ORIGINAL REPORT

CLINICAL OUTCOMES FOLLOWING EXERCISE REHABILITATION IN PEOPLE WITH MULTIMORBIDITY: A SYSTEMATIC REVIEW

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Objective: To determine the effectiveness of exercise rehabilitation in people with multimorbidity. Exercise capacity was the primary outcome. Secondary outcomes were: health-related quality of life, activities of daily living, cardiometabolic outcomes, mental health outcomes, symptom scores, resource utilization, health behaviours, economic outcomes, and adverse events.
Data sources: A search was conducted in MEDLINE, CINHAL, EMBASE, and Cochrane Central Register of Controlled Trials databases.
Study selection and extraction: Randomized and non-randomized controlled trials and cohort studies of exercise rehabilitation vs any comparison in people with multimorbidity.
Data synthesis: Forty-four reports (38 studies) were included. Rehabilitation ranged from 8 weeks to 4 years, with 1–7 sessions of rehabilitation weekly. Exercise included aerobic and resistance, limb training, aquatic exercises and tai chi. Compared with usual care, exercise rehabilitation improved 6-min walk distance (weighted mean difference (WMD) 64 m, 95% CI 45–82) and peak oxygen consumption (WMD 2.74 mL/kg/min, 95% CI –3.32 to 8.79). Effects on cardiometabolic outcomes and health-related quality of life also favoured rehabilitation; however; few data were available for other secondary outcomes.
Conclusion: In people with multimorbidity, exercise rehabilitation improved exercise capacity, health-related quality of life, and cardiometabolic outcomes.

LAY ABSTRACT

Chronic disease is a common health problem worldwide. It is increasingly common for people to have more than 1 chronic disease, which is called multimorbidity, and the interaction of their multiple health problems may worsen their health outcomes. Exercise rehabilitation is an effective and established treatment to improve health for people with different chronic diseases, such as heart and lung disease; however, the benefit of structured rehabilitation in people with multimorbidity has not been systematically reviewed. A literature search was performed to investigate the clinical outcomes following exercise rehabilitation in people with multimorbidity. Compared with usual medical care, the results showed that exercise rehabilitation improved exercise capacity, measured by walking distance in a formal test, health-related quality of life and the body's ability to use oxygen, in people with multimorbidity. There were few data regarding the benefit of rehabilitation on other outcomes, and more well-designed robust trials are needed.

Multimorbidity, defined as the co-existence of 2 or more chronic conditions (1), is common in clinical practice (2) and is associated with many negative consequences, including increased risk of disability (3), frailty (3) and mortality (4, 5), poorer functional status (6), reduced health-related quality of life (HRQoL) (7) and high healthcare costs (8). The increasing prevalence of multimorbidity generates financial pressures on healthcare systems, as expenditure increases almost exponentially with the number of chronic diseases in an individual (9).

Rehabilitation is integral to chronic disease management. It is described as therapies including exercise (aerobic and resistance) training, education and behaviour change (10), with interventions designed to optimize function and reduce disability in individuals with health conditions (11). Evidence has shown that exercise training, inclusive of aerobic and resistance regimens and education, improves outcomes, including exercise capacity, upper and lower limb function and muscular strength, and quality of life, and mitigates the progression of many chronic diseases (12). This accounts for the inclusion of exercise rehabilitation in clinical practice guidelines for several single diseases (12, 13).

Worldwide healthcare delivery tends to be organized around the treatment of single diseases (1, 14, 15). As a result, people with multimorbidity are often managed according to several single-disease guidelines. This is reflected in rehabilitation, which is frequently structured as single-disease programmes, such as cardiac and pulmonary rehabilitation. While meta-analyses of single-disease programmes have demonstrated improvements in exercise capacity, symptoms, and HRQoL (16–19), recent multimorbidity guidelines suggest that single-disease care may not be appropriate for people with multimorbidity (20). The low inclusion of people with multimorbidity in randomized controlled trials (RCT) reinforces the difficulty faced by healthcare professionals in creating appropriate clinical protocols (3) and guidelines. In a review of guidelines relevant to single-disease rehabilitation, 3 out of 7 did not mention coexisting conditions, and an additional 3 only briefly mentioned minor programme adaptations to accommodate multimorbidity (21). This highlights the need to investigate rehabilitation in people with multimorbidity.

A systematic review on the interventions for improving outcomes in patients with multimorbidity found mixed results about the effectiveness of interventions (2). The interventions were predominantly focused on organization of care, such as case management or multidisciplinary team-work, and educational or self-management support (2). It found no clear positive improvements in clinical outcomes, health service use, patient-related health behaviours or costs (2). The review suggests that interventions designed to target difficulties that people experience with daily functioning (e.g. physiotherapy) may be more effective (2). However, exercise rehabilitation was not delivered in the included studies and exercise capacity was not a reported outcome measure.

Exercise rehabilitation for people with multimorbidity may have a role to play in addressing common symptoms of multiple chronic diseases. This systematic review aimed to determine clinical outcomes following exercise rehabilitation in people with multimorbidity. This review was registered on PROSPERO on 29 August 2018 (CRD42018100512).

METHODS

This systematic review was reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (22).

Types of studies
Due to the emerging nature of the field of multimorbidity, RCTs, non-randomized control trials (NRCT) and cohort studies were eligible for inclusion. Studies published in a language other than English were excluded due to lack of access to translation services. Systematic reviews, cross-sectional and case studies were excluded.

Types of participants
Any participants with multimorbidity, defined as 2 or more chronic diseases, were included, and no age criteria were applied (1). This study used the World Health Organization (WHO) definition of chronic disease: health problems that require ongoing management over a period of years or decades (23). No criteria to confirm diagnosis of a specific chronic disease was applied. If multimorbidity was present in only a proportion of the participant population, studies were included if there were separate data for participants with multimorbidity.

Types of interventions
The study included rehabilitation programmes of at least 4 weeks' duration that included exercise with or without any form of education or psychological support (19, 24, 25), delivered in any setting (home-based, primary, secondary or tertiary care). These criteria are consistent with systematic reviews reporting on rehabilitation in chronic obstructive pulmonary disease, heart failure, and coronary heart disease populations (19, 24, 25). There were no criteria specified for exercise type, frequency or intensity or follow-up period, in order to enable widespread search results. The study excluded programmes without exercise training or those aimed at a single joint (e.g. hip), which focused on regaining function in the single joint via targeting range of motion or strength.

Comparisons of interest
Usual medical care (UMC) or other interventions that excluded exercise training (e.g. education or psychological support only) were comparisons of interest. Usual medical care was defined as general inpatient or outpatient care, including medical, nursing or allied health intervention. Studies comparing rehabilitation with UMC were analysed separately from those comparing with other interventions.

Types of outcomes
The primary outcome was exercise capacity, as measured by 1 or more of: laboratory-based exercise testing (e.g. cardiopulmonary exercise test; CPET) and/or field walking tests (e.g. 6-min walk test).

The secondary outcomes were: HRQoL (any generic or disease-specific questionnaires); activities of daily living (ADL) (any questionnaires); cardiometabolic

outcomes (e.g. blood pressure; BP), lipid profiles, body mass index (BMI)); mental health outcomes (e.g. depression and anxiety scores); symptom scores (e.g. dyspnoea, fatigue); resource utilization (e.g. hospital admissions, general practitioner visits); health behaviours (exercise or medication adherence, physical activity); economic outcomes (e.g. analysis measuring cost; effectiveness or impact); and adverse events.

The primary and secondary outcomes were selected as they are common measures within the field of rehabilitation research and in clinical practice. The studies included reported on at least 1 outcome of interest and did not have to include the primary outcome.

Search strategy

The search strategy used the following electronic databases in English only: up to 21 December 2021: MEDLINE, 1946 to present, In-process and other non-indexed citations, Ovid MEDLINE; Cumulative Index to Nursing and Allied Health Literature (CINAHL), 1981 to present, EBSCO CINAHL; EMBASE, 1947 to present, Ovid EMBASE; and Cochrane Central Register of Controlled Trials (CENTRAL), 1966 to present.

The search strategy for MEDLINE is shown in Table SI and was adapted for other databases. Reference lists of the identified articles were hand searched. The following trial registry was also searched: www.clinicaltrials.gov. Only studies with data published were included.

Selection of studies

Citations identified were collated via reference manager software (Endnote X7.8) and duplicates were removed. Two review authors (KB, ALL) screened titles and abstracts independently. Potential articles that met the inclusion criteria were identified and retrieved in full text for independent assessment by both reviewers. Any disagreements were resolved by consensus or a third reviewer (AH), where necessary.

Data extraction and management

Two review authors (KB, ALL) completed data extraction using an *a priori* data extraction template developed by the authors. The following data from included studies were extracted: (i) details of the intervention including: provider, delivery, location, dosage and tailoring (26); additional components (e.g. education or psychological support); (ii) participants: nature of multimorbidity and how it was defined; age; (iii) trial setting; (iv) study design; (v) comparators; (vi) outcome measures; and (vii) results. In the event that another report, referenced in the methods of an included study provided further detail of this data, this report was sourced and used to obtain the informa-tion required. WebPlotDigitizer (Pacifica, California, USA) (27) was used to extract data from studies that displayed results via figures and graphs only.

Assessment of risk of bias

The risk of bias of the RCT, NRCT and cohort studies were assessed independently using the Joanna Briggs Institute critical appraisal tools for specific study design (28). If necessary, authors were contacted to obtain further information. The risk of bias was assessed for the following domains: selection; performance; detection; attrition; reporting; and other (29). Two review authors (KB, ALL) independently extracted the data, and clarification was obtained via consensus discussion to confirm complete agreement.

Data analysis

For continuous variables (e.g. exercise capacity and HRQoL), the study recorded mean change from baseline or mean post-intervention values and standard deviation (SD). When 95% confidence intervals (95% CIs) and standard errors (SE) were reported, SDs were calculated. For dichotomous variables (e.g. health behaviours), risk ratios or odds ratios were calculated.

Meta-analysis

Meta-analysis was performed if trials were sufficiently clinically or statistically homogeneous, determined by factors including length of rehabilitation and outcome measure. Effect sizes (ES) were calculated using an online calculator (30) and Cohen's definition of ES of 0.2 as small, 0.5 as moderate and 0.8 or greater as large (31) was used to define magnitude.

Assessment of heterogeneity

Included studies were assessed in terms of clinical and statistical heterogeneity. Statistical heterogeneity was assessed by the inspection of forest plots and the I^2 statistics. The Cochrane guide to interpreting I^2 as follows, 0–40%: might not be important; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity; 75–100%: considerable heterogeneity (29). The fixed-effects model was used in the absence of heterogeneity; otherwise a random-effects model was used.

Subgroup analyses

Subgroup analyses were performed based on: (i) the definition of multimorbidity (i.e. 2 diseases vs 3 or more diseases), as these have been shown to have differences in prevalence (32, 33) and mortality (3); and (ii) the length of rehabilitation (4–8 weeks vs > 8 weeks); in clinical practice, it is common for rehabilita-

tion programmes to have durations of 4–8 weeks and research trials may have durations longer than 8 weeks.

Sensitivity analysis

Sensitivity analyses were performed to determine the potential effects of intervention components on outcomes, examining studies of exercise training only vs exercise training combined with education or psychological support.

RESULTS

The searches identified 23,999 studies (excluding duplicates), of which 23,862 were excluded based on title and abstract. Of the 137 full-text studies screened, 93 were excluded. The reasons for exclusion are detailed in Fig. 1. The final search outcome was 44 reports, resulting from 38 studies. Four studies had multiple reports that focused on different outcomes and met the inclusion criteria. Nine studies (10 reports) were reported only as abstracts (34–43). There were 17 RCTs, 1 randomized crossover trial, 19 cohort studies, and 1 quasi-experimental study.

Study characteristics are shown in Table I. The most common sample in the studies was chronic obstructive pulmonary disease (COPD) and comorbidities [diagnosis not specified] ($n=6$), followed by coronary heart disease (CHD) and diabetes ($n=4$). Multimorbidity groups were defined as 2 and 3 or more ($n=6$), 2–3 and 4 or more ($n=1$), distinct clusters (e.g. respiratory conditions, musculoskeletal conditions or neurological conditions) ($n=4$) or using a weighted comorbidity score (Charlson Comorbidity Index (CCI)) ($n=1$).

Intervention details are outlined in Table SII. Duration of interventions ranged from 8 weeks to up to 4 years, with a frequency of 1–7 sessions/week. The types of exercise included aerobic, aerobic and
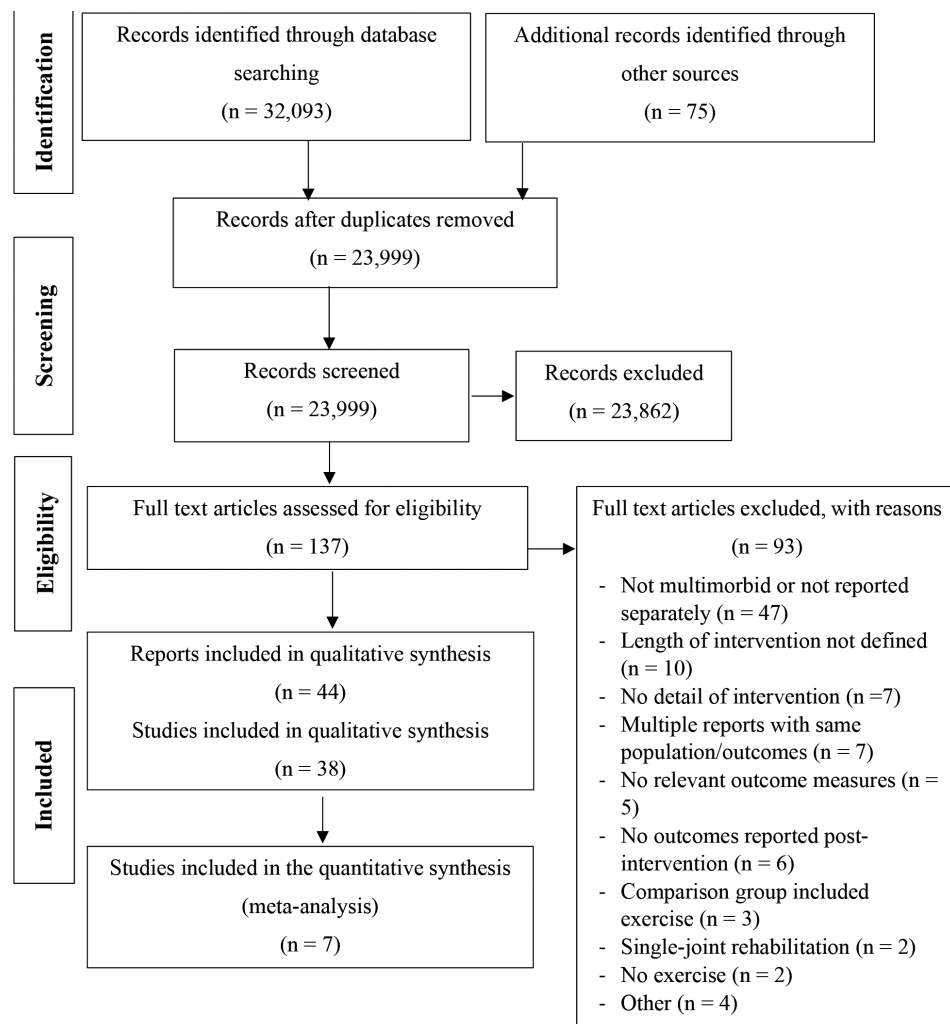

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Table I. Characteristics of included studies ($n = 38$)

Study	Country N	Study type	Diseases	Participants	Intervention	Duration of rehabilitation	Outcomes
Abdelbasset (2019) (54)	Saudi Arabia 69	Cohort	COPD HF	Age = range 45–61 74% males	Int 1 = low to moderate intensity aerobic exercise Int 2 = moderate intensity aerobic exercise Com = UC	12 weeks	PHQ-9
Abd El-Kader (2013) (44)	Saudi Arabia 80	RCT	Obesity Bronchial asthma	Age# (range) = 12–18 53% males#	Int = aerobic exercise; diet; medical treatment Com = usual medical care	8 weeks	BMI
Al-Jiffri (2013) (58)	Saudi Arabia 100	RCT	NAFLD Diabetes	Age# (range) = 35–55 100% males#	Int = aerobic exercise; diet Com = diet only (no exercise)	3 months	BMI HOMA-IR
Barnes (2009) (62)	Australia 12	Cohort	OSA Obesity	Age# = 42 (10.4) 25% males#	Int = aerobic and resistance exercise; diet Com = N/A	16 weeks	VO$_2$ peak BMI BP Lipids Insulin and glucose SF-36 POMS BDI FOCQ SASQ CRP
Beaudoin (2017) (46)	Canada 17	RCT	Cystic fibrosis Impaired glucose tolerance	Age* (mean, SEM) = 32 (24, 41) 38% males* Sedentary (< 100 min/wk structured exercise Age* (mean, SEM) = 36 (22, 57) 50% males* Sedentary (< 100 min/wk structured exercise)	Int = aerobic and resistance exercise Com = usual medical care	12 weeks	VO$_2$ peak Cystic fibrosis questionnaire-revised Physical activity questionnaire Physical activity monitor (steps) CRP
Bernocchi (2018) (47)	Italy 112	RCT	COPD Heart failure	Age* = 71 (9) 88% males* Age* = 70 (9.5) 75% males*	Int = aerobic and resistance exercises; education Com = usual medical care	4 months	6MWT MLHFQ CAT MRC PASE
Byrkjeland (2015) (48)	Norway 137	RCT	T2DM CAD	Age* = 65 (7.6) 87% males* Age* = 63 (7.2) 81% males*	Int = aerobic and resistance exercise Com = usual medical care	12 months	VO$_2$ peak HbA1c Glucose Insulin HOMA2-IR Adverse event (all medical events)
Castro (2015) (35)	Portugal 19	Cohort	CKD Diabetes	Age# = 72 (10) 33% males#	Int = aerobic and resistance exercise; haemodialysis Com = N/A	16 weeks	6MWT Accident or complication
Chiang (2020) (55)	Taiwan 50	RCT	Multimorbidity: 2 or more of HT, DM, HL, heart disease, metabolic syndrome, gout	Age = 60 (7.2) 72% males	Int = aerobic exercise Com = UC	12 weeks	IPAQ VO$_2$ peak SF-36
Collins (2010) (36)	USA 145	RCT	Diabetes PAD	Age# = 67 (10.1) 69% males#	Int = aerobic exercise; phone call Com = phone call only (no exercise)	6 months	Depressive symptoms
Crisafulli (2010) (63)	Italy 316	Cohort	COPD Comorbidities	Age# = 68 (7.6) 74% males#	Int = peripheral limb training; education; psychological support Com = N/A	21 sessions (9 weeks)	6MWT SGRQ MRC

(Continued)

Table I. (*contd.*)

Study	Country N	Study type	Diseases	Participants	Intervention	Duration of rehabilitation	Outcomes
de Groot (2012) (64)	USA 50	Quasi-experimental	Diabetes	Age$^\#$ = 57 (9.0) 32% males$^\#$	Int = aerobic and resistance exercise; cognitive behavioural therapy Com = N/A	12 weeks	VO$_2$ peak Diabetes quality of life measure SF-36 HbA1c Lipids BMI BDI Chronic illness resource survey Minutes exercise/week Steps
			Major depressive disorder				
Freitas (2018) (60)	Brazil 55	RCT	Asthma	Age* = 46 (7.7) 4% males* Performed <60 min structured or planned PA per week	Int = aerobic and resistance exercise; diet; education; psychological support	3 months	BMI HADS
			Obesity	Age* = 49 (9.6) 0% males* Performed <60 min structured or planned PA per week	Com = sham exercise (breathing and stretches); diet; education; psychological support		
Halvari (2017) (61)	Norway 137	RCT	CAD	Age$^\#$ = 63 (7.9) 81% males$^\#$	Int = aerobic and resistance exercise	12 months	HbA1c
			Diabetes	Physically active <150 min/wk	Com = usual physical activity		
Hassan (2016) (65)	Egypt 55	Cohort	COPD	Age$^\#$ = 60 (8.9) 93% males$^\#$	Int = aerobic and resistance exercise; education	8 weeks	6MWT VO$_2$ maximum mMRC SGRQ
			Comorbidities		Com = N/A		
Hsu (2021) (56)	Taiwan 66	RCT	Knee osteoarthritis Obesity	Age = range 60–70 53% males	Int 1 = Elastic band resistance exercise Int 2 = Elastic band resistance exercise, diet control Com = U/C	12 weeks	BMI
Johnson (2014) (38)	Not stated 30	Randomized crossover trial	Diabetes	Age$^\#$ = 68 (6.9) 53% males$^\#$	Int = aquatic exercise (details not provided)	12 weeks	6MWT
			Lower limb arthritis		Com = NS		
Khadanga (2016) (66)	USA 898	Cohort	CHD	Age$^\#$ = 64 (11.1) 73% males$^\#$	Int = aerobic and resistance exercise; education	3–4 months (maximum 36 sessions)	VO$_2$ peak Peak METS BMI
			Insulin resistance or diabetes		Com = N/A		
Kurian (2010) (39)	USA 22	Cohort	Diabetes	Age$^\#$ = elderly 68% males$^\#$	Int = resistance exercise	12 weeks	HbA1c Lipids
			Peripheral neuropathy		Com = N/A		
Listerman (2011) (67)	USA 749	Cohort	CHD	Age$^\#$ = 62 (10.6) 71% males$^\#$	Int = aerobic and resistance exercise; education; psychological support	24–36 sessions	6MWT BMI
			Comorbidities		Com = N/A		
Lo (2021) (57)	Taiwan 43	RCT	Multimorbidities: 2 of HT, HL, DM, stroke, cancer, heart disease, kidney disease, asthma, COPD, OP, degenerative arthritis, gout, depression, schizophrenia, bipolar disorder	Age range 40–≥65 49% males PA <150 min moderate intensity or <75 min vigorous intensity per week	Int 1 = aerobic exercise and MI Com 1 = MI Com 2 = UC	12 weeks	IPAQ SF-36 BMI VO$_2$ max
Martin (2016) (40)	Canada 15,927	Cohort	CHD	Age and sex details not stated	Int = details not provided	12 weeks	METs
			PAD		Com = N/A		
McNamara (2013) (50)	Australia 53	RCT	COPD	Age* = 73 (7) 50% males*	Int 1 = aerobic and resistance exercise (land-based)	8 weeks	6MWT ESWT ISWT CRDQ HADS
			Comorbidities	Age* = 72 (10) 28% males*	Int 2 = aerobic and resistance exercise (water-based)		
				Age* = 70 (9) 47% males*	Com = no exercise		

Table I. (*contd.*)

Study	Country N	Study type	Diseases	Participants	Intervention	Duration of rehabilitation	Outcomes
Mentz (2013) (51)	USA 2,331	RCT	Heart failure	Age# (median) = 59 72% males#	Int = aerobic exercise; education	Up to 4 years	VO_2 peak 6MWT
			COPD		Com = usual medical care; education		KCCQ
Mesquita (2015) (68)	Netherlands 213	Cohort	COPD	Age# = 64 (7) 59% males#	Int = details not provided	8 weeks (inpatient) Or 14 weeks (outpatient)	6MWT CWRT
			Comorbidities		Com = N/A		SGRQ
Mundra (2013) (41)	USA 120	Cohort	CVD	Age details not stated 70% males#	Int = details not provided	8–12 weeks	METs BMI BP
			Obesity		Com = N/A		Lipids Glucose BDI
Naz (2019) (69)	Turkey 211	Cohort	COPD	Age# (median, IQ range) = 64 (58, 68) 89% males#	Int = aerobic and resistance exercise	8 weeks	6MWT SGRQ mMRC
			Comorbidities		Com = N/A		HADS SF-36
Nonoyama (2016) (70)	Canada 1,247	Cohort	IHD	Age¥ = 61 (8.3) 96% males¥ [no comorbidities]	Int = aerobic and resistance exercise; education; psychological support	6–12 months	VO_2 peak BMI
			Comorbidities	Age¥ = 67 (10.1) 78% males¥ [non-respiratory comorbidity] Age¥ = 61 (10.1) 89% males¥ [respiratory comorbidity]	Com = N/A		
Servantes (2012) (52)	Brazil 50	RCT	Heart failure	Age* = 52 (9.83) 47% males*	Int 1 = aerobic exercise; education	3 months	VO_2 peak MLHFQ
			Sleep apnoea	Age* = 51 47% males*	Int 2 = aerobic and resistance exercise; education		
				Age* = 53 (8.19) 46% males*	Com = no exercise		
Soleimani (2009) (71)	Netherlands 284	Cohort	IHD	Age* = 57 (11.1) 72% males#	Int = aerobic exercise; diet counselling; psychological support	8 weeks	Resting HR Peak HR Post-exercise HR
			Diabetes		Com = N/A		HR recovery
Sridhar (2010) (53)	Malaysia 105	RCT	Diabetes	Age* = 62 (3.10) 55% males*	Int = aerobic exercise	12 months	BP HbA1c
			Hypertension	Age* = 59 (2.75) 56% males*	Com = no exercise		HR variability
Srinivasan (2014) (42)	USA 16	RCT	Major depressive disorder	Age# = 72 (5.24) Sex details not stated	Int = Tai Chi; antidepressant treatment	8 weeks	SIGHD
			Arthritis pain disorder	Age# = 74 (7.07) Sex details not stated	Com = mind-body education; antidepressant treatment		
Takaya (2014) (72)	Japan 528	Cohort	AMI	Age¥ = 62 (10) 81% males¥ [non-CKD]	Int = aerobic exercise; education	3 months	VO_2 peak BMI HR recovery
			CKD	Age¥ = 68 (9) 84% males¥ [CKD]	Com = N/A		
Tunsupon (2017) (73)	USA 165	Cohort	COPD	Age# (mean) = 70 96% males#	Int = aerobic and resistance exercise	8 weeks	6MWT MIET
			Comorbidities		Com = N/A		CWET CRQ
Verges (2004) (75)	France 95	Cohort	Acute coronary event	Age¥ = 57 (8.8) 86% males¥ [T2DM]	Int = aerobic exercise; education	2 months	VO_2 peak
			T2DM	Age¥ = 57 (11.3) 92% males¥ [Non-diabetic]	Com = N/A		

(Continued)

Table I. (*contd.*)

Study	Country N	Study type	Diseases	Participants	Intervention	Duration of rehabilitation	Outcomes
Wang (2013) (76)	Taiwan 90	Cohort	Heart failure	Age$^¥$ = 63 (2.10) 47% males$^¥$ [HF and non-anaemic]	Int = aerobic exercise	12 weeks	VO$_2$ peak
			Anaemia	Age$^¥$ = 64 (2.3) 40% males$^¥$ [HF and anaemic] Age$^¥$ = 62 (2.1) 47% males$^¥$ [Normal control]	Com = N/A		
Woodard (1994) (77)	USA 28	Cohort	CVD	Age$^¥$ = 61 (1.7) Sex details not stated [Comorbidity]	Int = aerobic exercise	6 months	METs
			Knee arthritis	Age$^¥$ = 59 (2.0) Sex details not stated [CVD only]	Com = N/A		
Zwerink (2010) (43)	Netherlands 6	Cohort	COPD	Age$^#$ = 70 (5) Sex details not stated	Int = aerobic and resistance exercise; education	10 weeks	6MWT ISWT
			Heart failure		Com = N/A		MLHFQ CRQ

Age is mean (standard deviation; SD) unless otherwise stated; $^#$whole population; *intervention group; $^¥$disease group.

n: number; RCT: randomized control trial; Int: intervention; Com: comparison; BMI: body mass index; NAFLD: non-alcoholic fatty liver disease; HOMA-IR: homeostasis model assessment-insulin resistance-index; MI: motivational interviewing; N/A: not applicable; OSA: obstructive sleep apnoea; VO$_2$: oxygen consumption; BP: blood pressure; SF-36: Short Form-36; POMS: Profile of Mood States; BDI: Beck Depression Index; FOCQ: Functional Outcomes of Sleep Questionnaire; SASQ: Sleep Apnoea Symptom Questionnaire; CRP: C-reactive protein; SEM: standard error of the mean; COPD: chronic obstructive pulmonary disease; 6MWT: 6-min walk test; MLHFQ: Minnesota Living with Heart Failure Questionnaire; CAT: COPD assessment test; MRC: dyspnoea by Medical Research Council; PASE: physical activity profile; T2DM: type 2 diabetes mellitus; CAD: coronary artery disease; HbA1c: haemoglobin A1c; HOMA2-IR: homeostasis model assessment 2-insulin resistance-index; CKD: chronic kidney disease; PAD: peripheral arterial disease; SGRQ: St George's respiratory questionnaire; HADS: Hospital Anxiety Depression Scale; mMRC: modified dyspnoea by Medical Research Council; NS: not stated; CHD: coronary heart disease; METs: metabolic equivalents; ESWT: Endurance Shuttle Walk Test; ISWT; Incremental Shuttle Walk Test; CRDQ: Chronic Respiratory Disease Questionnaire; KCCQ: Kansas City Cardiomyopathy Questionnaire; CWRT: constant work rate cycling test; IHD: ischemic heart disease; HR: heart rate; SIGHD: structured interview for Hamilton depression scale; AMI: acute myocardial infarct; MIET: maximal symptom-limited incremental cycle ergometer test; CWET: constant workload cycle endurance time test; CRQ: Chronic Respiratory Questionnaire; CVD: cardiovascular disease; wk: weeks.

resistance, peripheral limb training, aquatic exercise and tai chi. The rehabilitation was performed in several different locations, including supervised setting (*n* = 1), centre-based (*n* = 2), community exercise facility (*n* = 1), medical centre (*n* = 2), community-based (*n* = 3), home-based (*n* = 11) and hospital-based (*n* = 14); with some studies at multiple locations. Comparisons included UMC (*n* = 7), no exercise (*n* = 3), diet control (*n* = 1), motivational interviewing (*n* = 1), diet and sham exercise (*n* = 1) (sham exercise consisting of yoga pranayama breathing exercises and upper and lower limb stretches), phone call only (*n* = 1), diet (*n* = 1), usual physical activity (*n* = 1) and mind-body education (*n* = 1). There were no studies that measured ADL, resource utilization or economic outcomes.

Full details of the quality assessment for all study types are shown in Tables SIII, SIV and SV. For the RCTs and randomized crossover trial, 17 out of 18 reported not having participant or therapist blinding. Only 6 studies reported assessor blinding, and the remaining 9 studies did not specify whether assessors were blinded. For the cohort studies, 14 out of 19 studies showed that the exposures were measured in a valid and reliable way, with the other studies being unclear.

Meta-analysis was limited, as studies were clinically and methodologically heterogeneous, as defined in the methods section. Meta-analysis was performed for 3 outcomes: 6-min walk distance (6MWD), peak oxygen consumption (VO$_2$), and BMI.

Exercise rehabilitation vs usual medical care
Twelve studies (15 reports) compared exercise rehabilitation vs UMC (34, 38, 44–53, 54, 55, 57). The findings for studies are outlined in Table II.

Exercise capacity. The 6MWD was reported in 4 studies (6 reports) (38, 45, 47, 49–51), of which 2 (47, 50) were included in meta-analysis. Meta-analysis showed a weighted mean difference (WMD) of 64 m (95% CI 45–82) in favour of exercise rehabilitation (Fig. 2). A randomized crossover trial of a 12-week aquatic exercise programme showed an increased 6MWD from 395 m (SD 143.9) to 412 m (SD 147.9), *p* = 0.046 (38). However, no details of the comparison group were provided; the assumption was that the comparison group was UMC. The VO$_2$ peak (34, 45, 46, 48, 49, 51, 52, 55, 57) was reported in 6 studies (9 reports), of which 3 (46, 48, 52) were included in meta-analysis. Meta-analysis showed a WMD of 2.74 mL/kg/min (95% CI –3.32 to 8.79) in favour of exercise rehabilitation (Fig. 3) with significant heterogeneity, I^2 = 90%. One study (50) reported on endurance shuttle walk distance (ESWD) and incremental shuttle walk distance (ISWD). Significant improvement in both

Table II. Outcomes of studies of exercise-rehabilitation vs usual medical care

Study	Intervention (exercise type)	Outcome	Results (intervention)	Results (control)	Effect size	Notes
Exercise capacity						
Ambrosy (2018) (45)	Aerobic	6MWD (m)	HF+CKD: –7 (95% CI –13 to 0)	NR	NA	$p = 0.04$* Mean change (within group p-value)
Bernocchi (2018) (47)	Aerobic and resistance	6MWD (m)	60 (95% CI 22.2–97.8)	–15 (95% CI –40.3 to 9.8)	d = 0.69	$p = 0.004$* Mean change (between group p-value)
Johnson (2014) (38)	Details not provided	6MWD (m)	17	NR	–	$p = 0.046$ mean change (SD not stated)
McNamara (2013) (50)	Aerobic and resistance	6MWD (m)	land 43 (95% CI 22–63) water 48 (95% CI 22–70)	–16 (95% CI –34 to 1)	land d = 1.76 water d = 1.86	land vs Con: $p < 0.001$* water vs Con: $p < 0.0001$* Mean change (between group p-values)
Mentz (2013) (51)	Aerobic	6MWD (m)	19 (IQR –9 to 69)	1 (IQR –41 to 40)		$p = 0.16$ Median (IQR) change
Beaudoin (2017) (46)	Aerobic and resistance	VO$_2$ peak (mL/kg/min)	24.53 (SD 4.01)	25.35 (SD 6.79)	d = 0.15	ns Post-intervention
Byrkjeland (2015) (48)	Aerobic and resistance	VO$_2$ peak (mL/kg/min)	25.4 (SD 5.4)	25.2 (SD 6.7)	d = 0.03	$p = 0.0777$ Post-intervention
Chiang (2020) (55)	Aerobic	VO$_2$ peak (mL/kg/min)	27.3 (SD 7.1)	24.1 (SD 7.3)	d = 0.44	$p = 0.04$ Post-intervention (between group p-value)
Lo (2021) (57)	Aerobic	VO$_2$ peak (mL/kg/m^2)	25.9 (SD4.8)	MI: 24.2 (SD7.9) Con: 22.7 (SD 6.5)	Int vs Con: d = 0.49	Int vs Con: $p = 0.002$ Post-intervention (between groups p-value)
Mentz (2013) (51)	Aerobic	VO$_2$ peak (mL/kg/min)	0.2 (IQR –0.6 to 1.5)	0.1 (IQR –1.0 to 1.2)	–	$p = 0.82$ Median (IQR) change
Servantes (2012) (52)	Aerobic and resistance	VO$_2$ peak (mL/kg/min)	20.9 (SD 4.2)	12.8 (SD 3.2)	d = 2.17	$p = 0.951$ Post-intervention (between group p-value)
McNamara (2013) (50)	Aerobic and resistance	ESWD (m)	land 117 (95% CI –3 to 236) water 321 (95% CI 123–518)	–50 (95% CI –240 to 140)	land d = 0.69 water d = 1.21	land vs Con: $p = 0.456$ water vs Con: $p = 0.006$* Mean change (between group p-values)
McNamara (2013) (50)	Aerobic and resistance	ISWD (m)	land 13 (95% CI –16 to 43) water 49 (95% CI 26–73)	–1 (95% CI –24 to 22)	land d = 0.28 water d = 1.27	land vs Con: $p = 0.542$ water vs Con: $p = 0.005$* Mean change (between group p-values)
Health-related quality of life						
Bernocchi (2018) (47)	Aerobic and resistance	MLHFQ	–10.5 (95% CI –14.2 to –6.8)	–0.44 (95% CI –4.0 to 4.0)	d = 0.73	$p = 0.0007$* Mean change (between group p-value)
Servantes (2012) (52)	Aerobic and resistance	MLHFQ	25.1 (SD 16.5)	51.0 (SD 16.8)	d = 1.56	$p = 0.671$ Post-intervention (between group p-value)
Beaudoin (2017) (46)	Aerobic and resistance	QCFQR: physical functioning (%)	80.2 (SD 16.78)	81.93 (SD 16.82)	d = 0.10	ns Post-intervention
Beaudoin (2017) (46)	Aerobic and resistance	QCFQR: vitality (%)	58.33 (SD 19.2)	54.18 (SD 20.91)	d = 0.21	ns Post-intervention
Beaudoin (2017) (46)	Aerobic and resistance	QCFQR: emotional state (%)	81.66 (SD 12.73)	83.33 (SD 15.06)	d = 0.12	ns Post-intervention
Beaudoin (2017) (46)	Aerobic and resistance	QCFQR: eating disturbance (%)	98.61 (SD 3.92)	100 (SD 0)	d = unable to calc	ns Post-intervention
Beaudoin (2017) (46)	Aerobic and resistance	QCFQR: treatment burden (%)	65.29 (SD 28.14)	68.52 (SD 21.59)	d = 0.13	ns Post-intervention
Beaudoin (2017) (46)	Aerobic and resistance	QCFQR: health perception (%)	58.34 (SD 23.59)	74.1 (SD 15.17)	d = 0.79	ns Post-intervention
Beaudoin (2017) (46)	Aerobic and resistance	QCFQR: social limitations (%)	75.28 (SD 13.02)	72.22 (SD 18.24)	d = 0.19	ns Post-intervention
Beaudoin (2017) (46)	Aerobic and resistance	QCFQR: body image (%)	84.74 (SD 8.26)	81.5 (SD 18.13)	d = 0.23	ns Post-intervention
Beaudoin (2017) (46)	Aerobic and resistance	QCFQR: role limitations (%)	83.33 (SD 25.2)	84.73 (SD 21.99)	d = 0.06	ns Post-intervention
Beaudoin (2017) (46)	Aerobic and resistance	QCFQR: weight problems (%)	87.5 (SD 24.81)	83.33 (SD 40.82)	d = 0.12	ns Post-intervention
Beaudoin (2017) (46)	Aerobic and resistance	QCFQR: respiratory symptoms (%)	62.5 (SD 14.47)	65.75 (SD 8.17)	d = 0.28	ns Post-intervention
Beaudoin (2017) (46)	Aerobic and resistance	QCFQR: digestive symptoms (%)	84.74 (SD 10.17)	69.53 (SD 14.79)	d = 1.20	ns Post-intervention

(Continued)

Table II. (*contd.*)

Study	Intervention (exercise type)	Outcome	Results (intervention)	Results (control)	Effect size	Notes
Bernocchi (2018) (47)	Aerobic and resistance	CAT	5.3 (95% CI –6.9 to 3.7)	1.6 (95% CI –0.4 to 3.5)	d = 1.17	*p* = 0.0001* Mean change (between group *p*-value)
McNamara (2013) (50)	Aerobic and resistance	CRDQ -dyspnoea	land vs Con: 1.6 (95% CI –0.8 to 4.0) water vs Con: 3.3 (95% CI 0.9–5.6)	NA	–	land vs Con: *p* = 0.193 water vs Con: *p* = 0.007* Mean difference (between group *p*-values)
McNamara (2013) (50)	Aerobic and resistance	CRDQ - fatigue	land vs Con: 1.6 (95% CI –0.7 to 3.9) water vs Con: 4.7 (95% CI 2.4–7.0)	NA	–	land vs Con: *p* = 0.163 water vs Con: *p* < 0.001* Mean difference (between group *p*-values)
McNamara (2013) (50)	Aerobic and resistance	CRDQ - emotion	land vs Con: 0.1 (95% CI –2.8 to 3.1) water vs Con: 3.1 (95% CI 0.1–6.1)	NA	–	land vs Con: *p* = 0.921 water vs Con: *p* = 0.046* Mean difference (between group *p*-values)
McNamara (2013) (50)	Aerobic and resistance	CRDQ - mastery	land vs Con: 0.8 (95% CI –1.2 to 2.8) water vs Con: 1.9 (95% CI –0.2 to 4.0)	NA	–	land vs Con: *p* = 0.414 water vs Con: *p* = 0.070 Mean difference (between group *p*-values)
Ambrosy (2018) (45)	Aerobic	KCCQ	HF+CKD: 3 months: –1 (95% CI –2 to 0) HF+CKD: 12 months: –3 (95% CI –4 to –1)	NR	–	3 months: *p* = 0.06 12 months: *p* < 0.01* Mean difference within groups
Mentz (2013) (51)	Aerobic	KCCQ	2.1 (IQR –4.9 to 13.3)	3.9 (IQR –5.2 to 13.5)	–	*p* = 0.52 Median (IQR) change
Ambrosy (2018) (45)	Aerobic	EQ-5D	HF+CKD: 3 months: –1 (95% CI –3 to 0) HF+CKD: 12 months: –3 (95% CI –5 to –1)	NR	–	3 months: *p* = 0.09 12 months: *p* < 0.01* Mean difference within groups
Chiang (2020) (55)	Aerobic	SF-36	PCS 52.8 (SD 6.3) MCS 48.6 (SD 7.7)	PCS 49.4 (SD 7.4) MCS 51.4 (SD 6.6)	d = 0.49 d = 0.39	*p* = 0.03 *p* = 0.0.03 Post-intervention (between groups *p*-value)

Cardiometabolic

Study	Intervention (exercise type)	Outcome	Results (intervention)	Results (control)	Effect size	Notes
Abd El-Kader (2013) (44) Hsu (2021) (56) Lo (2021) (57)	Aerobic Resistance Aerobic	BMI (kg/m²) BMI (kg/m²) BMI (kg/m²)	27.15 (SD 2.38) Ex: 30.7 (SD 2.6) 66.5 (SD10.9)	32.14 (SD 2.16) 29.5 (SD 2.6) MI: 70.3 (SD 19.2) Con: 68.8 (SD 6.6)	d = 2.20 Ex vs Con: d = 0.46 d = 0.26	*p* < 0.05* Post-intervention (between group *p*-value) *p* < 0.001 Post-intervention (between group *p*-value) Int vs Con: *p* = 0.03 Int vs MI: *p* = NR Post-intervention (between group *p*-value)
Byrkjeland (2015) (48)	Aerobic and resistance	HOMA2-IR	1.10 (IQR 0.80–1.70)	1.25 (IQR 0.80–1.68)	NA	*p* = 0.31 Post-intervention: median (IQR)
Byrkjeland (2015) (48)	Aerobic and resistance	HbA1c (%)	7.2 (IQR 6.6–7.8)	7.4 (IQR 6.5–8.2)	–	*p* = 0.24 Post-intervention: median (IQR)
Sridhar (2010) (53)	Aerobic	HbA1c (%)	7.44 (SD 0.44)	9.84 (SD 0.53)	d = 4.93	*p* < 0.01* Post-intervention
Sridhar (2010) (53)	Aerobic	Systolic BP (mmHg)	135.53 (SD 3.54)	146.03 (SD 4.28)	d = 2.67	*p* < 0.05* Post-intervention
Sridhar (2010) (53)	Aerobic	Diastolic BP (mmHg)	82.82 (SD 1.07)	88.15 (SD 3.68)	d = 1.97	*p* < 0.05* Post-intervention
Byrkjeland (2015) (48)	Aerobic and resistance	Insulin (mmol/L)	49 (IQR 32–78)	48 (IQR 33–78)	NA	*p* = 0.56 Post-intervention: median (IQR)
Byrkjeland (2015) (48)	Aerobic and resistance	Glucose (mmol/L)	8.0 (IQR 6.7–9.3)	7.8 (IQR 6.7–9.0)	–	*p* = 0.63 Post-intervention: median (IQR)
Beaudoin (2017) (46)	Aerobic and resistance	CRP (mg/L)	2.1 (SD 1.37)	6.57 (SD 7.0)	d = 0.89	ns Post-intervention
Sridhar (2010) (53)	Aerobic	HR variability (bpm)	15.71 (SD 0.61)	13.02 (SD 0.54)	d = 4.67	ns Post-intervention

(Continued)

Table II. (*contd.*)

Study	Intervention (exercise type)	Outcome	Results (intervention)	Results (control)	Effect size	Notes
Hsu (2021) (56)	Resistance	Total cholesterol (mg/dL)	Ex: 165.8 (SD 26.9) Ex+Diet: 151.5 (SD 18.0)	160.1 (SD 20.2)	Ex vs Con: d=0.24 Ex+diet vs Con: d=0.45	Ex vs Con: $p < 0.001$ Ex+Diet vs Con: p=NR Post-intervention (between group p-value)
Mental health						
Abdelbassett (2019) (54)	Aerobic	PHQ-9	LMIE 3.65 (SD 1.2) MICE 3.1 (SD 1.2)	8.5 (SD 2.1)	LMIE vs Con: d=2.84 MICE vs Con: d=3.16	$p<0.001$ Post-intervention (between groups p-value)
McNamara (2013) (50)	Aerobic and resistance	HADS - anxiety	land vs Con: 0 (95% CI −2 to 2) water vs Con: −1 (95% CI −4 to 1)	NA	–	land vs Con: p=0.990 water vs Con: p=0.222 Mean difference (between group p-values)
McNamara (2013) (50)	Aerobic and resistance	HADS - depression	land vs Con: 0 (95% CI −2 to 1) water vs Con: −1 (95% CI −3 to 0)	NA	–	land vs Con: p=0.544 water vs Con: p=0.068 Mean difference (between group p-values)
Symptom score						
Bernocchi (2018) (47)	Aerobic and resistance	MRC	−0.17 (95% CI −0.3 to −0.02)	0.07 (95% CI −0.1 to 0.3)	d=0.37	p=0.05* Mean change (between group p-value)
Health behaviours						
Banks (2015) (34)	Aerobic	Exercise adherence (%)	HF+DM: 35.2%	NA		p=0.02*
Beaudoin (2017) (46)	Aerobic and resistance	Physical activity questionnaire (%)	76.27 (SD 8.47)	59.08 (SD 17.65)	d=1.24	ns Post-intervention
Chiang (2020) (55)	Aerobic	Total Physical Activity (METS-min/wk)	2898 (SD 2213)	1411 (SD 773)	d=0.89	p=0.003 Post-intervention (between group p-value)
Lo (2021) (57)	Aerobic	Total Physical Activity (Mets-min/wk)	1162 (SD 624)	MI: 1919 (SD 804) Con: 1068 (SD 781)	Int vs MI: d=1.05 Int vs Con: d=0.13	Int vs Con: p=0.011 Int vs MI: p=NR Post-intervention (between groups p-value)
Beaudoin (2017) (46)	Aerobic and resistance	Steps (no./day)	8644 (SD 1900)	8848 (SD 2730)	d=0.09	ns Post-intervention
Adverse events						
Byrkjeland (2015) (48)	Aerobic and resistance	No. adverse event (all medical events)	45	31	–	p=0.032*

Mean (SD) unless otherwise stated; *refers to whether study reported statistically significant improvement in this outcome; ns: not stated *p*-value; NR: no results; NA: not applicable; –: unable to calculate d.

6MWD: 6-min walk distance; HF: heart failure; CKD: chronic kidney disease; 95% CI: 95% confidence interval; Con: control; IQR: interquartile range; VO_2 peak: oxygen consumption; mL/kg/min: millilitres/kilogram/min; SD: standard deviation; ESWD: Endurance Shuttle Walk Distance; IWSD: Incremental Shuttle Walk Distance; MLHFQ: Minnesota Living with Heart Failure Questionnaire; QCFQR: Quality Of Life Cystic Fibrosis Questionnaire-revised; CAT: Chronic Obstructive Pulmonary Disease Assessment Test; CRDQ: Chronic Respiratory Disease Questionnaire; KCCQ: Kansas City cardiomyopathy questionnaire; BMI: body mass index; HOMA2-IR: Homeostasis Model Assessment2-Insulin Resistance index; HbA1c: haemoglobin A1c; BP: blood pressure; mmHg: millimetres of mercury; CRP: C-reactive protein; HR: heart rate; bpm: beats per min; HADS: Hospital Anxiety and Depression Scale; MRC: Medical Research Council dyspnoea scale; no.: number.
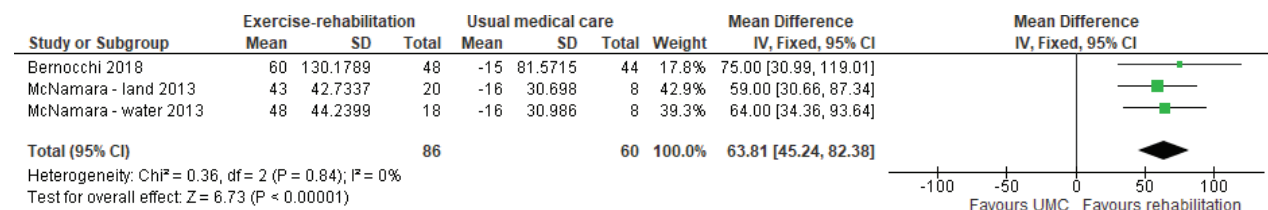
Study or Subgroup	Exercise-rehabilitation Mean	SD	Total	Usual medical care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bernocchi 2018	60	130.1789	48	-15	81.5715	44	17.8%	75.00 [30.99, 119.01]
McNamara - land 2013	43	42.7337	20	-16	30.698	8	42.9%	59.00 [30.66, 87.34]
McNamara - water 2013	48	44.2399	18	-16	30.986	8	39.3%	64.00 [34.36, 93.64]
Total (95% CI)			86			60	100.0%	63.81 [45.24, 82.38]

Heterogeneity: Chi² = 0.36, df = 2 (P = 0.84); I² = 0%
Test for overall effect: Z = 6.73 (P < 0.00001)

Fig. 2. Effect of exercise rehabilitation vs usual medical care (UMC) on 6-min walk distance (6MWD); reported in m. SD: standard deviation; IV: inverse variance; CI: confidence interval; df: degrees of freedom.

outcomes was found in the water-based rehabilitation group compared with UMC, with large ESs of 1.21 and 1.27, respectively. There was a moderate ES for ESWD and a small ES for ISWD in favour of land-based rehabilitation; however, these results were not statistically significant.

Subgroup analysis.
- *Duration.* One study (50) with a rehabilitation duration of 4–8 weeks had an ES for 6MWD of 1.76 (land-based) and 1.86 (water-based), whereas 1 study (47) with a duration of greater than 8 weeks (16 weeks) had an ES of 0.69. All 4 studies (7 reports)
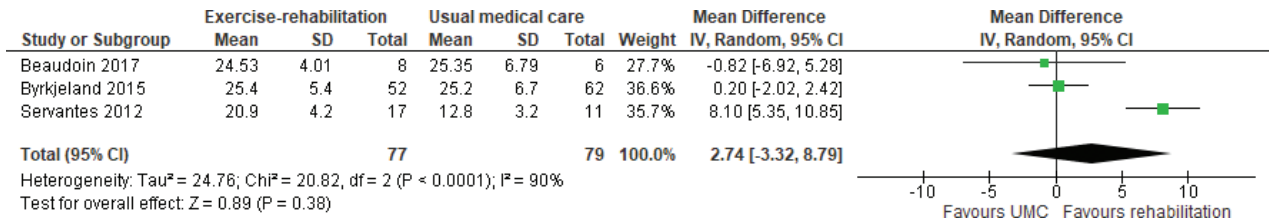
Study or Subgroup	Exercise-rehabilitation			Usual medical care			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Beaudoin 2017	24.53	4.01	8	25.35	6.79	6	27.7%	-0.82 [-6.92, 5.28]
Byrkjeland 2015	25.4	5.4	52	25.2	6.7	62	36.6%	0.20 [-2.02, 2.42]
Servantes 2012	20.9	4.2	17	12.8	3.2	11	35.7%	8.10 [5.35, 10.85]
Total (95% CI)			**77**			**79**	**100.0%**	**2.74 [-3.32, 8.79]**

Heterogeneity: Tau^2 = 24.76; Chi^2 = 20.82, df = 2 (P < 0.0001); I^2 = 90%
Test for overall effect: Z = 0.89 (P = 0.38)

Fig. 3. Effect of exercise rehabilitation vs usual medical care (UMC) on peak oxygen consumption (VO$_2$) peak (mL/kg/min). SD: standard deviation; IV: inverse variance; CI: confidence interval; df: degrees of freedom.

reporting VO$_2$ peak (34, 45, 46, 48, 49, 51, 52) had durations of greater than 8 weeks, and thus subgroup analysis for duration was not possible.

- *Number of coexisting conditions*. Insufficient data were available to determine whether effects on exercise capacity varied according to the number of coexisting conditions.

Sensitivity analysis. The effect of adding education, psychological support or motivational interviewing to an exercise programme varied across studies and outcomes. Studies of exercise only had ESs of 1.76–1.86 for 6MWD (50) and 0.03–0.44 for VO$_2$ peak (46, 47, 55). Studies of exercise plus education, psychological support or motivational interviewing has ESs of 0.69 for 6MWD (47) and 0.26–2.17 for VO$_2$ peak (52, 57).

Health-related quality of life. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) was reported in 2 studies (47, 52); both showed large ESs of 0.73 and 1.56, favouring exercise rehabilitation. One study (2 reports) (45, 51) showed a significant improvement in the Kansas City cardiomyopathy questionnaire following exercise rehabilitation (45). One study (46) applied the quality of life (QOL) cystic fibrosis questionnaire-revised, with no significant change in any of the 12 domains between exercise rehabilitation and UMC. One study (47) demonstrated significant improvement in the COPD assessment test in favour of exercise rehabilitation (ES of 1.17). One study (50) applied the chronic respiratory disease questionnaire (CRDQ); the water-based rehabilitation group compared with UMC showed significant difference in change for 3 out of 4 domains (dyspnoea, fatigue and emotion) in favour of exercise rehabilitation; however, it was not possible to calculate ESs. One study (55) applied the Short Form-26, with exercise training improving both the physical and mental composite score, with ESs of 0.49 and 0.39, respectively.

Subgroup analysis.
- *Duration*. Insufficient data were available to determine whether duration of rehabilitation impacted on QOL for the MLHFQ.

- *Number of coexisting conditions*. Insufficient data were available to determine whether effects on QOL varied according to the number of coexisting conditions.

Sensitivity analysis. Insufficient data were available to determine whether the components of rehabilitation impacted on QOL for the MLHFQ.

Cardiometabolic. BMI was significantly reduced with exercise rehabilitation (ES ranging from 0.26 to 2.20) (44, 57). Two studies (48, 53) reported improvement in haemoglobin A1c (HbA1c), with 1 (53) study showing a large ES (4.93) in favour of exercise rehabilitation. The other study (48) showed a non-significant reduction in HbA1c following exercise rehabilitation, and ES could not be calculated. One study (53) reported improvement in systolic blood pressure (BP) and diastolic BP, with ESs of 2.67 and 1.97, respectively, favouring exercise rehabilitation. One study (46) reported C-reactive protein (CRP); there was no significant difference in the change in CRP level between groups, despite a large ES of 0.89 favouring exercise rehabilitation. One study (48) reported homeostasis model assessment-insulin resistance-index (HOMA-IR), insulin and glucose, with no significant differences in change between groups for these outcomes (ESs could not be calculated). One study (53) reported heart rate (HR) variability, with a large ES (4.67) favouring exercise rehabilitation; however, this was not statistically significant.

Subgroup analysis.
- *Duration:* Insufficient data were available to determine whether duration of rehabilitation impacted on HbA1c.
- *Number of coexisting conditions*. Insufficient data were available to determine whether effects on cardiometabolic outcomes varied according to the number of coexisting conditions.

Sensitivity analysis. Insufficient data were available to determine whether the components of rehabilitation impacted on HbA1c.

Mental health. The Hospital Anxiety and Depression Scale (HADS) was reported in 1 study (50), with no significant differences between groups for either symptom. Exercise training at either a low to moderate

intensity or moderate intensity improved depression according to the Patient Health Questionnaire (54).

Symptoms. Dyspnoea, measured by the Medical Research Council dyspnoea scale (MRC), was significantly reduced in 1 study (47) following exercise rehabilitation, with a moderate ES of 0.37.

Health behaviours. One study (46) reported steps and physical activity, with no significant differences found for either outcome. The step count showed a small ES of 0.09, while the physical activity questionnaire had a large ES of 1.24, favouring exercise rehabilitation. Two studies (55, 57) reported improvements in total physical activity with exercise training compared with control, with ESs of 0.13–0.89.

Adverse events. Only 1 of the 9 included studies reported adverse events (48); however, the study was limited by a lack of detail reporting the types and relative severity of these events. Adverse events were defined as all medical events (including cardiovascular events (worsening stable angina/heart failure, unstable angina, acute myocardial infarction, stroke, cardiac arrest), hypoglycaemia and musculoskeletal events (skin ulcers, lower back pain, tendinitis, joint pain and fractures)). The incidence of serious events (primarily cardiovascular events (type not specified)) was equally distributed between the rehabilitation and control groups (11 vs 12), and no cardiovascular events occurred in close relation to the exercise sessions or CPET (48). The rehabilitation group did have a higher reported incidence of all medical events (45 vs 31, $p = 0.03$), which appeared to be musculoskeletal in nature (21 vs 11, $p = 0.077$), although the type and severity were not reported.

Exercise rehabilitation vs other intervention
Seven studies (9 reports) reported exercise rehabilitation vs other interventions (36, 37, 42, 56–61), including diet and sham exercise (59, 60), phone call only (36, 37), diet (56, 58), usual physical activity (61), motivational interviewing (57) and mind-body education (42) interventions. The findings for studies are outlined in Table III.

Exercise capacity. One study reported VO$_2$ peak (59) and demonstrated significant improvement post-intervention for aerobic and resistance exercise with diet compared with sham-exercise (breathing and stretches) with diet.

Health-related quality of life. The asthma QOL questionnaire was reported in 1 study (59), demonstrating better HRQoL post-intervention for aerobic and resistance exercise with diet compared with sham-exercise (breathing and stretches) with diet.

Cardiometabolic. BMI was reported in 4 studies (5 reports) (56–60). Meta-analysis showed a WMD of –2.92 kg/m^2 (95% CI –6.26 to 0.43) in favour of exercise rehabilitation and diet compared with sham exercise (breathing and stretches) and diet or diet only, but heterogeneity was high (Fig. 4). Diet alone resulted in a greater reduction in BMI and total cholesterol levels compared with resistance training (56). There was no difference in the effects of motivational interviewing and aerobic training (57). One study (61) reported HbA1c with no significant differences and a small ES of 0.01, comparing aerobic and resistance exercise rehabilitation with usual physical activity. One study (37) found no significant differences in CRP between aerobic exercise rehabilitation with a weekly phone call or a weekly phone call only. One study (58) reported homeostasis model assessment 2-insulin resistance-index (HOMA2-IR) and showed a large ES (1.26) in favour of exercise rehabilitation with low calorie diet, compared with low calorie diet alone. Total cholesterol, triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) were reported in 1 study (37) and there were no significant differences found for any of these outcomes, comparing aerobic and resistance exercise rehabilitation with usual physical activity.

Subgroup analysis.
- *Duration:* Insufficient data were available to determine whether duration of rehabilitation impacted on BMI.
- *Number of coexisting conditions:* Insufficient data were available to determine whether effects on cardiometabolic outcomes varied according to the number of coexisting conditions.

Sensitivity analysis. A study of exercise and diet had an ES of 1.51 for BMI, favouring exercise rehabilitation (58). A study of exercise and diet plus education or psychological support had an ES of 1.33 for BMI, favouring exercise rehabilitation and diet (60) compared with sham exercise (breathing and stretches) and diet.

Mental health. One study (60) reported significant reduction in depression measured on HADS, in favour of aerobic and resistance exercise rehabilitation with diet compared with sham-exercise (breathing and stretches) with diet. One study (36) reported depressive symptoms; however, the tool used was not stated and no significant difference was demonstrated, despite a large ES of 3.73 favouring exercise rehabilitation and weekly phone call compared with weekly phone call only. The structured interview for the Hamilton depression rating scale was reported in 1 study (42). No data were provided, but it stated there were statistically significant reductions in scores that demonstrated improvement for both the intervention (tai chi) and control (mind-body education) groups at the end of the intervention (42).

Symptoms. The asthma control questionnaire was reported in 1 study (59). There was improved asthma

Table III. Outcomes of exercise-rehabilitation vs other intervention

Study	Intervention	Outcome	Results (intervention)	Results (control)	Effect size (between groups)	Notes
Exercise capacity						
Freitas (2017) (59)	Int = aerobic and resistance exercise; Com = sham exercise (breathing and stretches)	VO$_2$ peak (mL/kg/min)	18.8 (IQR 16.8–21)	15 (IQR 13–17.5)	–	*p* < 0.001* Post-intervention: median (IQR)
Health-related quality of life						
Freitas (2017) (59)	Int = aerobic and resistance exercise; Com = sham exercise (breathing and stretches)	AQQ	4.7 (IQR 4.1–6.3)	3.8 (IQR 3.1–4.9)	–	*p* = 0.038* Post-intervention: median (IQR)
Cardiometabolic						
Al-Jiffri (2013) (58)	Int = aerobic exercise; Com = diet only (no exercise)	BMI (kg/m²)	27.25 (SD 2.68)	32.64 (SD 4.26)	d = 1.51	*p* = 0.0088* Post-intervention (between group *p*-value)
Freitas (2018) (60)	Int = aerobic and resistance exercise; Com = sham exercise (breathing and stretches)	BMI (kg/m²)	–2.6 (SD 1.3)	–1.0 (SD 1.1)	d = 1.33	ns Mean change
Freitas (2017) (58)	Int = aerobic and resistance exercise; Com = sham exercise (breathing and stretches)	BMI (kg/m²)	–2.7 (IQR –3.3 to –1.8)	–1.1 (IQR –1.8 to –0.4)	–	ns Post-intervention: median (IQR)
Hsu (2021) (56)	Int = resistance exercise; Com: diet advice	BMI (kg/m²)	30.7 (SD 2.6)	29.5 (SD 2.6)	d = 0.46	*p* < 0.001 Post-intervention (between group *p*-value
Lo (2021) (57)	Int = aerobic exercise; Com = motivational interviewing	BMI (kg/m²)	25.9 (SD 4.8)	24.2 (SD7.9)	d = 0.24	*p* = NR
Al-Jiffri (2013) (58)	Int = aerobic exercise; Com = diet only (no exercise)	HOMA-IR	2.64 (SD 1.37)	5.13 (SD 2.44)	d = 1.26	*p* = 0.0091* Post-intervention (between group *p*-value)
Halvari (2017) (61)	Int = aerobic and resistance exercise; Com = usual physical activity	HbA1c (%)	7.57 (SD 1.41)	7.56 (SD 1.23)	d = 0.01	ns Post-intervention
Collins (2011) (36)	Int = aerobic exercise; Com = phone call only (no exercise)	Total cholesterol (mmol/L)	–9.77 (SE 6.85)	NR	–	ns Change in intervention minus change in control
Collins (2011) (36)	Int = aerobic exercise; Com = phone call only (no exercise)	LDL (mmol/L)	–1.67 (SE 5.83)	NR	–	ns Change in intervention minus change in control
Collins (2011) (36)	Int = aerobic exercise; Com = phone call only (no exercise)	HDL (mmol/L)	–3.61 (SE 2.09)	NR	–	ns Change in intervention minus change in control
Collins (2011) (36)	Int = aerobic exercise; Com = phone call only (no exercise)	Triglycerides (mmol/L)	10.9 (SE 34.53)	NR	–	ns Change in intervention minus change in control
Collins (2011) (36)	Int = aerobic exercise; Com = phone call only (no exercise)	CRP (mg/L)	0.19 (SE 1.41)	NR	–	*p* > 0.2 Change in intervention minus change in control
Mental health						
Collins (2010) (36)	Int = aerobic exercise; Com = phone call only (no exercise)	Depressive symptoms	3.2 (SD 1.5)	–2.4 (SD 1.5)	d = 3.73	ns Mean change
Freitas (2018) (60)	Int = aerobic and resistance exercise; Com = sham exercise (breathing and stretches)	HADS	Anxiety: –4.0 (SD 4.6); Depression: –4.6 (SD 4.2)	Anxiety: –1.0 (SD 3.7); Depression: –0.4 (SD 3.3)	Anxiety: d = 0.72; Depression: d = 1.11	Anxiety: *p* = 0.63 Depression: *p* < 0.01* Mean change
Symptom score						
Freitas (2017) (59)	Int = aerobic and resistance exercise; Com = sham exercise (breathing and stretches)	ACQ	1.1 (IQR 0.4–1.6)	1.7 (IQR 1.4–2.0)	–	*p* = 0.003* Median (IQR)

Mean (SD) unless otherwise stated; *refers to whether study reported statistically significant improvement in this outcome; ns: not stated *p*-value; NR: no results; –: unable to calculate d.

Int: intervention; Com: comparison; VO$_2$ peak: oxygen consumption; IQR: interquartile range; AQQ: Asthma Quality of Life Questionnaire; BMI: body mass index; SD: standard deviation; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance index; HbA1c: haemoglobin A1c; SE: standard error; LDL: low-density lipoprotein; HDL: high-density lipoprotein; CRP: C-reactive protein; HADS: Hospital Anxiety and Depression Scale; ACQ: Asthma Control Questionnaire.

control in those who undertook aerobic and resistance exercise rehabilitation with diet compared with sham-exercise (breathing and stretches) with diet.

Exercise rehabilitation in cohort/quasi-experimental studies

Twenty studies (21 reports) reported the effects of exercise rehabilitation using cohort or quasi-experimental designs (35, 39–41, 43, 58–73) (Table IV).

Exercise capacity. Nineteen studies (20 reports) (35, 40, 41, 43, 62–77) reported measures of exercise capacity with clinically significant improvements following exercise rehabilitation in 6MWD (35, 67, 68), VO_2 peak (62, 64, 66, 70, 75, 76), metabolic equivalents (41, 66, 77), HR recovery (71), maximal symptom limited incremental cycle ergometer time (73) and peak HR (71).

Health-related quality of life. Eight studies (9 reports) (43, 62–65, 68, 69, 73, 74) reported measures of HRQoL with clinically significant improvements following exercise rehabilitation in Short Form-36 (62,64) and diabetes diabetes quality of life (QOL) measure questionnaire (64).

Cardiometabolic. Eight studies (39, 41, 62, 64, 66, 67, 70, 72) reported cardiometabolic measures with clinically significant improvements following exercise rehabilitation in BMI (62, 66, 67), HbA1c (39, 64), systolic BP (62), diastolic BP (41), CRP (62), insulin (62), glucose (41), total cholesterol (41,62), triglycerides (39, 41, 62), HDL (41, 62, 64) and LDL (41).

Mental health. Four studies (41, 62, 64, 69) reported measures of mental health with clinically significant improvements following exercise rehabilitation in the Beck Depression Index (41, 62, 64).

Symptoms. Three studies (62, 65, 69) reported symptom measures with no clinically significant improvements following exercise rehabilitation.

Health behaviours. One study (64) reported health behaviour measures with clinically significant improvements following exercise rehabilitation in the chronic illness survey.

Adverse events. One study (35) reported an adverse event outcome, defined as an accident or complication, but reported that this did not occur during the intervention.

DISCUSSION

This is the first systematic review of studies of exercise rehabilitation in people with multimorbidity. Compared with UMC, improvement in exercise capacity (peak exercise and selected measures of functional exercise tolerance), HRQoL and a mix of cardiometabolic outcomes were evident for exercise rehabilitation. These findings were consistent with outcomes from single-disease rehabilitation programmes, which included individuals with multimorbidities (78, 79), with noted improvements in BP and other cardiometabolic parameters. This suggests that either disease-specific or multimorbidity exercise rehabilitation programmes may be suitable for people with multimorbidities, in order to target improvements in these outcomes. A range of ES were identified for the included studies (range 0.03–4.93) which may be attributable to the type of programme applied (e.g. water-based vs land-based) (50) or difference in exercise prescription across studies. With the small number of included studies, it is not possible to establish the contribution of rehabilitation duration, adjuncts to exercise or the role of the number of coexisting conditions for exercise rehabilitation compared with UMC.

The majority of studies did not report on adverse events during rehabilitation. While a single study reported a greater number of medical events in the rehabilitation group (48), there was no difference in serious cardiovascular events, none occurred in proximity to rehabilitation classes or testing, and most were classified as musculoskeletal, with no reporting on the frequency of severe events (i.e. fractures). It is plausible that people participating in an exercise programme may encounter musculoskeletal events (80, 81), and the likelihood of this may be increased in the multimorbidity population with a history of sedentary behaviour. The absence of cardiovascular events in those with multimorbidity during exercise rehabilitation is reassuring, particularly as this population is likely to have several cardiovascular risk factors. Recently, the concerns regarding providing a safe exercise programme for the multimorbidity population have been illustrated (82, 83). We recommend that future studies report on adverse events, and specify the type, severity and timing of these events and their temporal relationship to the intervention.
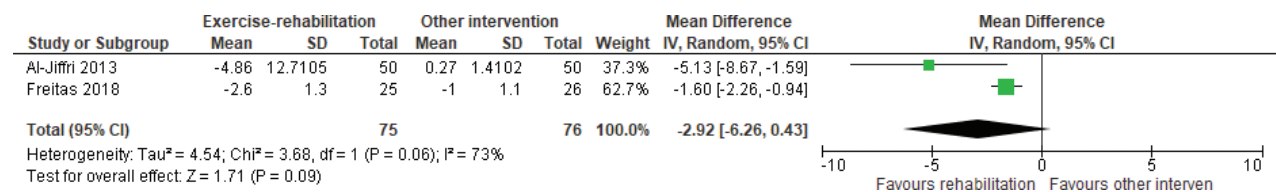
Study or Subgroup	Exercise-rehabilitation			Other intervention			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Al-Jiffri 2013	-4.86	12.7105	50	0.27	1.4102	50	37.3%	-5.13 [-8.67, -1.59]
Freitas 2018	-2.6	1.3	25	-1	1.1	26	62.7%	-1.60 [-2.26, -0.94]
Total (95% CI)			**75**			**76**	**100.0%**	**-2.92 [-6.26, 0.43]**

Heterogeneity: Tau² = 4.54; Chi² = 3.68, df = 1 (P = 0.06); I² = 73%
Test for overall effect: Z = 1.71 (P = 0.09)

Fig. 4. Effect of exercise rehabilitation vs other intervention on body mass index (BMI); reported in kg/m^2. SD: standard deviation; IV: inverse variance; CI: confidence interval; df: degrees of freedom.

Table IV. Outcomes of exercise-rehabilitation in cohort/quasi-experimental studies

Study	Intervention (exercise type)	Outcome	Subgroup	Results	Notes
Exercise capacity					
Castro[+] (2015) (35)	Aerobic and resistance	6MWD (m)	n/a	↑50	*p*<0.01*
Crisafulli[+] (2010) (63)	Peripheral limb training	6MWD (m)	1 comorbidity	45%	ns
			≥ 2 comorbidities	44%	no. of participants who achieved MCID
Hassan[+] (2016) (65)	Aerobic and resistance	6MWD (m)	1 comorbidity	↑173	ns
			> 1 comorbidity	↑149	
Listerman[+] (2011) (67)	Aerobic and resistance	6MWD (m)	1–2 comorbidities	↑77[¥]	ns
			> 2 comorbidities	↑61[¥]	Participants <56 years
Listerman[+] (2011) (67)	Aerobic and resistance	6MWD (m)	1–2 comorbidities	↑71[¥]	ns
			> 2 comorbidities	↑74[¥]	Participants 56–65 years
Listerman[+] (2011) (67)	Aerobic and resistance	6MWD (m)	1–2 comorbidities	↑56[¥]	ns*
			> 2 comorbidities	↑61[¥]	Participants >65 years
Mesquita[+] (2015) (68)	Details not provided	6MWD (m)	All participants	↑30	ns*
Naz[+] (2019) (69)	Aerobic and resistance	6MWD (m)	CCI 1	↑40	ns
			CCI 2	↑40	
			CCI ≥ 3	↑50	
Tunsupon[a] (2017)[+] (73)	Aerobic and resistance	6MWD (m)	1 comorbidity	↑44	ns
			≥ 2 comorbidities	↑28	
Tunsupon[b] (2017)[+] (74)	Aerobic and resistance	6MWD (m)	Obese	↑44	ns
			Morbidly obese	↑42	
Zwerink[+] (2010) (43)	Aerobic and resistance	6MWD (m)	n/a	↑2	ns
Barnes[+] (2009) (62)	Aerobic and resistance	VO$_2$ peak (mL/kg/min)	n/a	↑3.8	*p*=0.003*
de Groot[#] (2012) (64)	Aerobic and resistance	VO$_2$ peak (mL/kg/min)	n/a	↑1.1	*p*<0.01*
Khadanga[+] (2016) (66)	Aerobic and resistance	VO$_2$ peak (mL/kg/min)	Diabetes	Insufficient data	
			Insulin resistance	Insufficient data	
Nonoyama[+] (2016) (70)	Aerobic and resistance	VO$_2$ peak (mL/kg/min)	Respiratory comorbidity	↑1.2	ns*
			Non-respiratory comorbidity	↑2.6	
Takaya[+] (2014) (72)	Aerobic	VO$_2$ peak (mL/kg/min)	AMI+CKD	↑2.3	ns
Verges[+] (2004) (75)	Aerobic	VO$_2$ peak (mL/kg/min)	ACE+DM	↑2.4	ns*
Wang[+] (2013) (76)	Aerobic	VO$_2$ peak (mL/kg/min)	HF+A	↑3.6	ns*
Hassan[+] (2016) (65)	Aerobic and resistance	VO$_2$ max (mL/kg/min)	1 comorbidity	↑22.72	ns
			> 1 comorbidity	↑24.25	
Khadanga[+] (2016) (66)	Aerobic and resistance	Peak METS	Diabetes	Insufficient data	
			Insulin resistance	Insufficient data	
Martin[+] (2016) (40)	Details not provided	METs	IHD+PAD	↑0.76	ns
Woodard[+] (1994) (77)	Aerobic	METs	CVD+arthritis	↑0.92	*p*=0.005*
Zwerink[+] (2010) (43)	Aerobic and resistance	ISWD (m)	n/a	↑18	ns
Mesquita[+] (2015) (68)	Details not provided	CWRT (seconds)	All participants	↑202	ns*
Soleimani[+] (2009) (71)	Aerobic	Resting HR (bpm)	CAD+DM	↓6	*p*=0.852 Men
Soleimani[+] (2009) (71)	Aerobic	Resting HR (bpm)	CAD+DM	↓14	*p*=0.699 Women <50 years
Soleimani[+] (2009) (71)	Aerobic	Resting HR (bpm)	CAD+DM	↓10	*p*=0.753 Women ≥50 years
Soleimani[+] (2009) (71)	Aerobic	Peak HR (bpm)	CAD+DM	↑24	*p*=0.019* Men
Soleimani[+] (2009) (71)	Aerobic	Peak HR (bpm)	CAD+DM	0	*p*=0.012* Women <50 years
Soleimani[+] (2009) (71)	Aerobic	Peak HR (bpm)	CAD+DM	↑5	*p*=0.529 Women ≥50 years
Soleimani[+] (2009) (71)	Aerobic	Post-exercise HR (bpm)	CAD+DM	↑5	*p*=0.471 Men
Soleimani[+] (2009) (71)	Aerobic	Post-exercise HR (bpm)	CAD+DM	↑1	*p*=0.606 Women <50 years
Soleimani[+] (2009) (71)	Aerobic	Post-exercise HR (bpm)	CAD+DM	↓7	*p*=0.902 Women ≥50 years
Soleimani[+] (2009) (71)	Aerobic	HR recovery (bpm)	CAD+DM	↑18	*p*=0.029* Men
Soleimani[+] (2009) (71)	Aerobic	HR recovery (bpm)	CAD+DM	↑9	*p*=0.019* Women <50 years
Soleimani[+] (2009) (71)	Aerobic	HR recovery (bpm)	CAD+DM	↑14	*p*=0.913 Women ≥50 years
Takaya[+] (2014) (72)	Aerobic	HR recovery (bpm)	AMI+CKD	↑3	ns
Tunsupon[a] (2017)[+] (73)	Aerobic and resistance	MIET (W)	1 comorbidity	↑9.49	ns*
			≥ 2 comorbidities	↑15.01	

(Continued)

Table IV. (*contd.*)

Study	Intervention (exercise type)	Outcome	Subgroup	Results	Notes
Tunsupon[b] (2017)[+] (74)	Aerobic and resistance	MIET (W)	Obese	↑10.47	ns
			Morbidly obese	↑15.13	
Tunsupon[a] (2017)[+] (73)	Aerobic and resistance	CWET (seconds)	1 comorbidity	↑803.39	ns
			≥ 2 comorbidities	↑870.59	
Tunsupon[b] (2017)[+] (74)	Aerobic and resistance	CWET (seconds)	Obese	↑12.18	ns
			Morbidly obese	↑14.31	

Health-related quality of life

Study	Intervention (exercise type)	Outcome	Subgroup	Results	Notes
Barnes[+] (2009) (62)	Aerobic and resistance	SF-36	n/a	↑18.2	$p = 0.03$*
de Groot[#] (2012) (64)	Aerobic and resistance	SF-36	n/a	↑7.5	$p < 0.01$*
Naz[+] (2019) (69)	Aerobic and resistance	SF-36 – physical function	CCI 1	↑10	ns
			CCI 2	↑15	
			CCI ≥ 3	↑10	
Naz[+] (2019) (69)	Aerobic and resistance	SF-36 – social function	CCI 1	↑13	ns
			CCI 2	↑6	
			CCI ≥ 3	↑13	
Naz[+] (2019) (69)	Aerobic and resistance	SF-36 – physical role	CCI 1	0	ns
			CCI 2	↑25	
			CCI ≥ 3	0	
Naz[+] (2019) (69)	Aerobic and resistance	SF-36 – emotional role	CCI 1	0	ns
			CCI 2	0	
			CCI ≥ 3	0	
Naz[+] (2019) (69)	Aerobic and resistance	SF-36 – general	CCI 1	↑6	ns
			CCI 2	↑13	
			CCI ≥ 3	↑5	
Naz[+] (2019) (69)	Aerobic and resistance	SF-36 – mental	CCI 1	↑4	ns
			CCI 2	↑8	
			CCI ≥ 3	↑4	
Naz[+] (2019) (69)	Aerobic and resistance	SF-36 – pain	CCI 1	↑10	ns
			CCI 2	↑19	
			CCI ≥ 3	0	
Naz[+] (2019) (69)	Aerobic and resistance	SF-36 – vitality	CCI 1	↑10	ns
			CCI 2	↑15	
			CCI ≥ 3	↑10	
Zwerink[+] (2010) (43)	Aerobic and resistance	MLHFQ	n/a	↑3.3	ns
Crisafulli[+] (2010) (63)	Peripheral limb training	SGRQ	1 comorbidity	66%	ns
			≥ 2 comorbidities	71%	no. of participants who achieved MCID
Hassan[+] (2016) (65)	Aerobic and resistance	SGRQ	1 comorbidity	↓23.26	ns
			> 1 comorbidity	↓25.75	
Mesquita[+] (2015) (68)	Details not provided	SGRQ	All participants	↓4.0	ns
Naz[+] (2019) (69)	Aerobic and resistance	SGRQ	CCI 1	↓8	ns
			CCI 2	↓11	
			CCI ≥ 3	↓5	
Barnes[+] (2009) (62)	Aerobic and resistance	FOSQ	n/a	↑0.5	$p = 0.07$
de Groot[#] (2012) (64)	Aerobic and resistance	Diabetes quality of life measure	n/a	↑8.2	$p < 0.01$*
Tunsupon[a] (2017)[+] (73)	Aerobic and resistance	CRQ – score	1 comorbidity	↑7.0	ns
			≥ 2 comorbidities	↑14.31	
Tunsupon[b] (2017)[+] (74)	Aerobic and resistance	CRQ – score	Obese	↑12.73	ns
			Morbidly obese	↑8.13	
Zwerink[+] (2010) (43)	Aerobic and resistance	CRQ – dyspnoea	n/a	↓1.1	ns
Zwerink[+] (2010) (43)	Aerobic and resistance	CRQ – fatigue	n/a	↑0.5	ns
Zwerink[+] (2010) (43)	Aerobic and resistance	CRQ – emotional	n/a	↑0.1	ns
Zwerink[+] (2010) (43)	Aerobic and resistance	CRQ - mastery	n/a	↑0.4	ns

Cardiometabolic

Study	Intervention (exercise type)	Outcome	Subgroup	Results	Notes
Barnes[+] (2009) (62)	Aerobic and resistance	BMI (kg/m²)	n/a	↓6.0	$p < 0.001$*
de Groot[#] (2012) (64)	Aerobic and resistance	BMI (kg/m²)	n/a	↑0.6	ns
Khadanga[+] (2016) (66)	Aerobic and resistance	BMI (kg/m²)	Diabetes	Insufficient data	
			Insulin resistance	Insufficient data	
Listerman[+] (2011) (67)	Aerobic and resistance	BMI (kg/m²)	1–2 comorbidities	↓0.4	ns
			> 2 comorbidities	↓0.1	Participants < 56 years
Listerman[+] (2011) (67)	Aerobic and resistance	BMI (kg/m²)	1–2 comorbidities	↓0.7	$p < 0.001$* (1–2 comorbidities)
			> 2 comorbidities	↓0.3	Participants 56–65 years
Listerman[+] (2011) (67)	Aerobic and resistance	BMI (kg/m²)	1–2 comorbidities	↓0.5	$p < 0.001$* (1–2 comorbidities)
			> 2 comorbidities	↓0.3	Participants > 65 years
Nonoyama[+] (2016) (70)	Aerobic and resistance	BMI (kg/m²)	Respiratory comorbidity	↑0.3	ns
			Non-respiratory comorbidity	↑0.2	

(Continued)

Table IV. (*contd.*)

Study	Intervention (exercise type)	Outcome	Subgroup	Results	Notes
Takaya[+] (2014) (72)	Aerobic	BMI (kg/m²)	AMI+CKD	↓0.2	ns
de Groot[#] (2012) (64)	Aerobic and resistance	HbA1c (%)	n/a	↓0.4	$p<0.05$*
Barnes[+] (2009) (62)	Aerobic and resistance	Total cholesterol (mmol/L)	n/a	↓0.9	$p=0.006$*
de Groot[#] (2012) (64)	Aerobic and resistance	Total cholesterol (mg/dL)	n/a	↓7.2	ns
Barnes[+] (2009) (62)	Aerobic and resistance	LDL (mmol/L)	n/a	↓0.6	$p=0.04$*
de Groot[#] (2012) (64)	Aerobic and resistance	LDL (mg/dL)	n/a	↓11.1	$p<0.01$*
de Groot[#] (2012) (64)	Aerobic and resistance	HDL (mg/dL)	n/a	↑0.7	ns
Barnes[+] (2009) (62)	Aerobic and resistance	Triglycerides (mmol/L)	n/a	↓0.5	$p=0.003$*
de Groot[#] (2012) (64)	Aerobic and resistance	Triglycerides (mg/dL)	n/a	↑7.1	ns
Barnes[+] (2009) (62)	Aerobic and resistance	Systolic BP (mmHg)	n/a	↓5.3	$p=0.02$*
Barnes[+] (2009) (62)	Aerobic and resistance	Diastolic BP (mmHg)	n/a	↓4.0	$p=0.09$
Barnes[+] (2009) (62)	Aerobic and resistance	Insulin (mIU/L)	n/a	↓4.8	$p<0.001$*
Barnes[+] (2009) (62)	Aerobic and resistance	Glucose (mg/L)	n/a	↓0.3	$p=0.37$
Barnes[+] (2009) (62)	Aerobic and resistance	CRP (mg/L)	n/a	↓2.9	$p=0.01$*
Mental health					
Barnes[+] (2009) (56)	Aerobic and resistance	BDI	n/a	↓7.9	$p<0.001$*
de Groot[#] (2012) (64)	Aerobic and resistance	BDI	n/a	↓10.7	$p<0.01$*
Barnes[+] (2009) (62)	Aerobic and resistance	Profile of mood states	n/a	↑15.6	$p=0.11$
Naz[+] (2019) (69)	Aerobic and resistance	HADS - anxiety	CCI 1	↓2	ns
			CCI 2	↓2	
			CCI ≥ 3	↓2	
Naz[+] (2019) (69)	Aerobic and resistance	HADS - depression	CCI 1	↓1	ns
			CCI 2	↓2	
			CCI ≥ 3	0	
Symptom score					
Barnes[+] (2009) (62)	Aerobic and resistance	SAAQ	n/a	↓20.8	$p=0.08$
Crisafulli[+] (2010) (63)	Peripheral limb training	MRC	1 comorbidity	84%	ns
			≥ 2 comorbidities	70%	no. of participants who achieved MCID
Hassan[+] (2016) (65)	Aerobic and resistance	mMRC	1 comorbidity	↓1.35	ns
			>1 comorbidity	↓1.55	
Naz[+] (2019) (69)	Aerobic and resistance	mMRC	CCI 1	↓1	ns
			CCI 2	↓1	
			CCI ≥ 3	↓1	
Health behaviours					
de Groot[#] (2012) (64)	Aerobic and resistance	Chronic illness survey	n/a	↑6.3	$p<0.01$*
de Groot[#] (2012) (64)	Aerobic and resistance	Steps (no./week)	n/a	↓179	ns
de Groot[#] (2012) (64)	Aerobic and resistance	Exercise (min/week)	n/a	↑41.1	Ns

Mean (SD) unless otherwise stated; [+]cohort study; [#]quasi-experimental study; *refers to whether study reported statistically significant improvement in this outcome; ns: not stated *p*-value; [¥]distance converted from feet to meters; NA: not applicable; –: unable to calculate d.

6MWD: 6-min walk distance; SD: standard deviation; no.: number; MCID: minimally clinical important difference; CCI: Charlson Comorbidity Index; CI: confidence interval; IQR: interquartile range; VO₂: oxygen consumption; AMI: acute myocardial infarction; CKD: chronic kidney disease; ACE: acute coronary event; DM: diabetes mellitus; HF: heart failure; A: anaemia; SEM: standard error of the mean; METS: metabolic equivalents; IHD: ischaemic heart disease; PAD: peripheral arterial disease; CVD: cardiovascular disease; SE: standard error; IWSD: incremental shuttle walk distance; CWRT: constant work rate time; HR: heart rate; bpm: beats per min; CAD: coronary artery disease; MIET: maximal symptom limited incremental cycle ergometer time; W: Watts; CWET: constant workload endurance time; SF-36: Short Form-36; MLHFQ: Minnesota Living with Heart Failure Questionnaire; SGRQ: St George's Respiratory Questionnaire; FOSQ: Functional Outcomes of Sleep Questionnaire; CRQ: Chronic Respiratory Questionnaire; BMI: body mass index; HbA1c: haemoglobin A1c; LDL: low-density lipoprotein; HDL: high-density lipoprotein; BP: blood pressure; mmHg: millimeters of mercury; mIU/L: milli-international units/litre; CRP: C-reactive protein; BDI: Beck Depression Index; HADS: Hospital Anxiety and Depression Scale; SAAQ: Sleep Apnoa Symptom Questionnaire; MRC: Medical Research Council dyspnea scale; mMRC: modified Medical Research Council dyspnea scale.

Compared with other interventions (ranging from dietary advice, usual physical activity, distant support and education), improvement in exercise capacity, HRQoL, selected cardiometabolic parameters of BMI and HOMA2-IR, depression and asthma symptom were evident for exercise rehabilitation; however, the number of studies was very small. With the known benefits of exercise on exercise capacity, cardiometabolic parameters and depression (84), these findings support what has been previously demonstrated when comparing exercise rehabilitation with other interventions (85–87). The lack of difference between groups for HbA1c (61) may be attributed to the inclusion of exercise as part of usual physical activity (<150 min per week) in the comparative group. While there were no statistically significant differences found for CRP, cholesterol and triglyceride measures, ESs could not be calculated (37); therefore the results may have some clinical significance, with the magnitude unable to be determined.

A mix of approaches of varying intensities for exercise rehabilitation were tested in the included

studies, with findings demonstrating that multiple approaches can achieve improvements in those with multimorbidity. Some studies used existing single-disease exercise rehabilitation programmes, such as cardiac and pulmonary rehabilitation, which implies that rehabilitation programmes including aerobic exercise with or without resistance training appear to be beneficial in this population. Other studies have established new exercise rehabilitation programmes. This heterogeneity may impact the conclusions for the outcomes reviewed. Further research into the feasibility of multimorbidity rehabilitation programmes, the varying models of exercises, their prescription with regards to frequency and intensity and the outcomes achieved in those with multimorbidity will enhance the ability to make guidelines and recommendations for best-practice models of care for this cohort. It was not possible to determine whether there is an optimal length of rehabilitation programmes for multimorbidity, or whether effects differed according to the number of chronic conditions. The addition of education or psychological support appeared to have minimal impact, suggesting that the benefits achieved may be attributed to effects of exercise, although few studies included a comprehensive assessment of psychological outcomes. The lack of impact on anxiety, depression or dyspnoea may be attributable to the baseline levels of these psychological symptoms or severity of breathlessness in the participants; if baseline levels demonstrate minimal impact on an individual, there is limited room for improvement.

Few data were available to understand the impact of exercise rehabilitation on outcomes such as mental health, ADL, health behaviours such as physical activity or medication adherence, or healthcare costs. There is also limited information regarding the impact on resistance training on specific measures of strength in this population, despite 20 of the 38 included studies incorporating resistance training as part of the intervention. This lack of defined strength assessment as an outcome measure is also reflected in a recent Delphi study identifying the core outcome set for multimorbidity research (88). While physical activity and function is included (and perhaps represented in measures of exercise capacity in the studies included in this review), strength measurement is absent. This is despite recent reviews highlighting that exercise prescription for people with various diseases should include resistance training (12, 89). Collectively, each of these outcomes are likely to be of critical importance for people with multimorbidity and should be addressed in future trials. People with multimorbidity define good health and wellbeing as enjoyment of life, maintenance of independence, having social relationships and participating in society (90), which reinforces the importance of optimizing these outcomes. It has been suggested that optimal care for people with multimorbidity should focus on maximizing the health goals of individual patients, rather than on improving disease-focused outcomes (15). Whilst exercise rehabilitation directly addresses goals related to physical function and wellbeing, it should be acknowledged that goals related to psychological, social and participatory outcomes may require a more complex intervention, of which exercise may be only 1 component.

This systematic review had a number of limitations. Because this is a relatively new field, we chose to include studies with a broad range of designs, including non-randomized trials, to ensure that studies with relevant data were not excluded. As a result, risk of bias also varied widely across the studies, and interpretation of data from non-randomized trials was difficult. Subgroup analysis was not performed according to the number of coexisting conditions, as data were not reported in sufficient detail for this to occur. Although the current study did not limit the age of participants in the inclusion criteria, only 1 study was conducted in a paediatric population; the current findings are largely confined to studies of adults with multimorbidities. The exclusion of studies aimed at rehabilitation of a single joint (e.g. hip) may have led to exclusion of some that included interventions aimed at improving exercise capacity. Reporting of dosage, frequency and intensity of exercise were often very limited, which made it difficult to account for some of the changes, or lack of, in the outcome measures of interest. These factors can affect the magnitude of change for outcomes such as exercise capacity. The use of English language only may have had an effect by not including studies and data published in other languages. There is also a risk of publication bias through the impact of negative studies potentially being less likely to be published. The lack of ability to blind participants and therapists in rehabilitation trials, due to the nature of the intervention, may affect the outcomes achieved. For the RCTs, assessor blinding was unclear for 64% of the studies. This also could have a significant effect on outcomes such as bias towards positive results, particularly if assessors were not blinded. Sample sizes ranged from 6 to 2,331. Therefore, the results of some studies may be more powerful than others and the results from smaller sized studies should be considered with discretion.

In conclusion, in people with multimorbidity, improvement in exercise capacity, HRQoL and cardiometabolic outcomes were evident with exercise rehabilitation. Outcomes were similar to those seen following exercise rehabilitation in people with single diseases, regardless of the intervention type. Therefore, exercise rehabilitation can be effectively delivered to people with multimorbidity, both within current single-disease

rehabilitation programmes or in specialized multimorbidity exercise rehabilitation programmes.

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