The effect of exercise therapy on depressive and anxious symptoms in patients with ischemic heart disease

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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).

2.7. Analysis and syntheses

We distinguish the outcomes after short-term (< 12 weeks) follow up from the long-term (> 12 weeks) follow up, since both the multidisciplinary guideline for the treatment of depression and anxiety suggest that after three months of existing depressive or anxiety symptoms, the symptoms are considered more severe and therefore more intensive treatment is advised [32,33].

Data synthesis and analysis were conducted using Review Manager (V5.3.5, The Nordic Cochrane Centre Copenhagen; Denmark). We calculated the mean difference (MD) and 95% Confidence Interval (CI) for continuous outcomes. For dichotomous outcomes we calculated risk ratios (RR). When a standard error (SE) was published, we calculated the standard deviation (SD).

2.8. Heterogeneity

Clinical heterogeneity was explored by comparing the populations, interventions, comparator treatments, and outcome parameters. If the studies were clinically homogeneous, we explored statistical heterogeneity by means of eyeballing and the I^2 statistic [31]. We planned to use a fixed effects model if the I^2 was between 0% and 30%. A random effects model was used if the I^2 was between 30% and 75%. Publication bias was planned via funnel plot asymmetry. In case of sufficient studies, sensitivity analyses were considered to test whether the overall results were affected by the quality, the study population or the exercise intervention of the studies.

3. Results

3.1. Study selection

In total 4345 articles were identified. After titles and abstract screening, 31 articles were retrieved for detailed evaluation. Finally, we included 14 studies in this systematic review (SR) [34–47]. See Fig. 1 Flow diagram.

3.2. Study characteristics

Table 1 summarizes the study characteristics of the included studies. Eleven studies [34–38,40,41,43–45,47] included individuals with IHD with unclear depression or anxiety symptoms at time of inclusion. Four of these eleven studies had no depression or anxiety measurement at baseline. In the other seven studies, mean baseline measurement showed that anxiety and depression levels were not elevated. In the remaining three trials patients were selected because of high depressive or anxiety symptoms. These symptoms were measured before the start of the intervention as well as during the follow-up [39,42,46].

The exercise interventions in the studies varied in exercise activities, intensity, frequency and duration. Four trials had three or more intervention arms [38,39,46,47]. Exercise was mainly added as part of a multicomponent intervention in eight out of 14 trials [35,36,40–45]. These multicomponent interventions included also health education and behavior counseling. The comparison interventions varied widely, namely standard medical care delivered by the primary care specialist [35,37,38,42,44,46], stress management [38], relaxation therapy [34], psycho education [36,45], antidepressant medication [39], physiotherapy [40,43], home visits [41] and group counseling [46].

Eight studies measured both depression and anxiety [36,38,42–47], five studies measured depression [34,37,39–41] and one study assessed anxiety only [35]. The follow-up period varied from one week before Coronary Artery Bypass Graft (CABG) [43] until 52 weeks after the IHD diagnosis [37,42].

3.3. Risk of bias

Fig. 2 summarizes the risk of bias. There was a high risk of bias in 13 out of 14 trials [34–36,38–47]. Eleven studies did not report how the sequence generation to the treatment arms was generated, neither if the allocation was concealed [34,36,37,41–47]. Blinding of the primary outcome was not possible due to the use of self-report instruments in all studies. In three studies the outcome data were reported completely [35,38,44]. In three other studies attrition bias occurred [37,43,47] and in eight studies this item remains unclear [34,41,42,45,46]. Selective outcome reporting was present in nine trials, did not fully report depression or anxiety scores [34,37,39–42,46,47]. One study report baseline imbalances [37]. In eight studies other biases could not be repudiated, because there was incomplete information on funding [34,39,42,44,47], baseline comparability was not stated [37,40,41,43,46,47] or the sample size was not reached [36].

3.4. Heterogeneity

We considered a meta-analysis inappropriate for the following reasons; the included trials had small sample sizes making between trial heterogeneity with regard to the treatment effect very likely [48]. Also, the included trials varied markedly in terms of interventions, comparator treatments and outcome parameters. In this situation a formal synthesis of the available evidence is highly desirable [49].

3.5. Results of the studies

The primary and secondary results are shown in Table 2 and Table 3.

4. Depression

Depression was measured in thirteen studies [34,36–47]. Respectively three studies included patients with high depression symptoms at start of the study [39,42,46] and ten studies selected patients with unclear levels of depression at time of inclusion [34,36–38,40,41,43–45,47].

4.1. Patients with elevated depressive symptoms at time of inclusion

4.1.1. Short term < 12 weeks follow-up

Two RCTs included participants with elevated depression symptoms at baseline [42,46]. Stern et al. [46] found a significant decrease in depression scores in favour of exercise therapy (i.e. three one-hour sessions per week) compared to routine medical care given by a physician ($p < 0.02$). However, based on this study, it remains unclear if exercise therapy is also more effective than group counseling [46]. The second RCT did not find a significant effect comparing exercise with community care [33].

4.1.2. Long term > 12 weeks follow-up

Three RCTs included participants with high depressive symptoms [39,42,46]. Two RCTs had more than one intervention arm [39,46]. Blumenthal et al. [39] found a significant result in favour of the exercise intervention, when the results of antidepressant medication (Selective Sertonin Reuptake Inhibitor, SSRI) and the exercise group were combined and compared to placebo ($p < 0.034$). Exercise and SSRI were considered equally effective in reducing depressive symptoms ($p > 0.61$). It remains unclear if treadmill and cycling compared to community care reduced depressive symptoms after 16, 32 and 52 weeks follow-up [42]. It remains also unclear if exercise therapy is more effective than group counseling or routine medical care given by a physician after 24 or 52 weeks [46].

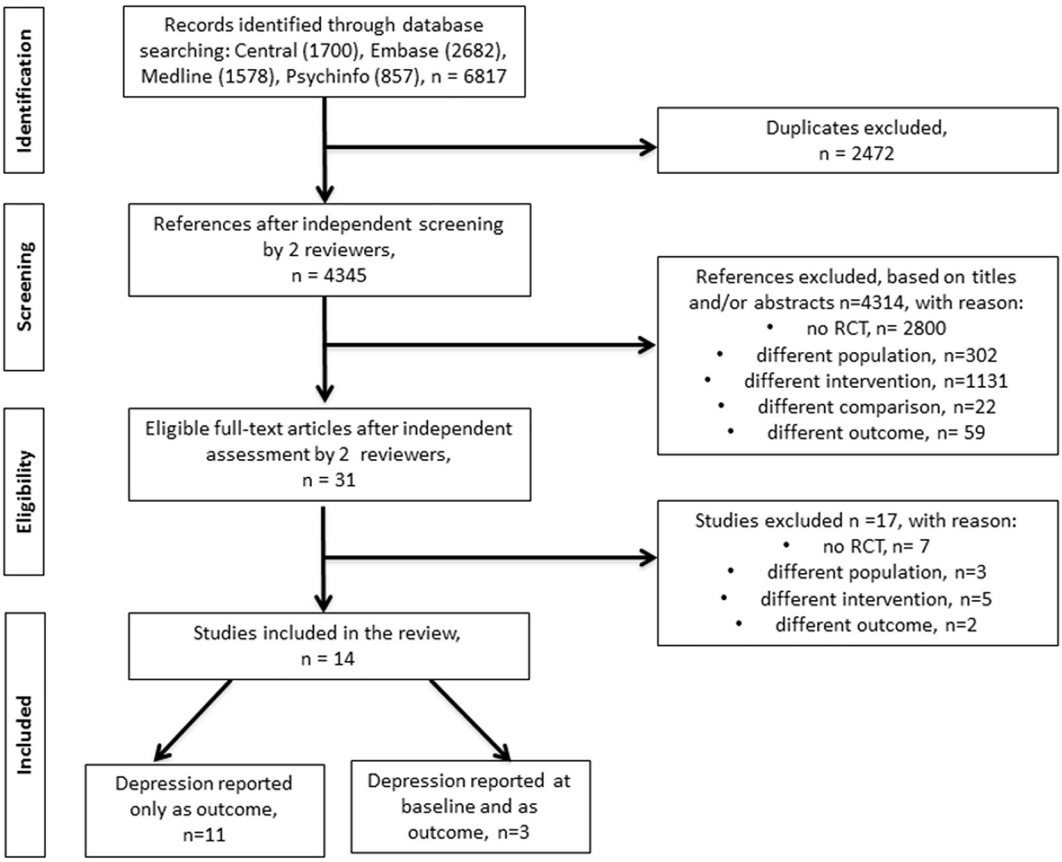

Fig. 1. Flow diagram.

4.2. Patients with unclear depressive symptoms at time of inclusion

4.2.1. Short term < 12 weeks follow-up

In five RCTs depressive symptoms were not explicitly described as inclusion criteria [40,41,43,45,47]. Three RCTs reported a significant effect of exercise on depression compared to varied types of comparators [41,43,45]. Newton et al. reported a significant decrease in depression scores in favour of running compared to visitations of a liaison nurse in combination with education ($p < 0.02$) [41]. Savci et al. found a significant reduction in depressive symptoms in favour of Inspiratory Muscle Training (MD -2.02; 95%CI -3.80to − 0.24) compared with postoperative mobilization [43]. It was also shown that fitness exercise, when compared to a pamphlet, significantly decreased depression rates after 4 weeks (MD -2.02; 95%CI -3.80 to − 0.24) and 8 weeks (MD -4.00; 95%CI -5.38 to − 2.62) [45]. A non-significant effect was found when combinations of exercises were compared with physiotherapy and individual cardiac care ($p > 0.05$) [40]. It remains unclear if gym training was more effective than a non-training intervention compared to a control intervention (not further specified) [47] or if aerobic training was compared to symptom monitoring [36].

4.2.2. Long term > 12 weeks follow-up

Six RCTs investigated the effect of exercise on depression symptoms after > 12 weeks follow-up [34,37,38,40,44,47]. Blumenthal et al. [38] found a significant effect of jogging and cycling in favour of regular medical regime after 16 weeks of follow-up.

(MD − 1.90; 95%CI − 3.57 to − 0.23). Taylor et al. [47] showed a significant reduction in depressive symptoms on the BDI and Hamilton Depression (HAM-D) after 26 weeks of gym training compared to a no training intervention ($p < 0.01$). No significant results were found when exercise was compared to relaxation and breathing therapy [34], stress management [38], physiotherapy and individually cardiac care [40], therapy by an individual physician [44] or a non-specified control intervention ($p > 0.05$) [47].

5. Anxiety

Overall anxiety was measured in nine studies [35,36,38,42–47]. Respectively two studies included patients with high anxiety symptoms at start of the study [42,46] and seven studies that selected patients with unclear levels of depression that only measured anxiety as outcome [35,36,38,43–45,47].

5.1. A. Patients with elevated anxiety symptoms at time of inclusion

5.1.1. Short term < 12 weeks follow-up

Two RCTs included participants with symptoms of anxiety at baseline [42,46]. Exercise compared to community care [42] or group counseling [46] significantly reduced symptoms of anxiety ($p < 0.05$ and $p < 0.007$).

5.1.2. Long term > 12 weeks follow-up

Two RCTs [42,46] included participants with elevated symptoms of anxiety at baseline. Both RCTs had more than one follow-up measurement. It remains unclear of treadmill and cycling or rowing [46], treadmill and cycling are effective in reducing anxiety symptoms [42].

5.2. B. Patients with unclear anxiety symptoms at time of inclusion

5.2.1. Short term < 12 weeks follow-up

In five RCTs, anxiety scores at time of inclusion were unclear [35,36,43,45,47]. Three RCTs [43,45,47] concluded that exercise, compared to different types of controls, had a significant effect on reducing symptoms of anxiety. Savci et al. [43] reported that Inspiratory

Table 1
Study characteristics.

Study	Population			Intervention				Comparison	Outcomes			
Study, year, country	No. of patients, (males %)	Years of age	Inclusion	Mode	Intensity	Frequency Length Duration	Multicomponent intervention		Follow-up	Depression assessment	Anxiety assessment	Secondary outcomes
Ades, 2005, USA [34]	51 (0%)	Mean age all woman 72 (SD 5)	Older women with CHD	Weight training	50–80% of 1 − / RM	3 days/week 24 weeks NR	No	Relaxation and breathing therapy 3 times per week	24 weeks	GDS		
Arthur, 2000, Canada [35]	249 (85%)	Mean age: intervention group 61.8 (SD 8.4); control group 63.8 (SD 7.8)	Awaiting CABG	Exercise training	NR	2 days/week 8 weeks NR	Yes: telephone calls, education and reinforcement.	Followed by primary care specialists	1 week for surgery, 6 weeks and 6 months after surgery		STAI-S, STAI-T	Re-events
Asbury, 2012, England [36]	42 (83%)	Mean age all adults 65.1 (SD 7.3)	Angina	Aerobic training	60–75% HRR	NR 8 weeks 80 min	Yes: weekly health promotion seminars, home exercise	NR except 'symptom monitoring'	8 weeks	HADS-D	HADS-A, HAQ	Risk factor
Bettencourt, 2005, Portugal [37]	126 (84%)	Mean age: intervention group 56 (SD NR); control group 58 (SD NR)	Acute Coronary Syndrome	Treadmill, cycling	MHR	3 days/week 12 weeks; followed by 1 per 4 weeks for rest of the year 60 min	No	3.5 consultations/ year	52 weeks	BDI		
Blumenthal, 2005, USA [38]	134 (69%)	Mean age; stress management training group 63 (SD 11.5); usual care group 63 (SD 9.0); exercise group 62 (SD 10.5).	IHD	Jogging, cycling	50–85% HRR	3 days/week 16 weeks 35 min	Yes; exercise plus usual care	[1] Stress management training; 16 weeks, 1.5 h per week plus usual care [2] UC: Regular medical regime.	16 weeks	BDI	STAI-S	
Blumenthal, 2012, USA [39]	101 (68%)	Mean age all adults: 63.9 (SD NR)	CHD and depression score on the BDI > 7 CABG	Walking, jogging	70–85% MHR	3 days/week 16 weeks 30 min	No	[1] SSRI; 50–200 mg per day [2] Placebo	16 weeks	HAM-D		
Engblom, 1992, Finland [40]	205 (NR)	Mean age: intervention group 54 (SD 6); control group 54 (SD 6).	CABG	Swimming, gymnastics ballgames, cycling	NR	NR Total of 24 h NR	Yes: Relaxation training, group discussion, dietary advice plus usual care	Usual care: Physiotherapy during hospital stay and verbal and written instructions on cardiac risk factors	8 and 32 weeks	BDI		Mortality Hospitalization
Newton, 1991, Schotland [41]	40 (73%)	NR	MI	Running	60–80% MHR	2 days/week 10 weeks 60 min	Yes: relaxation training, informal talk on risk factors	Visit of the liaison nurse, education on IHD.	10 weeks	BDI POMS		Mortality
Oldridge, 1991, Canada [42]	201 (88%)	Mean age: intervention group 52.9 (SD 9.5); control group 52.7 (SD 9.5)	AMI and BDI-SF > 5 and/or STAI-S > 43 or STAI-*T* > 42	Treadmill, cycling	65% MHR	2 days/week 8 weeks 50 min	Yes: behavioral counseling, and relaxation	NR except 'community care'	8, 16, 32 and 52 weeks	Unclear	Unclear	Mortality
Savci, 2011, Turkey [43]	43 (88%)	Mean age: intervention group 62.82 (SD 8.69); control group 57.48 (SD 11.48)	Awaiting CABG	IMT	15–45% MIP	2 times/day 5 days pre- and postoperative 30 min plus usual care	No	Postoperative mobilization therapy for 5 days	5 days pre and 5 days postoperative	HADS-D	HADS-A	
Seki, 2003, Japan [44]	38 (100%)	Mean age all men 70 (SD NR)	CAD	Walking, bicycling, jogging	NR	1 day/week 24 weeks 60 min	Yes: dietary and education	Followed by individual physician	24 weeks	SDS	STAI-S STAI-T	
Sharif, 2012, Iran [45]	80 (70%)	Mean age: intervention group 58.4 (SD NR); control group 59.2 (SD NR)	After CABG	Aerobic exercise	NR	2 days/week 4 weeks 45 min	Yes: education on drugs, diet, weight control, stress, smoking	Pamphlet about diet, activity and medication	4 and 8 weeks	BDI	STAI-S STAI-T	

(*continued on next page*)

Table 1 (*continued*)

Study	Population			Intervention				Comparison	Outcomes			
Study, year, country	No. of patients, (males %)	Years of age	Inclusion	Mode	Intensity	Frequency Length Duration	Multicomponent intervention		Follow-up	Depression assessment	Anxiety assessment	Secondary outcomes
Stern, 1983, USA [46]	106 (86%)	Mean age all adults: 54 (SD NR)	MI and TMAS > 19 and/or SDS > 40	Rowing, treadmill, cycling	85% MHR	3 days/week 12 weeks NR	No	1) Weekly group counseling 2) Follow-up by physician	12, 24, 52 weeks	SDS NIMH-SMS	TMAS	Mortality
Taylor, 1986, England [47]	210 (100%)	Mean age all adults: 52 (SD 9)	MI	NR except 'gym training'.	NR	NR 26 weeks NR	No	1) No training 2) Control; content NR	3 and 26 weeks	BHS HAM-D	STAI-S STAI-T	Re-events

BDI: Beck Depression Inventory; BDI-SF: Beck Depression Short Form; BHS: Beck Hopelessness Scale; CAD: Coronary Artery Disease; CR: Cardiac Rehabilitation; GDS: Geriatric Depression Scale; HADS: Hospital Anxiety and Depression Scale; HAM-D: Hamilton Depression Rating Scale; HAQ: Health Anxiety Questionnaire; HRR: Heart Rate Reserve; IHD: Ischemic Heart Disease; IMT: Inspiratory Muscle Training; LVEF: Left Ventricular Ejection Fraction; MHR: Maximum Heart Rate; MI: Myocardial Infarction; MIP: Maximal Inspiratory Pressure; NIMH-SMS: National Institute of Mental Health Self report Mood Scales; NR: Not Reported; POMS: Profile of Mood States; RM: Repetition Maximum; SDS: Zung Self Rating Depression Scale; SSRI: Selective Sertonin Reuptake Inhibitor; STAI: Spielberger State Trait Anxiety; TMAS: Taylor Manifest Anxiety Scale.

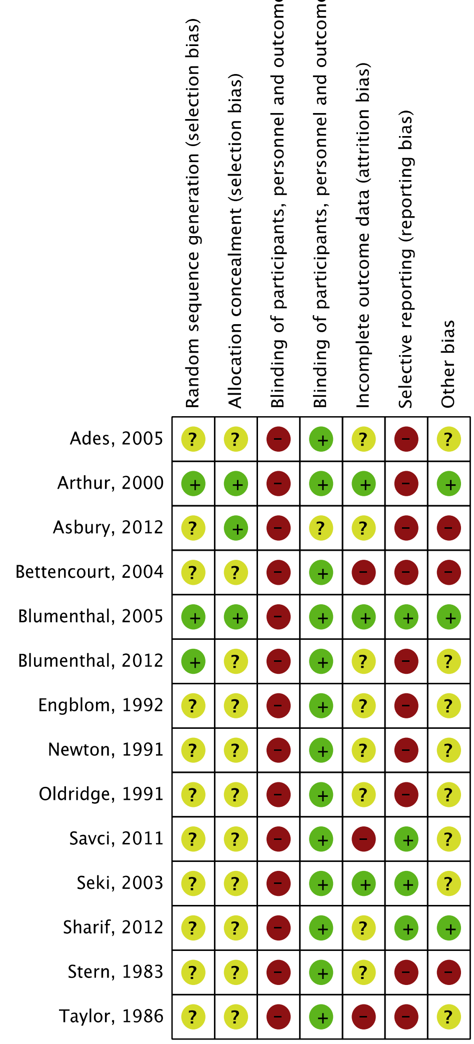

Fig. 2. Risk of bias.

Muscle Training (IMT) compared to postoperative mobilization was effective in reducing anxiety symptoms (MD − 4.19; 95%CI − 5.96 to − 2.42). Sharif [45] found a MD of − 4.00 (95%CI − 6.71 to − 1.29) in favour of fitness when fitness was compared to a pamphlet at 8 weeks follow-up [45]. Gym training was also effective when compared to no training intervention ($p < 0.05$) [47]. However, two other studies found no significant difference in anxiety scores when exercise was compared to standard care delivered by a primary care specialist ($p > 0.05$) [35], symptom monitoring (MD 1.07; 95%CI − 1.39 to 3.53) [36] or a pamphlet at 4 weeks follow-up (MD 3.00; 95%CI − 6.10 to 0.10) [45].

5.2.2. *Long term > 12 weeks follow-up*

Three RCTs provided data on the long-term effect of exercise [38,44,47]. Anxiety levels for these RCTs were unclear at time of

Table 2
Primary outcomes.

Study			Intervention				Comparison				Results	
Study, year	Outcome assessment	Follow-up	Intervention	Mean	SD	N	Comparison	Mean	SD	N	Mean Difference, 95% CI[a]	P-value
Patients with elevated depressive symptoms at time of inclusion												
Short term < 12 weeks follow-up												
Oldridge, 1991 [42]	Unclear	8 weeks	Treadmill, cycling	3.4	NR	78	Community care	3.6	NR	81		Exercise vs community care p > 0.05
Stern, 1983 [46]	SDS	12 weeks	Rowing, treadmill, cycling	33.5	NR	40	1) Group counseling	31.48	NR	31		ND
							2) Follow-up by physician	38.33	NR	27		Exercise vs control p < 0.02
Long term > 12 weeks follow-up												
Blumenthal, 2012 [39]	HAM-D	16 weeks	Walking, jogging	− 3.33 [b]	NR	37	1) SSRI	− 1.74 2	NR	40		Exercise vs SSRI equally effective p < 0.61
							2) Placebo	NR	NR	24		Exercise and SSRI vs placebo p < 0.034
Oldridge, 1991 [42]	Unclear	16 weeks	Treadmill, cycling	2.4	NR	78	Community care	3.1	NR	78		ND
		32 weeks	Treadmill, cycling	2.5	NR	78	Community care	2.8	NR	78		ND
		1 year	Treadmill, cycling	2.6	NR	78	Community care	2.7	NR	78		ND
Stern, 1983 [46]	SDS	24 weeks	Rowing, treadmill, cycling	33.26	NR	38	1) Group counseling	31.94	NR	31		ND
							2) Follow-up by physician	37.04	NR	25		ND
		1 year		34.49	NR	37	1) Group counseling	31.77	NR	31		ND
							2) Follow-up by physician	37.48	NR	25		
Patients with unclear depressive symptoms at time of inclusion												
Short term < 12 weeks follow-up												
Asbury, 2012 [36]	HADS-D	8 weeks	Aerobic training	NR	NR	19	Symptom monitoring	NR	NR	20		ND
Engblom, 1992 [40]	BDI	8 weeks	Swimming, gymnastics, ballgames, cycling	11.6	8.1	101	Physiotherapy, individually cardiac care	10.8	6.6	84	0.80 (− 1.22 to 2.92)	Exercise vs physiotherapy p > 0.05
Newton, 1991 [41]	BDI	10 weeks	Running	NR	NR	12	Visit of the liaison nurse, education on IHD.	NR	NR	10		Exercise vs visit of the liaison nurse p < 0.02
Savci, 2011 [43]	HADS-D	5 days	IMT	6.50	3.05	22	Postoperative mobilization	8.52	2.91	21	− 2.02 (− 3.80 to − 0.24)	Exercise vs post-operative mobilization p < 0.05
Sharif, 2012 [45]	BDI	4 weeks	Fitness	15	4.07	40	Pamphlet	17	3.6	40	− 2.00 (− 3.68 to − 0.32)	Exercise vs pamphlet p < 0.05
	BDI	8 weeks	Fitness	10	3.02	40	Pamphlet	14	3.28	40	− 4.00 (− 5.38 to − 2.62)	Exercise vs pamphlet p < 0.05
Taylor, 1986 [47]	BDI	3 weeks	Gym training	2.9	NR	45	1) No training	1.8	NR	24		ND
							2) Control	NR	NR	26		
	HAM-D	3 weeks	Gym training	5.1	NR	45	1) No training	3.5	NR	24		ND
							2) Control	NR	NR	26		
Long term > 12 weeks follow-up												
Ades, 2005 [34]	GDS	24 weeks	Weight training	NR	NR	21	Relaxation and breathing therapy 3 times per week	NR	NR	21		Exercise vs relaxation therapy p > 0.05
Bettencourt, 2005 [37]	BDI	52 weeks	Treadmill, cycling	8	NR	31	3.5 cardiac consultations per year	11	NR	95		ND
Blumenthal, 2005 [38]	BDI	16 weeks	Jogging, cycling	8.2[c]	0.6[d]	48	1) Stress management training	8.2[c]	0.6[d]	42	0.00 (− 1.67 to 1.67)	Exercise vs stress management p < 0.94
							2) Regular medical regime	10.1[c]	0.6[d]	38	− 1.90 (− 3.57 to − 0.23)	Exercise and stress management vs regular medical regime p < 0.02
Engblom, 1992 [40]	BDI	32 weeks	Swimming, gymnastics, ballgames, cycling	10	7.3	98	Physiotherapy, individually cardiac care	11.1	6.9	84	− 1.10 (− 3.17 to 0.97)	Exercise vs Physiotherapy p > 0.05

(*continued on next page*)

Table 2 (*continued*)

Study			Intervention				Comparison				Results	
Study, year	Outcome assessment	Follow-up	Intervention	Mean	SD	N	Comparison	Mean	SD	N	Mean Difference, 95% CI[a]	P-value
Seki, 2003 [44]	SDS	24 weeks	Aerobic and dynamic exercise	32.2	7.3	20	Followed by individual physician	33.2	10.3	18	− 1.0 (− 6.73 to 4.73)	Exercise vs followed by physician $p > 0.05$
Taylor, 1986 [47]	BDI	26 weeks	Gym training	2.4	NR	45	1) No training	2.0	NR	24		Exercise vs no training $p < 0.01$
							2) Control	3.3	NR	26		Exercise vs control $p > 0.05$
	HAM-D	26 weeks	Gym training	2.3	NR	45	1) No training	3.8	NR	24		Exercise vs no training $p < 0.01$
							2) Control	37.48	NR	25		ND
Patients with elevated anxiety symptoms at time of inclusion												
Short term < 12 weeks follow-up												
Oldridge, 1991 [42]	Unclear	8 weeks	Treadmill, cycling	42	NR	86	Community care	44	NR	84		Exercise vs community care $p < 0.05$
Stern, 1983 [46]	TMAS	12 weeks	Rowing, treadmill, cycling	13.48	NR	40	1) Group counseling	13.13	NR	31		Exercise vs control $p < 0.008$
							2) Follow-up by physician	15.92	NR	27		ND
Long term > 12 weeks follow-up												
Oldridge, 1991 [42]	Unclear	16 weeks	Treadmill, cycling	41	NR	86	Community care	43	NR	84		ND
		32 weeks		42	NR	86		42	NR	84		ND
		1 year		42	NR	86		41	NR	84		ND
Stern, 1983 [46]	TMAS	24 weeks	Rowing, treadmill, cycling	13.48	NR	38	1) Group counseling	11.13	NR	31		ND
							2) Follow-up by physician	14.64	NR	25		ND
		1 year		13.82	NR	38	1) Group counseling	12.19	NR	31		ND
							2) Follow-up by physician	15.12	NR	27		
Patients with unclear anxiety symptoms at time of inclusion												
Short term < 12 weeks follow-up												
Arthur, 2000 [35]	STAI-S	1 week before surgery	Exercise training	37	NR	123	Followed by primary care specialists	38	NR	123		Exercise vs followed by specialist $p > 0.05$
	STAI-T	1 week before surgery	Exercise training	NR	NR	NR	Followed by primary care specialists	NR	NR	NR		ND
Arthur, 2000 [35]	STAI-S	6 weeks	Exercise training	NR	NR	NR	Followed by primary care specialists	NR	NR	NR		ND
	STAI-T	6 weeks	Exercise training	NR	NR	NR	Followed by primary care specialists	NR	NR	NR		
Asbury, 2012 [36]	HADS-A	8 weeks	Aerobic training	7.25	4.25	19	Symptom monitoring	6.18	3.52	20	1.07 (− 1.39 to 3.53)	Exercise vs symptom monitoring $p > 0.05$
	HAQ	8 weeks	Aerobic training	NR	NR	NR	Symptom monitoring	NR	NR	NR		ND
Savci, 2011 [43]	HADS-A	5 days	IMT	6.14	2.8	22	Postoperative mobilization	10.33	3.12	21	− 4.19 (− 5.96 to − 2.42)	Exercise vs postoperative mobilization $p < 0.05$
Sharif, 2012 [45]	STAI-S & T	4 weeks	Fitness	31	6.29	40	Pamphlet	34	7.76	40	− 3.00 (− 6.10 to 0.10)	Exercise vs pamphlet $p > 0.05$
	STAI-S & T	8 weeks	Fitness	28	5.11	40	Pamphlet	32	7.08	40	− 4.00 (− 6.71 to − 1.29)	Exercise vs pamphlet $p < 0.05$
Taylor, 1986 [47]	STAI-S	3 weeks	Gym training	33.2	NR	45	1) No training	34.0	NR	24		ND
							2) Control	NR	NR	26		
	STAI-T	3 weeks	Gym training	32.8	NR	45	1) No training	33.4	NR	24		Exercise vs no training $p < 0.01$
							2) Control	NR	NR	26		ND
Long term > 12 weeks follow-up												

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Table 2 (*continued*)

Study		Intervention					Comparison				Results	
Study, year	Outcome assessment	Follow-up	Intervention	Mean	SD	N	Comparison	Mean	SD	N	Mean Difference, 95% CI[a]	P-value
Arthur, 2000 [35]	STAI-S	24 weeks	Exercise training	NR	NR	NR	Followed by primary care specialists	NR	NR	NR		ND
	STAI-T	24 weeks	Exercise training	NR	NR	NR	Followed by primary care specialists	NR	NR	NR		
Blumenthal, 2005 [38]	STAI-S	16 weeks	Jogging, cycling	35.2[c]	0.8[d]	48	1) Stress management training	36.4[c]	0.8[d]	42	− 1.20 (− 3.41 to 1.01)	Exercise vs stress management p > 0.05
							2) Regular medical regime (UC)	37.0[c]	0.8[d]	38	− 1.80 (− 4.00 to 0.40)	Exercise and stress management vs usual care p > 0.05
Seki, 2003 [44]	STAI-S	24 weeks	Aerobic exercise	32.9	7.8	20	Followed by physician	31.0	6.5	18	1.90 (− 2.65 to 6.45)	Exercise vs followed by physician p > 0.05
	STAI-T	24 weeks	Aerobic exercise	34.2	8.2	20	Followed by physician	34.6	11.0	18	− 0.40 (− 6.62 to 5.82)	Exercise vs followed by physician p < 0.05
Taylor, 1986 [47]	STAI-S	26 weeks	Gym training	28.7	NR	45	1) No training 2) Control	32.9 38.8	NR NR	24 26		Exercise vs control p < 0.01
	STAI-T	26 weeks	Gym training	29.9	NR	45	1) No training 2) Control	31.4 36.2	NR NR	24 26		Exercise vs control p < 0.05

NR: Not Reported; ND: No Data.
[a] Mean differences and 95% confidence intervals were given if applicable.
[b] Change score compared with placebo.
[c] Adjusted for age, sex, prior MI, pretreatment LVEF, pretreatment level of the corresponding outcome data.
[d] SD reported as fitted corrected mean.

inclusion. Taylor et al. [47] found a significant effect on the State Trait Anxiety Inventory-State (STAI-S) and State Trait Anxiety Inventory-Trait (STAI-T) when gym training was compared to a control intervention ($p < 0.05$). Seki et al. [44] reported a significant effect on the STAI-T when aerobic exercise was compared to follow-up by a physician (MD − 0.40; 95%CI − 6.62 to 5.82). Contradictory, in the same RCT no significant effect of the aerobic intervention was found when anxiety was established with the STAI-S (MD 1.90; 95%CI − 2.65 to 6.45) [44]. Exercise was also not effective in reducing anxiety when it was compared to stress management or standard care (MD − 1.80[1]; 95%CI − 4.00 to 0.40) [38].

6. Secondary outcomes

Six out of the 14 studies reported on clinical events [35,38,40–42,46] including mortality [35,38,41,42,46], recurrent events [35,46] and hospitalization [40]. Our results did not show a significant increase in the risk on mortality, recurrent cardiovascular events or hospitalizations. But these results must be interpreted with caution, as all studies were underpowered for the secondary outcome measures. See Table 3: secondary outcomes.

6.1. Publication bias

The number of included studies with appropriate data was insufficient to detect publication bias via funnel plot asymmetry.

7. Discussion

We systematically reviewed the existing literature on the effectiveness of exercise therapy to reduce depression and anxiety symptoms specifically in patients with IHD. Fourteen RCTs were included in this systematic review, but only three studies actually targeted patients with depressive or anxiety symptoms. The studies were clinically heterogeneous and reported varied results the majority of studies focused on depressive symptoms instead of anxiety symptoms. Some RCTs showed that exercise might be effective in reducing elevated depressive symptoms at the short and long term outcome. For anxiety, exercise seems valuable at a follow up period < 12 weeks and when there are high anxiety symptoms at the beginning of the exercise intervention. For the long term, this effect remains unclear.

We discuss potential explanations for the variety of results. First, the included RCTs differed in the presence of depression and anxiety symptoms in all patients at start of the exercise intervention, types of exercise interventions, comparators and duration of follow-up, making interpretation complicated. Second, the majority of studies [34-36,41,44,47] reported depressive and anxiety symptoms as secondary outcomes. This may affect our results because studies might be adequately powered for the primary outcome, but not necessarily for the secondary outcome [51]. Third, the non-conclusive results might be the result of the lack of clinical related outcomes blinding in all studies, which could have resulted in an over- or underestimation of the results. Fourth, the presence of floor effects may also limit the findings [52]. The RCTs that did not select patients with high depressive or anxiety symptoms, risk an underestimation of possible effects of the exercise intervention, making it incapable of detecting change across the entire clinically meaningful range of the study sample. Fifth, nine of the 14 RCTs included exercise as part of a multicomponent intervention. Interpretation of the results is therefore difficult, since it is impossible to attribute treatment related changes to exercise. Final, the overall quality of the RCTs included was low.

Our findings are corroborative to the conclusions of the already

[1] Adjusted for age, sex, prior MI, pretreatment LVEF, pretreatment level of the corresponding outcome data.

Table 3
Secondary outcomes.

Study	Intervention					Comparison					Results		
	Intervention	Mortality	Re-events	Hospitalization	N	Comparison	Mortality	Re-events	Hospitalization	N	Mortality Relative Risk, 95% CI	Re-events Relative Risk, 95% CI	Significance
Arthur, 2000 [35]	Exercise training	1	1		123	Relaxation and breathing therapy 3 times per week	0	2		123	3.00 (0.12 to 72.93)	0.50 (0.05 to 5.44)	
Blumenthal, 2005 [38]	Jogging, cycling	1			48	1) Stress Management Training	0			44	2.76 (0.12 to 65.92)		
						2) Regular medical regime	0			42	2.63 (0.11 to 62.95)		
Engblom, 2006 [40]	Swimming, gymnastics, ballgames, cycling	ND		26 patients, 49 hospital admission, 273 days in hospital	102	Physiotherapy, individually cardiac care	5		34 patients, 54 hospital admissions, 364 days in hospital	92			No significant differences, between hospital days and admission
Newton, 1991 [41]	Running	0			20		2			20	0.20 (0.01 to 3.92)		
Oldridge, 1991 [42]	Treadmill, cycling	4			99		3			102	1.37 (0.32 to 5.98)		
Stern, 1983 [46]	Rowing, treadmill, cycling	0	1		42	1) 75 Minutes weekly group counseling	0	3		35	NE	0.28 (0.03 to 2.55)	
						2) Followed by physician	1	1		29	0.20 (0.01 to 3.92)	0.69 (0.04 to 10.60)	

NE: Not Estimable.

available reviews on the effect of exercise in patients with depressive disorders [20], depressive disorder adjusted for publication bias [53], anxiety disorders [21], anxiety disorders and/or stress related disorders [54] and heart failure [27]. All five reviews report small effects of exercise training on depressive or anxiety symptoms. Although the effect of exercise as an independent treatment seems evident in those SRs, the existing literature is marked by small trials with weak methodological quality thus complicating the interpretation of the results presented in these reviews. At present, the existing body of evidence is not of sufficient rigor to recommended exercise as an independent treatment. However, exercise could be a useful, affordable and easy accessible treatment and may be serve as alternative for patients who - for different reasons - do not want traditional treatment [21,54].

The present SR adds to the available reviews for several distinctive reasons. First, this SR reports on the effect of exercise on both depression and anxiety, symptoms that are common in cardiovascular disease patients. Second, we explicitly separated the studies that selected patients with elevated depression and anxiety symptoms at baseline from studies without this selection criterion. Furthermore, we solely focused on exercise interventions that are movement based or were part of a multicomponent intervention and compared these exercise interventions with non-movement based interventions to understand the effect of exercise. Finally, we included a homogeneous group of cardiac participants with an identical underlying etiology, because exercise prevents the development of atherosclerosis and reduces symptoms in patients with established cardiovascular disease [55].

7.1. Implications for practice

Despite the unclear effects of exercise therapy on depression and anxiety, research has shown that cardiac patients benefit from exercise interventions [25]. Exercise programs have also proven to reduce mortality and re-hospitalization in a cardiac population [25].

7.2. Implications for further research

There appears to be a paucity of data from well-designed RCTs, so rigorous research on the effect of exercise on depressive and anxiety symptoms in patients with IHD is needed. Future research should require greater attention to critical methodological details, including adequate sample size, blinding of assessors and appropriate control groups. Future research should also include validated depressive or anxiety outcome measures, as well as measurements that adhere to an exercise regimen as a sole intervention. Since we are able to closely monitor physical activity directly using accelerometers. Furthermore, differences in effects due to type and intensity of exercise intervention should be explored in order to facilitate implementation into daily practice.

7.3. Conclusions

There is insufficient evidence that exercise is a compelling treatment for reducing depression and anxiety symptoms in a population with IHD. The small number of studies available, the heterogeneity between the studies and the risk of bias within the studies hamper firm conclusions.

7.4. Differences between protocol and review

Three changes from the protocol were made: [1] CHD was replaced by IHD. IHD reflects the underlying mechanism, atherosclerosis of the arteries, rather than heart valve diseases or arterial fibrillation; [2] because we only found three studies that selected patients with elevated depression or anxiety symptoms at baseline, we also included studies that selected patients with unclear levels of depression or anxiety at time of inclusion; [3] we did not find any cardiovascular risk factors defined as hypertension, high cholesterol (total/LDL/HLD/triglycerides) and Body Mass Index. Therefore, we deleted these secondary outcome.

Conflicts of interest

None.

Source of funding

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2017.11.018.

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