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Review article

# The effect of exercise therapy on depressive and anxious symptoms in patients with ischemic heart disease: A systematic review

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ABSTRACT

*Objective:* Depressive and anxiety symptoms are associated with Ischemic Heart Disease (IHD). Exercise interventions might improve both depressive and anxiety symptoms, but an overview of the evidence is lacking. Therefore, we systematically reviewed the existing literature on the effectiveness of exercise therapy to reduce depression and anxiety symptoms specifically in patients with IHD.

*Methods:* MEDLINE, EMBASE, PsycINFO and the Cochrane Central Register of Controlled Trials were searched until January 2016. The effectiveness of exercise was assessed within two groups: a) patients selected for study with severe depression or anxiety; and b) studies that did not exclusively targeted patients with increased levels of depression or anxiety. Secondary outcomes were mortality, cardiac events, re-hospitalizations and cardiovascular risk factors.

*Results:* We included fourteen studies. Clinical and methodological heterogeneity precluded meta-analysis. Three studies specifically included patients with high levels of depression or anxiety and eleven studies selected patients with unclear levels of depression or anxiety. Some RCTs showed that exercise was effective in lowering severe depressive symptoms (short and long term follow-up), but for the group with unclear depressive symptoms the results were non-conclusive. In the group with elevated anxiety symptoms, exercise had a positive effect on the short term follow-up. In the group with unclear anxiety symptoms the results were inconsistent (short and long term follow-up). No differences were found regarding the secondary outcomes.

*Conclusions:* There is a general paucity of data on the effect of exercise, precluding firm conclusions about the effectiveness of exercise for depressive and anxiety symptoms in IHD patients.

## 1. Introduction

Despite advances in therapy over the past decades, cardiovascular disease remains the leading cause of death worldwide [1]. Especially the incidence of ischemic heart disease (IHD), sometimes referred to as Coronary Heart Disease (CHD), is high, causing 15.9% of all deaths globally [2]. The pathophysiology and etiology of IHD are caused by atherosclerosis [3]. Important risk factors of IHD are high blood pressure, diabetes, dyslipidemia, and smoking [4].

Studies showed that up to 40% of patients with CHD suffer from depressive symptoms [5], and severe depressive symptoms are present in 15% of CHD patients [6]. The prevalence of anxiety symptoms is estimated between 20% and 60% [7]. Recent research suggested that 11% to 14% of CHD patients had a General Anxiety Disorder (GAD) [6].

*Abbreviations:* ACS, Acute Coronary Syndrome; CABG, Coronary Artery Bypass Graft; CI, 95% Confidence Interval; CHD, Coronary Heart Disease; BDI, Beck Depression Inventory; HAM-D, HAMilton Depression; IHD, Ischemic Heart Disease; IMT, Inspiratory Muscle Training; MD, Mean Difference; MI, Myocardial Infarction; RCT, Randomized Controlled Trial; RR, Risk Ratio; SE, Standard Error; SD, Standard Deviation; SMD, Standardized Mean Differences; SR, Systematic Review; SSRI, Selective Serotonin Re-uptake Inhibitors; STAI-S, State Trait Anxiety Inventory-State; STAI-T, State Trait Anxiety Inventory-Trait

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Also, depression and anxiety are risk factors for major adverse cardiac events [8] as well as all cause and cardiac mortality [9–12].

There are putative biological and psychological mechanisms that are linked to the etiology of depression and anxiety in IHD patients. Among these are the pro inflammatory cytokines hypothesis and the presence of psychological factors such as stress, life events and locus of control [13]. Depression, and to a lesser extent, anxiety, have been shown to be associated with hazardous clinical outcomes in patients with IHD such as greater rates of hospitalization and higher mortality rates [14,15]. Furthermore, it also appears to have negative effects on social and domestic activities [16].

Because of these hazardous effects, the treatment of depression and anxiety symptoms is recommended in clinical guidelines on cardiovascular disease [17]. The suggested interventions focus on empirically based psychotherapies and psychotropic medications [18]. It is shown that these interventions have only a minor effect on reducing depression rates, but not on hospitalization, re-events and cardiac mortality [19]. In case of anxiety symptoms, the effect of psychotherapies and psychotropic medications still remains unclear. This demonstrates the need for alternative interventions, which not solely reduce the depression and anxiety rates, but also improve cardiac outcomes.

Exercise may represent a promising, affordable and easily accessible treatment option for IHD patients with depression and anxiety symptoms. Exercise therapy is already often used as a treatment for depression [20] and anxiety [21] disorders and has shown to be effective in reducing symptoms of both disorders. There are several reasons why exercise may improve mood. First, it may act as a contributor to self-efficacy and self-esteem because of the mastery of new skills [22]. Second, it may have physiological benefits such as changes in endorphin and monoamine levels as well as a reduction in the stress hormone cortisol [23]. In addition to the effect of exercise on mood, exercise has shown to have direct benefits on the heart and coronary vasculature [24], resulting in a decrease in mortality and re-hospitalization rates [25].

There is evidence to support the introduction of exercise as a valuable treatment option for reducing depression and anxiety symptoms and cardiovascular risk, but an overview of the evidence specifically for IHD is lacking. The existing reviews include Heart Failure (HF) patients [26,27], a more severe heart condition than IHD because over time IHD can weaken the heart muscle and lead to HF [17]. To establish the effectiveness of exercise therapy for treating depression and anxiety symptoms in IHD patients an in-depth appraisal of the evidence is needed. Therefore, we systematically reviewed the existing literature on the effectiveness of exercise therapy to reduce depression and anxiety symptoms and improve cardiac outcomes specifically in patients with IHD.

## 2. Methods

### 2.1. Protocol and registration

The protocol was registered with number: CRD 42016035263. (http://www.crd.york.ac.uk/PROSPERO). We used the Preferred Reporting Items for Systematic reviews and Meta-Analysis recommendations for reporting the study [28].

### 2.2. Eligibility criteria

#### 2.2.1. Population

The population of interest are persons of > 18 years with IHD. IHD was defined as: [1] stable angina; [2] unstable angina; [3] myocardial infarction (MI) and [4] acute coronary syndrome (ACS). We included studies targeting patients with symptoms of anxiety and/or depression, as well as studies which did not explicitly select patients with increased levels of depressive or anxiety symptoms.

#### 2.2.2. Intervention

We included studies that investigated the effect of single exercise programs as well as studies that encompassed exercise as part of multiple-component interventions. Exercise could be any combination of aerobic, strength or balance training, offered over any length of time, in any frequency or modality. Yoga and tai-chi studies were included when they were movement based; if those interventions mainly existed of breathing exercises or gently postures, the study was excluded. Home-based exercises were excluded to assure that the patients would adhere to the intended exercise practices.

#### 2.2.3. Comparator

Studies were included if the exercise intervention was compared to standard medical treatment or any other intervention, e.g. education, antidepressant medications or stress management.

#### 2.2.4. Outcomes

The primary outcomes were [1] depression and [2] anxiety symptoms, identified by validated self-report instruments, such as the Hospital Anxiety and Depression Scale (HADS) and the Beck Depression Inventory (BDI) [29,30], standardized interviews, or judgment by qualified professionals. Secondary outcomes were: [1] mortality, defined as the number of deaths; [2] cardiac events, defined as non-fatal myocardial infarction; and [3] re-hospitalizations, defined as number of hospital readmissions.

### 2.3. Search

The databases MEDLINE, EMBASE, PsycINFO and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from database inception to January 2016. We used no limitation on language or publication date. We included only randomized controlled trials (RCTs) published in peer-reviewed journals. Reference lists of included articles were screened to find additional studies. Supplemental Files I shows the search strategy.

### 2.4. Study selection

Two reviewers (SV, AR) independently screened all titles and abstracts for potential eligible publications. Articles that passed the initial screening underwent full text review by both reviewers. Disagreement about study eligibility was resolved by discussion with the last author (WSoP).

### 2.5. Data collection process

Two reviewers (SV, AE) independently extracted data from each study using a predefined data extraction sheet. We collected data on trial characteristics (e.g. type of exercise, frequency, duration), outcome variables (e.g. anxiety and depression rates), results (mean, SD, follow-up). Discrepancies were resolved by discussion with the third reviewer (JM).

### 2.6. Risk of bias in individual studies

Based on the Cochrane Collaboration risk of bias tool, we identified the following domains as relevant for assessing the RCTs: sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting and other sources of bias [31]. Blinding was assessed at outcome level. Two reviewers (SV, AE) independently classified each domain as having low, high or unclear risk of bias. Disagreement about the risk of bias was resolved by discussion with the third reviewer (JM).