



SYSTEMATIC REVIEW

Self-management strategies in people with heart failure-related fatigue: a systematic review [version 1; peer review: awaiting peer review]

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Abstract

Introduction: Fatigue is a common symptom of heart failure which can be distressing for patients and negatively impact both their quality of life and prognosis. We report the efficacy of self-management strategies for people with heart failure-related fatigue.

Methods and results: We searched the MEDLINE, Psychinfo, Emcare and Cochrane Central Register of Controlled Trials (CENTRAL) databases from inception to August 2021 for relevant trials. Twenty-two papers were included describing 21 trials (15 RCTs), comprising 515 participants. Definitions of interventions are given and were grouped as either supported self-management or self-management interventions. Supported self-management included education and person-centred care interventions (n=5). Self-management interventions included mind-body therapies (10), and diet and supplements (6). The Cochrane risk of bias did not show significant high risk across the domains, however the number of participants recruited was small. There was heterogeneity in intervention type, delivery and outcome measures preventing meta-analysis.

Evidence for supported self-management interventions involving education and a person-centred approach, and self-management interventions such as CBT, mindfulness, and some supplements for heart failure-related fatigue is positive, but is limited to individual, small trials. Only eight trials provided a definition of fatigue, and 11 types of fatigue outcome measures were used.

Conclusion: The evidence base for the efficacy of supported self-management and self-management interventions for alleviating heart failure-related fatigue is modest in both study number, size, and quality. Further well-designed trials are needed, along with consensus work on fatigue definitions and reporting.

Keywords

heart failure, fatigue, self-management, systematic review

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Introduction

Fatigue is a common symptom affecting people with heart failure (HF) and can have a negative impact on their quality of life¹. For patients, the sensation of fatigue can be difficult to describe. Words like 'exhausted' and 'tired' can be used in place of fatigue. There is no universal definition of fatigue, and it can encompass both physical and psychological symptoms². The pathology of fatigue is related to the widespread activation of stress systems within the body when the heart is under strain³. The New York Heart Association (NYHA) classification system attempts to quantify the degree of limitation from HF symptoms such as breathlessness and fatigue experienced by a patient, but there is no similar scale for fatigue alone currently in use in clinical practice⁴.

A James Lind Alliance priority setting partnership identified the importance of self-management approaches, and the burden of fatigue for people with advanced HF and the challenges for health professionals to support them⁵. HF medications and rehabilitation are effective in improving quality of life for people with all stages of HF⁶. Self-management strategies are increasingly used in healthcare in addition to standard medical therapies⁷. It is important to distinguish between types of self-management. Guided by National Health Service UK definitions, we define supported self-management interventions as the ways that health and care services encourage, support and empower people to manage their ongoing physical and mental health conditions themselves, and self-management interventions as empowerment of people to manage their ongoing physical and mental health conditions themselves⁸. These approaches can be powerful adjuncts to traditional therapies for symptom control⁹. In this systematic review, we aimed to report the efficacy of supported self-management, and self-management interventions for people with HF-related fatigue.

Methods

Our overarching review question was, *what self-management interventions are used to help patients manage their symptoms of HF-related fatigue and which are most effective?* Our Prospero registered protocol is freely available¹⁰. The review is reported according to PRISMA guidance using the PRISMA checklist.

Scope

Population: adults aged 18+ with chronic HF.

Intervention: any supported self-management or self-management approach aimed at helping people with HF to manage fatigue, e.g., physical activity, nutritional or herbal therapies. We excluded formal cardiac rehabilitation as it is comprehensively reviewed elsewhere¹¹. We excluded treatments requiring a prescription by a medical practitioner.

Comparators: Usual care; comparative studies.

Outcomes: Primary: fatigue measured as a single entity or a component of a measure as self-report or with a formal measurement tool by a health professional. Secondary; safety,

adverse events, adherence. We also recorded any given definitions of fatigue and the outcome measure used.

Design: Randomised controlled trials (RCTs); non-randomised controlled trials.

Searches

MEDLINE, Psychinfo, Emcare (via OVID) and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched in July 2020 and updated in August 2021. The search was developed for MEDLINE and adapted for the other databases. [Search strategy available on request from authors] Authors of papers included at the full paper stage were contacted, and forward and backward reference searches of included papers were performed. There were no restrictions on basis of language.

Data extraction

The titles and abstracts of references were independently assessed for inclusion by two reviewers (LD, ALH). Disagreements were resolved through consultation with a third reviewer (RJ, BS). For studies of potential relevance, full papers were assessed in the same way. This process was facilitated by Rayyan¹².

The data extraction table was piloted with 10% of the included studies (LD, ALH) and adjusted as necessary. Data extraction was undertaken by LD, checked by AH, and discrepancies were discussed.

Risk of bias

Quality appraisal of randomised controlled trials and non-randomised controlled trials was conducted using the Cochrane risk of bias tool within Review Manager software (Version 5.4.1)¹³. The trials were appraised by ALH, checked by LD with discussion as needed.

Strategy for data synthesis

A meta-analysis for each intervention type was planned for the primary outcome of fatigue¹⁴. However, the data were not sufficiently homogenous for meta-analyses, varying in intervention, intensity, duration, fatigue outcome measure and timepoints measured. To give a visual presentation of fatigue data from individual trials, forest plots are presented with data from individual trials, grouped per type of self-management but without meta-analysis. The results of individual trials are reported as calculated mean differences in fatigue between intervention and control groups at the trial endpoint.

Results

Twenty-two papers describing 21 trials were included^{15–36}. [Figure 1]. Fifteen were RCTs, three were pilot RCTs, one was a controlled trial, and two were pilot controlled trials. [Table 1] Interventions were grouped either as supported self-management or self-management. Supported self-management interventions included education and person-centred care (n=5)^{15–19}. Self-management interventions included mind-body therapies (n=10)^{20–30}, and diet and supplements (n=6)^{31–36}.

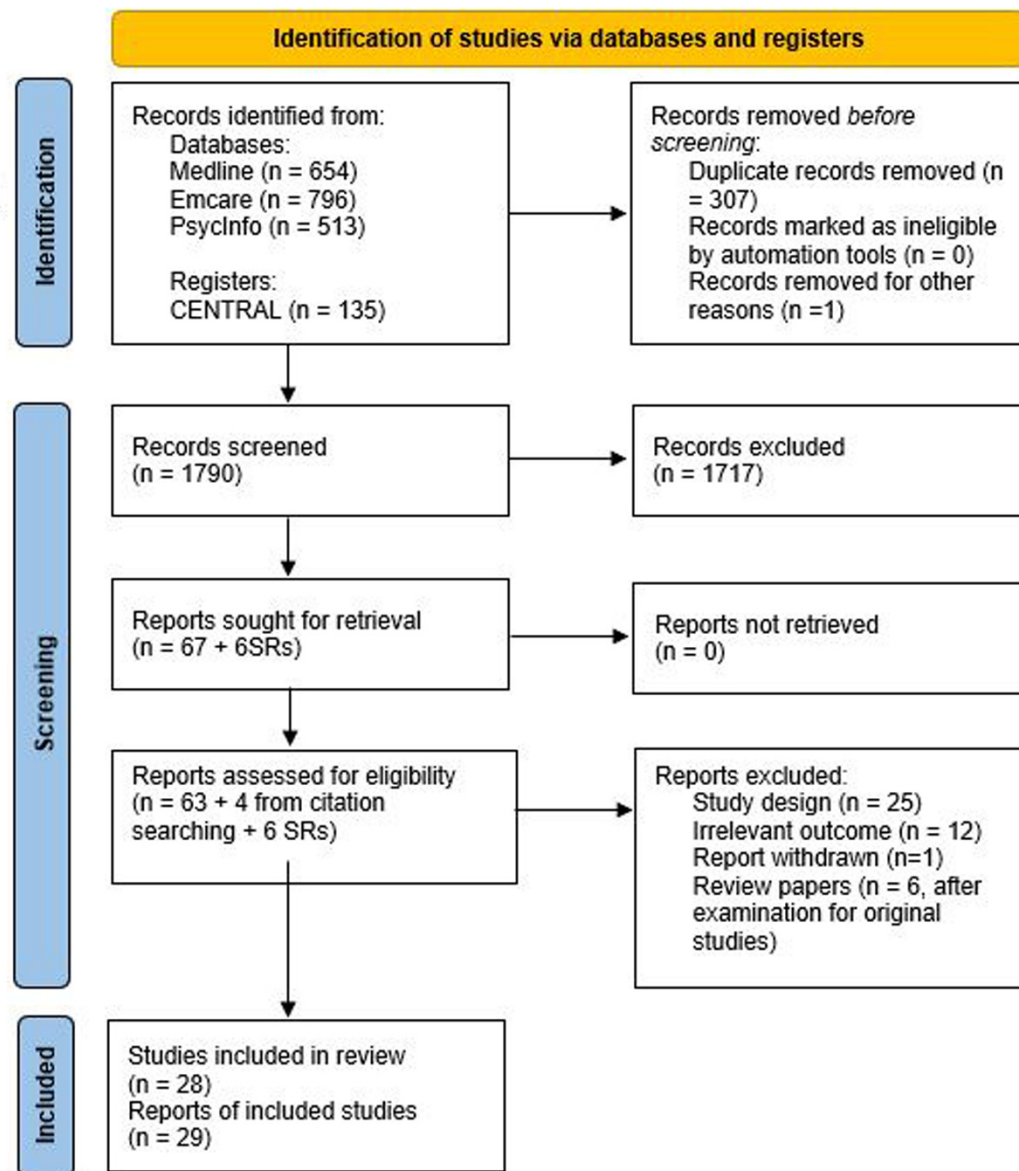


Figure 1. PRISMA flow diagram.

Participants

The mean age was ≤ 60 years in six trials^{16,23,24,27,30,32}, and 61–75 years in a further 12 trials^{17,18,20–22,25,26,28,29,31,33,35,36}. Only one trial recruited participants between 76–81 years¹⁹, and two trials gave age ranges from 30–76 years^{15,34}.

Women were not represented equally, with 14/21 trials having a mean of $<50\%$ women participants^{16,18–23,26,27,30,32–35}, of which 10 of the 14 trials recruited $<40\%$ ^{16,18,19,21,22,27,30–34}, and 5 of the 14 recruited $<25\%$ women^{16,21,22,30,32,33}.

NYHA status at recruitment was reported in most trials, and most participants were reported to be in NYHA classes I–III. Two trials focused on classes I–II^{20,24}, five trials focused on

classes I–III^{18,23,30,31,34}, one trial focused on classes II–III²⁶ four studies focused on class II only^{22,33,35,36}, four studies focused on classes II–III^{17,21,25,28,29}, and two studies focused on classes III–IV^{32,34}. When NYHA status was not reported, other descriptors were mean ejection fraction % (n=1)²⁷, and time since HF diagnosis (n=2)^{15,16}. In the remaining trial the outcome of fatigue was addressed in a sub-analysis, with only patients who had answered at least one dimension of the Multidimensional Fatigue Inventory 20 questionnaire at baseline being included¹⁹.

Country of study

The 21 trials were conducted worldwide although the USA was the most common location (7). Other locations were Iran (3),

[illegible]

Mind-body therapies n=9												
Author Year Setting Study	Aim (sample size calculation)	Participants Randomised Int. vs. Con	Mean age (yrs.) ± SD	% Female	Heart failure status NYHA class (%)	Intervention(s)	Control(s)	Fatigue Outcome measure	Fatigue outcome	Attrition	Adverse events/safety	
Hägglund 2017 Sweden Recruited via hospital outpatients RCT	To evaluate Tai Chi group training among PWHF aged 70 years and older (Sample size calculation based on QoL was 66 participants)	25,27	75.6, 75.5	24, 25	75% Class II & III based on physical scale of MFI-20	Tai Chi 2x 60 minutes per week for 16 weeks, could be performed sitting in a chair.	No Intervention	Multi-dimensional Fatigue Inventory (MFI-20 items)	Fatigue worse than baseline in <i>Int grp</i> at 16- weeks p = 036 6 months p = 042 At 6 month <i>Con vs. Int grp</i> rated more mental fatigue p=0.048	At the end of training period, data were available from n=21 <i>Int grp</i> and n=14 <i>Con grp</i> .	The authors reported that there were no adverse events	
Redwine 2012 USA Recruited via medical centres Pilot CT <i>CBT</i>	To measure whether a Tai chi effectively reduces somatic and/or cognitive symptoms of depression in PWHF and to examine the specific influence of fatigue	16,12	67.0, 72.6	17.8 (not including 4 dropouts in Tai chi grp)	Class II	Usual care plus Yang-style Tai Chi Chuan-Short Form (first third) training 2x week for 60min per session for 12 weeks plus home practice.	Usual care	Multi-dimensional Fatigue Symptom Inventory (MFSI) –Short Form. (30 items)	Decreased fatigue from baseline <i>Int. grp</i> p =0.05, <i>Int grp vs. Con</i> <i>grp.</i> p =0.19	n=4 of <i>Int grp</i> scheduling conflict (1), lack of interest (1), foot injury outside of class (1) & HF exacerbation unrelated to Tai chi (1)	The authors reported that there were no adverse events	
Freedland 2015 USA Recruited via hospital outpatients RCT	To determine the efficacy of an integrative CBT intervention for depression and HF self-care (Total of 240 based on main outcomes depression & self- care)	79,70	56.3, 55.5	50.6, 41.8	Classes I-II 58% III 42%	CBT delivered by experienced therapists plus usual care enhanced with structured HF education program Sessions tapered to bi-weekly and then monthly up to 6 months. Up to four telephone contacts were provided as needed between 6–12 months	Usual care enhanced with structured HF education program	Patient-Reported Outcomes Measure- ment Information System (PROMIS) assesses 7 PROM domains of which one is fatigue with 4 items	Decreased fatigue <i>Int. vs. Con.</i> <i>group</i> p=01 at 6 months	In the CBT group n=9 dropped out, n=8 discontinued due to ill health, n=5 lost to contact. No dropouts in usual care, just reduced assessments	The authors reported that there was no study related serious adverse events.	

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Mind-body therapies n=9	Author Year Setting Study	Aim (sample size calculation)	Participants Randomised Int. vs. Con	Mean age (yrs.) ± SD	% Female	Heart failure status NYHA class (%)	Intervention(s)	Control(s)	Fatigue Outcome measure	Fatigue outcome	Attrition	Adverse events/safety
	<i>Progressive muscle relaxation</i>											
	Selfi 2018 Iran Recruited hospitalised PWHF RCT	To compare the effects of Benson muscle relaxation (BMR) and nature sounds (NS) on fatigue in PWHF (Total of 32 based on fatigue outcome raised to 35 to allow for dropouts)	BMR vs. NS vs. Control 35,35,35	48.5, 51.1, 54.8	34,43, 33	Mean EF 29.57 ±4.9, 29.71±4.5, 31.11±4.9	<i>BMR group</i> Patients given 20min audio file via MP3 & headphones to use in morning & evening for 3 consecutive days. <i>NS grp</i> Patients closed their eyes & listened to nature sounds via MP3 & headphones for 20min with same schedule.	Usual care (US)	Fatigue severity scale (Farsi)	Decrease in fatigue from baseline for all groups. <i>BMR, NS vs. Control group</i> NS	Authors reported no missing data & no patients excluded after the randomization.	None reported
	Yu 2007a &b Hong Kong Recruited via hospital outpatients CT (Partly randomised)	To examine the effects of exercise training (ET) and Progressive muscle relaxation training (PMRT) on psychological outcomes and disease-specific QoL of older PWHF.	RT vs. ET vs. Control 59, 32, 62	74.9±8, 73 ±7.6, 77.4±7.5	44,72,44	II 59,44,68% III 40,56,32%	PMRT taught by a trained research nurse for 12-weeks. 2 PMRT sessions, 1 revision workshop, twice-daily PMRT home practices, and a biweekly telephone follow- up call. ET 12 weekly training sessions of resistance training and aerobic exercise and thrice weekly home exercise.	Research nurse made 8 phone calls on a weekly basis during the 12-week period.	Chronic Heart Failure Questionnaire (CHQ-C) comprises 20 items (scored on 7-point scale) divided into four domains: including fatigue (4 items) (Chinese version)	Fatigue reduced when all 3 groups analysed time x grps P<0.05 over 12 weeks Post-hoc analysis indicated effects of exercise in fatigue reduction (p =0.03) But NS for relaxation.	20 PMRT & 17 Con. grp Home visit refusal (n=4), Defaulted PMRT (n=5), hospital re- admission (n=10), Admission to care home (n=4) Emigration (n=3) Loss of contact (n=3), Death (n=8). Data from Yu 2007b - no numbers on exercise grp	None reported

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Mind-body therapies n=9	Author Year Setting Study	Aim (sample size calculation)	Participants Randomised Int. vs. Con	Mean age (yrs.) ± SD	% Female	Heart failure status NYHA class (%)	Intervention(s)	Control(s)	Fatigue Outcome measure	Fatigue outcome	Attrition	Adverse events/safety
	<i>Biofeedback</i>											
	Swanson 2009 USA Recruited via hospital outpatients RCT	To examine if a 6 week course of cardio-respiratory biofeedback training (BT) with PWHF with known NYHA Class I-III (No power calculation)	15,14	54 vs. 56	20, 21	Classes I-III	BT group received 45 mins training once weekly for 6 weeks & home practice, (Trainer unclear)	Quasi BT grp received false alpha-theta EEG biofeedback training with an identical schedule to BT group.	The Borg Scale (Dyspnoea and fatigue)	Decreased fatigue from baseline for BT group Fatigue worse from baseline Quasi BT grp p=0.05 with time <i>Int. vs. Con.</i> <i>group</i> NS at 6 or 18 weeks	n=4 financial reasons (2); transport issues (1); did not take hypertension medication (1)	None reported.
Dietary & supplements n=6	Author, Year Setting Study	Aim (Sample size calculation)	Participants Randomised Int. vs. Con	Mean age (yrs.) ± SD	% Female	Heart failure status NYHA class (%)	Intervention(s)	Control(s)	Fatigue Outcome measure	Fatigue	Attrition	Adverse events/safety
	<i>Diet</i>											
	Colin Ramirez 2004 Mexico Recruited via hospital outpatients RCT	To evaluate a dietary intervention focused on improvement of clinical & nutrition status, QoL & symptom relief (No power calculation)	30,35	64.2, 59.9	67,39	Classes I 58% II 26% III 6%	Na-restricted diet Restriction of total fluids to 1.5l/ day. Recommendations on nutritional content of diet by dietitian for 6 months.	Usual care & general nutritional advice	Questionnaire adapted from Kansas City Cardio- myopathy & medical consultation	Decrease in fatigue from baseline to 6mths <i>Int. group.</i> P =0.012 Con. group NS	<i>Int. group</i> n=3 non-adherence <i>Con group</i> n=1 excluded from clinic, n=3 were lost to follow-up;	None reported

Dietary & supplements n=6	Author, Year/Setting Study	Aim (Sample size calculation)	Participants Randomised Int. vs. Con	Mean age (yrs.) ± SD	% Female	Heart failure status NYHA class (%)	Intervention(s)	Control(s)	Fatigue Outcome measure	Fatigue	Attrition	Adverse events/safety
	<i>Supplements</i>											
	Berman 2004 Israel Recruitment of PWHF transplant list RCT	To assess the effect of CoQ10 on patients with end-stage heart failure and to determine whether CoQ10 can improve the pharmacologic bridge to heart transplantation. (No power calculation)	32 'randomly divided according to age and gender'	Overall 54.6 Range 40-67.	Overall 14.3	Class III & IV	3-month supply of capsules of CoQ10 60 mg/day	3-month supply of capsules of cornflour-based placebo. (Externally identical).	Adapted Multi-dimensional Assessment of Fatigue questionnaire	Fatigue decreased from baseline in Int. group (p<0.001). & were worse in Control group (NS)	n=5 death (1), heart transplant (1), drug-induced intestinal upset (1) transport problems (1) and lack of compliance (1)	Gastro-intestinal upset was reported with CoQ10 (No detail)
	Belcaro 2020 Italy Recruitment process unclear but study conducted by university cardiology department CT	To evaluate the positive benefits of Robuvit® (Oak wood extract) as a standardised supplement in PWHF (Calculation based on previous comparable study)	20/20	61.3±1.2, 60.2±2.3	Overall 0	Stable mild HF equal to Class II	Robuvit® (Oak wood extract) for 8 weeks in addition to usual care	Usual care	Multi-dimensional Assessment of Fatigue scale (MFIS) combining physical, cognitive, psychosocial items added together measured at 8 & 12 weeks	Decreased fatigue with Robuvit® vs. control group at 8 & 12 weeks P<0.05	Not reported	Author's report 'No side effects were observed'
	Jafari 2019 Iran Patients referred into medical training centre RCT	To investigate the impact of melatonin (M) and Branch chained amino acids (BCAA), on QoL, appetite, nutrition risk index (NRI), and fatigue status in PWHF & cardiac cachexia (21 patients per group based on changes in albumin levels and allowing for a 20% dropout rate)	M vs. BCCA vs. M & BCCA vs. placebo 21,21,21, 21	Age range 32-67	28, 29, 28, 29	Mostly I Class I & III n=3 IV	(1) melatonin 20 mg/d (1 tab/d); (2) BCAAs 10 g/d (5 caplets containing 2 g BCAAs/caplet) (3) melatonin & BCAAs 10 g/d (5 caplets containing 2 g BCAAs/caplet) Tablets taken at night before sleeping, and caplets in the evening for 8 weeks.	(4) Tablet-like melatonin and caplet-like BCAAs filled with corn starch taken as per treatment arms.	Fatigue Symptom Inventory (FSI)	Changes in fatigue from baseline within all groups. P < 0.05 overall 3 Int groups vs. control group P <0.001 at 8 weeks	Grp 1 n=3 lost to follow up Grp 2 n= 2 lost to follow up, 2 died Grp 3 n=1 lost to follow up, 2 Ht transplants. Grp4 n= 2 lost to follow up, 2 didn't take supplements	None reported

Dietary & supplements n=6	Author, Year/Setting Study	Aim (Sample size calculation)	Participants Randomised Int. vs. Con	Mean age (yrs.) ± SD	% Female	Heart failure status NYHA class (%)	Intervention(s)	Control(s)	Fatigue Outcome measure	Fatigue	Attrition	Adverse events/safety
	<i>Hawthorn</i>											
	Degenrung 2003 Germany Recruited from secondary and primary care RCT	To evaluate the efficacy and safety of Crataegisan® in PWHF (A total of 140 based on exercise tolerance outcome & assuming dropouts)	69,74	Overall 64.8 ±8.0 Range 44–79	49, 50	Class II diagnosed 3 months earlier	0.75 ml (30 drops) of extract* diluted in water taken orally before meals, 3x daily for 8 weeks of Crataegisan® Bioforce	Coloured drops (identical in look, odour & taste)	Subjective cardiac symptoms including fatigue were assessed by patient on a rating scale as none, mild, moderate or severe.	Changes in fatigue in or between groups were NS.	n=26 (Int, Con) withdrew at their own request (2, 1) protocol violations (12, 16), mainly due to medication compliance	9 Int. and 11 Con. group reported adverse events : Gastrointestinal, musculoskeletal , Respiratory, urinary, vascular and psychiatric disorders of mild to moderate severity unlikely to be related to study medication.
	Schmidt 1994 Germany RCT No details on recruitment	To investigate the efficacy and compatibility of this (relatively high) dose of Crataegus in PWHF (No power calculation)	40,38	60.4, 60.3	65, 58	Class II	Crataegus extract LI 132 administered as 3 x 1 (200mg) dragee/day corresponding to a daily dose of 600 mg. for 8 weeks plus a wash-out week.	Placebo dragees with same appearance as the INT, 3 x 1 dragee/day with same regime	subjective symptoms evaluated using 8 typical troubles ("general decrease in vitality", "exhaustion", "fatigability", "effort dyspnoea", "night dyspnoea" among others). Each item was assessed using the severity levels 0 to 3 ("none", "slight", "median", "severe").	No meaningful results	n=4 One from each group as the wash-out phase had not been adhered to Two participants were excluded due to poor compliance	No severe AEs reported. <i>Int. group</i> , (n=2) Temporary nausea (1) single cardiac trouble on one day (1) <i>Con. group</i> dryness of the mouth (1) internal restlessness (1)

Key: PWHF people with heart failure, **QoL** quality of life, **EF** ejection fraction, **NS** not statistically significant, **NHYA** New York Heart Association (classification of heart failure status), **CBT** Cognitive Behavioural Therapy

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Sweden (3), Germany (2), Taiwan (2), and one trial in each in Italy, Mexico, Israel, and Hong Kong.

Recruitment and power of trials

The number of participants recruited to each trial was small, with a total of 515 recruited across the 21 trials. Seven trials recruited less than 50 participants^{17,22,25,26,30,32,33}.

Recruitment was mostly via hospital outpatient clinics (12/21)^{17,20–24,26,28–31,33,34}. Five trials recruited from hospitalised patients^{15,16,19,25,27}, one trial recruited from both in and outpatients¹⁸. One trial recruited from a heart transplant list³² and another recruited via both secondary and primary care³⁵. In the remaining study it was not clear how participants were recruited³⁶.

Fatigue outcome measures and definitions

Eleven different outcome measures for fatigue were used in the trials. [Table 2] These included simple Likert scales for recording of symptom/signs, fatigue specific measures and fatigue subscales of more complex outcome measures. Definitions of fatigue were present in 11/21 trials. Fatigue was described in both physiological and psychological terms across the definitions, but some definitions were very brief. Eleven trials measured fatigue as a standalone outcome; and in 7 of these, fatigue was the primary outcome.

Three of the trials were not randomised and so were graded at high risk of bias for the two domains concerning randomisation and allocation concealment^{22,28,29,33}. [Figure 2] All the 15 RCTs described the random sequence process, 9/15 described allocation concealment^{16,20,23,27,30–32,35,36}.

Most trials were not suitable for participant and personnel blinding, but four trials did, three were supplement trials, the other the mindfulness trial (personnel blinding)^{26,32,34,35}. Only eight trials reported on the blinding of outcome assessment^{18,23,25,27,30–32,34}. Information regarding attrition and reporting bias was well reported. Whilst 11/15 RCTs and one pilot RCT recruited successfully on a sample calculation, all trials lost some participants to follow up^{15–21,23,24,27,34,35}. Two trials had significant attrition^{21,26}. Only three trials described a predefined analysis plan^{16,19,23}.

Efficacy and safety

Supported self-management interventions

The evidence for education and support and its impact on the fatigue of people with HF comprises five RCTs^{15–19}. [Table 1]

In an RCT by Abdolahi describing four weeks of education compared to regular hospital outpatient care, a statistically significant mean change in fatigue (Piper Fatigue Scale) was reported in favour of the intervention (Calculated MD -3.50 [95% CI -4.43, -2.57]¹⁵. An RCT by Albert and colleagues compared a video education package to standard HF education but did not provide sufficient data to examine the effect on fatigue¹⁶. The authors reported decreased fatigue (check list with Likert scale) at three months with the intervention compared to usual care ($p < 0.01$). [Figure 3a]

The remaining three RCTs on e-health education, supportive educational nursing care and patient centred care reported non-statistically significant improvements in fatigue compared to control groups (Chronic HF Questionnaire, Piper Fatigue Scale, Multidimensional Fatigue Inventory respectively) (Calculated MD 95% CI: -1.09 [-3.55,1.37], -4.12 [-7.67, -0.57], -4.65 [-10.55,1.25] respectively)^{17–19}. [Figure 3a] There were no adverse events reported with these RCTs.

Self-management interventions

Mind-body therapies. The evidence for mind-body therapies comprises five RCTs, four pilot trials, of which two did not randomise participants and one controlled trial^{22,28,29}. [Table 1] This includes one RCT of Qigong and two trials of Tai chi, two trials (one unrandomised) of Cognitive Behavioural Therapy (CBT), and one trial each of meditation, mindfulness, progressive muscle relaxation (unrandomised), nature sounds and biofeedback^{20–30}.

The RCT conducted by Chen investigated Chinese Qigong versus usual care alone for 12 weeks²⁰. They reported a statistically significant improvement in fatigue (Shortened Piper Fatigue Scale) compared with the usual care (Calculated MD -3.22 (95%CI -5.99, -0.45). [Figure 3b]

The pilot RCT and RCT of Tai chi did not show a statistically significant impact of the intervention on fatigue (both used the Multidimensional Fatigue Inventory)^{21,22}. The pilot RCT authors reported no significant difference between groups at 12 weeks ($p = 0.19$)²². The RCT authors reported that the usual care group had more mental fatigue than the intervention group at six months ($p = 0.048$)²¹. The authors were contacted to request further data, but no response was received.

Both trials of CBT reported a statistically significant reduction in fatigue (PROMIS, Multidimensional Assessment of Fatigue) at eight weeks and six months respectively, but only the RCT showed a statistically significant mean change compared with the control group [Calculated MD 95% CI: -2.90 [-8.82,3.02]; -4.00 [-0.679, -1.21] respectively)^{23,24}. [Figure 3b]

A pilot RCT by Jayadevappa compared transcendental meditation with a control group of listened to music or read twice daily²⁵. The authors reported no statistically significant difference in vitality (SF-36 scale) between the groups at six months. (Calculated MD 0.70 [95% CI -0.41,5.41]). [Figure 3b]

A further pilot RCT by Norman and colleagues described a mindfulness intervention which showed a statistically significant improvement in fatigue (Fatigue Severity Scale) compared to usual care alone at 10 weeks (Calculated MD -8.00 [-12.06,3.94])²⁶. [Figure 3b]

A three-arm RCT by Seifi and colleagues compared Benson muscle relaxation (BMR), nature sounds (NS) and usual care for hospital inpatients over three days²⁷. The authors reported an overall statistically significant improvement in fatigue (Fatigue Severity Scale) for all groups. (Calculated MD 95% CI -8.00 [-12.06, -3.94], -0.85 [-1.08, -0.62] respectively). [Figure 3b]

Table 2. Definitions of fatigue and measures used in the included studies.

Supported self-management	Definition or description	Measure used
Education		
Abdollahi 2020	'Physically, fatigue is absence of energy, cognitively it is a defect in senses concentration, and emotionally it is a decrease in motivation or interest'	Piper Fatigue Scale
Albert 2017	None	Checklist of 30 HF symptoms with blank spaces to write in other symptoms with a 36 item in-house Likert scale tool.
Tomita 2009	None	Congestive Heart Failure Questionnaire
Wang 2016	Fatigue is defined as a subjective, unpleasant feeling that involves the complex interaction of biological processes, psychosocial phenomena and behavioural manifestations. Patients with fatigue experience an overwhelming sustained sense of exhaustion and decreased capacity to engage in physical and mental activity that is not relieved by rest.	Shortened Piper Fatigue scale (Chinese)
Person centred care		
Wallstrom 2020	Fatigue is 'a subjective, unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition which interferes with individuals' ability to function to their normal capacity'. Fatigue is by nature subjective, which means that it can only be assessed by the affected and cannot be observed by another person. Being affected by a symptom such as fatigue can greatly affect wellbeing and the ability to live life as wanted.	Multidimensional Fatigue Inventory
Self-management		
Mind-body therapies		
Chen 2018	Patients with heart failure describe fatigue as " <i>a pervasive and unignorable bodily experience.</i> " Fatigue may cause limitations in performing daily and social activities, increased dependency on others, loss of self-esteem, and depression, thereby affecting patients' quality of life.	Shortened Piper Fatigue Scale (Chinese)
Hägglund 2017	In the embedded qualitative study, the experience of fatigue is interpreted as an 'inside experience where the body is like a barometer for limitations in daily activities and an existential awareness of vulnerability and mortality.'	Multi-dimensional Fatigue Inventory
Redwine 2012	Describes fatigue as a somatic symptom	Multi-dimensional Fatigue Symptom Inventory
Freedland 2015	None	Profile Physical and Mental Health Summary Scores (PROMIS)
Redeker 2015	None	Multi-dimensional Assessment of Fatigue
Jayadevappa 2007	None	Vitality on the SF-36 scale
Norman 2018	None	Fatigue Severity Scale
Selfi 2018	Used the The North American Nursing Diagnosis Association defines fatigue as 'an overwhelming sustained sense of exhaustion and decreased capacity for physical and mental work at usual level.' Fatigue as an internal and unpleasant symptom is accompanied by physical sensations such as exhaustion.	Fatigue Severity Scale (Farsi)

Yu 2017a&b	None	Chronic HF questionnaire (Chinese)
Swanson 2009	None	The Borg Scale (dyspnoea and fatigue)
Diet and supplements		
Colin Ramirez 2004	None	Questionnaire adapted from Kansas City Cardiomyopathy questionnaire & medical consultation
Berman 2004	None	Adapted Minnesota Living with Heart failure Questionnaire
Belcaro 2020	None	Multi-dimensional Fatigue Symptom Inventory
Jafari-Vayghan 2019	Fatigue (as a result of muscle wasting) and anorexia are the most commonly reported symptoms by cachectic HF patients. One-third of patients with mild HF and up to 50% of all HF patients are fatigued, which is defined as recurrent fatigue and is a disability in HF patients, making it difficult to perform daily activities. Decreased appetite in patients with HF can increase this disability and malnutrition and affects the prognosis of this medical condition.	Fatigue Symptom Inventory
Degenrung 2003	None	Subjective cardiac symptoms including fatigue were assessed by the patient on a categorical rating scale as none, mild, moderate or severe.
Schmidt 1994	None	The subjective symptoms were evaluated using a score system which included 8 typical troubles ("general decrease in vitality", "exhaustion", "fatigability", "effort dyspnoea", "night dyspnoea" among others).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abdollahi 2020	+	?	?	?	?	+	?
Albert 2017	+	+	?	?	?	+	?
Belcaro 2020	?	?	?	?	?	?	?
Berman 2004	+	+	+	+	?	+	+
Chen 2018	+	+	?	?	?	+	+
Collin Ramirez 2004	+	+	?	+	?	?	+
Degenrung 2003	+	+	+	?	?	+	+
Freedland 2015	+	+	?	+	+	?	+
Hagglund 2017	+	?	?	?	+	?	+
Jafari 2019	+	?	+	+	?	+	+
Jayadevappa 2007	+	?	+	+	+	+	+
Norman 2018	+	?	?	?	+	+	+
Redeker 2015	+	?	?	?	+	+	+
Redwine 2012	?	?	?	?	?	+	+
Schmidt 1994	+	+	?	?	?	+	?
Seifi 2018	+	+	?	+	+	?	+
Swanson 2009	+	+	?	+	+	+	?
Tomita 2009	+	?	?	+	?	+	?
Wallstrom 2020	+	?	?	+	?	?	+
Wang 2016	+	?	?	+	?	+	+
Yu 2007	+	+	?	+	?	+	?

Figure 2. Risk of Bias assessment.

In the controlled trial by Yu published over two papers, one of the trial groups received a progressive muscle relaxation intervention^{28,29}. The authors reported a non-statistically significant improvement in fatigue (Chronic HF Questionnaire) compared to the control group at 12 weeks [Calculated MD 0.28 [95% CI -0.03, 0.59]. [Figure 3b]

An RCT by Swanson investigated cardiorespiratory biofeedback training versus sham biofeedback over six weeks³⁰. The authors did not provide sufficient data to examine but reported that there was no significant difference in fatigue (Borg Scale) between the groups. [Figure 3b]

No adverse events were reported in four of the trials²⁰⁻²³ and a further four did not make a statement^{24,25,27-29}. The mindfulness trial reported an adverse event based on the statement of one participant who dropped out reporting a 'gloomy mood' related to increased bodily symptom awareness²⁶.

Diet and supplements. The evidence for diet and supplements comprises five RCTs and one pilot controlled trial³¹⁻³⁶. One RCT investigated a low salt, balanced dietary regime³¹. Three trials looked at dietary supplements: oakwood extract, Co-enzyme Q10, melatonin (Me) and branched chain amino acids (BCAA)³²⁻³⁴. The two remaining RCTs investigated the herbal supplement hawthorn (Crataegus)³⁵⁻³⁶.

There were insufficient data reported in the trials of low salt (only p values given), CoQ10 (no intergroup comparisons) and hawthorn trials (general statements) to determine any impact of the interventions^{31,32,35,36}. [Table 1].

A controlled trial by Belcaro investigated Robuvit® (Oak wood extract) compared to usual care alone. Participants in the Robuvit® group had a statistically significant reduction in fatigue (Multi-dimensional Assessment of Fatigue scale) compared to controls at 12 weeks (Calculated MD -36.10 (95% CI -37.43, -34.77)³³. [Figure 3c]

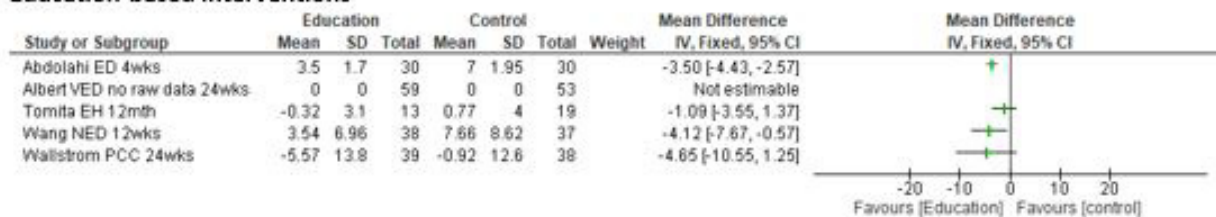
In a four-arm RCT by Jafari-Vayghan the impact of Me and BCAA supplementation, separately and together with an identical placebo group were investigated³⁴. All three supplement groups showed a statistically significant reduction in fatigue (Fatigue Symptom Inventory) compared to the placebo group at eight weeks (Calculated data M: MD -14.31 [95% CI -25.10, -3.52] BCAA: MD -21.76 [-31.36, -12.16], M & BCAA: MD -20.9 [-29.75, -10.43]) [Figure 3c]

Two RCTs did not report adverse events^{31,34}, and the Coenzyme Q10 RCT reported gastrointestinal upsets with the supplement but did not provide any numbers³². The two hawthorn RCTs gave detailed adverse events reporting as it was a primary outcome, but none of the serious adverse events were thought to be caused by the supplement^{35,36}. The Robuvit® trial reported that no side effects were observed³³.

Discussion

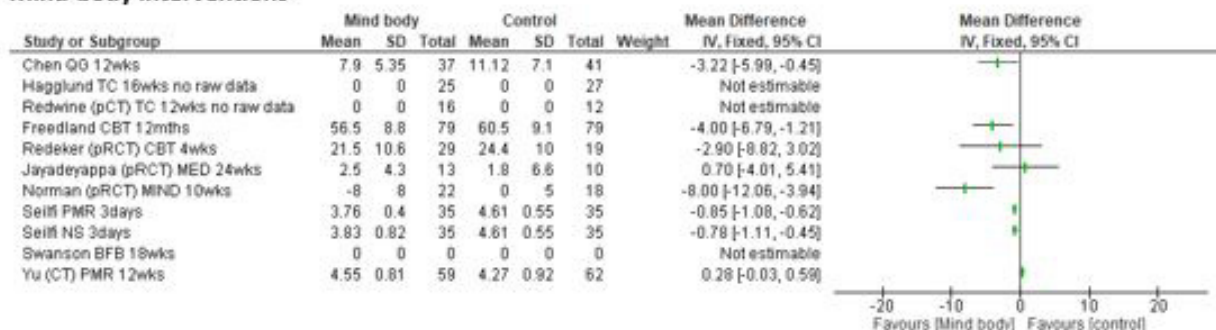
This systematic review includes 21 trials investigating the efficacy of a variety of supported self-management, and

a) Education-based interventions



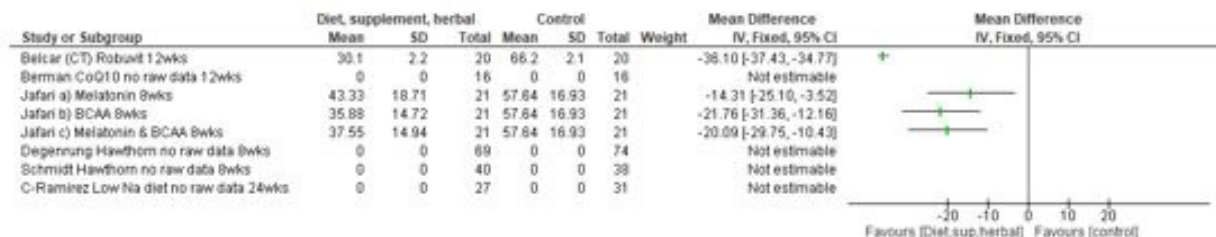
Key: All trials are randomised controlled trials (RCTs); ED education, VED video education, EH health education, NED nurse education, PCC person centred care

b) Mind-body interventions



Key: Trials are randomised controlled trials (RCTs) except (pRCT) pilot RCT, (pCT) pilot controlled trial (CT) controlled trial; QG Q Gong, TC Tai Chi, CBT cognitive behavioural therapy, MED meditation, MIND Mindfulness, PMR progressive muscle relaxation, BFB biofeedback

c) Diet and supplement interventions



Key: Trials are randomised controlled trials (RCTs) except (CT) controlled trial; BCAA branched chain amino acids

Figure 3. Forest plots for fatigue outcome per intervention group. Mean differences in fatigue outcome between intervention group and control group at end of trial.

self-management interventions for HF-related fatigue. A recent James Lind Alliance research prioritisation partnership for advanced HF highlighted the importance of fatigue to people with HF and supported the need for these types of interventions alongside medication and cardiac rehabilitation⁵. UK and European guidance suggests that a personalised, exercise-based cardiac rehabilitation programme should be offered to all people with HF, unless their condition is unstable^{6,37}. Furthermore, this provision should include psychological and educational content coupled with ongoing support^{6,37}. Many of the

interventions included in this systematic review are complementary to the recommendations of this guidance.

The supported self-management interventions in this review focused on education, support, and in one RCT, person-centred care¹⁵⁻¹⁹. Limited data for this type of intervention suggests a short term positive effect on fatigue, diminishing overtime. Related research in education for people with HF suggests that family-based education is preferable, but these studies do not identify fatigue as a standalone outcome³⁸. Future research

into the role of education should focus more on the important outcome of fatigue.

The self-management interventions in this systematic review formed two broad groupings of mind-body, and diet and supplements.

The group of mind-body therapies covered a range of interventions from CBT to biofeedback^{20–30}. Of note was the RCT of CBT showing a statistically significant effect on HF-related fatigue at 12 months²³. The pilot RCT of mindfulness also showed a statistically significant effect on HF-related fatigue at 10 weeks²⁶. These findings are supported by a recent systematic review of psychological interventions including CBT for HF which suggested a short term (<3 months) effect of a variety of psychological interventions on health related quality of life³⁹.

A 2020 systematic review and meta-analysis of the benefits of Tai Chi for HF reported that it improves exercise capacity, quality of life, depression, and decreased b-type natriuretic peptide expression⁴⁰. However, a more recent overview on the same topic concluded that more robust trials are needed, and that careful consideration is required in meta-analysis of these data⁴¹. Indeed, our review shows that fatigue data from the two Tai chi trials were not presented fully to allow proper interpretation.

Five of the seven diet and supplement trials did not provide sufficient detail on the fatigue outcome data. This lack of evidence is reflected in a recent systematic appraisal and evidence map of diet and supplements for people with HF which does not include the outcome of fatigue in its otherwise comprehensive approach⁴². Data from the Robuvit®, Melatonin and BCAA supplement trials in the current review both reported a statistically significant impact on fatigue in the short term^{33,34}.

A recent systematic review and meta-analysis of Co Q10 supplementation for HF suggested a possible benefit of coenzyme Q10 on all-cause mortality; the results for short-term functional outcomes were more modest or unclear⁴³. Fatigue was not included as a standalone outcome.

The supplement Robuvit® is less researched. The proposed mechanism of action involves the constituent polyphenols working to reduce oxidative stress in the body, and therefore impacting on energy capacity⁴⁴. The included trial for HF-related fatigue was a small non-randomised controlled trial and requires robust replication³³. Melatonin conversely has been investigated for its potential role in cardiovascular disease over the last two decades⁴⁵. The most recent RCT looking at melatonin supplementation for people with HF reports an improvement in quality of life compared to placebo over 24 weeks⁴⁶. There is little research on BCAA supplementation, and none of it in people with HF.

Overall, the participants of the included trials of supported self-management and self-management interventions do not represent the general HF population. The prevalence of HF slowly increases with age until about 65 years, after which it increases more rapidly. One in seven people have a diagnosis of HF at 84 years⁴⁷. Most of the participants in the included trials were under 75 years of age, and a significant number were 60 years or younger. A recent review of HF confirms that most interventional research is conducted with younger participants, whereas older, potentially more frail people with HF are the subject of qualitative studies⁴⁸.

The female gender is underrepresented in the trials and therefore caution is required when generalising from the results of studies with mostly male participants. A recent systematic review outlines the benefits of women-focused rehabilitation programmes for physical and mental dimensions of quality of life⁴⁹.

There was no language restriction in the conduct of this review, and the trials included were undertaken in a range of countries and included a range of ethnicities. We are aware that there is a lack of HF data generally from countries outside Europe and North America, especially from lower and middle-income countries, even though these are estimated to carry 80% of the global cardiovascular disease burden⁵⁰.

People with more severe HF (NYHA III and IV), who are likely to be experiencing greater fatigue, are under-represented in the studies included in this review. Only the CoQ10 and melatonin/BCAA RCTs included this profile of participants, with the former focusing on end stage HF, but the latter including only three participants with a NYHA status IV out of a total of 84^{32,33}.

A further aim of this systematic review was to examine how fatigue was defined and measured in these trials. Only half of the included trials gave a definition, and some of these were brief. This was in part because fatigue was only a primary or standalone outcome in eleven of the trials.

In the HF literature with a focus on physical activity and rehabilitation there is a tendency to focus on acute fatigue and its recovery after exercise exertion. Whilst this is an important area, it does not address the more global physical and psychological fatigue that people with HF experience on day-to-day. Over the 21 trials, eleven distinct fatigue outcome measures were used, from unvalidated, simple Likert scales based on symptoms, to fatigue items in established composite HF outcome measures. Further research is needed to be able to assess and quantify the patient experience of fatigue, potentially through the development of well-validated patient-reported outcome measures.

In conclusion, there is a limited evidence base for supported self-management and self-management interventions for

HF-related fatigue. However, these interventions are complementary to conventional HF management and may be of value if rehabilitation is not available or not appropriate. Supported self-management approaches involving education and ongoing support are likely to help people with HF generally in their quality of life, including managing fatigue despite the modest, short-term evidence. The efficacy evidence for a variety of self-management interventions such as CBT, mindfulness, and some supplements for HF-related fatigue is positive, but is limited to individual, small trials. All promising trials within this systematic review warrant replication.

In addition, this systematic review highlights two important issues associated with HF research. Firstly, that participant recruitment into supported self-management and self-management trials does not represent the real-world HF population in terms of age, gender, ethnicity and severity of disease. Secondly, it highlights the lack of focus of research on the everyday fatigue people with HF live with.

What is needed now is the acknowledgment of the importance of fatigue to people with HF, a better understanding of the impact of fatigue on quality of life, and more research into the promising interventions.

Further well-designed trials are needed to provide more robust evidence for self-management strategies for people with HF-related fatigue. These trials need to be designed to better

reflect the characteristics of the HF population. There is also a need for consensus work on fatigue definitions and outcome measures to allow clear and standardised reporting in future studies.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

Figshare: Appendix 2 Medline search strategy: systematic review of self-management of heart failure-related fatigue, <https://doi.org/10.6084/m9.figshare.21572856.v1>⁵¹.

Figshare: Appendix 3, intervention definitions: systematic review of self-management of heart failure-related fatigue, <https://doi.org/10.6084/m9.figshare.21572889.v1>⁵².

Reporting guidelines

Figshare: Appendix 1 PRISMA checklist: systematic review of self-management of heart failure-related fatigue, <https://doi.org/10.6084/m9.figshare.21572700.v1>⁵³.

Data are available under the terms of the [Creative Commons Attribution 4.0 International license \(CC-BY 4.0\)](#).

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