Exercise Rehabilitation for People with Multimorbidity

Submitted by

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List of tables

The list of tables includes only tables that are not part of published or submitted manuscripts.

There are no figures in this thesis apart from those in published or submitted manuscripts.

List of abbreviations

ADL	Activities of daily living
AFO	Ankle-foot orthosis
AQoL	Assessment of quality of life
BMI	Body mass index
BP	Blood pressure
CCI	Charlson comorbidity index
CHD	Coronary heart disease
CHF	Chronic heart failure
CI	Confidence interval
CIRS(G)	Cumulative illness rating scale for geriatrics
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
CRP	C-reactive protein
CRQ	Chronic respiratory questionnaire
DSRG	Disease-specific rehabilitation group
DUSOI	Duke severity of illness checklist
ED	Emergency department
EQ-5D-5L	EuroQol-5D-5L
ES	Effect size
ESWD	Endurance shuttle walk distance
FCI	Functional comorbidity index
GP	General practitioner
HADS	Hospital anxiety and depression scale
HbA1c	Haemoglobin A1c

HDL	High-density lipoprotein
HF	Heart failure
HOMAR-IR	Homeostasis model assessment insulin-resistance-index
HR	Heart rate
HREC	Human research ethics committee
HR-QOL	Health-related quality of life
ILD	Interstitial lung disease
IQR	Interquartile range
ISWD	Incremental shuttle walk distance
Katz ADL index	Katz index of independence in activities of daily living
kg	Kilograms
LDL	Low-density lipoprotein
m	Metres
MI	Myocardial infarction
MCID	Minimal clinical important difference
MID	Minimal importance difference
Min	Minute
mL	Millilitres
MLHF	Minnesota living with heart failure questionnaire
MMRG	Multimorbidity rehabilitation group
MRC	Medical research council dyspnoea scale
MULTIPleS	Multimorbidity illness perception scale
NRCT	Non-randomised controlled trial
OR	Odds ratio
RCT	Randomised controlled trial
RM	Repetition maximum

RPE	Rating of perceived exertion
RPG	Rehabilitation program group
SD	Standard deviation
SE	Standard error
SF-36	36-item short form health survey questionnaire
SGRQ	St George's respiratory questionnaire
SPSS	Statistical Package for the Social Sciences
UHEC	University human ethics committee
UK	United Kingdom
UMC	Usual medical care
UMCG	Usual medical care group
VO_2	Oxygen consumption
WHO	World Health Organization
WMD	Weighted mean difference
6MWD	6-minute walk distance
6MWT	6-minute walk test

Abstract

Multimorbidity, the co-existence of two or more chronic conditions, is common in clinical practice and is associated with many negative consequences. Rehabilitation is integral to chronic disease management, but people with multimorbidity are often excluded from trials of disease-specific rehabilitation interventions. The research described in this thesis investigated the current evidence for exercise rehabilitation in people with multimorbidity and the feasibility of multimorbidity rehabilitation programs.

A systematic review (34 studies) showed that in people with multimorbidity, clinically important improvements in exercise capacity, quality of life and cardiometabolic outcomes were evident following exercise rehabilitation. Compared to usual care, exercise rehabilitation improved 6-minute walk distance (weighted mean difference 64 m, 95% CI 45–82). Two pilot randomised controlled trials (RCTs) were conducted to evaluate the feasibility of multimorbidity rehabilitation studies. In a pilot RCT of exercise rehabilitation versus usual medical care, 100 people were screened to recruit 16 participants, with a 71% completion rate. In a pilot RCT of multimorbidity rehabilitation versus disease-specific rehabilitation, 61 people were screened to recruit 17 participants; the multimorbidity group averaged 12 sessions and the disease-specific group attended 11 sessions. Both trials successfully collected outcome data for exercise capacity and health-related quality of life, which will provide data to underpin power calculations for future trials.

The results show that rehabilitation can be delivered to people with multimorbidity within single-disease or multimorbidity-specific rehabilitation programs. While studies to date demonstrate improvements in exercise capacity, quality of life and cardiometabolic outcomes, there are few data to understand the impact of exercise rehabilitation on mental health, daily activities or healthcare costs. The pilot studies will inform the design of future trials that could address outcomes that are meaningful to people with multimorbidity and healthcare services. This will contribute to the development of optimal models of care for people with multimorbidity.

Statement of authorship

This thesis includes work by the author that has been published or accepted for publication as described in the text.

Except where reference is made in the text of the thesis, this thesis contains no material published elsewhere or extracted on whole or in part from a thesis accepted for the award of any other degree or diploma.

No other person's work has been used without due acknowledgement in the main text of the thesis.

This thesis has not been submitted for the award of any degree or diploma in any other tertiary institution.

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Candidate's declaration

In the case of chapters two, three and four of this thesis, the extent of the candidate's contribution was as follows:

Thesis Chapter	Publication Title	Publication Status	Extent of Contribution
2	The effects of exercise-based rehabilitation on clinical outcomes in people with multimorbidity: A systematic review	Submitted	50%
3	A rehabilitation programme for people with multimorbidity versus usual care: A pilot randomized controlled trial	Published	55%
4	Multimorbidity rehabilitation versus disease-specific rehabilitation in people with chronic diseases: a pilot randomized controlled trial	Published	50%

Kathryn Barker

2nd November 2020

Publications

All manuscripts (accepted and submitted) presented in this thesis were written and based on work conducted during the period of candidature for the purpose of obtaining the degree of Master of Applied Science (Research). Each manuscript was prepared in accordance with the requirements of the relevant journal.

The contributions of the candidate and her co-authors towards each study are stated in the prefaces of chapters two to four. Permissions to use publications for this thesis were permitted by the corresponding journals.

Published manuscripts

- Barker K, Holland AE, Lee AL, et al. A rehabilitation programme for people with multimorbidity versus usual care. Journal of Comorbidity 2018; 8(1):1-11.

- Barker K, Holland AE, Lee AL, et al. Multimorbidity rehabilitation versus disease-specific rehabilitation in people with chronic diseases: a pilot randomized controlled trial. Pilot and Feasibility Studies 2018; 4(1):181. doi: 10.1186/s40814-018-0369-2

Submitted manuscript

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CHAPTER 1 – INTRODUCTION

1.1 Multimorbidity

1.1.1 Definition and prevalence of multimorbidity

Multimorbidity is defined as the co-existence of two or more chronic conditions (1). It is the most common presentation of chronic disease (2), with nearly one in four Australians (23%) estimated to have two or more chronic conditions (3), which increases to two thirds of adults over the age of 60 years (4). The prevalence of multimorbidity is higher in women and people from low socioeconomic status backgrounds (5). Previously multimorbidity and comorbidity have been used interchangeably. It is now accepted that comorbidity should be used when there is a specific index condition (6). Comorbidity places one disease in a central position and any other condition as secondary (6). Multimorbidity acknowledges that with the existence of multiple diseases within a person, there may be different priorities of conditions throughout the lifespan.

Although multimorbidity is often thought of as a problem of older people, a study following participants over a 20-year period showed a significant increase in multimorbidity prevalence across the 20-year period for all age groups, which had baseline approximate ages of 15, 35 and 55 years (7). A cross-sectional study of 1751841 patients from Scottish medical practices showed that the absolute number of people with multimorbidity was higher in those younger than 65 years (1). Therefore, it is an issue that has impact across the age span of the population.

Socioeconomic status and lifestyle risk factors affect the prevalence and severity of multimorbidity. People living in more socioeconomically deprived areas have a higher probability of developing multimorbidity, with the inequality being most evident between 50 and 70 years of age (7). The probability of developing multimorbidity is significantly higher in people who are overweight, current or ex-smokers, have a poor diet, and consume alcohol (7).

1.1.2 Health consequences of multimorbidity

People living with multimorbidity are a high-need, vulnerable population; they face complex and interrelated cultural, social, economic and systemic barriers to access to services (2). Multimorbidity is an important problem in most healthcare systems and is common in clinical practice (8). It is associated with increased risk of disability (9), frailty (9), mortality (10, 11), poorer functional status (10, 12-14) and reduced health-related quality of life (HR-QOL) (15).

Measuring function is important in the heterogeneous multimorbidity population, because it offers a way to compare the impacts of different types of disease on different populations (16). Functional levels may be used as markers of the existence, severity and impact of a disease (16). Optimising function is a common goal of healthcare and functional status is highly valued by patients, therefore it is an essential outcome (17). These factors make function a useful outcome in multimorbidity.

Recently there has been a shift from a focus on health in terms of survival to an emphasis on the person's ability to perform their daily activities, and more recently to social and emotional wellbeing and quality of life (16). Health-related quality of life has been used to evaluate the impact of multimorbidity, because it provides a multidimensional perspective that encompasses a person's physical, emotional and social functioning (13). A study in primary care found that HR-QOL was adversely affected by multimorbidity when controlling for confounding variables, such as age, sex, household income and education. It also found that physical HR-QOL was more affected than mental HR-QOL in people with multimorbidity (13).

1.1.3 Healthcare burden and costs of multimorbidity

People with multimorbidity have high healthcare costs (5). The increasing prevalence of multimorbidity generates financial pressures on healthcare systems, as expenditure on healthcare rises almost exponentially with the number of chronic diseases per person (18). Healthcare utilisation and costs in primary and secondary care are significantly higher among people with multimorbidity, including primary care consultations, hospital outpatient visits, hospital admissions and total healthcare costs (19). This effect has been reported to occur independent of age, gender and socioeconomic status (19). People with multimorbidity are more likely to have unplanned admissions to hospital than people without multimorbidity (20). One study showed that people with four or more physical health conditions had a predicted probability of admission about 14 times greater than of people with no physical conditions (20). It has been found that in a diabetic population, those who have complex management, through having multimorbidity, polypharmacy and multiple health professionals, spent more time on health-related activities (21) which increases the individuals' burden of care. Multimorbidity often demands specialist attention, knowledge and skills, and creates an increased need for social, medical and healthcare services (22).

1.1.4 Challenges for the management of multimorbidity – fragmented healthcare

Healthcare systems worldwide are often structured on the single disease model (23) and have become specialised to deliver increasingly technical treatments for individual

diseases (24). In the management of a person with multimorbidity, the common approach to the presence of another disease is to refer to another specialist (24). This model of care is based on the working assumption that the optimal treatment for someone with more than one condition is to prescribe the treatments for all the individual conditions (24). This fragmented approach to healthcare for people with multimorbidity can lead to incomplete, inefficient, ineffective and potentially harmful interventions (1, 23). People with multimorbidity are often faced with complex and conflicting treatment plans (25). Lack of communication between the specialist and primary care physicians involved in one person's healthcare can add to the treatment burden and challenges faced by the individual. The fragmented healthcare between specialists, general practitioners (GPs) and allied health professionals also leads to increased treatment burden arising from multiple investigations and locations of healthcare services, especially in rural or regional areas (26). People with multimorbidity and their families navigate a mix of programs in the community, such as disease management, secondary prevention or numerous allied health professionals, many of which have their own entry criteria, waiting lists and assessment tools (27). Healthcare professionals need to navigate multiple separate guidelines for single chronic diseases, often with conflicting advice and priorities when managing patients with multimorbidity. Qualitative research shows that doctors identify the lack of guidelines and decision-making as one of several challenges in treating people with multimorbidity (28, 29). These single disease guidelines are also developed based on research in which people with multimorbidity have been excluded, which is discussed further in section 1.2.4. With the fragmentation of healthcare, important co-existing conditions can go unnoticed; an example is depression, which is overrepresented and underdiagnosed in patients presenting with other chronic diseases (26). This can reduce the effectiveness of treatment plans through the lack of identification and treatment of all factors that may be barriers to overall care. Individual preferences may be overlooked, with goals of care being predominantly medical, without the patient's wishes and lifestyle preferences being considered or integrated into the care of the whole person. Health professionals have been found not to factor information from patient experience into their opinions about systems improvements (30). Their focus tends to be on their own resources and behaviours of other health professionals (30). Patient priorities should be highlighted in the decision-making process, thus enabling people to remain in control of their health (2, 26, 31).

1.1.5 Problems for people with multimorbidity – barriers to accessing care

People with multimorbidity experience barriers to accessing healthcare, some of which are similar to those documented by patients with single chronic diseases. Qualitative studies

have been performed to identify barriers to healthcare in the multimorbidity population (27, 32). Qualitative studies focused on single diseases have reported that barriers to self-care include concerns about knowledge deficits, physical and financial access to care, adverse effects of medications, negative emotions, personal struggles and difficulties with lifestyle changes (32). In one study, the majority of people reported that symptoms of one of their conditions interfered with self-care for another condition (32). Lifestyle changes for two conditions often seemed incompatible and "stress" from one condition would often aggravate another (32). The compounding effects of multiple conditions often centred on physical limitations or complex recommendations for lifestyle changes (32). In another study focusing on access to care for people with multimorbidity, barriers were failing to qualify for services, coping with wait times, struggling with service scarcity and negotiating the location of care (27). This led to people experiencing disappointment, frustration and uncertainty regarding their future health (27). Barriers to service delivery were unreliable care, unmet needs, and incongruent and inflexible care (27). These barriers led to a lack of confidence and trust in care providers, stress, frustration and receiving suboptimal care (27). When someone believes that they lack the ability to control a situation, it is more likely that no action will be taken (e.g. taking medication to control hypertension) (31). Understanding the barriers that exist within the multimorbidity population can contribute to identifying solutions or guide the design of healthcare models. When developing and implementing such models in the multimorbidity population, these barriers should be considered to reduce their impact on outcomes for individuals.

1.1.6 Management strategies for multimorbidity

Disease management strategies that are common across most chronic diseases include healthy eating, being physically active, avoiding tobacco use and coping emotionally (2). There are also common daily challenges for people living with chronic diseases: dealing with symptoms, disability, emotional impacts, complex medical regimens, difficult lifestyle adjustments and obtaining helpful medical care (33). Given the prevalence of multimorbidity and the commonality in management approaches, fragmented single-disease management must be replaced with integrated care of the whole person to attain both efficiencies in the healthcare system and a more patient-centred approach (2). Healthcare providers need to ensure people with multimorbidity have the confidence and skills to manage their conditions and are provided with the most appropriate treatment to achieve optimal disease control and prevention of complications (33). The Chronic Care Model is an approach to improving services with a focus on six areas; 1) self-management support; 2) decision support; 3) delivery system design; 4) clinical information systems; 5) health care organisation and 6) community resources (34). Studies suggest that

redesigning care using this model leads to improved patient care and better health outcomes (34). The adoption of integrated approaches to improving health care for chronic diseases, such as the Chronic Care Model, could assist in the move away from the current fragmented, silo structure of disease management. Rehabilitation programs may offer a model of care to address a broad range of chronic disease management strategies using integrated care. They may also assist with confidence and skill development, disease control and prevention of complications.

1.2 Rehabilitation in multimorbidity and chronic disease

1.2.1 Definition of rehabilitation

Rehabilitation is a set of interventions designed to optimise function and reduce disability in individuals with health conditions, in interaction with their environment (35). Rehabilitation has been described as therapies including, but not limited to, exercise training, education and behaviour change (36). With its objective of optimising function, rehabilitation assists those with health conditions to remain as independent as possible, to participate in education, to be economically productive, and fulfil meaningful life roles (37). Rehabilitation is integral to chronic disease management as it aims to address many of the negative consequences resulting from chronic diseases.

1.2.2 Benefits of rehabilitation in chronic disease

Rehabilitation provided along a continuum of care, ranging from in-hospital care to rehabilitation in the community, can improve health outcomes, reduce costs by shortening hospital length of stay, reduce disability and improve quality of life. Rehabilitation that begins early in the disease process produces better functional outcomes for almost all health conditions associated with disability (38). The improvement of a person's ability to participate more fully in everyday life, as a consequence of rehabilitation, reduces costs related to ongoing care and support, and may also accelerate a return to education, employment (39) or independent living.

Pulmonary and cardiac rehabilitation are examples of well-accepted chronic disease rehabilitation programs that are underpinned by strong evidence (40, 41). Clinical guidelines and statements strongly recommend the widespread implementation of these programs in people living with pulmonary or cardiac conditions (42-45). The findings of systematic reviews of trials investigating these single-disease programs are described in Table 1.

Table 1. Systematic reviews of cardiac, heart failure and pulmonary rehabilitation.

	Anderson et al., 2016 (40)	**Davies et al., 2010 (46)**	**McCarthy et al., 2015 (41)**
Title	Exercise-based cardiac rehabilitation for coronary heart disease	Exercise based rehabilitation for heart failure	Pulmonary rehabilitation for chronic obstructive pulmonary disease
Population	•MI •coronary artery bypass graft •percutaneous coronary intervention •angina •coronary artery disease	•chronic systolic heart failure •ischaemic or non-ischaemic cardiomyopathy	•COPD (more than 90% of participants)
No. studies	63 RCTs	19 RCTs	65 RCTs
No. participants	14,486	3,647	3,822
Program	•exercise-based interventions with at least 6 months follow-up •supervised or unsupervised •inpatient; outpatient; community or home based	•exercise-based interventions with at least 6 months follow-up •exercise with or without education and psychological intervention	•exercise training for at least 4 weeks, with or without education and/or psychological support •community or home-based •physical activity considered to be

	•includes some form of exercise training that is applied to a cardiac population •exercise training with or without psychological or educational interventions		aerobically demanding
Comparison	Standard medical care	Usual medical care as defined by the study	•conventional care •only verbal advice given
Measures	•mortality •MI •revascularisation •hospitalisation •HR-QOL •costs	•mortality •hospitalisation •HR-QOL •health-care utilisation and costs	•HR-QOL •functional or maximal exercise capacity
Findings	•exercise-based cardiac rehabilitation reduced cardiovascular mortality compared with control (no exercise) • overall risk of hospital admissions	•a reduction in the hospitalisation rate was demonstrated with exercise training programs •hospitalisations due to systolic heart failure were reduced with exercise	•both functional exercise and maximal exercise showed statistically significant improvement •statistically significant improvement for all included outcomes (Chronic Respiratory

	was reduced with cardiac rehabilitation • evidence of significant improvement in most or all the HR-QOL sub-scales with exercise-based cardiac rehabilitation compared to control at follow-up •indicated exercise-based cardiac rehabilitation to be a potentially cost-effective use of resources in terms of gain in quality-adjusted life years	• significant improvement in HR-QOL	Questionnaire and St George's Respiratory Questionnaire)

COPD = chronic obstructive pulmonary disease; No. = number; RCTs = randomised controlled trials; MI = myocardial infarction; HR-QOL = health-related quality of life

1.2.3 Outcomes for people with multimorbidity in single-disease programs

Several studies have investigated the impact of multimorbidity on the outcomes of single-disease programs, such as pulmonary and cardiac rehabilitation. Most studies have reported that people with multimorbidity still achieve improvements in outcomes such as exercise capacity and HR-QOL (47-50). However, for patients included in cardiac, heart failure (HF) and pulmonary rehabilitation who have been identified as having multimorbidity, their clinical outcomes may be less optimal compared to people with single diseases (51-53). The reported impact varies across outcomes.

A systematic review of the influence of comorbidities on outcomes of pulmonary rehabilitation in patients with COPD found that multimorbidity can have a negative influence on some outcomes (48). This review found that 70% of patients with COPD who

were enrolled in pulmonary rehabilitation had multimorbidity. Pulmonary rehabilitation programs were beneficial in patients with multimorbidity and COPD, and COPD alone. However, the presence of specific conditions had a varied impact on outcomes. Participants with osteoporosis were less likely to show improvements in functional exercise capacity (odds ratio (OR) = 0.28, 95% CI: 0.11–0.70, 1 study) (54). People with cardiovascular disease were less likely to experience positive change in QOL (OR range 0.20–0.67, 2 studies) (55, 56). Improvements in dyspnoea and health status were significantly smaller in patients with multimorbidity. It was acknowledged that the data were scarce, with only four articles included, and formal meta-analysis was not possible due to heterogeneity of the methods and outcomes (48). Another study published since this systematic review examined the impact of comorbidities on pulmonary rehabilitation outcomes in people with COPD and interstitial lung disease (ILD) (47). It found a similar number of comorbidities between COPD (3.3±2.1, n=242) and ILD groups (3.2±1.9, n=66) ($p>0.05$), and described the impact in terms of improvers following pulmonary rehabilitation. Improvers were defined as people who achieved minimal clinical important difference (MCID) for exercise capacity (6-minute walk distance (6MWD)) and HR-QOL (chronic respiratory disease questionnaire). In people with ILD, clinically meaningful improvement in exercise capacity was less likely in those who had diseases of the circulatory system (53.8% vs 86.4%, $p=0.027$) or musculoskeletal system (47.4% vs 82.8%, $p=0.013$). There were no significant associations between type or number of comorbidities and response to pulmonary rehabilitation in terms of exercise capacity for people with COPD.

Similar impacts of multimorbidity have been demonstrated in cardiac rehabilitation. In a study on the outcomes of cardiac rehabilitation in people with coronary heart disease (CHD) (49), most participants demonstrated statistically significant improvements in exercise capacity, measured by 6-minute walk test (6MWT), body mass index (BMI) and the physical and mental components of an HR-QOL measure (the 36-item short form health survey questionnaire – SF-36), regardless of multimorbidity. However, age appeared to moderate the impact of multimorbidity on outcomes, with more impact in younger people. In individuals younger than 56 years, those with no multimorbidity had statistically greater improvements in all outcomes than people with multimorbidity. In individuals aged 56 to 65 years, those with no multimorbidity had statistically greater improvements in exercise capacity (mean difference in 6MWD 90 vs 74 metres) and BMI (-0.6 vs -0.3 kg/m^2), with no difference in HR-QOL (49). In people aged more than 65 years, those with no multimorbidity had statistically greater improvements in exercise capacity only, than those with multimorbidity (mean difference in 6MWD 70 vs 61 metres)

(49). Another study investigated the impact of respiratory and non-respiratory comorbidities, such as diabetes, cancer and peripheral vascular disease, on patients undergoing cardiac rehabilitation (50). For peak oxygen consumption (VO_2), there were significant differences among all three groups (respiratory, non-respiratory and no comorbidities) ($p = 0.02$) after cardiac rehabilitation (50). Savage et al. (2009) (57) found that more than 20% of patients enrolled in cardiac rehabilitation failed to improve their peak VO_2, with one of the identified reasons being medical comorbidities (57).

The heterogeneity of cohorts and interventions in these studies may be a partial explanation for their varied findings about the impact of multimorbidity on reported outcomes. Differences in how multimorbidity is defined and reported, patient populations and length and type of exercise rehabilitation programs also affect the ability to translate findings reported to date into clinical practice.

1.2.4 Problems with current models of chronic disease rehabilitation, research and guidelines

Healthcare delivery around the world tends to be organised around the treatment of single diseases (1, 58, 59). As previously highlighted, while rehabilitation is integral to chronic disease management, it is frequently structured in single-disease programs such as cardiac, HF and pulmonary rehabilitation. As a result, people with multimorbidity are often managed according to several single-disease guidelines. In clinical practice, the health of people attending disease-specific rehabilitation programs is increasingly complex with more co-existing health conditions. In the United Kingdom (UK), 46% of patients in cardiac rehabilitation have comorbidities (60). A review of recent guidelines relevant to single-disease rehabilitation for people with chronic diseases showed that three out of seven sets of guidelines do not mention coexisting conditions, and an additional three only make passing mention of minor program adaptations (52). This raises the question of whether the rehabilitation needs of people with multimorbidity can be adequately addressed in disease-specific programs. Internationally, improvement of care for people with complex healthcare and social care needs has been identified as a priority for both government and health service providers (61-63).

One advantage of utilising disease specific rehabilitation programs is that a well-established model of care is already in existence in many developed countries. However there remain significant barriers to uptake and participation. Poor access to rehabilitation is commonly identified as a barrier to uptake, and hampers the performance of healthcare systems worldwide (64). Factors contributing to the access barrier and the unmet need for rehabilitation services include location, transport, high out-of-pocket expenses and long

waiting times (27, 39, 64, 65). Development of a novel model of multimorbidity rehabilitation, involving flexible access to programs, may enable some of the recognised barriers to be lowered or removed. Such programs may also allow a broader range of rehabilitation goals and educational needs to be addressed than might be possible in a disease-specific model. Investigation comparing the outcomes of disease-specific and rehabilitation could guide healthcare providers to the optimal model of rehabilitation.

Access is not only related to healthcare services or delivery, but relates to the demographic, social and economic characteristics of the individual (64, 66). A person's access to the services they require may be affected by their ability to perceive, seek, reach, pay and engage (64). People with chronic diseases have many of these individual access barriers due to lower health literacy (67) and socioeconomic levels (68), which are exacerbated within the multimorbidity population by the impact of multiple chronic diseases and increased treatment burden. Access empowers people to make the steps that enable them to obtain healthcare (64), which could be described as active self-management. Rehabilitation programs can use self-management strategies that aim to effect positive change in health behaviours, resulting in improved health outcomes. The multimorbidity rehabilitation model may allow for adaptability in addressing aspects of chronic disease management that suit the individual's priorities, which can shift or change throughout a period of rehabilitation, rather than focus on a single disease.

Recognising the importance of and unmet need for rehabilitation, the World Health Organization (WHO) held a meeting in 2017 titled 'Rehabilitation 2030: a call for action'. The meeting report highlights that more people than ever are living with noncommunicable diseases and other chronic conditions. Health systems need to be equipped to provide services that optimise functioning in light of impairments, injuries or health conditions, both acute or chronic (69). This reflects the need for the complex and growing multimorbidity population to have access to evidence-based and sustainable rehabilitation programs. There is a clear need for rehabilitation programs that are relevant for people with multimorbidity and have evidence of efficacy. This need was addressed by the pilot studies in Chapters 3 and 4, which investigated exercise rehabilitation in multimorbidity populations.

1.2.5 Potential solutions to lack of rehabilitation for people with multimorbidity

Several approaches could be taken to include people with multimorbidity in exercise rehabilitation programs. Two possible approaches, which are examined in this thesis, are;

1. The participation of people with multimorbidity, who currently do not have access to disease-specific exercise rehabilitation programs, in a multimorbidity

rehabilitation program. Chapter 3 describes an investigation of the feasibility of this approach, and its outcomes compared to usual medical care.

2. The inclusion of people with multimorbidity, who would be eligible to participate in established disease-specific exercise rehabilitation, in a multimorbidity rehabilitation program. Chapter 4 outlines the feasibility of this approach, and its outcomes in comparison to a disease-specific rehabilitation program.

Multimorbidity rehabilitation programs: The lack of access to exercise rehabilitation programs for people with many specific chronic diseases highlights the importance of investigating multimorbidity rehabilitation. Access to healthcare is defined as access to a service, a provider or an institution, which translates to the opportunity or ease with which consumers or communities are able to use appropriate services in proportion to their needs (64). People with multimorbidity may benefit from a modified rehabilitation structure which accommodates all conditions. Multimorbidity rehabilitation addresses recommendations that a care model should aim to improve HR-QOL by reducing treatment burden (70). Multimorbidity rehabilitation would not limit participation due to disease type and would aim to improve the management of multiple diseases.

Including people with multimorbidity in existing programs: It has been suggested that rather than using resources to increase delivery of single-disease interventions, multimorbidity interventions should be integrated into existing healthcare systems to support implementation and sustainability (71). Another suggestion is to apply and build on the evidence regarding effective interventions for single diseases to people with multimorbidity (8). Many healthcare systems already offer well-established disease-specific rehabilitation programs, and although their outcomes may vary in those with multiple underlying conditions, existing studies suggest clinically meaningful outcomes can be achieved (47-53). These systems are well placed to provide rehabilitation for people with multimorbidity or to adapt successful existing models, such as pulmonary rehabilitation, to more comprehensively address the needs of people with multimorbidity (52). The idea of a generic, symptom-based exercise rehabilitation program, focusing on symptoms and common disability rather than primary organ disease, has been investigated in the UK (72). This concept has been developed in people with chronic heart failure (CHF) and COPD, who experience similar symptoms of exertional breathlessness and fatigue, as well as common secondary impairments such as skeletal muscle dysfunction. Whilst pulmonary rehabilitation is well established in the UK for people with COPD, the CHF population is much less likely to participate in rehabilitation programs (72). Rather than devoting resources to new interventions, it was proposed that people with CHF could improve their exercise capacity and HR-QOL by participating in existing pulmonary rehabilitation

programs. A consensus conference reported high level of agreement that the same principles of exercise can be used for CHF and COPD; in addition, 75% of stakeholders supported symptom-based rather than disease-based rehabilitation for breathlessness (73). This concept is supported by a study showing that people with CHF achieved statistically significant improvements in exercise capacity and HR-QOL by participating in a seven-week pulmonary rehabilitation program alongside people with COPD (72). There was no adaptation of the program for people with CHF and no negative consequences on the outcomes for people with COPD. However, in this study the participants only had a single disease, either CHF or COPD, as those with combined disease were excluded. Therefore, whilst this research was progressive in considering alternative models of exercise rehabilitation, such as symptom-based or generic exercise rehabilitation programs, it did not address outcomes for people with multimorbidity.

Identifying clinically relevant comparators for multimorbidity rehabilitation: Many people living with multimorbidity lack access to any form of exercise rehabilitation and are being managed via the medical care model alone. However, in many settings, people with multimorbidity are eligible to attend traditional disease-specific rehabilitation programs (e.g. those with pulmonary or cardiac disease). This makes it important to establish whether multimorbidity rehabilitation offers any benefits beyond those of participation in these established services. Thus, there are two comparators for studies of multimorbidity rehabilitation: usual care and disease-specific rehabilitation. Feasibility studies conducted using these comparators are reported in Chapters 3 and 4.

1.3 The current literature on multimorbidity rehabilitation

Multimorbidity rehabilitation programs are currently uncommon in both research and clinical practice. Whilst several studies have evaluated the impact of comorbidities on rehabilitation outcomes, as described in section 1.2.3, there are few randomised trials that have examined a multimorbidity rehabilitation model. Randomised trials of single-disease rehabilitation models frequently exclude people with multimorbidity (9), although a few trials have specifically targeted these patients (74). Research funding which places an emphasis on tight outcome measures has also contributed to the current lack of evidence in the multimorbidity population. The challenges of determining a core set of outcomes and need for more robust outcomes for the multimorbidity population is further discussed in section 1.4.

A systematic review of interventions for improving outcomes in patients with multimorbidity found mixed results about their effectiveness, with no clear positive improvements in clinical outcomes, health service use, patient-related health behaviours or costs (8). The review suggests that interventions designed to target difficulties that people experience with daily functioning (e.g. physiotherapy) are more effective (8). The interventions were predominantly focused on organisation of care, such as case management or multidisciplinary teamwork, and educational or self-management support (8). However, exercise rehabilitation was not delivered in any of the included studies, and exercise capacity was not a reported outcome measure.

No previous authors had conducted a systematic review of rehabilitation for multimorbidity. Such a review is necessary to determine whether effective models are available, and highlight areas needing further research. Relevant comparisons for such a review include usual medical care and other types of interventions. A systematic review of exercise rehabilitation for multimorbidity is presented in Chapter 2.

1.3.1 Rehabilitation research populations and methods

The evaluation of interventions for a complex, heterogeneous multimorbidity population poses numerous methodological challenges in study design, outcome measurement and analysis (75). These challenges include identification of appropriate outcome measures and tools to capture the extent and impact of multimorbidity. These measurement issues are discussed in the following section.

1.4 Measurement of patient characteristics and outcomes in multimorbidity rehabilitation

Rehabilitation aims to alter activities (i.e. behaviour) or participation (i.e. role functioning in the community) (76). Assessment of its feasibility and effectiveness requires measurement of change in function, patient-centred outcomes and use of resources. For these reasons, research on exercise rehabilitation may examine program and process feasibility, exercise capacity, HR-QOL, performance of activities of daily living (ADL) and healthcare resource utilisation. In a study in the UK, where expert stakeholders were asked to rank categories of outcome measures for an exercise rehabilitation program for combined COPD and HF populations, the most important categories for both clinical and research purposes were HR-QOL, exercise capacity and symptom evaluation (77).

A study published in 2018 used the Delphi process to identify a core set of outcomes that should be used in multimorbidity research, namely HR-QOL, mental health outcomes and mortality (78). However, the authors also stated that researchers should consider the full range of outcomes when designing studies to capture important domains in multimorbidity depending on individual study aims and interventions (78). The choice of tools used in the studies in Chapters 3 and 4 was influenced by its validity, reliability, sensitivity, feasibility of use, frequency of use in similar trials ,and availability of MCID and population norms to suit the intervention, population, environment and resources. A description of the measures included in the studies (Chapters 3 and 4), and the rationale for their selection, is given in the following sections.

1.4.1 Feasibility measures

Feasibility studies involve a realistic assessment of study design and processes to inform further clinical trials (79). This process includes assessing factors including internal and environmental capacity, study design, dose of intervention, comparator and patient type (79). The findings of feasibility studies determine whether an intervention should be recommended for efficacy testing (80). With multimorbidity rehabilitation being a new model of care, it is important to establish whether it is feasible to recruit to such a study, and realistic to deliver the intervention. In the clinical trials reported in Chapters 3 and 4, program feasibility was measured by the numbers screened to achieve target sample sizes, the number of those who agreed to participate, and the number who completed the intervention.

1.4.2 Functional exercise capacity

Functional exercise capacity is a vital outcome in chronic disease rehabilitation that is sensitive to change with exercise-based interventions. The 6MWT is an important and relatively simple test of functional capacity. It is useful for assessing the degree of functional exercise impairment, prognosis, and response to therapy in patients who are moderately to severely impaired due to a range of cardiopulmonary and other conditions (81). For patients with moderate-to-severe cardiopulmonary disease, the 6MWT is the most commonly used tool for the objective assessment of functional exercise capacity in patient management and research (81). It also has the advantage of wide acceptance and experience in both research and clinical settings (81).

In the studies described in this thesis, the outcome of change in functional exercise capacity was measured by the 6MWT. The 6MWT has demonstrated validity and reliability in patients with chronic respiratory disease (82), HF (83), arthritis, diabetes, cognitive dysfunction and depression (84), and in patients with cardiac disease and multimorbidities

(85). A multidisciplinary and international group of clinicians and researchers developed a standard operating procedure for the 6MWT (86). The 6MWTs performed during the studies reported in this thesis were administered according to this procedure.

1.4.3 Health-related quality of life

Quality of life is the person's own evaluation of all of their life, including perceptions of pathology, impairments, activities, and participation interpreted in the light of their own context (76). Health-related quality of life incorporates health status (physical, psychologic, social functioning) and may also measure impairment, symptoms or disability (87). However, as the health of individuals is more than the absence of disease, HR-QOL measures usually incorporate perceptions, role functions, social health and general wellbeing, and may even measure aspects of spirituality, sexual function, life satisfaction and environment (87). Health-related quality of life can be a broad generic measure or a disease-specific measure. The use of both generic and disease-specific HR-QOL tools in the studies in Chapters 3 and 4 reflected the models of exercise rehabilitation investigated, namely, disease-specific and multimorbidity rehabilitation programs. Over 1200 QOL measures exist in the literature, and they vary greatly in their content (76). Whilst some are valid in populations that may contain people with multimorbidity, there are currently no quality of life tools specifically developed for people with multimorbidity. Nevertheless, the use of generic instruments permits comparisons across disease categories (16).

In the research presented herein, HR-QOL was measured using two generic instruments, the Assessment of Quality of Life (AQoL) (88, 89) and EuroQol-5D-5L (EQ-5D-5L) (90, 91). The AQoL and EQ-5D-5L are valid and reliable instruments, with moderate levels of responsiveness and sensitivity in a wide range of health conditions (88, 91). The AQoL is widely used in Australian health research (92) and with Australian population norms (93). It measures five dimensions: illness, independent living, social relationships, physical senses and psychological wellbeing (89). The EQ-5D-5L is widely used in clinical trials, observational studies and other health surveys (94), and measures five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (90). The inclusion of two widely used but different HR-QOL tools within the feasibility studies in Chapters 3 and 4 allowed for the identification of the most suitable tool for future use.

For the study comparing multimorbidity to disease-specific rehabilitation, disease-specific HR-QOL measures were also performed. These were the Minnesota Living with Heart Failure Questionnaire (MLHF) for participants with a primary diagnosis of HF, and St George's Respiratory Questionnaire (SGRQ) for participants with a primary diagnosis of respiratory disease. The SGRQ and MLHF are reliable and valid instruments that are

sensitive and responsive to change after pulmonary rehabilitation (95) and trials for people with HF (96).

1.4.4 Activities of daily living

Functional status assessments measure the ability of an individual to perform activities required in daily life (97). A person can be considered disabled when an activity is limited in its nature, duration, or quality of performance (97). Activities of daily living include the fundamental skills generally required to manage basic physical needs, and are comprised of the following areas: grooming/personal hygiene, dressing, toileting/continence, transferring/ambulating and eating (98). Rehabilitation contributes to alleviating disability (97), and is evaluated through the assessment of an individual's functional status. Therefore, the measurement of disability or functional status is an essential component of rehabilitation (97). There are several tools available for the measurement of ADL.

In the studies described in this thesis, functional ADL were measured using the Katz Index of Independence in Activities of Daily Living (Katz ADL index). The Katz ADL index is used in older people to measure function (99) and has been used in people with chronic diseases (100). It is a simple and quick measure to administer, with yes/no answers for basic ADL (99). The Katz ADL index has been found to be reliable and have construct validity when used as a basic ADL measure in the elderly (101).

1.4.5 Healthcare resource utilisation

Economic evaluation is increasingly used to inform the decisions of various healthcare systems about which healthcare interventions to fund from available resources (102) and to curb costs without decreasing the quality of healthcare provided (103). For economic evaluation, it is first necessary to know the quantities of resources utilised, for example, number of doctors' visits or number of days in hospital. Once healthcare resource utilisation is known, the costs of the resources can be calculated (103).

Resource utilisation for the studies in Chapters 3 and 4 was focused on healthcare utilisation. It was measured by collecting data on emergency department presentations, hospital admissions and GP presentations during the trial periods and any health event necessitating hospital admission during the intervention period. Participants also maintained a daily diary recording all medical consultations with their GP or consultant physician and hospital admissions.

1.4.6 Measures of multimorbidity

Unlike single-disease trials, where measures of severity are well established (e.g. forced expiratory volume in COPD), there is no accepted measure of the severity or disease characteristics of people with multimorbidity. Because multimorbidity measures are used to describe a complex population, significant challenges exist in its definition, classification and measurement (75). An optimal comorbidity index to adequately describe or reflect the characteristics of people with multimorbidity, or to predict the impact of comorbidities on rehabilitation outcomes, has not been determined (104). Such descriptive tools are important to understand the characteristics of trial participants, to compare across studies and allow replication. Methods of quantifying multimorbidity in studies of costs and healthcare resource utilisation have tended to concentrate on diagnosis-based indices (105), such as the Charlson comorbidity index (CCI). Other important components include the severity, complexity and burden of each condition, and the overall impact on the individual (e.g. a few conditions that are very severe, versus a larger number of mild conditions).

There is also no gold standard measure of multimorbidity, and the tools currently available examine differing aspects of disease and burden (106). Several multimorbidity measures were included in the studies in Chapters 3 and 4, to determine which would be most suitable for larger-scale trials in terms of ease of use and quality of information obtained. These measures, their key features and measurement properties are described in Table 2.

Table 2. Components of multimorbidity measures.

	Cumulative Illness Rating Scale for Geriatrics	**Functional Comorbidity Index**	**Multimorbidity Illness Perception Scale**	**Duke Severity of Illness Checklist**
Population	Medically impaired elderly subjects	General population	Multimorbid patients	General population
Component measured	Illness severity	Physical function index	Illness perception	Illness severity
Content	14 body system categories	18-item index based on diagnosis of diseases	22 items •5 domains	Up to 10-item index based on health

	•severity scale for each domain: 0 = no problem 1 = current mild problem or past significant problem 2 = moderate disability or morbidity / requires first-line therapy 3 = severe / constant significant disability/ uncontrollable chronic problems 4 = extremely severe / immediate treatment required / end organ failure / severe impairment in function)	•yes/no response	•4-point Likert scale (for 4 domains) •6-point Likert scale (for 1 domain – emotional representations)	problems or diagnosis •4 parameters for each diagnosis •severity coding: 0 = none 1 = questionable 2 = mild 3 = moderate 4 = major
Domains	•heart •vascular •hematopoietic •respiratory	•arthritis (rheumatoid & osteoarthritis) •osteoporosis •asthma	•emotional representations •treatment burden •prioritising conditions •causal links	•symptoms •complications •prognosis without treatment •treatment potential

	•eyes, ears, nose, throat & larynx •upper gastrointestinal •lower gastrointestinal •liver •renal •genitourinary •musculoskeletal / integument •neurological •endocrine / metabolic & breast •psychiatric illness	•COPD, respiratory distress syndrome or emphysema •angina •congestive heart failure (or heart disease) •heart attack (myocardial infarct) •neurological disease (such as multiple sclerosis or Parkinson's) •stroke or transient ischemic attack •peripheral vascular disease •diabetes types I & II •upper gastrointestinal disease (ulcer, hernia, reflux)	•activity limitations	

		•depression •anxiety or panic disorders •visual impairment (such as cataracts, glaucoma, macular degeneration) •hearing impairment (very hard of hearing, even with hearing aids) •degenerative disc disease (back disease, spinal stenosis or severe chronic back pain) •obesity &/or BMI > 30		
Score	•score yields 5 numbers: 1. total number of categories endorsed 2. total score	•cumulative score (1 point per item) •single total score	•22-item summary scale •score for each domain	•overall severity score (calculated using equation which gives full weight to the

	3. severity index 4. number of categories at level 3 severity 5. number of categories at level 4 severity			diagnosis or health problem with the highest diagnosis severity score, and which gives progressively diminishing weights to the diagnoses with lower scores) •score for each diagnosis = % (sum of 4 parameter scores / 16 x 100)
Key features / remarks	•relies on clinical expertise of assessor – determine severity or complexity of medical conditions •need to obtain results of comprehensive investigations & tests •guide available to aid decisions	•simple to administer •the higher the score, the greater number of comorbidities	•unidimensional measure •allows for comparisons between patients and within patients over time	•assessor selects categories •score based on the clinical knowledge & judgement of health provider •measures burden of illness at a point in time •high severity parameter

	•scoring allows to see whether a total score reflects a few serious problems or multiple problems of mild to moderate severity			ratings indicate the presence of more symptoms, more complications, worse prognosis without treatment & worse expected response to treatment •score; 0 = lowest & 100 = highest
Reliability / validity	Good interrater reliability and face validity	Not stated	Demonstrated validity and reliability (preliminary evidence)	Modest level of reliability

COPD = chronic obstructive pulmonary disease; BMI = body mass index

Cumulative Illness Rating Scale for Geriatrics (107-109); Functional Comorbidity Index (110); Multimorbidity Illness Perception Scale (111); Duke Severity of Illness Checklist (112)

1.5 Summary

Given both the high prevalence and impact of multimorbidity, there is an urgent need for the development of more effective interventions. Evidence has shown that exercise rehabilitation can improve outcomes and mitigate the progression of many chronic diseases (113) and is recommended in guidelines and management for many single diseases (114). Therefore, exercise rehabilitation for people with multimorbidity may have a role to play in addressing common symptoms and risk factors of multiple chronic

diseases. It is important to determine if exercise-based rehabilitation that includes people with multimorbidity is feasible and can improve clinical outcomes for this population.

1.5.1 Aims and outline

The overarching aim of the research was to determine the current status and feasibility of delivering exercise rehabilitation programs for people with multimorbidity. To achieve this aim, three studies were conducted, each with its own specific aims.

Chapter 2 contains a systematic review and meta-analysis of the literature on the effects of exercise rehabilitation on clinical outcomes in people with multimorbidity. The review compared exercise rehabilitation to usual medical care and other interventions in people with multimorbidity. The primary outcome was exercise capacity; secondary outcomes were HR-QOL, ADL, cardiometabolic outcomes, mental health outcomes, symptom scores, resource utilisation, health behaviours, economic outcomes and adverse events.

Chapter 3 presents a pilot RCT comparing multimorbidity rehabilitation to usual medical care. The aims were to:

- evaluate the feasibility of a rehabilitation program for people with multimorbidity compared to usual medical care in people unable to access traditional disease-specific rehabilitation;
- gather preliminary data about the effects of these interventions on functional exercise capacity, ADL, HR-QOL and resource utilisation; and
- determine which multimorbidity measures were the most suitable for use in a larger-scale trial (115).

Chapter 4 presents a pilot RCT comparing multimorbidity rehabilitation to disease-specific rehabilitation. The aims were to:

- evaluate the safety and feasibility of multimorbidity rehabilitation compared to a disease-specific rehabilitation program in people with multimorbidity; and
- gather data about change in functional exercise capacity, ADL, HR-QOL and resource utilisation (the proposed outcomes for use in a future trial) (106).

CHAPTER 2

The effects of exercise rehabilitation on clinical outcomes in people with multimorbidity: A systematic review and meta-analysis.

The systematic review presented in Chapter 2 has been prepared for and submitted to the European Journal of Physical and Rehabilitation Medicine and is currently under review.

Declaration of Authorship – Chapter 2

Student's declaration

The nature and extent of contributions to Chapter 2 of this thesis are as follows.

Name	**Nature of contribution**	**Extent of contribution**	**Signature**
Kathryn Barker	Study concept & design; protocol development; literature review; data extraction & analysis; quality assessment; writing of manuscript & review	50%	
Annemarie Lee	Study concept & design; protocol development; literature review; quality assessment; data analysis; review of manuscript	20%	

Anne Holland	Study concept & design; protocol development; review of manuscript	20%
Elizabeth Skinner	Study concept & design; protocol development; review of manuscript	10 %

The effect of exercise rehabilitation on clinical outcomes in people with multimorbidity: A systematic review.

Running title: Exercise rehabilitation in multimorbidity

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Abstract

Introduction: A systematic review and meta-analysis to determine the effectiveness of exercise rehabilitation on clinical outcomes in people with multimorbidity. The primary outcome was exercise capacity and the 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.

Evidence acquisition: MEDLINE, CINHAL, EMBASE and the Cochrane Central Register of Controlled Trials databases were searched from inception to November 2019. Randomized and non-randomized controlled trials and cohort studies of exercise rehabilitation versus usual medical care or other interventions in people with multimorbidity were eligible for inclusion.

Evidence synthesis: Meta-analysis was performed where trials were sufficiently clinically or statistically homogeneous. Forty reports, for 34 studies were included. Rehabilitation ranged from eight weeks to four years, with 1-7 sessions of rehabilitation each week. Exercise included aerobic, aerobic and resistance, peripheral limb training, aquatic exercises and Tai Chi. The most common group was COPD and comorbidities. Compared to usual care, meta-analysis showed effects favouring exercise rehabilitation for 6-minute walk distance (weighted mean difference (WMD) 64 m, 95% CI 45 to 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 exercise rehabilitation, however few data were available for mental health, symptoms, health behaviours and cost-effectiveness.

Conclusions: In people with multimorbidity, improvement in exercise capacity, health-related quality of life and cardiometabolic outcomes were evident following exercise rehabilitation.

Keywords: rehabilitation; exercise; multimorbidity; comorbidity; chronic disease

Introduction

Multimorbidity, defined as the co-existence of two or more chronic conditions (1), is common in clinical practice (8) and is associated with many negative consequences, including increased risk of disability (9), frailty (9) and mortality (10, 11), poorer functional status (32), reduced health-related quality of life (HR-QOL) (15) and high healthcare costs (5). The increasing prevalence of multimorbidity generates financial pressures on healthcare systems, as expenditure on an individual's healthcare rises almost exponentially with the number of chronic diseases (18).

Rehabilitation is integral to chronic disease management. It has been described as therapies including exercise training, education and behavior change (36), with interventions designed to optimize function and reduce disability in individuals with health conditions (35). Evidence has shown that exercise and education can improve outcomes and mitigate the progression of many chronic diseases (113) and is recommended in guidelines and management for several single diseases (114). Worldwide healthcare delivery tends to be organized around the treatment of single diseases (1, 58, 59). As a result, people with multimorbidity are often managed according to several single-disease guidelines and this is reflected in rehabilitation, which is frequently structured as single-disease programs such as cardiac and pulmonary rehabilitation. While meta-analyses of single-disease programs have demonstrated improvements in exercise capacity, symptoms, HR-QOL, and reduced hospitalisation (46, 116-118), recent multimorbidity guidelines suggest that single-disease care may not be appropriate for people with multimorbidity (70). The low inclusion of people with multimorbidity in randomized control trials (RCT) reinforces the difficulty faced by healthcare professionals in creating appropriate clinical protocols (9) and guidelines. In a review of guidelines relevant to single-disease rehabilitation, three out of seven did not mention coexisting conditions and an additional three only briefly mentioned minor program adaptations to accommodate multimorbidity (52). 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 (8). The interventions were predominantly focused on organization of care, such as case management or multidisciplinary team-work, and educational or self-management support (8). It found no clear positive improvements in clinical outcomes, health service use, patient-related health behaviors or costs (8). The review suggests that interventions designed to target difficulties that people experience with daily functioning (e.g.

physiotherapy) may be more effective (8). However, exercise rehabilitation was not delivered in any of 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 aims to determine the effectiveness of exercise rehabilitation on clinical outcomes in people with multimorbidity, with the primary outcome of exercise capacity. This review was registered on PROSPERO on 29/08/2018 (CRD42018100512).

Materials and Methods

This systematic review was reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (119).

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 English only were included due to lack of access to translation services. We excluded systematic reviews, case studies and cross-sectional studies.

Types of participants

We included any participants with multimorbidity, defined as two or more chronic diseases (1), and used the World Health Organization definition of chronic disease: health problems that require ongoing management over a period of years or decades (120). 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

We included rehabilitation programs of at least four weeks duration that included exercise with or without any form of education or psychological support (40, 41, 46), 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 (40, 41, 46). There was no criteria specified for exercise type, frequency or intensity or follow-up period to enable widespread search results. We excluded programs without exercise

training or those aimed at a single joint (e.g. hip) that 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 did not include exercise training (e.g. education or psychological support only). Usual medical care was defined as general inpatient or outpatient care, including medical, nursing or allied health intervention. Studies comparing rehabilitation with UMC were analyzed separately to those comparing to other interventions.

Types of outcomes

The primary outcome was exercise capacity as measured by one or more of: laboratory-based exercise testing (e.g. cardiopulmonary exercise test [CPET]) and / or field walking tests (e.g. six-minute walk test, incremental shuttle walk test).

The secondary outcomes were: HR-QOL (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. dyspnea, fatigue); resource utilization (e.g. hospital admissions, general practitioner visits); health behaviors (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 one 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 1/11/2019: 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 Supplementary Table 1 and was adapted for use in the other databases. Reference lists of the identified articles were hand searched. We also searched the following trial registry, using the same search strategies: 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, AL) 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, AL) completed data extraction using a priori data extraction template developed by the authors. The following data from included studies were extracted: (1) details of the intervention including: provider, delivery, location, dosage and tailoring (121); additional components (e.g. education or psychological support); (2) participants: nature of multimorbidity and how it was defined; age; (3) trial setting; (4) study design; (5) comparators; (6) outcome measures; and (7) results. Where another report was referenced in the methods for further detail, this report was sourced and used to obtain the detailed information required. The software program WebPlotDigitizer (122) was used to extract data from studies that displayed via figures and graphs only.

Assessment of risk of bias

The risk of bias of the RCT, NRCTs and cohort studies were independently assessed using the Joanna Briggs Institute critical appraisal tools for the specific study design (123). 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 (124). Two review authors (KB, AL) independently extracted the data and clarification was obtained using consensus discussion to confirm complete agreement.

Data analysis

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

Meta-analysis

Meta-analysis was performed where 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 (125) and Cohen's definition of ES of 0.2 as small, 0.5 as moderate and 0.8 or greater as large (126) 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% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity (124). The fixed-effects model was used in the absence of heterogeneity; otherwise a random-effects model was used.

Subgroup analyses

Subgroup analyses was performed based on (1) the definition of multimorbidity (i.e. two diseases vs three or more diseases), as these have been shown to have differences in prevalence (127, 128) and mortality (9); and (2) the length of rehabilitation (four to eight weeks vs >eight weeks), as in clinical practice, it is common for rehabilitation programs to have durations of four to eight weeks and research trials may have durations greater than eight weeks.

Sensitivity analysis

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

Results

The searches identified 23,995 studies (excluding duplicates), of which 23,862 were excluded based on title and abstract. Of the 133 full text studies screened, 93 were excluded. The reasons for exclusion are detailed in Figure 1. The final search outcome was 40 reports, resulting from 34 studies. Nine studies (ten reports) were reported only

as abstracts (129-138). There were 13 RCTs, one randomized crossover trial, 19 cohort studies and one quasi-experimental study.

Study characteristics are in Table 1. The most common sample in the studies was COPD and comorbidities [diagnosis not specified] (n = 6), followed by CHD and diabetes (n = 4). Multimorbidity groups were defined as two and three or more (n = 4), two to three and four or more (n = 1), distinct clusters (e.g. respiratory conditions, musculoskeletal conditions or neurological conditions) (n = 2) or using a weighted comorbidity score (Charlson comorbidity index (CCI)) (n = 1).

Intervention details are outlined in Supplementary Table 2. Duration of the rehabilitation interventions ranged from eight weeks to up to four years, with frequency of exercise sessions 1-7 sessions/week. The types of exercise included aerobic, aerobic and resistance, peripheral limb training, aquatic exercises and Tai Chi. The rehabilitation was performed in several different locations, including supervised setting (n = 1), center-based (n = 1), community exercise facility (n = 1), medical center (n = 2), community-based (n = 3), home-based (n = 9) and hospital-based (n = 14); with some studies at multiple locations. Comparisons included UMC (n = 5), no exercise (n = 3), diet and sham exercise (n = 1), 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 Supplementary Tables 3, 4 and 5. For the RCTs and randomized crossover trial, 13 out of 14 reported not having participant or therapist blinding. Only five studies reported assessor blinding and the remaining nine 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 heterogenous, as defined in the methods section. Meta-analysis was performed for three outcomes: 6-minute walk distance (6MWD), peak oxygen consumption (VO_2) and BMI.

Exercise rehabilitation versus usual medical care

Nine studies (12 reports) compared exercise rehabilitation versus UMC (74, 129, 133, 139-147). The findings for studies are outlined in Table 2.

Exercise capacity

The 6MWD was reported in four studies (six reports) (74, 133, 140, 142, 144, 145), of which two (74, 142) were included in meta-analysis. Meta-analysis showed a weighted mean difference (WMD) of 64m (95% CI 45 to 82) in favor of exercise rehabilitation (Figure 2). A randomized crossover trial of a 12-week aquatic exercise program showed an increased 6MWD from 395 meters (m) (143.9) to 412m (147.9), p=0.046 (133). However, no details of the comparison group were provided, an assumption was that the comparison group was usual medical care. The VO_2 peak (129, 140, 141, 143-146) was reported in four studies (seven reports), of which three (141, 143, 146) were included in meta-analysis. Meta-analysis showed a WMD of 2.74 ml/kg/min (95% CI -3.32 to 8.79) in favor of exercise rehabilitation (Figure 3) with significant heterogeneity, I^2 = 90%. One study (74) reported on endurance shuttle walk distance (ESWD) and incremental shuttle walk distance (ISWD). Significant improvement in both outcomes were found in the water-based rehabilitation group compared to 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 favor of land-based rehabilitation, however these results did not reach statistical significance.

Subgroup analysis

Duration: One study (74) with a rehabilitation duration of four to eight weeks had an ES for 6MWD of 1.76 (land-based) and 1.86 (water-based), whereas one study (142) with a duration of greater than eight weeks (16-weeks) had an ES of 0.69. All four studies (seven reports) reporting VO_2 peak (129, 140, 141, 143-146) had durations of greater than eight 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 or psychological support to an exercise program varied across studies and outcomes. Studies of exercise only had ESs of 1.76 to 1.86 for 6MWD (74) and 0.03 to 0.15 for VO_2 peak (141, 142). Studies of exercise plus education or psychological support has ESs of 0.69 for 6MWD (142) and 2.17 for VO_2 peak (146).

HR-QOL

The Minnesota living with heart failure questionnaire (MLHFQ) was reported in two studies (142, 146); both showed large ESs of 0.73 and 1.56, favoring exercise rehabilitation. One study (two reports) (140, 145) showed a significant improvement in

the Kansas City cardiomyopathy questionnaire following exercise rehabilitation (140); ES was unable to be calculated. One study (141) 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. Effect size ranged from small 0.06 (nine domains) to large 1.20 (two domains) favoring exercise rehabilitation. One study (142) demonstrated significant improvement in the COPD assessment test in favor of exercise rehabilitation with a large ES of 1.17. One study (74) applied the chronic respiratory disease questionnaire (CRDQ); the water-based rehabilitation group compared to UMC showed significant difference in change for three out of four domains (dyspnea, fatigue and emotion) in favor of exercise rehabilitation, however ESs were unable to be calculated.

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

Body mass index was significantly reduced with exercise rehabilitation and had a large ES of 2.20 (139). Two studies (143, 147) reported hemoglobin A1c (HbA1c), with one (147) study showing a large ES, of 4.93, in favor of exercise rehabilitation. The other study (143) showed a reduction in HbA1c following exercise rehabilitation, however it was not significant, and ES was unable to be calculated. One study (147) reported systolic BP and diastolic BP, both showed a large ESs of 2.67 and 1.97 respectively, favoring exercise rehabilitation. One study (141) reported C-reactive protein (CRP); there was no significant difference in change between groups, despite a large ES of 0.89, favoring exercise rehabilitation. One study (143) reported homeostasis model assessment-insulin resistance-index (HOMA-IR), insulin and glucose and did not show significant differences in change between groups for these outcomes, and ESs were unable to be calculated. One study (147) reported heart rate (HR) variability with a large ES, of 4.67, favoring exercise rehabilitation, however this did not reach statistical significance.

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 one study (74), with no significant differences between groups for either anxiety or depression.

Symptoms

Dyspnea, measured by the medical research council dyspnea scale (MRC), was reported in one study (142) with a significant reduction in dyspnea in favor of exercise rehabilitation and a moderate ES of 0.37.

Health behaviours

One study (141) reported steps and physical activity with no significant differences found for either outcome. The step count showed a small ES of 0.09, while physical activity questionnaire had a large ES of 1.24, favoring exercise rehabilitation.

Adverse events

Only one of the nine included studies reported on adverse events (143), 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], hypoglycemia 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 (143). 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 versus other intervention

Five studies (seven reports) reported exercise rehabilitation versus other interventions (131, 132, 137, 148-151), including diet and sham exercise (149, 150), phone call only (131, 132), diet (148), usual physical activity (151) and mind-body education (137) interventions. The findings for studies are outlined in Table 3.

Exercise capacity

One study reported VO_2 peak (149) and demonstrated significant improvement post-intervention for aerobic and resistance exercise with diet compared to sham-exercise (breathing and stretches) with diet.

HR-QOL

The asthma QOL questionnaire was reported in one study (149), demonstrating better HR-QOL post-intervention for aerobic and resistance exercise with diet compared to sham-exercise (breathing and stretches) with diet.

Cardiometabolic

Body mass index was reported in two studies (three reports) (148-150). Meta-analysis showed a WMD of -2.92 kg/m^2 (95% CI -6.26 to 0.43) in favor of exercise rehabilitation and diet compared to sham exercise (breathing and stretches) and diet or diet only, but heterogeneity was high (Figure 4). One study (151) reported HbA1c with no significant differences and a small ES of 0.01, comparing aerobic and resistance exercise rehabilitation to usual physical activity. One study (132) found no significant differences in CRP between aerobic exercise rehabilitation with a weekly phone call or a weekly phone call only. One study (148) reported HOMA2-IR and showed a large ES, of 1.26, in favor of aerobic exercise rehabilitation with low calorie diet, compared to low calorie diet alone. Total cholesterol, triglycerides, low density lipoprotein (LDL) and high density lipoprotein (HDL) were reported in one study (132) and there were no significant differences found for any of these outcomes, comparing aerobic and resistance exercise rehabilitation to 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, favoring exercise rehabilitation (148). A study of exercise and diet plus education or psychological support had an ES of 1.33 for BMI, favoring exercise rehabilitation and diet (150) compared to sham exercise (breathing and stretches) and diet.

Mental health

One study (150) reported significant reduction in depression measured on HADS with a large ES of 1.11, in favor of aerobic and resistance exercise rehabilitation with diet compared to sham-exercise (breathing and stretches) with diet. While the anxiety domain did not show a significant difference, there was a large ES of 0.72. One study (131) reported depressive symptoms, however the tool used was not stated and no significant difference was demonstrated, despite a large ES of 3.73 favoring exercise rehabilitation and weekly phone call compared to weekly phone call only. The structured interview for Hamilton depression scale was reported in one study (137). No data were provided but it stated there were statistically significant reductions in scores which demonstrated improvement for both the intervention (Tai Chi) and control (mind-body education) groups at the end of intervention (137).

Symptoms

The asthma control questionnaire was reported in one study (149). There was improved asthma control in those who undertook aerobic and resistance exercise rehabilitation with diet compared to sham-exercise (breathing and stretches) with diet.

Exercise rehabilitation in cohort/quasi-experimental studies

Twenty studies (21 reports) reported effects of exercise rehabilitation using cohort or quasi-experimental designs (49, 50, 54, 130, 134-136, 138, 152-164) (Table 4).

Exercise capacity

Nineteen studies (20 reports) (49, 50, 54, 130, 135, 136, 138, 152-164) reported measures of exercise capacity with clinically significant improvements following exercise rehabilitation in 6MWD (49, 130, 156), VO_2 peak (50, 152, 153, 155, 162, 163), metabolic

equivalents (136, 155, 164), HR recovery (158), maximal symptom limited incremental cycle ergometer time (160) and peak HR (158) (Table 4).

HR-QOL

Eight studies (nine reports) (54, 138, 152-154, 156, 157, 160, 161) reported measures of HR-QOL with clinically significant improvements following exercise rehabilitation in short form-36 (152, 153) and diabetes QOL questionnaire (153) (Table 4).

Cardiometabolic

Eight studies (49, 50, 134, 136, 152, 153, 155, 159) reported cardiometabolic measures with clinically significant improvements following exercise rehabilitation in BMI (49, 152, 155), HbA1c (134, 153), systolic BP (152), diastolic BP (136), CRP (152), insulin (152), glucose (136), total cholesterol (136, 152), triglycerides (134, 136, 152), HDL (136, 152, 153) and LDL (136) (Table 4).

Mental health

Four studies (136, 152, 153, 157) reported measures of mental health with clinically significant improvements following exercise rehabilitation in the Beck depression index (136, 152, 153) (Table 4).

Symptoms

Three studies (152, 154, 157) reported symptom measures with no clinically significant improvements following exercise rehabilitation (Table 4).

Health behaviours

One study (153) reported health behavior measures with clinically significant improvements following exercise rehabilitation in the chronic illness survey (Table 4).

Adverse events

One study (130) reported an adverse event outcome, defined as accidents or complications, and reported that none occurred during the intervention.

Discussion

This is the first systematic review of studies of exercise rehabilitation in people with multimorbidity. When compared to UMC, improvement in exercise capacity (peak exercise and selected measures of functional exercise tolerance), HR-QOL and a mix of

cardiometabolic outcomes were evident for exercise rehabilitation. These findings were consistent with outcomes from single-disease rehabilitation programs which included individuals with multimorbidities (47, 165), with noted improvements in blood pressure and other cardiometabolic parameters. This suggests that either disease-specific or multimorbidity exercise rehabilitation programs may be suitable for people with multimorbidities to target improvements in these outcomes. A range of ES were identified for the included studies (range 0.03 to 4.93) which may be attributable to the type of program applied (e.g. water vs land-based) (74) 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 to 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 (143), 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 program may encounter musculoskeletal events (166, 167), and likelihood of this may be increased in the multimorbidity population with a history of sedentary behavior. 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 program for the multimorbidity population have been illustrated (168, 169). We recommend future studies report on adverse events and specify the type, severity and timing and their temporal relationship to the intervention.

When compared to other interventions (ranging from dietary advice, usual physical activity, distant support and education), improvement in exercise capacity, HR-QOL, 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 (170), these findings support what has been previously demonstrated when comparing exercise rehabilitation to other interventions (171-173). The lack of difference between groups for HbA1c (151) may be attributed to the inclusion of exercise as part of usual physical activity (<150 minutes per week) in the comparative group. While there were no statistically significant differences found for CRP, cholesterol and triglyceride measures, ESs were not able to be calculated for this study (132);

therefore the results may have some clinical significance, with the magnitude unable to be determined.

A mix of approaches 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 programs, such as cardiac and pulmonary rehabilitation, whilst others established new exercise rehabilitation programs. This heterogeneity may impact the conclusions for the outcomes reviewed. Further research into the feasibility of multimorbidity rehabilitation programs and the outcomes achieved, within single-disease or new programs, 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 programs 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 the benefits achieved may be attributed to effects of exercise, although few studies included a comprehensive assessment of psychological outcomes. For symptoms, the lack of impact on anxiety and depression or symptom of dyspnea may be attributable to the baseline levels of depression and anxiety 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 behaviors such as physical activity or medication adherence, or healthcare costs. Such 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 (174), 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 (59). 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 one 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. 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 it was unclear regarding assessor blinding for 64% of the studies. This also could have a significant affect on outcomes such as bias towards positive results, particularly if it was that the assessors were not blinded. Sample sizes ranged from six 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.

Conclusions

In people with multimorbidity, improvement in exercise capacity, HR-QOL and cardiometabolic outcomes were evident for 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 programs or in specialized multimorbidity exercise rehabilitation programs.

Conflicts of Interest

The authors certify that there is no conflict of interest with any financial organisation regarding the material discussed in the manuscript.

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Author Contributions

KB and AL have given substantial contributions to the conception or design of the manuscript, to acquisition, analysis and interpretation of the data. AH have given substantial contributions to the conception or design of the manuscript, to analysis and interpretation of the data. All authors have participated to drafting the manuscript and revising it critically. All authors read and approved the final version of the manuscript.

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Table 1. Characteristics of included studies (n = 34).

Study	Country n	Study Type	Diseases	Participants	Intervention	Duration of Rehabilitation	Outcomes
Abd El-Kader 2013(139)	Saudi Arabia 80	RCT	Obesity Bronchial asthma	Age# (range) = 12 to 18 53% males#	Int = aerobic exercise; diet; medical treatment Com = usual medical care	8 weeks	BMI
Al-Jiffri 2013(148)	Saudi Arabia 100	RCT	NAFLD Diabetes	Age# (range) = 35 to 55 100% males#	Int = aerobic exercise; diet Com = diet only (no exercise)	3 months	BMI HOMA-IR
Barnes 2009(152)	Australia 12	Cohort	OSA Obesity	Age# = 42 (10.4) 25% males#	Int = aerobic & resistance exercise; diet Com = N/A	16 weeks	VO_2 peak BMI BP Lipids Insulin & glucose SF-36 POMS BDI FOCQ SASQ CRP

Beaudoin 2017(141)	Canada 17	RCT	Cystic fibrosis	Age* (mean, SEM) = 32 (24, 41) 38% males*	Int = aerobic & resistance exercise	12 weeks	VO_2 peak Cystic fibrosis questionnaire-revised Physical activity questionnaire Physical activity monitor (steps) CRP
			Impaired glucose tolerance	Age* (mean, SEM) = 36 (22, 57) 50% males*	Com = usual medical care		
Bernocchi 2018(142)	Italy 112	RCT	COPD	Age* = 71 (9) 88% males*	Int = aerobic & resistance exercises; education	4 months	6MWT MLHFQ CAT MRC PASE
			Heart failure	Age* = 70 (9.5) 75% males*	Com = usual medical care		
Byrkjeland 2015(143)	Norway 137	RCT	T2DM	Age* = 65 (7.6) 87% males*	Int = aerobic & resistance exercise	12 months	VO_2 peak HbA1c Glucose Insulin HOMA2-IR Adverse event (all medical events)
			CAD	Age* = 63 (7.2) 81% males*	Com = usual medical care		
Castro 2015(130)	Portugal 19	Cohort	CKD	Age# = 72 (10) 33% males#	Int = aerobic & resistance exercise; hemodialysis	16 weeks	6MWT Accident or complication
			Diabetes		Com = N/A		

Collins 2010(131)	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(54)	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
de Groot 2012(153)	USA 50	Quasi-experimental	Diabetes Major depressive disorder	Age[#] = 57 (9.0) 32% males[#]	Int = aerobic & resistance exercise; cognitive behavioral 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
Freitas 2018(150)	Brazil 55	RCT	Asthma	Age[*] = 46 (7.7) 4% males[*]	Int = aerobic & resistance exercise; diet; education; psychological support	3 months	BMI HADS

			Obesity	Age* = 49 (9.6) 0% males*	Com = sham exercise (breathing & stretches); diet; education; psychological support		
Halvari 2017(151)	Norway 137	RCT	CAD Diabetes	Age# = 63 (7.9) 81% males#	Int = aerobic & resistance exercise Com = usual physical activity	12 months	HbA1c
Hassan 2016(154)	Egypt 55	Cohort	COPD Comorbidities	Age# = 60 (8.9) 93% males#	Int = aerobic & resistance exercise; education Com = N/A	8 weeks	6MWT VO_2 maximum mMRC SGRQ
Johnson 2014(133)	Not stated 30	Randomized crossover trial	Diabetes Lower limb arthritis	Age# = 68 (6.9) 53% males#	Int = aquatic exercise (details not provided) Com = NS	12 weeks	6MWT
Khadanga 2016(155)	USA 898	Cohort	CHD Insulin resistance or diabetes	Age# = 64 (11.1) 73% males#	Int = aerobic & resistance exercise; education Com = N/A	3-4 months (maximum 36 sessions)	VO_2 peak Peak METS BMI
Kurian 2010(134)	USA 22	Cohort	Diabetes Peripheral neuropathy	Age# = elderly 68% males#	Int = resistance exercise Com = N/A	12 weeks	HbA1c Lipids
Listerman 2011(49)	USA 749	Cohort	CHD	Age# = 62 (10.6) 71% males#	Int = aerobic & resistance exercise; education; psychological support	24-36 sessions	6MWT BMI

			Comorbidities		Com = N/A		
Martin 2016(135)	Canada 15,927	Cohort	CHD PAD	Age & gender details not stated	Int = details not provided Com = N/A	12 weeks	METs
McNamara 2013(74)	Australia 53	RCT	COPD Comorbidities	Age* = 73 (7) 50% males* Age* = 72 (10) 28% males* Age* = 70 (9) 47% males*	Int 1 = aerobic & resistance exercise (land-based) Int 2 = aerobic & resistance exercise (water-based) Com = no exercise	8 weeks	6MWT ESWT ISWT CRDQ HADS
Mentz 2013(145)	USA 2,331	RCT	Heart failure COPD	Age# (median) = 59 72% males#	Int = aerobic exercise; education Com = usual medical care; education	Up to 4 years	VO_2 peak 6MWT KCCQ
Mesquita 2015(156)	Netherlands 213	Cohort	COPD Comorbidities	Age# = 64 (7) 59% males#	Int = details not provided Com = N/A	8 weeks (inpatient) Or 14 weeks (outpatient)	6MWT CWRT SGRQ
Mundra 2013(136)	USA 120	Cohort	CVD Obesity	Age details not stated 70% males#	Int = details not provided Com = N/A	8-12 weeks	METs BMI BP Lipids Glucose BDI

Naz 2019(157)	Turkey 211	Cohort	COPD Comorbidities	Age[#] (median, IQ range) = 64 (58, 68) 89% males[#]	Int = aerobic & resistance exercise Com = N/A	8 weeks	6MWT SGRQ mMRC HADS SF-36
Nonoyama 2016(50)	Canada 1,247	Cohort	IHD Comorbidities	Age[¥] = 61 (8.3) 96% males[¥] [no comorbidities] Age[¥] = 67 (10.1) 78% males[¥] [non-respiratory comorbidity] Age[¥] = 61 (10.1) 89% males[¥] [respiratory comorbidity]	Int = aerobic & resistance exercise; education; psychological support Com = N/A	6-12 months	VO_2 peak BMI
Servantes 2012(146)	Brazil 50	RCT	Heart failure Sleep apnea	Age[*] = 52 (9.83) 47% males[*] Age[*] = 51 47% males[*] Age[*] = 53 (8.19) 46% males[*]	Int 1 = aerobic exercise; education Int 2 = aerobic & resistance exercise; education Com = no exercise	3 months	VO_2 peak MLHFQ

Soleimani 2009(158)	Netherlands 284	Cohort	IHD Diabetes	Age[#] = 57 (11.1) 72% males[#]	Int = aerobic exercise; diet counselling; psychological support Com = N/A	8 weeks	Resting HR Peak HR Post-exercise HR HR recovery
Sridhar 2010(147)	Malaysia 105	RCT	Diabetes Hypertension	Age[*] = 62 (3.10) 55% males[*] Age[*] = 59 (2.75) 56% males[*]	Int = aerobic exercise Com = no exercise	12 months	BP HbA1c HR variability
Srinivasan 2014(137)	USA 16	RCT	Major depressive disorder Arthritis pain disorder	Age[#] = 72 (5.24) Gender details not stated Age[#] = 74 (7.07) Gender details not stated	Int = Tai Chi; antidepressant treatment Com = mind-body education; antidepressant treatment	8 weeks	SIGHD
Takaya 2014(159)	Japan 528	Cohort	AMI CKD	Age[¥] = 62 (10) 81% males[¥] [non-CKD] Age[¥] = 68 (9) 84% males[¥] [CKD]	Int = aerobic exercise; education Com = N/A	3 months	VO_2 peak BMI HR recovery
Tunsupon 2017a(160)	USA 165	Cohort	COPD Comorbidities	Age[#] (mean) = 70 96% males[#]	Int = aerobic & resistance exercise Com = N/A	8 weeks	6MWT MIET CWET

							CRQ
Verges 2004(162)	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		
Wang 2013(163)	Taiwan 90	Cohort	Heart failure	Age¥ = 63 (2.10) 47% males¥ [HF & non-Anemic]	Int = aerobic exercise	12 weeks	VO_2 peak
			Anemia	Age¥ = 64 (2.3) 40% males¥ [HF & Anemic]	Com = N/A		
				Age¥ = 62 (2.1) 47% males¥ [Normal control]			
Woodard 1994(164)	USA 28	Cohort	CVD	Age¥ = 61 (1.7) Gender details not stated [Comorbidity]	Int = aerobic exercise	6 months	METs
			Knee arthritis	Age¥ = 59 (2.0) Gender details not stated	Com = N/A		

				[CVD only]			
Zwerink 2010(138)	Netherlands 6	Cohort	COPD Heart failure	Age# = 70 (5) Gender details not stated	Int = aerobic & resistance exercise; education Com = N/A	10 weeks	6MWT ISWT MLHFQ CRQ

Age is mean (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; OSA = obstructive sleep apnea; N/A = not applicable; 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 apnea symptom questionnaire; CRP = C-reactive protein; SEM = standard error mean; COPD = chronic obstructive pulmonary disease; 6MWT = 6-minute walk test; MLHFQ = Minnesota living with heart failure questionnaire; CAT = COPD assessment test; MRC = dyspnea by Medical Research Council; PASE = physical activity profile; T2DM = type 2 diabetes mellitus; CAD = coronary artery disease; HbA1c = hemoglobin A1c; HOMA2-IR = homeostasis model assessment 2-insulin resistance-index; CKD = chronic kidney disease; USA = United States of America; PAD = peripheral arterial disease; SGRQ = St George's respiratory questionnaire; HADS = hospital anxiety depression scale; mMRC = modified dyspnea 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

Table 2. Outcomes of studies of exercise-rehabilitation versus usual medical care.

Study	Intervention (exercise type)	Outcome	Results (intervention)	Results (control)	Effect size	Notes
Exercise capacity						
Ambrosy(140)	Aerobic	6MWD (m)	HF+CKD: -7 (95% CI -13 to 0)	NR	NA	p = 0.04* Mean change (within group p-value)
Bernocchi(142)	Aerobic & resistance	6MWD (m)	60 (95% CI 22.2 to 97.8)	-15 (95% CI -40.3 to 9.8)	d = 0.69	p = 0.004* Mean change (between group p-value)
Johnson(133)	Details not provided	6MWD (m)	17	NR	--	p = 0.046 mean change (SD not stated)
McNamara(74)	Aerobic & resistance	6MWD (m)	land 43 (95% CI 22 to 63) water 48 (95% CI 22 to 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(145)	Aerobic	6MWD (m)	19 (IQR -9 to 69)	1 (IQR -41 to 40)		p = 0.16 Median (IQR) change
Beaudoin(141)	Aerobic & resistance	VO2 peak (ml/kg/min)	24.53 (SD 4.01)	25.35 (SD 6.79)	d = 0.15	ns Post-intervention
Byrkjeland(143)	Aerobic & resistance	VO2 peak (ml/kg/min)	25.4 (SD 5.4)	25.2 (SD 6.7)	d = 0.03	p = 0.0777 Post-intervention
Mentz(145)	Aerobic	VO2 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(146)	Aerobic & resistance	VO2 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(74)	Aerobic & resistance	ESWD (m)	land 117 (95% CI -3 to 236) water 321 (95% CI 123 to 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(74)	Aerobic & resistance	ISWD (m)	land 13 (95% CI -16 to 43) water 49 (95% CI 26 to 73)	-1 (95% CI -24 to 22)	land d = 0.28	land Vs Con: p = 0.542 water Vs Con: p = 0.005*

						water d = 1.27	Mean change (between group p-values)
Health-related quality of life							
Bernocchi(142)	Aerobic 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(146)	Aerobic 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(141)	Aerobic resistance	&	QCFQR: physical functioning (%)	80.2 (SD 16.78)	81.93 (SD 16.82)	d = 0.10	ns Post-intervention
Beaudoin(141)	Aerobic resistance	&	QCFQR: vitality (%)	58.33 (SD 19.2)	54.18 (SD 20.91)	d = 0.21	ns Post-intervention
Beaudoin(141)	Aerobic resistance	&	QCFQR: emotional state (%)	81.66 (SD 12.73)	83.33 (SD 15.06)	d = 0.12	ns Post-intervention
Beaudoin(141)	Aerobic resistance	&	QCFQR: eating disturbance (%)	98.61 (SD 3.92)	100 (SD 0)	d = unable to calc	ns Post-intervention
Beaudoin(141)	Aerobic resistance	&	QCFQR: treatment burden (%)	65.29 (SD 28.14)	68.52 (SD 21.59)	d = 0.13	ns Post-intervention
Beaudoin(141)	Aerobic resistance	&	QCFQR: health perception (%)	58.34 (SD 23.59)	74.1 (SD 15.17)	d = 0.79	ns Post-intervention
Beaudoin(141)	Aerobic resistance	&	QCFQR: social limitations (%)	75.28 (SD 13.02)	72.22 (SD 18.24)	d = 0.19	ns Post-intervention
Beaudoin(141)	Aerobic resistance	&	QCFQR: body image (%)	84.74 (SD 8.26)	81.5 (SD 18.13)	d = 0.23	ns Post-intervention
Beaudoin(141)	Aerobic resistance	&	QCFQR: role limitations (%)	83.33 (SD 25.2)	84.73 (SD 21.99)	d = 0.06	ns Post-intervention
Beaudoin(141)	Aerobic resistance	&	QCFQR: weight problems (%)	87.5 (SD 24.81)	83.33 (SD 40.82)	d = 0.12	ns Post-intervention
Beaudoin(141)	Aerobic resistance	&	QCFQR: respiratory symptoms (%)	62.5 (SD 14.47)	65.75 (SD 8.17)	d = 0.28	ns Post-intervention
Beaudoin(141)	Aerobic resistance	&	QCFQR: digestive symptoms (%)	84.74 (SD 10.17)	69.53 (SD 14.79)	d = 1.20	ns Post-intervention

Bernocchi(142)	Aerobic 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(74)	Aerobic resistance	&	CRDQ -dyspnea	land Vs Con: 1.6 (95% CI -0.8 to 4.0) water Vs Con: 3.3 (95% CI 0.9 to 5.6)	NA	--	land Vs Con: p = 0.193 water Vs Con: p = 0.007* Mean difference (between group p-values)
McNamara(74)	Aerobic resistance	&	CRDQ - fatigue	land Vs Con: 1.6 (95% CI -0.7 to 3.9) water Vs Con: 4.7 (95% CI 2.4 to 7.0)	NA	--	land Vs Con: p = 0.163 water Vs Con: p < 0.001* Mean difference (between group p-values)
McNamara(74)	Aerobic resistance	&	CRDQ - emotion	land Vs Con: 0.1 (95% CI -2.8 to 3.1) water Vs Con: 3.1 (95% CI 0.1 to 6.1)	NA	--	land Vs Con: p = 0.921 water Vs Con: p = 0.046* Mean difference (between group p-values)
McNamara(74)	Aerobic 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(140)	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(145)	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(140)	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
Cardiometabolic							
Abd El-Kader(139)	Aerobic		BMI (kg/m^2)	27.15 (SD 2.38)	32.14 (SD 2.16)	d = 2.20	p < 0.05*

							Post-intervention (between group p-value)
Byrkjeland(143)	Aerobic & resistance		HOMA2-IR	1.10 (IQR 0.80 to 1.70)	1.25 (IQR 0.80 to 1.68)	NA	p = 0.31 Post-intervention: median (IQR)
Byrkjeland(143)	Aerobic & resistance		HbA1c (%)	7.2 (IQR 6.6 to 7.8)	7.4 (IQR 6.5 to 8.2)	--	p = 0.24 Post-intervention: median (IQR)
Sridhar(147)	Aerobic		HbA1c (%)	7.44 (SD 0.44)	9.84 (SD 0.53)	d = 4.93	p < 0.01* Post-intervention
Sridhar(147)	Aerobic		Systolic BP (mmHg)	135.53 (SD 3.54)	146.03 (SD 4.28)	d = 2.67	p < 0.05* Post-intervention
Sridhar(147)	Aerobic		Diastolic BP (mmHg)	82.82 (SD 1.07)	88.15 (SD 3.68)	d = 1.97	p < 0.05* Post-intervention
Byrkjeland(143)	Aerobic & resistance		Insulin (mmol/L)	49 (IQR 32 to 78)	48 (IQR 33 to 78)	NA	p = 0.56 Post-intervention: median (IQR)
Byrkjeland(143)	Aerobic & resistance		Glucose (mmol/L)	8.0 (IQR 6.7 to 9.3)	7.8 (IQR 6.7 to 9.0)	--	p = 0.63 Post-intervention: median (IQR)
Beaudoin(141)	Aerobic & resistance		CRP (mg/L)	2.1 (SD 1.37)	6.57 (SD 7.0)	d = 0.89	ns Post-intervention
Sridhar(147)	Aerobic		HR variability (bpm)	15.71 (SD 0.61)	13.02 (SD 0.54)	d = 4.67	ns Post-intervention
Mental health							
McNamara(74)	Aerobic & 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(74)	Aerobic & 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(142)	Aerobic 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 behaviors							
Banks(129)	Aerobic		Exercise adherence (%)	HF+DM: 35.2%	NA	--	p = 0.02*
Beaudoin(141)	Aerobic resistance	&	Physical activity questionnaire (%)	76.27 (SD 8.47)	59.08 (SD 17.65)	d = 1.24	ns Post-intervention
Beaudoin(141)	Aerobic resistance	&	Steps (no./day)	8644 (SD 1900)	8848 (SD 2730)	d = 0.09	ns Post-intervention
Adverse events							
Byrkjeland(143)	Aerobic 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-minute walk distance; m = meters; HF = heart failure; CKD = chronic kidney disease; CI = confidence interval; Con = control; IQR = interquartile range; VO2 peak = oxygen consumption; ml/kg/min = milliliters/kilogram/minute; 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; kg/m^2 = kilograms/meters^2; HOMA2-IR = Homeostasis Model Assessment2-Insulin Resistance index; HbA1c = hemoglobin A1c; BP = blood pressure; mmHg = millimeters of mercury; mmol/L = millimoles/liter; CRP = C-reactive protein; mg/L = milligrams/liter; HR = heart rate; bpm = beats per minute; HADS = hospital anxiety & depression scale; MRC = Medical research council dyspnea scale; no. = number

Figure 1. PRISMA flow diagram

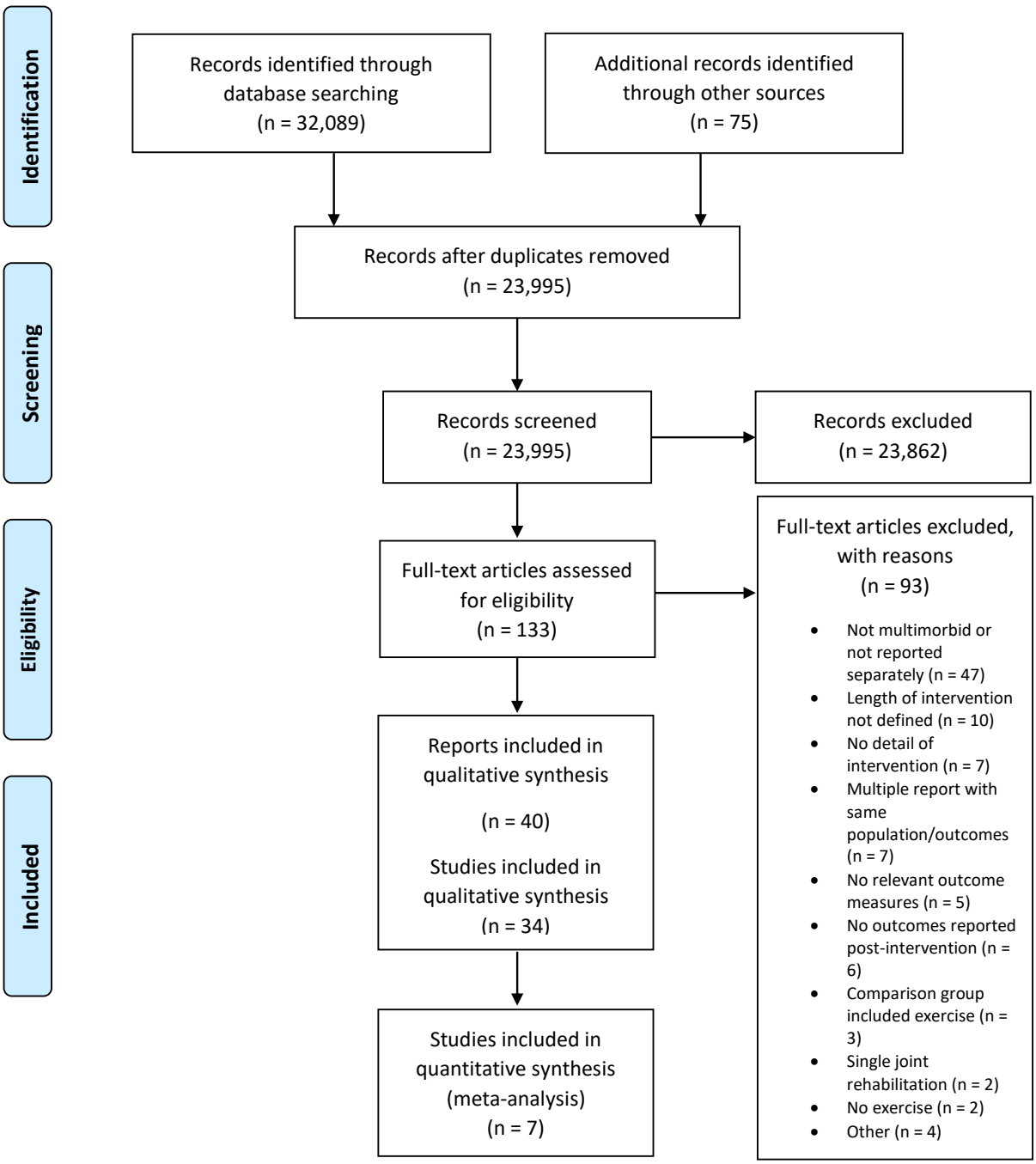
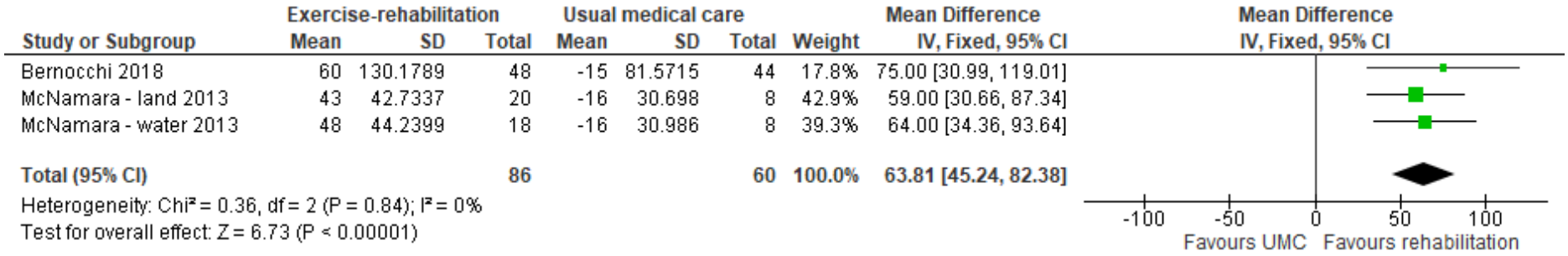


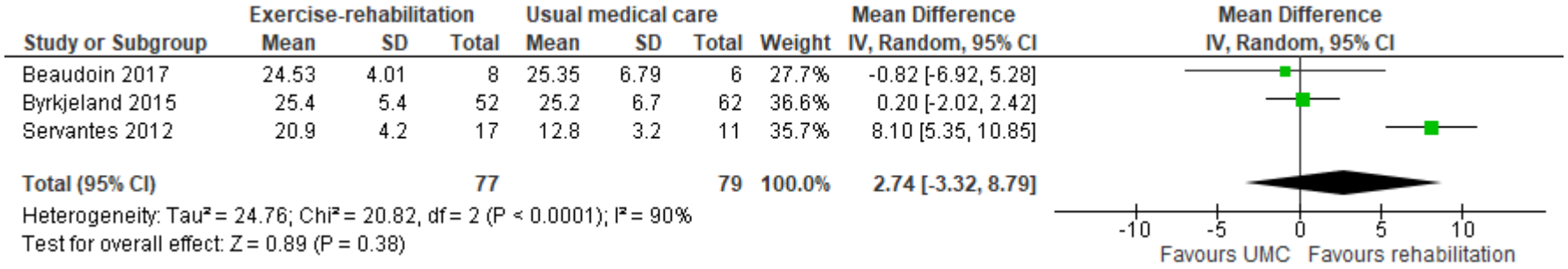
Figure 2. Effect of exercise rehabilitation versus usual medical care on 6MWD



6MWD reported in meters

6MWD = six-minute walk distance; SD = standard deviation; IV = inverse variance; CI = confidence interval; df = degrees of freedom; UMC = usual medical care

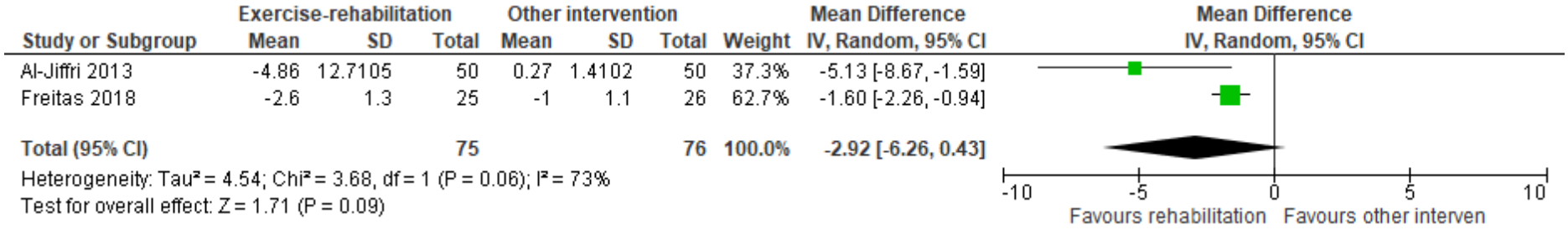
Figure 3. Effect of exercise rehabilitation versus usual medical care on VO_2 peak



VO_2 peak reported in ml/kg/min

VO2 = peak oxygen consumption; SD = standard deviation; IV = inverse variance; CI = confidence interval; df = degrees of freedom; UMC = usual medical care

Figure 4. Effect of exercise rehabilitation versus other intervention on BMI



BMI reported in kg/m^2

BMI = body mass index; SD = standard deviation; IV = inverse variance; CI = confidence interval; df = degrees of freedom

Supplementary Document to Chapter 2

The effect of exercise rehabilitation on clinical outcomes in people with multimorbidity: A systematic review and meta-analysis.

Table 1. Search strategy for Medline.

Comorbidity/ OR comorbid* OR co-morbid*
Multimorbidity OR multimorbid* OR multi-morbid* OR multidisease* OR multi-disease*
1 OR 2
Exercise/ OR exercise
Rehabilitation/ OR rehab*
Exercise therapy/ OR “exercise therap*”
4 OR 5 OR 6
3 AND 7

Note: All searches were limited to English and human

Table 2. Intervention details (n = 34).

Study	Intervention	Other interventions	Frequency (sessions/week)	Duration of Rehabilitation	Duration of session (minutes)	Intensity	Supervision (exercise)	Location
Abd El-Kader 2013(139)	Int = exercise training: treadmill; basic physical fitness movements (running, jumping & playing with medicine ball)	Diet regime & medical treatment	4	8 weeks	15-35	Treadmill: 60-80% max HR	Physical education expert	NS
	Com = usual medical care	Nil						
Al-Jiffri 2013(148)	Int = aerobic exercise training: treadmill	Prescribed low-calorie diet	3	3 months	30	65-75% max HR	NS	NS
	Com = prescribed low-calorie diet	Nil						
Barnes 2009(152)	Int = aerobic & resistance exercise: combination of cycling, walking and jogging; resistance exercises – 7 exercises for upper & lower limb muscle groups	Very low-energy diet (with meal replacement)	3 (resistance) And 5 (aerobic)	16 weeks (resistance) And 12 weeks (aerobic)	3 sets of 12 repetitions (resistance) And 40 (aerobic)	80% 1-RM (resistance) And 80% VO_2 peak (aerobic)	Exercise physiologist & physiotherapist	Hospital-based & home-based
	Com = N/A							
Beaudoin 2017(141)	Int = aerobic & resistance exercise: walking, jogging, cycling or elliptical trainer; resistance exercises – 5-7 exercises for large muscle groups	Nil	3	12 weeks	20-40 (aerobic) And 1-3 sets of 8-15 repetitions (resistance)	60-80% VO_2 peak (aerobic) And 30-50% 1-RM (resistance)	NS	Hospital-based
	Com = usual medical care	Nil						

Bernocchi 2018(142)	Int = exercise: mini-ergometer, callisthenic exercises, free walking OR mini-ergometer, muscle reinforcement exercises (with weights), free walking	Education	3-7	4 months	45-55 (aerobic) And 30-40 (resistance)	Moderate or high level of dyspnea on Borg scale	Physiotherapist	Home-based
	Com = usual medical care	Nil						
Byrkjeland 2015(143)	Int = aerobic & resistance exercise: supervised - alternating between: circuit training/interval training (uphill walking or step)/spinning [resistance components used free weights]; home - walking/swimming/cycling/cross-country skiing	Nil	2 (supervised) And 1 (home-based)	12 months	60 (duration of class) 10-15 repetitions (resistance)	High intensity: RPE ≥ 15 (5-15 minutes) And Moderate intensity: RPE = 12-14 (remaining time)	Qualified instructors	Hospital-based & home-based
	Com = control group (usual care with GP)	Nil						
Castro 2015(130)	Int = aerobic & resistance exercise: cycle-ergometer or treadmill; resistance - elastic bands and dumbbells	Hemodialysis	3	16 weeks	20 (aerobic) And 20 (resistance)	NS (aerobic & resistance)	NS	Hospital-based
	Com = N/A							
Collins 2010(131)	Int = home-based walking program	Bi-weekly phone call	3 (minimum)	6 months	50	NS	Exercise instructor	Home-based
	Com = bi-weekly phone call	Nil						
Crisafulli	Int = pulmonary rehabilitation (peripheral limb training)	Educational sessions, chest physiotherapy,	3	21 sessions	180 (specific duration of	NS	Physiotherapist	Hospital-based

2010(54)		and psychological and nutritional counselling when indicated		(9 weeks)	exercise NS)			
	Com = N/A							
de Groot 2012(153)	Int = aerobic & strengthening exercise: free-walking, treadmills, stationary cycling or elliptical machines; resistance exercises – sit-to-stand, single-arm curl, shoulder press, wall push-ups, side bends & forwards lunges (using body weight or commonly available items)	Cognitive behavioral therapy	150 minutes per week	12 weeks (aerobic) And 4-6 weeks (resistance)	20-30 (aerobic) And NS (resistance)	55-75% HRR (aerobic) And Appropriate intensities using the RPE method	Exercise physiologist & community fitness director	Community exercise facility
	Com = N/A							
Freitas 2018(150)	Int = aerobic & resistance exercise: treadmill, bike or elliptical machine; resistance - targeting major muscle groups (pectoral, deltoid, quadriceps & hamstrings)	Education and diet regime (low-calorie) with nutritionist & psychologist input	2	3 months	NS (aerobic) And 2 sets of 10 repetitions per exercise	50-75% VO_2 peak (aerobic) And 50-70% 1-RM (resistance)	Physiotherapist	Hospital-based
	Com = sham exercise: breathing (based on yoga's pranayama breathing exercises) & stretches - targeting major muscle groups: (trapezius, pectoralis, gluteus, hamstrings, quadriceps femoris, paraspinal, latissimus dorsi, and pubis adductors)	Education and diet regimen (low-calorie) with nutritionist & psychologist input	2	3 months	NS (breathing) And 10 seconds per stretch	no intensity progression (breathing) And no progression (stretches)	NS	NS

Halvari 2017(151)	Int = aerobic & resistance exercise: spinning classes; endurance & resistance circuit training; interval training – uphill walking/jogging; weight room training	Nil	3	12 months	60	High intensity: RPE ≥ 15 (5-15 minutes) And Moderate intensity: RPE = 12-14 (remaining time)	Students with Masters degrees from the Norwegian School of Sports Sciences	Hospital-based & home-based
	Com = usual physical activity	Nil						
Hassan 2016(154)	Int = pulmonary rehabilitation (exercise training targeting upper & lower limbs); treadmill (interval training); resistance - free weights	Education	3	8 weeks	NS (aerobic) And 30 repetitions (resistance)	60-80% max HR (aerobic) And According to patient's tolerance (resistance)	NS	NS
	Com = N/A							
Johnson 2014(133)	Int = aquatic exercise program – details not described	NS	NS	12 weeks	NS	NS	NS	Community-based
	Com = NS							
Khadanga 2016(155)	Int = cardiac rehabilitation (aerobic & resistance exercise): treadmill and arm ergometer, stepper, trampoline or rower; resistance – 6 exercises (leg extension, leg curl, bench press, shoulder press, lateral pulldown & bicep curl), using weight-lifting equipment or free weights	Education	Up to 3	3-4 months (maximum 36 sessions)	45-60 (aerobic & resistance combined) 10 repetitions per exercise (resistance)	70-85% max HR (aerobic) And 50% 1-RM (resistance)	Cardiac rehabilitation specialist	Medical centre
	Com = N/A							

Kurian 2010(134)	Int = resistance exercise training – details not described Com = N/A	NS	NS	12 weeks	NS	NS	NS	NS
Listerman 2011(49)	Int = cardiac rehabilitation (aerobic & resistance exercise): details not described Com = N/A	Individual counselling & group education	2-3	24-36 sessions	60	Each participant was given an individualized prescription based on baseline functional capacity	NS	Medical centre
Martin 2016(135)	Int = cardiac rehabilitation (exercise-based program): details not described Com = N/A	NS	NS	12 weeks	NS	NS	NS	NS
McNamara 2013(74)	Int 1 = land-based exercise (aerobic & resistance): upper & lower limb aerobic exercises (punching, kicking, stationary marching, walking: treadmill or free-walking, stationary cycling); upper & lower limb & thoracic cage stretches; resistance exercises – 3 unsupported arm exercises	Nil	3	8 weeks	60 (aerobic & resistance combined) And 3 sets of 10 repetitions (resistance)	80% average 6MWT speed (walking) And 3-5 on modified Borg Scale (0-10) for dyspnea & RPE	Physiotherapist	Hospital-based
	Int 2 = water-based exercise (aerobic & resistance): upper & lower limb aerobic exercises (extensive variety of exercises); upper & lower limb & thoracic cage stretches; resistance exercises – 3 unsupported arm exercises	Nil	3	8 weeks	60 (aerobic & resistance combined) And	3-5 on modified Borg Scale (0-10) for dyspnea & RPE	Physiotherapist	

					3 sets of 10 repetitions (resistance)			
	Com = no exercise	Nil						
Mentz 2013(145)	Int = aerobic exercise - walk (treadmill or walking-independently) or stationary cycling	Self-management education program	3 (supervised) And 5 (home exercise)	Up to 4 years	30-35 supervised & 40 home-based	60-70% HRR	NS	Supervised setting & home-based
	Com = usual medical care	Self-management education program						
Mesquita 2015(156)	Int = pulmonary rehabilitation: details not described	NS	5 (inpatient) Or 3 (outpatient)	8 weeks (inpatient) Or 14 weeks (outpatient)	NS	NS	NS	Hospital-based
	Com = N/A							
Mundra 2013(136)	Int = cardiac rehabilitation – details not described	NS	NS	8-12 weeks	NS	NS	NS	NS
	Com = N/A							
Naz 2019(157)	Int = pulmonary rehabilitation (aerobic & resistance exercise): treadmill & stationary bike; resistance exercises - free weights (upper & lower limb)	Breathing exercises and stretching exercises	2	8 weeks	30 (aerobic) And 8-10 repetitions (resistance)	Treadmill walking speed: (6MWT distance x 10)/1000 x 0.8 km/h Cycling workload: (Watt = 103.217 + (30.500 x sex)	Physiotherapist	Hospital-based
	Com = N/A							

					120 (total exercise time)	+ (-1.613 x age) + ((0.002 x distance x weight)) sex; male = 1 female = 0) And 4-6 modified Borg scale (aerobic & resistance)		
Nonoyama 2016(50)	Int = cardiac rehabilitation (aerobic & resistance exercise): walking; resistance exercises - lower & upper body & trunk-stabilizing exercises Com = N/A	Education and psychological & dietary counselling	1 per week (6-12 months) And 1 per month (4-12 months)	6-12 months	90 (duration of class) 60 maximum (aerobic) And 10-15 repetitions (resistance)	60-80% VO_2 peak (aerobic) And NS (resistance)	Physiotherapist & kinesiologist	Hospital - based
Servantes 2012(146)	Int 1 = aerobic training: walking	Education	3 (first and second months) And 4 (third month)	3 months	30-45	Borg exertion scale (0-15) to evaluate intensity Heart rate levels that correspond to anaerobic threshold (10 heart rates up & down)	Physiotherapist	Home-based

	Int 2 = aerobic & resistance training: walking; resistance exercises – 3 exercises for upper limb & 4 exercises for lower limb (free weights)	Education	3 (first and second months) And 4 (third month)	3 months	30-45 (aerobic) And 1 set of 12-16 repetitions each exercise (resistance)	Borg exertion scale (0-15) to evaluate intensity Heart rate levels that correspond to anaerobic threshold (10 heart rates up & down) And 30-40% 1-RM (resistance)	Physiotherapist	
	Com = untrained group	Nil						
Soleimani 2009(158)	Int = cardiac rehabilitation (aerobic exercise): treadmill	Psychological & dietary counselling	3	8 weeks	20	Intensity of exercise was patient dependent: no further details provided	Physical therapist	Hospital-based
	Com = N/A							
Sridhar 2010(147)	Int = aerobic exercise: treadmill or cycling	Nil	5	12 months	30	NS	Physiotherapist	Hospital-based
	Com = no exercise	Nil						
Srinivasan 2014(137)	Int = Tai Chi	Antidepressant treatment	2	8 weeks	60	NS	Certified instructor	NS
	Com = mind-body education	Antidepressant treatment	2	8 weeks	60		Trained personnel	
Takaya	Int = cardiac rehabilitation: walking, cycling & calisthenics	Education	5	3 months	30-60	50-60% HRR (aerobic)	NS	Centre-based &

2014(159)	Com = N/A Com = N/A		(weeks 1-2 = 5 supervised sessions & remaining 10 weeks = 2 supervised session & home-based)			Or 12-13 Borg RPE scale (6-20)		home-based
Tunsupon 2017a(160)	Int = pulmonary rehabilitation: treadmill; stationary cycle; stretching; light floor exercises (with or without weights) Com = N/A	Nil	3	8 weeks	90 (duration of class)	NS	NS	NS
Verges 2004(162)	Int = cardiac rehabilitation: treadmill, cycle and arm ergo Com = N/A	Education	3	2 months	60	65-80% max HR And 13-15 Borg RPE scale	Exercise physiologist	NS
Wang 2013(163)	Int = aerobic interval training: bicycle ergometer Com = N/A	Nil	3	12 weeks	15 (5, 3-minute intervals)	80% VO_2 peak	NS	Hospital-based
Woodard 1994(164)	Int = cardiac rehabilitation: walking or stationary cycling Com = N/A	Nil	3	6 months	45	50-85% symptom-limited HRR	NS	Community-based
Zwerink 2010(138)	Int = exercise program: cycling; walking; lifting; functional strength exercises	2 self-management sessions	2 (community-physio practice)	10 weeks	NS	NS	NS	Community-based &

	Com = N/A	And 1 (home-based)	home-based

Int = intervention; Com = comparison; max = maximum; HR = heart rate; NS = not stated; N/A = not applicable; RM = repetition maximum; VO_2 peak = peak oxygen consumption; GP = general practitioner; RPE = rating of perceived exertion; HRR = heart rate reserve; 6MWT = 6-minute walk test

Table 3. Quality assessment – Randomized Controlled Trials and Randomized Crossover Trial.

Study	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	Groups treated identically other than intervention	Follow up complete	Analyzed in group randomized to	Outcomes measured in same way	Outcomes measured in a reliable way	Appropriate statistical analysis	Appropriate trial design for RCT
Abd El-Kader(139)	UC	UC	Y	N	UC	UC	Y	Y	UC	Y	Y	Y	Y
Al-Jiffiri(148)	UC	UC	UC	N	N	UC	Y	Y	Y	Y	Y	Y	UC
Beaudion(141)	Y	N	Y	N	N	UC	Y	Y	Y	Y	Y	Y	Y
Bernocchi(142)	Y	N	N	N	N	UC	Y	Y	Y	Y	UC	Y	Y
Byrkjeland(143)	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y
Collins(131)	UC	UC	Y	N	N	UC	Y	UC	UC	UC	UC	Y	UC
Freitas(150)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Halvari(151)	Y	Y	N	N	N	UC	Y	Y	Y	Y	Y	Y	Y
Johnson(133)	UC	UC	UC	N	N	UC	UC	UC	UC	UC	UC	UC	UC
McNamara(74)	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y
Mentz(145)	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y
Servantes(146)	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y
Sridhar(147)	UC	UC	Y	N	N	UC	Y	Y	Y	Y	Y	Y	Y
Srinivasan(137)	UC	UC	Y	N	N	UC	UC	Y	Y	Y	Y	UC	UC

Y = yes; N = no; UC = unclear

Table 4. Quality assessment – cohort studies.

Study	Groups similar & recruited from same population	Exposures measured similarly in both groups	Exposures measured in a valid &reliable way	Identified confounding factors	Strategies to deal with confounding factors	Groups/participants free of outcome at start	Outcomes measured in a valid &reliable way	Follow up time reported & sufficient	Follow up complete & reasons why not	Strategies for incomplete follow up	Appropriate statistical analysis
Barnes(152)	NA	NA	Y	Y	N	NA	Y	Y	N	NA	Y
Castro(130)	NA	NA	Y	N	N	NA	Y	Y	N	N	UC
Crisafulli(54)	NA	NA	Y	NA	NA	NA	Y	Y	N	N	Y
Hassan(154)	NA	NA	Y	N	NA	Y	Y	Y	Y	N	Y
Khadanga(155)	NA	Y	Y	Y	N	NA	Y	Y	Y	N	Y
Kurian(134)	UC	UC	UC	UC	UC	UC	UC	Y	UC	UC	UC
Listerman(49)	NA	Y	Y	Y	Y	Y	Y	Y	Y	UC	Y
Martin(135)	UC	UC	UC	UC	UC	UC	UC	Y	UC	UC	UC
Mesquita(156)	NA	NA	UC	Y	Y	Y	UC	Y	Y	NA	Y
Mundra(136)	Y	Y	UC	N	N	Y	UC	Y	N	N	UC
Naz(157)	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y
Nonoyama(50)	NA	NA	Y	Y	Y	Y	Y	Y	Y	UC	Y
Soleimani(158)	Y	Y	Y	NA	NA	Y	UC	Y	Y	NA	Y
Takaya(159)	Y	NA	Y	NA	NA	Y	Y	Y	Y	NA	Y
Tunsupon[a](160)	NA	NA	Y	Y	Y	Y	UC	Y	Y	Y	Y
Verges(162)	Y	NA	Y	NA	NA	Y	Y	Y	Y	NA	Y
Wang(163)	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y
Woodard(164)	Y	NA	Y	N	N	Y	Y	Y	N	N	Y
Zwerink(138)	NA	NA	UC	Y	Y	Y	UC	Y	Y	UC	Y

Y = yes; N = no; UC = unclear; NA = not applicable

Table 5. Quality assessment – quasi-experimental studies.

Study	**Clear 'cause'& 'effect'**	**Participants similar**	**Participants receiving similar treatment other than intervention**	**Control group**	**Outcome measures pre- & post-intervention**	**Follow up complete & reasons why not**	**Outcomes measured in same way**	**Outcomes measured in a reliable way**	**Appropriate statistical analysis**
de Groot(153)	Y	Y	Y	N	Y	Y	Y	Y	Y

Y = yes; N = no

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CHAPTER 3

A rehabilitation programme for people with multimorbidity versus usual care: A pilot randomized controlled trial

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Declaration of Authorship – Chapter 3

Student's declaration

The nature and extent of contributions to Chapter 3 of this thesis are as follows.

Name	**Nature of contribution**	**Extent of contribution**	**Signature**
Kathryn Barker	Study concept & design; protocol development; data collection & analysis; writing of manuscript & review	55%	
Anne Holland	Study concept & design; protocol development; review of manuscript	10%	
Annemarie Lee	Study concept & design; protocol development; data collection & analysis; review of manuscript	10%	

Elizabeth Skinner	Study concept & design; protocol development; review of manuscript	10%
Kathryn Ritchie	Study design; recruitment; data collection & analysis; manuscript review	5%
Claire Boote	Study design; recruitment; manuscript review	2%
Stephanie Lowe	Study design; recruitment; data collection; manuscript review	2%
Fiona Pazsa	Recruitment; data collection; manuscript review	2%
Lee Thomas	Recruitment; data collection; manuscript review	2%
Monica Turczyniak	Study design; recruitment; data collection; manuscript review	2%

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A rehabilitation programme for people with multimorbidity versus usual care: A pilot randomized controlled trial

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Abstract

Background: Multimorbidity, the coexistence of two or more chronic conditions, is common in clinical practice. Rehabilitation for people with multimorbidity may provide access to a rehabilitation programme that can address common symptoms and risk factors for multiple chronic diseases. **Objective:** The aims of this study were to (1) evaluate the feasibility of a rehabilitation programme compared to usual medical care (UMC) in people with multimorbidity and (2) gather preliminary data regarding clinical effects and impact on functional exercise capacity, activities of daily living, health-related quality of life and resource utilization. **Design:** A pilot feasibility parallel randomized controlled trial was undertaken. Adults with multimorbidity were randomized to the rehabilitation programme (intervention) or UMC (control). The duration of the rehabilitation programme was 8 weeks and comprised exercise (1 h, twice weekly) and education (1 h, once weekly). The UMC group did not participate in a structured exercise programme. **Results:** One hundred people were screened to recruit 16 participants, with a 71% completion rate for the intervention group. The rehabilitation group achieved a mean (standard deviation) improvement in 6-minute walk distance of 44 (41) m and the UMC group of 23 (29) m. **Conclusions:** This study suggests that it would be feasible to conduct a larger randomized control trial investigating a rehabilitation programme for people with multimorbidity. Low uptake of the study suggests that refinement of the inclusion criteria, recruitment sources and programme model will be needed to achieve the number of participants required.

Keywords

Multimorbidity, rehabilitation, randomized control trial, exercise, education

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Introduction

Multimorbidity, defined as the coexistence of two or more chronic conditions,[1] is an important problem in most healthcare systems and is common in clinical practice.[2] It is associated with increased mortality,[3,4] poorer functional status[5] and reduced health-related quality of life (HRQoL).[6] Multimorbidity is a rising healthcare burden internationally,[7–9] and as a result, policy and guideline makers need to ensure that this complex population have access to evidence-based and sustainable interventions.

A systematic review on interventions for improving outcomes in people with multimorbidity identified 18 randomized control trials (RCTs), testing heterogeneous interventions.[2] Findings suggested that interventions that focused on areas where people have difficulties, such as functional outcomes, led to modest improvements.[2] Even when clinical practice guidelines (such as pulmonary or cardiac rehabilitation) exist with recommendations based on high-level evidence and rehabilitation programmes focused on single diseases are well established, gaps remain in implementation.[10–12] Current chronic disease-specific clinical guidelines for rehabilitation do not meet the challenges of multimorbidity,[13] by overlooking the potential interaction of multiple diseases and their management, or fail to address or exclude people with multimorbidity.[13,14] It was shown that in a review of recent guidelines relevant to single-disease rehabilitation for people with chronic diseases, three of the seven do not mention coexisting conditions and an additional three only make passing mention of minor programme adaptations.[13] Within the research field on disease-specific rehabilitation programmes, there has been debate over the inclusion of people with complex conditions. This is highlighted in the analysis conducted on the studies on a Cochrane review of pulmonary rehabilitation in chronic obstructive pulmonary disease, which shows that 51% and 48% of the included studies excluded people with cardiac and musculoskeletal disease, respectively.[13] Due to the multitude of presentations within the multimorbidity population, many people do not fit the single-disease rehabilitation models. There are also several perceived barriers that prevent healthcare professionals from referring to rehabilitation programmes, which include awareness and familiarity, belief in health benefits, motivation and prioritization and the complexity of behavioural change required by the patient.[10,12]

Rather than using resources to increase the proportion of single-disease interventions, it has been suggested that multimorbidity interventions should be integrated into existing healthcare systems to support implementation and sustainability[15] and to apply and build on the evidence regarding effective interventions for single diseases to people with multimorbidity.[2] Many healthcare systems already include well-established disease-specific rehabilitation programmes and, therefore, are well placed to provide rehabilitation for people with multimorbidity, or to evolve the successful existing models, such as pulmonary rehabilitation, to more comprehensively address the needs of people with multimorbidity.[13] As evidence has shown that exercise and education can improve outcomes and mitigate the progression of many chronic diseases[16] and is recommended in guidelines for many single diseases, exercise-based rehabilitation for people with multimorbidity may have a role to play in addressing common symptoms and risk factors for multiple chronic diseases, rather than only focusing on management of one disease.

Objectives

The study aims were to (1) evaluate the feasibility of a rehabilitation programme for people with multimorbidity compared to usual medical care (UMC) in people with multimorbidity who are unable to access traditional disease-specific rehabilitation; (2) gather preliminary data regarding effects of these interventions on functional exercise capacity, activities of daily living (ADL), HRQoL and resource utilization; and (3) determine which multimorbidity measures would be most suitable for use in a larger scale trial.

Materials and methods

Study overview, design and setting

This trial was a pilot feasibility parallel RCT, conducted at Sunshine Hospital, Victoria, Australia. Participants were recruited from November 2014 to February 2015 and sourced from inpatient medical wards, outpatient clinics and the community-based rehabilitation service at Western Health. Informed consent was gained from all participants. Ethical approval was obtained from Melbourne Health Human Research Ethics Committee and La Trobe University. The trial was registered with Australian New Zealand Clinical Trials Registry (ACTRN 12614001187639) and reported according to Consolidated Standards of Reporting Trials (CONSORT) guidelines.[17]

Eligibility criteria

The inclusion criteria were adults (aged >18 years) with a physician diagnosis of two or more chronic conditions who met the defined list of multimorbidity by Barnett et al. (Online Supplementary Table 1).[1] This defined list of multimorbidity was used to ensure a consistent selection criterion for this trial, as there are no agreed clear and comprehensive criteria for the selection of chronic conditions which qualify for multimorbidity.[18] Participants were not eligible for traditional disease-specific rehabilitation programmes (cardiac, heart failure and pulmonary rehabilitation), because their primary diagnosis was another condition or their cardiorespiratory disease was deemed to be stable and not contributing to a decline in function. Exclusion criteria were an inability to walk 50 m, severe cognitive impairment, unstable cardiovascular

disease or diabetes and current participation in a structured exercise programme.

Randomization

Eligible participants were randomized in a 1:1 allocation. The allocation sequence was generated using computer-generated random numbers, and group allocation was placed into sealed opaque envelopes by an independent investigator not involved in recruitment or outcome measurement. Randomization occurred after the completion of the baseline data collection.

Interventions

Participants were randomized to either a rehabilitation programme (intervention) or UMC (control). The duration of the rehabilitation programme was 8 weeks and comprised exercise (1 h, twice weekly) and education (1 h, once weekly) in a group setting. The rehabilitation programme structure was developed according to current evidence-based cardiac, heart failure and pulmonary rehabilitation programmes. UMC included general inpatient or outpatient medical care, potentially including allied health; however, they did not participate in a structured exercise programme during the study period.

Exercise. The exercise programme consisted of aerobic and resistance exercises.

Aerobic component. Comprises walking (corridor or treadmill) and stationary cycling, for a total of 30 min, with 15 min for each activity. The initial walking prescription was calculated at 80% of peak walking speed or distance,[19,20] and stationary cycling intensity was calculated at 60–80% of the maximum work rate estimated from the 6-min walk test (6MWT).[21] Exercise prescription was progressed using a rating of perceived exertion (RPE) Borg scale (6–20) and dyspnoea modified Borg scale, aiming for an RPE score of 12–14 and a dyspnoea score of 3–4, correlating to moderate intensity exercise.[22]

Resistance component. Upper and lower limb exercises using free weights with four upper limb and three lower limb exercises. Components of the resistance exercise routine were based on functional exercises. The initial load corresponded to 10–12 repetition maximum (RM). A 10–12 RM is the weight that can be lifted correctly and comfortably at least 10 times but not more than 12.[23] Progression was undertaken using an RPE Borg scale (6–20), aiming for an RPE score of 12–14.

Cessation/withdrawal and safety criteria included a change in a participant's medical condition that deemed him/her unsuitable for exercise (for further detail, see Online Supplementary Material). The exercise prescription was modified for a participant's individual requirements, related to change in symptoms or limitations due to comorbidities. For example, a second walking session was included to replace cycling if the participant was unable to use a stationary bike due to back pain. A physiotherapist and a nurse were present during the exercise sessions.

Table 1. Education sessions.

1	Nursing
	What is multimorbidity?
	Managing multimorbidity – risk factors and setting goals.
	Finding useful resources.
2	Nursing
	Communication with healthcare professionals, family and friends.
	Smoking cessation.
	Blood pressure and cholesterol – how to manage.
3	Physiotherapy
	Why is exercise important?
	Types of exercise and how much to do.
	Precautions and warnings for exercise.
4	Dietetics
	Healthy eating.
	Weight management.
	Finding useful resources.
5	Diabetes educator
	What is diabetes?
	Managing blood sugar levels.
	Signs and symptoms of low/high blood sugar levels.
6	Pharmacy
	General medicine advice.
	Why am I taking so many medications?
	Home medicine review.
7	Occupational therapy
	Performing activities of daily living.
	Energy conservation.
	Relaxation and stress management.
8	Psychology
	Anger/shock/numbness/denial/disbelief.
	Acceptance and building problem-solving skills.
	Action towards achieving a modified healthy lifestyle.

Education. Education for the rehabilitation programme was delivered by multidisciplinary professionals using a didactic approach with handouts provided (Table 1). The rehabilitation programme education sessions aimed to enhance skills in general disease self-management and focused on common risk factor modification for chronic diseases.[24] Participants were directed towards finding relevant information and resources in disease management. The 'managing multimorbidity' session aimed to teach participants to recognize when their disease symptoms changed and consult their general practitioner (GP) for management. A diabetes education session was included due to the prevalence of diabetes in the study population. The pharmacy session focused on awareness of community services available through local pharmacies to assist people with managing polypharmacy, such as home medication review and medication distribution packs.

Pre- and post-assessments were conducted at baseline and following the intervention period, completed by blinded assessors.

Participant characteristics

Baseline demographics, medical history and multimorbidity measures[6] were collected. The use of multiple multimorbidity measures was to determine which would be most suitable for a larger scale trial for ease of use and information obtained. These included the Cumulative Illness Rating Scale for Geriatrics (CIRS(G)),[25] the Functional Comorbidity Index (FCI)[26] and the Duke Severity of Illness Checklist (DUSOI).[27] Illness perception was measured using the Multimorbidity Illness Perception Scale (MULTIPleS).[28] Detailed information regarding these measures is available in the Online Supplementary Document.

Feasibility measures

Feasibility of the trial was measured by numbers screened to achieve the target sample size, the number who agreed to participate and the number who completed the intervention. Programme completion was defined as attendance at 12 or more of the 16 sessions.[29]

Outcome measures

Primary outcome: Functional exercise capacity. The 6MWT was used to measure the primary outcome of change in functional exercise capacity. The 6MWT is a measure of functional exercise capacity in populations with multiple chronic diseases including cardiovascular disease, lung disease, arthritis, diabetes, and cognitive dysfunction and depression.[30] The 6MWT was administered according to standardized guidelines, with two tests conducted and the longest distance recorded.[31]

Secondary outcomes

Activities of daily living. The Katz Index of Independence in Activities of Daily Living (Katz ADL index) was used to measure functional ADL. It has been used in people with chronic disease[32] and in the older population[33] to measure function.

Health-related quality of life. Two generic instruments, the Assessment of Quality of Life (AQoL)[34,35] and EuroQol-5D-5L (EQ-5D-5L),[36,37] were used to measure HRQoL. The AQoL and EQ-5D-5L are valid and reliable instruments, with moderate levels of responsiveness and sensitivity in a wide range of health conditions.[34,37] The AQoL has Australian population norms, which was relevant to the participants in this trial.[38]

Resource utilization. Data on emergency department (ED) presentations, hospital admissions and GP presentations during the intervention period were collected to measure healthcare utilization. Consultant physician appointments, GP consultations and hospital admissions were also recorded by participants via a daily diary. Diary information was verified by participant interview at the post-intervention assessment. Hospital admissions and length of stay were verified from Western Health patient medical records.

Statistical methods

Sample size. Being a pilot trial, no sample size calculation was undertaken.[39] A sample of 16 participants was recruited due to the resources available and time frame to complete the intervention.

Statistical analysis. Feasibility was described in numbers and percentages. Continuous variables were reported as mean and standard deviation (SD) or median and interquartile range depending on data distribution. Continuous variables were analysed using paired or independent *t*-tests for normally distributed data and χ^2 or Mann–Whitney *U* test for non-normally distributed data. Data were analysed through Statistical Package for the Social Sciences Windows Version 23.0. Power calculations for a future, definitive randomized trial were conducted via online tools (www.sealedenvelope.com).[40]

Results

One hundred people were screened to recruit 16 participants (Figure 1). Of the 84 not included in the trial, 34 (40%) did not meet the inclusion criteria. The most common reasons were an inability to walk 50 m ($n = 6$) and neutropenia ($n = 6$). Fifty (60%) people met the inclusion criteria but did not participate in the trial, with 38 (45%) declining to participate and 12 (14%) identifying other reasons. Six people were not interested, and four stated it was too far to travel. Another common reason for not participating in the trial was work commitments ($n = 4$). Refer to Figure 1 for further details.

Randomization allocated eight participants each to the intervention and control groups. Seven of the eight participants in the rehabilitation programme group (RPG) received the intervention, with one participant withdrawing from the trial. One participant from each group was lost to follow-up. The primary outcome measure of 6MWT was analysed in six participants in the RPG and seven in the usual medical care group (UMCG).

Participant demographics are summarized in Table 2. The mean (SD) age was 65 (12) years, and body mass index (BMI) was 33 (8) kg/m^2. There was a total of five men (31%). The most common main diagnosis was cancer for both groups. The RPG's most common comorbidities were hypertension (88%), diabetes (63%) and cancer (38%). The UMCG's most common comorbidities were diabetes (50%), cancer (50%) and coronary heart disease (50%).

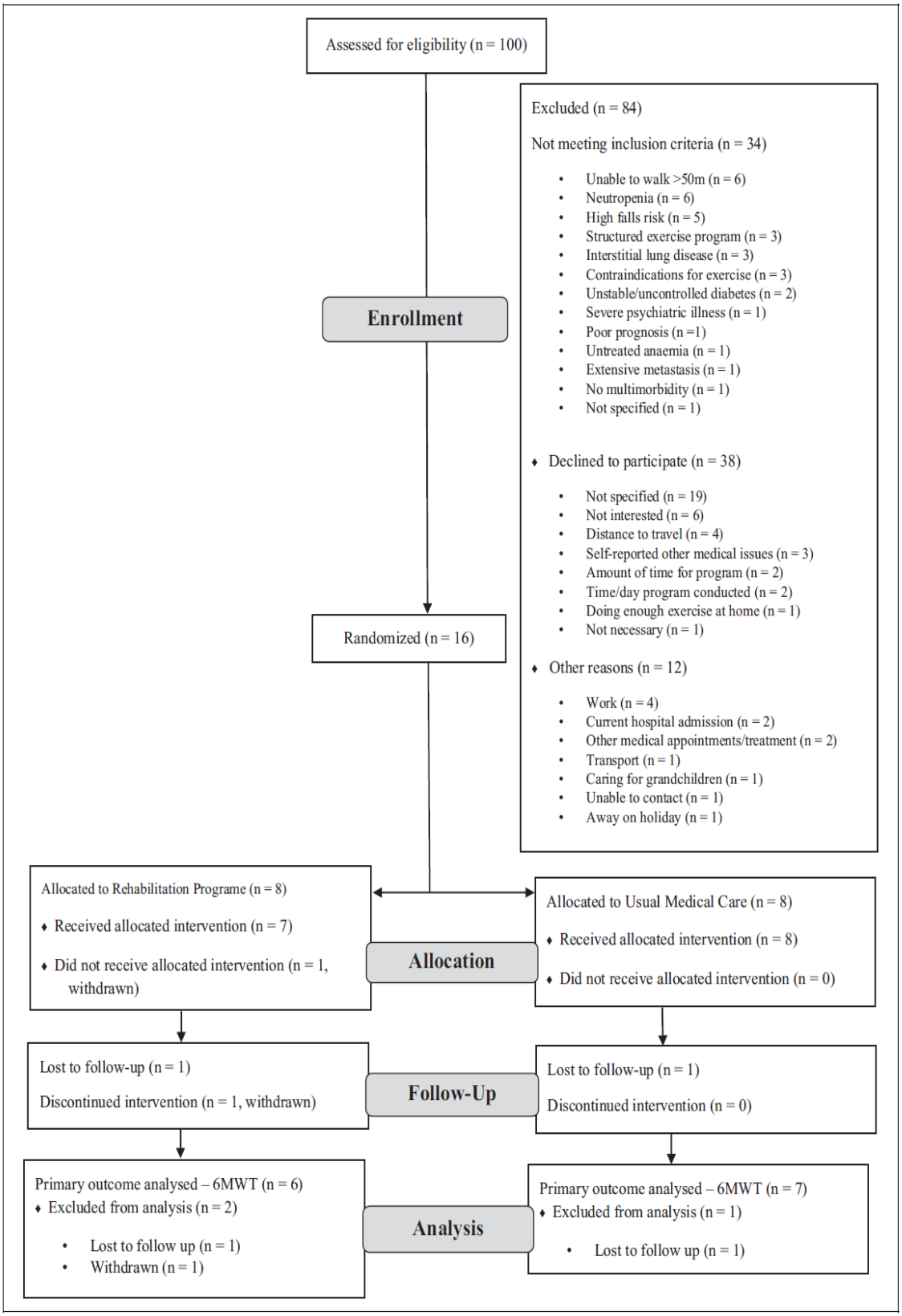

Figure 1. The CONSORT flow diagram of patient flow through the study.

Table 2. Participant characteristics.

	Rehabilitation programme ($n = 8$)	Usual care ($n = 8$)
Age (years), mean (SD)	67 (8)	63 (15)
Male, *n* (%)	1 (13)	4 (50)
BMI, mean (SD)	34 (10)	32 (5)
Main diagnosis, *n* (%)		
Cancer	2 (25)	2 (25)
Smoking status, *n* (%)		
Current	2 (25)	1 (13)
Ex-smoker	3 (38)	4 (50)
Never	3 (38)	3 (38)
Baseline 6MWD, mean (SD)	289 (135)	449 (88)
Other comorbidity, *n* (%)		
Hypertension	7 (88)	3 (38)
Diabetes	5 (63)	4 (50)
Cancer	3 (38)	4 (50)
Coronary heart disease	2 (25)	4 (50)
Number of comorbidities, mean (SD)	4 (2)	4 (1)
Functional Comorbidity Index, mean (SD)	6 (2)	6 (2)
Multimorbidity Illness Perception Scale, mean (SD)		
Treatment burden	3 (5)	6 (5)
Prioritization	7 (4)	7 (3)
Causal relationships	3 (3)	2 (2)
Activity restriction	5 (3)	3 (3)
Emotional representations	10 (11)	13 (11)
Summary scale	28 (22)	31 (21)
Cumulative Illness Rating Scale for Geriatrics, mean (SD)		
Total number of categories endorsed	6 (2)	6 (2)
Total score	10 (5)	11 (5)
Severity Index	2 (0)	2 (0)
Number of categories at level 3 severity	1 (1)	1 (1)
Number of categories at level 4 severity	0 (0)	0 (1)

SD: standard deviation; *n*: number; BMI: body mass index; 6MWD: 6-minute walk distance.

Each group had a similar number of comorbidities (mean (SD): RPG 4 (2) and UMCG 4 (1)). The UMCG had a higher baseline 6-min walk distance (6MWD) of 449 (88) m compared to the RPG with 289 (135) m.

Both groups had a similar FCI with a mean (SD) of 6 (2), indicating similar physical function.[26] The higher MULTIPleS summary scale in the UMCG indicated worse perception of their multiple diseases.[28] The total score, indicating medical burden,[25] in the CIRS(G) was slightly higher for the UMCG mean 11 (5) compared to the RPG with 10 (5). The severity index was the same, with similar numbers of categories at level three and four severity in both groups (Table 2), indicating little difference in disease severity or number of chronic problems between groups. The DUSOI data were not reported due to issues encountered in tool use. All assessors found the tool difficult to use, and several assessors administered the tool incorrectly, by asking participants rather than clinicians to select categories.

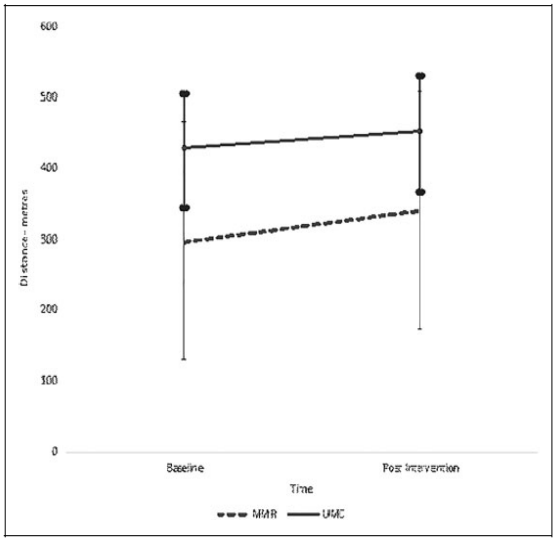

Figure 2. Six-minute walk distance.
MMR: multimorbidity rehabilitation programme; UMC: usual medical care. Data are presented as mean and standard deviation.

In the RPG, 71% of participants completed the rehabilitation programme, with a mean of 11 (6) sessions (of the 16 possible sessions) attended. One adverse event occurred during the intervention. A participant fell while performing the walking component of the rehabilitation programme. The participant tripped while walking, and this occurred as they were no longer wearing an ankle–foot orthosis (AFO) previously prescribed (due to poor fit). No injuries were sustained, and the participant resumed the programme at the following session, with follow-up organized to have the AFO refitted.

The RPG achieved a mean improvement in 6MWD of 44 (41) m and the UMCG of 23 (29) m, $p = 0.13$ (Figure 2 and Table 3). Only the RPG achieved the minimal important difference (MID) of least 30 m[31] for the mean change in 6MWD. However, in both groups, 25% of participants individually achieved the MID. One participant in the RPG became very unwell for reasons unrelated to the intervention and had a lengthy hospital admission (16 days). They were unable to complete the intervention and as a result, their change in 6MWD (−127 m) did not reflect the intervention. Data for this participant were removed as an extreme outlier.

No significant differences were observed between groups for improvement in the AQoL, Katz ADL index and EQ-5D-5L (Table 3). There was a mean increase in the AQoL utility score for both groups, with a greater increase in the UMCG; however, it was not significantly different ($p = 0.81$). Four participants from each group achieved the MID of 0.06 in the AQoL.[41]

Seven participants returned their daily diaries (RPG 2 and UMCG 5) with resource utilization recorded. Four participants in the UMCG reported GP visits, with a mean

Table 3. Primary and secondary outcome measures.

	Rehabilitation programme ($n = 6$)			Usual medical care ($n = 7$)			
	Baseline	Post	Change	Baseline	Post	Change	p Value[a]
Primary							
6MWD (m), mean (SD)	296 (170)	340 (167)	44 (41)	430 (77)	453 (86)	23 (29)	0.13
Secondary							
AQoL utility, mean (SD)	0.513 (0.278)	0.560 (0.361)	0.047 (0.271)	0.482 (0.275)	0.675 (0.272)	0.193 (0.203)	0.81
Usual care ($n = 6$)							
Katz ADL index, mean (SD)	5.33 (0.52)	5.67 (0.52)	0.33 (0.52)	4.86 (1.68)	5.14 (1.22)	0.29 (0.95)	0.84
EQ-5D-5L visual analogue scale, mean (SD)	70 (18)	77 (16)	7 (17)	69 (21)	76 (16)	8 (15)	0.88

n: number; 6MWD: six-minute walk distance; SD: standard deviation; AQoL: assessment of quality of life; ADL: activities of daily living; EQ-5D-5L: EuroQol-5D-5L.
[a]*p* Value represents comparison between groups for change over the course of the programme.

(SD) of 3 (3) visits and no visits for the RPG. Two participants, one from each group, presented to ED, and three participants (RPG 2 and UMCG 1) were admitted to hospital during the intervention period.

Due to error during the trial period, an outcome measure reported in the trial registry (Short Form 36 (SF-36)) was not collected, with the SF-36 form not included in the outcome measure packs during data collection.

Discussion

Summary

This study suggests that it would be feasible to conduct an RCT of a rehabilitation programme for people with multimorbidity compared to UMC. Outcomes relevant to a larger trial, including exercise capacity and HRQoL, could be collected consistently, and there was preliminary evidence of benefit for functional capacity. The study has provided direction on outcome measures, education and models of care which will inform the design of a suitably powered study.

Comparison with existing literature

This study is focused on interventions that are organizationally based and professionally led, which are targeting functional limitations. This is similar to the design of the OPTIMAL trial, an occupational therapy-led self-management support programme for people with multimorbidity.[42] The OPTIMAL trial showed significantly improved frequency of participation, self-efficacy and quality of life.[42] The intervention for the OPTIMAL trial was completed using some of the same health professionals as this study, including physiotherapy, occupational therapy and pharmacy. A study that used a home-based occupational and physical therapy intervention to address functional limitations showed improvements in survival; the home-based model used may have contributed to the excellent retention seen in this study.[43] The difference in location of therapy compared to this study should also be considered for the model of a future RCT as this may have contributed to a greater recruitment rate.

Strengths and limitations

Our study required screening six times the number of participants needed to achieve full recruitment. Most people who did not participate in the trial met the criteria, but frequently declined. Lack of willingness to attend/participate or travel to attend was frequently cited as a reason for refusal. The low recruitment rate of this trial may have impacted on the representation of the multimorbidity population studied and potentially accounting for the disparity in baseline measures between groups of the primary outcome measure (6MWT); this may also limit the applicability of the findings in a larger RCT. A potential solution is the recruitment process. Increasing the recruitment areas, such as including endocrinology outpatient clinics and GP practices, may increase the rate of recruitment and allow for a more comprehensive representation of the multimorbidity population. Other factors that could be refined in the design of a larger RCT are inclusion criteria and model of rehabilitation. To ensure consistency in the selection criteria, a defined list of diseases was used. However, as shown in a systematic review on multimorbidity indices, there is a lack of clear and comprehensive criteria for the chronic conditions which qualify for multimorbidity.[18] The use of wider criteria of chronic diseases may allow for recruitment of participants who were not considered for this trial.

Once recruited, people were willing to attend the rehabilitation programme, with a programme completion rate of 71%. The rehabilitation classes were successfully conducted with a physiotherapist and a nurse present. Informal feedback from the blinded assessors and participants indicated that the assessment process was lengthy and some outcome measures were difficult to administer and complete, particularly the CIRS(G) and DUSOI. There was also a poor return rate of the daily diaries. To improve the

processes in a larger RCT, a more efficient approach of reducing the number of measures and including the simplest to complete is required.

The small number of participants in this feasibility trial limits the conclusions that can be drawn from the primary and secondary outcome measures. A larger RCT will be required to determine the effect of rehabilitation for people with multimorbidity on function, HRQoL and resource utilization. This trial did not address whether the method of delivery of rehabilitation, twice weekly exercise and weekly education group sessions in a hospital outpatient setting, is the most suitable from the participant's perspective. This model of rehabilitation and the setting and access may have impacted on the uptake of participation in the trial. Further qualitative data collection using consumer focus groups or individual participant interviews may allow for constructive information on the model of rehabilitation provided and the most suitable service delivery model.

Multimorbidity measures were used in this trial to describe a complex population. Interventions could have varied the effects depending on the degree of multimorbidity.[2] A systematic review has highlighted the variation in definitions of multimorbidity and a need for clear reporting of participant characteristics.[2] The FCI appeared to be the most suitable for a larger scale RCT in terms of population suitability, ease of use, information obtained and relevance to intervention. The FCI is simple to administer and score and was designed to focus on physical function.[33] Physical function is an important aspect of exercise rehabilitation, and therefore, the FCI is a valuable measure. The DUSOI was a difficult measure to use with several issues encountered. The CIRS(G) was a time-consuming measure to administer. It was also difficult to obtain all required information to accurately score each category, with participants not undergoing investigations or results not available. The clinical expertise of blinded assessors can affect accurate scoring of the CIRS(G) due to the decision process required to clarify complex medical problems or their severity.[25]

Future research implications

Healthcare resources are limited, and in most high-income countries, health policy focuses on the reduction of spending growth and strategies to increase efficiency.[44] Addressing multimorbidity in a single rehabilitation programme is potentially a more cost-effective and sustainable model of delivering rehabilitation compared to single-disease models. Currently, there is limited clinical guidance on the optimal modality of exercise and rehabilitation programmes for people with several chronic diseases, such as diabetes and cancer.[45,46] Many people with chronic diseases do not have access to any rehabilitation programme, despite significant limitations in physical function. This is particularly true for the people living with cancer, the largest group in our trial, in whom there is emerging evidence for exercise-based rehabilitation programmes[47–49] but access is extremely poor.[50] The rehabilitation programme model for people with multimorbidity, including exercise and education, offers a potential solution for improved healthcare access and addressing the needs of the multimorbidity population. Addressing and evaluating some of the components of access being approachability, acceptability, availability and accommodation, affordability and appropriateness[51] in a larger RCT could be of value to shape the implementation of this new model of care. Previous research suggests that interventions that are more likely to be effective for multimorbidity are those that are targeted at areas where people have difficulties, such as functional ability.[2] Further development of this model should ensure that it addresses these features and is inclusive of the range of people with multimorbidity, including those with low physical capacity.

Developing a novel model of rehabilitation for people with multimorbidity allows for a renewed approach to content and delivery of education, compared to disease-specific focus approaches. In this trial, the education sessions were presented with a focus on self-management and resource awareness, delivered in a didactic method, which was anecdotally well received by participants. In a larger RCT, formal evaluation of the education topics and content could inform the development of an education programme that best addresses the needs of the multimorbidity population. How to most effectively deliver education in rehabilitation programmes is another question that is currently under consideration. In disease-specific rehabilitation, alternative delivery models are being investigated, such as DVD,[52] manuals[53] and digital technology.[54] Development of flexible programmes may best accommodate different people's needs and choices.[55]

Both groups had a mean BMI that would be classified as obese. Obesity is a known risk factor for a number of chronic diseases, including diabetes, cardiovascular disease and cancer,[56] and therefore, it is likely that the multimorbidity population will have a higher prevalence of obesity. This may have an impact on programme development, design and implementation, as exercise prescription and equipment might need modifying to accommodate this and potentially highlighting a need for nutritional management and counselling as a core component of the programme. This was evident in this trial with factors such as ensuring equipment, for example, exercise bikes, had suitable load capacities and appropriate seating was available.

The results of this study allow estimation of sample sizes for a future RCT comparing a rehabilitation programme for people with multimorbidity to UMC. We calculate that 92 participants would be required to have an 80% chance of detecting, as significant at the 5% level, an increase in the primary outcome measure 6MWD of 30 m.[40] This is based on the MID for the 6MWD in patients with chronic respiratory disease[31] and assumes an SD of change in 6MWD of 51 m, based on data collected in this trial. Given the large confidence intervals, this estimation

for adequate power should be interpreted with caution. Given this number of participants and the screening required for this study, it is likely a multicentre trial would be needed to achieve recruitment.

Conclusion

This study suggests that it would be feasible to conduct an RCT of a rehabilitation programme for people with multimorbidity compared to UMC. Our data suggest that a future large RCT is feasible, with adequate power to reach conclusions about the primary and secondary outcomes of exercise capacity, HRQoL and resource utilization. It is likely that a multicentre trial would be required. Further refinement of the study design, including inclusion criteria, recruitment sources and programme model, is needed to improve recruitment rates to achieve the number of participants required.

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Supplemental material

Supplementary material for this article is available online.

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Supplementary Document for Chapter 3

Methods

Multimorbidity diagnosis

A detailed list of chronic conditions that meet the definition of multimorbidity are outlined in Table S1 (1).

Table S1. List of conditions for definition of multimorbidity

Condition	Diagnosis	Condition	Diagnosis
Hypertension	Ever recorded	Alcohol problems	Ever recorded
Depression	Recorded in past 12 months OR ≥ 4 anti-depressant prescriptions (excluding low-dose tricyclics) in last 12 months	Other psychoactive substance misuse	Ever recorded
Painful condition	≥ 4 prescription only medicine analgesic prescriptions in last 12 months OR ≥ 4 specified anti-epileptics in the absence of epilepsy	Treated constipation	≥ 4 laxative prescriptions in last year
Asthma	Ever recorded and any prescription in the past 12 months	Stroke and transient ischemic attack	Ever recorded
Coronary heart disease	Ever recorded	Chronic kidney disease	Ever recorded
Treated dyspepsia	≥ 4 prescriptions in the last 12 months BNF 0103% excluding antacids AND NOT ≥ 4 NSAIDS or ≥ 4 aspirin/clopidogrel	Diverticular disease of intestine	Ever recorded
Diabetes	Ever recorded	Atrial fibrillation	Ever recorded
Thyroid disorders	Ever recorded	Peripheral vascular disease	Ever recorded
Rheumatoid arthritis, other inflammatory polyarthropathies and systematic connective tissue disorders	Ever recorded	Heart failure	Ever recorded
Hearing loss	Ever recorded	Prostate disorders	Ever recorded
Chronic obstructive pulmonary disease	Ever recorded	Glaucoma	Ever recorded
Anxiety, neurotic, stress related and somatoform disorders	Recorded in past 12 months OR ≥ 4 anxiolytic/hypnotic prescriptions in last 12 months OR ≥ 4 10/25mg amitriptyline in last 12 months and don't meet Pain criteria	Epilepsy (currently treated)	Ever recorded AND antiepileptic prescription in last 12 months

Irritable bowel syndrome	Ever recorded OR ≥ 4 prescription only antispasmodic prescription in past 12 months	Dementia	Ever recorded
New diagnosis of cancer in past 5 years	Recorded in past 5 years	Schizophrenia (and related psychosis) or bipolar disorder	Ever recorded/in last 12 months OR lithium prescribed in last 168 days
Psoriasis or eczema	Ever recorded AND ≥ 4 prescriptions in last 12 months	Migraine	≥ 4 prescription only medicine anti-migraine prescriptions in last year
Inflammatory bowel disease	Ever recorded	Blindness/low vision	Ever recorded
Chronic sinusitis	Ever recorded	Anorexia or bulimia	Ever recorded
Learning disability	Ever recorded	Bronchiectasis	Ever recorded
Parkinson's disease	Ever recorded	Viral hepatitis	Ever recorded
Multiple sclerosis	Ever recorded	Chronic liver disease	Ever recorded

Full exclusion criteria

Full exclusion criteria were:

- an inability to walk greater than fifty meters;
- severe cognitive impairment;
- psychiatric or intellectual disability which would limit the ability to participate in a class with distant supervision or the ability to complete outcome measures (defined as mini-mental state exam (MMSE) <= 18 points) (175);
- pulmonary hypertension with recent history of dizziness or syncope on exertion (must have medical clearance if mean pulmonary artery pressure > 50 mm Hg);
- acute pulmonary embolus;
- interstitial lung disease;
- unstable cardiovascular disease (e.g. unstable angina, uncontrolled arrhythmia, New York Heart (NYH) Class 4 chronic heart failure (CHF), uncontrolled hypertension, diastolic pressure > 95 mm Hg);
- absolute contraindications to exercise (e.g. severe orthopaedic/neurological deficit; severe uncontrolled pain: surgical or medical (including active transmissible infectious disease) restrictions to mobilization/rehabilitation (e.g. diabetic foot);
- severe ischemic vascular disease;

- advanced neuropathy/retinopathy which would compromise the ability to safely exercise);
- people already participating in a structured exercise rehabilitation program from a community or external provider;
- uncontrolled diabetes;
- uncontrolled epilepsy or seizures;
- extensive brain, skeletal or visceral metastases, life expectancy considered to be less than 12 months;
- known thrombocytopenia (<50×109/l) or severe neutropenia (neutropenia defined as absolute neutrophil count < 500/µL; profound neutropenia defined as ANL < 100 neutrophils/mm^3 (176);
- room air desaturation at rest < 85%;
- abnormal and untreated moderate anaemia (80-109 g/L);
- pregnant women.

Usual cessation/withdrawal criteria for multimorbidity rehabilitation applied to all participants as follows:

- a change in a participant's medical condition that made them unsuitable for exercise;
- non-attendance (if patient fails to attend six consecutive sessions);
- a participant withdrawal from the program.

For the safety criteria, exercise was ceased, during the corresponding exercise session, if a participant displayed the following observations during group exercise:

- heart rate (HR) > 160bpm;
- blood pressure (BP) > 180 mmHg or <90 mmHg (systolic) and > 110 mmHg or < 60 mmHg (diastolic);
- SpO_2 < 88% (exercise temporarily ceased and resumed when SpO2 reached 88% or supplemental oxygen supplied);
- diaphoretic, pale or dizzy;
- room air desaturation at rest < 85%;
- syncope, dizziness, onset of angina or chest pain;

Exercise was not commenced if the participants displayed the following observations:

- fever > 38.0,
- new known thrombocytopenia (<50×109/l) or severe neutropenia (neutropenia defined as absolute neutrophil count < 500/µL; profound neutropenia defined as ANL < 100 neutrophils/mm^3 (176).

Outcome measures

Measures of multimorbidity included:

The Cumulative Illness Rating Scale for Geriatrics (CIRS(G)) (107) is composed of 14 body system categories, with a severity scale for each domain (109). It has been used to successfully classify medically impaired elderly subjects with good interrater reliability and face validity (107). The Functional Comorbidity Index (FCI) (110) is an 18-item index based on diagnosis of comorbid diseases. One point per disease is scored with the scores summed to provide a single total score; the higher the score, the greater number of an individual's co-morbidities. The Duke Severity of Illness Checklist (DUSOI) (112) assesses the severity of a person's illness based on four parameters for each diagnosis, including symptoms, complications, prognosis without treatment and treatment potential.

Measures of illness perception included:

The Multimorbidity Illness Perception Scale (MULTIPleS) (111) explores five domains of emotional representations, treatment burden, prioritizing conditions, causal links and activity limitations. This assesses the impact of multimorbidity on illness perceptions, adjustments, clinical outcomes, quality of life and costs in this population, and is valid and reliable.

Results

Table S2. Main Diagnoses*

Main Diagnosis, n (%)	**Rehabilitation Program (n = 8)**	**Usual Care (n = 8)**
Acute Polyarthritis	0 (0%)	1 (13%)
Atrial Fibrillation	0 (0%)	1 (13%)
Benign Prostatic Hyperplasia	0 (0%)	1 (13%)
Bleeding Stoma	0 (0%)	1 (13%)
Cancer	2 (25%)	0 (0%)
Diabetes	1 (13%)	0 (0%)
Diarrhoea & Lethargy	1 (13%)	0 (0%)
Fractured Ribs	1 (13%)	0 (0%)
Laminectomy	1 (13%)	0 (0%)
Pneumonia	0 (0%)	1 (13%)
Rheumatoid Arthritis	1 (13%)	0 (0%)
Stroke	0 (0%)	1 (13%)
Transverse Myelitis	1 (13%)	0 (0%)
Tumour	0 (0%)	2 (25%)

*main diagnoses as determined by the treating clinician at referral or hospital admission

Overall prevalence of co-existing conditions by group

Table S3. Prevalence of co-existing conditions

Other Co-existing Condition (n, %)	**Rehabilitation Program (n = 8)**	**Usual Care (n = 8)**
Alcohol Problems	0 (0%)	1 (13%)
Anxiety	1 (13%)	1 (13%)
Asthma	1 (13%)	2 (25%)
Atrial Fibrillation	0 (0%)	1 (13%)
Cancer (newly diagnosed)	3 (38%)	4 (50%)
Chronic Kidney Disease	1 (13%)	0 (0%)
Chronic Obstructive Pulmonary Disease	2 (25%)	3 (38%)
Chronic Sinusitis	0 (0%)	1 (13%)
Coronary Heart Disease	2 (25%)	4 (50%)
Depression	2 (25%)	2 (25%)
Diabetes	5 (63%)	4 (50%)
Diverticular Disease of Intestines	1 (13%)	0 (0%)
Hearing Loss	1 (13%)	0 (0%)
Heart Failure	1 (13%)	0 (0%)
Hypertension	7 (88%)	3 (38%)
Peripheral Vascular Disease	1 (13%)	0 (0%)
Prostate Disorders	0 (0%)	1 (13%)
Rheumatoid Arthritis	1 (13%)	0 (0%)
Stroke/Transient Ischaemic Attack	1 (13%)	2 (25%)
Thyroid Disorders	0 (0%)	1 (13%)
Treated Constipation	1 (13%)	0 (0%)

Treated Dyspepsia	2 (25%)	2 (25%)

Supplement References for Chapter 3

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CHAPTER 4

Multimorbidity rehabilitation versus disease-specific rehabilitation in people with chronic diseases: a pilot randomized controlled trial

The clinical trial presented in Chapter 4 has been published in Pilot and Feasibility Studies – 29/11/18.

- Barker K, Holland AE, Lee AL, et al. Multimorbidity rehabilitation versus disease-specific rehabilitation in people with chronic diseases: a pilot randomized controlled trial. Pilot and Feasibility Studies 2018; 4(1):181. doi: 10.1186/s40814-018-0369-2

Declaration of Authorship – Chapter 4

Student's declaration

The nature and extent of contributions to Chapter 4 of this thesis are as follows.

Name	**Nature of contribution**	**Extent of contribution**	**Signature**
Kathryn Barker	Study concept & design; protocol development; recruitment; data collection & analysis; writing of manuscript & review	50%	
Anne Holland	Study concept & design; protocol development; review of manuscript	10%	

Annemarie Lee	Study concept & design; protocol development; data collection & analysis; review of manuscript	10%
Elizabeth Skinner	Study concept & design; protocol development; review of manuscript	10%
Terry Haines	Study design; review of manuscript	3%
Kathryn Ritchie	Study design; recruitment; data collection & analysis; manuscript review	5%
Claire Boote	Study design; recruitment; manuscript review	2%
Joanne Saliba	Study design; recruitment; data collection; manuscript review	2%
Stephanie Lowe	Study design; recruitment; data collection; manuscript review	2%
Fiona Pazsa	Recruitment; data collection; manuscript review	2%
Lee Thomas	Recruitment; data collection; manuscript review	2%

Monica Turczyniak	Study design; recruitment; data collection; manuscript review	2%

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Pilot and Feasibility Studies

RESEARCH Open Access

Multimorbidity rehabilitation versus disease-specific rehabilitation in people with chronic diseases: a pilot randomized controlled trial

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Abstract

Background: Multimorbidity (the co-existence of two or more chronic conditions in an individual) is a growing healthcare burden internationally; however, healthcare and disease management, including rehabilitation, is often delivered in single-disease siloes. The aims of this study were to (1) evaluate the safety and feasibility of multimorbidity rehabilitation compared to a disease-specific rehabilitation program in people with multimorbidity and (2) gather preliminary data regarding clinical outcomes and resource utilization to inform the design of future trials.

Methods: A pilot feasibility randomized controlled trial with concealed allocation, assessor blinding, and intention-to-treat analysis. Seventeen individuals with a chronic disease eligible for disease-specific rehabilitation (pulmonary, cardiac, heart failure rehabilitation) and at least one other chronic condition were recruited. The intervention group attended multimorbidity exercise rehabilitation and the control group attended disease-specific exercise rehabilitation. Participants attended twice-weekly exercise training and weekly education for 8 weeks. Feasibility measures included numbers screened, recruited, and completed. Other outcome measures were change in functional exercise capacity (6-minute walk test (6MWT)), health-related quality of life (HRQoL), activities of daily living (ADL), and resource utilization.

Results: Sixty-one people were screened to recruit seventeen participants (nine intervention, eight control); one withdrew prior to rehabilitation. Participants were mostly male (63%) with a mean (SD) age of 69 (9) years and body mass index of 29 (6). The intervention group attended a mean (SD) of 12 (6) sessions, and the control group attended 11 (4) sessions. One participant (6%) withdrew after commencing; two (12%) were lost to follow-up. The intervention group 6MWT distance increased by mean (SD) of 22 (45) meters (95% confidence interval −16 to 60) compared to 22 (57) meters (95% confidence interval −69 to 114) (control).

Conclusions: It was feasible to recruit people with multimorbidity to a randomized controlled trial of rehabilitation. A large RCT with the power to make significant conclusions about the impact on the primary and secondary outcomes is now required.

Trial registration: The trial was registered with the Australian and New Zealand Clinical Trials Registry available at http://www.anzctr.org.au ACTRN12614001186640. Registered 12/11/2014.

Keywords: Multimorbidity, Rehabilitation, Exercise, Randomized controlled trial, Cardiac, Pulmonary, Heart failure

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Background

Multimorbidity (the co-existence of two or more chronic conditions in an individual) [1] is a growing healthcare burden internationally [2–4]. Two thirds of adults over 60 years have multimorbidity [5], the severity increasing with age [6]. With an estimation that 25% of our population will be over 65 years of age by 2015 [7], the prevalence of multimorbidity will rise significantly. This is of importance to the healthcare system with multimorbidity associated with increased premature mortality [8, 9], poorer functional status [10], and reduced health-related quality of life (HRQoL) [11].

Worldwide healthcare delivery focuses on single diseases [1, 12, 13]. This challenges those caring for patients with chronic disease, as multimorbidity has direct management implications. Single-disease clinical guidelines are not developed in a multimorbidity context nor consider multimorbidity [14–16]. People with multimorbidity are managed with multiple single-disease guidelines. However, recent multimorbidity guidelines suggest that single-disease care may not be appropriate for people with multimorbidity, due to the potential interactions between diseases and drugs as well as total treatment burden [17].

Rehabilitation is integral to chronic disease management but is frequently structured in single-disease siloes such as cardiac and pulmonary rehabilitation. Meta-analyses demonstrated improvements in exercise capacity, symptoms, HRQoL, and reduced hospitalization in people with chronic disease [18–21]. However, patients attending the disease-specific rehabilitation programs are increasingly complex with more co-existing health conditions. In the United Kingdom (UK), 46% of patients in cardiac rehabilitation have comorbidities [22]. While patients with multimorbidity are included in cardiac, heart failure (HF), and pulmonary rehabilitation, their clinical outcomes are less optimal compared to people with single diseases [23–25].

An alternative option is multimorbidity rehabilitation, with inclusive criteria that do not limit participation due to disease type. Understanding whether the provision of multimorbidity rehabilitation for this population is at least equivalent in health outcomes to disease-specific rehabilitation has considerable implications. People with multimorbidity may benefit from a modified structure which accommodates all conditions and which influences their benefit from rehabilitation. Multimorbidity rehabilitation also addresses recommendations that a care model should aim to improve HRQoL by reducing treatment burden, adverse events, and unplanned care [17].

The aims of this study were to (1) evaluate the safety and feasibility of a multimorbidity rehabilitation compared to a disease-specific rehabilitation program in people with multimorbidity and (2) to gather preliminary data regarding proposed outcomes for the main trial which were change in functional exercise capacity, activities of daily living (ADL), HRQoL, and resource utilization.

Methods

Study overview, design, and setting

This trial was a pilot feasibility single-blind parallel randomized controlled trial (RCT), conducted at Sunshine Hospital, Victoria, Australia. Participants were recruited from November 2014 to February 2015 and sourced from referrals to pulmonary, cardiac, and HF rehabilitation programs, inpatient medical, respiratory, and cardiology wards, and the community-based rehabilitation service at Western Health. Ethical approval was obtained from the Melbourne Health Human Research Ethics Committee and La Trobe University. The trial was registered with Australian New Zealand Clinical Trials Registry (ACTRN 12614001186640) and reported according to CONSORT guidelines [26].

Eligibility criteria

The inclusion criteria were adults (aged > 18) with a physician diagnosis of a single disease for which usual care rehabilitation was indicated (i.e., Chronic Obstructive Pulmonary Disease (COPD), bronchiectasis [27], HF, coronary artery disease or ischemic heart disease [28]), and at least one other chronic condition, such as diabetes, hypertension, and cancer [1]. Exclusion criteria were an inability to walk 50 m, severe cognitive impairment, unstable cardiovascular disease or diabetes, and confirmed pre-existing participation in a structured exercise program. A detailed list of eligible chronic conditions and exclusion criteria are included in Additional file 1.

Randomization

Eligible participants were randomized in a 1:1 allocation. The allocation sequence was generated using computer-generated random numbers and group allocation was placed into sealed opaque envelopes by an independent investigator not involved in intervention delivery or outcome measurement. Randomization occurred after the signing of the consent form and completion of the baseline data collection.

Interventions

Participants were randomized to either usual care disease-specific rehabilitation program (pulmonary, cardiac, or HF rehabilitation) (control) or a multimorbidity rehabilitation program (intervention). Both rehabilitation programs were 8 weeks duration and comprised exercise (1 h, twice-weekly) and education (1 h, once weekly) performed in an outpatient setting. The interventions were delivered by health professionals experienced in

the delivery of disease-specific rehabilitation programs. A face to face instruction session was conducted prior to the commencement of the intervention period to ensure consistent delivery of exercise.

Exercise

Exercise prescription and delivery was equivalent in the disease-specific and multimorbidity rehabilitation programs. Clinicians were encouraged to individualize the exercise program to accommodate participants' chronic conditions. For example, a second walking session was included to replace cycling if the participant was unable to use a stationary bike due to back pain. The program consisted of aerobic (walking and cycling) and strengthening (upper and lower limb) exercises (see Additional file 1 for exercise details).

Education

Education for the disease-specific and multimorbidity rehabilitation programs was delivered by multidisciplinary team members using a didactic approach with handouts provided. (Table 1). The disease-specific topics were consistent with the current recommendations [28, 29]. The multimorbidity rehabilitation program education sessions aimed to enhance skills in general disease self-management and focused on common risk factor

Table 1 Education sessions

	Multimorbidity	Usual disease-specific		
		Pulmonary rehab	Cardiac rehab	Heart failure rehab
1	Nursing What is multimorbidity? Managing multimorbidity—risk factors and setting goals Finding useful resources	Speech pathology Managing shortness of breath and eating and talking Finding useful resources	Social work Services and supports Social supports Finding useful resources	Social work Services and supports Social supports Finding useful resources
2	Nursing Communication with health care professionals, family, and friends Smoking cessation Blood pressure and cholesterol—how to manage.	Nursing What is respiratory disease? Managing your disease (action plans) Smoking cessation	Nursing What is heart disease? Managing your disease (action plans) Risk factor modification	Nursing What is CHF? Managing your disease (action plans) Risk factor modification
3	Physiotherapy Why is exercise important? Types of exercise and how much to do Precautions and warnings for exercise	Physiotherapy Why is exercise important? Types of exercise and how much to do Precautions and warnings for exercise	Physiotherapy Why is exercise important? Types of exercise and how much to do Precautions and warnings for exercise	Physiotherapy Why is exercise important? Types of exercise and how much to do Precautions and warnings for exercise
4	Dietetics Healthy Eating Weight management Finding useful resources	Dietetics Healthy Eating Weight management Finding useful resources	Dietetics Healthy Eating Weight management Finding useful resources	Dietetics Healthy Eating Weight management Finding useful resources
5	Diabetes Educator What is diabetes? Managing blood sugar levels Signs and symptoms of low/high blood sugar levels	Continence What is incontinence? Managing incontinence Finding useful resources	Diabetes educator What is diabetes? Managing blood sugar levels Signs and symptoms of low/high blood sugar levels	Diabetes educator What is diabetes? Managing blood sugar levels Signs and symptoms of low/high blood sugar levels
6	Pharmacy General medicine advice Why am I taking so many medications? Home medicine review	Pharmacy Inhalers and medications Why am I taking so many medications? Home medicine review	Pharmacy Classes of medications Why am I taking so many medications? Home medicine review	Pharmacy Classes of medications. Why am I taking so many medications? Home medicine review
7	Occupational therapy Performing activities of daily living Energy conservation Relaxation and stress management	Occupational therapy Performing activities of daily living Energy conservation Relaxation and stress management	Occupational therapy Performing activities of daily living Energy conservation Relaxation and stress management	Occupational therapy Performing activities of daily living Energy conservation Relaxation and stress management
8	Psychology Anger/shock/numbness/denial/disbelief Acceptance and building problem-solving skills Action towards achieving a modified healthy lifestyle	Psychology Anger/shock/numbness/denial/disbelief Acceptance and building problem-solving skills Action towards achieving a modified healthy lifestyle	Psychology Anger/shock/numbness/denial/disbelief Acceptance and building problem-solving skills Action towards achieving a modified healthy lifestyle	Psychology Anger/shock/numbness/denial/disbelief. Acceptance and building problem-solving skills Action towards achiving a modified healthy lifestyle.

modification for chronic diseases [30]. Participants were directed towards finding relevant information and resources in disease management. The "managing morbidity" session aimed to teach participants to recognize when their disease symptoms changed and to develop their relationship with their general practitioner (GP) to manage these changes or exacerbations, rather than addressing disease-specific action plans. The multidisciplinary team presenting the education did not cover any disease-specific topics, but addressed specific questions that arose during the sessions. A diabetes education session was included in the multimorbidity education due to the high prevalence of diabetes in the study population. The pharmacy education session did not present the common medication classes or device techniques for specific diseases, as is usual in disease-specific rehabilitation, but focused on awareness of community services commonly available through local pharmacies to assist people with managing polypharmacy, such as home medication review and medication distribution packs. Some of the presentations were developed collaboratively by the study team (i.e., managing multimorbidity) and others by individual disciplines (i.e., dietetics and psychology). Several of the presentations were adapted from existing disease-specific presentations. Goal setting was a core component of the sessions, without the use of specific behavior change techniques.

Outcome measures

Initial and discharge assessments were conducted at baseline and following rehabilitation completion by blinded assessors. The blinded assessors were provided with a face to face instruction session and manuals for performing the measures prior to the commencement of the data collection.

Baseline demographics, medical history, and multimorbidity measures [11] were collected. The use of multiple multimorbidity measures was to determine which measures would be most suitable for a larger scale trial for ease of use and information obtained. These included the Cumulative Illness Rating Scale for Geriatrics (CIRS(G)) [31], the Functional Comorbidity Index (FCI) [32], the Multimorbidity Illness Perception Scale (MULTIPleS) [33], and the Duke Severity of Illness Checklist (DUSOI) [34]. The detailed information regarding these measures is in the Additional file 1.

Feasibility and process outcomes

The program feasibility was measured by numbers screened to achieve target sample size, the number of those who agreed to participate; and the number who completed the intervention. Program completion was defined a priori as attendance at 12 out of 16 sessions for pulmonary rehabilitation [35]; similar cutoffs for cardiac, HF, and multimorbidity rehabilitation were applied for consistency.

Patient-centered outcomes

Functional exercise capacity

The primary outcome proposed for the main trial was change in functional exercise capacity, measured by the 6-min walk test (6MWT). The 6MWT has demonstrated validity and reliability in patients with chronic respiratory disease [29], HF [36], and in patients with cardiac disease and multi-morbidities [37]. The 6MWT was administered according to guidelines, with two tests conducted, with the longest distance recorded [38]. Supplemental oxygen was delivered during the 6MWT for any participant who was normally prescribed with domiciliary exertional oxygen with the same flow rate used at each assessment.

Secondary outcomes proposed for the main trial included ADL and HRQoL questionnaires and resource utilization.

Activities of daily living

Functional ADL were measured using the Katz Index of Independence in Activities of Daily Living (Katz ADL index). The Katz ADL index is used in older people to measure function [39] and has been used in people with chronic diseases [40].

Health-related quality of life

HRQoL was measured with all participants using two generic instruments, the Assessment of Quality of Life (AQoL-4D) [41, 42] and EuroQol-5D-5 L (EQ-5D-5 L) [43, 44]. The AQoL-4D and EQ-5D-5 L are valid and reliable instruments, with moderate levels of responsiveness and sensitivity in a wide range of health conditions [41, 44]. The EQ-5D-5 L may be considered as a second potential primary outcome. Disease-specific HRQoL measures were the Minnesota Living with Heart Failure Questionnaire (MLHF) for participants with a primary diagnosis of HF and St. George's Respiratory Questionnaire (SGRQ) for participants with a primary diagnosis of respiratory disease. The SGRQ and MLHF are reliable and valid instruments that are sensitive and responsive to change after pulmonary rehabilitation or exercise training for people with HF [29, 45].

Resource utilization

Resource utilization was measured by collecting data on emergency department (ED) presentations, hospital admissions, GP presentations during the trial period, and any health event necessitating hospital admission during the intervention. Participants also maintained a daily diary recording all medical consultations with their GP or consultant physician and hospital admissions. Diary information was verified by participant interview at the

post-intervention assessment. Hospital admissions and length of stay were verified using Western Health patient medical records.

Statistical methods

Sample size

As this was a pilot trial, no sample size calculation was undertaken [46]. A sample of sixteen participants was recruited due to the resources available and the timeframe to complete the intervention.

Statistical analysis

Feasibility was described in numbers and percentages. Continuous variables were reported as mean and standard deviation (SD), or median and interquartile range [IQR] depending on data distribution. Continuous variables were analyzed using a paired or independent t-tests for normally distributed data and Chi-square or Mann-Whitney U test for non-normally distributed data. All patient-centered outcomes were presented with a 95% confidence interval (CI). Data analysis was by intention-to-treat. The study was not powered to detect differences in patient-centered outcomes and therefore, the results of hypothesis testing should be interpreted with caution. Data were analyzed through the Statistical Package for the Social Sciences (SPSS) Windows Version 23.0.

Results

Sixty-one people were screened to recruit 17 participants (Fig. 1). The original aim was to recruit 16 participants; however, one participant withdrew prior to intervention

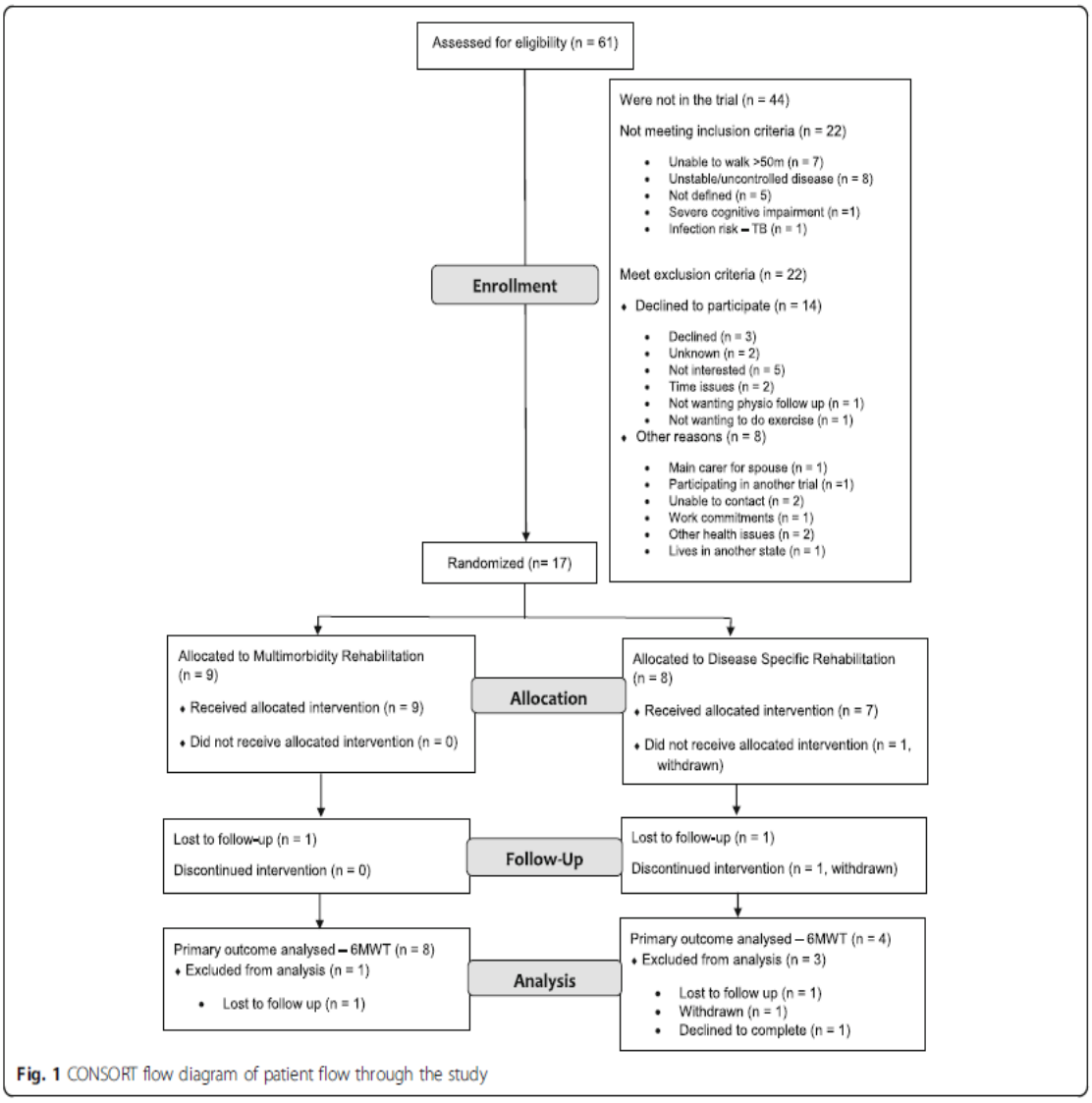

Fig. 1 CONSORT flow diagram of patient flow through the study

and therefore an additional participant was recruited. Of the 44 not in the trial, 22 did not meet the inclusion criteria. Of these, eight had unstable or uncontrolled disease. Seven were excluded as they were not able to walk more than 50 m. Of the 22 who met the criteria but were not recruited, 14 declined to participate with the most common reason "not being interested" in five. Other reasons for declining are in the Additional file 1. Of the 17 participants recruited and randomized, nine were randomized to the Multimorbidity Rehabilitation Group (MMRG) and eight to the Disease-Specific Rehabilitation group (DSRG). All nine of the MMRG received the intervention and seven in the DSRG received the intervention, with losses to follow up detailed in Fig. 1. Two participants from the MMRG (none from the DSRG) who did not complete the rehabilitation program were included in the analysis as they completed all post-intervention outcome measures.

Participant demographic characteristics are summarized in Table 2. A total of 63% were male, with a mean (SD) age of 69 (9) and body mass index of 29 (6). The MMRG had a higher baseline 6-min walk distance (6MWD) of 446 (102) meters (m) compared to the DSRG with 335 (141) m.

The DSRG had a higher FCI compared to the MMRG, indicating lower physical function [32]. The higher summary score for the MULTIPleS in the DSRG indicated worse perception of their multiple diseases [33]. For the CIRS(G), the higher total score for the DSRG compared to the MMRG suggests greater medical burden in this group [31]. However, the severity index score was the same for both groups with a small difference in the total number of categories endorsed (Table 2), indicating a higher level of severity of disease or more chronic problems in the DSRG. The DUSOI data was not reported due to issues encountered in tool use. All assessors found the tool difficult to use and several assessors administered the tool incorrectly, by asking participants to select categories rather than the clinician deciding.

Fifty percent of the participants required individual adjustments to their exercise program to accommodate their multimorbidity. The causes of the adjustments were pain located in the knee ($n = 6$), hip ($n = 1$), and back ($n = 3$), and balance issues in two participants. Of the eight participants requiring modification to the exercise prescription, three had multiple causes and five had a single cause. Both participants with balance issues required adjustment of the step exercise (a lower limb strengthening exercise), where they were unable to hold weights in their hands and safely complete the step action. Therefore, one participant held a weight in one hand and placed the other on a rail and one placed both their hands on rails and did not hold any weights. The pain (hip, knee, and back) issues affected participants' ability to perform the following exercises: squats, steps, sit to stand (lower limb strengthening exercises), cycling (aerobic exercise), and upper limb weights (upper limb strengthening exercise). The adjustments included repetition of an alternative exercise component (e.g., walking, sit to stand, and squats), not performing that exercise, performing the upper limb exercises in a seated position, or increasing the sets and repetitions of another exercise component.

Post-intervention

Overall, 63% of the participants completed the rehabilitation programs (67% in MMRG compared to 57% in DSRG). The MMRG attended a mean number of 12 (6) sessions and the DSRG attended 11 (4) sessions. No adverse events related to the interventions or testing were recorded.

There was no significant difference in mean change in 6MWD from baseline to post-intervention between the groups, with the MMRG achieving a mean improvement of 22 (45) m (95% CI − 16 to 60) and the DSRG achieved a mean improvement of 22 (57) m (95% CI − 69 to 114) (Fig. 2). The data displayed in Fig. 2 reflect the numbers analyzed for each group accounting for withdrawals and losses to follow up (detailed in Fig. 1). In both groups, 50% of participants achieved the minimal important difference (MID) of at least 30 m [38].

There were no significant differences between the groups for improvement in AQoL, Katz ADL index, and EQ-5D-5 L (Table 3). There was a mean increase in the AQoL utility score for both groups, with a greater mean increase in the DSRG compared to the MMRG. Two participants from each group achieved the MID of 0.06 in the AQoL [47].

Nine of the participants returned their daily diaries, with resource utilization recorded (MMRG $n = 5$; DSRG $n = 4$). All the participants had GP visits during the trial. The total number of GP visits were similar between groups (MMRG 10 vs DSRG 11). There was no significant difference in the mean number of GP visits between groups (MMRG 2 (1) vs DSRG 3 (2)). No participants had ED presentations, but two participants were admitted to the hospital, one from each group. Due to an error during the trial period, an outcome measure reported in the trial registry (Short Form 36 (SF-36)) was not collected, with the SF-36 form not included in the outcome measure packs during data collection.

Discussion

This pilot study showed that it was feasible to conduct multimorbidity rehabilitation programs in people with multiple chronic diseases. The lack of adverse events during the multimorbidity program suggests this model was safe to conduct. This pilot trial supports the performance of a larger RCT in regard to recruitment, enrolment,

Table 2 Participant characteristics

	Multimorbidity Rehabilitation Group (MMRG) ($n = 9$)	Disease-Specific Rehabilitation Group (DSRG) ($n = 7$)
Age (in years), mean (SD)	68 (10)	71 (8)
Male, *n* (%)	7 (78%)	3 (43%)
BMI, mean (SD)	27 (6)	32 (5)
Main diagnosis, *n* (%)		
- Acute myocardial infarction	2 (22%)	1 (14%)
- Percutaneous coronary intervention—stent	0 (0%)	3 (43%)
- Coronary artery bypass graft surgery	2 (22%)	0 (0%)
- Mitral valve replacement/repair	1 (11%)	0 (0%)
- Chronic obstructive pulmonary disease	3 (34%)	2 (29%)
- Asthma	0 (0%)	1 (14%)
- Congestive heart failure	1 (11%)	0 (0%)
Disease-Specific Program Originally Referred to, *n* (%)		
- Cardiac	5 (56%)	4 (57%)
- Heart failure	1 (11%)	0 (0%)
- Pulmonary	3 (33%)	3 (43%)
Smoking status, *n* (%)		
- Current	1 (12%)	1 (14%)
- Ex-smoker	4 (44%)	4 (57%)
- Never	4 (44%)	2 (29%)
Baseline 6MWD, mean (SD)	446 (102)	335 (141)
Other comorbidities, *n* (%)		
- Coronary heart disease	8 (89%)	4 (57%)
- Hypertension	8 (89%)	5 (71%)
- Diabetes	4 (44%)	4 (57%)
Number of comorbidities, mean (SD)	4 (1)	4 (1)
Functional Comorbidity Index, mean (SD)	4 (2)	8 (1)
Multimorbidity Illness Perception Scale, mean (SD)		
- Treatment burden	4 (3)	5 (4)
- Prioritization	6 (4)	9 (2)
- Causal relationships	3 (3)	3 (3)
- Activity restriction	4 (3)	4 (2)
- Emotional representations	9 (12)	16 (9)
- Summary scale	26 (20)	37 (16)
Cumulative Illness Rating Scale for Geriatrics, mean (SD)		
- Total number of categories endorsed	4 (2)	5 (1)
- Total score	6 (3)	9 (2)
- Severity index	2 (0)	2 (0)
- Number of categories at level 3 severity	0 (1)	1 (1)
- Number of categories at level 4 severity	0 (0)	0 (0)

SD standard deviation, *n* number, *BMI* body mass index, *6MWD* 6-min walk distance

consent, randomization, and undertaking of multimorbidity rehabilitation exercise and education sessions.

The similar number of sessions attended in both groups shows that people were willing to attend an outpatient exercise rehabilitation program that focused on multimorbidity compared to disease-specific groups. The prescribed exercise program was completed by participants when delivered by physiotherapy and nursing staff concurrently supervising people with different disease types. The completion rates for both groups were similar or better than those reported for disease-specific programs worldwide. In the UK, completion rates have been reported at 7% of those enrolled in pulmonary rehabilitation [48] and completion rates of cardiac rehabilitation in South Australia were 13% [49].

The procedures required to conduct a RCT were feasible in this trial. The well-established disease-specific rehabilitation programs of cardiac, HF, and pulmonary rehabilitation at the health network contributed to the ability to fully recruit. Only 61 people were required to be screened to fully recruit to this trial, which was 3.6 times the number required for enrollment. This should translate into achievable recruitment targets for a larger RCT. It was anecdotally reported by assessors and some participants that assessments were time-consuming due to questionnaire burden and outcome measures used. To make a larger trial less cumbersome and costly, refining the number of questionnaires and outcome measures would be beneficial. The reasons for non-enrollment in the trial were similar to the anecdotal barriers experienced for people attending existing disease-specific services at the health network, including unstable or uncontrolled disease, poor exercise capacity (an inability to walk 50 m), not interested in attending an exercise program, not wanting physiotherapy, and work commitments.

The education sessions for the MMRG were a novel part of this trial, with the objective of enhancing skills in disease self-management. It has been reported that

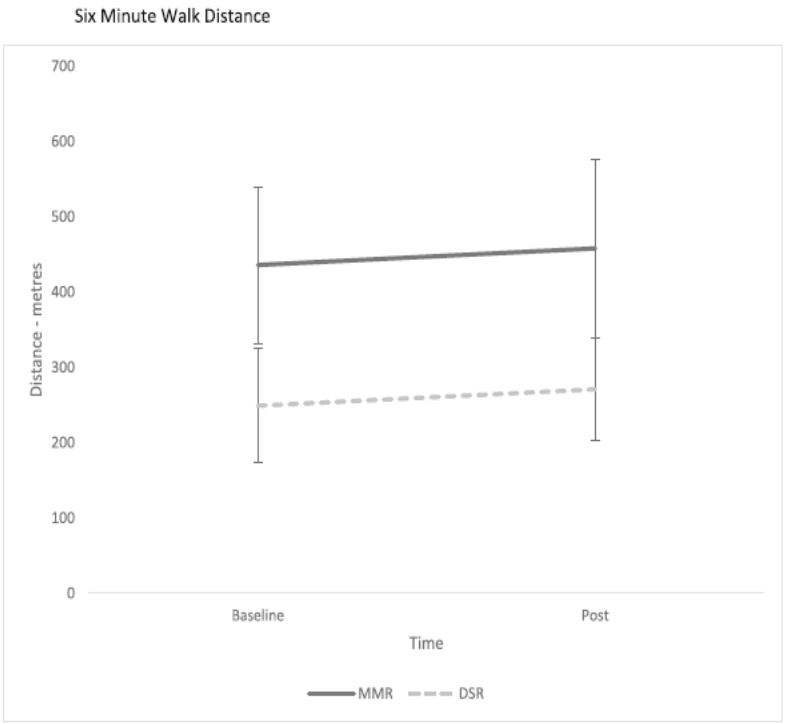

Fig. 2 Six-minute walk distance

education programs using self-management skill training are more effective in improving clinical outcomes than information-only education [50]. In future research, potential options for measuring the impact of the difference in the education sessions may include identifying a suitable tool for measuring education. The new model of multimorbidity rehabilitation had the novel aspect of participants attending a rehabilitation program with other people who had different diseases compared to them. There is potential value in investigating participants' perceptions of peer support within rehabilitation and whether this influences satisfaction, attendance, and completion rates. Presently, an investigation into peer support largely focuses on programs delivered by trained individuals and not that achieved by informal support between peers within a rehabilitation group. For these novel aspects of multimorbidity rehabilitation, using focus groups with the participants and educators to gather qualitative data could provide meaningful information. This was not performed in this trial due to resources, but would be very valuable data to collect to inform the optimal design of a rehabilitation intervention for any future large trial.

Multimorbidity measures were used in this trial to describe a complex population. There is no gold standard measure of multimorbidity, and the tools available examine differing aspects of disease and burden. The FCI and MULTIPleS appeared to be the most suitable for a larger scale trial in terms of population suitability, ease of use, and information obtained. The FCI is simple to administer and score, with yes/no responses and a total of single scores [32]. This is an appropriate measure for use in a trial researching exercise capacity and rehabilitation as it was designed to focus on physical function [32]. The MULTIPleS measures a participant's illness perception, which can affect people's self-management of diseases and enable them to make sense of their conditions [33]. Physical function and disease self-management are important aspects of exercise rehabilitation, and therefore, the FCI and MULTIPleS are valuable measures. As previously stated, the DUSOI was a difficult measure to use with several issues encountered. The CIRS(G) was a time-consuming measure to administer. It was also difficult to obtain all required information to accurately score each category, with participants not undergoing investigations or results not being available. The clinical

Table 3 Patient-centered outcome measures

	Multimorbidity Rehabilitation Group (MMRG) ($n = 8$)				Disease-Specific Rehabilitation Group (DSRG) ($n = 5$)				Difference between groups	
	Baseline	Post	Change	95% CI	Baseline	Post	Change	95% CI	Mean	95% CI
Six-min walk distance (m), mean (SD)	436	458	22 (45)	− 16–60	249 ($n = 4$)	271 ($n = 4$)	22 (57)	− 69–114	0	− 67–67
AQoL utility, mean (SD)	0.684 (0.204)	0.709 (0.222)	0.025 (0.136)	− 0.089–0.139	0.566 (0.271)	0.620 (0.257)	0.054 (0.363)	− 0.397–0.505	− 0.029	− 0.336–0.278
EQ-5D-5 L visual analogue scale, mean (SD)	73 (10)	76 (19)	3 (18)	− 12–18	55 (17) ($n = 4$)	53 (5) ($n = 4$)	− 3 (13) ($n = 4$)	− 24–19	6	− 17–28
St George Respiratory Questionnaire, mean (SD)	49 (16) ($n = 3$)	37 (20) ($n = 3$)	− 12 (19) ($n = 3$)	− 60–36	48 ($n = 1$)	49 ($n = 1$)	1 ($n = 1$)	N/A	− 12	− 109–84
Minnesota Living with Heart Failure Questionnaire	22 ($n = 1$)	13 ($n = 1$)	− 9 ($n = 1$)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Katz ADL index, mean (SD)	5.38 (1.79)	5.88 (0.34)	0.5 (2)	− 1.05–2.05	4.8 (0.84)	4.8 (1.10)	0 (2)	− 2.15–2.15	0.50	− 1.77–2.77

95% confidence interval represents comparison between groups for change over the course of the program

n number, *CI* confidence interval. *AQoL* assessment of quality of life, *SD* standard deviation, *ADL* activities of daily living, *EQ-5D-5 L* EuroQol-5D-5 L, *N/A* not applicable

expertise of blinded assessors can affect the accurate scoring of the CIRS(G) due to the decision process required to clarify complex medical problems or their severity [51]. For a future larger scale trial, these difficulties could be avoided by carefully selecting the most relevant and applicable outcome measures.

This trial was limited in the estimate of potential intervention effect due to the small sample size, as expected in a feasibility study. This sample size was chosen to accommodate the number of participants who could attend the MMRG with available resources, an acceptable approach in pilot trials [46]. A larger RCT is needed to draw conclusions about the impact of a multimorbidity rehabilitation program on clinical outcomes. However, the ability of multimorbidity rehabilitation to accommodate people with different disease types and allow people to attend programs that run at different times throughout a week may create a more flexible model which may positively influence reported barriers of program timing and disruption to usual routines [52]. This is important with current pressure on healthcare resources and the growing burden of chronic diseases.

The results of this study allow estimation of sample sizes for a future randomized controlled trial comparing multimorbidity and disease-specific rehabilitation. To detect a clinically meaningful improvement for the primary outcome measure of 6MWT with 80% power, 114 participants are required [53]. This assumes a clinically meaningful difference between groups of 30 m, based on the well-established minimal important difference for 6MWT derived in patients with chronic respiratory disease [38], and assumes a SD of change in 6MWD of 57 m, based on data collected in this trial for the DSRG. To detect a clinically meaningful improvement for the secondary outcome of EQ-5D-VAS with 80% power, 214 participants are required [53]. This assumes a difference between groups of 6.9 points, which is the MID for the EQ-5D-VAS derived in the COPD population [54], and a SD of change in EQ-5D of 18, based on data from Table 3. Given the large confidence intervals, these estimations for adequate power should be interpreted with caution. Through the high prevalence of multimorbidity, these sample sizes should be readily achieved.

Conclusions

It was feasible to conduct multimorbidity rehabilitation programs in people with chronic diseases. This provides a sound basis upon which to conduct a larger RCT comparing disease-specific and multimorbidity rehabilitation exercise and education sessions, from which definitive conclusions regarding efficacy can be made. This may assist in the development of effective healthcare models in the multimorbidity population.

Additional file

Additional file 1: Supplemantary material. (DOC 103 kb)

Abbreviations

6MWD: 6-min walk distance; 6MWT: 6-min walk test; ADL: Activities of daily living; AQoL-4D: Assessment of Quality of Life; CI: Confidence interval; CIRS(G): Cumulative Illness Rating Scale for Geriatrics; COPD: Chronic obstructive pulmonary disease; DSRG: Disease-specific rehabilitation group; DUSOI: Duke Severity of Illness Checklist; ED: Emergency department; EQ-5D: EuroQol-5D-5 L; FCI: Functional Comorbidity Index; GP: General practitioner; HF: Heart failure; HRQoL: Health-related quality of life; IQR: Interquartile range; Katz ADL index: Katz Index of Independence in Activities of Daily Living; MID: Minimal important difference; MLHF: Minnesota Living with Heart Failure Questionnaire; MMRG: Multimorbidity Rehabilitation Group; MULTIPleS: Multimorbidity Illness Perception Scale; RCT: Randomized controlled trial; SD: Standard deviation; SF-36: Short form 36; SGRQ: St. George's Respiratory Questionnaire; SPSS: Statistical Package for the Social Sciences; UK: United Kingdom

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Availability of data and materials

The dataset analyzed during the current study is available for reproducibility reasons from the corresponding author on reasonable request and with approval of the overseeing Human Research Ethics Committee.

Authors' contributions

KB was involved in the study conception and design, recruitment, data collection, analysis and interpretation, and completed the first draft of the manuscript. AH was involved in the study design, data analysis and interpretation, and reviewed the manuscript for intellectually important content. AL was involved in the study design, data analysis and interpretation, and reviewed the manuscript for intellectually important content. TH was involved in the study design and reviewed the manuscript for intellectually important content. KR was involved in the study design, recruitment, and data collection and analysis. CB was involved in the study design and recruitment. SL was involved in the study design, recruitment, and data collection. FP was involved in the recruitment and data collection. JS was involved in the study design, recruitment, and data collection. LT was involved in the recruitment and data collection. MT was involved in the study design, recruitment, and data collection. ES was involved in the study conception and design, recruitment, data collection, analysis and interpretation, and reviewed the manuscript for intellectually important content. All authors approved the final manuscript.

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Ethics approval and consent to participate
Ethical approval was obtained from Melbourne Health Human Research Ethics Committee (Protocol number: 2014.029) and La Trobe University. Signed consent was gained from the participants and a copy of the participant consent information form was provided to them.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

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Supplementary Document for Chapter 4

Methods

Multimorbidity diagnosis

A detailed list of chronic conditions that meet the definition of multimorbidity are outlined in Table 1 (1).

Table 1. List of conditions for definition of multimorbidity

Condition	Diagnosis	Condition	Diagnosis
Hypertension	Ever recorded	Alcohol problems	Ever recorded
Depression	Recorded in past 12 months OR ≥ 4 anti-depressant prescriptions (excluding low-dose tricyclics) in last 12 months	Other psychoactive substance misuse	Ever recorded
Painful condition	≥ 4 prescription only medicine analgesic prescriptions in last 12 months OR ≥ 4 specified anti-epileptics in the absence of epilepsy	Treated constipation	≥ 4 laxative prescriptions in last year
Asthma	Ever recorded and any prescription in the past 12 months	Stroke and transient ischemic attack	Ever recorded
Coronary heart disease	Ever recorded	Chronic kidney disease	Ever recorded
Treated dyspepsia	≥ 4 prescriptions in the last 12 months BNF 0103% excluding antacids AND NOT ≥ 4 NSAIDS or ≥ 4 aspirin/clopidogrel	Diverticular disease of intestine	Ever recorded
Diabetes	Ever recorded	Atrial fibrillation	Ever recorded
Thyroid disorders	Ever recorded	Peripheral vascular disease	Ever recorded
Rheumatoid arthritis, other inflammatory polyarthropathies and systematic connective tissue disorders	Ever recorded	Heart failure	Ever recorded
Hearing loss	Ever recorded	Prostate disorders	Ever recorded
Chronic obstructive pulmonary disease	Ever recorded	Glaucoma	Ever recorded
Anxiety, neurotic, stress related and somatoform disorders	Recorded in past 12 months OR ≥ 4 anxiolytic/hypnotic prescriptions in last 12 months OR ≥ 4 10/25mg amitriptyline in last 12 months and don't meet Pain criteria	Epilepsy (currently treated)	Ever recorded AND antiepileptic prescription in last 12 months

Irritable bowel syndrome	Ever recorded OR ≥ 4 prescription only antispasmodic prescription in past 12 months	Dementia	Ever recorded
New diagnosis of cancer in past 5 years	Recorded in past 5 years	Schizophrenia (and related psychosis) or bipolar disorder	Ever recorded/in last 12 months OR lithium prescribed in last 168 days
Psoriasis or eczema	Ever recorded AND ≥ 4 prescriptions in last 12 months	Migraine	≥ 4 prescription only medicine anti-migraine prescriptions in last year
Inflammatory bowel disease	Ever recorded	Blindness/low vision	Ever recorded
Chronic sinusitis	Ever recorded	Anorexia or bulimia	Ever recorded
Learning disability	Ever recorded	Bronchiectasis	Ever recorded
Parkinson's disease	Ever recorded	Viral hepatitis	Ever recorded
Multiple sclerosis	Ever recorded	Chronic liver disease	Ever recorded

Full exclusion criteria:

- an inability to walk greater than fifty meters;
- severe cognitive impairment;
- psychiatric or intellectual disability which would limit the ability to participate in an exercise class with distant supervision or the ability to complete outcome measures (defined as mini-mental state exam (MMSE) <= 18 points) (175);
- pulmonary hypertension with recent history of dizziness or syncope on exertion (must have medical clearance if mean pulmonary artery pressure > 50 mm Hg);
- acute pulmonary embolus;
- interstitial lung disease;
- unstable cardiovascular disease (e.g. unstable angina, uncontrolled arrhythmia, New York Heart (NYH) Class 4 chronic heart failure (CHF), uncontrolled hypertension, diastolic pressure > 95 mm Hg);
- absolute contraindications to exercise (e.g. severe orthopedic/neurological deficit; severe uncontrolled pain: surgical or medical (including active transmissible infectious disease) restrictions to mobilization/rehabilitation (e.g. diabetic foot);
- severe ischemic vascular disease;

- advanced neuropathy/retinopathy which would compromise the ability to safely exercise;
- people already participating in a structured exercise rehabilitation program from a community or external provider;
- uncontrolled diabetes;
- uncontrolled epilepsy or seizures;
- extensive brain, skeletal or visceral metastases, life expectancy considered to be less than 12 months;
- known thrombocytopenia (<50×109/l) or severe neutropenia (neutropenia defined as absolute neutrophil count < 500/µL; profound neutropenia defined as ANL < 100 neutrophils/mm^3 (176);
- room air desaturation at rest < 85%;
- abnormal and untreated moderate anemia (80-109 g/L);
- pregnant women.

Exercise details

Aerobic component: Comprising of walking (corridor or treadmill) and stationary cycling; a total of 30 minutes, for 15 minutes each. The initial walking prescription was calculated at 80% of peak walking speed or distance (95, 177) and stationary cycling intensity was calculated at 60-80% of maximum work rate estimated from the 6-minute walk test (6MWT) (178). Exercise prescription was progressed using a rating of perceived exertion (RPE) Borg scale (6-20) and dyspnea modified Borg scale, aiming for a RPE score of 12-14 and a dyspnea score of 3-4, correlating to moderate intensity exercise (179).

Resistance component: Upper and lower limb exercises using free weights with four upper limb and three lower limb exercises. The initial load corresponded to 10-12 repetition maximum (RM). A 10-12 RM is the weight that can be lifted correctly and comfortably at least 10 times, but not more than 12 (180). Progression was undertaken using a RPE Borg scale (6-20), aiming for a RPE score of 12-14. Usual cessation/withdrawal and safety criteria for chronic disease rehabilitation applied to all participants, which included a change in a participant's medical condition that deemed them unsuitable for exercise (for further detail, see section below). Supplemental oxygen was delivered if SpO_2 was <88% during exercise on room air and was titrated to maintain a $SpO_2 \geq 90\%$.

Usual cessation/withdrawal criteria for chronic disease rehabilitation applied to all participants as follows:

- a change in a participant's medical condition that made them unsuitable for exercise;
- non-attendance (if patient fails to attend six consecutive sessions);
- a participant withdrawal from the program.
- For the safety criteria, exercise was ceased if a participant displayed the following observations during group exercise:
- heart rate (HR) > 160bpm;
- blood pressure (BP) > 180 mmHg or <90 mmHg (systolic) and > 110 mmHg or < 60 mmHg (diastolic);
- SpO_2 < 88% (exercise temporarily ceased and resumed when SpO2 reached 88% or supplemental oxygen supplied);
- diaphoretic, pale or dizzy;
- room air desaturation at rest < 85%;
- syncope, dizziness, onset of angina or chest pain;
- Exercise was not commenced if the participants displayed the following observations:
- fever > 38.0,
- new known thrombocytopenia (<50×109/l) or severe neutropenia (neutropenia defined as absolute neutrophil count < 500/µL; profound neutropenia defined as ANL < 100 neutrophils/mm^3 (176).

Outcome measures

Measures of multimorbidity included:

The Cumulative Illness Rating Scale for Geriatrics (CIRS(G)) (107), which consists of 14 body system categories, providing a severity scale for each domain (109). The CIRS(G) has been successfully applied in medically impaired elderly subjects with good interrater reliability and face validity (107). The Functional Comorbidity Index (FCI) (110) is an 18-item index based on diagnosis of comorbid diseases such as arthritis, COPD, depression and diabetes. The index is scored with one point per disease with the scores summed to provide a single total score; the higher the score, the greater number of co-morbidities in an individual. The Multimorbidity Illness Perception Scale (MULTIPleS) (111) examines five domains of emotional representations, treatment burden, prioritizing conditions, causal

links and activity limitations. This measures the impact of multimorbidity on illness perceptions, adjustments, clinical outcomes, quality of life and costs in this population, with demonstrated validity and reliability. The Duke Severity of Illness Checklist (DUSOI) (112) measures the severity of a person's illness. It comprises of four parameters for each diagnosis, including symptoms, complications, prognosis without treatment and treatment potential.

Results

Other reasons for declining to participate in the trial (n = 1 each):

- time issues
- not wanting any physiotherapy
- not wanting to do exercise
- being main carer for a spouse
- participating in another trial
- work commitments
- living in another state

Overall prevalence of comorbidities by group

Table 2. Prevalence of comorbidities		
Other Comorbidity (n, %)	**Multimorbidity (n = 9)**	**Disease Specific (n = 7)**
Anxiety	2 (22%)	0 (0%)
Asthma	2 (22%)	1 (14%)
Atrial Fibrillation	1 (11%)	1 (14%)
Chronic Kidney Disease	0 (0%)	1 (14%)
Chronic Liver Disease	1 (11%)	0 (0%)
Chronic Obstructive Pulmonary Disease	3 (33%)	2 (29%)
Coronary Heart Disease	8 (89%)	4 (57%)
Depression	1 (11%)	3 (43%)
Diabetes	4 (44%)	4 (57%)
Diverticular Disease of Intestines	0 (0%)	1 (14%)
Glaucoma	1 (11%)	0 (0%)
Heart Failure	1 (11%)	2 (29%)
Hypertension	8 (89%)	5 (71%)
Rheumatoid Arthritis	0 (0%)	2 (29%)
Schizophrenia/Bipolar Disorder	0 (0%)	1 (14%)
Stroke/Transient Ischaemic Attack	1 (11%)	0 (0%)
Thyroid Disorders	0 (0%)	1 (14%)
Treated Dyspepsia	0 (0%)	3 (43%)

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CHAPTER 5

Conclusions and recommendations

5.1 Overview of main findings

The three studies presented in this thesis (Chapters 2–4) extend our knowledge about exercise rehabilitation in people with multimorbidity. This thesis has presented evidence to support the feasibility of delivering exercise-based rehabilitation programs in people with multimorbidity, either within existing single-disease rehabilitation programs or as new, multimorbidity-specific programs. This evidence should assist in the development of new healthcare models in the multimorbidity population.

As outlined in Chapter 2, research to date has demonstrated that people with multimorbidity can improve their exercise capacity, HR-QOL and cardiometabolic outcomes via 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 either within current single-disease rehabilitation programs or in specialised multimorbidity exercise rehabilitation programs. However, few data are available to understand the impact of rehabilitation on mental health, ADL, health behaviours or healthcare costs.

The research described in Chapters 3 and 4 shows that it is feasible to conduct multimorbidity rehabilitation programs in people with chronic diseases. These feasibility studies support the ability to recruit, consent, enrol and randomise participants in larger RCTs of multimorbidity rehabilitation exercise and education sessions. Moreover, the work shows that outcomes relevant to larger trials, including exercise capacity, HR-QOL, ADLs and resource utilisation, can be collected consistently. The pilot studies provide direction on outcome measures, education and models of care which will inform the design of suitably powered studies.

Other key findings from the studies in Chapters 3 and 4 are:

- physiotherapist and nurse were able to deliver the exercise component of the multimorbidity rehabilitation program, and participants were able to complete it;
- completion rates of the multimorbidity rehabilitation program were similar to those reported for disease-specific rehabilitation programs worldwide;
- the assessors and participants found the assessments to be time-consuming, so a reduction of the number of assessment questionnaires is required for larger RCTs;

- of several multimorbidity measures, the FCI and MULTIPleS were the most suitable for use in a larger RCT; and
- refinement of the recruitment process, by targeting more outpatient medical clinics (e.g. endocrinology and general medical clinics), would assist in achieving the numbers required for adequately powered larger RCTs.

5.2 Clinical significance of the research

The findings presented in this thesis support inclusion of people with multimorbidity within current single-disease rehabilitation programs, such as cardiac, HF and pulmonary rehabilitation programs. The studies in thesis provide evidence that improvements in exercise capacity, HR-QOL and cardiometabolic outcomes are achievable and that it is safe for people with multimorbidity to participate in such programs. They also suggest that the development of specialised multimorbidity rehabilitation models of care may be useful to improve outcomes in this group and are worthy of consideration if a healthcare service is establishing new programs. This could eliminate the current confusion in trying to implement multiple single-disease guidelines and exercise prescriptions for people with multiple chronic diseases. It may also assist in relieving the burden of care for people living with multiple chronic diseases by having one model of care and consistent advice about how to manage and improve their health, rather than the current model of disease-specific information being delivered in a siloed fashion. Ensuring the removal of the siloes of healthcare in the domain of rehabilitation is an important factor that should considered in the decision about the providing the ideal rehabilitation program. Consideration of the model of rehabilitation, whether it be inclusion into disease-specific rehabilitation, establishing multimorbidity rehabilitation or other novel models such as limitation-based rehabilitation, for chronic conditions may assist with the best use of finite resources.

People with multimorbidity already participate in current disease-specific programs such as cardiac and pulmonary rehabilitation (47-50); therefore, they are able to access rehabilitation through established referral pathways. In the development of specialised multimorbidity rehabilitation programs, it is important to ensure appropriate referral pathways are established. This would involve engagement of relevant stakeholders, such as doctors (both GPs and specialist physicians), allied health professionals, nurses and patients. Exercise capacity and HR-QOL emerged as important outcome measures for an exercise-based rehabilitation program. This is evident via their widespread use within clinical and research settings for disease-specific rehabilitation programs, and from the expert opinion regarding desirable outcome measures for rehabilitation programs in the

development of symptom-based rehabilitation (77) and multimorbidity research (78). Consideration of other outcome measures that are also commonly used in clinical and research settings for rehabilitation, such as symptom evaluation, mental health, ADL and function, must depend on individual program aims and resources. Whilst there is no gold standard tool for multimorbidity measurement, it remains important to implement one to allow for the quantification and evaluation of multimorbidity in healthcare programs. The findings presented in this thesis suggest that the FCI and MULTIPleS are suitable options for use in an exercise-based rehabilitation program (106, 115). The impact of education and psychological support, and the most effective models for their delivery, remain unclear from the current evidence. However, the complex nature of multimorbidity makes it likely that exercise alone will be insufficient to meet the needs of many patients, so multicomponent programs will be necessary. The inclusion of other disease management strategies, such as health coaching, may work well within rehabilitation programs to achieve the aims of risk-factor reduction, self-management and improved health outcomes for the multimorbidity population. Potential research on multimorbidity rehabilitation programs is discussed in the following section.

5.3 Future research directions

The systematic review in Chapter 2 showed that few data were available to understand the impact of exercise-based rehabilitation for people with multimorbidity on mental health, ADL, health behaviours and healthcare costs. As these outcomes are likely to be of critical importance to people with multimorbidity, they should be included in future trials. Ongoing evaluation of the outcomes of exercise capacity, HR-QOL and cardiometabolic outcomes would build upon the current findings and provide additional evidence for these outcomes. Further investigation of the type, dose and frequency of exercise within exercise rehabilitation programs will provide more detailed insight into the optimal components of programs and their effects on key outcomes. In addition, further investigation into the inclusion or exclusion of education or psychological support in rehabilitation programs could establish the significance of the influence of these components of care. Some of the questions that could be addressed in RCTs are:

- Do people with multimorbidity achieve equivalent outcomes for exercise capacity, HR-QOL and cardiometabolic outcomes participating in multimorbidity rehabilitation compared to disease-specific rehabilitation?

- What is the impact of multimorbidity rehabilitation on mental health, ADL, health behaviours and healthcare costs?
- What is the optimal type, dose and frequency of exercise in people with multimorbidity to improve health?

Findings from the studies presented in Chapters 3 and 4 raised possible areas of future research to be considered as part of larger RCTs on multimorbidity rehabilitation versus disease-specific rehabilitation or usual medical care. Embedded qualitative research would provide a better understanding of the experience of participants and gather more meaningful information about the method of delivery of the rehabilitation programs, peer support and education and healthcare professionals' acceptability of delivering and referring to these services. This could be incorporated into trials via co-design methods, in the form of focus groups with the participants and educators, or individual interviews. Some of the questions that could be addressed are:

- Is the typical structure of rehabilitation, such as twice-weekly exercise and weekly education group sessions in a hospital outpatient setting, the most suitable from the participant's perspective?
- What outcome measures are most important to participants, clinicians and healthcare services?
- What are participants' perceptions of peer support within the rehabilitation program and does this influence satisfaction, attendance and completion rates?
- What is the optimal method of delivery of the education sessions?
- What should be included in the education (topics and content)?
- Does a person's perceived treatment burden impact their decision to participate in a rehabilitation program?
- What are healthcare professionals' perceptions of delivering multimorbidity rehabilitation?
- What are healthcare professionals' perceptions of referring to multimorbidity rehabilitation?

Another question prompted by the current research was how the impact of the education component of a rehabilitation program should be evaluated, particularly given the difference in topics addressed in multimorbidity and disease-specific rehabilitation. Answering this question would involve comparing the impact of education on generic risk factor modification and self-management strategies delivered in the multimorbidity rehabilitation program to that of disease-specific management (e.g. specific symptoms and

medication management) delivered in a corresponding program. Outcome measures such as the Patient Activation Measure (181), which assesses patient knowledge, skill and confidence for self-management (182), may be used to in health care settings to evaluate education programs. Therefore, future research should attempt to include measures that identify any difference in outcomes attributable to these differing educational approaches.

5.4 Strengths & limitations of the thesis

While the systematic review is considered the highest level of evidence, it should be noted that the studies presented in Chapters 3 and 4 were pilot feasibility studies. Feasibility studies have an important role to play in ensuring larger trials are optimally designed and implemented. This assists in the best use of limited resources in healthcare.

The studies presented here had several limitations. First was the lack of a co-design approach to the intervention. For future trials, it will be important to ensure that patients are involved at all steps of the design process, particularly regarding the content of education and support components. Second, there was no investigation of the optimal exercise prescription for the multimorbidity population. The strategies used in the studies presented here were adopted from those known to be effective in single-disease programs but may not be optimal for people with multimorbidity. This should be investigated in future studies. Third, the program involved centre-based settings only; home-based and telehealth programs, including the use of new technology such as telehealth, were not considered. Whilst centre-based rehabilitation remains the most common method of delivering chronic disease rehabilitation, other models are emerging, such as home rehabilitation (146, 183) and telerehabilitation (142, 184). Technology-enabled programs may also facilitate remote monitoring, delivery of education, and peer support. Such strategies have the potential to improve access by reducing the burden of travel and transport to centre-based programs. Fourth, the studies were performed at a single centre in the western suburbs of Melbourne, Australia, so their applicability to other patient cohorts is uncertain. However, the use of specific tools to describe the nature, severity and burden of multimorbidity in trial participants will enhance the ability to perform comparisons across studies, as described earlier in this thesis.

The multimorbidity rehabilitation program implemented in this body of work was based on well-established programs conducted in single-disease groups. The structure of single-disease exercise rehabilitation programs is familiar to clinicians in daily practice, and this may assist in implementation for a new cohort of patients with multimorbidity. The step

from research findings to implementation into clinical practice takes time, but familiarity with this model may help to combat this problem. However, as mentioned previously, the single-disease rehabilitation program structure may also be a limitation; consultation with patients, as outlined in the co-design section above, is required to determine if this is the most suitable model of care for this population. The multimorbidity population is a complex cohort, and therefore a single approach to delivering a rehabilitation model of care may not suit all. Inclusion of varied options in the format and delivery of rehabilitation programs may improve outcomes in this population.

5.5 Conclusion

The body of work presented in this thesis indicates that exercise rehabilitation can be delivered to people with multimorbidity within current single-disease programs, or within multimorbidity-specific exercise programs. The pilot studies indicate that it is feasible to conduct RCTs on exercise rehabilitation programs in people with multimorbidity. They simultaneously highlight the need for further research, with suitable statistical power, to make definitive conclusions about the effects on mental health, ADL, health behaviours and resource utilisation. The multimorbidity exercise rehabilitation model of care has the potential to mitigate common symptoms and risk factors, improve clinical outcomes and reduce health care costs for the multimorbidity population.

Appendices

Appendix A: Copyright permissions

Permissions to use publications in Chapters 2-4 of this thesis were permitted by the corresponding journals.

Appendix B: Ethics Approval Certificates

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MELBOURNE HEALTH

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MELBOURNE HEALTH HUMAN RESEARCH ETHICS COMMITTEE

ETHICAL APPROVAL OF A RESEARCH PROJECT

Dr Elizabeth Skinner
Western Health
Department of Physiotherapy
Gordon Street
FOOTSCRAY VIC 3011

25th July 2014 (Updated 22nd August 2014)

Dear Dr Skinner,

MH Project Number: 2014.029

Project Title: What is the effect of a generalised compared to a disease-specific outpatient exercise rehabilitation program on functional exercise tolerance in people with multimorbidity: two pilot parallel randomized controlled trials

HREC Approval Date: 25th July 2014

I am pleased to advise that the above project has received ethical approval.

Participating Sites:

- Western Health – Footscray Hospital
- Western Health – Sunshine Hospital
- Western Health – Williamstown Hospital

Approved Documents:

- Protocol Version 2.0 dated 17th July 2014
- Western Health Participant Information and Consent Form Version 3 dated 25th July 2014
- AQoL-4D Basic Data Collection
- EQ-5D-5L Health Questionnaire English Version for the UK Version 2.0 dated 2009
- Katz Index of Independence in Activities of Daily Living
- Minnesota Living with Heart Failure Questionnaire dated 1986
- St George's Respiratory Questionnaire Original English Version (SGRQ) dated 14th March 2013
- SF-36 Your Health and Well-Being Version 2 dated 1996, 2000
- Six-Minute Walk Test Protocol
- Six-Minute Walk Test Recording Sheet
- Multimorbidity Rehabilitation – Initial Assessment form
- Multimorbidity Rehabilitation – Exercise Record
- Informed Consent Form Script

The Melbourne Health HREC operates and is constituted in accordance with the National Statement on Ethical Conduct in Human Research 2007.

- Daily Diary
- Duke Severity of Illness Checklist (DUSOI) dated 1996-2014
- Cumulative Illness Rating Scale for Geriatrics (CIRS-G) Scoring Sheet
- Multimorbidity Illness Perceptions Scale (MULTIPleS)
- The Functional Comorbidity Index

Site Specific Assessment:

Please note: Please forward this HREC approval certificate to the Director of Research at Western Health together with your Research Governance-Site Specific Assessment application. You cannot commence this study until you have completed all the requirements of the Site Specific Assessment and have received written approval to conduct your research project at Western Health.

Conditions of Ethics Approval:

In order to comply with the National Statement on Ethical Conduct in Human Research 2007, Guidelines for Good Clinical Research Practice and Melbourne Health Research Policies and Guidelines you are required to:

- Submit a copy of this letter to the Radiation Safety Officer (RSO) at Western Health, for addition of the project to the Licence for Research Involving Human Volunteers held by the Department of Human Services Radiation Safety Section Radiation Safety Licence (if your project involves exposure to ionising radiation). Note: You cannot commence the project until you have received notification from the RSO that the project has been added to the Licence;
- Notify the HREC of the actual start date of the project;
- *Submit to the HREC for approval any proposed amendments to the project including any proposed changes to the Protocol, Participant Information and Consent Form/s and the Investigator Brochure;*
- *Notify the HREC of any adverse events in accordance with the Melbourne Health Guidelines for Monitoring and Reporting of Safety in Clinical Trials Involving Therapeutic Products and Other Clinical Research, July 2009;*
- *Notify the HREC of any unforseen events;*
- *Notify the HREC of your inability to continue as Principal Investigator or any other change in research personnel involved in the project;*
- *Notify the HREC if a decision is taken to end the study prior to the expected date of completion or failure to commence the study within 12 months of the HREC approval date;*
- *Notify the HREC of any other matters which may impact the conduct of the project.*

Reporting

You are required to submit to the HREC:

- *An Annual Progress Report every 12 months (or more frequently as requested by the reviewing HREC) for the duration of the project. This report is due on the anniversary of HREC approval. Continuation of ethics approval is contingent on submission of an annual report in a timely manner; and*
- *A comprehensive Final Report upon completion of the project.*

The HREC may conduct an audit of the project at any time.

Please refer to the Office for Research website to access forms such as the Amendment Form, Annual Report/Final Report Form, Guidelines for Monitoring and Reporting of Safety in Clinical Trials Guidelines and Adverse Event Report Forms, and other information and news

concerning research at Melbourne Health:
http://www.mh.org.au/www/342/1001127/displayarticle/1001352.html

A list of those HREC members present at the review of this project can be obtained from the above website.

Yours sincerely

Ms. Jessica Turner
Manager - Human Research Ethics Committee

LA TROBE UNIVERSITY

University Human Ethics Committee

RESEARCH OFFICE

MEMORANDUM

To: **Dr Anne Holland, La Trobe University Clinical School, Alfred Health**

From: **Senior Human Ethics Officer, Ethics and Integrity**

Subject: **UHEC acceptance of Melbourne Health HREC approved project - 2014.029**

Title: **What is the effect of a generalised compared to a disease-specific outpatient exercise rehabilitation program on functional exercise tolerance in people with multimorbidity: two pilot parallel randomized controlled trials**

Date: **26 February 2016**

Thank you for submitting the above protocol to the University Human Ethics Committee (UHEC). Your material was forwarded to the UHEC Chair for consideration. Following evidence of a full review and subsequent final approval by the **Melbourne Health HREC**, the UHEC Chair agrees that the protocol complies with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and is in accordance with La Trobe University's *Human Research Ethics Guidelines*.

Endorsement is given for you to take part in this study in line with the conditions of final approval outlined by **Melbourne Health HREC.**

Limit of Approval. La Trobe UHEC endorsement is limited strictly to the research protocol as approved by **Melbourne Health HREC**.

Variation to Project. As a consequence of the previous condition, any subsequent modifications approved by **Melbourne Health HREC** for the project should be notified formally to the UHEC.

Annual Progress Reports. Copies of all progress reports submitted to **Melbourne Health HREC** must be forwarded to the UHEC. Failure to submit a progress report will mean that endorsement for your involvement this project will be rescinded. An audit related to your involvement in the study may be conducted by the UHEC at any time.

Final Report. A copy of the final report is to be forwarded to the UHEC within one month of it being submitted to **Melbourne Health HREC.**

If you have any queries on the information above please e-mail: **humanethics@latrobe.edu.au** or contact me by phone.

On behalf of the La Trobe University Human Ethics Committee, best wishes with your research!

Kind regards,

Sara Paradowski
Senior Human Ethics Officer
Executive Officer – University Human Ethics Committee
Ethics and Integrity / Research Office
La Trobe University Bundoora, Victoria 3086
P: (03) 9479 – 1443 / F: (03) 9479 - 1464
http://www.latrobe.edu.au/researchers/ethics/human-ethics

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