at present do not indicate substantial benefits (108–110).

Exercise may be effective improving several biomarkers that have been implicated in depression (e.g., impaired neuroplasticity, autonomic, and immune imbalances). However, at present, evidence derived from non-depressed individuals still needs to be replicated among clinical populations (111). Nevertheless, recent trials have begun to show efficacy in treating patients with severe mood disorders (112–114) and individuals with treatment-resistant depression, either alone or as an add-on to medications (115, 116). Lastly, exercise can be effective for individuals who may present concerns about drug treatment, such as women with pregnancy or post-partum depression (117) and adolescents (118, 119).

At present, research is still needed to establish the efficacy of exercise in the long-term course of major depression. Some analyses suggest that the antidepressant effects may diminish beyond the duration of the exercise intervention (92). However, individuals who regularly engage in moderate physical activity maintain reduced risk of incurring depressive episodes (120, 121).

EFFECTIVENESS OF EXERCISE IN LATE LIFE DEPRESSION

The clinical features and pathophysiology of late-life depression are largely distinct from that encountered among younger adults (122–124). Specifically, depression in late life is associated with a higher prevalence of physical illnesses, greater prevalence of cognitive impairments and inadequate response to antidepressant drugs (125–128). Despite these differences, late-life depression seems to respond to exercise as well as adult depression (129–131). Moreover, among studies appraised in recent meta-analyses, participants receiving exercise

did not report any significant side effects. More recently, the SEEDS study showed that exercise was an effective add-on to antidepressant drugs for mild to moderate depression (132). Interestingly, adding exercise to antidepressant drugs primarily affected core symptoms of depression rather than somatic symptoms (133). Moreover, individuals receiving aerobic exercise plus antidepressants displayed greater improvements in cognition and autonomic balance compared to those only receiving antidepressants (134, 135). The intervention was well-received by patients and physicians alike (136).

Despite these promising results, the available evidence remains insufficient to conclude whether exercise can improve cognition in patients with late-life depression (108, 109). At present, studies suggest that exercise may not improve cognition among non-impaired, non-depressed individuals (137), but it may, to some extent, improve cognitive performance among individuals diagnosed with cognitive impairment (irrespective of depression), dementia, or physical diseases (138–141).

HOW SHOULD EXERCISE BE PRESCRIBED TO INDIVIDUALS WITH DEPRESSION?

Depression is usually treated by primary care physicians, psychiatrists, and psychologists. Exercise interventions can be delivered by professionals with a variety of disciplinary backgrounds, including group exercise leaders, personal trainers, clinical exercise physiologists, wellness specialists, and physical therapists. Given the challenging cognitive and affective features of depression, it is recommended that exercise for individuals with depression should be delivered by professionals with specific experience in mental health care (142). In other words, a well-integrated, collaborative approach is essential.

A collaborative approach begins with physicians willing to introduce the idea of exercise as a possible treatment options to individuals expressing depression complaints. However, proposals to introduce exercise to the armamentarium of interventions for the treatment of depression are often met with skepticism by physicians due to various perceived barriers (143, 144). These barriers may stem, at least in part, from high-profile reviews and treatment recommendations that downplay the relevant evidence. A recent review, for example, characterized any benefits of exercise, even against non-active control interventions, as merely “modest,” alleged that “high-quality clinical studies investigating the effect of exercise for treating depression among older patients are lacking,” and raised doubt about whether older individuals with depression would be “willing to participate actively in an exercise program” (145). A counterpoint is that, to a large extent, such statements reflect a limited or outdated assessment of the evidence (146, 147). While the evidence base continues to evolve, there are already several randomized controlled trials with positive results that satisfy the standard criteria for high methodological quality (91). Furthermore, provided that proper therapeutic alliances are established within a stepped-care collaborative framework

(136), many individuals with subthreshold, mild, and moderate depressive symptoms will opt for exercise and will demonstrate satisfactory adherence.

Several groups have published recommendations for developing exercise prescriptions for individuals with depression, based on both empirical evidence and clinical experience (148–152). While we endorse these recommendations, we should note that the optimal exercise prescription for the treatment of depression remains unknown, insofar as the relation between the “dose” of exercise (i.e., intensity, frequency, session duration) and the therapeutic response remains understudied. Therefore, any prescription recommendations at the present stage are essentially derived from general exercise prescription guidelines, which were developed primarily for the improvement and maintenance of physical fitness and cardiometabolic health (153). Therefore, we wish to highlight an emerging trend in exercise prescription, which may be especially relevant to the treatment of depression, namely affect-based exercise prescription (154). This method expands the traditional focus of exercise prescriptions from the dual goal of maximizing fitness gains while minimizing risk to a model that also aims to ensure that participants consistently derive pleasant affective experiences. The inclusion of pleasure as a central consideration is intended to enhance what is often the Achilles’ heel of lifestyle or behavior-change interventions, namely adherence. In a typical affect-based prescription, the exercise participant is shown a simple rating scale (e.g., one ranging from +5: “I feel very good” to –5: “I feel very bad”) and is instructed to self-regulate his or her exercise intensity and duration to maintain a rating of +3 or higher.

Individuals with depression can experience exercise as pleasant and affect-enhancing (155–157). Among non-depressed adults, affective responses to a bout of exercise have been found in correlational studies to be associated with the amount of physical activity individuals choose to do (158), while experimental manipulations resulting in improved affective responses have been shown to increase the amount of physical activity performed over a subsequent period of 6 months (159). Early evidence among individuals with depression indicates that affective responses to a bout of exercise may predict treatment response (160, 161). While randomized controlled trials investigating the efficacy, effectiveness, and cost-effectiveness of affect-based exercise prescriptions for the treatment of depression are not yet available, this method seems to hold promise for clinical application due to its simplicity, making it appealing to physicians who lack specialized training in exercise and to healthcare organizations concerned about implementation costs.

CONCLUSIONS

The premature mortality of individuals with depression is an alarming public health concern, which is exacerbated by the present inability to offer satisfactory treatments. Physical exercise represents an underutilized intervention that may uniquely address both concerns at the same time.

First, exercise offers numerous physical benefits, which can counteract several mechanisms postulated to increase mortality risk in depression. Second, if prescribed and delivered correctly, exercise can be as effective as other first-line treatments, while being mostly free of adverse side-effects.

While there is a need of pragmatic trials to evaluate the long-term effects of exercise and its cost-effectiveness, clinicians in the mental health sector should acknowledge this ancient, yet new treatment option and should start to use it to the benefit of patients.

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AUTHOR CONTRIBUTIONS

MB and PE conceived and drafted the work. MM, DZ, SC, PC, LC, GS, SZ, and MA contributed to revising it critically and approving the content.

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