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Exercise as a therapeutic modality for the prevention and treatment of depression

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Abstract

While maintaining an active lifestyle and engaging in regular exercise are known to promote cardiovascular (CV) health, increasing evidence has emerged to indicate that these lifestyle behaviors also can promote psychological health and well-being. This has led to research to determine if exercise can serve as a potential therapeutic modality for major depressive disorder (MDD), which is a leading cause of mental-health impairment and overall disability worldwide. The strongest evidence to support this use comes from an increasing number of randomized clinical trials (RCTs) that have compared exercise to usual care, placebo controls, or established therapies in healthy adults and in various clinical populations. The relatively large number of RCTs has led to numerous reviews and meta-analyses, which generally have been concordant in indicating that exercise ameliorates depressive symptoms, improves self-esteem, and enhances various aspects of quality of life. Together, these data indicate that exercise should be considered as a therapeutic modality for improving CV health and psychological well-being. The emerging evidence also has led to a new proposed subspecialty of "lifestyle psychiatry", which promotes the use of exercise as an adjunctive treatment for patients with MDD. Indeed, some medical organizations have now endorsed lifestyle-based approaches as foundational aspects of depression management, with adoption of exercise as a treatment option for MDD. This review summarizes research in the area and provides practical suggestions for the use of exercise in clinical practice.

Keywords

Cardiovascular disease; Exercise; Depression; Lifestyle medicine; Cardiac rehabilitation

Lifestyle medicine is an evolving medical specialty that uses therapeutic lifestyle interventions as a primary modality to treat chronic, noncommunicable diseases. Lifestyle medicine focuses on health behaviors and psychological factors that promote health and

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decrease disease risk (Fig. 1). For instance, poor diet, obesity, physical inactivity, substance abuse, and smoking are negative health behaviors that contribute to chronic medical conditions, such as coronary heart disease (CHD), type 2 diabetes, and hypertension.[1] Psychological determinants of disease include depression, anxiety, social isolation and poor social support, various forms of chronic stress, pessimism, and vital exhaustion.[2–6]

A central tenet of lifestyle medicine is the bi-directional relationship between physical health behaviors and psychological well-being. Substantial evidence indicates that health-damaging behaviors can lead to a decrease in psychological well-being. Conversely, negative psychological states such as depression, anxiety and anger can adversely impact health-promoting behaviors. Indeed, common negative moods such as depression, anxiety, and anger along with low social support are commonly associated with a higher concentration of poor health habits.

The present review will briefly discuss the assessment of depression and distinguish between physical activity (PA) and exercise. Next, we will summarize available evidence regarding the amelioration of depression with physical activity and exercise in general and cardiac populations, with specific emphasis on the conduct of randomized clinical trials (RCTs), which have compared the efficacy of exercise versus standard of care, placebo controls, or established treatments for major depressive disorder (MDD). We will then overview emerging data regarding how the combination of exercise and other lifestyle interventions may be used as a treatment modality for depressive symptoms in medical practice. Finally, we will evaluate how these new findings can be incorporated into the current practice of clinical medicine and may be leading to a new sub-specialty of ‘lifestyle psychiatry’.

Definition and assessment of depression

Depression is a term that has been used to describe a mood state that may range from mild unhappiness to intense sadness and despair. It also may refer to a clinical syndrome or cluster of symptoms, or to a diagnosed clinical disorder. Major depressive disorder is one of the most common psychiatric conditions in the United States and worldwide. It is estimated that 21 million adults in the United States will have at least one major depressive episode during their lifetimes. This number represents 8.4% of all U.S. adults.[7] The prevalence of MDD is higher among adult females (10.5%) compared to males (6.2%) and also is consistent across high, middle and low income countries, emphasizing the global burden of this condition.[8]

Clinical depression is relatively common in patients with CHD, with estimates of 15% to 20% of cardiovascular disease (CVD) patients meeting criteria for MDD and an additional 20% reporting elevated depressive symptoms.[9–11] A number of studies have reported that the presence of clinical depression is associated with more than a doubling of risk for mortality and nonfatal CVD events[12,13] and that even subclinical elevations in depressive symptoms are associated with a worse prognosis in patients with established CHD.[10,11]

According to the most recent Diagnostic and Statistical Manual of Mental Disorders (DSM-V), MDD is one of a number of depressive disorders. The common feature of these disorders

is feeling of sadness, loss of interest, and/or irritable mood, accompanied by related changes that significantly affect the individual's capacity to function (including somatic symptoms and impaired cognition). The severity of depression is typically based on three considerations: 1) the presence of symptoms (which may vary in frequency and intensity); 2) the duration of the disorder; and 3) the impact on personal and social functioning. The general criteria for MDD diagnosis are provided in Table 1.

MDD is formally diagnosed by clinical interview, while symptom severity is typically quantified by clinical ratings or psychometric questionnaires. The more commonly used questionnaires are listed in Table 2. Among these, the Patient Health Questionnaire (PHQ)-2 has been suggested by the American Heart Association as a screening tool for depression among CVD patients.[14]

Exercise, physical activity and depression

Although the terms physical activity and exercise are often used interchangeably, physical activity and exercise are considered distinct constructs.[15] PA is defined as any bodily movement that requires energy expenditure, while exercise is defined as structured PA that aims to maintain or improve physical fitness; PA defined in this manner is broader in scope, and includes such activities as gardening, housework, physical labor, and leisure type activities such as bowling, golf, and pickleball. Exercise, on the other hand, is a subcategory of physical activity and is considered more purposeful in that it is designed to improve or maintain aerobic capacity, muscular strength and endurance, and/or flexibility.

The beneficial impact that PA and exercise have upon mental health is well-documented. The earliest studies were observational and examined the relationship between physical activity and incidence of depression within communities. An example of an early epidemiologic study was conducted in Alameda County California in 1965.[16] A PA index was computed based upon the frequency and presumed intensity of self-reported PA (e.g., playing sports, swimming, walking, and gardening). Men and women who reported low levels of PA at baseline were more likely to be depressed and were twice as likely to subsequently develop depression compared to those individuals who reported high PA at baseline. Interestingly, persons who were active but who subsequently became sedentary also were more likely to become depressed. As an extension of these findings, recent Mendelian randomization research has demonstrated that people who are more active and are genetically predisposed to MDD are less likely to develop MDD compared to people of equal genetic risk for MDD and low PA levels.[17] Because these observational studies are correlational in nature, such studies cannot be used to establish causal relationships. For example, factors such as illness and declining health could also be responsible for these associations. People who are sick and disabled are less likely to engage in PA and are more likely to get depressed.

The study of the relationship between exercise and depression in general populations has led to subsequent investigations as to whether promotion of PA and exercise can be used as therapy for the prevention and treatment of psychiatric disorders. This is particularly important insofar as it has been estimated that mental, neurological and substance-use

disorders (i.e. schizophrenia, mood and anxiety disorders, epilepsy, dementia, alcohol dependence) account for 13% of the global burden of disease, placing mental illness as the greatest burden, exceeding both heart disease and cancer.[18] The potential use of exercise therapy for treating depression is especially relevant insofar as MDD and CHD are both highly prevalent and each is considered a risk factor for the other.

RCTs of exercise in depressed populations

The most convincing evidence for the causal effects of exercise in reducing depressive symptoms can be derived from RCTs. Over the past two decades, the number of RCTs of exercise on depression has accrued substantially.[19,20] In the most recent Cochrane review of the literature by Cooney et al.,[19,21] 39 trials (2326 participants) fulfilled inclusion criteria, of which 37 provided data for the meta-analyses. For the 35 trials (1356 participants) comparing exercise versus no treatment or a control intervention, the pooled standardized mean difference (SMD) for the primary outcome of depression at the end of treatment was −0.62, indicating a moderate clinical effect. However, when only the six trials (464 participants) with adequate allocation concealment, intention-to-treat analysis, and blinded outcome assessment were considered, the pooled SMD for this outcome was no longer statistically significant.

A subsequent meta-analysis by Schuch et al.[22] of 25 RCTs compared exercise to a number of control or comparison groups, with adjustment for publication bias. Nine of the trials included participants with MDD. Exercise was associated with a large and significant reduction in depression (Fig. 2). The anti-depressant effect of exercise was greater for studies that included individuals diagnosed with MDD. Adjusted analyses found that publication bias generally resulted in an underestimation of the beneficial effects of exercise upon depression. Further, larger effect sizes were observed for studies involving supervision of exercise by qualified exercise professionals. However, it also should be noted that many studies suffer from methodological shortcomings, which detract from the strength of these findings.

RCTs of exercise for depression compared to established antidepressant medications

A series of studies at Duke University have examined the benefits of exercise compared to established pharmacotherapy for depression. In 1999, researchers conducted the first in a series of RCTs designed to examine the effects of exercise in patients with MDD compared to standard antidepressant medication.[23] Initially, there was a great deal of skepticism among those in the mental health field: Would sufficient numbers of patients with MDD volunteer for an exercise study? Could patients with MDD engage in exercise and stick to it? And of course, would exercise help ease depression? The answer to each of these questions was a resounding ‘yes’!

In the first RCT, 156 patients with MDD were recruited and randomized to one of three conditions: aerobic exercise, antidepressant medication (sertraline) or a combination of exercise and sertraline. Results revealed that all three groups showed significant, and

comparable, improvements in depressive symptoms. Remission rates (i.e., no longer met criteria for MDD) were 60.4% of patients in the exercise group, 65.5% in the medication group, and 68.8% in the combined group. Surprisingly, even patients with more severe depression appeared to benefit from exercise as much as those who received the medication, and there was no advantage for those who received both exercise and sertraline compared to those who received either sertraline or exercise alone—even in those with more severe depression.

Interestingly, in a 6-month follow up report,[24] participants in the exercise group exhibited lower rates of depression (30%) compared to participants in the sertraline (52%) and combined group (55%). Moreover, only 8% of those patients who were remitted after treatment in the exercise condition suffered a relapse, compared to 31% in the sertraline condition and 38% in the combination sertraline and exercise condition.

The study provided some answers, but also raised other questions. Because most patients improved, the improvements could be attributed to any number of explanations–a placebo effect, spontaneous remission, demand characteristics (i.e., trying to 'please' the researchers), regression to the mean, or due simply to the increased attention provided by study staff. Because participants exercised in a group setting, there was a possibility that social support provided to participants during their exercise workouts further enhanced the benefits of exercise. A second study attempted to address these concerns.[25] In this study, 202 adults with MDD were randomly assigned to supervised exercise in a group setting; home-based exercise; antidepressant medication (sertraline, 50–200 mg daily); or placebo pill. After 4 months of treatment, 41% of the participants achieved remission, defined as no longer meeting the criteria for MDD and a score of <8 on the Hamilton Rating Scale for Depression. Both exercise and medication groups achieved higher remission rates compared with placebo; 45% of MDD patients undergoing supervised exercise, 40% undergoing home-based exercise, and 47% receiving medication were in remission after 16 weeks of treatment, compared with only 31% receiving placebo. The efficacy of exercise in patients was generally comparable to those patients receiving antidepressant medication, and medication and exercise tended to be better than the placebo. Not surprisingly, placebo response rates were high, suggesting that some of the therapeutic response was due to patient expectations, ongoing symptom monitoring, attention, and other nonspecific factors.

These studies involved patients with MDD, but did not specifically target patients with CHD, for whom the presence of comorbid depression has important prognostic significance. Subsequently, 101 patients with stable CHD and elevated depressive symptoms, in a study known as UPBEAT,[26] were randomized to aerobic exercise (3 times/week), sertraline (50–200 mg/day), or placebo. After 4 months, participants in the aerobic exercise program and those who received sertraline had larger reductions in depressive symptoms compared to patients in the placebo group (Fig. 3). In addition, exercise and antidepressant medication tended to result in greater improvements in heart rate variability compared with placebo, and exercise tended to result in greater improvements in heart rate variability compared with sertraline. This study was important because it demonstrated that the improvements in depression from exercise training were comparable to an established antidepressant

medication and had the added benefit of also improving some CHD biomarkers that could improve clinical outcomes.

RCTs of aerobic exercise for depression in heart failure (HF)

While depression is common among CHD patients, its presence is accentuated among patients with HF. Depression among heart failure patients is associated with both diminished quality of life (QoL) and a higher risk for adverse clinical outcomes, especially if depression worsens over time.[27,28] A systematic review and meta-analysis of 16 RCTs involving 3226 patients with HF found that exercise training was associated with a significant decrease in depressive symptoms compared to patients with HF who did not undergo exercise training.[29,101] In perhaps the largest, multi-site RCT of exercise in HF patients, known as HF-ACTION, participants randomized to exercise reported lower levels of depression after 3 and 12 months compared to usual care controls. Findings were similar among patients undergoing exercise training in center-base, home-based, or combined settings.

RCTs of resistance training for depression

Most studies of exercise and depression focus on aerobic exercise. However, an important aspect of physical fitness involves muscular strength and endurance, which is improved by resistance training. There is now evidence that resistance training can also improve mental health. In a meta-analysis of 33 RCTs, involving 1877 participants,[30] resistance exercise training was associated with a moderate-sized mean effect upon reduction of depressive symptoms. There was significant heterogeneity in the findings, however, due in part to small samples and disparate baseline conditions. Accordingly, more studies regarding the impact of resistance training upon depression are needed.

Impact of cardiac rehabilitation (CR) on depression

Although CR was initially introduced primarily as an exercise intervention, it has subsequently expanded in scope to become a more comprehensive lifestyle intervention, with aerobic exercise as the core and four additional elements including dietary modification, risk factor management (including smoking cessation), stress reduction, and patient education (Fig. 4). This development is relevant because there is increasing evidence that besides exercise, dietary modification,[31–34] smoking cessation,[35–37] and sleep hygiene,[38–41] either alone or acting additively[42] or synergistically[43–45] with exercise can contribute to improvements in depression.

In a series of reports from the Ochsner Clinic, participation in exercise-based CR has been shown to be associated with reduced depression in women,[46] older adults,[47] and in patients with risk factors for CHD such as diabetes.[48] In one study of 338 consecutive patients who were referred for exercise-based CR,[49] 69 patients were depressed at study entry. After 12 weeks of CR and exercise training (CRET), depression was reduced significantly in two thirds of patients and improvements on several measures of QoL were noted. In a subsequent study of 522 consecutive CHD patients enrolled in CRET and a control group of 179 CHD patients who did not complete CRET, the prevalence of depression decreased 63% after

CRET (from 17% to 6%).[50] Depressed patients who completed cardiac rehabilitation also had a 73% lower mortality rate.

To assess the relative benefit of each of the core components of CR, Kabboul et al.[51] performed a meta-analysis of 148 RCTs, involving 50,965 participants, which evaluated the comparative effectiveness of each of the core components on mortality and morbidity. The two components that had the most significant impact on reducing all cause-mortality were exercise training and psychosocial interventions (Table 3). In an important RCT of patients referred for exercise-based CR, Blumenthal et al.[52] reported that stress management provided added value to traditional exercise-based CR on depression and a composite measure of stress, as well as on major adverse CVD events.

There also are emerging data that suggest that dietary interventions also may reduce the risk of MDD,[32] whereas diets high in ultra-processed foods may be associated with an increased risk of depressive symptoms.[53] Meta-analyses of clinical trials that use whole food diet interventions have provided preliminary evidence that they significantly reduced depressive symptoms and several small RCTs have reported improvements in depressive symptoms when randomized to receive Mediterranean-style dietary intervention compared to controls.[33,54–56] Clearly, a promising area for future research is to further assess the impact of dietary interventions upon depression as well as the combined effects of diet and exercise.

Mechanisms of beneficial effects of exercise on depression

A growing literature suggests that exercise can reduce depression through both biological and psychological mechanisms. However, these mechanisms are complex and not yet fully elucidated. For instance, some early investigations focused rather narrowly on beta endorphins and it was thought that the release of beta endorphins during exercise might explain the anti-depressant effects of exercise.[57] However, this notion was subsequently considered overly simplistic since endorphin levels measured in the periphery are not necessarily reflective of levels in the brain.

A current understanding of the mechanistic relationship between exercise and depression, including the influence of potential moderators and confounders has been summarized by Kandola et al.[58] (Fig. 5). Some of the principal biological derangements associated with depression include disruptions in the neuroplasticity pathways of the brain, the effects of chronic low grade inflammation, vulnerability of the brain to oxidative stress, and the impact of neuroendocrine dysfunction. There is supportive evidence that exercise can favorably retard each of these mechanistic pathways toward depression.

Some of the plausible biological and psychological mechanisms that could be responsible for the beneficial effects of exercise include stimulation of brain-derived neurotrophic factor (BDNF),[59,60] increased core body temperature,[61] reduced inflammation,[62,63] stimulation of the pre-frontal cortex and hippocampus,[64] enhanced aminergic transmission including alterations in central norepinephrine activity,[65–68] enhanced activity of the hypothalamic-

pituitary-adrenocortical axis, including structural brain changes that can be induced by prolonged cortisol exposure,[69] and reductions in oxidative stress.[70]

The psychological benefits of exercise are broad-based, including evidence that exercise can promote one's sense of self-efficacy and mastery, and lead to improved self-esteem.[58] Exercise also can provide a greater sense of hope, purpose and meaning, and can serve as a method for coping with stress. In addition, exercise, particularly in a group setting such as the programs offered through cardiac rehabilitation, can increase social support by providing opportunities to socialize and interact with others. It is likely that the improvement in mood that can follow from the initiation of exercise involve a synergistic interplay of the biological, psychological, and social pathways that are promoted by regular exercise and increased PA.

Clinical implications

Evidence accumulated over the past two decades indicates that physically active individuals and individuals who engage in regular exercise are less likely to be depressed at the time of baseline measurements and less likely to become depressed when followed over time. As reviewed herein, the results of numerous RCTs generally indicate that exercise improves depressive symptoms even among people with MDD. Meta-analyses of RCTs also demonstrate that exercise can significantly improve other psychological domains including self-esteem, quality of life, neurocognition,[71] and sleep.[72,73] Therefore, based upon available evidence, exercise has become increasingly considered as a viable treatment option for patients with mild to moderate MDD and it can be combined with other established therapies such as cognitive behavior therapy, interpersonal psychotherapy, and/or pharmacotherapy in particular for more severe MDD.

These psychological benefits raise practical questions as to how to use exercise as a therapeutic modality for the prevention and treatment of depression. First, what is the "therapeutic dose" of exercise that aids its anti-depressive effects? Second, how can one best motivate depressed patients to exercise? And third, what are useful strategies to help patients maintain exercise, especially those who may be depressed? The following sections will briefly address these practical concerns.

Exercise "dose" for treating depression.

The issue of exercise dose has recently been evaluated by Pearce et al. in a meta-analysis of exercise activity and depression among 15 studies, involving 191,130 participants.[74] An inverse curvilinear association between PA and incident depression was observed. This dose response relationship was similar among patients diagnosed with MDD versus patients with depressive symptoms with steeper gradients at lower PA volumes (Fig. 6). Relative to those adults not reporting any activity, those accumulating half the recommended volume of PA (i.e., ~ 75 min of moderate intensity of exercise/week) had 18% lower risk of depression, while those reportedly engaged in the recommended volume of exercise (i.e., ~ 150 min of moderate intensity exercise per week) had 25% lower risk, with diminishing benefits beyond that exposure level. Importantly, the greatest differences in risk for depression were observed among those who were totally sedentary versus those engaging in low doses of

PA. This parallels the general finding that clinical health benefits accrue most dramatically among patients who shift from being sedentary to initiating even low levels of PA.[75,76] One relatively small RCT of depressed patients determined that the optimal dose of exercise was 150 min/wk. of aerobic exercise,[77] but because the methodologies of exercise RCTs generally tend to be of lower quality compared to drug trials[78] there remains uncertainty as to the optimal dose of exercise to treat depression in clinical populations.

Motivating Patients with Clinical Depression to Exercise.

One of the pressing challenges in clinical practice is how to motivate patients who are depressed and sedentary to initiate an exercise regimen. A full discussion of this issue is beyond the scope of this review, but we favor using principles applied from motivational interviewing,[79] action planning concepts,[80,81] and the transtheoretical model of health behavior change.[82] Among these principles, it is best to look for opportunities to assess patients' willingness to consider initiating exercise. This might involve asking patients open-ended questions about their PA habits or garnering the same information from questionnaires, such as the two-item exercise vital sign that is recommended by the American Academy of Sports Medicine.[83] Using such information, patients can then be asked if they are willing to consider the benefits of exercise. If so, then the present and future-oriented benefits of exercise can be shared with patients, followed by querying patients as to their thoughts about this information.

A related counseling principle is helping patients to make action plans according to their sense of "self-efficacy". This principle is based on the well-demonstrated recognition that patients are less likely to initiate goals if they believe they are beyond their capability. Thus, the goal with depressed sedentary patients should be to achieve "small wins" or psychological successes by encouraging them to engage in whatever level of exercise or PA that the feel they can initiate. This is best accomplished by setting modest goals to maximize the likelihood of success and providing patients with encouragement. This could mean as little as 5–10 min of walking every day or a few days per week, which is consistent with a new directive within the 2018 Physical Activity Guidelines for Americans that suggests that any amount of exertion, regardless of duration, can count toward one's weekly total of physical activity.[84]

In our experience, movement begets movement and the first goal among patients who are sedentary is to get them to take the first step—literally and figuratively. This is particularly helpful because many depressed patients may be easily fatigued, have unrealistic fears about being able to exercise safely, and/or have little confidence that they can succeed.

It is important that providers not just prescribe exercise but follow-up at regular intervals to reinforce patients' exercise behaviors so that it becomes a habit. If the physician provides an exercise prescription but never follows up, the unintended message to the patient may be that exercise is just not that important. Ultimately, we have found that patients who exercise regularly will transition from considering exercise as a means to an end (i.e., increased fitness, greater survival) to an end in itself.[85] Other guidelines for incorporating exercise as a treatment for patients with depression are listed in Table 4.

Barriers to Begin and Sustain an Exercise Regimen.

In anticipation of difficulty sustaining an exercise program, it can be useful for patients to identify potential barriers to exercise, to anticipate obstacles to exercise, and to brainstorm potential solutions. External factors may include inclement weather, unsafe neighborhoods, and time demands of family and work. Internal factors include low motivation (e.g., low energy, belief that exercise may not be helpful or is beyond the person's abilities), unpleasant sensations from exercise (e.g., pain, fatigue, shortness of breath), or fear of injury or of a catastrophic event (e.g., myocardial infarction or stroke). The presence of significant anxiety is another factor that can diminish the effectiveness of exercise in reducing depression. In one exercise RCT of depressed patients, Herman and colleagues[86] showed that high anxiety levels at study entry predicted early dropout from exercise programs and the presence of comorbid anxiety has also been shown to diminish the effectiveness of exercise in reducing depression.[87,88] Therefore, anxious patients with comorbid depression may require more attention to initiate and maintain an exercise program.

Summary and conclusions

Based upon the available evidence, a number of medical organizations, such as the American Heart Association, American College of Sports Medicine, and American College of Lifestyle Medicine have called for the routine assessment of PA in healthcare settings. However, the emerging evidence regarding the psychological benefits of exercise for depressed patients suggests that there is also fertile opportunity for mental health professionals to use exercise therapy and other lifestyle interventions in their management of patients with depression and related disorders in what may be considered a new subspecialty of "lifestyle psychiatry". This emerging field recognizes the important contribution of health behaviors on mental, as well as physical health, including the benefits derived from healthy nutrition,[89,90] smoking abstinence,[91,92] sleep,[93,94] and physical activity.[95,96]

Notably in this regard, a number of organizations including the Royal Australia and New Zealand Royal College of Psychiatrists[97] now endorse lifestyle-based approaches as foundational aspects of depression management. Furthermore, exercise is also now recommended as a treatment option for MDD by a number of mental health organizations, including the European Psychiatric Association,[98] and the World Federation of Societies for Biological Psychiatry suggest that exercise be considered as an adjunctive treatment to supplement pharmacotherapy.[99]

The National Institute for Health and Care Excellence (NICE) guidelines, which set forth evidence-based recommendations for health and care in England, also endorse exercise and physical activity as a treatment modality for mild depression. According to the NICE Guidelines,[100] doing any form of physical activity on a regular basis could help enhance feelings of wellbeing and further suggest that the benefits could be enhanced if this activity is performed outdoors.

In summary, accumulated evidence from both observational studies and RCTs indicate that exercise diminishes depressive symptoms, even among individuals with MDD. These findings add to the extant literature suggesting that exercise can enhance self-esteem,

increase self-confidence, and improve QoL. Thus, in addition to the cardiovascular benefits of exercise, exercise now may be considered an effective therapeutic modality for aiding in the prevention and treatment of depression.

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Abbreviations:

CHD	coronary heart disease
CR	cardiac rehabilitation
CRET	cardiac rehabilitation and exercise training
CVD	cardiovascular disease
HF	heart failure
MDD	major depressive disorder
NICE	National Institute for Health and Care Excellence
PA	physical activity
PHQ	Patient Health Questionnaire
QoL	quality of life
RCTs	randomized clinical trials
SMD	Standard mean difference

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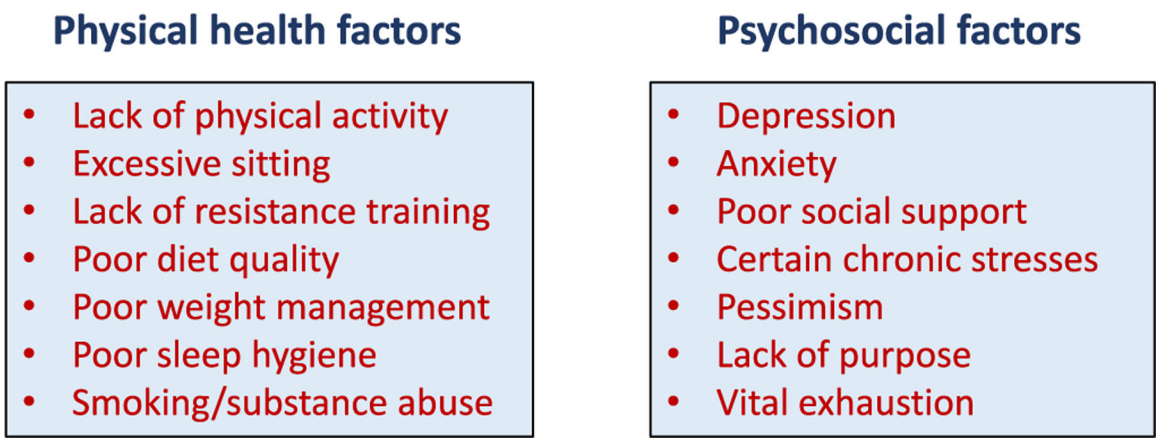

Fig. 1.
Physical health and psychosocial risk factors for disease.

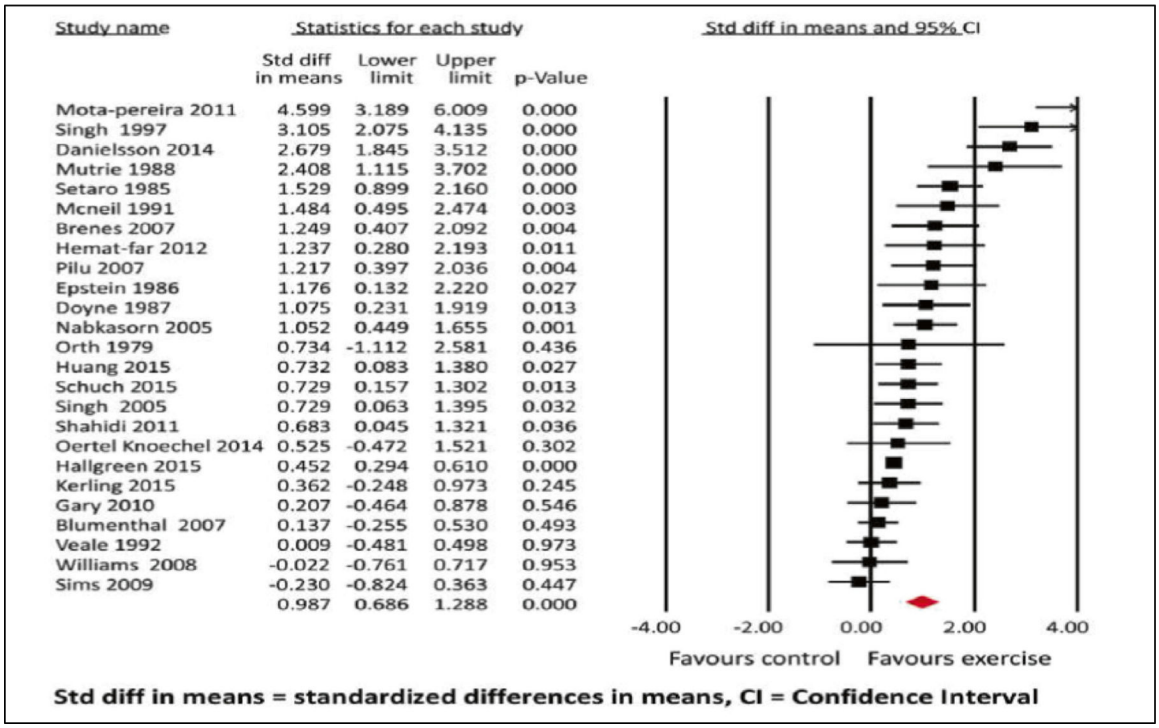

Fig. 2.

Results of meta-analysis of 25 randomized controlled trials of exercise interventions versus control conditions among individuals with major depressive disorder or depressive symptoms, indicating a large treatment effect. (Reprinted with permission from Schuch et al.[22]).

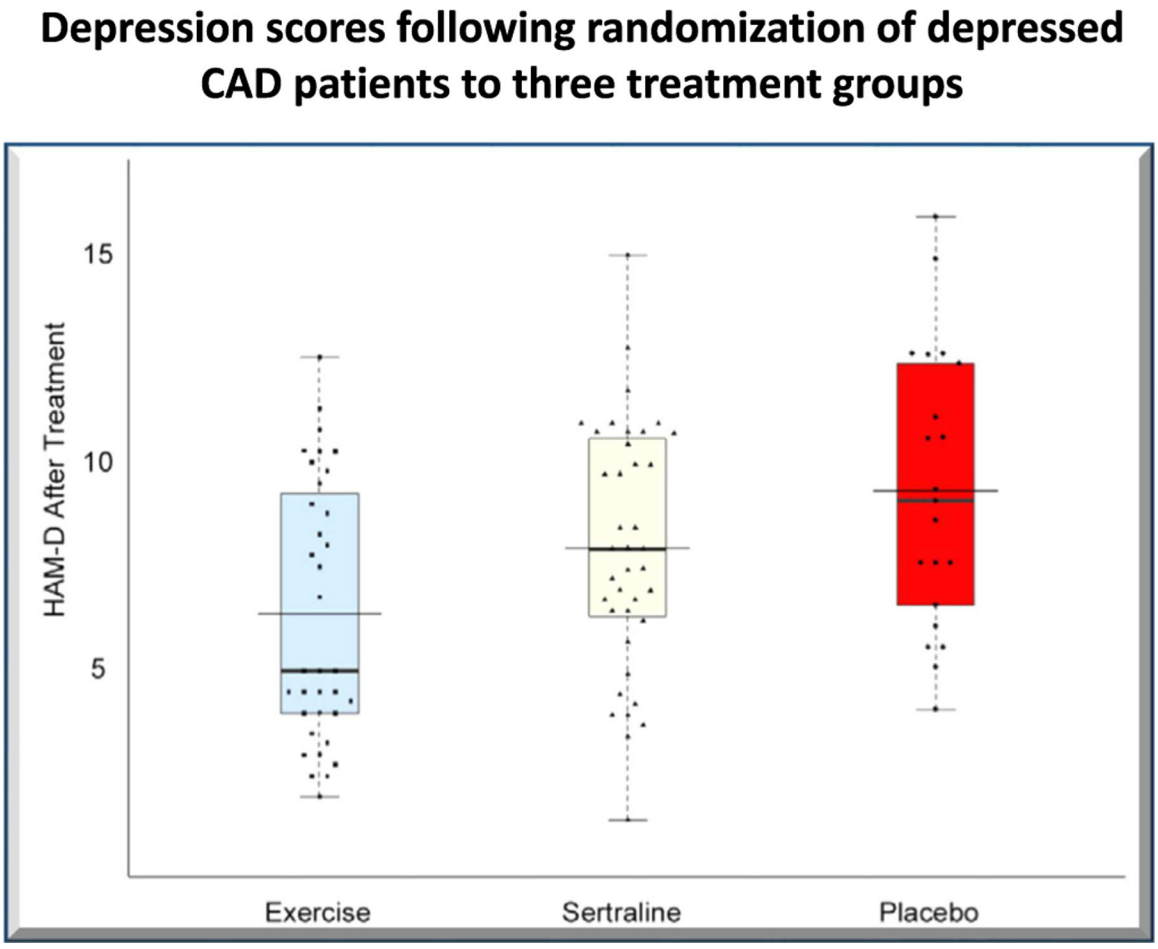

Fig. 3.

Hamilton-D (HAM—D) scores for depression among 101 cardiac patients with elevated depression symptoms, randomized to three groups, after completion of their randomized treatments. The exercise group had the lowest depression scores. (Reprinted with permission from Blumenthal et al.[26]).

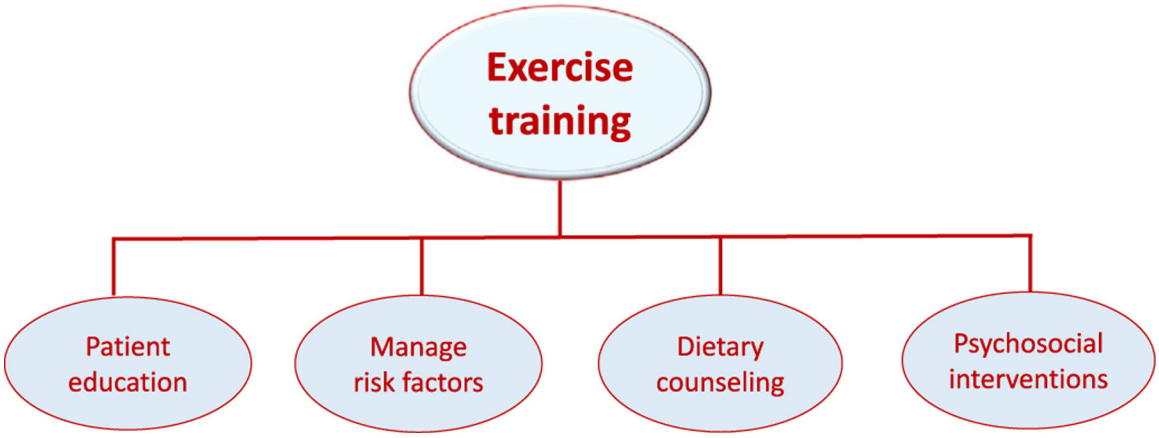

Fig. 4.

Cardiac rehabilitation is based on the promotion of exercise training and the inclusion of four other core components, including stress management and psychotherapy (e.g., interpersonal therapy or cognitive behavior therapy) specifically for patients with depression when indicated.

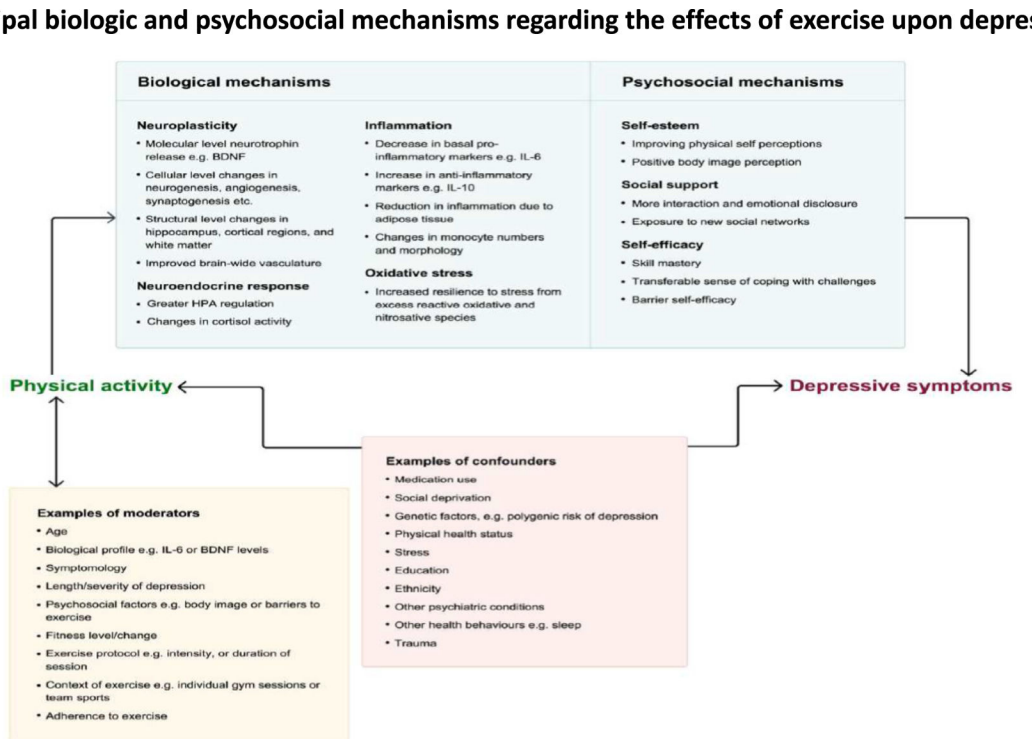

Fig. 5.

Biological and psychosocial mechanisms that may contribute to the anti-depressant effects of exercise, along with examples of moderators and cofounding factors that may influence the study of these mechanistic relationships. (Reprinted with permission from Kendola et al.[58]).

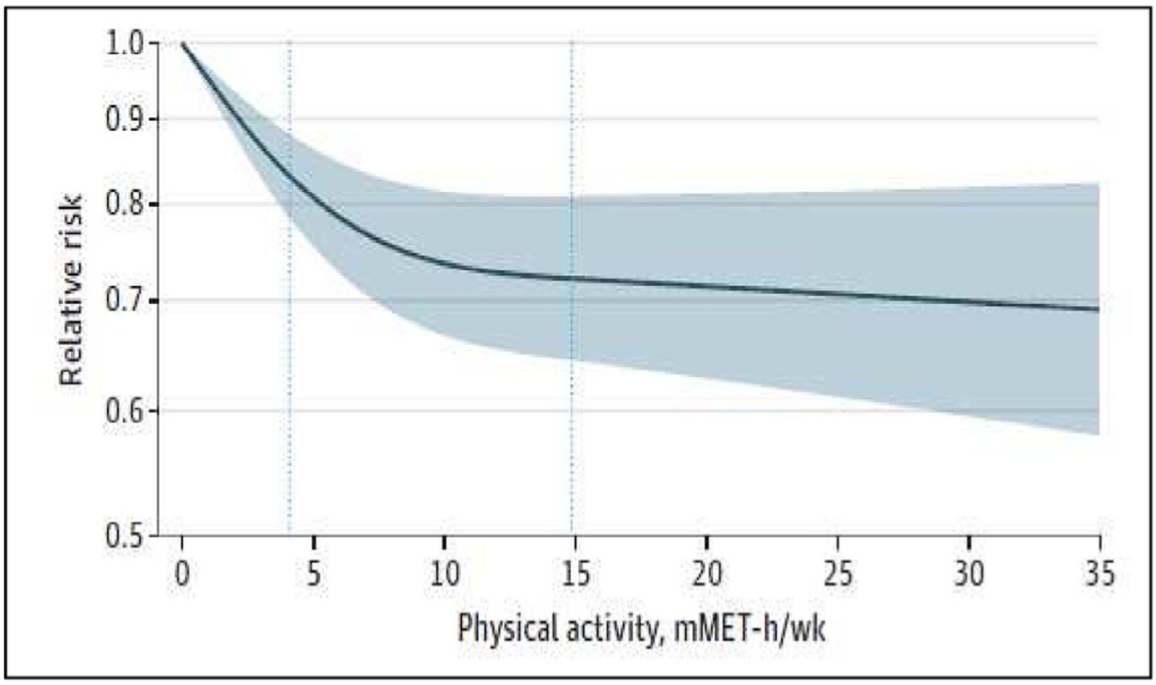

Fig. 6.

Association between physical activity level and risk for depression, from meta-analysis of 119,130 participants in 15 studies. An inverse curvilinear relationship between dose of physical activity and depression is noted, with the greatest reduction occurring at low levels of physical activity. (Reproduced with permission from Pearce et al.[74]).

Table 1

Diagnosis of major depression based on DSM-5 criteria.*

A. **Required symptoms.** At least one of the following:

- Depressed Mood: Most of the day, nearly every day; may be subjective (e.g., feels sad, empty, hopeless) or observed by others (e.g., appears tearful).
- Loss of interest: Markedly diminished interest/pleasure in all (or almost all) activities most of the day, nearly every day.

B. **Associated symptoms.** ≥4 of the following additional symptoms during the same 2-week period that are a change from previous functioning:

- Weight loss or gain
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Feeling worthless or excessive/inappropriate guilt
- Decreased concentration
- Thoughts of death or suicide

* When symptoms not attributable to effects of substance abuse, underlying medical condition, or better explained by other psychiatric conditions.

Table 2

Common psychometric instruments used to assess depression.

Instrument	# of items
Beck Depression Inventory-II (BDI-II)	21
Center for Epidemiological Studies-Depression Scale (CES-D)	20
Hamilton Rating Scale for Depression (HAM-D)*	17
Hospital Anxiety and Depression Scale-Depression (HADS-D)	7
Patient Health Questionnaire-9 (PHQ-9)	9
PHQ-2 subscale of PHQ-9	2
Symptom Checklist-90 Depression scale (SCL-90 D)	12
Zung Self-Rating Depression Scale (SDS)	20

* Note: The HAM-D scale is administered and scored by a health care professional and contains 21 items, but the score is based on 17 items.

Table 3

Estimates of the effects of the five core components of cardiac rehabilitation upon all-cause mortality according to meta-analysis by Kabboul et al.[51]

Core component	Estimate and 95% CI
Exercise training	0.74 (0.60–0.92)
Nutritional counseling	1.07 (0.78–1.46)
Risk factor modification	0.87 (0.66–1.15)
Patient education	0.98 (0.78–1.20)
Psychosocial management	0.68 (0.54–0.85)

Table 4

Guidelines for exercise prescription for depressed patients.

- Evaluate patient's ability to safely engage in exercise. Refer patients who require medical clearance (e.g., sedentary patients with cardiac, metabolic, or renal disease) for evaluation prior to recommending exercise.
- Work with patients to develop specific exercise prescription that includes details about patients' preferred mode, intensity, frequency, and duration of physical activity.
- Help patients establish a "minimal floor" of physical activity if they are unable to achieve the CDC recommendation of exercise most days of the week.
- Walking programs are generally easiest to implement.
- Begin at relatively low level of intensity, frequency, and duration of physical activity.
- Encourage exercise with a partner or group. Social support can reinforce exercise routine and add important element of accountability for regular exercise. The structure of formal, exercise-based cardiac rehabilitation provides an ideal setting for patients with CHD.
- Identify potential 'barriers' to regular exercise and help patients to problem solve potential solutions.
- Reinforce health promoting aspects of exercise.
- Encourage the use of exercise logs to document adherence. Step counts also can be useful.
- Review progress with patient at regular intervals.
- Remember special considerations for exercising in inclement weather or in cold or hot conditions.
- Monitor depression and refer to mental health specialist if symptoms persist or worsen.