**Cardiac rehabilitation and physical activity levels in heart failure**

Submitted by Grace Olivia Dibben to the University of Exeter
as a thesis for the degree of
Doctor of Philosophy in Medical Studies
In April 2020.

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## Abstract

### Background

Maintenance of adequate physical activity (PA) is a key recommendation for people with and without chronic disease, with well-established health benefits. However, there is uncertainty in the level of objectively assessed PA in people with heart failure (HF) and how exercise-based cardiac rehabilitation (CR) interventions can impact upon PA levels (chapter 1).

### Methods

Four linked research studies were undertaken. A systematic review and meta-analysis to determine whether participation in exercise-based CR increases PA levels of patients with coronary heart disease and HF (chapter 2). A laboratory-based calibration study to estimate HF specific accelerometer intensity thresholds for moderate-to-vigorous PA (MVPA) and inactivity (chapter 3). A cross-sectional study to quantify the PA levels of 247 HF patients participating in a randomised controlled trial of a home-based CR intervention (REACH-HF) in HF patients (chapter 4). A pooled analysis study to assess the effects on PA of the REACH-HF intervention in HF patients and explore the patient characteristics associated with a change in PA level (chapter 5).

### Results

The systematic review and meta-analysis identified 40 randomised controlled trials (6480 patients). Moderate evidence was found to support that CR positively impacts PA levels of patients with coronary heart disease and HF compared to control. The calibration study determined HF specific accelerometer values relating to inactivity (right wrist: 18.6mg (95% CI 8.8 to 28.4mg), left wrist: 16.7mg (95% CI 7.8 to 25.6mg), waist: 7.6mg (95% CI -3.1 to 18.4mg)) and moderate intensity PA (right wrist: 45.5mg (95% CI 31.9 to 59.1mg), left wrist: 43.6 (95% CI 38.5 to 56.3mg), waist: 40.6mg (95% CI 24.3 to 57.0)), lower than the non-specific thresholds used in most HF patient studies based on healthy adults. PA levels of 247 HF patients were examined and 45% were found to meet current PA recommendations of 150 minutes per week of MVPA. However, MVPA ranged widely from 0 to 375.2 minutes per week. HF patient age, body composition, employment status, New York Heart Association

class, smoking status, NT-proBNP level, and exercise tolerance were associated (P<0.05) with baseline MVPA levels. At final follow-up, there was evidence of an increase in light PA (26.9 mins/day, 95% CI: -0.05 to 53.8, p=0.05) and a decrease in inactivity (-38.31 mins/day, 95% CI: -72.1 to -4.5, p=0.03) during weekdays in HF patients undertaking home-based CR compared to control. Exercise tolerance, HADS anxiety score, presence of diabetes, and living with a parent or child >18 years were associated with a change in PA.

**Conclusions**

Objective measurement of PA in HF remains under researched. This thesis discusses methodological, and clinical implications for the future measurement of PA, and exercise-based CR interventions in people with HF (chapter 6).

**Acknowledgements**

I would like to especially thank my supervisors Professor Rod Taylor, Associate Professor Melvyn Hillsdon, and Dr Hasnain Dalal for giving me the opportunity to conduct this PhD research. I will be forever grateful for your encouragement, support, wisdom and inspiration throughout this process, in shaping this thesis and in my confidence and growth as a researcher.

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Thank you to Professor Lora Fleming and the European Centre for Environment and Human Health staff. I feel lucky to have been part of this group and experience the value of collaboration and learning from each other. Thank you to my fellow PhD students in the centre, for their support and understanding and sharing the trials and tribulations of undertaking a PhD.

To my dearest friends Aileen, Zowie and Charlotte, thank you for always being there for me, and for your encouragement and confidence in me. Last but not least, thank you to my parents, Dianne and George, and my brother James for their love, care and belief in me.

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## Authors Declaration

I declare that all the research reported in this thesis is my own work, and each of the chapters and the empirical research reported in chapters 2-5 was planned, conducted and written by me.

The thesis contains four empirical research studies that have been written as manuscripts for publication in peer-reviewed journals. At the time of submission of this thesis, Chapter 2 has been published, Chapters 3 and 4 have been submitted for publication, and Chapter 5 has been prepared for submission. Each of these manuscripts are co-authored, but all are primarily the result of my own work as the result of this PhD thesis. All the manuscripts are written by me.

Throughout the PhD, supervisory guidance was provided by the co-supervisors, Prof Rod Taylor (RS), Dr Melvyn Hillsdon (MH), and Dr Hasnain Dalal (HD), with some additional advisory guidance from Prof Patrick Doherty (PD) and Dr Lars Hermann Tang (LT).

Detailed below is my substantial contribution to each of the co-authored manuscripts.

**Chapter 2**: Cardiac rehabilitation and physical activity: systematic review and meta-analysis

This manuscript was submitted to a call for systematic reviews in cardiac rehabilitation in the journal '*Heart*'. The paper was accepted for full submission and published in 2018. I developed the protocol for the systematic review and meta-analysis, conducted the searches, screening, data extraction, quality appraisal, data analysis and manuscript writing. RT, MH and HD commented on the protocol, conducted double full paper screening, quality appraisal and data extraction of the full text articles, and provided advice at all stages of the review. RT provided statistical advice. All authors commented on the manuscript and signed off on the final version.

**Chapter 3**: Physical activity assessment by accelerometry in people with heart failure.

This manuscript is currently under review (April 2020) for publication in the journal '*BMC Sports Science, Medicine and Rehabilitation*'. I developed the protocol, (including presenting the work to a local HF public and patient involvement group, to discuss common physical activities for inclusion in the protocol), submitted the study to the Health Research Authority for ethical approval, recruited patients, took informed consent, collected the study data, ran the data analysis, and manuscript writing. Guidance from RT, MH, and HD was provided at all stages of the study. PD and LT commented on the study protocol prior to submission for ethical approval. Dr Manish Gandhi provided recruitment support and access to patients from the heart failure clinic at the Royal Devon and Exeter NHS Foundation Trust cardiology department. Statistical support for the accelerometer data was provided by Dr Brad Metcalf (BM), and for the leave-one-out cross validation by Dr Mark Kelson (MK). All authors commented on the manuscript drafts and signed off on the final version.

**Chapter 4**: Factors associated with objectively assessed physical activity levels of heart failure patients

This manuscript is currently under review (April 2020) for publication in the journal '*Journal of Clinical and Experimental Cardiology'*. For this study, I developed the statistical analysis plan, merged the two trial data sets, conducted the statistical analyses, interpreted the results and drafted the manuscript. RT, MH, and HD were involved in the study conception. RT and BM provided advice with the statistical analysis plan and conducting the analysis. All other authors advised on the interpretation of the results, commented on the manuscript drafts, and signed off on the final version for submission.

**Chapter 5**: Effect of home-based cardiac rehabilitation on objectively assessed physical activity in heart failure patients.

This study is currently being prepared for submission for publication. For this study I developed the statistical analysis plan, ran the statistical analyses, interpreted the results and drafted the manuscript. RT, MH and HD were involved in the study conception and interpretation of results. RT provided

guidance with the statistical analysis. All authors provided comments on the manuscript and signed off on the final version.

Chapters 1 (Introduction) and 6 (Discussion) were written by myself with review by my supervisors (RT/MH/HD).

**Publications relating to this thesis**

Four papers for publication were produced from this PhD project. Chapters 2 to 5 present a version of each manuscript.

Chapter 2 has been published as:

Dibben GO, Dalal HM, Taylor RS, Doherty P, Tang LH, Hillsdon M. Cardiac rehabilitation and physical activity: systematic review and meta-analysis. Heart 2018;104:1394-1402.

Chapter 3 has been submitted as:

Dibben GO, Gandhi MM, Taylor RS, Dalal HM, Metcalf B, Doherty P, et al. (submitted) Physical activity assessment by accelerometry in people with heart failure. BMC Sports Science, Medicine and Rehabilitation.

Chapter 4 has been submitted as:

Dibben GO, Hillsdon M, Dalal HM, Metcalf B, Doherty P, Tang LH, et al. (submitted) Factors associated with objectively assessed physical activity levels of heart failure patients. Journal of Clinical and Experimental Cardiology.

Chapter 5 has been prepared for submission as:

Dibben GO, Dalal HM, Hillsdon M, Tang LH, Doherty P, Taylor RS. (in preparation) Effect of home-based cardiac rehabilitation on objectively assessed physical activity in heart failure patients.

A letter was published in relation to work completed in this thesis. This is presented in appendix 3.8 and is published as:

Dibben GO, Taylor RS, Dalal HM, Hillsdon M. One size does not fit all – application of accelerometer thresholds in chronic disease. *International Journal of Epidemiology* 2019;48:1380.

**Abbreviations**

| | |
|---|---|
| ACE | Angiotensin converting enzyme |
| AF | Atrial fibrillation |
| ARB | Angiotensin II receptor blocker |
| AUC | Area under the curve |
| BACPR | British Association for Cardiovascular Prevention and Rehabilitation |
| BMI | Body mass index |
| CHD | Coronary heart disease |
| CI | Confidence interval |
| COPD | Chronic obstructive pulmonary disease |
| CPM | Counts per minute |
| CR | Cardiac rehabilitation |
| CRT | Cardiac resynchronisation therapy |
| EF | Ejection fraction |
| ENMO | Euclidean norm minus one |
| HADS | Hospital anxiety and depression scale |
| HF | Heart failure |
| HFmrEF | Heart failure with mid-range ejection fraction |
| HFpEF | Heart failure with preserved ejection fraction |
| HFrEF | Heart failure with reduced ejection fraction |
| HR | Hazard ratio |
| ICD | Internal cardioverter-defibrillator |
| IPAQ | International physical activity questionnaire |
| IQR | Interquartile range |
| ISWT | Incremental shuttle walk test |
| LVEF | Left ventricular ejection fraction |
| MAD | Mean amplitude deviation |
| MCID | Minimal clinically important difference |
| MD | Mean difference |
| METS | Metabolic equivalents |
| MLHFQ | Minnesota living with heart failure questionnaire |
| MRA | Mineralcorticoid receptor antagonists |
| MVPA | Moderate-to-vigorous physical activity |
| NICE | National Institute for Health and Care Excellence |

| | |
|---|---|
| NIHR | National Institute for Health Research |
| NT-proBNP | N-terminal-pro B-Type natriuretic peptide |
| NYHA | New York Heart Association |
| PA | Physical activity |
| RCT | Randomised controlled trial |
| REACH-HF | Rehabilitation enablement in chronic heart failure |
| RMR | Resting metabolic rate |
| ROC | Receiver operator characteristic |
| RPE | Rating of perceived exertion |
| RR | Relative risk |
| SCHFI | Self-care of Heart Failure Index |
| SD | Standard deviation |
| SIGN | Scottish Intercollegiate Guidelines Network |
| SVM | Sum of vector magnitude |
| WHO | World Health Organisation |
| WMD | Weighted mean difference |

# Chapter 1: Introduction

This chapter provides an overview of the concept of physical activity (PA) (section 1.1), summarises the relevant evidence for its key benefits to health (section 1.2), and discusses the current challenges in its assessment (section 1.3), particularly with accelerometry (section 1.4). This is then followed by a description of heart failure (HF) (section 1.5.1), PA levels of HF patients (section 1.5.2), evidence for PA benefits (section 1.5.3), and the impact of exercise based cardiac rehabilitation (CR) (section 1.5.4). The overarching aim of this thesis, and specific aims of each of the empirical studies is also described (section 1.7).

## 1.1 Physical activity – definitions and guidelines

PA is defined as any bodily movement produced by skeletal muscles resulting in energy expenditure beyond resting expenditure. [1] PA includes, in addition to sports and structured exercise, occupational, household, personal care, leisure time and transportation activity. [1] PA is a different concept to physical fitness, although the two are often related. [2] Physical fitness comprises multiple components (i.e. health-related and skill-related) that enable an individual to perform PA without undue fatigue. [1]

PA patterns are often quantified according to the following four dimensions:

- Frequency: how often the PA occurs, e.g. three times per week,
- Duration: the length of time one bout of PA is sustained for,
- Type: the mode of PA performed, i.e. walking, swimming, etc,
- Intensity: the effort required to undertake PA.

The majority of PA guidelines and recommendations are based on systematic reviews and consensus statements of studies using subjective measures of PA and have consistently identified 150 minutes per week of moderate-to-vigorous intensity PA (MVPA) as providing considerable health benefits. [3-5] Internationally, the current PA recommendation for the health of adults and older adults is at least 150 minutes of MVPA per week, or 30 minutes MVPA on at least 5 days per week. In addition, individuals should undertake activities

aimed at improving or maintaining muscular strength, balance and flexibility on at least two days per week. [6-9] This is also the standard PA recommendation for cardiac patients by the British Association for Cardiovascular Prevention and Rehabilitation (BACPR) and the Scottish Intercollegiate Guidelines Network (SIGN). [10-12] World Health Organisation (WHO) guidelines indicate that MVPA minutes should be obtained in bouts of at least 10 minutes for potential health benefits. [7] A bout refers to the duration a session of PA is sustained for. Emerging research is suggesting that PA undertaken in bouts of <10 minutes may also have positive health benefits. [13-15] This has led to updated United Kingdom and United States guidelines, where MVPA can be accumulated in bouts of any length. [6, 8]

When examining the total profile of human behaviour in terms of movement or energy expenditure, sedentary behaviour should also be considered. Sedentary behaviour refers to a combination of sitting or reclining and low energy expenditure (<1.5 METS) during waking hours. [16]. A large body of research has recognised the detrimental effects to health of prolonged sedentary time, and report that sedentary time is a risk factor for poor health outcomes, independent of MVPA levels. [17-19] However, some epidemiological studies have demonstrated that associations between sitting time and all-cause mortality and cardiovascular disease are dependent on MVPA (Figure 1.1). [20-22] Furthermore, the evidence base for sedentary behaviour is not as strong as for PA, with unclear biological mechanisms and reliance on surrogate outcomes, such as time spent watching television, and so specific quantitative guidelines for sedentary time have not been established yet. Therefore in a recent review, authors recommend clinicians prioritise a message focussed on increasing PA at any intensity, until the evidence base for sitting or sedentary time is more robust. [20]

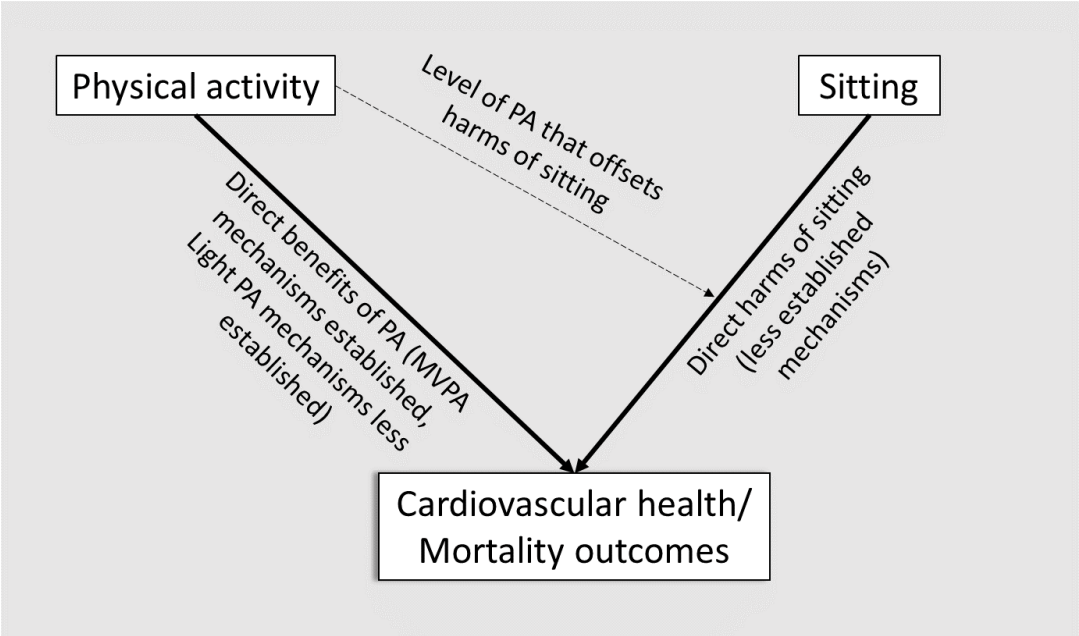


Figure 1.1: Conceptualisation of the associations between health outcomes and sitting, with physical activity as an effect modifier (adapted from Stamatakis et al. [20]).

### 1.2 Evidence for PA and health benefits

In the 1950s the first epidemiological studies suggesting a link between PA at work being beneficial to health began to emerge, when Morris et al. found that London bus drivers developed a higher rate of coronary heart disease (CHD) than the bus conductors, and likewise in postal clerks compared to postmen. [23] Similarly, Paffenberger et al. showed those with more sedentary jobs compared to physically active on the San Francisco docks had higher rates of CHD, [24] and the Harvard alumni study showed that men who expended more energy per week in sports, walking and stair climbing had a lower risk of developing CHD than less physically active classmates. [25]

Since then, it has been estimated that physical inactivity is responsible for 6-10% of the major non-communicable diseases worldwide, making it comparable to smoking and obesity as a risk factor for disease. [26] It is widely accepted that engagement in MVPA is an important primary prevention strategy to promote health, and secondary prevention strategy to manage and minimise the severity of disease. [27] Many studies have shown the long-term health benefits

of self-reported PA in the general population, across the life course, with risk reductions for all-cause mortality, and reduced rates of non-communicable diseases such as CHD, obesity, type 2 diabetes mellitus, and dementia. [28-30] Other benefits include reduced risk factors for chronic diseases; reduction in inflammatory biomarkers, systolic and diastolic blood pressure, reduced cholesterol levels, and improved cardiovascular fitness. [31-33] PA is also associated with reduced risk of functional limitations and disability in older age, and improved health related quality of life (HRQoL). [3, 34]

In more recent studies, relationships between health outcomes and objectively measured PA levels have been assessed. Ekelund et al. performed a harmonised meta-analysis of 8 studies, involving 36,383 adults (mean age 62.6 years; 72.8% women) and showed a non-linear dose-response relationship between accelerometer measured PA and improvement in all-cause mortality in adults. [35] Saint-Maurice et al. showed risk reductions for all-cause mortality with increased amounts of accumulated sporadic or bouted MVPA range from 60-80%. [15] Loprinzi showed that a 60 minute increase in light PA (independent of MVPA) resulted in a 16% reduction in hazard of all-cause mortality. [36] Rees-Punia et al. performed a statistical computation, and showed a hypothetical replacement of 30 minutes/day sitting time with light intensity PA was associated with a 14% mortality risk reduction, and replacement with MVPA was associated with 45% mortality risk reduction. [37] Associations between accelerometer measured PA and cardiovascular disease risk factors, physical function, and frailty in older populations have also been reported. [38, 39]

### 1.3 PA measurement methods

There are a wide range of tools available to researchers to measure PA that vary in feasibility and accuracy. Ideally, PA assessment methods should measure all four of the dimensions of PA. Some methods are more appropriate for measuring PA in terms of energy expenditure, for example doubly labelled water or indirect calorimetry, however these methods are expensive, and aren't feasible for use in larger scale studies. [40] Tools that are appropriate for measuring PA in terms of behaviour include direct observation, activity diaries,

questionnaires, accelerometers, pedometers, and even commercial devices such as Fitbits and smartphones, for example. These methods can be further categorised as subjective or objective approaches.

Subjective methods of assessing PA include questionnaires (self- or interview administered), and PA diaries or logs (i.e. records kept over a specific timeframe), which vary in length, depth of information captured and recall periods. [40] These methods rely on self-report, and are often cost-effective and convenient ways to collect PA data from large samples in a relatively short period of time.

Objective methods of assessing PA levels often continuously measure energy expenditure or bodily movement and are generally considered more accurate as they are not subject to response and recall bias as with subjective methods. Advances in technology has meant body-worn devices (such as acceleromters, pedometers or Fitbits) have become smaller, and data capacity and battery power have increased alongside capability to measure multiple integrated responses to PA, therefore these devices are increasing in popularity. [41] Over recent years, accelerometers have become the most popular PA monitors for research purposes and have been used successfully in many large-scale, population studies, with proven acceptability to participants. [36, 42, 43]

Both approaches have their relative advantages and disadvantages and vary in their ability to assess the multiple dimensions of PA, i.e. frequency, duration, type and intensity, which are summarised below.

### *1.3.1 Frequency*

Subjective PA measures in the form of questionnaires or diaries are able to capture PA frequency, often by asking individuals to recall the frequency of performing activities from a given list, or using rating scales (e.g. never, sometimes, mostly, always). Recall durations range from a day to up to a year, and many require individuals to determine the frequency of PA over a ‘usual’ or ‘typical’ period of time. Since frequency of many activities fluctuates over weeks or monthly periods, sometimes due to seasonal changes, individuals are likely to report their highest recent or desired frequency of participation. [44] Reliance on individuals accurately recalling PA over long time frames or a ‘typical’ period

may lead to recall and response bias, and have been found to be unreliable methods of measuring PA in older adults and cardiac patients. [45, 46] For example, cardiac patients answering the Health Survey for England PA interview often overestimated the number of days they were active compared to accelerometer measured PA, resulting in the survey misclassifying 63% of participants. [47]

Objective assessment methods will provide varying degrees of information about PA frequency. Pedometers and doubly labelled water are unable to determine PA frequency. But, accelerometers, heart rate monitors and direct observation methods are able to provide much more detailed records of daily and weekly PA. [46] Accelerometers continuously record acceleration, and are able to collect data on the number of bouts of continuous or intermittent activity for up to 60 days. [48] Many accelerometers are now waterproof, and have enough battery power to last for measurement periods of at least a week, placing minimal burden on the participant to remember to remove the device to bathe or charge the device. These methods are also advantageous as they do not rely on self-report, so recall and response biases are diminished. [46, 49]

### *1.3.2 Duration*

Similar to PA frequency, subjectively assessed PA duration data are often collected from questions regarding the length of time spent in hours or minutes performing specific PAs over the different recall periods, or on each PA occasion. As well as being limited by the above-mentioned misreporting and recall biases, intermittent, sporadic or unstructured PAs are difficult to measure and recall using subjective assessment methods. Some questionnaires do not take into account PAs that have a duration of less than 10 or even 30 minutes. [44, 47] This may be particularly important information to gather in older individuals or those with chronic diseases, as the majority of their PA will be made up of short bouts of activity that occur as part of routine daily activity. [50]

Indirect calorimetry and heart rate monitors are able to capture PA duration by assessing the time spent in activities which gives outputs over predetermined intensity thresholds such as heart rate zones or metabolic equivalents (METS) values. [46] Accelerometers collect data continuously over pre-defined time periods (epochs) ranging from 1-60 seconds. [51] Selection of smaller epochs

will capture greater levels of variation in PA patterns, and will enable researchers to pick up continuous, intermittent and sporadic activities. [52] Accelerometers also record PA with a time stamp, which allows for examination of both duration and timing of PA, which may be valuable information for interventions targeting sedentary periods throughout the day. [53]

### *1.3.3 Type*

Whilst the absolute values for frequency and duration may be subject to inaccuracies and bias with recall, they can provide useful insight into the context of PA behaviour, with information about the type of activities performed. By understanding not only the volume of activity undertaken, but the type of activities or sedentary behaviours undertaken, researchers may be able to provide more personalised or targeted interventions. However, some self-report methods can influence the number and type of activities reported by individuals through the use of leading questions or providing a set list of PAs, which may not cover activities older adults or those with chronic diseases would typically undertake such as household chores and walking. [44]

Although objective PA assessment methods are generally considered to be superior to subjective methods, methods such as accelerometry and pedometry are limited in their ability to capture certain PA types such as swimming, cycling and walking on an incline or stairs. [2, 46, 54] Current advancements in accelerometer measured PA are attempting to use machine learning methods to identify patterns in the raw data which represent specific types of PA, however these methods remain in early stages of development. [55] In contrast, such activity monitors are generally believed to provide better assessments of ambulatory activities such as walking that have proved difficult to capture via self-report, and make up the majority of adult, and particularly older adults PA. [2, 56, 57]

### *1.3.4 Intensity*

Subjective PA assessment methods often express PA intensity in one of two ways. Firstly, to ask the individual to rate the activity themselves using descriptive cues (e.g. moderate, hard, very hard, or breathing normally, slightly out of breath, too out of breath to carry on a conversation). [46] Perceptions and

reporting of PA intensity can be influenced by a number of factors including the perceived desirability of a given response and often result in individuals misclassifying PAs, with a tendency to overestimate time spent in MVPA. [40, 44, 51, 58]

The second method is to assign a MET value, a measure of energy expenditure, to the PA. METS are defined as the ratio of the working metabolic rate to the resting metabolic rate. The standard definition of one MET, which represents the energy used whilst at rest, is equal to 3.5 ml/kg/min or 1.0 kcal/kg/hour in adults. METS are used to categorise PA into intensity levels, namely: sedentary/inactivity (<1.5 METS), light PA (1.5-2.9 METS), moderate PA (3.0-5.9 METS), vigorous PA (>6.0 METS). METS can be expressed in absolute terms, i.e. as an absolute value relative to body mass or resting metabolism (assuming everyone expends energy in the same way), or in relative terms, i.e. relative to peak exercise capacity.

Often, MET values are obtained via standard tables such as the Compendium of Physical Activities which consists of a wide-ranging list of PAs that have been categorised, coded and given a corresponding MET value. [59] However, employing this method focuses on the absolute rather than the relative intensity of PAs, not taking into account large inter- and intraindividual variations in energy expenditure depending on age, sex and body mass. [47] For example, asking individuals to specify the speed at which they walk, and using that to assign a MET value. Researchers have demonstrated weak relative agreement between accelerometer and self-reported (International Physical Activity Questionnaire – Long Form) estimations of PA intensity, with participants self-reporting higher MVPA levels (r=0.12, 95% CI 0.08 to 0.14). [60] In addition, MET values in these tables are based on data from young healthy adults. Both exercise capacity and resting metabolism decline with age, resulting in higher metabolic costs of PAs, so whilst these estimates may be suitable for the general adult population, they may not be appropriate for the unfit, elderly or those with capacity limiting chronic diseases. [44, 50, 58, 61-64]

A further issue with subjective PA assessment methods is the fact that many do not capture data for low intensity PAs, with some not counting PAs with intensities lower than brisk walking. [44, 46, 50] Studies have shown that lower

intensity PAs are more difficult to recall accurately. [65] However capturing this information in older adults and those with chronic disease is important as this is the type of PA these populations tend to participate in most frequently. [50]

Objective PA assessment approaches are able to determine PA intensity via various methods. Most pedometers are able to accurately record accumulated steps during walking, but are less useful for measuring PA intensity. [2] Indirect calorimetry uses average oxygen consumption to gauge PA intensity, however the need for bulky equipment to measure this severely limits its use beyond laboratory experiments into free-living environments. Accelerometers will estimate PA intensity through identifying periods or bouts activity where accelerometer signals lie above predetermined thresholds or cut-points for the various intensity categories (i.e. sedentary, light, moderate and vigorous). [46] However, these methods are also subject to similar limitations as subjective PA assessments in the use of absolute cut-points to categorise PA intensity, based on studies of young healthy adults. Further discussion around the complexity of measuring PA intensity via accelerometer will be presented in the following section (section 1.4.2).

### *1.3.5 Comment on consensus*

In general, objective PA assessment methods demonstrate less variability in validity and reliability compared to self-report measures in a variety of populations including older adults and CR participants. [40, 45, 46, 49] However, there exists extreme variability in the methodological quality of studies, as well as choice of criterion or comparison measure, and reported outcome metrics. [45, 46] This has meant that data synthesis is challenging, and many reviews are only able to report comparisons between total energy expenditure or PA rather than examining the four dimensions of PA in detail. Furthermore, many of the studies that compared self-report to objective measures of PA examined the relationship using correlations and did not report the level of agreement between methods. This means only the strength of the relationship between the two methods is known, and does not rule out that moderate-highly correlated measures are not assessing different PA constructs. [46, 49]

Given the complexity of PA, its dimensions and measurement there remains a lack of consensus on a gold standard assessment method. Researchers must weigh up the various pros and cons of the different tools available to measure PA levels, considering the population under investigation, and the outcome measures of interest. [66] Accelerometers are able to provide detailed information on the frequency, duration and intensity of PA, and wrist-worn accelerometers have been used successfully in multiple large-scale population studies such as NHANES, UK Biobank, and Whitehall II studies, with high adherence rates. [42, 43, 51] PA measured via accelerometer has also been reported to have stronger associations with cardiometabolic biomarkers compared to self-report measured PA. [67] Developments in raw-accelerometry, and transparent data processing methods means that comparisons and harmonisation between studies are now much more achievable, which enables better understanding of the relationship between PA and health. [35] Chapters 2-5 of this thesis use wrist-worn accelerometer measured PA data, therefore further information about accelerometers is provided in the following section.

## 1.4 Accelerometry

Accelerometers are small electronic devices, usually worn at the waist or on the wrist but can also be worn on the upper arm, thigh or ankle. They measure the direction and magnitude of acceleration associated with bodily movement, in 1-3 axes (mediolateral (x), vertical (y), and anteroposterior (z); figure 1.2) [48, 69].The signal is then summarised over a user-defined time period or epoch, into a summary metric (i.e. activity count, vector magnitude).

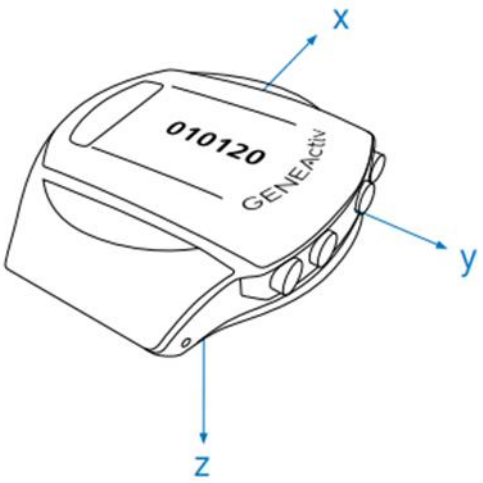


Figure 1.2: The directions of the mediolateral (x), vertical (y) and anteroposterior (z) axes. [68]

Early accelerometers such as the Actigraph GT1M (Pensacola, FL) produced proprietary outcome metrics, ‘activity counts’ which are collected over pre-defined time periods (epochs), ranging from 1-60 seconds. [51] The key limitation with such accelerometers is that the proprietary algorithm used to derive the brand-specific activity counts is kept confidential, making comparison, interpretation or harmonisation of data across accelerometer brands and studies challenging. Comparatively, accelerometers that undertake no onboard processing and provide the raw acceleration in gravitational units (g or mg), are now more available as small, low-cost devices enabling researchers to collect raw accelerometer data continuously for extended periods.

Chapters 3-5 of this thesis will focus on accelerometer measured PA in HF patients using the GENEActiv accelerometer (Activinsights Ltd, Cambridgeshire, UK) which provides high resolution accelerometer data in its raw format (figure 1.3). The GENEActiv accelerometer has been validated for both wrist and hip worn use in adults for measurement of PA and sedentary time. [69-71] It has strong relations with habitual PA patterns measured by the Actigraph GT3X+, another popular tri-axial raw accelerometer, and are therefore comparable. [72]


Figure 1.3: GENEActiv accelerometer

It is also worthwhile to note that with the vast technological developments over recent years, there is now a wealth of commercially available fitness trackers and smart watches, often equipped with multiple sensors including accelerometers, which provide health and PA information to consumers via mobile apps and proprietary algorithms. However, the rate at which companies release new devices means that few well-established brands and models are thoroughly validated for use in research. [73]

### *1.4.1 Data processing of raw acceleration*

Data collected from accelerometers is only a proxy for PA and therefore needs to be translated into meaningful behavioural units. An advantage of using raw accelerometer data in health research is that new data processing techniques can be applied to previously collected PA data sets, providing opportunities for data harmonization and comparisons and therefore better understanding of PA levels on a public health level, or population specific.

Methods for data reduction and analysis of raw accelerometer data are well-defined, openly available and reproducible. In this thesis three data reduction techniques are explored and are described below. Each are designed to quantify the magnitude of acceleration during a given epoch, combining the signals from the three axes to a single vector magnitude expressed in

milligravity units, where higher values correspond to higher intensity of PA. [69, 74, 75]

Firstly, Euclidean Norm Minus One (ENMO), developed by van Hees et al. where the vector magnitude is calculated in each epoch, and 1000mg (one earth gravitational unit) is removed, negative ENMO values are rounded to 0. The argument for this process is that negative values are potentially a result of calibration error rather than bodily movement. [74]

$$ENMO = \sqrt{x^2 + y^2 + z^2} - 1g$$

Mean amplitude deviation (MAD), developed by Vaha-Ypya et al in 2015, describes the mean distance of data points about the mean, and gives output in mg. This method was shown to successfully classify different PAs based on the intensity, regardless of accelerometer brand. [75]

$$MAD = \frac{1}{n} \times \sum |r_i - \bar{r}|$$

Where;

$$r_i = \sqrt{x_i^2 + y_i^2 + z_i^2}$$

$$\bar{r} = mean\ vector\ magnitude\ within\ the\ time\ period\ of\ interest$$

Finally, gravity-subtracted sum of vector magnitudes (SVM), where the vector magnitude is calculated in each epoch and 1g is subtracted, when the accelerometer is static and the earth's gravitation pull is the only acceleration, the result is 0. [69]

$$SVM = \sum |\sqrt{x^2 + y^2 + z^2} - 1g\ |$$

### *1.4.2 PA analysis with accelerometers*

Figure 1.4 (adapted from Bai et al. [76]) depicts the data reduction methods and pathways that can be used to analyse raw accelerometer data to answer specific research questions that may be relevant in HF patients.

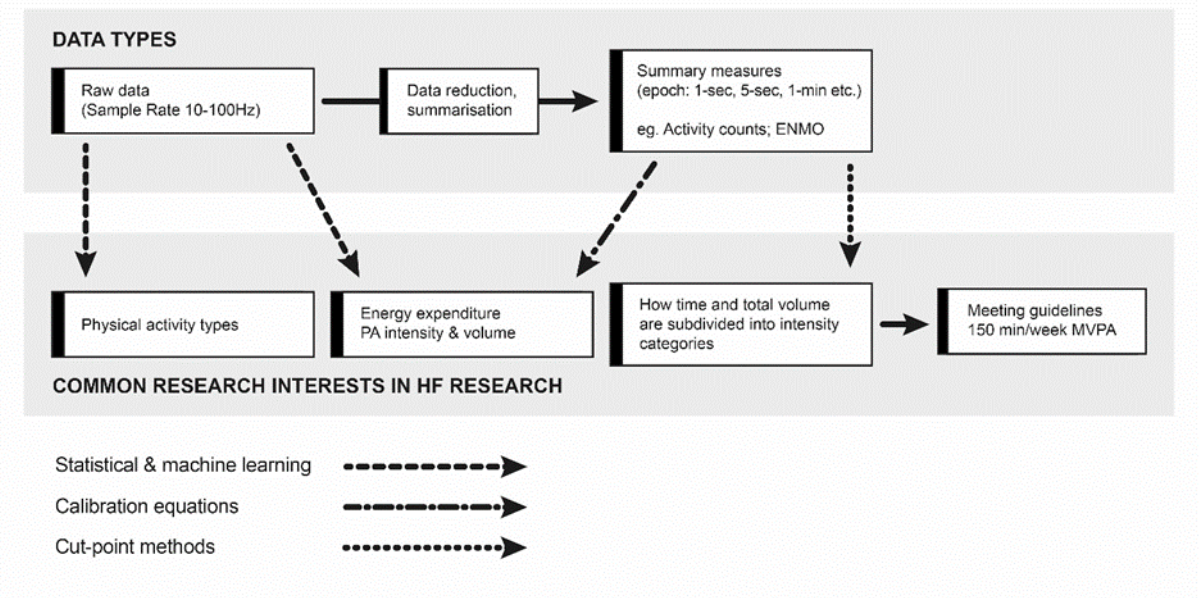


Figure 1.4 Analysis pathways in accelerometer measured PA research. Adapted from Bai et al. [76].

Given that international PA recommendations are intensity specific, it is important to be able to differentiate between PA intensities. A key feature of accelerometers is the ability to determine the intensity of PA by using the acceleration data captured per unit of wear time through the application of intensity thresholds or cut-points (calibration equations and cut-point methods pathways (figure 1.4).

The accelerometer thresholds or cut-points for PA intensities are derived from calibration studies where accelerometer values that relate to the intensity of interest (i.e. sedentary (<1.5 METS), light (1.5-2.9 METS), moderate (3.0 – 5.9 METS) or vigorous (>6.0 METS)) are calibrated against an objective gold standard measure of energy expenditure such as indirect calorimetry. These are usually derived from regression equations or receiver operator characteristic (ROC) curves. [52]

The majority of early calibration studies were performed with uniaxial ActiGraph accelerometers, and cut-points denoted in proprietary counts per minute (CPM) ranging from 1810-2743 CPM for the lower bound of moderate intensity PA. Common to all these early calibration studies was the use of young and healthy individuals (mean age range 22-30 years) performing treadmill based running or

walking activity. [51, 77-80] Accelerometer thresholds based on treadmill or indoor track running and walking have been shown to be less accurate in assessing free-living PA than when based on larger numbers of more typical lifestyle activities. [81]

Over more recent years, with the emergence of tri-axial and raw accelerometers, and new methods to process raw data in ways that are more transparent and comparable, cut-points and intensity thresholds have been derived and reported in gravitational units (g or mg). There have also been improvements in the calibration protocols, including more 'typical' lifestyle activities such as household chores and sedentary activities, improving applicability to measuring both PA and sedentary behaviour in free living conditions. [69, 82, 83] However, much like early calibration studies the samples of participants were young, healthy adults (mean age range 34-49). Furthermore, many of these cut-points tend to be based on absolute MET values, using standard MET calculations (i.e. assuming a resting metabolic rate of 3.5 ml/kg/min), which as mentioned previously in section 1.3.4 does not take into account the inter- and intraindividual variability of energy expenditure. [47]

Currently, there is no universally accepted and standardised approach for measuring PA using accelerometers in health research, particularly in special populations such as the elderly or those with chronic disease. Researchers have proposed guidelines and protocols for best practices in using accelerometers for PA measurement in health research, [56] which aids in making decisions about device placement and data collection, and how to report use in publications, yet there is still uncertainty around which published intensity thresholds to use. [84] When different thresholds for MVPA are used to predict PA levels and whether individuals are meeting PA guidelines it becomes difficult to compare results. [54] Furthermore, multiple studies in both adults and children have demonstrated that application of different intensity thresholds to the same data set can result in wide variations in MVPA minutes and different conclusions about PA levels, with cut-point choice having a larger influence on PA estimations than accelerometer wear site. [81, 85-87] In light of these challenges there has been a call for standardisation of PA monitor calibration, along with data collection, processing and analysis, preferably with the use of raw accelerometer data where possible. [88, 89]

### *1.4.3 Effects of age, exercise capacity and chronic disease on accelerometer output*

Multiple studies have applied the various cut-points identified above to samples of older adults and those with chronic disease including HF, without evidence that it is appropriate to do so. [43, 51, 90-92] A fundamental flaw of these methods is the application of a single threshold to all within a population.

Increasing age is associated with decreases in both cardiorespiratory fitness or exercise capacity and resting metabolic rate, which results in higher metabolic costs of PAs including walking and daily lifestyle activities compared to younger adults. [62, 64] Knaggs et al. demonstrated that metabolic costs of activities are further increased with the presence of mobility issues. [63] Hall et al. also confirmed that those with chronic conditions demonstrated significantly greater work rates in terms of METS compared to healthy counterparts for a given task. [61] Consequently, estimating PA intensity based on accelerometer thresholds that were derived from studies of healthy adults would likely lead to misclassification of PA in certain populations, i.e. participants who are elderly or living with chronic disease may not be credited for engaging in MVPA if the accelerometer threshold used to determine MVPA is too high. Therefore there has been a call for researchers to perform calibration studies in other populations, including older adults, and those with chronic disease to establish appropriate thresholds that relate more closely to the metabolic cost of activities within the specific population.

A number of calibration studies have been performed in older adults without exercise-limiting chronic disease. [64, 92-95] The majority of these studies used actigraph accelerometers and were lab-based with a mixture of daily lifestyle activities or treadmill walking. However, derived cut-points were expressed in single axis, proprietary counts per minute over different epochs, which means comparison is still limited. With the exception of the calibration of the Actical by Hooker et al., [64] all authors demonstrated that cut-points for MVPA in older adults (mean age range 52-75.5 years) were lower than those published based on younger adults.

In addition to the effect of age, the effect of exercise capacity or fitness has also been investigated. In a study of 106 older adults (mean age 77.6 +/- 4.0 years)

Pruitt et al. calculated individual activity count thresholds for ‘meaningful’ PA collected during a 400m walk and found that individualised thresholds were more effective in differentiating PA levels of participants than accelerometry variables of overall activity (eg. activity counts per day). [96] The individual thresholds varied widely (between 149 to 3133 counts per minute), and authors applied previously published cut-points and demonstrated that this would likely have resulted in misinterpretation of PA levels in their sample of older adults.

Similarly, Ozemek et al. demonstrated the extreme variability in individual accelerometer values when undertaking activities at moderate intensity relative to the individual (~2000-7500 cpm), with low and moderate fitness groups having significantly lower cut-points compared to the high fit group. [97] Rejeski et al. also observed large variability in activity counts achieved during supervised walking at a moderate intensity (rating of perceived exertion (RPE) 13), emphasising that MVPA is a relative construct. These studies support the concept that exercise capacity influences energy expenditure during PA, and that application of standard accelerometer cut-points to individuals with low exercise capacity risks underestimating their PA level. [98]

Although individualised cut-points may be preferable, this is often not feasible in public health or large-scale studies, nor for providing clinical advice or guidance to chronic disease patients in order to increase their PA levels. Furthermore, PA is often measured as a secondary outcome in clinical studies of chronic disease patients, which would make it difficult to dedicate valuable resources towards establishing individual thresholds for MVPA. Therefore, in order to better estimate the energy cost of activities from accelerometer data in adults with chronic disease, the best solution at present requires population specific thresholds of accelerometer data.

There are a small number of studies that have performed accelerometer calibration or validation studies in chronic disease populations including Parkinson’s, [99] diabetes, [100] multiple sclerosis, [101] and chronic obstructive pulmonary disease (COPD). [102] Clearly there is a need for further research in this area, with focus on other exercise limiting chronic diseases. Appropriate, accurate, reliable and valid assessment of PA in the elderly and chronic disease populations is an important area of research. Improving the way

in which we measure PA in these populations will enable researchers to better understand relationships between PA levels and health outcomes. One important chronic disease population that requires further investigation is HF.

## 1.5 Heart failure (HF)

### *1.5.1 Definitions, treatment and incidence*

HF is a complex, long-term clinical syndrome defined as the reduced ability of the heart to pump and/or fill with blood, meaning there is inadequate cardiac output to meet the metabolic demands of the body. [103] In the UK, approximately 900,000 people are living with HF, it is responsible for approximately 5% of all emergency hospital admissions and costs the NHS around £1bn per year, up to 2% of all NHS expenditure. [104] It is an important public health issue, the burden of HF is increasing with rising prevalence due to population growth, an ageing population, and increasing prevalence of HF risk factors, especially diabetes, hypertension and obesity. [105, 106] Another postulation for these increases is that advances over recent years in cardiovascular surgery and medicine, have led to a decrease in the mortality rates of acute cardiac syndromes such as myocardial infarction, valvular and congenital heart diseases, hypertension and arrhythmias. However, in prolonging these patients' lives, many are living with resultant myocardial damage and are at risk of developing HF. Incidence of HF is increasing in people aged over 85 years, a group of patients who are often excluded from randomised controlled trials (RCTs). Data are often extrapolated to these patients, so there remains uncertainty as to whether standard HF therapies are as safe and effective in the very elderly. [106] In addition, patient profiles appear to be changing, with HF patients increasingly surviving into older years and therefore living with greater numbers of associated comorbidities, such as hypertension, atrial fibrillation, osteoarthritis and COPD. As a result, HF management is becoming more complex. [105]

The typical symptoms of HF include dyspnoea or shortness of breath, fatigue, weakness or tiredness, reduced exercise tolerance and increased time to recover after exercise, fluid retention presenting as peripheral and/or abdominal

oedema. Other symptoms may also include difficulty sleeping, wheezing, nocturnal cough, loss of appetite, feeling bloated, dizziness, and depression. [103]

HF is categorised into three subtypes, namely HF with preserved ejection fraction (HFpEF), HF with reduced ejection fraction (HFrEF), and HF with mid-range ejection fraction (HFmrEF) [103] Ejection fraction is usually >50% in patients with HFpEF, where the volume of the left ventricle is typically normal, but the left ventricular wall is thicker and more stiff with a high ratio of left ventricular mass/end-diastolic volume. HFpEF has historically been harder to diagnose due to its more complex and heterogeneous nature compared to HFrEF. [107] HFmrEF patients have an ejection fraction between 40-50%. Ejection fraction in HFrEF patients is <40%, with dilated left ventricles, and normal or reduced left ventricular mass/end-diastolic volume ratio.[108] Ischaemic heart disease and previous myocardial infarction are more common in HFrEF patients, whereas hypertension and valve disease are more common in HFpEF patients [104]. It is currently estimated that about half of HF patients have HFpEF, with the proportion of HFpEF patients increasing, and expected to rise to about 65% of hospitalised patients with HF by 2020. There is no data currently on the trends on the emerging HFmrEF category. [109]

Clinically, HF is classified into four functional classes defined by the New York Heart Association (NYHA) described in table 1.1, as follows:

Table 1.1: Definitions of the NYHA functional classes

| Functional Class | Description |
|---|---|
| I | No limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, or dyspnoea. |
| II | Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitations, or dyspnoea. |
| III | Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitations, or dyspnoea. |
| IV | Unable to carry on any physical activity without discomfort. Heart failure symptoms are present even at rest or with minimal exertion. |

The updated 2018 National Institute for Health and Care Excellence (NICE) guidelines in the UK recommend the following pharmacological treatment to alleviate symptoms and extend survival: diuretics, for the relief of congestive symptoms and fluid retention; then for HFpEF patients, medical management of comorbidities such as hypertension, atrial fibrillation, ischaemic heart disease and diabetes. For HFrEF patients, management of symptoms controlled with a combination of renin-angiotensin-aldosterone system blockers (ACE inhibitors, ARBs), β-adrenoreceptor blockers, mineralocorticoid receptor antagonists (MRA) and further or alternative medications if symptoms persist or patients experience intolerances to certain medications. Some patients are also offered surgical interventions, with placement of internal devices such as pacemakers and implanted cardioverter defibrillators, or cardiac resynchronisation therapy. In addition to the pharmacological treatments, NICE guidelines also recommend a number of non-pharmacological treatments for all HF patients including CR. Lifestyle advice should be offered, with information regarding salt and fluid restriction, smoking and alcohol consumption. [110]

Prior to the 1990s, patients with HF were generally discouraged from exercising, and bedrest was recommended. [111] Since then, numerous studies have demonstrated the safety and efficacy of exercise programmes in patients

with HF, and as a result, national and international guidelines now recommend that stable HF patients participate in CR. [103, 110, subsection 1.9]

Despite major advances in the treatment of HFrEF over recent years, there has been little progress made in therapy for HFpEF patients, who have not been shown to respond well to standard pharmacological treatments. [104, 108] The mechanisms causing this type of HF are not well understood, nor are the mechanisms underlying these patients exercise intolerance which is often the primary chronic symptom, resulting in poor health related quality of life (HRQoL). [112] However, recent research indicates that exercise and PA interventions are beneficial for patients with HFpEF, with improvements in both exercise capacity and HRQoL. [113] Further, patients have indicated a preference for HRQoL rather than length of life, so the focus of research is shifting in this direction. [114] Exercise capacity, PA, and HRQoL present important alternative clinical outcomes, and targets for interventions.

### *1.5.2 PA levels of HF patients*

A small number of studies have assessed PA levels of patients with HF, however these studies are limited by PA measurement methods that may not be accurate or appropriate in this population.

Studies using self-reported measures of PA have demonstrated that many patients are non-compliant with non-pharmacological recommendations, and indicated that many HF patients do not engage in any form of regular exercise. [115, 116] In the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial) trial, [117] HFpEF patients PA levels were subjectively assessed, by asking participants “What has the subject’s usual pattern of exercise been during the past 2 weeks?”, and calculating the product of the number of minutes, and frequency of activities per week for three intensity categories of activity corresponding to MET estimations from the Compendium of physical activities. [59] It was found that only 11% of patients were meeting the national recommended guidelines for PA. Those with poor PA levels were more likely to be female and NYHA class III, and those that did meet PA guidelines were less likely to have a number of comorbidities or risk factors including high BMI, diabetes, chronic kidney disease, and less likely to have a history of prior HF hospitalisation.

Yates et al. [118] measured PA levels of 29 HFrEF patients both objectively via Actiheart accelerometer and subjectively via Modified 7-day PA Recall Questionnaire, which has been validated in older people with cardiac problems, but not specifically patients with HF. [119] Based on subjective data, only 38% of patients met PA guidelines of 150 minutes of MVPA, but based on accelerometer data no patients met PA guidelines, and engaged in <1 minute of MVPA per day. The authors applied absolute cut-points for categorising PA intensity from Freedson et al. [77], which were developed in a study of healthy adults, and have been shown to be unsuitable for application in populations with low exercise capacity. [97]

Dontje et al. measured PA levels of 68 HF patients via accelerometry using the SenseWear® Pro3 Armband (BodyMedia, Inc., Pittsburgh, PA), a bi-axial accelerometer, which has not been specifically validated for HF patients, and PA intensity was categorised via proprietary algorithms to calculate energy expenditure in Kcal. Results showed that around half performed less than 30 minutes of moderate intensity PA per day, alongside findings that those with higher NYHA classes and lower self-efficacy had reduced PA levels. [120] Yavari et al. also measured PA levels of HF patients using the SenseWear Mini Armband (BodyMedia, Inc., Pittsburgh, PA), a tri-axial accelerometer, which also has not been validated specifically in HF patients. Again, PA intensity was calculated using the energy expenditure output of the accelerometer. The authors found that HF patients had highly sedentary lifestyles (78-79% of waking time) and suggested that HFpEF patients achieved virtually no continuous MVPA. [121]

Most recently, Barker et al. compared accelerometer measured PA levels of people with chronic disease to healthy individuals of the same age, and reported that patients with cardiovascular disease, and HF in particular have low levels of PA. However, the authors applied the same cut-points for MVPA to all study participants, whether healthy or living with chronic disease, which assumes that a moderate intensity activity for a healthy adult has the same energy expenditure for a patient with HF of the same age. Given the limitations to exercise capacity with chronic disease, including HF, this method may not be appropriate. [90]

HF patients are often elderly and the most common symptom of HF is limited exercise tolerance, [105] both of which are factors that have been demonstrated to affect energy expenditure and result in lower accelerometer thresholds for MVPA. Studies have shown that for HF patients the energy requirements to perform simple daily lifestyle activities may require a much greater percentage of their peak aerobic capacity, potentially leading to early onset of fatigue, early termination of a given activity, and an overall reduction in the volume of daily activity. Furthermore, it has been shown that resting metabolic rate decreases in HF patients with increasing NYHA class. [121, 122]

Although HF patients may perform less PA than healthy adults of a similar age, the magnitude of the difference, and reports that patients perform little to no daily MVPA may be exaggerated by use of inappropriate PA measurement methods. In a systematic review that aimed to assess whether activity monitors were appropriately validated for use in populations with chronic diseases, Van Remoortel et al. [123] found most validation studies were highly heterogeneous and had been performed in healthy adults, with only 12% validation studies performed in those with chronic diseases (1 in patients with HF). Moreover, common limitations amongst the studies included in this systematic review include small sample sizes, and inclusion of younger patients which may not be representative of the wider HF population. In addition, use of proprietary accelerometers limits comparisons across studies and accelerometer brands. At present, there are no accelerometer calibration studies in HF patients. Therefore, further studies investigating PA levels of HF patients using raw accelerometry, and transparent data reduction and analysis techniques that allow better comparison to other studies and other populations are warranted to improve our understanding of PA in this population.

### *1.5.3 Effect of PA on HF and associated mechanisms*

Several systematic reviews and meta-analyses have clearly demonstrated the importance of HF patients engaging in regular exercise for health benefits including improvements in exercise capacity, reduced all-cause and HF-specific hospital admissions, and health related quality of life. [124-127] The benefits of PA are less well researched. Exercise training or regular PA is recommended by national and international guidelines and supported by a class I

recommendation (i.e. evidence or general agreement that the treatment or procedure should be performed) for HF patients who are able to participate. [103, 110, 128]

Higher PA levels have been shown to be important prognostic predictors in HF patients. Loprinzi measured free-living PA via accelerometry of 189 patients who identified as having congestive HF, and found that for every 60 minute increase in free-living PA (which included total engagement of PA per week, i.e. all non-sedentary movement), HF patients had a 35% reduced risk of all-cause mortality (figure 1.5).[129] This was double the reduction found in the coronary artery disease patients of the same study where a 60 minute increase in PA resulted in a 16% reduced risk of all-cause mortality. [130]

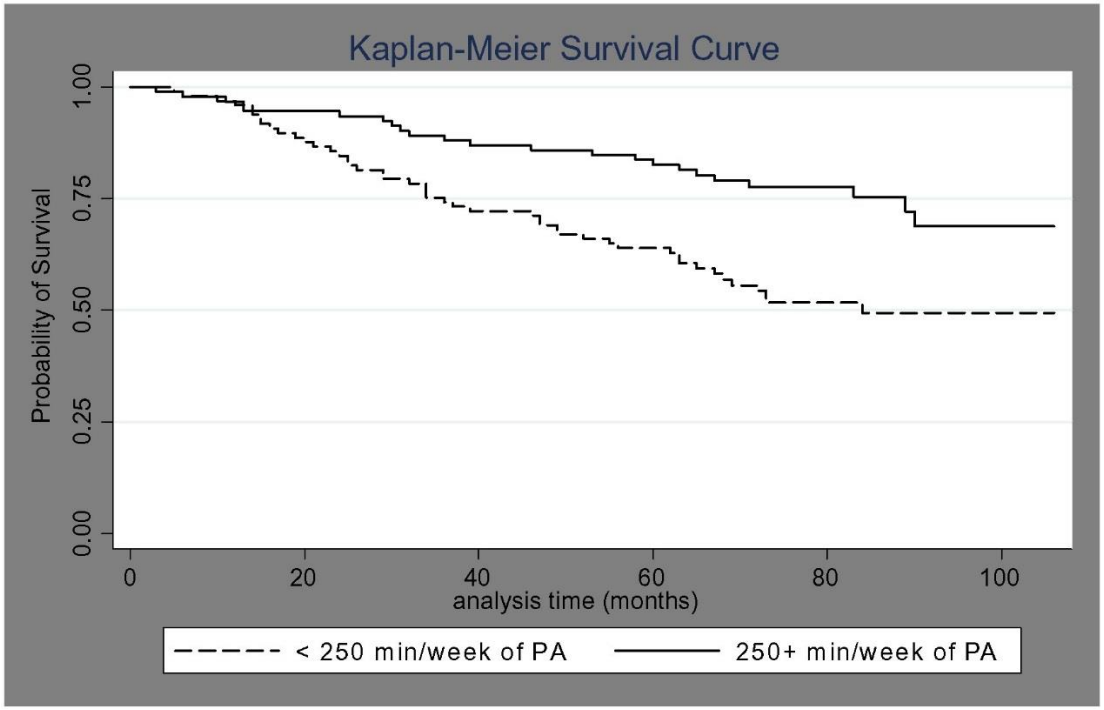


Figure 1.5: Kaplan-Meier all-cause mortality survival curve across PA level above or below 250 min/week total PA (light-to-vigorous intensity). Reproduced from Loprinzi [129].

In the TOPCAT trial of HFpEF patients, PA levels lower than the national recommendations was associated with a greater risk of HF hospitalisation (HR, 1.93; 95% CI, 1.16–3.22), cardiovascular mortality (HR, 4.36; 95% CI, 1.37–13.83), and all-cause mortality (HR, 2.95; 95% CI, 1.44–6.02) after adjustment

for potential confounders. [117] Similarly, Cacciatore et al. showed that self-reported PA levels of patients with advanced HF (NYHA IIIb) is a predictor of mortality, regardless of comorbidities, disability and physical function. [131]

Daily PA levels have also been shown to have strong associations with exercise capacity, rehospitalisation, clinical prognosis, NYHA class, along with burden of comorbidities, health related quality of life, depression and sleep apnoea in HF patients. [132-136] Lee et al. [137] showed that maintaining PA is a key component alongside improving functional status and enhancing exercise self-efficacy for maintaining and improving health related quality of life and independence in HF patients, which HF patients express preference for, over length of life. [116]

There are a number of mechanisms by which PA can be beneficial to health in HF patients, including cardiac, cognitive, vascular and cardiovascular disease risk factors, summarised below in figure 1.6. [32, 138-140] The mechanisms for benefits of PA in patients with HFpEF are less well established. However, researchers have proposed the following potential explanations; reduced left ventricular filling pressures, less diastolic stiffness and favourable left ventricular structure and function. [141]

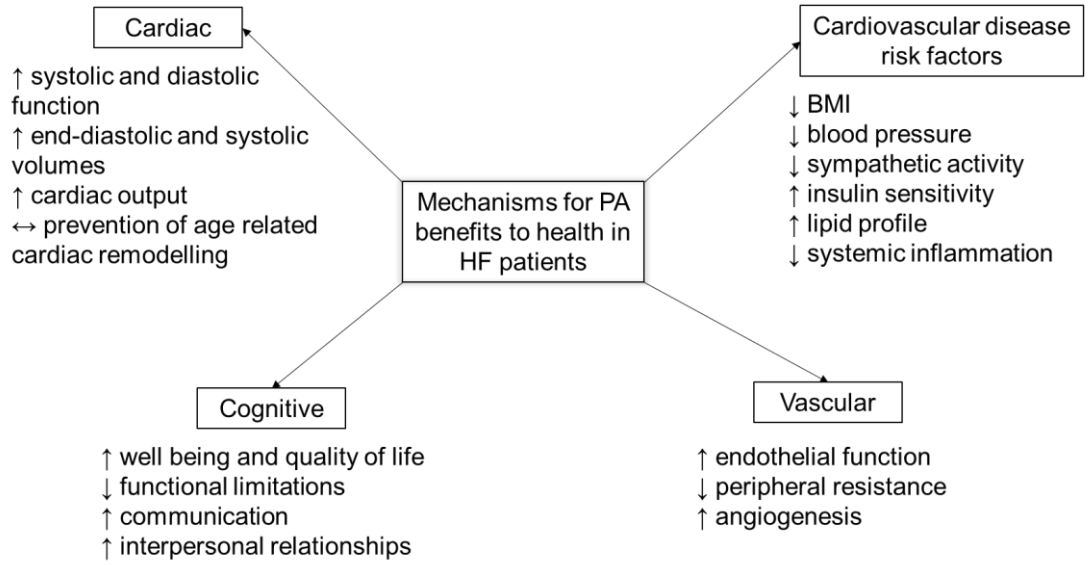


Figure 1.6: Mechanisms for PA benefits to health in patients with HF. Adapted from Vanhees et al. [32], Gielen et al. [138], Crimi et al. [139], and Rego et al. [140]

Current understanding about the relationship between PA and HF outcomes is mostly based on self-reported PA measures, or studies that have inappropriately applied accelerometer data analysis methods based on studies of healthy young adults, which could impact upon the strength of associations seen. For example, Loprinzi et al. demonstrated that application of different accelerometer cut-points for MVPA influenced estimates for associations between PA and health outcomes such as obesity, high C-reactive protein levels and low high-density lipoprotein levels. [142] More precise, population specific measurement of PA in HF patients should enable aetiological, epidemiological and observational studies to confirm, clarify and better understand the relationships between PA and health benefits in this challenging population.

### *1.5.4 Impact of exercise-based CR in HF on PA*

CR is a complex intervention defined by the BACPR as “The coordinated sum of activities required to influence favourably the underlying cause of cardiovascular disease, as well as to provide the best possible physical, mental and social conditions, so that the patients may, by their own efforts, preserve or resume optimal functioning in their community and through improved health behaviour, slow or reverse progression of disease”. [10] It comprises components of health education with advice on cardiovascular risk reduction, psychosocial care and stress management alongside structured exercise. [10, 143]

Considerable evidence exists in support of CR for HF patients, and it is now recommended in international guidelines for HF management, with a class IIa recommendation (i.e. evidence or opinion that it is reasonable to perform the treatment or procedure).[103, 104, 128, 144, 145] Recent trial level and individual patient level meta-analyses have shown CR has significant benefits for HF patients. Pooled data from 44 randomised trials showed exercise-based CR reduces overall hospital admissions (relative risk RR 0.70, 95% CI 0.60 to 0.83, p=0.0001), and HF-specific hospitalisation (RR 0.59, 95% CI 0.42 to 0.84, p=0.003). CR also showed potentially clinically important improvements in HRQoL up to 12 months follow-up (standardised mean difference -0.60, 95% CI

-0.82 to -0.39, p<0.0001). [124] In a recent individual patient data meta-analysis, participation in CR resulted in improvements in exercise capacity, measured via 6-min walk test (mean 21.0m, 95% CI 1.57 to 40.4m, p=0.034) and Minnesota Living with HF score (mean improvement 5.9; 95% CI 1.0 to 10.9, p=0.018). [127]

Traditionally, CR programmes have prioritised increasing exercise capacity or fitness as a priority, rather than increasing overall PA levels. Whilst it is established that CR can improve exercise capacity with programmes as short as 4 weeks, an increase in PA requires a more profound change in behaviour of the patients as improvements in exercise capacity do not necessarily result in a more active lifestyle. [146] Patients report that adherence to exercise recommendations are more difficult than other behavioural changes required for HF including smoking and alcohol cessation, medication, and follow-up appointments. [147] Two systematic reviews investigating the effect of CR on PA in CHD patients have been previously conducted in 1998 and 2015 and both concluded that there was insufficient evidence of CR impacting PA levels of patients. [148, 149] Neither of these studies included HF patients, nor did they attempt meta-analysis. Therefore the impact of CR on PA of HF patients remains uncertain.

Ideally, CR interventions should lead to long-term, maintained lifestyle change, with both improved exercise capacity and PA level, resulting in better HRQoL at a cost that represents good value for the NHS. [150] However, Ramadi et al. [151] found that although patients maintained exercise capacity improvements 6 months post-CR, many patients failed to maintain PA levels post-CR, with MVPA and sedentary time comparable to pre-CR levels. Other studies have also indicated the need for CR interventions that successfully increase PA levels and reduce sedentary time, and maintain these healthy lifestyle changes in the long-term post-intervention. [152-153] The potential reasons for these findings have not been explored in the literature, therefore it is unclear whether it may be due to poor PA measurement methods in this population, or due to behavioural changes. With a lack of gold standard PA measurement, data processing, analysis and reporting methods, PA outcomes previously reported in CR trials are often confusing, not suitable for comparison and not necessarily measuring PA behaviour change. Many studies have relied on self-reported

measures of PA, and where accelerometers have been used researchers have applied inappropriate accelerometer cut-points, both of which risk misclassifying PA levels of HF patients, and makes it difficult to tease out small changes in PA levels. Furthermore, single, aggregated measures of PA such as weekly MVPA levels may mask important patterns of change in PA data. For example, an observational study in older adults showed that an aerobic exercise training program resulted in an increase in exercise capacity, but PA increases were offset by a compensatory decline in PA outside the training programme. [154] Therefore, improvements in PA measurement in HF patients, using population appropriate cut-points to determine PA intensity, and looking beyond a single measure of PA may help to provide better understanding of how CR interventions work.

### *1.5.5 REACH-HF research programme*

Despite the strong evidence base for CR in HF, uptake remains poor, in the UK less than 20% of patients are offered CR post-discharge after HF diagnosis, and less than 5% attend at least one CR session. [104] Similar statistics demonstrating suboptimal rates of uptake are true across Europe and the US. [155, 156] Reasons for this underutilisation of CR in HF patients include lack of endorsement by physicians, which may be due to their perceived benefit of CR. [157] Other barriers to participation in and referral to CR include patient demographics such as age, lower socioeconomic status, distance to travel, and burden of comorbidities. [155-157] Therefore strategies are required to increase CR participation to ensure HF patients are accessing this important treatment for secondary prevention. Alternative models for CR such as telehealth, community- or home-based interventions have been shown to produce similar reductions in cardiovascular risk factors, with similar costs after myocardial infarction and coronary revascularisation, and may provide a different approach to widen participation in CR for HF patients. [158, 159]

Rehabilitation Enablement in Chronic Heart Failure (REACH-HF) is a National Institute for Health Research (NIHR) funded research programme with the aim of developing and evaluating a health professional facilitated home-based self-help manual CR intervention to improve self-care and HRQoL in people with HF

and their caregivers. [160, 161] It was developed with involvement of a local Patient and Public Involvement group consisting of HF patients and caregivers of people with HF. [162] Within the REACH-HF research programme there are two completed RCTs (both comparing REACH HF intervention (HF manual, Chair based exercise DVD, Caregiver resource and Progress tracker) plus usual care to usual care alone) – a full multicentre RCT in 216 patients (mean age 70 years, 22% female) with HFrEF with 12-months follow-up, [163] and a single centre pilot trial in 50 patients (mean age 73.9 years, 54% female) with HFpEF with 6-months follow-up. [164] In addition to a number of other outcomes these two trials collected 7-day raw accelerometry measured PA in all patients at baseline and follow-up time points.

The findings of the pilot study support the acceptability of the REACH-HF intervention, and emerging evidence of the impact of exercise-based CR interventions in patients with HFpEF. Although the pilot study was not statistically powered to definitively assess the efficacy of the REACH-HF intervention, results were promising with a number of favourable patient outcomes including disease-specific HRQoL.

The results of the full RCT in HFrEF patients showed clinically important improvements in disease specific HRQoL at 12 months follow-up with the REACH-HF intervention compared to usual care alone. REACH-HF was also associated with improved ratings of self-care maintenance, indicating greater engagement in activities such as monitoring weight and fluid retention, engaging in exercise and using a system to remember medication. However, no differences were seen in other secondary outcomes including accelerometer measured PA. Average daily PA outcomes reported utilised mg values for sedentary activities and MVPA based on healthy adults, therefore application of HF population specific accelerometer thresholds may reveal different patterns in the data.

### 1.6 Summary

Lack of PA is a well-accepted risk factor of ill health in the general population. Maintenance of adequate PA is also a key recommendation for many chronic

disease populations, including HF. Although, often assessed in the past in larger population studies using self-report, a number of methods (including accelerometry) are now available to objectively assess PA levels. These methods have their relative pros and cons. PA measurement is complex across all populations, and as evidence shows, PA measurement in the elderly, and chronic disease populations involves additional challenges. In particular, accelerometer data reduction and analysis techniques such as cut-point and calibration studies that are based on samples of young healthy adults are likely to be inappropriate for use in HF populations, and may result in misinterpretation, misclassification or underestimation of PA levels of HF patients.

To date, there has only been a small body of research on objectively assessed PA in HF patients. Well conducted studies, using improved, population specific PA assessment techniques are therefore needed to understand and clarify the PA patterns of this population, and the relationships between PA levels and patient level characteristics i.e. sociodemographics, exercise capacity and quality of life. A substantive body of RCT evidence shows that participation in exercise-based CR improves exercise capacity and HRQoL, and reduces risk of hospital admissions in people with HF. However, the impact of exercise-based CR on PA levels in HF remains uncertain.

PA measurement in HF patients is under researched, and further work is needed to improve PA measurement methods, and understanding of PA levels in this population, and how exercise-based CR interventions can impact upon these levels.

### 1.7 Aims of the thesis

The overarching aim of this thesis is to contribute to the further knowledge and understanding on PA in people with HF and how exercise-based CR can impact this.

The specific aims were to:

(1) Undertake a systematic review to assess the evidence as to whether participation in exercise-based CR increases PA levels of cardiac patients, including those with HF (Chapter 2),

(2) Undertake an accelerometer calibration study and develop HF specific accelerometer intensity thresholds for MVPA and inactivity (Chapter 3),

(3) Examine the PA levels of HF patients, and associations between baseline PA and patient-level factors including sociodemographics, exercise capacity, and HRQoL (Chapter 4),

(4) Determine whether a home-based, self-help CR intervention improves PA levels of people with HF, and the sociodemographic, exercise capacity and HRQoL factors are associated with a change in PA level (chapter 5).

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# Chapter 2: Cardiac rehabilitation and physical activity: systematic review and meta-analysis

## 2.1 Abstract


Objective

To undertake a systematic review and meta-analysis to assess the impact of cardiac rehabilitation (CR) on physical activity (PA) levels of patients with heart disease and the methodological quality of these studies.

Methods

Databases (MEDLINE, EMBASE, CENTRAL, CINAHL, PsychINFO and SportDiscus) were searched without language restriction from inception to January 2017 for randomised controlled trials (RCTs) comparing CR to usual care control in adults with heart failure or coronary heart disease (CHD) and measuring PA subjectively or objectively. The direction of PA difference between CR and control was summarised using vote counting (i.e. counting the positive, negative and non-significant results) and meta-analysis.

Results

Forty RCTs, (6480 patients: 5825 CHD, 655 HF) were included with 26% (38/145) PA results showing a statistically significant improvement in PA levels with CR compared to control. This pattern of results appeared consistent regardless of type of CR intervention (comprehensive vs. exercise-only) or PA measurement (objective vs. subjective). Meta-analysis showed PA increases in the metrics of steps/day (1423, 95% CI 757.07 to 2089.43, $p<0.0001$) and proportion of patients categorised as physically active (relative risk 1.55, 95% CI 1.19 to 2.02, $p=0.001$). The included trials were at high risk of bias, and the quality of the PA assessment and reporting was relatively poor.

Conclusion

Overall, there is moderate evidence of an increase in PA with CR participation compared to control. High quality trials are required, with robust PA

measurement and data analysis methods, to assess if CR definitely leads to important improvements in PA.

## 2.2 Introduction

Physical activity (PA) is defined as any bodily movement produced by skeletal muscles resulting in energy expenditure beyond resting expenditure. [1] The current UK recommendation for PA in adults and older adults is ≥150 min of moderate intensity PA per week. [2] This is based on a number of systematic reviews and consensus statement, consistently identifying 150 min/week as providing considerable health benefits, including reduced all-cause mortality, reduced risk factors for chronic diseases, improved cardiovascular fitness and quality of life. [2, 3] This is also the standard PA recommendation for patients with cardiac disease by the British Association for Cardiovascular Prevention and Rehabilitation and the Scottish Intercollegiate Guidelines Network. [4, 5]

The benefits of cardiac rehabilitation (CR) participation for those with coronary heart disease (CHD) and heart failure (HF) are well established and include reduced cardiovascular mortality, reduced risk of hospital admissions, improved exercise capacity and health-related quality of life. [6, 7] A key aim of CR is to increase total daily energy expenditure in addition to exercise capacity. [2] However, previous observational studies demonstrated that many patients with heart disease (pre-CR and post-CR) are failing to meet recommended daily PA levels [8, 9] and the extent that CR impacts on PA levels of patients remains unclear.

While two systematic reviews to date have indicated inadequate evidence of an impact of CR participation on PA levels of patients with CHD, [10, 11] these studies have limitations. Neither included studies involving patients with HF nor attempted meta-analysis due to the heterogeneity of CR interventions. Therefore, an updated systematic review with an improved search strategy and broader population inclusion criteria is justified.

The aim of this systematic review and meta-analysis of randomised controlled trials (RCTs) was twofold. First, to clarify the impact of CR participation on PA

levels of patients with CHD and HF. Second, to review the methodological quality of PA outcomes reported in these trials.

## 2.3 Methods

The protocol was registered on PROSPERO (CRD42017055137). We conducted and report this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyse statement. [12]

### *2.3.1 Search strategy and inclusion criteria*

Details of the search strategy and inclusion criteria are provided in appendix 2.1. The full search strategy is provided in appendix 2.2.

### *2.3.2 Data extraction and risk of bias assessment*

A standardised data extraction form was used to extract study characteristics, patient characteristics, intervention and control details, PA measurement method and outcome data at all follow-up time points. Multiple publications of the same study were assessed for additional data and presented as a single RCT (appendix 2.3).

The Cochrane Collaboration's tool for assessing risk of bias was used to assess the quality of included studies.[13] Data extraction and risk of bias assessment were initially completed by a single reviewer (GD) and then checked for accuracy by one other reviewer (MH, HD or RST). Disagreement was resolved by discussion.

### *2.3.3 Data synthesis and meta-analysis*

Due to the wide range of PA metrics reported across studies, we first summarised the direction of PA results using a vote counting approach [13] (quantifying studies on the basis of their positive, negative or non-significant results). Given the wide range of PA measures, we decided against using standardised effect size for meta-analysis and instead conducted meta-analysis where two or more studies reported the same units of PA measurement. Meta-analysis was completed on all follow-up time points apart from one outcome

measure (proportion of patients categorised as physically active) where there was sufficient data to separate into short-term (≤12 months post-CR) and long-term (>12 months post-CR) follow-up.

Given the clinical heterogeneity of the included studies, random-effects models were used to pool data. Statistical heterogeneity was assessed using the $I^2$ statistic. Binary outcomes for each study were pooled as relative risks (RR) and continuous outcomes as mean differences (MD). Meta-analysis results were reported as means and 95% CIs. A two-tailed p value of ≤0.05 was considered statistically significant. Analyses were performed in Review Manager (RevMan V.5.3, The Cochrane Collaboration) or Stata V.14.

We explored the effect of various potential treatment effect modifiers by stratifying the vote counting results, that is, setting of CR (centre vs home based), patient group (CHD vs HF), publication date (pre-1990, representing the time of major changes in drug and device management of CHD and HF), dose of exercise intervention (dose=number of weeks of exercise training×average sessions/week×average duration of session in minutes. Dose ≥2000 units (median) vs dose <2000 units); objective versus subjective PA measures and method of PA statistical analysis. Studies lacking enough information to calculate dose were omitted from the analysis.

## 2.4 Results

### *2.4.1 Study selection*

Figure 2.1 summarises the screening process resulting in 47 publications across 40 RCTs included in the review.

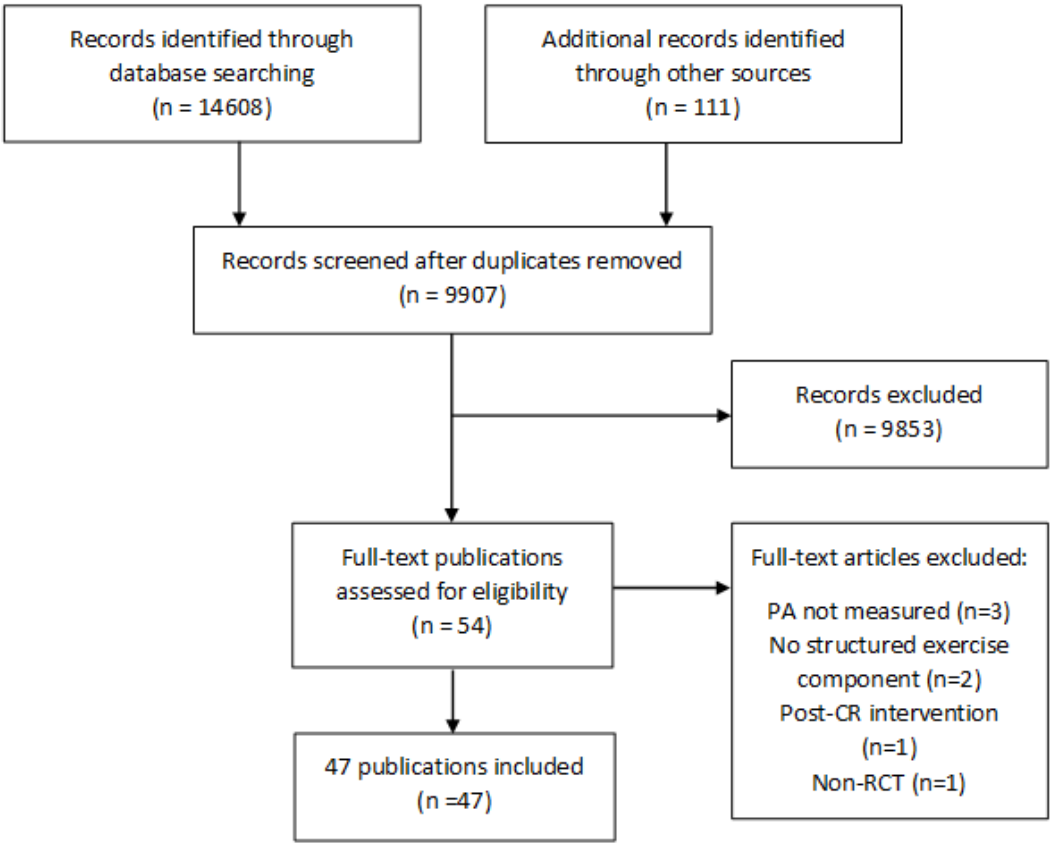


Figure 2.1: Preferred Reporting Items for Systematic Reviews and Meta-analyses flow chart of search process.

### *2.4.2 Characteristics of included studies*

The 40 RCTs, all published in English, included a total of 6480 patients with cardiac disease (5825 CHD, 655 HF). A summary of study characteristics is shown in table 2.1. Individual study characteristics are detailed in appendix 2.4.

Table 2.1: Summary of study characteristics

| Characteristic | Number of studies (%) or Median (range) |
|---|---|
| **Multicentre RCT** | 10 (25) |
| **Exercise only** | 17 (42.5) |
| **CR location** | |
| Home-based | 10 (25) |
| Centre-based | 23 (57.5) |
| Both | 7 (17.5) |
| **Sample size** | 89.5 (19-1813) |
| <50 | 10 (25) |
| 51-100 | 14 (35) |
| >100 | 16 (40) |
| **Publication date** | |
| 1970-1979 | 1 (2.5) |
| 1980-1989 | 5 (12.5) |
| 1990-1999 | 12 (30) |
| 2000-2009 | 10 (25) |
| 2010-2017 | 12 (30) |
| **Study location** | |
| Europe | 25 (62.5) |
| North America | 10 (25) |
| Asia/Australia | 5 (12.5) |
| **Sex** | |
| Male only | 6 (15) |
| Female only | 1 (2.5) |
| Both | 32 (80) |
| Not reported | 1 (2.5) |
| **Age (years)*** | 58.3 (47-81) |
| **Diagnosis** | |
| CHD | 28 (70) |
| HF | 10 (25) |
| Both | 2 (5) |
| **Follow up (months)** | 12 (1.5-120) |

* Median of study means

### *2.4.3 PA measures reported*

In total, 28 studies measured PA using subjective approaches, 10 studies used objective methods and two studies used a combination of both. Across all studies, 45 different PA metrics were used (median 1.5, range 1–10). Details of individual study PA measurement methods including a summary is presented in appendix 2.5.

### *2.4.4 Risk of bias assessment*

Risk of bias assessments for each study are summarised in figure 2.2. All studies were assigned high risk in blinding of participants and personnel due to the nature of CR. The most prevalent methodological issues were non-adequate description of randomisation (25/40, 62.5%), allocation concealment (27/40, 67.5%) and blinding of PA outcome assessment (26/40, 65%). There was high risk of bias in 50% (20/40) trials for incomplete outcome data. Most trials were low risk for selective reporting (33/40, 82.5%), balanced groups at baseline (34/40, 85%) and were free of cointerventions (35/40, 87.5%).

| | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data addressed | Selective reporting | Groups balanced at baseline | Both groups received the same treatment except intervention |
|---|---|---|---|---|---|---|---|---|
| Astengo et al. 2010 [40] | ? | ? | - | ? | + | ? | + | + |
| Bengtsson 1983 [33] | ? | ? | - | ? | - | + | + | + |
| Bertie et al. 1992 [41] | ? | ? | - | ? | - | + | + | + |
| Borland et al. 2014 [14] | + | + | - | + | + | + | + | + |
| Carlsson et al. 1997 [29] | ? | ? | - | ? | + | + | + | + |
| Cowie et al. 2011 [17] | ? | + | - | + | - | + | - | + |
| DeBusk et al. 1979 [42] | ? | ? | - | ? | + | + | + | - |
| Devi et al. 2014 [18] | + | + | - | + | + | + | + | + |
| Engblom et al. 1992 [24] | ? | ? | - | + | + | + | + | + |
| Erdman et al. 1986 [30] | + | ? | - | ? | - | + | ? | - |
| Gottlieb et al. 1999 [43] | ? | ? | - | ? | + | - | + | + |
| Gulanick 1991 [44] | ? | ? | - | ? | + | + | + | ? |
| Hämäläinen et al. 1989 [25] | ? | ? | - | ? | - | - | + | + |
| Hambrecht et al. 1993 [19] | ? | ? | - | ? | - | + | + | + |
| Heath et al. 1987 [20] | ? | ? | - | ? | ? | + | - | - |
| Higgins et al. 2001 [13] | ? | ? | - | ? | - | + | + | - |
| Houle et al. 2011 [15] | + | ? | - | ? | - | + | + | + |
| Lidell & Fridlund 1996 [31] | ? | ? | - | ? | - | + | + | + |
| Maddison et al. 2015 [45] | + | ? | - | + | + | - | + | + |
| Mueller et al. 2007 [21] | ? | ? | - | ? | - | + | + | + |
| Naser et al. 2008 [46] | + | + | - | ? | + | + | + | + |
| Oldenburg et al. 2014 [47] | ? | ? | - | ? | + | + | + | + |
| Oliveira et al. 2014 [22] | + | + | - | + | - | - | + | + |
| Ornish et al. 1998 [48] | ? | ? | - | + | - | + | + | + |
| Otterstad et al. 2003 [28] | ? | + | - | ? | ? | + | + | + |
| Reid et al. 2011 [16] | + | + | - | + | - | + | + | + |
| Ribeiro et al. 2012 [23] | + | + | - | + | + | - | + | + |
| Senden et al. 2005 [49] | ? | ? | - | ? | - | + | + | + |
| Sivarajan et al. 1982 [50] | + | ? | - | ? | - | + | + | + |
| Ståhle et al. 1999 [51] | ? | ? | - | ? | + | + | + | + |
| Todd & Ballantyne 1992 [52] | + | ? | - | ? | - | + | - | + |
| Toobert et al. 1998 [53] | ? | ? | - | ? | + | - | + | + |
| Van den Berg-Emons et al. 2004 [54] | ? | ? | - | ? | ? | + | - | + |
| Wall et al. 2009 [55] | ? | ? | - | ? | - | + | + | + |
| Wang et al. 2016 [56] | + | + | - | ? | + | + | + | + |
| West et al. 2012 [27] | ? | + | - | + | + | + | + | + |
| Willenheimer et al. 2001 [57] | ? | ? | - | + | - | + | + | + |
| Witham et al. 2007 [58] | + | + | - | + | - | + | + | + |
| Witham et al. 2012 [59] | + | + | - | + | + | + | - | + |
| Zwisler et al. 2008 [32] | + | + | - | + | - | + | + | + |

Figure 2.2: Quality appraisal. + (green), low risk of bias; ? (yellow), unclear risk of bias; − (red), high risk of bias. [40-59]

### *2.4.5 Impact of CR participation on PA levels*

*Vote counting*

A total of 145 CR versus control PA comparisons were reported across all studies (appendix 2.6). Overall, 26% of results showed a statistically significant improvement in PA with CR (table 2.2).

Table 2.2: Vote counting

| **Direction of result** | **Number of results (%)** |
|---|---|
| PA in CR same as control (P>0.05) | 100 (69%) |
| PA in CR higher than control (P≤0.05) | 38 (26%) |
| PA in control higher than CR (P≤0.05) | 2 (1%) |
| PA difference between CR and control not clear (no P-value reported) | 5 (3%) |
| Total | 145 |

*Stratified analysis*

The pattern of results was similar whether PA measurement was objective or subjective (appendix 2.7). The statistical methods used across the studies were varied. The majority reported a p value for between-group differences. Comparing the direction of results by statistical method showed a greater number of positive results reported when the p value for interaction time×group was used (appendix 2.8). As numbers were small, this is unlikely to be of significance.

There was a higher proportion of non-significant results (86% vs 63%) and fewer positive results (10% vs 32%) in studies including patients with HF compared with studies with CHD (appendix 2.9). Removing the results from studies conducted prior to 1990 or those based on exercise frequency did not affect the direction of results (appendix 2.10).

*CR intervention*

Table 2.3 shows an increased number of positive results with home-based CR interventions compared with centre-based interventions. Studies with a higher exercise dose also produced a slightly increased number of positive results compared with studies with a lower exercise dose (appendix 2.11). The pattern of results was similar when comparing studies of comprehensive CR to exercise-only CR studies (appendix 2.12).

Table 2.3: vote counting – comparing centre based cardiac rehabilitation (CR) to home based CR and combined RCTs

| **Direction of result** | **Number of results** | | |
|---|---|---|---|
| | **Centre based CR intervention** | **Home based CR intervention** | **Combined centre and home based or RCT included both** |
| PA in CR same as control (P>0.05) | 63 (77%) | 22 (51%) | 15 (75%) |
| PA in CR higher than control (P≤0.05) | 15 (18%) | 19 (44%) | 4 (20%) |
| PA in control higher than CR (P≤0.05) | 1 (1%) | 0 | 1 (5%) |
| PA difference between CR and control not clear (no P-value reported) | 3 (4%) | 2 (5%) | 0 |
| Total | 82 | 43 | 20 |

### *2.4.6 Meta-analyses*

*Steps/day*

Five studies used mean steps/day as a measure of PA assessed by either pedometer [14–16] or accelerometer. [17, 18] Pooling results across studies showed compared with control, CR participation was associated with an

increase in mean steps/day (1423, 95% CI 757.07 to 2089.43, p<0.0001; figure 2.3) at short-term follow-up (median 3, range 1.5–12 months). With no evidence of statistical heterogeneity ($I^2$=0%, p=0.845).

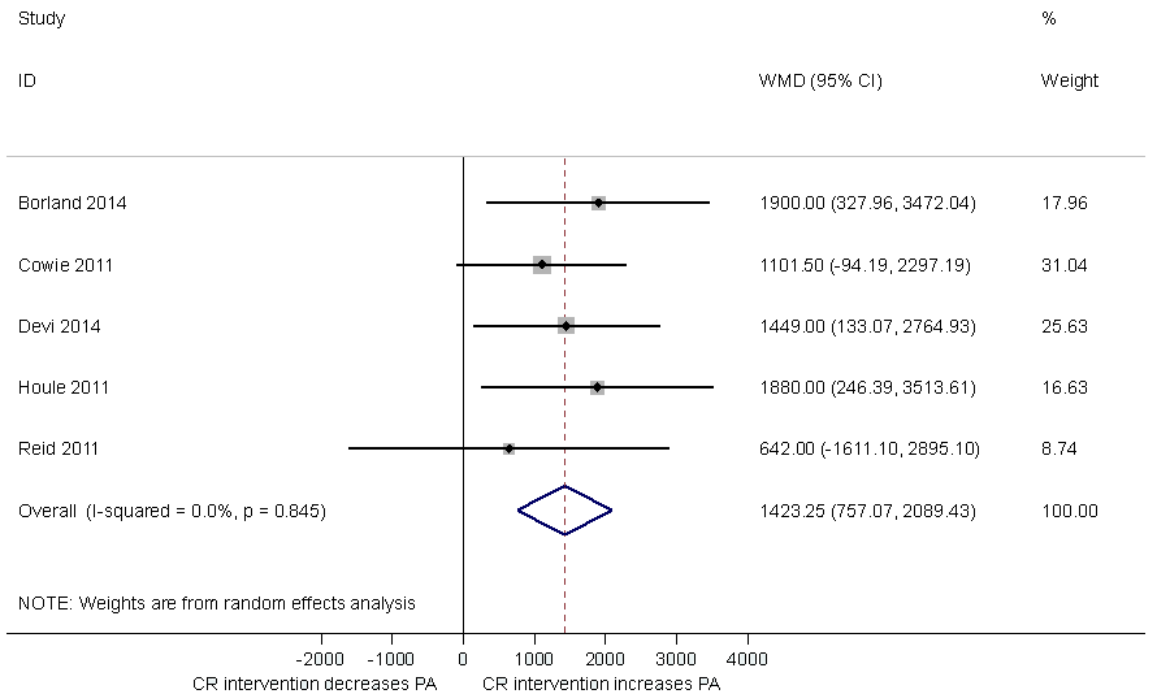


Figure 2.3: Impact of cardiac rehabilitation on mean steps/day at short-term follow-up (median 3 months, range 1.5–12 months). CR, cardiac rehabilitation, PA, physical activity; WMD, weighted mean difference.

*Energy expenditure*

Energy expenditure (kcal/week) was estimated via questionnaire in three studies (median follow-up time 12 months, range 32 weeks–72 months). [19–21] Meta-analysis showed that CR participation was associated with an increase in energy expenditure compared with control (878.4, 95% CI 433.83 to 1323.01, p=0.0001). Test for statistical heterogeneity was significant ($I^2$=70%, p=0.04).

*Sedentary time, light PA and moderate–vigorous PA (min/day)*

There was no impact on mean min/day spent sedentary or sitting between CR and control (−10.9, 95% CI −39.02 to 17.20, p=0.45; figure 2.4A) based on two

studies estimating this objectively via accelerometer [14, 18] and subjectively via International Physical Activity Questionnaire (IPAQ), [22] at 9 weeks follow-up (median, range 6–12 weeks). There was no evidence of a difference in mean min/day spent in light intensity PA in CR compared with control (−6.6, 95% CI −45.09 to 31.92, p=0.74; figure 2.4B) based on two studies reporting this outcome via accelerometer [23] and IPAQ, [22] at 9.5 weeks follow-up (median, range 9–10 weeks). There was no difference in mean min/day spent in moderate–vigorous PA in CR compared with control (8.5, 95% CI −1.44 to 18.44, p=0.09; figure 2.4C), measured via accelerometer [18, 23] and IPAQ, [22] at 9 weeks follow-up (median, range 6–10 weeks).

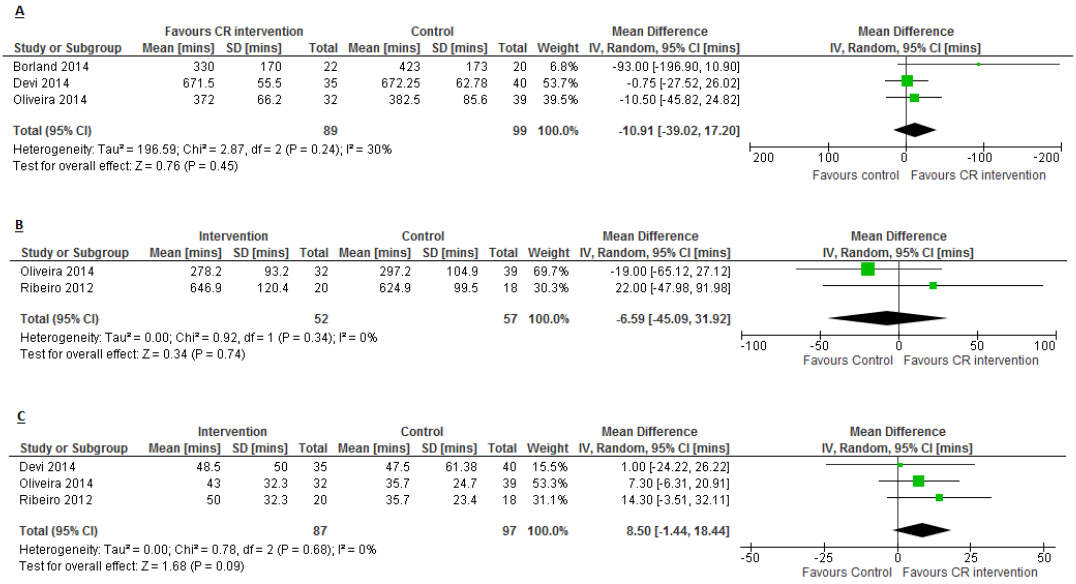


Figure 2.4: Impact of cardiac rehabilitation on (A) min/day spent sedentary or sitting; (B) min/day spent in light intensity PA and (C) min/day spent in moderate–vigorous PA.

*Proportion of patients categorised as physically active (short-term follow-up ≤12 months)*

CR increased the proportion of patients categorised as 'physically active', measured at short-term follow-up (median 6 months, range 0–12 months) across nine studies (RR 1.55, 95% CI 1.19 to 2.02, p=0.001; figure 2.5A). There was evidence of substantial statistical heterogeneity ($I^2$=87%, p<0.00001). The

definition of ‘physically active’ varied across studies: that is, exercise frequency ≥3×/week, [24] exercising ≥3×/week for 20 min, [25, 26] exercising >100 kcal/day, [27] average daily steps >7500,15 exercising for >1 hour/week, [28] regularly training (defined as either walking or cycling ≥30 min daily, sport activities once weekly or vigorous physical training) [29] and two studies did not provide any definition. [30, 31]

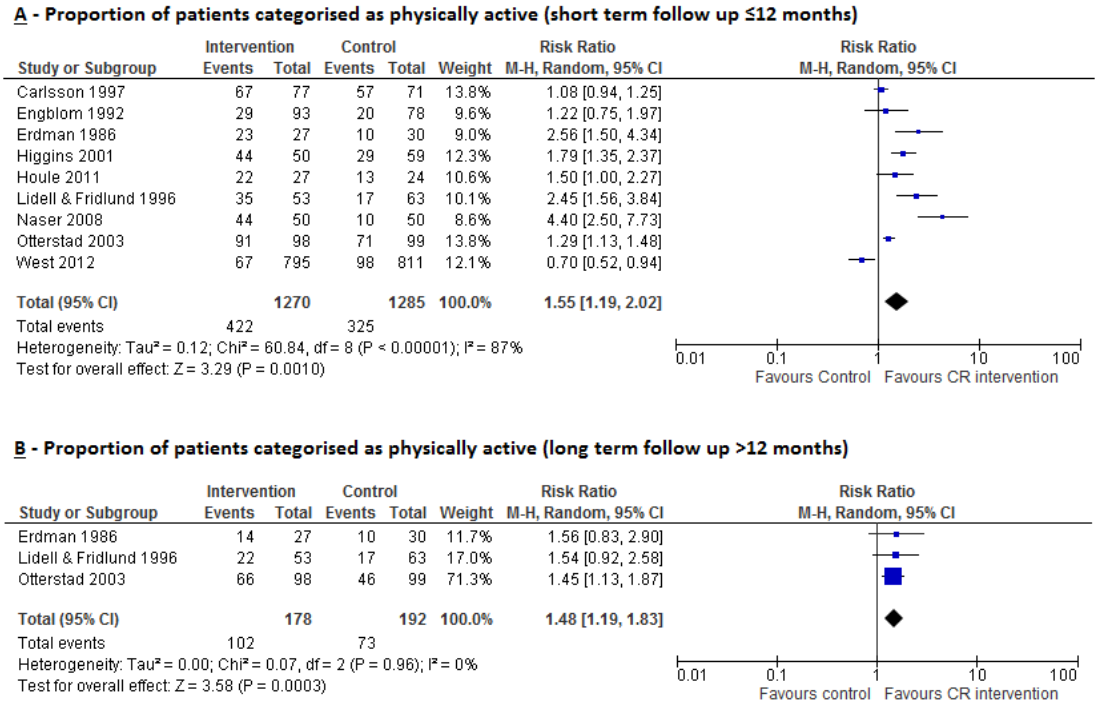


Figure 2.5: Impact of cardiac rehabilitation on proportion of patients categorised as physically active measured at (A) short-term follow-up (≤12 months) and (B) long-term follow-up (>12 months).

*Proportion of patients categorised as physically active (long-term follow-up >12 months)*

CR increased the proportion of patients considered physically active, measured at long-term follow-up (median 5 years, range 2–5 years) in three studies [28, 30, 31] (RR 1.48, 95% CI 1.19 to 1.83, p=0.0003; figure 2.5B) with no evidence of statistical heterogeneity ($I^2$=0.0%, p=0.96).

*Proportion of patients categorised as sedentary or not physically active*

Five studies reported the proportion of patients considered sedentary, [29] exercising <4 hours per week [32] or undertaking no exercise, [24, 28, 33] at 12 months (median, range 12–24 months) follow-up. There was a reduction in CR participants categorised as sedentary or not physically active (RR 0.76, 95% CI 0.61 to 0.95, p=0.02), with no evidence of statistical heterogeneity ($I^2$=36%, p=0.18).

## 2.5 Discussion

This systematic review of RCTs shows moderate evidence of an increase in PA with CR participation with 26% (38/145) of comparisons reporting a statistically significant result in favour of CR compared with control. This pattern of results appear consistent regardless of whether studies assessed PA using subjective or objective methods, or the CR intervention was comprehensive or exercise only. Studies involving patients with HF appeared less likely to have positive results in favour of CR. There was an increased proportion of positive results with higher doses of CR suggesting that higher doses of exercise training may be more effective in improving PA levels. Similarly, results suggest that home-based interventions may be more effective in improving PA levels.

Meta-analyses showed that CR participation compared with control is associated with an increase in some PA outcomes: steps/day at short-term follow-up, energy expenditure (kcal/week) at short-term follow-up, proportion of patients categorised as physically active both at short-term and long-term follow-up and reduced proportion of patients categorised sedentary or not physically active at short-term follow-up. CR was not shown to have a significant impact on minutes/day spent sedentary or in light or moderate-vigorous PA at short-term follow-up.

It remains uncertain if the mean increase of 1423 steps/day that we observed with CR is clinically meaningful. In patients with chronic obstructive pulmonary disease undergoing rehabilitation, the minimal clinically important difference (MCID) was calculated to lie between 600 and 1100 steps/day and resulted in a reduction in hospital admissions. [34] However, we know of no published MCID for patients with CHD or HF.

We believe there are two potential reasons why we saw improvements in some outcomes, but not others. First, categorising continuous PA data to PA categories (eg, sedentary, light moderate or vigorous) may have resulted in a loss of sensitivity to change. Second, some studies may have been susceptible to measurement bias as they used subjective PA measures.

### *2.5.1 Comparison of findings to previous studies*

Our results build on previous systematic reviews [10, 11] that found some evidence to indicate that CR positively impacts on PA in patients with CHD, but little evidence in long term and recommended CR programmes place more emphasis on improving the long-term PA levels of patients. [10] Ter Hoeve et al concluded that centre-based CR was not sufficient to improve and maintain PA levels and suggested home-based CR programmes may be more successful; however, literature is limited in this area. [11] In accord with recent Cochrane systematic reviews of CR, [9, 10] the participating patients were relatively young (<60 years), predominantly male, with large differences in the programme location, duration, intensity, modality and length of follow-up.

### *2.5.2 Strengths and limitations*

We believe this to be the first meta-analysis to assess the impact of CR on PA levels of patients with both CHD and HF. Strengths of this review include extensive literature searches, use of RCTs and inclusion of both subjective and objective PA assessment. Compared with the previous systematic reviews, we identified an additional 23 RCTs (2432 additional patients), 10 of which specifically involved patients with HF (655 patients).

However, this review has limitations. With the wide range of PA outcomes reported across the studies, at various follow-up time points, we were limited in the extent of meta-analysis we were able to complete. That only small numbers of studies were suitable for inclusion in the meta-analysis, limits our ability to draw firm conclusions from these pooled results. Vote counting was done to give a quantitative overview of the results. However, this method has limitations: (1) large and small studies carry the same weight, (2) studies reporting multiple PA outcome results contribute more weight and (3) results from multiple outcomes within study may not be independent. Furthermore, judgements by

the authors on levels of PA were not based on national recommendations, leading to uncertainty about the clinical meaningfulness of PA improvements.

Key issues raised in risk of bias assessments were insufficiently described randomisation and allocation concealment procedures, leading to difficulty rating the quality of the RCTs. Additionally, 65% of studies had unclear risk of bias with regard to blinding of outcome assessment. This is particularly important in PA measurement since awareness of being assessed may cause both the intervention and control group patients to alter their behaviour and increase their PA on assessment days, potentially introducing bias to results. Small study numbers meant we were unable to generate a funnel plot to assess potential publication bias.

There were numerous limitations in approaches studies took to assessing PA. Where questionnaires were used, few had been evidently validated for use in cardiac populations. Self-report commonly considered the frequency of exercise sessions undertaken as opposed to overall PA per se. Self-reported measures of PA are less valid and reliable than direct measures in patients with CR, generally overestimating PA and relying on patient recall. [35] Despite accelerometers being the most commonly used objective PA measurement method, a variety of devices were used, with sensors placed at different body sites, and a wide range of outcome metrics reported across studies, limiting the ability to meta-analyse these data. Additionally, data handling methods were poorly reported; no studies adequately explained the minimum wear time requirement for inclusion in data analysis or data reduction techniques. Where accelerometer thresholds were used to estimate intensity, they were derived from studies in young, healthy adults which may mean the PA level is underestimated in patients with cardiac disease. [36] Resting metabolic rate in patients with cardiac disease has been previously demonstrated to be significantly lower (23%–36%) than the typically utilised value of 3.5 mL/kg/min, [37] which may have implications in underestimating energy expenditure during higher intensity activities. Therefore, researchers should consider using thresholds specifically established for patients with cardiac disease.

There was inconsistency in statistical methods used across the studies. Baseline adjusted regression methods are recommended for analysis of RCTs.

[38] However, only 35% reported a p value that took the baseline PA level into account. Although many studies showed between group differences in fitness outcomes, 26% of results demonstrated a statistically significant difference in PA outcomes. This is likely because individual studies were often small and underpowered to detect small differences in PA. Only 13 (32%) of the included studies included formal sample size calculations and of these only 4 (31%) were based on PA outcomes.

### *2.5.3 Implications for clinical practice and future research*

That our results showed no difference in PA outcomes in studies that employed comprehensive CR compared with exercise-only CR suggest that improvements in PA with CR are the result of exercise training rather than components of education and psychosocial interventions. Improved reporting of adherence and intervention fidelity would provide useful information to further understand the efficacy of comprehensive CR intervention components. Additionally, improvement in exercise capacity may not be directly related to increases in PA levels. CR programmes should consider supplementing their existing exercise-training intervention with interventions that specifically aim to increase PA level. For example, the ongoing PATHway I trial, where the basis of the CR intervention is PA promotion and the primary outcome is objectively measured PA level. [39]

Further research is required to validate interventions that promote PA in cardiac populations. Furthermore, objective measurement of PA requires population-specific calibration studies to establish intensity thresholds. The use of inconsistent PA measures and units made formal pooling of data problematic. We therefore recommend that future studies use objective measures of PA such as accelerometers, be statistically powered to detect small differences in PA, use appropriate data handling and analysis methods, and PA outcomes are reported in relation to national PA recommendations. Studies should assess PA outcomes over the long term.

## 2.6 Conclusions

This systematic review and meta-analysis provides moderate evidence of an increase in PA with CR participation compared with control. However, the included trials were at risk of bias, and the quality of PA assessment and reporting was relatively poor. It is unclear whether increases in PA with CR are clinically meaningful. Further high-quality trials are required to assess if CR leads to important improvements in PA, such as the UK recommended target of 150 min of moderate intensity PA per week, especially in long term.

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# Chapter 3: Physical activity assessment by accelerometry in people with heart failure

## 3.1 Abstract


Background

International guidelines for physical activity (PA) recommend at least 150 minutes per week of moderate-to-vigorous PA (MVPA). There is yet to be consensus on the most appropriate way to categorise raw accelerometer data into behaviourally relevant metrics such as intensity, especially in chronic disease populations. Therefore the aim of this study was to estimate acceleration values corresponding to inactivity and MVPA during daily living activities of patients with heart failure (HF), via calibration with oxygen consumption (VO2) and to compare these values to previously published PA intensity thresholds.

Methods

Twenty-one adults with HF (mean age 71±14 years) undertook a range of daily living activities (including laying down, sitting, standing and walking) whilst measuring PA via wrist- and hip-worn accelerometers and VO2 via indirect calorimetry. Raw accelerometer output was used to compute PA in units of milligravity (mg). Energy expenditure across each of the activities was converted into measured METS (VO2/resting metabolic rate) and standard METS (VO2/3.5 ml/kg/min). PA energy costs were also compared with predicted METS in the compendium of physical activities. Location specific activity intensity thresholds were established via multilevel mixed effects linear regression and receiver operator characteristic curve analysis. A leave-one-out method was used to cross-validate the thresholds.

Results

Accelerometer values corresponding with intensity thresholds for inactivity (<1.5METS) and MVPA (≥3.0METS) were >50% lower than previously published intensity thresholds for both wrists and waist accelerometers

(inactivity: 16.7 to 18.6mg versus 45.8mg; MVPA: 43.1 to 49.0 mg versus 93.2 to 100 mg). Measured METS were higher than both standard METS (34-35%) and predicted METS (45-105%) across all standing and walking activities.

Conclusion

HF specific accelerometer inactivity and MVPA intensity thresholds are lower than previously published thresholds based on healthy adults, due to lower resting metabolic rate and greater energy expenditure during daily living activities for HF patients.

### 3.2 Background

Accurate monitoring of physical activity (PA) is increasingly important as exemplified by PA being a stated a key target in the lifestyle recommendations to heart failure (HF) patients. [1] Progressively, clinical trials are relying on accelerometers to objectively measure PA to investigate the relationship between PA and HF disease progression, [2] or to evaluate the effect of a PA or exercise programme in primary or secondary prevention in HF. [3] However, there is yet to be consensus on the most appropriate way to convert raw acceleration data into behaviourally relevant metrics, particularly in chronic disease populations.

International PA recommendations for public health and cardiac patients are based on time spent in moderate-to-vigorous PA (MVPA). In order to derive this information from accelerometers, the raw data must be categorised into levels of intensity using thresholds or cut-points derived from calibration studies. Previous studies in HF patients have tended to use proprietary outcomes, ‘activity counts’, and/or applied previously published intensity thresholds to express time spent in MVPA. [4-8] These proprietary outcomes and thresholds are typically based on calibration studies in young, healthy individuals. Applying these thresholds to HF patients assumes the energy cost for a given activity is the same for everyone, which may lead researchers to underestimate PA levels of people with HF due to the lack of consideration for an individual’s exercise

tolerance. [9] Therefore recent publications have called for population specific calibration studies. [9,10]

We conducted a laboratory-based calibration study to estimate acceleration values for hip- and wrist-worn accelerometers corresponding to inactivity and MVPA in patients with HF, by calibrating with oxygen consumption ($VO_2$) and comparing derived thresholds to current generic intensity thresholds.

## 3.3 Methods

### *3.3.1 Participants*

A sample of 22 adults with HF were recruited from the Royal Devon and Exeter NHS Foundation Trust between March 2018 and October 2018. Inclusion criteria were adult (≥18 years) outpatients with a diagnosis of HF confirmed by a hospital specialist, New York Heart Association (NYHA) class I to III symptoms, who were able to give informed consent. Exclusions were: acute decompensated HF, contraindication to exercise testing or PA, resident in a long term care facility, unwilling or unable to travel to the research site, patients unable to understand the study information, and judged unable to participate for any other reason.

The study protocol conforms to the 1975 Declaration of Helsinki, ethical approval was granted by Cambridge South Research Ethics Committee (18/EE/0019), and the trial registration ID is: NCT03659877. Participants gave informed consent prior to data being collected.

### *3.3.2 Activities*

Participants attended the sports science laboratory at University of Exeter St Luke's campus in the UK. They were asked to not eat or drink caffeinated or calorie containing foods or drinks prior to the visit which was scheduled in the morning, and instructed to take their medication as normal. The laboratory protocol consisted of a series of activities (listed in order of completion below), chosen based on previous calibration studies [7-8,11] and to be representative of daily living activities for HF patients, selected with the help of a local HF patient and public involvement group.

- Laying down on a bed for 30 minutes,
- Sitting on the bed for 5 minutes,
- Incremental shuttle walk test (ISWT) performed until stopping criteria met, [12-13]
- Sitting watching TV for 5 minutes,
- Standing washing & drying dishes for 5 minutes,
- Sitting quietly for 5 minutes,
- Walking at a pace perceived to be light for 3-5 minutes,
- Walking at a pace perceived to be moderate for 3-5 minutes,
- Light pace walk carrying 2x1.5kg shopping bags for 3-5 minutes.

Resting metabolic rate (RMR) was measured during minutes 10-20 of a 30 minute period laying down in low- or semi-Fowler's position (as per patient preference). [14] Breakfast was then provided prior to any physical activities being performed. ISWT was performed to measure exercise capacity and gauge rating of perceived exertion (RPE) over the completed stages, which informed the light (RPE 11) and moderate (RPE 13) walking paces.

Standardised instructions were given prior to the test, and no encouragement given throughout. [12-13] Stopping criteria were when the participant was too breathless to continue, or unable to maintain the required speed.

The duration of each activity was chosen to optimise the likelihood of steady state metabolism being achieved. Patients unable to complete 5 minutes walking did a minimum of 3 minutes. At the end of the ISWT and each walking activity, participants were asked to sit and rest quietly until they felt ready to complete the next task. Other activities had a 1 minute transition period. Participants that used walking aids in their daily life, were allowed to do so throughout the activities as required. The patient visit lasted approximately 3 hours in total.

### *3.3.3 Measures*

Prior to the activities, weight was measured without shoes, to the nearest 0.1kg using an electronic scale (Seca, Hamburg, Germany), height was measured without shoes to the nearest 0.1cm using a stadiometer (Seca, Hamburg, Germany) and blood pressure was assessed using a manual

sphygmomanometer (Accoson, England). Body mass index was calculated using weight and height ($kg/m^2$).

Throughout each activity, participants wore 3 GENEActiv accelerometers (Activinsights, Kimbolton, UK); one on each wrist, secured using a watch strap; and on the waist, placed on the left iliac crest, secured using an elasticated waist band. GENEActiv accelerometers measure acceleration between -8g and 8g, and recorded raw triaxial acceleration at 100Hz. The GENEActiv accelerometer has been validated for both hip- and wrist-worn measurement of PA, and to distinguish between inactivity, light PA, and MVPA in healthy adults. [15]

VO2 was measured throughout each activity with a portable Oxycon mobile breath-by-breath ergospirometry system, (VIASYS Healthcare GmbH, Hoechburg, Germany). This system has been shown to be a reliable and valid method of measuring energy expenditure. [16] Standardised gas and volume calibration was performed within one hour before each participant visit according to manufacturer's specifications. [17] The flow meter was calibrated automatically. $VO_2$ was expressed in millilitres per kilogram per minute (ml/kg/min).

Before starting any activities, participants were instructed on how to use the Borg 6-20 RPE scale, [18] which was reported during the last 30 seconds of each ISWT level and during the last minute of all other activities.

### *3.3.4 Data reduction*

Immediately after testing was completed, the accelerometers and ergorespirometry system were removed and data were downloaded to a personal computer.

*Oxygen consumption data*

$VO_2$ was averaged over minutes 10-20 of lying down, over the last 30 seconds of each stage of the ISWT, and over the last minute of all other activities. $VO_2$ data for each individual for each activity was converted into metabolic equivalents (METS) in two different ways; standard METS calculated using the standard formula ($VO_2$/3.5ml/kg/min), and measured METS using each

individual participants measured RMR ($VO_2$/RMR). Predicted METS for each activity were taken from the compendium of physical activities. [19]

*Accelerometer data*

GENEActiv data were downloaded using GENEActiv PC software (version 3.2; Activinsights, Kimbolton, Cambridge, UK) and averaged over 5 second epochs, which is considered adequate for reporting different activities. [20]

Each axis (x, y, z) of the raw tri-axial data was multiplied by 1000 to transform the signals from g to milligravity units (mg), to ensure the subsequent accelerometer thresholds would be comparable to prior literature. Raw tri-axial data were then summarized into a single vector magnitude using three common approaches, which are described in table 3.1.

As other studies have identified, at low magnitude of acceleration, ENMO returned a high frequency of 0's, making it severely limited in classifying inactivity and light PA. [23] Therefore ENMO was excluded from further analysis.

In line with the $VO_2$ data, MAD and SVM values were averaged over minutes 10-20 of lying down, the last 30 seconds of each ISWT stage, and the last minute of all other activities.

Table 3.1: Details of the three data reduction approaches used in this study

| Data reduction approach | Description | Strengths/Limitations |
|---|---|---|
| Gravity-subtracted sum of vector magnitudes (SVM) [19]<br>$SVM = \frac{1}{n} \times \sum \lvert\sqrt{x^2 + y^2 + z^2} - 1000\mathrm{m}g\rvert$ | Vector magnitude is calculated in each epoch and 1000mg is subtracted. When the accelerometer is static and the earth's gravitation pull is the only acceleration, the result is 0. | Gravity correction taken into account within the algorithm.<br>Rotation invariant.<br>The absolute value of negative vector magnitudes are used,<br>Fewer studies have used this method, so comparability is more limited. |
| Mean amplitude deviation (MAD) [25]<br>$MAD = \frac{1}{n} \times \sum \lvert r_i - \bar{r}\rvert$<br>Where;<br>$r_i = \sqrt{x_i^2 + y_i^2 + z_i^2}$ | Describes the typical distance of data points around the mean. Represents the mean value of the dynamic acceleration component. | Gravity correction taken into account within the algorithm.<br>Rotation invariant.<br>Appears to account well for calibration error. |

| | | |
|---|---|---|
| $period\ of\ interest$ | | Fewer studies have used this method, so comparability is more limited. |
| Euclidean Norm Minus One (ENMO) [26]<br><br>$ENMO = \sqrt{x^2 + y^2 + z^2} - 1000\mathrm{m}g$ | Vector magnitude is calculated in each epoch and 1000mg is subtracted. Negative ENMO values rounded to 0 | Gravity correction taken into account within the algorithm.<br><br>Rotation invariant.<br><br>More widely used in studies, and is the output from the only currently available open source accelerometer data processing package, GGIR.<br><br>Sensitive to poor calibration.<br><br>Negative values are rounded up to zero, hypothesised that this corrects for errors in subtraction in gravitational component.<br><br>Studies shown that ENMO less sensitive at low levels of movement. |

### *3.3.5 Data analysis*

Conservatively assuming a ROC AUC of 0.85 (based on lowest AUC previously reported, [7-8,11] and assumed null AUC of 0.5 (no association) at 90% power and 5% alpha, a minimum sample size of 18 patients was required.

Based on methods used in previous calibration studies [7-8,11] we used a combination of receiver-operator characteristic (ROC) analysis and mixed effects regression model analysis methods to establish accelerometer thresholds for inactivity (<1.5 METS) and MVPA (≥3 METS). Because of the low exercise capacity of HF patients, a threshold for vigorous intensity was not generated. Data from the ISWT were not included in the threshold generation analysis due to the short interval times for each ISWT level, and the small numbers of participants that reached the latter stages.

Correlations between SVM, MAD and METS were checked using Pearson's correlation and interpreted according to Cohen's effect size i.e. weak, r=0.1 to 0.29; moderate r=0.3 to 0.49; strong r≥0.5.

ROC analysis was performed using the 'roctab' and 'roccomp' STATA commands. The continuous MET values were coded into the following intensity categories: inactivity (<1.5 METS: yes/no), MVPA (≥3.0 METS: yes/no) to create binary indicators. The mg values that maximised the combination of sensitivity and specificity were selected as the threshold values. AUC values for each ROC curve calculated were defined as excellent (≥0.90), good (0.80-0.89), fair (0.70-0.79), poor (0.60-0.69) or failure (<0.60).

Multilevel mixed effects linear regression modelled the accelerometer-derived mg values across the range of METS achieved during the different activities. This analysis was performed using the 'xtmixed' STATA command where METS was entered into the model as both a fixed and random effect. This allowed the 'mg against METS' slopes and intercepts to vary between individuals. The resulting regression equation was used to calculate intensity thresholds for inactivity (<1.5 METS) and MVPA (≥3.0 METS). A different model was produced for each combination of 'body location by 'mg' method' separately.

Sensitivity analyses were undertaken to explore the impact of excluding participants that used a walking aid, as this may have affected accelerometer readings, and excluding washing up as an activity, as this involves high levels of wrist movement, but little waist movement.

In order to validate the derived intensity thresholds a leave-one-out method was used. One observation was left out and used as the test dataset, and a multilevel mixed effects linear regression model was fitted and used to predict the left out observation, this was then repeated sequentially for all possible observations. A median split of the actual acceleration values and the predicted values were cross-tabulated to obtain a 'percentage of correct predictions'.

We applied both the derived thresholds and the Hildebrand thresholds to a baseline accelerometer measured PA data set of 247 HF patients recruited to two home-based cardiac rehabilitation randomised controlled trials, details of which are published elsewhere. [3,24] Cohen's K was run to determine the level of agreement between the derived HF specific intensity thresholds and Hildebrand thresholds for classing patients as meeting current PA guidelines.

Statistical analyses were performed using Stata (V.15.0; StataCorp, College Station, Texas, USA). Leave-one-out cross validation analysis was performed using the R programming language and environment (V3.6.1). All data are expressed as mean values and standard deviations unless otherwise stated. The level of significance was set at $p<0.05$.

### 3.4 Results

Table 3.2 details the characteristics of the study participants.

Table 3.2: Patient characteristics

| Characteristic | N= 22 patients<br>Mean ± SD unless otherwise stated |
|---|---|
| Male (n, %) | 17 (77) |
| Age (years) | 70.7 ± 14.1 |
| Body Mass Index (kg/m$^2$) | 28.1 ± 4.4 |
| LVEF (%) | 34.5 ± 14.0 |
| Reduced LVEF <40% (n, %) | 14 (64) |
| Mid-range LVEF 40-49% (n, %) | 4 (18) |
| Preserved EF ≥50% (n, %) | 4 (18) |
| NYHA class (n, %) | |
| I | 1 (4) |
| II | 18 (82) |
| III | 3 (14) |
| IV | 0 |
| Dilated cardiomyopathy (n, %) | 14 (64) |
| Ischaemic heart disease (n, %) | 8 (36) |
| ICD/CRT/Pacemaker (n, %) | 13 (59) |
| ACE/ARB/ARNI (n, %) | 21 (95) |
| Beta-blocker (n, %) | 22 (100) |
| MRA (n, %) | 14 (64) |
| Loop diuretic (n, %) | 17 (77) |
| Hypertension (n, %) | 11 (50) |
| Diabetes (n, %) | 6 (27) |
| COPD (n, %) | 4 (18) |
| Arthritis (n, %) | 2 (9) |
| AF (n, %) | 11 (50) |
| Stroke (n, %) | 5 (23) |
| Comorbidities (hypertension, diabetes, COPD, arthritis, AF, stroke) (n, %) | 6 (27) |
| 0 comorbidity | 4 (18) |
| 1 comorbidity | 5 (23) |

| | |
|---|---|
| 2 comorbidities | 4 (18) |
| 3 comorbidities | 3 (14) |
| 4+ comorbidities | |
| ISWT distance (m) | 286.4 ± 190.6 |
| RMR (mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) | 2.67 ± 0.66 |

Data presented as mean ± standard deviation or as number (percentage). LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronisation therapy; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin II receptor blocker neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; ISWT, incremental shuttle walk test.

### *3.4.1 Accelerometry and METS*

All participants completed all activities within the study protocol. All three accelerometers failed to record for one participant so they were omitted from analysis. For a second participant, the left wrist accelerometer failed to record, so only their right wrist and waist data was included.

Accelerometer outputs (SVM and MAD), METS (standard, measured and predicted), and RPE scores for each of the activities are reported in table 3.3. For all activities, measured METS were 33-35% higher than standard METS. Similarly, measured METS were (7-105%) higher than the compendium predicted METS. [19]

Table 3.3: Mean (SD) accelerometer output via SVM and MAD calculations, METS calculated via measured and standard formula, and RPE score for each activity performed

| Physical activity (N=21) | Accelerometer values: SVM | | | Accelerometer values: MAD | | | METS (measured RMR)* | METS (standard RMR)† | Predicted METS‡ | RPE score |
|---|---|---|---|---|---|---|---|---|---|---|
| | Right wrist (m*g*) | Left wrist (m*g*) | Waist (m*g*) | Right wrist (m*g*) | Left wrist (m*g*) | Waist (m*g*) | | | | |
| Laying down | 4.7 (1.9) | 4.8 (2.3) | 3.7 (0.8) | 3.3 (4.7) | 2.1 (4.2) | 0.4 (0.3) | 1.0 (0.0) | 0.8 (0.2) | 1.0 | 6.5 (1.2) |
| Sitting (fasted) | 7.3 (2.7) | 8.7 (4.8) | 4.3 (0.9) | 13.0 (19.9) | 13.8 (13.6) | 0.6 (0.5) | 1.2 (0.2) | 0.9 (0.2) | 1.3 | 6.5 (1.1) |
| Sitting watching TV | 8.4 (3.2) | 6.6 (2.8) | 4.1 (0.9) | 14.3 (14.1) | 10.4 (12.2) | 0.9 (1.5) | 1.3 (0.2) | 1.0 (0.2) | 1.3 | 6.4 (0.8) |
| Standing washing & drying dishes | 74.4 (22.4) | 55.1 (18.9) | 8.7 (2.5) | 54.3 (24.7) | 45.4 (16.7) | 2.0 (2.7) | 2.6 (0.5) | 1.9 (0.4) | 1.8 | 8.9 (2.3) |
| Sitting quietly | 9.8 (4.8) | 14.4 (14.1) | 4.3 (1.0) | 18.5 (24.0) | 34.8 (35.0) | 0.8 (0.7) | 1.4 (0.2) | 1.1 (0.3) | 1.3 | 7.1 (1.7) |
| Light pace walk (average pace 1.6 mph) | 57.8 (17.3) | 62.6 (25.1) | 62.9 (28.8) | 27.9 (23.3) | 24.4 (23.3) | 3.2 (2.5) | 4.1 (1.0) | 3.0 (0.6) | 2.0 | 10.6 (2.2) |
| Moderate pace walk | 79.2 (27.3) | 76.9 (31.1) | 86.0 (40.2) | 34.1 (23.9) | 26.7 (17.0) | 4.3 (2.5) | 4.7 (1.1) | 3.5 (0.8) | 2.8 | 12.9 (1.5) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (average pace 2.2 mph) | | | | | | | | | | |
| Light pace walk carrying shopping bags (2 x 1.5kg) (average pace 1.6 mph) | 55.5 (20.7) | 56.9 (20.9) | 66.5 (29.8) | 24.7 (33.2) | 16.4 (27.3) | 3.3 (1.4) | 4.4 (0.9) | 3.2 (0.6) | 2.5 | 13 (2.5) |

SVM, sum of vector magnitude; MAD, mean amplitude deviation; METS, metabolic equivalents; RPE, rating of perceived exertion; ISWT, incremental shuttle walk test.

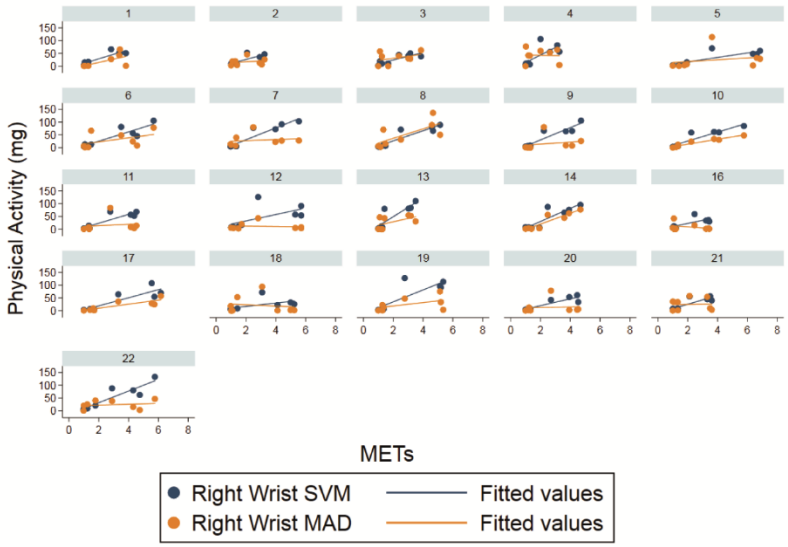
*Measured METS = VO2 (ml/kg/min) measured during each activity / VO2 (ml/kg/min) measured at rest (resting metabolic rate).

†Standard METS = VO2 (ml/kg/min) measured during each activity / 3.5 (ml/kg/min).

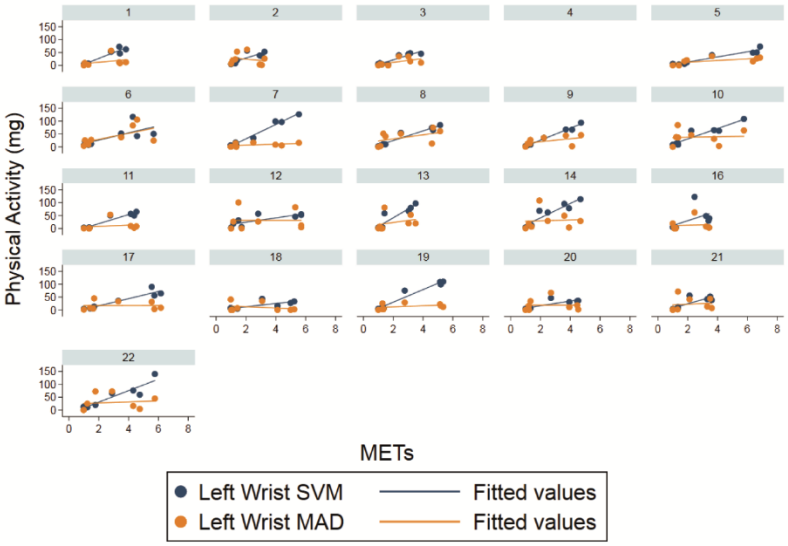
‡Predicted METS taken from most similar activity in the compendium of physical activity.

Figure 3.1 shows the relationships between SVM and measured METS and MAD and measured METS for each participant at each accelerometer wear location. Accelerometer values increased in line with the increase in METS. Correlations between SVM and METS were strong (left wrist r=0.78, right wrist r=0.76, waist r=0.80). Correlation between left and right wrist MAD and METS was weak (left wrist r=0.18, right wrist r=0.28), and between waist MAD and METS was strong (r=0.61).

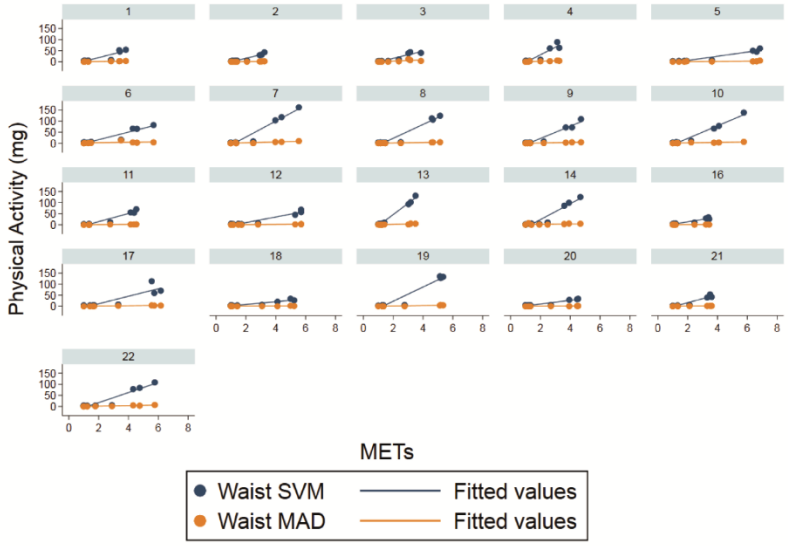
A




B




C




Graphs by Patient ID

Figure 3.1: Trellis plot showing acceleration values in mg vs intensity in METS for each activity and fitted regression lines, for SVM (blue) and MAD (orange), for (A) right wrist, (B) left wrist, (C) waist worn accelerometers.

### *3.4.2 ROC curve analysis*

ROC analysis results are presented in appendix 3.6. GENEActiv accelerometers at all locations were able to discriminate between inactivity, and MVPA. SVM gave more precise discrimination across all three accelerometer wear locations, and both inactivity and MVPA (AUC=0.93 to 0.99) compared to MAD (AUC=0.61 to 0.97). All derived inactivity and MVPA thresholds were lower than the commonly used thresholds previously published at all wear locations. [7-8]

### *3.4.3 Multilevel mixed effects regression analysis*

Table 3.4 shows the multilevel mixed effects regression model coefficients and constants, and the derived inactivity and MVPA intensity thresholds calculated by inputting 1.5 METS and 3.0 METS respectively. All derived thresholds for inactivity were much lower than the threshold for inactivity of 45.8 mg commonly applied to all populations. [8] Right wrist: SVM=13.3-18.6mg, MAD=14.2-18.4mg. Left wrist: SVM=14.4-16.9mg, MAD=15.4-18.8mg. Waist: SVM=7.6-11.1mg, MAD=1.0mg.

Crucially, even the highest HF-derived MVPA threshold (49mg) is much lower than the MVPA threshold of 93.2mg or 100mg that are commonly applied to all populations. [7] Right wrist: SVM=43.1-49mg, MAD=24.7-29.5mg. Left wrist: SVM=43.6-47.0mg, MAD=20.7-24.2mg. Waist: SVM=40.6-47.2mg, MAD=2.4-2.6mg. MVPA thresholds did not differ by location (wrist or waist) for SVM, but were much lower at the waist compared to the wrist for MAD.

Table 3.4: Mixed effect regression model coefficients, constants and resulting intensity thresholds for inactivity and MVPA with confidence intervals for SVM and MAD

| | **Coefficient (95% CI)** | **Constant (95%CI)** | **Inactivity Threshold (<1.5 METS) (m*g*) (95% CI)†** | **MVPA Threshold (≥3.0 METS) (m*g*) (95% CI)†** |
|---|---|---|---|---|
| *SVM* | | | | |
| *Right wrist* | | | | |
| All patients (n=21, obs=168) | 17.9 (15.4 to 20.5)*** | -8.3 (-14.2 to -2.3)** | 18.6 (8.8 to 28.4) | 45.5 (31.9 to 59.1) |
| Excluded aided walking activity data‡ (n=21, obs=159) | 20.2 (17.6 to 22.9)*** | -11.7 (-17.6 to -5.9)*** | 18.6 (8.7 to 28.5) | 49.0 (35.1 to 62.9) |
| Excluded aided walking activity data and washing up activity data §(n=21, obs=138) | 19.8 (17.7 to 22.0)*** | -16.4 (-19.9 to -13.0)*** | 13.3 (6.7 to 19.9) | 43.1 (33.3 to 52.9) |
| *Left wrist* | | | | |
| All patients (n=20, obs=160) | 18.0 (15.5 to 20.5)*** | -10.3 (-15.4 to -5.2)*** | 16.7 (7.8 to 25.6) | 43.6 (38.5 to 56.3) |
| Excluded aided walking activity data‡ (n=20, obs=151) | 20.1 (17.7 to 22.5)*** | -13.2 (-18.2 to -8.2)*** | 16.9 (8.3 to 25.5) | 47.0 (34.8 to 59.2) |
| Excluded aided walking activity data and washing up activity data § (n=20, obs=131) | 19.9 (17.6 to 22.2)*** | -15.5 (-19.6 to -11.5)*** | 14.4 (6.8 to 21.85) | 44.3 (33.2to 55.2) |
| *Waist* | | | | |

| | | | | |
|---|---|---|---|---|
| All patients (n=21, obs=168) | 22.0 (18.3 to 25.7)*** | -25.4 (-30.5 to -20.2)*** | 7.6 (-3.1 to 18.4) | 40.6 (24.3 to 57.0) |
| Excluded aided walking activity data‡ (n=20, obs=159) | 22.9 (19.6 to 26.2)*** | -26.6 (-31.7 to -21.5)*** | 7.7 (-2.3 to 17.8) | 42.0 (27.1 to 57.0) |
| Excluded aided walking activity data and washing up activity data § (n=21, obs=138) | 24.0 (20.2 to 27.9)*** | -24.9 (-29.5 to -20.4)*** | 11.1 (0.78 to 21.49) | 47.2 (31.0 to 63.32) |
| *MAD* | | | | |
| *Right wrist* | | | | |
| All patients (n=21, obs=168) | 5.3 (2.5 to 8.0)*** | 10.4 (3.1 to 17.8)** | 18.3 (6.9 to 29.7) | 26.2 (10.7 to 41.7) |
| Excluded aided walking activity data‡ (n=21, obs=159) | 7.4 (4.5 to 10.3)*** | 7.3 (-0.1 to 14.6) | 18.4 (6.6 to 30.1) | 29.5 (13.4 to 45.6) |
| Excluded aided walking activity data and washing up activity data § (n=21, obs=138) | 7.0 (4.2 to 9.8)*** | 3.7 (-2.6 to 10.0) | 14.2 (3.6 to 24.8) | 24.7 (9.9 to 39.5) |
| *Left wrist* | | | | |
| All patients (n=20, obs=160) | 2.8 (0.3 to 5.2)* | 14.6 (7.5 to 21.7)*** | 18.7 (7.9 to 29.5) | 22.8 (8.3 to 37.3) |
| Excluded aided walking activity data‡ (n=20, obs=151) | 3.7 (1.0 to 6.3)** | 13.3 (6.1 to 20.5)*** | 18.8 (7.6 to 29.9) | 24.2 (9.1 to 39.4) |
| Excluded aided walking activity data and washing up activity data § (n=20, obs=131) | 3.5 (0.8 to 6.2)* | 10.1 (3.2 to 17.0)** | 15.4 (4.4 to 26.3) | 20.7 (5.7 to 35.6) |
| *Waist* | | | | |

| | | | | |
|---|---|---|---|---|
| All patients (n=21, obs=168) | 0.9 (0.7 to 1.2)*** | -0.5 (-0.9 to 0.0) | 1.0 (0.2 to 1.7) | 2.4 (1.3 to 3.5) |
| Excluded aided walking activity data‡ (n=21, obs=159) | 1.0 (0.8 to 1.2)*** | -0.6 (-1.1 to -0.1)* | 1.0 (0.2 to 1.8) | 2.5 (1.4 to 3.6) |
| Excluded aided walking activity data and washing up activity data § (n=21, obs=138) | 1.1 (0.8 to 1.3)*** | -0.6 (-1.0 to -0.2)** | 1.0 (0.3 to 1.7) | 2.6 (1.5 to 3.6) |

MVPA, moderate-to-vigorous physical activity; SVM, sum of vector magnitudes; MAD, mean amplitude deviation; METS, metabolic equivalents

†95% CI calculated using upper and lower bounds of coefficient and constant in formula.

* p<0.05, ** p<0.01, *** p<0.001

‡ Excluded walking activity data for n=3 patients using walking aids. § Excluded walking activity data for n=3 patients using walking aids and all washing up activity data.

### *3.4.4 Sensitivity analysis*

Two sensitivity analyses were performed (excluding walking data of patients who used walking aids, and walking data of patients who used walking aids, plus all washing and drying dishes data). Neither made considerable difference to the thresholds derived through ROC analysis or multilevel mixed effect regression analysis.

### *3.4.5 Validation analysis*

Leave-one-out cross validation (appendix 3.7) of the multilevel models showed that the model fit for SVM at each wear location was acceptable but appeared to under predict at high PA and MET levels. Proportion of correct predictions were high (right wrist: 96%; left wrist: 99%, waist: 95%). Models using MAD performed less well with lower proportions of correct predictions (right wrist: 69%; left wrist: 64%; waist: 87%).

Cohen's K test showed 63% agreement (95% CI 57% to 69%, K= 0.19, $p<0.001$) between HF specific and adult intensity thresholds in classification of patients meeting PA guidelines. [7]

## 3.5 Discussion

This is the first study to derive HF specific accelerometer intensity thresholds for time spent inactive and in MVPA. Intensity thresholds corresponding to inactivity were much lower than those previously published based on young healthy adults. [8] Sedentary time is defined as a combination of sitting or reclining and low energy expenditure during waking hours. [25] The time spent below 1.5 METS measured by wrist worn accelerometry can only measure inactivity, and not the specific posture required to be defined as sedentary time, therefore we use the term inactivity. Although less investigated than MVPA, inactivity thresholds of <50mg or <40mg have been previously proposed for GENEActiv accelerometers. [8, 26-27] This suggests the possibility that researchers using generic intensity thresholds are concluding that HF patients are more inactive when they may actually be engaging in light intensity activities.

Similarly, accelerometer thresholds corresponding to MVPA were much lower than those derived from other calibration studies both in healthy adults and older adults. [7,10] Applying intensity thresholds developed in younger, healthier populations to HF patients assumes the energy cost for a given activity is the same for everyone, with no consideration for an individual's exercise capacity. [9] In line with previous studies, we showed HF patients require greater energy expenditure to complete walking and self-paced daily living activities, where METS calculated using measured RMR were higher than METS calculated using the standard RMR estimate of 3.5 ml/kg/min [28-31]. Additionally, measured METS were higher than the predicted METS from the compendium of physical activities. [19] Often, self-reported PA measures use the compendium to inform activity estimates and it is also used to prescribe PA. [32-33] This clearly highlights the limitations of using existing MET tables to estimate the time HF patients spend in MVPA.

The average RMR for this sample of HF patients was 2.67 ml/kg/min, 24% less than the standard 3.5 ml/kg/min, consistent with RMRs reported previously in older adults,[28] and HF patients. [30] The application of standard RMR for MET calculations is common, including in previous calibration studies, [7-8] however several studies have shown the inaccuracy of using estimated RMR in elderly and clinical populations including HF patients. [28, 30-31] Although the mechanism for decreased RMR in HF patients is currently unknown, decline with increasing NYHA class has been shown, and may be influenced by changes in skeletal muscle physiology associated with a reduced cardiac output in HF. [30] It may be argued that our lower RMR is due, to some extent, to being measured whilst supine, rather than sitting, however we measured supine RMR in line with current best practices. [12]

### *3.5.1 Data reduction and analysis techniques*

We explored 3 data reduction approaches for generating a single value of acceleration from the x, y, z axes. We found that ENMO returned a high frequency of 0's across all activities, which has been observed by others, [23] and therefore excluded it from further analysis. SVM had stronger correlations with METS, produced higher AUC values in the ROC analysis, and returned

better model fit predictions in the leave-one-out cross validation analysis compared to MAD.

ROC analysis was less robust than multilevel mixed effect regression analysis when using MAD, with poor-fair AUC for wrist accelerometers. This may be due to the dichotomisation of MET data in the ROC analysis, which leads to a loss of statistical power, whereas the absolute MET values are used in the multilevel mixed effect regression analysis. Furthermore, the multilevel mixed effect regression correctly accounts for the clustering of measures within individuals which ROC analysis does not.

Therefore we recommend studies measuring PA levels in HF patients use the thresholds derived using SVM and multilevel mixed effect regression for all patients, i.e. inactivity (right wrist: 18.6mg, left wrist: 16.7mg, waist: 7.6mg) and MVPA (right wrist: 45.5mg, left wrist: 43.6, waist: 40.6mg).

### *3.5.2 Strengths and limitations*

Strengths of this study include the use of both wrist- and waist-worn accelerometers with known reliability and validity, comparison of multiple data reduction algorithms, and comprehensive data analysis of raw acceleration data captured at a high sampling frequency. We were thus able to generate HF specific intensity thresholds, enabling more accurate differentiation between inactivity, and MVPA behaviours of HF patients. In contrast to previous calibration studies we have individually measured RMR, and used this to more accurately measure METS for each activity for each individual. [7-8]. We selected representative HF patients from a hospital clinic, who were heterogeneous in exercise capacity and age, factors known to affect PA measurement, [10-11,28] and determined activities with the assistance of a HF Patient and Public Involvement group to represent typical daily living, with the majority of PA and exercise from walking and household activities.

We recognise that this study has some limitations. It was based on small, single-centre sample of HF patients, therefore we are unable to determine how the thresholds may vary between NYHA classes. In addition, it is difficult to determine whether HF medications taken by the patients (100% patients taking β-blockers) influenced VO2 or heart rate. Attempting to apply a single threshold

to all within a population may not be possible since individual capacities vary. [34] Employing a threshold or cut-point technique to derive PA metrics from accelerometers may not be as accurate as newer techniques such as machine learning that are being explored in public health studies. [35-36] However, whilst PA recommendations are based on classes of PA intensity rather than specific behaviours, these techniques are still pragmatic to use until consensus is reached.

### *3.5.3 Implications and future research*

We have developed a new approach that better captures PA in HF patients using accelerometry. Our results suggest that application of previously published intensity thresholds based on calibration studies of adults without chronic disease potentially risks underestimation and misclassification of PA in HF patients. Larger studies, using our approach are now required to clarify PA levels in the various severity levels of HF, taking account of comorbidity. We suggest power calculations should take into account the small numbers of patients that reach the latter stages of the ISWT to ensure spread of patients fitness levels represented.

This study also has important implications for PA and exercise prescription. It is vital both the patient and the clinician are aware of the PAs that will count as MVPA and benefit the patient, as prescribing activities that are too intense may lead to decreased motivation and adherence to PA guidelines or CR. [37] Our results show that any walking activity, including at a slow speed, would be sufficient for HF patients to accumulate minutes of MVPA.

## 3.6 Conclusions

HF specific accelerometer intensity thresholds for both inactivity and MVPA were substantially lower (<50%) than previously published and commonly used intensity thresholds. Using cut-points or intensity thresholds based on calibration studies of younger, healthy adults assumes energy expenditure is the same for everyone, regardless of an individual's exercise capacity. We demonstrated that HF patients require more energy to perform typical daily

living activities, including walking and household activities, with higher measured MET values compared to METS calculated using assumed RMR, or METS predicted from the compendium of physical activities. We thereby demonstrate that the application of generic PA thresholds may result in a misclassification and underestimation of the true amount of MVPA undertaken by HF patients.

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# Chapter 4: Factors associated with objectively assessed physical activity levels of heart failure patients

## 4.1 Abstract


Aims

To determine the level of objectively measured moderate-to-vigorous physical activity (MVPA) in patients with heart failure (HF), and to assess the association between MVPA and patient sociodemographic, exercise capacity, and health status factors.

Methods

Baseline MVPA data was available in 247 HF patients with 7-day wrist-worn accelerometry from two randomised controlled trials. Associations between MVPA and patient sociodemographic, exercise capacity, and health status factors were assessed using univariate and multivariable linear regression models.

Results

247 patients (28% female, mean age 71±10 years) with HF with reduced ejection fraction (n=198) and preserved ejection fraction (n=49) were included in the analysis. Average MVPA was 283.3 min/week and ranged widely from a minimum of 0 mins/week to maximum of 2626.7 mins/week (standard deviation: 404.1 mins/week). 111 (45%) of patients had a level of PA that met current guidelines of at least 150 minutes/week of MVPA. Multivariable regression showed patient's age, body mass index, employment status, smoking status, New York Heart Association class, NT-proBNP and exercise capacity to be strongly associated ($p<0.001$) with the level of MVPA ($p<0.001$).

Conclusion

Whilst 45% of HF patients had objectively measured levels of MVPA that met current PA recommendations, we observed a wide range in the level of MVPA across this patient sample. As a number of factors were found to be associated

with MVPA our findings provide important information for future interventions aiming to increase MVPA in HF patients.

## 4.2 Introduction

There are numerous benefits of regular physical activity (PA) that persist across the life course, including prevention and management of chronic disease, prolonging functionality and increasing health-related quality of life [1]. To achieve these health benefits, it is recommended that adults perform at least 150 minutes per week (i.e. ≥30 minutes/day over 5 or more days per week) of moderate-to-vigorous PA (MVPA) [1].

A small number of studies to date have quantified the PA levels of HF patients and consistently report daily MVPA levels much lower than the recommended 30 minutes [2-5]. Some studies have reported that HF patients undertake on average as little as 1 minute of MVPA per day [2-5]. However, these previous studies are limited by small sample sizes (N<100), [2-4] and/or reliance on self-report measures of PA, [5] which have been shown to be less reliable than objective measures [6]. Moreover, studies that did use objective PA methods are based on proprietary algorithms that assess levels of MVPA from data in healthy adults [2-4].

The aims of this study were to: (1) determine the level of objectively measured PA and MVPA in HF patients using HF-specific intensity algorithms and (2) assess the association between MVPA and patient sociodemographic, exercise capacity, and health status factors.

## 4.3 Methods

### *4.3.1 Study design*

This study used baseline data pooled from two randomised controlled trials of a home-based cardiac rehabilitation intervention for HF patients (REACH-HF): a single centre study in patients with HF with preserved ejection fraction (HFpEF)

(ISRCTN78539530) and a multicentre study in patients in HF reduced ejection fraction (HFrEF) (ISRCTN86234930) [7-10].

Both trials were conducted in accord with the principles of the Declaration of Helsinki and ethical approval was granted by the East of Scotland Research Ethics Service (15/ES/0036) [9] and by the North West Lancaster Research Ethics Committee (14/NW/1351) [10].

### *4.3.2 Study participants*

Participating HF patients were recruited from primary and secondary care settings in five UK centres (Birmingham, Cornwall, Dundee, Gwent, and York) between January 2015 and February 2016 [9-10]. A total of 266 patients completed the baseline visit, 216 with HFrEF (defined as left ventricular ejection fraction <45%) and 50 with HFpEF (defined as left ventricular ejection fraction ≥45%). The patients were aged ≥18 years and had a confirmed diagnosis of HF on echocardiography or angiography within the last 6 months [7-8]. A full list of trial inclusion and exclusion criteria are provided in appendix 4.1. All study participants provided written informed consent.

### *4.3.3 Data collection*

*Medical history, demographics, blood test, and exercise capacity*

During their baseline clinic visit the following categories of data were collected: (1) medical history, i.e. comorbidities, New York Heart Association (NYHA) class, HF aetiology, concomitant HF medication and presence of implantable cardiac devices; (2) sociodemographic information i.e. age, ethnicity, weight, employment status, and smoking status; (3) blood sample was taken for measurement of N-terminal Brain Natriuretic Peptide (NT-proBNP); (4) health outcome questionnaires – i.e. disease-specific health-related quality of life assessed by Minnesota Living with Heart Failure Questionnaire, and the Health Related Quality of Life (HeartQoL) questionnaire; psychological wellbeing using the Hospital Anxiety and Depression Scale questionnaire; generic health-related quality of life using the EQ-5D-5L questionnaire; and Self-care of HF Index questionnaire; (5) exercise capacity assessed by an incremental shuttle walk test (ISWT) – the ISWT was performed twice with at least 30 minutes rest

between the tests, administered by the PI or research nurse. Standardised instructions were given to patients, and no encouragement was given throughout the test [7-8]. The peak distance (m) walked in either of the two tests was recorded.

*Physical Activity – Accelerometry*

At baseline visit, patients were also provided a GENEActiv triaxial accelerometer (GENEActiv, Activinsights, Kimbolton, Cambridge, UK) and instructed to wear the accelerometer on their non-dominant wrist for 7 days during waking and sleeping hours [9-10]. Monitors were returned using postage-paid envelopes. Data were downloaded using GENEActiv PC software (version 3.2; Activinsights, Kimbolton, Cambridge, UK) and analysed in R (R Core Team, Vienna, Austria) using the GGIR software package (version 1.5-18, http://cran.r-project.org). Initial processing included autocalibration, the detection of abnormally high values and non-wear [11-12]. Data were averaged over 5 second epochs and Euclidean Norm Minus One was used to quantify the acceleration related to movement registered and was expressed in units of milligravity (mg) [13]. The Euclidean norm (magnitude) of the 3 raw signals minus 1000mg, with negative numbers rounded to zero was calculated using the following formula:

$$\sqrt{x^2 + y^2 + z^2} - 1000mg$$

Non-wear was determined over 60 minute windows using 15 minute increments, and was apparent when 2 of the 3 axes had a data range <50 mg and a standard deviation <13 mg [14]. To be included in analysis patients were required to have ≥16 hours per day and ≥7 days of wear. The first seven days that met the criteria were used for analysis.

For each patient, the following PA metrics were calculated: (1) minutes per week of MVPA, (2) whether patients meet the PA recommendation of ≥150 minutes of MVPA per week, (3) average daily PA levels (over all days, weekdays only, and weekend days only) broken down into minutes of inactivity, light PA, and MVPA. These metrics were calculated using both bouted PA i.e. periods of PA sustained for at least 10 minutes where accelerometer readings

lie above the intensity threshold (with a 20% allowance for values to fall outside the threshold) and unbouted i.e. PA accumulated in bouts of any length.

These metrics were calculated using HF population specific accelerometer intensity thresholds for inactivity of 16.7mg (left wrist) and 18.6mg (right wrist) and MVPA of 43.6mg (left wrist) and 45.5mg (right wrist). These intensity thresholds were determined by a recent calibration study in 21 HF patients with concurrently assessed acceleration values and directly measured oxygen uptake across a range of activities of daily living [15]. We considered the potential effects of application of HF specific intensity thresholds which were derived using an alternative data reduction method (SVM rather than ENMO), and concluded that the difference in the calculated PA patterns would be minimal, and would not affect the conclusions of the study.

### *4.3.4 Statistical analysis*

Descriptive statistics were used to summarise patient characteristics and levels of PA. Continuous variables are presented as means and standard deviations (SD) and discrete variables presented as counts or percentages.

Univariate linear regression analysis was conducted to examine the association between MVPA in minutes/week and each group of potential predictor variables (i.e. medical history/sociodemographics, exercise capacity, health status outcomes) separately. Univariate logistic regression was used to examine the association with these groups of variables and the binary outcome of whether patients meet PA guidelines or not. Variables were selected for multivariable analysis if there was statistical evidence of ($p<0.15$) of their association in univariate analysis.

Three multivariable PA regression models were developed for both MVPA in minutes/week and binary outcome of meeting PA guidelines or not: (1) model 1 – medical history sociodemographic variables only, (2) model 2 - exercise capacity and health status variables only, and (3) model 3 - medical history sociodemographic and health and disease status variables that were identified as statistically significant ($p<0.05$) in models 1 and 2. Checks and diagnostics were performed for model assumptions, residuals, multicollinearity (variance inflation factor) and influential observations (Cook’s distance). Akaike

information criterion and $R^2$ values (proportion of variance explained) were used to inform model comparison and selection. We performed two groups of sensitivity analyses: (1) including the patients previously excluded with high residuals and Cook's distances and (2) MVPA was recalculated without the requirement for PA to be in bouts of at least 10 minutes (unbouted).

Statistical analyses were performed using Stata (V.15.0; StataCorp, College Station, Texas, USA).

### 4.4 Results

Of the 266 patients who completed baseline visits, 247 were included in the analysis (see table 4.1). Overall, patients had a mean age of 70.9 years and were predominantly male (72%) and NYHA class I to III (99%). Alongside differences in medications, HFpEF patients were more likely to be older and female, have higher BMI, live alone, have hypertension, chronic renal impairment, arthritis and COPD, have lower generic health-related quality of life (EQ-5D-3L) Hospital Anxiety and Depression Scale depression scores depression, and self-care maintenance scores, and lower ISWT distance. Four patients had missing accelerometer data, and 15 patients were excluded due to inadequate accelerometer wear time (<7 days of wear with ≥16 hours per day). Apart from a higher proportion in employment (26 vs 13%, p=0.01), excluded patients were similar to those included in the PA analysis.

Table 4.1: Sociodemographic characteristics and disease and health status factors at baseline of patients included in the analysis. N (%) unless otherwise stated

| Characteristic | All patients N=247 patients | HFrEF patients N=198 | HFpEF patients N=49 |
|---|---|---|---|
| Mean (SD) age (years) | 70.9 (10.4) | 70.1 (10.7) | 74.3 (8.0)** |
| Female sex | 70 (28) | 43 (22) | 27 (55)*** |
| Median (IQR) BMI (kg/m$^2$) | 29.2 (25.9-33.6) | 25.4 (28.1-32.2) | 31.2 (27.4-36.5)** |
| Employment status | | | |
| Retired | 199 (81) | 153 (77) | 46 (94) |
| In employment or self-employment | 31 (12) | 30 (15) | 1 (2) |
| Other | 17 (7) | 15 (7) | 2 (4) |
| Ethnic origin | | | |
| White | 236 (96) | 187 (94) | 49 (100) |
| Other | 11 (4) | 11 (6) | 0 (0) |
| NYHA class | | | |
| I | 40 (16.2) | 38 (19) | 2 (4) |
| II | 147 (59.5) | 117 (59) | 30 (61) |
| III | 59 (23.9) | 42 (21) | 17 (35) |
| IV | 1 (0.4) | 1 (1) | 0 (0) |
| Median (IQR) LVEF (%) | 35 (30-44) | 34 (25-38) | 62 (58-64)*** |
| LVEF <45% | 114 (46) | 144 (73) | 0 (0) |
| LVEF>45% | 43 (17) | 0 (0) | 44 (90) |
| Unknown | 59 (24) | 54 (27) | 5 (10) |
| Time since HF diagnosis (years) | | | |
| <1 | 74 (30) | 65 (33) | 9 (18) |
| 1-2 | 47 (19) | 34 (17) | 13 (27) |
| >2 | 126 (51) | 99 (50) | 27 (55) |
| Live alone | 66 (27) | 44 (22) | 22 (45)** |
| Current smoker | 14 (6) | 10 (5) | 4 (8) |

| | | | |
|---|---|---|---|
| Cause of heart failure | | | |
| Ischaemic | 115 (47) | 91 (46) | 24 (49) |
| Non-ischaemic | 116 (47) | 93 (47) | 23 (47) |
| Unknown/Not classified | 16 (6) | 14 (7) | 2 (4) |
| Trial site | | | |
| Truro | 56 (23) | 56 (29) | 0 (0) |
| Gwent | 44 (18) | 44 (22) | 0 (0) |
| Birmingham | 48 (19) | 48 (24) | 0 (0) |
| York | 50 (20) | 50 (25) | 0 (0) |
| Dundee | 49 (20) | 0 (0) | 49 (100) |
| Comorbidities | | | |
| Diabetes mellitus | 59 (24) | 44 (22) | 15 (31) |
| Myocardial infarction | 70 (28) | 61 (31) | 9 (18) |
| Hypertension | 113 (46) | 82 (41) | 31 (63)** |
| Stroke | 29 (12) | 26 (13) | 3 (6) |
| Asthma | 28 (11) | 20 (10) | 8 (16) |
| Chronic renal impairment | 45 (18) | 32 (16) | 13 (27)* |
| Arthritis | 107 (43) | 77 (39) | 30 (61)** |
| Atrial fibrillation or atrial flutter | 118 (48) | 99 (50) | 19 (39) |
| COPD | 27 (11) | 17 (9) | 10 (20)* |
| Depression | 61 (25) | 46 (23) | 15 (31) |
| Median (IQR) Number of comorbidities | 3 (2-5) | 3 (2-5) | 4 (3-6) |
| Medication | | | |
| ACE inhibitor/ARB | 220 (89) | 182 (92) | 38 (78)* |
| Aldosterone antagonist | 118 (48) | 109 (55) | 9 (18)*** |
| Anticoagulant | 114 (46) | 96 (48) | 18 (37) |
| Beta blocker | 194 (79) | 163 (82) | 31 (63)** |
| Digoxin | 39 (16) | 33 (17) | 6 (12) |
| Loop diuretic | 170 (69) | 127 (64) | 43 (88)** |
| Nitrate | 38 (15) | 24 (12) | 14 (29)** |
| Mean (SD) NT-proBNP (pg/ml) | 1326.82 (1696.67) | 1467.58 (1809.23) | 758.04 (952.35)** |

| | | | |
|---|---|---|---|
| Mean (SD) ISWT (m) (N=232) peak | 230.4 (150.8) | 245.3 (147.7) | 171.9 (150.4)** |
| Mean (SD) MLHFQ overall | 32.1 (23.8) | 30.9 (23.1) | 36.9 (26.2) |
| Mean (SD) HADS | | | |
| Anxiety | 5.6 (4.4) | 5.6 (4.3) | 5.8 (4.8) |
| Depression | 4.8 (3.5) | 4.5 (3.3) | 5.8 (4.0)* |
| Mean (SD) HeartQoL global | 1.8 (0.78) | 1.8 (0.74) | 1.5 (0.87) |
| Mean (SD) EQ-5D-3L | 0.70 (0.26) | 0.73 (0.24) | 0.58 (0.30)*** |
| Mean (SD) SCHFI | | | |
| Maintenance | 54.5 (15.8) | 55.8 (15.6) | 49.0 (15.3)** |
| Management | 40.7 (22.5) | 41.8 (23.6) | 38.0 (19.6) |
| Confidence | 62.7 (24.3) | 63.6 (24.3) | 59.2 (24.1) |

SD, standard deviation; IQR, interquartile range; BMI, body mass index; NYHA, New York heart association; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, NT-pro-brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; ACE, Angiotensin-converting enzyme; ARB, angiotensin II receptor antagonist; ISWT, incremental shuttle walk test; MLHFQ, Minnesota living with heart failure questionnaire; HADS, hospital anxiety and depression scale; SCHFI, self-care of heart failure index. *P<0.05, **P<0.01, ***P<0.001 HFpEF vs HFrEF groups.

### *4.4.1 Level of PA in HF patients*

The average level of MVPA across the HF patients was 283.3 mins/week. MVPA ranged widely across the study population from minimum of 0 mins/week to maximum of 2626.7 mins/week (standard deviation: 404.1 mins/week). A total of 111 (45%) patients had a level of PA that met current guidelines of 150 minutes/week of MVPA. Daily PA of HF patients categorised by intensity, days, and bout rule is reported in table 4.2. Patients undertook 40.5 ± 57.7 mins/day bouted MVPA and 175.9 ± 86.4 min/day unbouted MVPA averaged across all days of the week. Unbouted MVPA levels were higher during the week days compared to weekend days ($p<0.001$), but bouted MVPA levels did not differ. Levels of bouted and unbouted light PA were higher during weekdays than weekend days ($p<0.001$) and both bouted and unbouted inactivity levels were higher at the weekend than during the week ($p<0.001$).

Table 4.2: Mean (SD) PA mins/day of different intensity (inactivity, Light PA, MVPA) over all days, weekend days and week days

| | All Days | Weekend Days | Week Days |
|---|---|---|---|
| Bouted* | | | |
| Inactivity | 1199.6 (145.7) | 1214.5 (150.4) | 1193.6 (150.9)*** |
| Light PA | 200.0 (108.0) | 187.9 (114.1) | 204.8 (112.2)*** |
| MVPA | 40.5 (57.7) | 37.6 (58.7) | 41.6 (60.5) |
| Unbouted† | | | |
| Inactivity | 1075.1 (110.1) | 1089.3 (115.7) | 1069.4 (113.1)*** |
| Light PA | 189.0 (46.8) | 183.0 (50.9) | 191.4 (48.4)*** |
| MVPA | 175.9 (86.4) | 167.7 (86.6) | 179.1 (89.2)*** |

PA, physical activity; MVPA, moderate-to-vigorous physical activity.
*Bouted: activity accumulated in continuous 10 minute duration
†Unbouted: activity accumulated in any duration
*** $p<0.001$ t-test weekend days vs week days

Table 4.3 summarises the characteristics and reported MVPA levels of HF patients in this study and across previous HF studies. Daily MVPA levels of the HF patients in the present study are higher than the majority of PA levels reported in previous studies [2-5].

Table 4.3: Summary of studies reporting MVPA levels of patients with heart failure.

| Lead study author (year), country | N patients included | PA measurement method | Level of MVPA (minutes/day) | % patients meeting PA guidelines* |
|---|---|---|---|---|
| Dontje (2014) Netherlands [2] | N=68<br>Mean age 62±14 years<br>71% male<br>NYHA I-II 60%<br>NYHA III 40% | Accelerometer – SenseWear Pro3 Armband worn for 2 consecutive weekdays | Mean 53 ± 54 min/day | 56% |
| Yates (2017) USA [3] | N=29<br>Median age 74 (range 61-85) years<br>65% male<br>NYHA not reported | Modified 7 day physical activity recall questionnaire (self-report)<br>Accelerometer – Actiheart worn for 7 consecutive days | Not reported (self-report)<br>Median 0.78 (range 0-8.38) min/day (accelerometer) | 38% (self-report)<br>0% (accelerometer) |
| Yavari (2017) Canada [4] | HFpEF N=53<br>Median age 75 (IQR 66-81) years<br>58% male<br>NYHA I-II 75%<br>NYHA III 23%<br>HFrEF N=16 | Accelerometer – SenseWear Mini Armband worn for 4 consecutive days | HFpEF – median 12 (first quartile-third quartile 6-30) mins/day<br>HFrEF – median 36 (first quartile-third quartile 6-84) mins/day | Not reported |

| | | | | |
|---|---|---|---|---|
| | Median age 72.5 (IQR 63-81) years<br>81% male<br>NYHA I-II 75%<br>NYHA III 25% | | | |
| Hedge (2017) USA, Canada, Brazil, Argentina [5] | N= 1751<br>Mean age 68.6 ± 9.6 years<br>50% male<br>NYHA I 6%<br>NYHA II 59%<br>NYHA III 34%<br>NYHA IV 1% | Non-validated (self-report) question “What has the subject’s usual pattern of exercise been during the past 2 weeks?” for 3 categories of activity (heavy, medium, light) | Not reported | 11% |
| Present study | N=247<br>Mean age 70.9 ± 10.4 years<br>72% male<br>NYHA I 16%<br>NYHA II 60%<br>NYHA III-IV 24% | Accelerometer – GENEActiv worn for 7 consecutive days | mean 40.5 ± 57.7 min/day | 45% |

HF, heart failure; PA, physical activity; MVPA, moderate-vigorous physical activity; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

* i.e. 150 minutes per week MVPA or 30 min/day MVPA

### *4.4.2 Predictors of PA in HF patients*

*MVPA minutes per week*

*Univariate analyses*

Appendix 4.2 shows the results of the univariate linear regressions between MVPA (min/week) and the sociodemographic, exercise capacity and health status factors. MVPA (min/week) was positively ($p<0.05$) associated with cause of HF, smoking history, ISWT distance, HEART QoL global and physical scores, and overall EQ-5D-3L score. PA was negatively ($p<0.05$) related to age, body mass index (BMI), employment status, NYHA class I-III, NT-pro-BNP, living alone, living with child >18 years, diabetes, number of comorbidities, number of cardiorespiratory-metabolic comorbidities, taking loop diuretics, Minnesota Living with Heart Failure Questionnaire overall, physical and emotional scores (where lower scores indicate better QoL), and Hospital Anxiety and Depression Scale depression scores. Variables that were closely related to MVPA ($0.05<p<0.15$) included living with a parent, osteoporosis, angina and taking nitrates.

*Multivariable analyses*

In model 1: NYHA class I-III, age, BMI, smoking history and employment status were all included in the final model as significant contributors, and the model accounted for 30% of the observed variance in MVPA (table 4.4). Two patients were removed from multivariable analysis due to having both high residual (e=2178, e=2040) and Cook's distance (D=0.07, D=0.15).

In model 2: ISWT distance was the only significant contributor and explained 27% of the observed variance in MVPA (table 4.4). Two patients identified with high residual (e=2288, e=2182) and Cook's distance (D=0.17, D=0.14) were removed from the analysis.

In model 3: two patients removed with high residual (e=2202, e=2141) and Cook's distance (D=0.10, D=0.14). ISWT distance, age, BMI, and smoking history remained as significant contributors and accounted for 36% of the variance in MVPA (table 4.4).

The variance inflation factor ranged from 1.1-1.2 across the three models indicating a low level of multicollinearity (variance inflation factor >5 indicates a level high correlation that may be problematic for modelling).

Including the patients with high residuals and Cook's distances decreased the $R^2$ across all three models, and resulted in the removal of employment status in model 1, and NYHA class being replaced by smoking status in model 3. Running a model containing all variables with $p<0.15$ from the univariate analysis produced findings consistent to model 3. Analysis with unbouted (< 10 minutes in duration) MVPA data, which decreased $R^2$ across all models, and NT-proBNP replaced employment status in model 1, no other differences were observed.

Table 4.4: Comparison of multivariable linear regression models to predict minutes/week PA.

| Multivariable model | Variables included in model (p<0.05) | Unstandardized beta coefficient (95% CI) | t-statistic | Variable P-value | Model Adjusted $R^2$ (p-value) |
|---|---|---|---|---|---|
| **1. Socio-demographic** | NYHA class | -133.06 (-196.85 to -69.26) | -4.11 | <0.001 | 0.30 |
| | Age | -13.36 (-17.25 to -9.47) | -6.77 | <0.001 | (<0.001) |
| | BMI | -13.50 (-20.06 to -6.94) | -4.05 | <0.001 | |
| | Smoking history | 84.41 (19.49 to 149.32) | 2.56 | 0.011 | |
| | Employment status | -40.94 (-81.66 to -0.22) | -1.98 | 0.049 | |
| | constant | 1786.0 (1348.48 to 2223.52) | 8.04 | <0.001 | |
| **2. Exercise capacity and health status** | ISWT peak | 1.2 (0.94 to 1.46) | 9.06 | <0.001 | 0.27 |
| | constant | -12.62 (-85.00 to 59.76) | -0.34 | 0.73 | (<0.001) |
| **3. Socio-demographic, exercise capacity and health status*** | ISWT peak | 0.84 (0.57 to 1.11) | 6.17 | <0.001 | 0.36 |
| | Age | -10.55 (-14.39 to -6.71) | -5.41 | <0.001 | (<0.001) |
| | BMI | -11.17 (-17.54 to -4.80) | -3.45 | 0.001 | |
| | Smoking history | -65.09 (2.11to -128.07) | 2.04 | 0.04 | |
| | constant | 1001.40 (560.16 to 1442.63) | 4.47 | <0.001 | |

PA, physical activity; NYHA, New York heart association; BMI, body mass index; NT-proBNP, NT-pro-brain natriuretic peptide; ISWT, incremental shuttle walk test.

* all variables p<0.05 from multivariate models 1 and 2

*MVPA meeting PA recommendations*

*Univariate analyses*

Appendix 4.3 shows the results of the univariate logistic regressions between meeting PA guidelines and the sociodemographic, exercise capacity and health status factors. The association between meeting PA guidelines was statistically significant with age, BMI, employment status, NYHA class I-III, NT-proBNP, living alone, living with partner, diabetes, number of comorbidities, number of cardiorespiratory-metabolic comorbidities, taking anticoagulants, taking loop diuretics, ISWT distance, Minnesota Living with Heart Failure Questionnaire overall, physical and emotional scores, Hospital Anxiety and Depression Scale depression scores and overall EQ-5D-3L. Variables that were closely related to meeting PA guidelines ($0.05<p<0.15$) included cause of HF and trial site.

*Multivariable analyses*

In model 1: NYHA class I-III, NT-proBNP level, age, and BMI were statistically significant contributors included in the model (table 4.5). One patient with high residual (e=5.96) was removed.

In model 2 (exercise capacity and health status variables), only ISWT distance was included in the model, all patients were included in this model (table 4.5).

In model 3 (overall model with all variables identified in models 1 and 2), ISWT distance and NT-proBNP level were the only significant variables included in the model (table 4.5), all patients were included in this model.

*Sensitivity analysis*

Including the patient previously excluded with high residuals and Cook's distances in model 1, which made no difference to the included variables, but decreased the pseudo $R^2$. Running a model containing all variables $p<0.15$ made no difference to the included variables but decreased the pseudo $R^2$.

Table 4.5: Comparison of multivariable logistic regression models to predict meeting PA guidelines.

| Multivariable model | Variables included in model (p<0.05) | OR (95% CI) | z-statistic | Variable P-value | Model Pseudo $R^2$ (p-value) |
|---|---|---|---|---|---|
| **1. Socio-demographic** | NYHA | 0.39 (0.23 to 0.66) | -3.51 | <0.001 | 0.18 |
| | NT-proBNP | 1.00 (1.00 to 1.00) | -3.76 | <0.001 | (<0.001) |
| | Age | 0.96 (0.93 to 0.99) | -2.90 | 0.004 | |
| | BMI | 0.93 (0.88 to 0.98) | -2.56 | 0.01 | |
| | Constant | 2235.99 (103.71 to 48209.83) | 4.92 | <0.001 | |
| **2. Exercise capacity and health status** | ISWT peak | 1.01 (1.00 to 1.01) | 5.17- | <0.001 | 0.11 |
| | constant | 0.21 (0.12 to 0.38) | 5.18 | <0.001 | (<0.001) |
| **3. Socio-demographic, exercise capacity and health status*** | ISWT peak | 1.01 (1.00 to 1.01) | 5.00 | <0.001 | 0.15 |
| | NT-proBNP | 1.00 (1.00 to 1.00) | -3.07 | 0.002 | (<0.001) |
| | Constant | 0.34 (0.18 to 0.65) | -3.31 | 0.001 | |

PA, physical activity; NYHA, New York heart association; BMI, body mass index; NT-proBNP, NT-pro-brain natriuretic peptide; ISWT, incremental shuttle walk test.

* all variables p<0.05 from multivariate models 1 and 2

## 4.5 Discussion

We found that some 45% of HF patients had objectively assessed levels of activity that meet current recommendation of at least 150 minutes per week of MVPA. HF patients undertook an average of 283.3 min/week MVPA. However, the level of MVPA across patients ranged widely from a minimum of 0 mins/week to a maximum of 2626.7 mins/week. Results also showed that HF patients have higher levels of MVPA and light PA, and lower levels of inactivity during the week compared to the weekends.

Our results differ somewhat from the majority of previous studies reporting very low levels of MVPA in HF patients [3-5]. However, these previous studies have relied on less accurate methods of measuring PA intensity, either using self-reported measures, or categorising accelerometer measured PA intensity using thresholds derived from studies of healthy adults. In this study, we used recently developed HF specific accelerometer intensity thresholds for MVPA to determine MVPA levels of HF patients. Using HF population specific accelerometer intensity thresholds provides a more accurate estimation of PA intensity as the increased energy cost of physical activities and limited exercise tolerance of HF patients are taken into account. Were we to have used the standard thresholds [16-17], it would have been concluded that HF patients undertook 33.2 ± 74.1 mins/week MVPA, and only 19 (8%) of patients met PA guidelines of 150 minutes of MVPA/week.

The three multivariable linear regression models, and three multivariable logistic regression models revealed that lower PA levels were associated with older patients, those with higher BMI, patients who were unemployed, higher NYHA classes, current smokers, higher NT-proBNP levels, and lower ISWT peak distances. Since PA has been shown to have stronger associations with mortality in HF patients than measures of physical fitness [18], these variables may be useful for clinicians to identify those patients for whom PA promoting interventions may be most beneficial, and to tailor the information, PA and exercise plans provided, as recommended in current cardiac rehabilitation guidelines [19-20].

Our results build upon previous studies that showed PA is associated with a number of HF patient clinical characteristics [18, 21-25]. Previous studies have also shown that patients with lower PA levels had a higher burden of comorbidities [18]. In our univariate analyses, we found that apart from diabetes, the presence of other comorbidities in isolation were not associated with PA level. However, the total number of comorbidities was significantly associated with PA level. We found that the number of cardiorespiratory and metabolic comorbidities was associated with PA whereas the number of physical and musculoskeletal was not associated with PA. We also confirm that reduced PA is moderately associated with reduced exercise capacity in HF patients, with ISWT peak distance giving the highest univariate $R^2$ value.

### *4.5.1 Strengths and limitations*

Our study has a number of strengths. We believe this to be the first study objectively assessed PA levels of HF patients using accelerometry and HF-specific intensity thresholds, That PA is measured and reported using a range of methods and metrics makes direct comparison across studies difficult [26]. It is common practice to estimate levels of MVPA from accelerometer data using previously reported PA intensity thresholds, or proprietary, private algorithms from commercially available activity monitors [15-17, 27]. However, these thresholds and algorithms are based on studies using young, healthy adults, therefore may not be applicable to chronic disease or elderly populations [15, 28]. As HF patients have limited exercise capacity, the energy cost of physical activities are higher, [15, 29] so applying these intensity thresholds risks misclassification of PA of HF patients, which is highlighted by our previous comment on MVPA conclusions, had we used the standard intensity thresholds. Using improved MVPA assessment methods, with HF specific intensity thresholds as a potentially more accurate measure in this patient population should provide more precise understanding of the relationships between sociodemographics, exercise capacity, and health and disease status factors and PA levels of HF patients. This study also benefits from a relatively large HF patient sample from two clinical trials and recruited from a number of sites across UK [9-10].

Our study also has some limitations. Because of tolerability, dose of medication was not optimized in all patients. Although each of the multivariable models identified factors with significant associations with PA, over 50% of the variance in MVPA mins/week remained unexplained. Studies have identified motivation, exercise self-efficacy and fear of PA to be barriers to PA in HF patients although these were not assessed in this study [30-31]. Sedentary time has been shown to be a risk factor for poor outcomes in cardiac rehabilitation participants independent of PA level [32]. Inclusion of heart rate data has also been shown to improve accuracy of energy expenditure estimation [33]. Future studies may consider measurement of these additional factors in order to improve PA prediction models.

Although our study sample size was larger than previously reported studies of PA levels in HF patients and associations with various factors in HF [18, 25], the frequency count of some of the demographic variables was low such as ethnic minorities, presence of some comorbidities and taking particular medications. Given the cross-sectional nature of this study, the associations found between PA and sociodemographics, exercise capacity and health status factors cannot be implied to be causal. Longitudinal studies of objectively assessed PA in HF patients using population specific accelerometer intensity thresholds are needed to confirm the results of the present study.

### 4.6 Conclusions

Almost half of the HF patients in this study had objectively assessed levels of MVPA that met current PA recommendations of at least 150 minutes per week of MVPA. However, we also found the level of MVPA to range widely across patients in our study. Patients were less inactive and performed more PA during the week compared to the weekend. Multivariable regression analyses showed that patient age, BMI, employment status, NYHA class I-III, current smoking status, NT-proBNP level, and ISWT peak distance to be strongly associated with the PA levels of HF patients. These factors may be useful to help inform clinicians and researchers how best to target subgroups of HF patients who could most benefit from interventions to increase their PA. Future accelerometry

studies of PA in chronic disease populations need to consistently apply population specific thresholds when estimating MVPA.

### 4.7 References


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**Chapter 5: effect of home-based cardiac rehabilitation (REACH-HF) on objectively assessed physical activity in people with heart failure: pooled analysis of two randomised controlled trials.**

## 5.1 Abstract


Objectives

To quantify the impact of home-based cardiac rehabilitation (CR) on objectively assessed physical activity (PA) of heart failure (HF) patients and to explore the extent by which patient characteristics are associated with a change in PA.

Methods

PA data from two randomised controlled trials of a home-based CR intervention (REACH-HF) plus usual care versus usual care alone (control) were pooled across a total of 247 HF patients. Objective PA was assessed via GENEActiv triaxial accelerometer for 24-consecutive hours for 7 days at baseline (pre-randomisation), post-intervention (4 months) and final follow-up (6-12 months).

Results

There was no difference in PA between REACH-HF and control groups in 7-day PA levels post-intervention or at final follow-up. At final follow-up there was evidence of an increase in weekday moderate-to-vigorous PA (MVPA) (10.9 mins/day, 95% CI: -2.94 to 24.69), and light PA (26.9 mins/day, 95% CI: -0.05 to 53.8) and decrease inactivity (-38.31 mins/day, 95% CI: -72.1 to -4.5) in favour of REACH-HF. Factors associated with an increase in PA from baseline to final follow-up were baseline MVPA, incremental shuttle walk test (ISWT) distance, and HADS anxiety score, and living with a child >18 years ($p<0.05$). Living with a parent was associated with a decrease in MVPA ($p<0.05$).

Conclusion

Whilst participation in the REACH-HF home-based CR intervention did not increase overall weekly activity, week day PA levels were increased and period

of inactivity reduced. CR programmes and related research need to focus on the importance improving levels of objectively assessed PA of people with HF.

## 5.2 Introduction

Physical activity (PA) has numerous health benefits for heart failure (HF) patients including reduced HF mortality and HF hospitalisation, and improved quality of life [1-3]. Current PA guidelines recommend 150 mins/week moderate-to-vigorous PA (MVPA) or the equivalent of 30 mins/day on 5 or more days/week [4, 5].

Traditionally, cardiac rehabilitation (CR) interventions have prioritised increasing exercise capacity rather than PA behaviour, and evidence that CR increases PA toward recommended levels is lacking [6]. To date, only a small number of studies have assessed the impact of CR on PA levels in HF patients, mainly using self-report measures that are known to be prone to over-reporting.[7] HF specific accelerometer intensity thresholds for categorising PA intensity from raw accelerometer data have recently been developed, taking into account the lower resting metabolic rate and requirement for greater energy expenditure during PA in people with HF.[8] Due to the wide range of health benefits associated with increased PA, further studies examining the impact of CR on levels of MVPA in HF patients are required using more objective, population specific PA measurement techniques.

Home-based programmes are increasingly being used to promote the availability and uptake of CR.[9] The primary aim of this study was to assess the impact of home-based CR programme (Rehabilitation Enablement in Chronic Heart Failure (REACH-HF))[10-13] on objectively measured PA using HF specific accelerometer thresholds for estimating intensity. In addition we also explored the patient level characteristics associated with a change in PA level.

## 5.3 Methods

### *5.3.1 Study design*

This study used data pooled from two controlled trials that randomised HF patients 1:1 to a home-based CR intervention consisting of a HF manual, chair based exercise DVD, caregiver resource and progress tracker plus usual care (REACH-HF group) to usual care alone (control group), stratified by site and N-terminal Brain Natriuretic Peptide (NT-proBNP) (ISRCTN78539530 and ISRCTN86234930). Details of these trials are presented elsewhere.[10-13] Ethical approval was granted for the two trials by East of Scotland Research Ethics Service (15/ES/0036) and the North West Lancaster Research Ethics Committee (14/NW/1351).

### *5.3.2 Participants*

A total of 266 HF patients (216 HF with reduced ejection fraction (HFrEF), 50 HF with preserved ejection fraction (HFpEF)) were recruited and completed the baseline visit between January 2015 and February 2016, from primary and secondary care settings in five UK centres (Birmingham, Cornwall, Dundee, Gwent and York). Full inclusion and exclusion criteria are published elsewhere.[12-13] In summary, eligible participants were aged ≥18 years with a confirmed diagnosis of HF on echocardiography, radionuclide ventriculography or angiography within the last 6 months. All participants provided written informed consent.

### *5.3.3 Data collection*

PA data were collected via accelerometry on three occasions; at baseline (pre-randomisation), post-intervention (4 months) and final follow-up (6-12 months). The final follow-up visit varied between the two trials (6 months for HFpEF patients, and 12 months for HFrEF patients) and have therefore been combined for this study.

During the baseline visit, the following data were collected: past medical history (i.e. comorbidities, New York Heart Association (NYHA) class, concomitant medication), sociodemographic information (i.e. age, ethnicity, employment status, smoking status), NT-proBNP measurement via blood sample, exercise tolerance via incremental shuttle walk test (ISWT), and health outcome questionnaires i.e. disease-specific health related quality of life (HRQoL) using the Minnesota Living with Heart Failure Questionnaire (MLHFQ), and the Health

Related Quality of Life (HeartQoL) questionnaire; psychological wellbeing using the Hospital Anxiety and Depression Scale (HADS) questionnaire; generic HRQoL using the EQ-5D-5L questionnaire; and Self-care of HF Index questionnaire (SCHFI).

*Physical activity – accelerometry*

At the clinic visits, participants were provided with and instructed to wear a GENEActiv triaxial accelerometer (GENEActiv, Activinsights, Kimbolton, Cambridge, UK) for 24-consecutive hours for 7 days. Accelerometers were returned to the clinical trials unit using postage-paid envelopes. Data were downloaded using GENEActiv PC software (version 3.2; Activinsights, Kimbolton, Cambridge, UK) and processed in R (R Core Team, Vienna, Austria) using the GGIR software package (version 1.5-18, http://cran.r-project.org). Initial processing included autocalibration, and detection of abnormally high values and non-wear.[14-15] Data were averaged over 5 second epochs and Euclidean Norm Minus One (ENMO) was used to quantify the acceleration related to movement registered and expressed in milligravity units (mg) using the following formula.[16]

$$\sqrt{x^2 + y^2 + z^2} - 1000mg$$

Once the raw accelerometer data was processed, HF specific accelerometer intensity thresholds (inactivity: 16.7mg (left wrist), 18.6mg (right wrist), MVPA: 43.6mg (left wrist), 45.5mg (right wrist)) were applied to calculate the average minutes per day spent inactive, in light PA and MVPA, over all days, weekend days and week days. These thresholds were established by a recent accelerometer calibration study in 21 HF patients.[8] Average weekly MVPA was used to calculate the proportion of patients meeting current PA guidelines. For the primary analysis these metrics were calculated using bouted data, i.e. sustained periods of 10 minutes or more where accelerometer data lies above the intensity threshold (with a 20% allowance for values to fall outside the threshold) in line with current National PA recommendations.[4,5] For secondary analyses, these metrics were calculated using unbouted data, i.e. allowing PA to be accumulated in bouts of any duration.

### *5.3.4 Statistical analysis*

Descriptive statistics were calculated as means and standard deviations or counts and percentages unless otherwise stated.

Data from final follow-up were used for primary analysis in line with the primary end-points of the two trials.[12-13] The intervention effects (i.e. REACH-HF vs control) on average min/day PA (inactivity, light PA and MVPA) over all days, week days and weekend days were examined using linear regression analysis, adjusting for baseline PA (inactivity, light PA or MVPA respectively), treatment group and trial stratification variables (NT-proBNP, centre). Similarly, intervention effects on the proportion of patients meeting PA guidelines was examined using logistic regression. These analyses were repeated at post-intervention follow-up, and using unbouted PA data for secondary analyses.

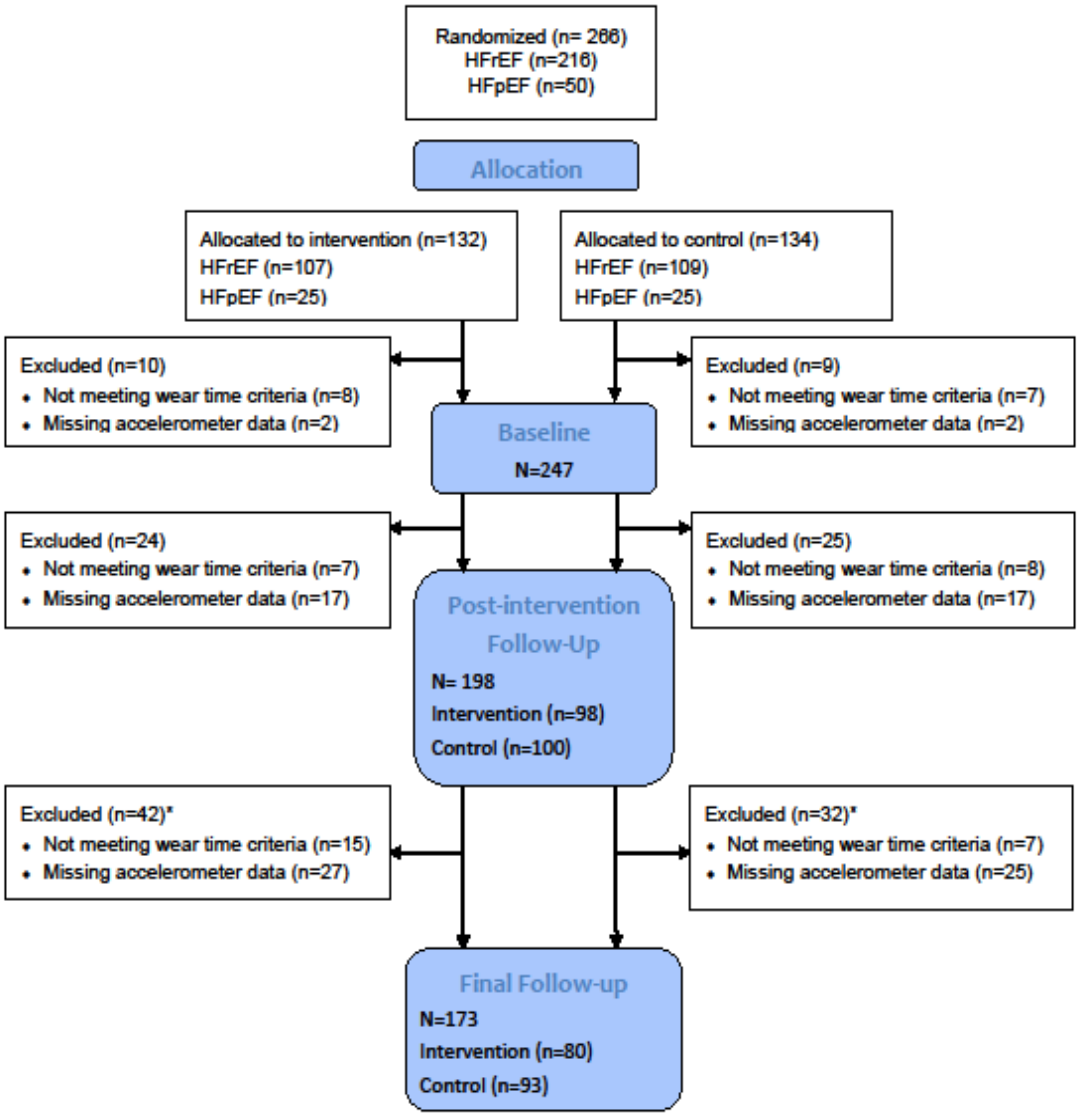
Linear regression was used to investigate the baseline sociodemographic (e.g. age, sex, ethnicity), medical history (e.g. NYHA class, medication), ISWT and health status variables (e.g. HRqOL) associated with change in MVPA, adjusting for baseline MVPA treatment group and trial stratification variables (NT-proBNP, centre).

Variables with statistical evidence of univariate association with change in MVPA ($p<0.15$) were selected for entry into a series of multivariable regression models to establish which variables were independently and most strongly associated with change in PA at final follow-up and post-intervention, mutually adjusting for trial stratification variables, baseline MVPA and treatment group. Model 1 – sociodemographic and medical history variables only, model 2 – exercise capacity and health status variables only, and model 3 – sociodemographic, medical history, exercise capacity and health status variables identified as significant ($p<0.05$) predictors in models 1 and 2. Checks and diagnostics were performed for model assumptions, residuals, multicollinearity (variance inflation factor) and influential observations (Cook's distance). AIC and $R^2$ values were used to inform model comparison and selection.

Statistical analyses were performed using Stata (V.15.0; StataCorp, College Station, Texas, USA).

## 5.4 Results

247 patients had accelerometer data at baseline which met the criteria for inclusion in analysis. Post-intervention, 198 patients were included, and at final follow-up 173 patients were included in the analysis (figure 5.1). Patients were predominantly male (72%), had a mean age of 70.9 ± 10.4 years, and majority NYHA II (60%), full baseline characteristics are described in table 5.1. PA levels did not differ between HFrEF and HFpEF patients at any time point (data not shown).




*14 patients excluded from post-intervention follow-up analysis (for missing data or not enough valid days) were included in the final follow-up with sufficient accelerometer data.

Figure 5.1: Participant flow diagram

Table 5.1: Patient characteristics at baseline. Data are presented as N(%) unless otherwise stated.

| | REACH-HF N=122 | Control N=125 |
|---|---|---|
| Mean (SD) Age (years) | 70.5 (10.0) | 71.3 (10.7) |
| Female Sex | 40 (33) | 30 (24) |
| Mean (SD) BMI (kg/m$^2$) | 29.9 (6.6) | 30.0 (5.9) |
| Employment status | | |
| In employment/ Self- | 15 (12) | 16 (13) |
| employed | 98 (80) | 101 (81) |
| Retired | 0 (0) | 1 (1) |
| Housework | 7 (6) | 3 (2) |
| Unemployed | 2 (2) | 4 (3) |
| Other | | |
| Ethnicity (white vs other) | 7 (6) | 4 (3) |
| NYHA class | | |
| NYHA I | 24 (20) | 16 (13) |
| NYHA II | 71 (58) | 76 (61) |
| NYHA III-IV | 27 (22) | 33 (26) |
| Time since HF diagnosis | | |
| 0 years | 37 (30) | 37 (30) |
| 1 year | 24 (20) | 23 (18) |
| 2 years | 61 (50) | 65 (52) |
| Cause of HF | | |
| Ischaemic | 52 (43) | 63 (50) |
| Non-ischaemic | 63 (52) | 53 (43) |
| Not known/ classified | 7 (5) | 9 (7) |
| Mean (SD) LVEF (%) | 38.4 (14.7) | 38.1 (15.5) |
| Mean (SD) NT-proBNP (pg/ml) | 1288.3 (1794.3) | 1364.4 (1602.1) |
| Living alone | 32 (26) | 34 (27) |
| Living with partner | 79 (65) | 79 (63) |
| Living with child>18 | 7 (6) | 10 (8) |
| Living with child<18 | 3 (2) | 2 (2) |
| Living with parent | 2 (2) | 3 (2) |

| | | |
|---|---|---|
| Smoking history | | |
| Current smoker | 7 (6) | 7 (5) |
| Ex-smoker | 67 (55) | 72 (58) |
| Never smoked | 48 (39) | 46 (37) |
| Trial site | | |
| Truro | 27 (22) | 29 (23) |
| Gwent | 22 (18) | 22 (18) |
| Birmingham | 24 (20) | 24 (19) |
| York | 25 (20) | 25 (20) |
| Dundee | 24 (20) | 25 (20) |
| Comorbidities | | |
| Angina | 32 (26) | 33 (26) |
| Diabetes | 31 (25) | 28 (22) |
| MI | 29 (24) | 41 (33) |
| Hypertension | 59 (48) | 54 (43) |
| Osteoporosis | 11 (9) | 6 (5) |
| Stroke | 14 (11) | 15 (12) |
| Asthma | 14 (11) | 14 (11) |
| Chronic back pain | 40 (33) | 36 (29) |
| Chronic renal impairment | 17 (14) | 28 (22) |
| Arthritis | 57 (47) | 50 (40) |
| Atrial fibrillation | 51 (42) | 67 (54) |
| COPD | 13 (11) | 14 (11) |
| Depression | 30 (25) | 31 (25) |
| Total number of comorbidities | 3 (2-5) | 3 (2-5) |
| Medication | | |
| Angiotensin II receptor | 38 (31) | 27 (22) |
| antagonist | 71 (58) | 84 (67) |
| ACE inhibitor | 62 (51) | 56 (45) |
| Aldosterone antagonist | 52 (43) | 62 (50) |
| Anticoagulant | 99 (81) | 95 (76) |
| Beta blocker | 23 (19) | 16 (13) |
| Digoxin | 5 (4) | 8 (6) |
| Ivabradine | 83 (68) | 87 (70) |
| Loop diuretic | 22 (18) | 16 (13) |

| | | |
|---|---|---|
| Nitrate | 1 (1) | 3 (2) |
| Thiazide diuretic | | |
| Type of HF (HFrEF vs HFpEF) | 24 (20) | 25 (20) |
| Mean (SD) ISWT (peak distance, m) | 241.9 (157.1) | 219.1 (144.2) |
| Mean (SD) MLHFQ | | |
| Overall | 33.5 (24.5) | 30.7 (23.0) |
| Physical | 17.3 (11.8) | 16.1 (11.6) |
| Emotional | 7.7 (7.7) | 7.1 (7.0) |
| Mean (SD) HADS | | |
| Anxiety | 5.3 (4.5) | 5.9 (4.4) |
| Depression | 4.8 (3.6) | 4.8 (3.4) |
| Mean (SD) HeartQoL | | |
| Global | 1.8 (0.8) | 1.8 (0.8) |
| Physical | 1.6 (0.8) | 1.6 (0.8) |
| Emotional | 2.1 (0.9) | 2.1 (0.9) |
| Mean (SD) EQ-5D-5L | 0.7 (0.3) | 0.7 (0.3) |
| Mean (SD) SCHFI | | |
| Maintenance | 56.0 (16.1) | 53.0 (15.4) |
| Management | 42.0 (24.7) | 39.6 (20.4) |
| Confidence | 61.9 (25.2) | 63.6 (23.4) |

REACH-HF: Rehabilitation enablement in chronic heart failure; SD: standard deviation; BMI: body mass index; NYHA: New York Heart Association; HF: heart failure; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal proB-type natriuretic peptide; MI: myocardial infection; COPD: chronic obstructive pulmonary disease; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; ISWT: incremental shuttle walk test; MLHFQ: Minnesota living with heart failure questionnaire; HADS: hospital anxiety and depression scale; SCHFI: self-care in heart failure index.

### *5.4.1 Intervention analysis*

The average change in daily MVPA (over all 7 days) at final follow-up in the REACH-HF group was 4.0 mins/day, but varied greatly (minimum -91.2, maximum 291.7, SD 51.5 min/day). The control group average MVPA change at final follow-up was -5.1 mins/day (min -135.7, max 173.2, SD 34.2 min/day). No between group differences were seen in PA changes over all days or weekend days (table 5.2). However, an increase in at least light intensity, bouted PA on weekdays and a decrease in weekday inactivity (mins/day) was seen in the REACH-HF group with the reverse found in the control group (between group differences in favour of REACH-HF: light PA: 26.87 (95% CI -0.05 to 53.78), p=0.05, inactivity: -38.31 (95% CI -72.13 to -4.5), p=0.03).

In terms of prevalence of meeting PA guidelines, no differences were found between REACH-HF and control group at final follow-up (table 5.3). There was an increase in unbouted weekday MVPA and a decrease in weekday inactivity in the REACH-HF group, with the reverse found in control group, (between group differences showing a trend in favour of REACH-HF (MVPA: 15.18 (95% CI -0.32 to 30.67), p=0.06; inactivity: -21.25 (95% CI -43.24 to 0.75), p=0.06; appendix 5.1).

At post-intervention follow-up, the average change in daily MVPA (over all 7 days) in the REACH-HF group was 1.7 mins/day (minimum -76.9, maximum 177.7, SD 26.4 min/day). In the control group average MVPA change was 2.0 min/day (minimum -96.3, maximum 150.6, SD 33.1 min/day). There were no significant differences between REACH-HF group and control for all PA intensities, days (all, weekend or week), and bouted or unbouted PA, or proportion of patients meeting PA guidelines (appendices 5.2-5.4).

Table 5.2: Intervention effects on PA outcomes at final follow-up

| | Baseline | | Final follow-up | | Δ to final follow-up | | Between group difference (mean, 95% CI) p-value |
|---|---|---|---|---|---|---|---|
| | REACH-HF mean (SD, N) | Control mean (SD, N) | REACH-HF mean (SD, N) | Control mean (SD, N) | REACH-HF mean (SD, N) | Control mean (SD, N) | |
| *All days Bouted* | | | | | | | |
| MVPA (min/day) | 43.62 (51.15, 80) | 49.66 (73.98, 93) | 47.61 (67.78, 80) | 44.56 (72.10, 93) | 3.99 (51.53, 80) | -5.10 (34.23, 93) | 7.61 (-5.11 to 20.33) p=0.24 |
| Light (min/day) | 213.80 (110.94, 80) | 219.93 (114.73, 93) | 221.92 (129.57, 80) | 209.50 (120.90, 93) | 8.12 (87.01, 80) | -10.43 (87.85, 93) | 16.87 (-8.79 to 42.54) p=0.20 |
| Inactive (min/day) | 1182.58 (144.43, 80) | 1170.41 (164.42, 93) | 1170.47 (170.47, 80) | 1185.78 (167.52, 93) | -12.12 (115.83, 80) | 15.53 (10.52, 93) | -24.77 (-56.69 to 7.16) p=0.13 |
| *Weekend Days Bouted* | | | | | | | |
| MVPA (min/day) | 43.72 (56.62, 80) | 41.0 (69.84, 93) | 38.67 (61.04, 80) | 36.43 (62.10, 93) | -5.05 (52.27, 80) | -4.57 (43.31, 93) | 0.14 (-12.92 to 13.21) p=0.98 |
| Light (min/day) | 208.10 (123.23, 80) | 202.18 (118.25, 93) | 201.36 (128.36, 80) | 206.22 (123.41, 93) | -6.75 (107.42, 80) | 4.04 (103.72, 93) | -8.38 (-37.96 to 21.20) p=0.58 |
| Inactive (min/day) | 1188.18 (161.84, 80) | 1196.82 (160.52, 93) | 1199.98 (162.57, 80) | 1197.35 (158.21, 93) | 11.80 (131.33, 80) | 0.53 (121.78, 93) | 8.27 (-27.01 to 43.55) p=0.64 |
| *Week Days Bouted* | | | | | | | |
| MVPA (min/day) | 43.58 (50.71, 80) | 53.12 (79.66, 93) | 51.19 (71.70, 80) | 47.82 (78.90, 93) | 7.61 (55.14, 80) | -5.31 (37.46, 93) | 10.87 (-2.94 to 24.69) p=0.12 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Light (min/day) | 216.08 (112.68, 80) | 227.03 (120.85, 93) | 230.15 (135.37, 80) | 210.81 (125.37, 93) | 14.07 (90.71, 80) | -16.22 (92.74, 93)* | 26.87 (-0.05 to 53.78) p=0.05 |
| Inactive (min/day) | 1180.34 (143.59, 80) | 1159.85 (174.23, 93) | 1158.66 (178.56, 80) | 1181.37 (178.59, 93) | -21.68 (122.78, 80) | 21.53 (106.40, 93)* | -38.31 (-72.13 to -4.5) p=0.03 |

REACH-HF: Rehabilitation enablement in chronic heart failure; SD: standard deviation; MVPA: moderate-to-vigorous physical activity; PA: physical activity

* $p<0.05$ REACH-HF group vs control

Table 5.3: Intervention effects on proportion of patients meeting PA guidelines at final follow-up

| | Baseline | | Final follow-up | | OR (95% CI) p-value |
|---|---|---|---|---|---|
| | REACH-HF (n, N, %) | Control (n, N, %) | REACH-HF (n, N, %) | Control (n, N, %) | |
| Bouted | | | | | |
| Proportion meeting guidelines | 42, 80, 53% | 45, 93, 48% | 43, 80, 54% | 39, 93, 42% | 0.43 (0.16 to 1.14) p=0.09 |
| Unbouted | | | | | |
| Proportion meeting guidelines | 80, 80, 100% | 93, 93, 100% | 79, 80, 99% | 93, 93, 100% | - |

REACH-HF: Rehabilitation enablement in chronic heart failure; OR: odds ratio

### *5.4.2 Univariate regression analysis*

Appendix 5.5 shows the associations between baseline sociodemographic, clinical and behavioural patient variables and change in MVPA at final follow-up. Older patients were more likely to show a decrease in MVPA ($p<0.05$), whereas patients living with a child >18 years, with greater ISWT distance, and higher HADs anxiety score were more likely to increase their MVPA ($p<0.05$).

Post-intervention, presence of diabetes and SCHFI maintenance scores at baseline were associated with a decrease in MVPA ($p<0.05$), whereas individuals with greater ISWT distance at baseline were more likely to increase their MVPA ($p<0.05$; appendix 5.6).

### *5.4.3 Multivariable regression analysis*

Table 5.4 shows the multivariable prediction models at final follow-up. In model 1: baseline MVPA and living with a parent was associated with a decrease in MVPA and living with a child aged >18 years was associated with an increase in MVPA. This model accounted for 15% of the variance in change in MVPA. Three patients were removed with high residual (e=211.5, e=258.3 and e=182.0) and Cook's distance d=0.35, d=0.39 and d=0.04). In model 2: baseline MVPA was associated with a decrease in MVPA, and ISWT distance and HADS anxiety score were associated with an increase in MVPA. This model accounted for 9% of the variance in MVPA change. In model 3: ISWT distance, living with a child aged over 18 years, and HADS anxiety score were strongly associated with an increase in MVPA, and living with a parent and baseline MVPA were associated with a decrease in MVPA. The model explained 15% of the variance in MVPA change at final follow-up.

Multivariable models to predict change in MVPA post-intervention are presented in appendix 5.7. In model 1: living with a parent was associated with an MVPA increase, and baseline MVPA and presence of diabetes with an MVPA decrease. This model explained 10% of the variance in MVPA change. In model 2: baseline MVPA was associated with a decrease in MVPA, and ISWT distance was most strongly associated with an increase in MVPA. The model accounted for 10% of the variance in MVPA change. In model 3: living with a parent and ISWT distance were associated with MVPA increases, and baseline

MVPA and presence of diabetes were strongly associated with MVPA decrease. This model accounted for 14% of the variance in MVPA change.

Variance inflation factor ranged from 1.06 – 1.18 across the 6 models indicating a low level of multicollinearity.

Table 5.4: Comparison of multivariable models to predict change in minutes/day MVPA at final follow-up.

| Multivariable model | Variables included in model (p<0.05) | Unstandardized beta coefficient (95% CI) | t-statistic | Variable P-value | Model Adjusted $R^2$ (p-value) |
|---|---|---|---|---|---|
| **1. Socio-demographic** | Group | -4.03 (-12.19 to 4.12) | -0.98 | 0.33 | 0.15 |
| | Baseline MVPA | -0.15 (-0.22 to -0.09) | -4.64 | <0.001 | (<0.001) |
| | Centre | -0.28 (-3.0 to 2.45) | -0.20 | 0.84 | |
| | BNP 2000 | -6.58 (-17.27 to 4.10) | -1.22 | 0.23 | |
| | Live with parent | -41.81 (-72.96 to -10.67) | -2.65 | 0.009 | |
| | Live with child >18 | 16.04 (0.05 to 32.02) | 1.98 | 0.049 | |
| | constant | 5.89 (-4.92 to 16.70) | 1.08 | 0.28 | |
| **2. Exercise capacity and health status** | Group | -6.72 (-19.81 to 6.37) | -1.01 | 0.31 | 0.09 (0.001) |
| | Baseline MVPA | -0.20 (-0.31 to -0.09) | -3.47 | 0.001 | |
| | Centre | 0.13 (-4.34 to 4.60) | 0.06 | 0.95 | |
| | BNP 2000 | -7.39 (-25.08 to 10.30) | -0.83 | 0.41 | |
| | ISWT peak | 0.07 (0.02 to 0.11) | 2.69 | 0.008 | |
| | HADs anxiety | 1.90 (0.41 to 3.38) | 2.52 | 0.013 | |
| | constant | -12.91 (-37.03 to 11.21) | -1.06 | 0.29 | |
| **3. Socio-demographic, exercise capacity and health status*** | Group | -8.37 (-21.13 to 4.38) | -1.3 | 0.20 | 0.15 |
| | Baseline MVPA | -0.21 (-0.33 to -0.10) | -3.73 | <0.001 | (<0.001) |
| | Centre | -0.11 (-4.47 to 4.25) | -0.05 | 0.96 | |
| | BNP 2000 | -6.21 (-23.44 to 11.01) | -0.71 | 0.48 | |

| | | | | |
|---|---|---|---|---|
| | ISWT peak | 0.08 (0.03 to 0.12) | 3.16 | 0.002 |
| | Live with child >18 | 30.48 (5.92 to 55.04) | 2.45 | 0.02 |
| | HADS anxiety | 1.89 (0.44 to 3.33) | 2.58 | 0.01 |
| | Live with parent | -52.60 (-100.16 to -5.05) | -2.19 | 0.03 |
| | constant | -14.51 (-38.05 to 9.04) | -1.22 | 0.23 |

MVPA: moderate-to-vigorous physical activity; BNP 2000: NT-proBNP above or below 2000 pg/ml; ISWT: incremental shuttle walk test; HADS: hospital anxiety and depression score

* all variables $p<0.05$ from multivariate models 1 and 2

## 5.5 Discussion

We believe this to be the first analysis of randomised controlled trial data of a CR intervention (REACH-HF) objectively assessing PA levels of people HF using intensity thresholds specifically developed for HF. Compared to control, participation in REACH-HF had no impact on daily PA levels when averaged over the 7 days of the week. However, separating weekend and weekdays revealed important different patterns in the PA response. Average weekday PA levels showed a consistent trend where MVPA and light PA increased, and inactivity decreased in the REACH-HF group. Over weekend days, the reverse appeared to be true, with an increase in inactivity and decrease in PA.

As some 45% of patients in the REACH-HF trials were already meeting UK PA guidelines at baseline (based on bouted data), it may be that there was a ceiling effect, where those already physically active would have difficulty further improving upon MVPA levels, making small changes in PA difficult to pick up statistically. This has often been the case in other CR trials.[6] Our findings also suggest that the REACH-HF participants compensated for increased PA during the week by being less active at the weekend. Understanding of the behavioural effects of a home-based CR intervention could provide a key target for clinicians to encourage patients to increase PA and reduce inactivity at the weekend as well as during the week, which could lead to more marked increases in overall weekly PA levels.

### *5.5.1 Regression analysis*

Given the large variation in PA differences from baseline up to final follow-up in MVPA, we were interested to investigate potential factors associated with a change in MVPA. Living with a parent, presence of diabetes, baseline MVPA and ISWT distance, living with a child >18 years and baseline HADS anxiety score were closely associated with a change in MVPA up to 12 months follow-up. Only baseline ISWT distance was consistently associated with an increase in MVPA across both follow-up time points. This finding suggests that individuals with higher exercise tolerance may find it easier to increase their PA levels. Our results also showed that particular living situations of the patient had a strong association with PA change (living with a parent or child >18 years),

which may indicate involvement of family members is associated with PA behaviour change and self-care of HF patients.[19] Understanding the factors associated with change in PA with CR intervention could potentially enhance development of tailored interventions targeting particular sub-groups where a change in PA is either more or less likely to occur.

Although some studies have shown that PA levels are associated with a number of factors including age, BMI, exercise capacity and disease severity in HF patients, these have been limited by cross-sectional design that do not measure within-person PA change. [20-22] Therefore it is difficult to compare our results to other HF or chronic disease studies.

### *5.5.2 Strengths and limitations*

This study has a number of strengths. Firstly, the objective measurement of PA, and robust and rigorous accelerometer data processing and analysis. Literature reporting accelerometer measured PA in HF patients with CR intervention is limited, especially in large, representative samples. The use of population specific intensity thresholds provides a more reliable estimate of PA levels of HF patients, compared to application of commonly used thresholds based on healthy adults.[8] However, we acknowledge that these are based on a small heterogeneous sample of patients, and is not a perfect method. Application of a single threshold for MVPA to a population will always lead to a proportion of patients PA being misclassified due to heterogeneity in exercise tolerance. Therefore further studies are required to find an alternative approach.

This study highlights the benefit of extracting more detailed PA data, looking beyond a single PA metric (i.e. average weekly MVPA), and considering within-week differences in PA patterns. Looking at the unbouted data also provides useful information in HF patients as performing continuous bouts of exercise for 10 minutes or more may be challenging with limited exercise tolerance. However, in increasing granularity, statistical power is reduced and future studies should consider this in sample size calculations. Future studies could also consider the distribution of PA both between- and within-days in HF patients, since research has shown that afternoon and evening PA decreases with increasing age.[23] This could inform future intervention development,

targeting inactive periods throughout both the week and the day best placed for PA modification.

As this was an exploratory study, multiple repeated independent tests were conducted comparing treatment groups, and between baseline predictors and change in MVPA. Given the dangers of multiple testing, which may have led to increased Type 1 errors, our results must be treated with caution. In addition, variables associated with MVPA change were inconsistent across the two follow-up points and explained only a small proportion (10-15%) of the variance in MVPA change and combining the final follow-up data sets from 6 and 12 months may have introduced variation to the data. Whilst the sample size was sufficient for this exploratory study, some of the frequency counts of variables included in the multivariable models were low. Further studies using objective PA assessment are needed in order to clarify the impact of exercise-based CR interventions in HF patients and the patient factors associated with change in PA.

## 5.6 Conclusion

This pooled analysis of randomised controlled trials shows that participation in a home-based CR intervention has no impact objectively measured on 7-day PA of HF patients but did appear to increase weekday PA levels.

## 5.7 References

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## Chapter 6: Discussion

Exercise-based CR is considered a key element in the management of HF with strong evidence of improvements in patient exercise capacity and health-related quality of life and reduction in the risk of hospitalisation. [1] In addition, exercise-based CR seeks to increase PA levels so that HF patients meet the national PA recommendations of at least 150 minutes per week of MVPA. [2, 3] With developments in PA measurement technology in recent years, there has been an increasing shift away from self-reported, subjective measures of PA that are prone to recall and social desirability bias, towards objective measures of PA. Accelerometry has become the most widely used objective method, with wrist-worn devices often used in large population assessment studies, due to minimal burden to participants and high levels of precision and adherence. [4] Accelerometers do not directly measure PA, but acceleration, and estimates of PA levels are based on the relationship between accelerometer values and PA intensity.

Studies measuring PA levels of HF patients with accelerometers have consistently reported HF patients have low levels of PA. [5-7] but are limited by small sample sizes and use of proprietary accelerometer algorithms. [5, 6] Proprietary accelerometers use closed, commercially owned algorithms to transform the raw data into units of activity, such as activity counts, which complicates comparison and interpretation of results across studies using different brands of accelerometer. Although more reliable than self-report, another fundamental limitation of previous studies of PA measurement is that they have applied thresholds of acceleration to estimate PA intensity based on studies of healthy adults rather than HF-specific populations. [7] Given the limitations in physical function of patients with HF compared to healthy adults, these previous accelerometry studies are at high risk of misclassifying and underestimating HF patient PA levels. [8] Reliable and accurate classification of PA levels in HF patients, is needed to not only determine the impact of interventions (such as exercise-based CR) on the PA levels of participants but also to quantify the potential associations of PA with patient health outcomes, such as HRQoL.

The overarching aim of this thesis was to contribute to the further knowledge and understanding of PA in people with HF, and how exercise-based CR can impact this.

The specific aims were to:

(1) Undertake a systematic review to assess the evidence as to whether participation in exercise-based CR increases PA levels of cardiac patients, including those with HF (Chapter 2),

(2) Undertake an accelerometer calibration study and develop HF specific accelerometer intensity thresholds for MVPA and inactivity (Chapter 3),

(3) Examine the PA levels of HF patients, and associations between baseline PA and patient-level factors including sociodemographics, exercise capacity, and health-related quality of life (Chapter 4),

(4) Determine whether a home-based, self-help CR intervention improves PA levels of people with HF, and the sociodemographic, exercise capacity and HRQoL factors associated with a change in PA level (chapter 5).

This discussion chapter presents: (1) an overview of the key findings of each of the empirical chapters 2, 3, 4 and 5, (2) discussion of the overarching strengths and limitations of the research work undertaken (3) an overview of clinical and policy implications of the results, and (4) identification of directions for future research in this field.

## 6.1 Overview of the findings

*Systematic review of exercise-based CR*

This study (presented in chapter 2) which built upon two previous reviews [9, 10] identified forty RCTs comparing exercise-based CR to control (usual care or no CR) which measured pre- and post-CR PA levels of 6480 patients (655 HF and 5825 CHD). Only 25% (38/145) of reported comparisons reported statistically significant increases in PA in favour of CR over control. However,

meta-analyses of studies showed participation in CR was associated with an increase in some of the PA outcomes i.e. steps/day (1423 steps, 95% CI 757.1 to 2089.4, p<0.001) and energy expenditure (878.4 kcal/week, 95% CI 433.8 to 1323.0, p=0.0001) at short term follow-up, proportion of patients categorised as physically active both at short and long term follow-up (short term: RR 1.55, 95% CI 1.19 to 2.02, p=0.001; long term: RR 1.48, 95% CI 1.19 to 1.83, p=0.0003), and reduced proportion of patients categorised sedentary or not physically active at short term follow-up (RR 0.76, 95% CI 0.61 to 0.95, p=0.02). The study concluded that there was moderate evidence to support that CR positively impacts PA levels of patients with CHD and HF compared to control. Increases appeared to be consistent regardless of whether studies used subjective or objective measures of PA and improvements appeared to be the result of the exercise training component of PA rather than the education or psychosocial elements of the intervention. [11]

However, the review identified few studies that fully characterised the frequency, intensity and duration of PA undertaken. This study highlighted the need for a more complete characterisation of PA and HF specific methods for measuring PA, in order to make firm conclusions and determine whether PA improvements are clinically meaningful.

*Accelerometer calibration study to develop HF specific intensity thresholds*

This study (presented in chapter 3) sought to determine the accelerometer threshold values that correspond to ‘inactivity’ (<1.5 METS) and ‘MVPA’ (≥3.0 METS) in patients with HF during daily living activities with direct assessment of oxygen consumption.

Twenty-one patients with HF were included in the analysis out of 22 recruited. Patients had a mean age of 71 years, were majority male (77%), and NYHA class II (82%). The HF specific intensity thresholds identified for inactivity were (right wrist: 18.6mg (95% CI 8.8 to 28.4mg), left wrist: 16.7mg (95% CI 7.8 to 25.6mg), waist: 7.6mg (95% CI -3.1 to 18.4mg)) and MVPA (right wrist: 45.5mg (95% CI 31.9 to 59.1mg), left wrist: 43.6 (95% CI 38.5 to 56.3mg), waist: 40.6mg (95% CI 24.3 to 57.0)). These values are much lower than previously published and frequently applied thresholds based on healthy adults i.e. inactivity: wrist 45.8mg, waist 46.9mg; MVPA: wrist 93.2mg, waist 68.7mg. [12,

13] It was shown that HF patients had lower mean resting metabolic rate than the assumed metabolic rate used in standard MET calculations (2.67 vs 3.5 ml/kg/min) and required more energy to perform daily living activities. For example, walking at any speed or perceived effort level constituted a moderate intensity (≥3 METS) activity for the majority of patients. This study demonstrates the problem of applying accelerometer thresholds derived from healthy population studies to patient populations such as HF who typically have low exercise capacity. Doing so can result in misclassification of PA intensity, and underestimation of PA levels and proportions of patients meeting PA recommendations. This study demonstrated that a 'one size fits all' approach to acceleration cut point methods is not appropriate in HF patients. [8]

*Secondary analysis of REACH-HF trials: level and predictors of baseline PA*

Using the accelerometer thresholds determined in chapter 3, this study (chapter 4) sought to assess the PA levels of HF patients and then to examine the sociodemographic, exercise capacity and health status outcomes associated with MVPA levels. The study used data from the two RCTs of a home-based CR intervention (REACH-HF). [14, 15] A total of 247 patients were included with mean age 70.9 years, 72% male, 99% NYHA I-III. Almost half (45%) of the patients were found to meet current PA recommendations of 150 minutes per week of MVPA at baseline. However, MVPA ranged widely across the patients from 0 to 375.2 minutes per week. Multivariable regression analyses showed that patient age, BMI, employment status, NYHA class, smoking status, NT-proBNP level, and ISWT peak distance were each strongly associated ($P<0.05$) with baseline MVPA levels of patients with HF.

*Secondary analysis of REACH-HF trials: intervention effect and on PA*

Using the data from the REACH-HF trials and the HF-specific PA intensity thresholds (chapter 3), this study (chapter 5) sought to determine whether a CR intervention improved PA levels of people with HF, and the sociodemographic, exercise capacity and health status outcome predictors of change in PA level. No differences in PA levels at post-intervention follow-up at any PA intensity, days (all, weekend or week) and bouted or unbouted PA data were found between REACH-HF compared to control group. However, at final follow-up there was evidence of an increase in weekday light PA (26.9 mins/day, 95% CI:

-0.05 to 53.8, p=0.05) and a decrease in inactivity (-38.31 mins/day, 95% CI: -72.1 to -4.5, p=0.03), in favour of the REACH-HF group. Over weekend days, the reverse appeared to be true, with an increase in inactivity and decrease in PA.

PA differences from baseline up to final follow-up in the REACH-HF group varied greatly from -91.2 to 291.7 mins/day. Multivariable regression analyses showed that baseline ISWT distance and HADS anxiety score, baseline MVPA levels, presence of diabetes and living with a parent or child >18 years were associated with a change in PA. However, these factors were inconsistent across the two follow-up time points, and only explained a small percentage (10-15%) of the variation in PA change.

### 6.2 Strengths and limitations

The strengths and limitations specific to the four studies above are presented within each of the respective chapters. There were some important overarching strengths and limitations of the research work undertaken and presented in this thesis – (1) systematic and comprehensive approach, (2) use of accelerometry and data reduction methods, (3) calibration study methods; (4) generalisability of study population samples.

*(1) Systematic and comprehensive approach*

An overarching strength of this thesis was its focus on the understanding of PA in people with HF, and how exercise-based CR can impact this. The thesis was planned with each of the four linked research studies that build upon and feed into the next. For example, the systematic review highlighted several limitations to the evidence base such as the poor quality of PA measurement with considerable variation in the adopted PA assessment techniques and PA metrics reported. This warranted the subsequent calibration study to develop HF specific acceleration values for estimating the time spent in different PA intensities. The HF-specific accelerometer intensity thresholds were then applied to the REACH-HF data set to provide valuable information regarding the objectively measured PA levels of a large, representative sample of HF patients

prior to exercise-based CR and the sociodemographic, exercise capacity and health status variables closely associated with PA levels. Finally, bringing together all the findings of the previous studies to determine whether a home-based CR intervention impacts the PA levels of HF patients, and what sociodemographic, exercise capacity and health status factors at baseline may predict a change in PA.

Rigorous methods were used in each research stage. The systemic review (chapter 2) was conducted and reported in line with Cochrane guidelines and Preferred Reporting Items for Systematic Reviews and Meta-analyses statement [16, 17] ensuring systematic and transparent methods of searching, screening and data extraction. After extensive literature searches, only RCTs with control groups involving usual care or no exercise were included to ensure high quality evidence, and methodological quality was assessed using the Cochrane risk of bias tool [16]. This study provides a comprehensive summary of the evidence base for exercise-based CR on PA levels of patients with HF and CHD and is the first meta-analysis in this area. In chapter 3, novel HF population specific accelerometer intensity thresholds were developed after multiple data reduction and analysis techniques were explored in order to find the best model fit, and validation analysis performed to check the performance of the derived intensity thresholds. This then enabled accurate quantification of PA levels and investigation into the factors associated with PA in a cohort of HF patients in chapter 4, and detailed assessment of the impact of a home-based CR programme (REACH-HF [14, 15]) on the PA levels of HF patients compared to usual care control in chapter 5. In both chapters 4 and 5 statistical model checks and diagnostics were performed along with sensitivity analyses in order to obtain the best model fit for the data.

*(2) Use of accelerometry and data reduction methods*

A strength of the linked nature of the research studies in this thesis was the consistent use of accelerometer technology, i.e. GENEActiv accelerometer devices (chapters 3-5) and comprehensive, robust and transparent data processing and analysis techniques. As noted in the systematic review, although accelerometery data have been reported in previous CR intervention studies, inconsistency in data processing methods, choice of intensity

thresholds and researcher decisions regarding device wear time criteria, location and outcome metrics make comparisons across studies challenging. GENEActiv devices have known reliability and validity and allow acceleration data captured at a high sampling frequency in its raw format. [18, 19] Devices that produce raw acceleration values offer researchers increased opportunity for development of new and innovative data processing techniques and facilitate the comparison between studies. GENEActiv accelerometers have been shown to be comparable to other accelerometer brands that also produce raw data. [20, 21] The use of the open source R package GGIR also facilitates transparent data processing. Accelerometer data collection, processing, reduction and analysis techniques used in chapters 3-5 were comprehensive, and reported according to best practice papers [22, 23], ensuring reproducibility and transparency, as consensus on gold standard methodology, particularly in chronic disease populations is yet to be established. [24]

However, accelerometers are not without limitations. Accelerometers are unable to accurately distinguish activities that require upper body effort (i.e. carrying a load). This was demonstrated in the calibration study, where measured MET values for walking whilst carrying shopping bags were slightly higher than walking at the same pace without carrying any load, whereas accelerometer values were lower (table 3.2). In addition to this, accelerometers are not able to distinguish walking on an incline from walking on a flat surface, or walking up flights of stairs, each of which requires greater energy expenditure [25]. Accelerometer placement location on different parts of the body also impacts measurement accuracy, and it is not clear which placement location provides the best recording of whole-body movement. For example, activities requiring large amounts of upper body movement whilst stationary are challenging to capture with a single accelerometer, as demonstrated by the washing up activity of the calibration study, where the wrist accelerometer values were much higher (recording values similar to walking), than the waist worn accelerometer (table 3.2). A single accelerometer will also be unable to accurately capture other activities such as non-ambulatory forms of locomotion i.e. driving or cycling, and swimming. [26] However, the majority of HF patients' PA will tend to consist of walking and household activity, which both wrist- and hip-worn GENEActiv accelerometers have been proven to be accurate at measuring. [18, 19]

Within the calibration study (chapter 3), multiple data reduction algorithms were explored. SVM, MAD and ENMO [18, 27, 28] are commonly used methods to summarise raw triaxial accelerometer data into a single vector magnitude. It was found that ENMO was not suitable for further analysis because of the low level of movement performed by the HF patients, which led to a large amount of 0s returned for activities. The data reduction method that performed best in the calibration study was SVM, thus the derived accelerometer thresholds were SVM based. GGIR was then used in the two secondary analyses of chapters 4 and 5 to process the accelerometer data of participants. GGIR is designed for use with ENMO, and not SVM. However, there is currently no universally accepted method for data reduction, analysis and presentation of accelerometer outcome data in chronic disease populations. [29, 30] Since other comparable intensity thresholds are based on ENMO, and GGIR is currently the only openly available processing package for accelerometer data, the accelerometer data was run through GGIR the same way for consistency.

*(3) Calibration study methods*

The calibration study methods were informed by studies undertaken by researchers in the field of public health, who have identified that cut-points or intensity thresholds for adults may not be applicable in elderly populations. [31, 32] Although there is a large literature base for accelerometer validation and calibration studies in children and healthy adults, very few accelerometer calibration studies have been undertaken in chronic disease populations and none in patients with HF, therefore there have been calls for studies in this area [33].

The thresholds were developed using robust data reduction and analysis methods, after multiple techniques were explored in order to obtain the best model fit, and individual resting metabolic rate was measured and used to calculate the metabolic cost of physical activities, in contrast to previous calibration studies. [12, 13] Leave-one-out cross validation analysis was used to validate the derived intensity thresholds. This statistical approach demonstrated that the models fit was generally acceptable but performed less well at higher PA and MET levels. In an attempt to maximise the applicability of the laboratory based activities to daily life, the daily living activities selected for the protocol

were determined with the assistance of a HF patient and public involvement group as activities they typically undertake on a day to day basis, and that would make up the majority of their overall daily PA.

It is acknowledged that this study has methodological limitations, which are common among all laboratory calibration studies. The study is limited by a small heterogeneous sample recruited from a single centre. In addition, the physical activities were undertaken in a laboratory rather than free living conditions. Laboratory based studies can only include a narrow range of specific activities, whereas in a free living scenario many more activities are undertaken that may look similar to laboratory based activities in terms of raw acceleration, but may in fact be entirely different behaviours with different intensities. Overall, these limitations mean that the derived cut-points may only be applicable to the small sample of patients performing the specific activities undertaken as part of the protocol.

The key challenge with this methodological approach to categorising accelerometer measured PA intensity is the substantive level of between subject variability in METS and accelerometer values in populations with compromised resting metabolic rate and exercise tolerance. [31-34] Multiple studies have shown that application of the various available cut-points and intensity thresholds for adults and children to the same sample results in largely discrepant conclusions as to the volume of MVPA undertaken, and prevalence of meeting PA recommendations. [33-40] When both the HF specific and adult intensity thresholds for MVPA were applied to the REACH-HF patient data set significantly different conclusions regarding PA levels of the patients was found depending on the threshold used (i.e. 45% patients met PA guidelines using the HF specific thresholds vs 8% using the adult thresholds) with 63% agreement using Cohen's K test (95% CI 57% to 69%, K= 0.19, $p<0.001$). However, application of a single cut point based on small, heterogeneous samples performing laboratory-based activities will always fail to generalise to the entire population performing free living activities.

A downside of the ability to develop new and innovative techniques with raw accelerometry data, is that it has led to considerable methodological inconsistencies in research, and consensus regarding best practice methods

has yet to be reached, which means data harmonization is still a challenge. Studies in public health have shifted towards more advanced statistical methods such as machine learning. [41, 42] These methods move beyond intensity classification, and enable researchers to identify specific behaviours. However, because national PA recommendations are based on PA intensity, cut-point methods are still used in epidemiological and interventional studies, [7, 43] despite knowledge that this may not be appropriate. [8] Therefore, even with limitations in terms of the level of precision, intensity classification via calibration studies remains useful until a better solution is agreed upon.

*(4) Generalisability of study population samples*

A limitation common to each of the studies that make up this thesis is their limited sample size that can limit the generalisability to the wider HF population. Many of the studies included in the systematic review and meta-analyses had small samples recruited from a single centre, and an average patient age of 58 years, lower than the national average of patients undertaking CR (centre based 65 years, home based 67 years), and much lower than the mean age of HF patients at diagnosis in the UK of 77 years. [44, 45] Individual studies were often underpowered to detect small differences in PA, with only 4 of the studies including formal sample size calculations based on PA outcomes.

The calibration study presented in chapter 3 is limited by a small heterogeneous sample recruited from a single centre. The patient sample of 21 was small in comparison to some previous calibration studies [12, 13] and heterogeneous. However, power calculations suggested a minimum sample size of 18 patients. Nevertheless, this limits our ability to draw firm conclusions, in particular regarding how disease severity may influence the accelerometer values relating to MVPA, since few patients at higher NYHA class (i.e. III-IV) were included in the study. Due to the limitations of PhD budget, timeline and logistics the sample was chosen for convenience. The patients included in the calibration study were comparable to the REACH-HF patients in terms of age and comorbidities, however the REACH-HF patients performed better in their baseline ISWT.

Although the study samples of the multicentre REACH-HF studies are larger and more representative of the wider HF population, [12, 13, 46-52] the

frequency counts of some of the predictors such as ethnic minorities, presence of particular comorbidities and taking particular medications were low, and few patients classified as NYHA class IV were included, limiting generalisability. In chapter 5, it was demonstrated how aggregating PA behaviour into a single metric, i.e. average weekly MVPA, can mask other important associations in PA data. Increasing the granularity of the data in order to observe differences in weekend and weekday PA, provided valuable information about the ways in which exercise-based CR can impact PA behaviour. However, the limited sample size in the REACH-HF data set, combined with the increased granularity of the PA data meant the analysis may be underpowered. The results should also be interpreted with some degree of caution as multiple repeated tests were conducted.

## 6.3 Implications for practice and policy

The findings presented in this thesis have several important implications for both clinical practice and healthcare policy relating to two broad topics – (1) practice of PA assessment, and (2) implications for CR practice.

*(1) PA assessment*

Accelerometer PA measurement in chronic disease populations is under-researched and consensus regarding the most appropriate and accurate way to measure PA in chronic disease populations is urgently required. The calibration study presented in chapter 3 aimed to develop an improved approach to categorising PA intensity in HF patients and provide a signal to clinicians and researchers that thresholds for moderate intensity based on healthy adults are not appropriate for application in HF patients. In line with many previous studies reporting low PA levels of HF patients which used accelerometer intensity thresholds based on healthy adults, [5-7] application of the Hildebrand thresholds [12, 13] to the REACH-HF data set led to the conclusion that 8% (9/247) of patients met PA recommendations. In contrast, application of the HF specific thresholds derived for MVPA in the calibration study concluded that 45% (111/247) of patients met PA recommendations, with an average daily MVPA of around 40 minutes. The HF specific thresholds for MVPA were lower

than the Hildebrand thresholds for inactivity, which demonstrates how application of thresholds based on healthy adults risks misclassification of PA intensity of HF patients. Despite the limitations of this method detailed in the previous section, it is suggested that researchers measuring PA levels of HF patients with raw accelerometers use these thresholds until a better method is published.

Chapter 5 demonstrated the value of taking a more in-depth and detailed analysis approach with accelerometer data. Simply considering a single aggregated PA outcome such as overall weekly minutes of MVPA may mask important associations, preventing further understanding of how exercise-based interventions could be working, or not working. The analysis of the REACH-HF cohort revealed differences in PA patterns between days, i.e. more PA and less inactivity during the week compared to weekends. There is also evidence in older adults that with increasing age, PA tends to be compressed into the morning, with increased inactivity during the afternoons and evenings, [53] supporting the recommendation for accelerometer data to be studied in greater detail. Increasing the granularity of the data, however, decreases the statistical power of the analyses, therefore sample size calculations for future studies should reflect this. Researchers should carefully consider the PA outcome metrics of interest to be extracted from the raw data, and how best to present these data.

Conventionally, in line with National PA recommendations for MVPA to be accumulated in bouts of at least 10 minutes, accelerometer data is usually processed and reported in terms of bouts. [3] The most common bout criteria used in accelerometer data processing are bouts of 10 minutes or more above the threshold for MVPA with an 80% allowance (i.e. allowing for up to 2 minutes of acceleration values to be below the threshold). In the United States and UK, updated PA recommendations have recently been developed, removing the need for PA to be accumulated in bouts of a minimum duration, informed by emerging research showing that PA of any bout length has significant health benefits. [3, 52] Current methods for defining bouts of PA based on intensity are potentially flawed, for example a 20 minute bout of PA at an accelerometer value just below the threshold for moderate intensity would not be classed as MVPA, whereas 8 minutes (allowing for up to 2 minutes interruption) at a value

just over the threshold for moderate intensity would count as MVPA, despite the former PA accumulating a greater volume. Since some HF patients limited exercise capacity restricts them from being able to perform extended bouts of continuous PA, PA of all durations is also useful to report, as in chapters 4 and 5 of this thesis. Researchers may uncover interesting relationships or data trends in intermittent PA that would not be seen if only sustained PA (≥10 minutes) is reported. Other authors support this, stating that researchers should consider sample characteristics when investigating PA accumulated in bouts of varying durations [34].

*(2) Implications for CR practice*

The findings of the systematic review and meta-analysis (chapter 2) and the secondary analysis of the REACH-HF individual patient data set (chapter 5), provide evidence that exercise-based CR can have a modest positive impact on PA levels of HF patients. These findings, in conjunction with other recent individual patient data meta-analyses and an updated Cochrane review [55-57] continue to support the class 1A recommendation for CR in HF. [58] Therefore, one of the key implications for practice is that we should continue to encourage HF patient participation in CR, whether it be a centre- or home-based intervention as recommended by the updated NICE guidelines [1].

Traditionally CR programmes have focussed on aerobic exercise training with the main aim to increase exercise capacity rather than PA promotion. Whilst increases in exercise capacity can be achieved with CR programmes as short as 4 weeks, [55] increases in PA may require a long-term change in behaviour and habits of the patient. Across all the studies in this thesis, the close relationship between exercise capacity and PA level has been evident. For example, REACH-HF patients who achieved a greater ISWT distance at baseline were more likely to be physically active at baseline, but also more likely to increase their PA levels up to 12 months follow-up. In its current format, we have shown modest positive influences of CR on PA levels of HF patients. But with studies demonstrating the close relationships between PA and key measures of exercise capacity and HF severity, and some indicating that PA levels are more important than exercise capacity in relation to mortality [46-51]

CR programmes may need to adapt, placing greater emphasis on increasing PA levels in the long term specifically.

In addition to a greater focus of CR on PA levels, there may be benefits to gain from simplifying the PA advice given to HF patients. A key target of CR is for patients to meet current National PA recommendations for adults and older adults of 150 minutes per week of MVPA. It is important to note that these current PA guidelines have been developed based predominantly on self-reported measures of PA. [1] The calibration study presented in chapter 3 showed that for the majority of participating HF patients, any walking activity, even walking at a pace perceived by the patient to be light, constituted a moderate intensity PA (≥ 3 METS). Given this finding, clinicians may consider encouraging patients simply to walk more, not necessarily aiming to reach any particular speed, or effort level, as this is likely to have significant health benefits [43]. The interventional analysis presented in chapter 5 showed that the REACH-HF intervention increased weekday PA, thereby decreasing weekday inactivity, whereas the opposite appeared to be true at the weekend. This may present a tangible target for clinicians and CR professionals to encourage patients to increase PA both during the week and the weekend; making a conscious effort not to compensate for exercise by sitting. A simple message of sit less, move more, every day, could be easier for patients to understand and implement into their lifestyle in the long term, and may lead to more marked increases in overall PA levels and reduction in sedentary time rather than a message that focuses on 150 minutes or more per week of PA at a minimum of moderate intensity [43].

This approach has also been suggested by other researchers, since cardiac patients have been observed to have consistently high levels of sedentary time regardless of whether the patient was entering, completing or long removed from a CR programme [59]. Freene and colleagues [60] recently reported that participation in a 6 week hospital-based CR programme did not affect accelerometer measured time spent in MVPA or sedentary behaviour despite increases in self-reported MVPA, but did improve time spent in light intensity PA along with exercise capacity. In this study, thresholds for activity intensity based on healthy adults were applied, so where an improvement in objectively measured light intensity PA is seen, this may in fact be MVPA if population

specific thresholds had been applied. Nevertheless, the authors conclude that alternative approaches to increasing PA should be considered such as sit less, move more, which this thesis supports for HF patients. Studies in the context of public health also suggest that the approach of ‘sit less, move more’ may be a better alternative. Ekelund et al. [43] showed that higher levels of total PA, regardless of intensity, and less time spent sedentary are associated with reduced risk of all-cause mortality in middle aged and older adults in a non-linear dose-response relationship. However, this study was cross-sectional in design, and so changes in PA over time and their effect on mortality and other health outcomes remain unclear. [61]

The cross-sectional study reported in chapter 4 identified a number of sociodemographic, exercise capacity and health factors that are closely associated with PA levels of HF patients prior to intervention. Lower levels of PA were associated with patients who: were older, had a higher BMI, were unemployed or retired, had a higher NYHA class, were current smokers, had a higher NT-proBNP level or walked less distance on their ISWT. These factors may be important for clinicians and researchers to inform development of interventions and target specific subgroups of HF patients who could benefit most from PA interventions.

Chapter 5 presents the sociodemographic, exercise capacity and health status variables that were related to a change in PA level up to 12 months follow-up. The variables that were closely associated with a change in PA level were baseline ISWT distance, HADS anxiety sore, presence of diabetes, and living with a parent or child >18 years. However, these associations were inconsistent across the two follow-up time points, and the multivariable regression models only explained a small amount of the variance in PA change. Nevertheless, since this is the first study to investigate the patient characteristics associated with changes in PA level, these results provide an early indication to potential subgroups of patients who may require more or less intensive intervention in order to maximise intervention efficacy.

### 6.5 Future research directions

The research studies undertaken in this thesis identified a number of areas for future research.

*(1) Accelerometer measured PA intensity*

Objective, accelerometer measured PA and sedentary behaviour is likely to remain a feature of CR and HF trials as technology becomes more advanced and devices become less expensive. Therefore, until consensus is reached on the gold standard, criterion measure of PA, continued improvements are needed in the methods used to extract the clinically meaningful information researchers require from raw accelerometer data, specifically in chronic disease populations such as HF patients. It is essential that we measure PA accurately in order to further examine the relationships between PA and various health outcomes and assess the effectiveness of CR interventions.

Multiple data reduction methods to extract a single accelerometer value from the raw triaxial data were explored within the calibration study. ENMO was found to return a high number of 0 values and so was excluded from further analysis. This has been found previously, [28] and it seems likely that in populations where a large proportion of activity is at low intensity, ENMO may be an inappropriate method for calculating a single accelerometer value from multi-axis devices. GGIR is the only open source, freely available raw accelerometer processing package, which at present can only return ENMO values. Therefore, caution is advised for future studies using this method in HF populations, until a solution to this is agreed upon. A data reduction method more appropriate for use in populations where the majority of physical activities are a low intensity should be explored in greater depth. In addition, new open access code that has a user defined summary measure of acceleration is required.

In accordance with the findings in this thesis for HF patients, studies in older adults have shown that application of accelerometer thresholds for adults may not be applicable. [35, 36, 62] Although an improved method of estimating absolute PA intensity specifically in the HF population has been developed as described in chapter 3, calibration studies are limited in their ability to generalise to a wider population than the small sample used. Future studies should ensure recruitment of the often underrepresented HF groups, i.e. NYHA classes III-IV,

HFpEF patients, and also accounting for the smaller number of patients that reach the latter stages of the ISWT so that a range of fitness levels are also represented. Power calculations to inform the appropriate sample size will enable researchers to examine potential differences between NYHA classes.

In the field of PA and public health, there has been a shift towards machine learning based methods for device calibration and validation in order to measure PA and sedentary behaviour more accurately. Machine learning based modelling is a more advanced statistical method, which utilises artificial intelligence to automatically learn and improve from experience. This enables the ability to capture nonlinearities and complex relationships in raw accelerometry data in order to identify thresholds without the need for laboratory-based calibration studies. [41, 42] It provides opportunities beyond identifying the intensity of PA, to also predict the type of activity and energy expenditure. [41] An advantage of this method is the use of the raw acceleration data, with no need for reduction into a single summary measure of acceleration in epochs. However, Farrahi et al. [41] recently performed a systematic review of machine-learning approaches to calibration and validation of accelerometers and showed that the capability of machine learning based models to generalise to independent populations in free living settings still remains a challenge, without consensus on a gold standard, criterion measure. The heterogeneity of previous studies, and wide-ranging parameters and methodological decisions that affect the model results made it difficult to provide recommendations on the optimal parameters, and consensus remains in question. Nevertheless, studies applying these advanced methods in HF populations are also required to further understand PA levels in this population, and how they differ from healthy adults.

While PA recommendations remain based on estimates of PA intensity based on single values of acceleration, there will be difficulty in accurately classifying what ‘moderate intensity’ is for an entire population, particularly in a population of people with compromised but very heterogeneous exercise capacity such as HF patients. Using absolute, fixed accelerometer thresholds or cut-points to define intensity will always misclassify the relative intensity of PA for a given person, due to heterogeneity of capacity within a population. One solution is to calculate individualised intensity thresholds, relative to the individual’s exercise capacity. A small number of previous studies have investigated relative intensity

thresholds in other populations (i.e. healthy adults, healthy older adults and postmenopausal women), demonstrating the strong influence of exercise capacity on the inter-individual variability in accelerometer values and resulting relative activity thresholds [63-67]. Common among all the findings of these studies is the increased accuracy of PA level estimations using relative intensity thresholds compared to absolute thresholds. For example, Shrack et al., [67] using a combination of heart rate and accelerometer measurement, compared relative to absolute cut-points to assess PA levels of older adults. Data showed that time spent in MVPA, relative to the individual, contradicted the general consensus that older people are less active, after considering the changes in physiology, functional ability and subclinical burden. Future studies need to perform multiple maximal and submaximal exercise tests, in order to determine measures such as $VO_2$ max, lactate threshold and heart rate reserve to inform individualised relative accelerometer thresholds. However, such detailed exercise protocols may be challenging and burdensome for patients. These methods would also be expensive and time consuming limiting their applicability to larger scale surveillance studies. Nevertheless, improved methods for capturing the frequency, intensity, duration and type of PA in HF patients would provide more accurate estimates and further understanding of PA levels in this population, and requires additional investigation.

Studies in public health are also now beginning to investigate whether lower intensities of PA have health benefits, with results suggesting light intensity PA is inversely associated with all-cause mortality risk and cardiometabolic health, independent of confounders including age and MVPA. [43, 68, 69] Since a single accelerometer threshold was applied to estimate intensity in this population-wide study, it may be that relative MVPA has been detected rather than light intensity PA. The same may also be true of HF patients, however until we are better able to categorise accelerometer measured PA intensity in this patient group, the health benefits of PA at differing intensities remain unclear.

As outlined in the previous section, the increasing popularity of commercially available fitness trackers, activity monitors and smart watches that provide consumers with an abundance of health information including daily step counts, heart rate, and activity intensity could prove to be useful tools in CR interventions, providing patients with goals and targets, and providing

immediate feedback. However, these commercial devices will be limited by proprietary algorithms to measure the different PA metrics, which will limit comparability with other PA measurement methods such as raw accelerometers. However, since their popularity is increasing, and the next generation of HF patients are very likely to be more technologically adept, validation studies will be required before they can be used in clinical practice.

*(2) Alternative PA metrics*

National PA guidelines are primarily based on self-reported PA data, and recommendations for HF patients are the same as for healthy adults. Alongside intensity, PA can also be categorised according to frequency, duration, type, and pattern. There are now a wealth of opportunities to explore new subcategories of data, or physiologically meaningful patterns of behaviour, which may prove to be better indicators of overall PA, and show stronger associations with health outcomes. As accelerometer derived PA outcome metrics evolve, becoming less influenced by individual or population specific characteristics, they could be used to inform new PA guidelines, both for the general population, and specifically for CR participants including those with HF. [70]

Whilst emerging studies have suggested that PA of light intensity also has benefits, with a curvilinear relationship between PA and health outcomes, [43, 68, 69, 71] results presented within this thesis have shown that the application of a single accelerometer threshold to determine PA intensity across a population is not appropriate, and for some within the population, PA labelled as light intensity may in fact be at least moderate intensity and vice versa. Therefore, it may be that a measure of overall PA, which is not subject to categorisation based on intensity is more appropriate. This, theoretically, would also overcome the need for multiple cut-points and calibration studies for different subpopulations such as age categories and different chronic disease groups. For example, the UK Biobank and Whitehall II studies [7, 72] report overall ENMO as a PA metric. However, this single value currently has little clinical meaning, and is difficult for those not familiar with accelerometer data to understand. Future research using an overall PA metric should aim to

determine the value at which associations with health outcomes such as mortality, which would aid understanding with a reference or target value.

In addition to this, exploring differences in the duration of bouts of PA, i.e. sustained activity versus intermittent activity in HF patients may provide important additional information. Since longer, sustained bouts of aerobic activity may be more difficult for the less fit HF patients, or those with HFpEF to achieve, [73] this may offer an alternative target for PA interventions. For example, a patient at the start of an exercise-based intervention may accrue intermittent activity in very short bouts, requiring lots of breaks, but by the end of the intervention is able to complete a longer continuous bout of activity. Would this have health benefits if the patient is not necessarily completing a greater volume of PA overall? Melin et al. [74] explored accelerometer measured walking patterns in HF patients and found that variability in PA (characterised by low walking speed and frequent pauses) had an additive value over and above exercise capacity in a prognostic model. Studies should therefore explore differences in activity bout durations, and their association with health outcomes in HF patients.

Since accelerometers assess PA continuously with a time stamp, within- and between-day patterns of how PA is accrued can be monitored. Chapter 5 demonstrated the value of looking at PA data in more detail, and showed a trend for both MVPA and light intensity PA to increase only during the week with REACH-HF intervention. Other studies have identified a diurnal pattern of PA in older, non-working populations with a mid-morning peak and gradual decline with age in activity in afternoon and evening activity. [53] Understanding these types of patterns of PA behaviour in HF patients, who experience higher levels of fatigue than the general population, may help to identify potential windows throughout the day where PA modification will be best placed. Further research is needed here, and measures of within- and between-day variability in PA accrual should be explored.

Identifying alternative PA metrics based on duration, timing, or type of PA as well as intensity, and their relationships with health outcomes in HF patients, may enable researchers to determine an ideal ‘dose’ of PA, or prescriptions similar to medications. As many previous studies have been observational or

cross sectional in design, larger, longitudinal studies are required. Researchers should also ensure sample sizes are large enough to detect differences in the PA data, especially when the outcome measures of interest are more granular.

*(3) CR interventions*

There has been a large increase in the volume of studies measuring PA level as a secondary outcome of RCTs of CR over recent years, as PA and sedentary time have become key targets of CR. [2] However, much like the field of public health, the primary challenge facing researchers is developing effective, sustainable and cost-effective interventions to generate long term PA behaviour change to successfully reduce rehospitalisation, and improve HF patient's symptoms and quality of life. Traditionally, the exercise training element of CR intervention has focussed on increasing functional exercise capacity ($VO_2$) as the key target. Major benefits of increased PA levels in HF patients, independent of exercise capacity include improvements in quality of life, and reductions in all-cause mortality, HF mortality, and HF hospitalisation. [75-77] In addition, many HF patients are not keen to undergo tests of maximal exercise capacity such as cardiopulmonary exercise tests on treadmills or bicycle ergometers and may be more amenable to PA measurement via accelerometer [78]. Although the results of the studies presented in this thesis have shown how closely associated exercise capacity (measured via ISWT) and PA levels are, it appeared the fitter patients at baseline were more likely to increase their PA levels with REACH-HF intervention. However, it is the less fit, and less active patients that may need to be targeted for more intense intervention, as these patients will have the most to gain from increasing their PA. Therefore, more intense interventions specifically tailored or targeted at those with lower PA levels could be explored.

New models of CR intervention that specifically target PA levels of participants are emerging. The PATHway I trial which has now completed recruitment for a multicentre pilot RCT, proposes an internet-enabled and sensor-based home exercise platform for individualised CR, where PA promotion is the basis of the intervention, and objectively measured PA level is the primary outcome. [79] Other such trials would provide valuable longitudinal data to further

understanding of the ways in which CR intervention can impact PA levels in patients with HF.

Although exercise-based CR effects appear to be consistent regardless of delivery method (i.e. centre vs home based), research should continue to pursue alternative modes of delivery in order to improve CR uptake in HF patients (in the UK, less than 20% of patients discharged from hospital after HF diagnosis are offered CR, and less than 5% attend at least one session of CR [50]), and in line with NICE guidelines that recommend a 'personalised, exercise-based CR programme in a format and setting that is easily accessible'. [1] One such potential mode of delivery is through mobile or electronic health, which includes internet based interventions, mobile applications or various wearable devices. Potential benefits of this mode of delivery include access to the intervention at any location, at any time, which allows programmes to be more tailored to fit into the individual's lifestyle and overcomes barriers of face-to-face contact. [80] It may be that these home-based mobile interventions are more suitable for increasing daily PA than structured group exercise programmes as it is easier to implement into daily life. There is increasing evidence that these types of health interventions are feasible, acceptable and can support lifestyle modification in those with CHD, however use of these interventions to increase PA levels of those with HF is yet to be investigated thoroughly, and there is concern that some of these interventions have been developed with little theoretical underpinning, or poor description of the behaviour change techniques utilised. [80, 81]  Future studies investigating the integration of theoretically informed, mobile or internet technology applications and their impact on increasing HF patient participation in CR and improving PA levels are warranted.

Buys et al. have shown that cardiac patients express interest for technology enabled home-based CR. [82] PA technology continues to develop rapidly, and availability and popularity of commercially available wearable activity monitors or fitness trackers are increasing, even within clinical research. [83] Popular devices include Fitbits, Garmin, Misfit, Apple and Polar, and commonly contain sensors such as pedometers, accelerometers and photoplethymography (to estimate heart rate). [83] ter Hoeve et al. [84] found that the addition of pedometer-based, face-to-face group counselling sessions to a standard CR

programme increased daily step counts and time spent in prolonged MVPA. Advances in device quality offer both researchers and patients new opportunities with access to an abundance of PA information which may be useful tools in CR interventions. Although these devices are limited by proprietary algorithms for converting the raw data into meaningful PA units, and often only display a limited set of PA metrics on the device or associated mobile app, they may be useful for enhancing the delivery of PA and CR interventions, facilitating activity tracking, goal setting and feedback. [85] Thorough validation of these newer devices would be required however, especially in chronic disease populations such as elderly HF patients with multiple morbidities. [45]

In addition to development of new, accessible and PA focussed models of CR intervention, chapter 2 of this thesis identified there is a paucity of studies reporting PA outcomes over the long-term, therefore studies with long term follow-up of a year or longer are also required. Furthermore, patients with more severe symptoms of HF, i.e. NYHA class IV have been greatly underrepresented in the studies that make up this thesis, so conclusions as to whether accelerometer thresholds for MVPA and inactivity differ across the different NYHA classes remains unknown, along with associations between PA level and other factors in the more severely limited patients. This is also true of the majority of HF and CR research, and studies including underrepresented groups such as older, NYHA class IV, HFpEF patients have been called for. [55]

## 6.6 Conclusions

Maintaining PA levels is important to the health of patients with chronic disease including HF. Nevertheless, objective measurement of PA in these groups remains under researched. The body of research presented in this thesis provides new and important information in this field including: (1) improved methods for the objective and reliable assessment of PA in chronic disease and HF specifically; (2) better understanding of the PA levels of HF patients and (3) how exercise-based CR interventions can impact upon PA in HF patients.

Overarching research limitations included small patient samples and therefore the potentially limited generalisability of findings to the wider HF population.

There are also major limitations in accelerometer calibration methods, both within this thesis and in the wider field of research, with a lack of consensus on the gold standard method of measuring PA intensity in chronic disease populations.

HF patients should continue to be encouraged to participate in exercise-based CR, and clinicians and practitioners are urged to refocus CR to enhance PA rather than simply improving exercise capacity. New modes of delivery such as internet based and technology enabled interventions should be explored to assess their impact on both CR uptake and changes in levels of PA. Researchers and clinicians should also explore the possibility of moving beyond a single PA metric, which could inform intervention design (i.e. identifying and targeting inactive periods throughout the day or week), and provide alternative goals for interventions beyond increasing weekly MVPA. Research into PA measurement in HF patients should follow the developing sophisticated methods being explored by public health researchers, ensuring that HF patients' PA measurement continues to improve, and patients' PA behaviour is not misclassified. Further research is required towards identifying a better solution and consensus on the best methodological approach to extracting behaviourally meaningful metrics from raw accelerometer data.

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## Appendix 2.1

### Search strategy

A search strategy was developed in consultation with information specialists experienced in systematic review searching. The following databases were searched from inception to January 2017 for relevant RCTs: MEDLINE, EMBASE, CENTRAL, CINAHL, PsychINFO and SportDiscus. A copy of the full strategy is provided (appendix 2.2). We also undertook supplementary searches of the following catalogues for grey literature (i.e. publications beyond the control of commercial publishers): EThOS, Open Grey, Zetoc and PQDT; trial registries: ClinicalTrials.gov, The WHO International Clinical Registry Platform (ICTRP), UK Clinical Trials Gateway, ISRCTN registry; forward and backward citation checking and searched the reference lists of included studies and previous systematic reviews.[14,15].

A single reviewer (GD) initially screened the titles and abstracts and discarded clearly irrelevant studies. Full papers were checked for inclusion by two reviewers (GD and MH, HD or RST) and disagreements about inclusion of studies were resolved by discussion.

### Inclusion criteria

Studies were eligible if they fulfilled the following criteria:

- Design: RCT
- Study population: adults with heart failure or CHD (including myocardial infarction, revascularisation or stable angina).
- Intervention: CR, defined as structured exercise or PA programme alone or in combination with education and psychosocial interventions – in any setting (home, centre or community based).
- Control: usual care that did not include a structured exercise programme.
- Outcomes: PA measured objectively (e.g. accelerometer, pedometer) or subjectively (e.g. interview, questionnaire). We included studies that used amount of exercise undertaken as an acceptable proxy of PA.

We excluded studies if participants had previously received any form of CR.

## Appendix 2.2

## Search strategy for MEDLINE database

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)**

1946 to Present

Search Strategy:

| # | Searches | Results |
|---|---|---|
| 1 | exp Heart Failure/ | 113505 |
| 2 | ((heart or cardiac or myocardial or ventricular) adj5 failure).ti,ab. | 165648 |
| 3 | "congestive heart failure".ti,ab. | 37916 |
| 4 | ((right-sided or left-sided or diastolic or systolic) adj5 failure).ti,ab. | 6991 |
| 5 | exp Myocardial Ischemia/ | 432299 |
| 6 | (myocard* adj5 isch*mi*).ti,ab. | 50649 |
| 7 | exp Heart Diseases/ | 1109082 |
| 8 | (((heart or coronary) adj5 disease) or CHD or CAD).ti,ab. | 258469 |
| 9 | ("ischemic heart disease" or "ischaemic heart disease" or IHD).ti,ab. | 33856 |
| 10 | "acute coronary syndrome".ti,ab. | 16465 |
| 11 | ((myocard* or heart) adj5 infarct*).ti,ab. | 187996 |
| 12 | (atherosclerosis or arteriosclerosis).ti,ab. | 119767 |
| 13 | ("percutaneous coronary intervention*" or PCI).ti,ab. | 31306 |
| 14 | angioplasty.ti,ab. | 42533 |
| 15 | exp Myocardial Infarction/ | 175310 |
| 16 | stent*.ti,ab. | 85371 |
| 17 | exp Angina Pectoris/ | 46071 |
| 18 | angina.ti,ab. | 52590 |
| 19 | "angina pectoris".ti,ab. | 19708 |
| 20 | "stable angina".ti,ab. | 7629 |
| 21 | revasculari*.ti,ab. | 53414 |
| 22 | exp Coronary Artery Bypass/ | 52957 |
| 23 | exp Myocardial Revascularization/ | 92398 |
| 24 | ("coronary artery bypass graft" or "coronary artery bypass surgery" or CABG).ti,ab. | 26816 |
| 25 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 | 1456929 |
| 26 | exp Rehabilitation/ | 193650 |
| 27 | rehabilitat*.ti,ab. | 140077 |

| | | |
|---|---|---|
| 28 | exp Sports/ | 170759 |
| 29 | sport.ti,ab. | 22280 |
| 30 | exertion.ti,ab. | 14324 |
| 31 | exp Exercise/ | 168685 |
| 32 | exercise.ti,ab. | 232301 |
| 33 | ((lifestyle or life-style or risk factor) adj3 (intervent* or program* or modification or change* or treatment* or therap*)).ti,ab. | 25424 |
| 34 | ((physical or exercise or fitness) adj5 (training or therap* or intervent* or program* or treatment* or prescription)).ti,ab. | 96583 |
| 35 | (aerobic adj3 (training or exercise or activit*)).ti,ab. | 13005 |
| 36 | exp "Physical and Rehabilitation Medicine"/ | 23492 |
| 37 | "cardiac rehabilitation".ti,ab. | 5131 |
| 38 | "heart rehabilitation".ti,ab. | 24 |
| 39 | "cardio* rehabilitation".ti,ab. | 431 |
| 40 | telerehabilitation.ti,ab. | 433 |
| 41 | telemedicine.ti,ab. | 8069 |
| 42 | telecare.ti,ab. | 580 |
| 43 | (prescribed adj2 (exercise or activity)).ti,ab. | 649 |
| 44 | 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 | 719391 |
| 45 | exp Motor Activity/ | 270112 |
| 46 | "physical activity".mp. | 90007 |
| 47 | "physical inactivity".mp. | 6506 |
| 48 | "activity level".mp. | 10982 |
| 49 | ((habitual or leisure or daily) adj3 activity).mp. | 15283 |
| 50 | ((lifestyle or life-style) adj2 (activ* or behaviour* or behavior*)).mp. | 6433 |
| 51 | exp "Activities of Daily Living"/ | 66589 |
| 52 | "activit* of daily living".mp. | 74413 |
| 53 | (habitual adj3 exercise).mp. | 533 |
| 54 | (exercise adj2 (habit* or participation)).mp. | 2571 |
| 55 | (adherence adj2 exercise).mp. | 1045 |
| 56 | (sedentary adj2 (behaviour or behavior or time)).mp. | 4821 |
| 57 | "energy expenditure".mp. | 23370 |
| 58 | "risk factor".mp. | 175935 |
| 59 | acceleromet*.mp. | 12894 |

| | | |
|---|---|---|
| 60 | pedomet*.mp. | 2434 |
| 61 | IPAQ.mp. | 774 |
| 62 | (step adj2 count*).mp. | 1283 |
| 63 | walk*.mp. | 108945 |
| 64 | ((direct or indirect) adj2 calori*).mp. | 7768 |
| 65 | (MVPA or "moderate-vigorous physical activity" or "moderate to vigorous physical activity").mp. | 4455 |
| 66 | ("doubly labelled water" or "doubly labeled water").mp. | 1436 |
| 67 | "activity monitor".mp. | 1265 |
| 68 | 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 | 657045 |
| 69 | exp Randomized Controlled Trial/ | 508365 |
| 70 | ("randomised controlled trial" or "randomized controlled trial").mp. | 530710 |
| 71 | "controlled clinical trial".mp. | 110323 |
| 72 | "clinical trial".mp. | 710202 |
| 73 | "controlled trial".mp. | 540481 |
| 74 | 69 or 70 or 71 or 72 or 73 | 961974 |
| 75 | 25 and 44 and 68 and 74 | 3707 |
| 76 | limit 75 to (("young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") and humans) | 3230 |

## Appendix 2.3

## Supplementary References

### *Linked papers used in data extraction:*

I Houle J, Doyon O, Vadeboncoeur N, et al. Effectiveness of a pedometer-based program using a socio-cognitive intervention on physical activity and quality of life in a setting of cardiac rehabilitation. *Can J Cardiol* 2012;28(1):27-32.

II Dubach P, Myers J, Dziekan G, et al. Effect of exercise training on myocardial remodelling in patients with reduced left ventricular function after myocardial infarction. *Circulation* 1997;95(8):2060-7.

III Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary heart disease? The lifestyle heart trial. *Lancet* 1990;336:129-33.

IV Sandström L, Ståhle, A. Rehabilitation of elderly with coronary heart disease – improvement in quality of life at a low cost. *Advances in Physiotherapy* 2005;7:60-6.

V Hage C, Mattsson E, Ståhle A. Long term effects of exercise training on physical activity level and quality of life in elderly coronary patients – a three- to six-year follow up. *Physiother Res Int* 2003;8(1):13-22.

VI Ståhle A, Mattsson E, Rydén L, et al. Improved physical fitness and quality of life following training of elderly patients after acute coronary events. *Eur Heart J* 1999;20(20):1475-84.

VII Todd IC, Ballantyne D. Antianginal efficact of exercise training: a comparison with β blockade. *Br Heart J* 1990;64:14-9.

VIII Toobert DJ, Glasgow RE, Radcliffe JL. Physiologic and related behavioural outcomes from the women's lifestyle heart trial. *Ann Behav Med* 2000;22(1):1-9.

IX Wang W, Thompson DR, Chow A, et al. An education booklet to aid cardiac patients' recovery at home. *Int Nurs Rev* 2014;61(2):290-4.

X Witham MD, Gray JM, Argo IS, et al. Effect of a seated exercise program to improve physical function and health status in frail patients ≥70 years of age with heart failure. *Am J Cardiol* 2005;95:1120-4.

XI Zwisler AD, Schou L, Soja AM, et al. A randomized clinical trial of hospital-based, comprehensive cardiac rehabilitation versus usual care for patients with congestive heart failure, ischemic heart disease, or high risk of ischemic heart disease (the DANREHAB triL) – design, intervention, and population. *Am Heart J* 2005;150(5):899.

***Questionnaires used in studies:***

XII Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003;35:1381-95.

XIII Taylor HL, Jacobs DR, Schucker B, et al. A questionnaire for the assessment of leisure time physical activities. *J Chron Dis* 1978;31(12):741-55.

XIV Paffenbarger RS, Wing Al, Hyde RT. Physical activity as an index of heart attack risk in college alumni. *Am J Epidemiol* 1978;108(3):161-75.

XV Voorrips LE, Ravelli AC, Dongelmans PC, et al. A physical activity questionnaire for the elderly. *Med Sci Sports Exerc* 1991;23(8):974-9.

XVI Richardson MT, Ainsworth BE, Jacobs DR, et al. Validation of the Stanford 7-day recall to assess habitual physical activity. *Ann Epidemiol* 2001;11(2):145-53.

XVII Toobert DJ, Hampson SE, Glasgow RE. The summary of diabetes self-care activities measure. *Diabetes Care* 2000;23:943-50.

XVIII Dipietro L, Caspersen CJ, Ostfeld AM et al. A survey for assessing physical activity among older adults. *Med Sci Sports Exerc* 1993;25(5):628-42.

XIX Gulanick M, Holm K, Kim M. Psychometric data for self efficacy scales used with recovering cardiac patients. *J Cardiopulm Rehabil* 1987;7:502.

XX Godin G, Jobin J, Bouillon J. Assessment of leisure time exercise behaviour by self-report: a concurrent validity study. *Can J Public Health* 1986;77:359-62.

XXI Lindskog BD, Sivarajan ES. A method of evaluation of activity and exercise in a controlled study of early cardiac rehabilitation. *Journal of Cardiac Rehabilitation* 1982;2(2):156-65.

XXII Thompson DR, Jenkinson C, Roebuck A. Development and validation of a short measure of health status for individuals with acute myocardial infarction: the myocardial infarction dimensional assessment scale (MIDAS). *Qual Life Res* 2002;11(6):535-43.

**Appendix 2.4: Characteristics of included studies**

| Author | Study design | Population* | Intervention | Control |
|---|---|---|---|---|
| Astengo et al. 2010 | Sweden<br>Multicentre RCT | CHD – stable angina<br>N=62 (intervention 33, control 29)<br>Age: Intervention 62±7, control 65±8 years<br>Sex: Intervention 21%, control 24% female<br>Ethnicity: not reported | Exercise only<br>Home-based<br>Duration: 250 days (mean), ≥5 sessions/ week, ≥30 mins/ session<br>Intensity: approx. 70% maximal capacity.<br>Modality: Exercise bike, allowed to replace cycling with other aerobic training twice per week.<br>Resistance training included. | Maintain usual sedentary life |
| Bengtsson 1983 | Sweden<br>Single centre RCT | CHD – MI<br>N=171 (intervention 81, control 90)<br>Age: Intervention: 55.3±6.6, control: 57.1±6.6 years<br>Sex: Intervention 14%, control 16% female<br>Ethnicity: not reported | Comprehensive rehabilitation - Exercise, counselling and social measures<br>Centre-based<br>Duration: 3 months, 2 sessions/week, 30 mins/session<br>Intensity: 90% maximum HR at exercise tolerance test.<br>Modality: Ergometer cycling, calisthenics and jogging. No | Usual care |

| | | | | |
|---|---|---|---|---|
| | | | resistance training. Supervised by physiotherapist. | |
| Bertie et al. 1992 | UK<br>Single centre<br>RCT | CHD – AMI<br>N=110 (intervention 57, control 53)<br>Age: Intervention 52.1±1.3, control 52.7±1.3 years<br>Sex: not reported<br>Ethnicity: not reported | Comprehensive rehabilitation - Exercise, relaxation technique and information reinforcement<br>Centre-based<br>Duration: 4 weeks, 2 sessions /week. Intensity not described.<br>Modality: Pulse monitored, group circuit training, supervised by physiotherapist. | Standard hospital care |
| Borland et al. 2014 | Sweden<br>Single centre<br>RCT | HF<br>Intervention group: NYHA II/III (n=10/14) LVEF 26±10. Control group: NYHA II/III (n=11/12) LVEF 27±11<br>N=48 (intervention 25, control 23)<br>Age: Intervention: 70±6, control: 71±9 years<br>Sex: Intervention 25%, | Exercise only<br>Centre-based<br>Duration: 3 months, 2 sessions/week, 60 mins/session<br>Intensity: Borg RPE 12-13 and/or Category ratio scale, dyspnoea 2-3.<br>Modality: peripheral muscle training, aerobic exercise on ergometer cycle and balance exercises. Resistance training | Asked to continue with their usual lives. |

| | | | | |
|---|---|---|---|---|
| | | control 28% female<br>Ethnicity: not reported | included. Supervision not described. | |
| Carlsson et al. 1997 | Sweden<br>Single centre<br>RCT | CHD – AMI<br>N=168 (intervention 87, control 81)<br>Age: Intervention: 62.2, control: 61.9 years (SD not reported)<br>Sex: Intervention 25%, control 25% female<br>Ethnicity: not reported | Comprehensive rehabilitation - Exercise and education<br>Centre-based<br>Duration: 10-12 weeks, 2-3 sessions/week, 40 mins/session.<br>Intensity: not reported<br>Modality: interval training, cycling and jogging. Supervision not reported. | Usual care |
| Cowie et al. 2011 | UK<br>Single centre<br>RCT | HF<br>NYHA II/III (37(62%)/23(38%)<br>LV impairment: Mild, n=0, Mild-moderate, n=0, Moderate, n=8(13%), Moderate-Severe, n=17(29%), Severe, n=35(58%)<br>N=60 (home intervention 20, hospital intervention 20, control 20)<br>Age: Home: 65.5 (35-82), | Comprehensive rehabilitation - Exercise and some education on symptoms of unstable HF<br>Home-based or centre-based<br>Duration: 8 weeks, 2 sessions/week, 60 mins/session.<br>Intensity: 40-60% HRR, or 12-13 Borg RPE<br>Modality: Aerobic exercise, circuit training.<br>Resistance exercise not included.<br>Hospital group supervised by | Usual care |

| | | | | |
|---|---|---|---|---|
| | | Hospital: 71.2 (59-85), Control: 61.4 (39-79)<br>Sex: 15% female<br>Ethnicity: not reported | physiotherapist, home group given DVD and physiotherapist contact every two weeks. | |
| DeBusk et al. 1979 | USA<br>Multicentre RCT | CHD – MI<br>N=70 (gym intervention 28, home intervention 12, control 30)<br>Age: Gym: 52±8, Home: 55±7, Control: 54±8 years<br>Sex: 0 female<br>Ethnicity: not reported. | Exercise only<br>Centre-based or home-based<br>Duration: 8 weeks, gym group 3 sessions/week and 60 minutes/session, home group 7 sessions/week and 40 minutes/session.<br>Intensity: 70-85% peak HR attained during cycle testing.<br>Modality: Gym group – calisthenics, walking, jogging and stationary cycling. Home group – stationary cycling. Resistance training not included. | No exercise training |
| Devi et al. 2014 | UK<br>Multicentre RCT | CHD – stable angina<br>N=94 (intervention 48, control 46)<br>Age: Intervention 66.27±8.35, control: 66.20±10.06 years | Comprehensive rehabilitation – education on secondary prevention of CHD and goal setting for PA, diet, managing emotions and smoking. | Usual treatment from GP |

| | | | | |
|---|---|---|---|---|
| | | Sex: Intervention 29%, control 22% female<br>Ethnicity: Intervention 92% white British, 8% other, Control: 91% white British, 9% other. | Home-based – online program<br>Duration: 6 weeks, encouraged to log into program 3-4 times per week.<br>Intensity: not reported.<br>Modality: individualized tailored goals focussed on exercise, access to cardiac nurses via email. | |
| Engblom et al. 1992 | Finland<br>Single centre RCT | CHD – CABG<br>N=201 (intervention 93, control 78)<br>Age: Intervention: 54±6, Control: 54±6 years<br>Sex: 0 female<br>Ethnicity: not reported | Comprehensive rehabilitation - exercise, education, relaxation training and psychosocial<br>Centre-based<br>Duration: 8 months, sessions/week and time/session not described<br>Intensity: 70% HR achieved during exercise test<br>Modality: floor and swimming pool gymnastics, cycle ergometer, swimming and ball games, resistance training included. Supervised exercise. | Reference, hospital based treatment, with written information provided. |

| | | | | |
|---|---|---|---|---|
| Erdman et al. 1986 | Netherlands<br>Single centre<br>RCT | CHD – MI, CABG and severe stable angina<br>N=80 (intervention 40, control 40)<br>Age: 51 (range 35-60)<br>Sex: 0 females<br>Ethnicity: not reported | Exercise only<br>Centre-based<br>Duration: 6 months, 2 sessions/week, 90 minutes/session<br>Intensity: Not reported<br>Modality: Gymnastics, jogging and sports such as volleyball, soccer and hockey. No resistance training included. Supervised by cardiologist. | Home rehabilitation – patients received a brochure with guidelines and advice about physical fitness training and jogging. |
| Gottlieb et al. 1999 | USA<br>Single centre<br>RCT | HF<br>Intervention group: NYHA class II 45%, NYHA class III 55%, LVEF 22±8.<br>Control group: NYHA class II 29%, Class III 71%, LVEF 25±10<br>N= 33 (intervention 17, control 16)<br>Age: Intervention: 67±7, Control: 64±10 years | Exercise only<br>Centre-based<br>Duration: 6 months, 3 sessions/week, goal of 30 minutes/session<br>Intensity: Borg RPE 12-13<br>Modality: Initially rode a Schwinn Aerdyne bike, gradually introduced to walking on a treadmill. Final exercise program consisted of 15ft on bike and 30ft on treadmill. Resistance training not included. | Usual care |

| | | | | |
|---|---|---|---|---|
| | | Sex: Intervention 0, control 21% female<br>Ethnicity: Intervention: Black 73%, White 27%, Control: Black 71%, White 29% | Supervised by nurse or exercise physiologist. | |
| Gulanick 1991 | USA<br>Single centre RCT | CHD – MI or cardiac surgery patients<br>N= 40 (intervention (1) – 11, intervention (2) – 15, control - 14)<br>Age: 57±11.3<br>Sex: 30% female<br>Ethnicity: not reported | (1) Comprehensive rehabilitation – exercise and education<br>(2) Education only<br>Hospital based<br>Duration: 5 weeks, 3 sessions/week, 30 minutes/session.<br>Intensity: 70-80% maximum HR response<br>Modality: not described.<br>Supervised by cardiac rehabilitation staff. | Usual care |
| Hämäläinen et al. 1989 | Finland<br>Multicentre RCT | CHD – AMI<br>N=375 (intervention 188, control 187)<br>Age: <65 years<br>Sex: 25% female<br>Ethnicity: not reported | Comprehensive rehabilitation – exercise, education (smoking, dietary and physical activation advice) and psychosocial discussions<br>Centre-based | FU by patients own doctors and did not participate in any organized rehabilitation programmes |

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|---|---|---|---|---|
| | | | Duration: 3 months, sessions/week and minutes/session not described.<br>Intensity: not described<br>Modality: not described.<br>Supervised exercise in one centre only. | |
| Hambrecht et al. 1993 | Germany<br>Single centre<br>RCT | CHD – Stable angina<br>N=88 (intervention 45, control 43)<br>Age: Intervention: 53±6, control 54±7 years<br>Sex: 0 females<br>Ethnicity: not reported | Exercise only<br>Initially hospital based, then home-based<br>Duration: 12 months, 7 sessions/week, <30 minutes/session.<br>Intensity: 75% $VO_2$ max HR<br>Modality: cycle ergometer and group training (jogging, calisthenics and ball games).<br>Resistance training not included.<br>Hospital exercise was supervised, home exercise was not. | 1 week on ward, received instructions about necessity of regular physical activity and ways of lowering fat consumption. Then received usual care from private physician. |
| Heath et al., 1987 | USA<br>Single centre<br>RCT | CHD – CABG | Exercise only<br>Home-based or centre-based | No exercise |

| | | | | |
|---|---|---|---|---|
| | | N=65 (home exercise 17, group exercise 28, control 20)<br>Age: Control: 63±6, Home exercise: 56±11, Group exercise: 58±8 years<br>Sex: 25% female<br>Ethnicity: not reported | Duration: 12 weeks, 5 sessions/week, 30-40 minutes exercise/session (90 minutes supervised group sessions)<br>Intensity: 70-100% peak heart rate during treadmill test, and 13-15 Borg RPE scale.<br>Modality: walking, stationary cycling or similar. Resistance training not included. Group sessions only were supervised. | |
| Higgins et al. 2001 | Australia<br>Single centre RCT | CHD – post PCI<br>N=105 (intervention 54, control 51)<br>Age: Intervention: 48 (range 31-63), Control: 47 (range 26-63) years<br>Sex: Intervention 17%, control 4% female<br>Ethnicity: not reported | Comprehensive rehabilitation - Exercise, education and psychosocial support<br>Home-based<br>Duration: 12 months, sessions/week and minutes/session not described<br>Intensity: moderate, RPE guided.<br>Modality: Walking program with graded increase in frequency in duration of exercise. No resistance | Standard care and telephone follow up |

| | | | | |
|---|---|---|---|---|
| | | | training. Clinician made 3 home visits and monthly telephone calls. | |
| Houle et al. 2011 | Canada<br>Multicentre RCT | CHD – ACS<br>N=65 (intervention 32, control 33)<br>Age: Intervention: 58±8, Control: 59±9 years<br>Sex: Intervention 19%, control 24% female<br>Ethnicity: not reported | Comprehensive rehabilitation – pedometer based programme, exercise (daily step target), education regarding PA, and psychosocial support<br>Home-based<br>Duration: 12 months, sessions/week and minutes/session not described.<br>Intensity: moderate according to Borg RPE scale<br>Modality: walking. Resistance training not included, and exercise unsupervised. | Usual care (no restriction to go to centre based CR or consult a health care professional) |
| Lidell & Fridlund 1996 | Sweden<br>Single Centre RCT | CHD – MI<br>N=116 (intervention 53, control 63)<br>Age: Intervention: 55, Control: 57.6 years (SD not reported) | Exercise and education<br>Centre and home-based<br>Duration: 6 months, 1 session/week plus home exercise, 120 minutes/session (60 mins exercise).<br>Intensity: not described | Usual care |

| | | | | |
|---|---|---|---|---|
| | | Sex: Intervention 13.2%, control 12.7% female<br>Ethnicity: not reported | Modality: bicycle ergometer and calisthenics. Resistance not included. Supervision not described. | |
| Maddison et al. 2015 | New Zealand<br>Multicentre RCT | CHD - Ischaemic heart disease<br>Heart attack – 74%, Angina – 50%<br>N=171 (intervention 85, control 86)<br>Age: Intervention: 61.4±8.9, Control: 59.0±9.5 years<br>Sex: intervention 19%, control 19% female<br>Ethnicity: Intervention group - NZ Maori – 7%, Pacific – 6%, Asian – 9%, NZ European/other – 78%<br>Control group - NZ Maori – 8%, Pacific – 6%, Asian – 10%, NZ European/other – 76% | Exercise only<br>Home-based<br>Duration: 24 weeks, at least 5 sessions/week, at least 30 mins/session<br>Intensity: moderate to vigorous<br>Modality: aerobic based activity, resistance training not included.<br>No supervision. | Usual care with encouragement to be physically active and attend a cardiac club |

| | | | | |
|---|---|---|---|---|
| Mueller et al. 2007 | Switzerland<br>Single centre<br>RCT | HF<br>(LVEF <40%)<br>N=50 (intervention 25, control 25)<br>Age: 55.0 ± 10 years<br>Sex: 0 females<br>Ethnicity: not described | Comprehensive rehabilitation - Exercise, education and diet<br>Centre-based<br>Duration: 1 month, 5 cycling and 14 walking sessions/week, 30 mins per cycling session, 45 minutes per walking session<br>Intensity: 60-80% HRR and work rate, 12-14 RPE Borg Scale<br>Modality: walking and indoor cycling. No resistance training.<br>Supervised by physician or medical resident. | Usual care |
| Naser et al. 2008 | Iran<br>Single centre<br>RCT | CHD – First MI<br>N=100 (intervention 50, control 50)<br>Age: Intervention: 53.2, Control: 54.8 years (SD not reported)<br>Sex: intervention 10%, control 22% female.<br>Ethnicity: not reported | Comprehensive rehabilitation - exercise, lifestyle counselling<br>Centre-based<br>Duration: 2 years, 2 sessions/week, reducing to 1 session/week from month 2 onwards. 60 mins/session<br>Intensity: not reported<br>Modality: heart targeting aerobic exercise. Resistance training not | Usual care |

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|---|---|---|---|---|
| | | | included. Supervised by program manager and exercise leader. | |
| Oldenberg et al. 1995 | Australia<br>Single centre<br>RCT | CHD – CABG<br>N=91 (intervention 43, control 43)<br>Age: Intervention: 60±7.1, Control: 59±8.1 years<br>Sex: intervention 7%, control 12% female<br>Ethnicity: not reported | Comprehensive rehabilitation – exercise, education (focussed on key areas of CVD risk) and psychologist led support<br>Centre-based<br>Duration: 12 months, 6 weekly meetings, which began between 4 and 8 weeks following hospital discharge and booster sessions at 8 months and 1 year post baseline. 3 hours/session<br>Intensity: not described<br>Modality: Stretching, calisthenics, cycle ergometer and walking. Resistance training not included.<br>Supervised by physiotherapist and registered nurse. | Standard medical and nursing care |
| Oliveira et al. 2014 | Portugal<br>Single centre<br>RCT | CHD – AMI<br>N=96 (intervention 49, control 47) | Exercise only<br>Centre-based<br>Duration: 8 weeks, 3 sessions/week, 50 mins/session. | Usual care |

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| | | Age: Intervention: 54.8 ± 10.6, Control: 58.6 ± 10.7 years<br>Sex: intervention 14.9%, control 17.8% female<br>Ethnicity: not reported | Intensity: 70-85% maximal heart rate achieved in the exercise test<br>Modality: Aerobic exercise, cycle ergometer or treadmill. No resistance training. Supervised exercise. | |
| Ornish et al. 1998 | USA<br>Multicentre RCT | CHD<br>N=48 (intervention 28, control 20)<br>Age: Intervention: 56.1 ± 7.5, Control: 59.8 ± 9.1 years<br>Sex: intervention 5%, control 21% female<br>Ethnicity: not reported | Comprehensive rehabilitation - exercise, stress management, psychosocial support, education and diet<br>Centre-based<br>Duration: 5 years, up to 6 sessions/week, at least 30 mins/session<br>Intensity: 50-80% of max heart rate achieved during treadmill test or age-adjusted maximum.<br>Modality: Aerobic exercise, typically walking. No resistance training. Supervision not described. | Usual care |
| Otterstad et al. 2003 | Norway | CHD – AMI, UAP, PCI or CABG | Comprehensive rehabilitation – exercise, dietary advice, smoking | Usual care |

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| | Single centre RCT | N=197 (intervention 98, control 99)<br>Age: Intervention: 54 ± 8, Control: 55 ± 8 years<br>Sex: intervention 19%, control 16% female<br>Ethnicity: not reported | cessation, physical activity counselling, risk factor management, psychosocial management and health education.<br>Centre-based<br>Duration: 2 years, 2 sessions/week, 1 hour/session<br>Intensity: First 6 weeks: 11-13 Borg RPE scale. Following 9 weeks: 13-15 Borg RPE scale.<br>Modality: dynamic endurance training. Resistance training not included. Supervised by physiotherapist for first 15 weeks, then encouraged to exercise at home alone or in organised groups | |
| Reid et al. 2011 | Canada<br>Multicentre RCT | CHD – MI and PCI<br>N= 223 (intervention 115, control 108)<br>Age: Intervention: 56.7 ± 9.0, Control: 56.0 ± 9.0 years | Exercise only<br>Home-based (internet)<br>Duration: 6 months, daily activity, minutes/session not reported<br>Intensity: not described | Usual care |

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| | | Sex: intervention 15.7%, control 13.9% female<br>Ethnicity: not reported | Modality: not described, not supervised. | |
| Ribeiro et al. 2012 | Portugal<br>Single centre RCT | CHD – First MI<br>N= 42 (intervention 22, control 20)<br>Age: Intervention: 54.3 ± 10.8, Control: 57.0 ± 7.6 years<br>Sex: intervention 10%, control 27.8% female<br>Ethnicity: not reported | Exercise only<br>Centre-based<br>Duration: 8 weeks, 3 sessions/week, 55 mins/session<br>Intensity: 65-75% maximal heart rate achieved during exercise test.<br>Modality: Aerobic exercise, cycle ergometer or treadmill. No resistance training. Exercise supervised. | Usual care |
| Senden et al. 2005 | Netherlands<br>Single centre RCT | HF<br>NYHA class II/III<br>Intervention group: LVEF 27.9 ± 8.3%<br>Control group: LVEF 26 ± 7%<br>N= 77 (intervention 44, control 33)<br>Age: 59.8 ± 9.3 years<br>Sex: Intervention 20%, control 31% female | Exercise only<br>Home and centre based<br>Duration: 26 weeks, at least 4 sessions/week (2 home, 2 centre), home sessions 11 minutes, centre sessions 1 hour<br>Intensity: Cycle ergometer: 50% of maximum short-term exercise performance determined by steep ramp test. Adjusted version of | Usual care |

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| | | Ethnicity: not reported | home training programme: >70% peak HR measured during steep ramp test.<br>Modality: Aerobic interval training (stationary running or cycle ergometer), with strength, flexibility and coordination exercises. Resistance training included.<br>Centre sessions supervised by physiotherapist. | |
| Sivarajan et al. 1982 | USA<br>Multicentre RCT | CHD – MI<br>N=258 (intervention 1: 88, intervention 2: 86, control: 84)<br>Age: Intervention 1: 55.6±9.3, Intervention 2: 56.3±8.3, Control: 57.1±7.3 years<br>Sex: <20% female in each group<br>Ethnicity: >80% Caucasian in each group | Intervention 1 – exercise only, intervention 2 – Comprehensive rehabilitation – exercise, education sessions and teaching-counselling<br>Home-based<br>Duration: 3 months, 2 sessions per week, reducing to 1 once patient has returned to work. Minutes per session not described<br>Intensity: progressive, no further information | Conventional medical and nursing management |

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| | | | Modality: Calisthenics and walking. Resistance training not included. No supervision. | |
| Ståhle et al. 1999 | Sweden<br>Single centre<br>RCT | CHD (some HF patients) – ACS<br>N=101 (intervention 50, control 51)<br>Age: Intervention: 71 ± 3.9, Control: 71 ± 4.7 years<br>Sex: Intervention 18%, control 22% female<br>Ethnicity: not reported | Exercise only<br>Centre-based<br>Duration: 3 months, 3 sessions/week, 50 mins/session<br>Intensity: (1) ≥50% based on the relation between maximal heart rate and maximal oxygen uptake for at least 40 minutes<br>(2) ≥80% of estimated maximal oxygen uptake during three periods of 3-4 minutes engaging large muscle groups for training the central circulation<br>Modality: Aerobic exercise, group training. Strength training also included. Supervised by specialised physiotherapist | Usual care – instructed to restart usual physical activity |
| Todd & Ballantyne 1992 | UK<br>Single centre<br>RCT | CHD – stable angina<br>N= 40 (intervention 20, control 20) | Exercise only | Usual care |

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| | | Age: Intervention: 53 (range 45-60), Control: 51 (range 37-60) years<br>Sex: 0 female<br>Ethnicity: not reported | Home-based, with weekly centre-based sessions early on in the programme<br>Duration: 1 year, 7 sessions/week, 11 minutes/session<br>Intensity: progressive, no further information.<br>Modality: calisthenics, no resistance training. Initial in-hospital sessions supervised by physiotherapist, otherwise no supervision. | |
| Toobert et al. 1998 | USA<br>Single centre RCT | CHD<br>N=28 (intervention 16, control 12)<br>Age: Intervention: 64 ± 9, Control: 62 ± 11 years<br>Sex: 100% female<br>Ethnicity: Intervention group: Caucasian 94%, Native American, Alaskan 6%, Hispanic 0%, African American 0%, Other 0% | Comprehensive rehabilitation – exercise, cooking classes, stress management, group discussions<br>Centre-based<br>Duration: 24 months, daily sessions, then at least 3 sessions/week, 1 hour/session.<br>Intensity: Individually prescribed based on treadmill test, no further details | Usual care |

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| | | Control group:<br>Caucasian 83%, Native American, Alaskan 0%, Hispanic 8%, African American 0%, Other 8% | Modality: Aerobic exercises or walking, no resistance training included. Supervised by exercise physiologist. | |
| Van den Berg-Emons et al. 2004 | Netherlands<br>Single centre<br>RCT | HF<br>Intervention group: LVEF – 23.9 ± 9.4%, NYHA class II/III – 56/44%. Control group: LVEF – 27.6±6%, NYHA II/III – 63/37%<br>N= 34 (intervention 18, control 16)<br>Age: Intervention: 58.6 ± 12.1, Control: 58.6 ± 10.6 years<br>Sex: intervention 33%, control 19% female<br>Ethnicity: not reported | Exercise only<br>Centre-based<br>Duration: 3 months, 2 sessions/week, 1 hour/session<br>Intensity: Individually prescribed target heart rate (resting HR + (60% difference between resting and maximal HR)<br>Modality: Aerobic exercise, predominantly cycling, walking and games. No resistance training included, supervision not described. | Standard medical treatment without special advice for activities |
| Wall et al. 2009 | USA<br>Single centre<br>RCT | HF<br>LVEF ≤60%, mean not reported. | Comprehensive rehabilitation - Exercise and education (nutrition, medication, disease management and monitoring symptom changes | 12 month outpatient, home-based, multidisciplinary disease |

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| | | NYHA class – Intervention 2±0, Control 2.13±0.13.<br>N= 19 (intervention 9, control 10)<br>Age: Intervention: 69 ± 4.44, Control: 70 ± 4.05 years<br>Sex: intervention 33.3%, control 50% female)<br>Ethnicity: 100% white. | and disease status<br>Home-based<br>Duration: 12 months, 3 sessions/week, >15 mins/session.<br>Intensity: not reported<br>Modality: Aerobic exercise, treadmill. No resistance training included. Supervised by cardiac rehabilitation specialist. | management programme, which included multiple home visits and follow-up phone calls. |
| Wang et al. 2016 | Singapore<br>Single centre RCT | CHD – MI<br>N=128 (intervention 64, control 64)<br>Age: Intervention: 54.9±8.7, Control: 55.8±10.3 years<br>Sex: intervention 9.4%, control 10.9% female<br>Ethnicity: not reported | Comprehensive rehabilitation – exercise plan and education booklet focussed on psychologically related content (relaxation, stress management, CHD symptom monitoring)<br>Home-based<br>Duration: not described<br>Intensity: not described<br>Modality: not described | Usual care |
| West et al. 2012 | UK<br>Multicentre RCT | CHD – AMI<br>N= 1813 (intervention 903, control 913) | Comprehensive rehabilitation – exercise, health education and counselling | All patients in the trial had similar care in all respects other |

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| | | Age: Intervention: 64.2±11.2, Control: 64.7±10.9 years<br>Sex: intervention 27.4%, control 25.6% female<br>Ethnicity: not reported | Centre-based<br>Duration: 6-8 weeks, 1-2 sessions/week, averaged 20 hours over 6-8 weeks<br>Intensity: not described<br>Modality: Warm up, cool down and used exercise equipment in physiotherapy gyms, no further information. Use of resistance training not described. In most centres led by nurses with previous acute cardiac care experience, and in a few by occupational therapists or physiotherapists. | than referral to cardiac rehabilitation, receiving available explanatory booklets, being advised to see their GP and attend routine outpatient follow up, with referral for further cardiac investigations or interventions as appropriate. |
| Willenheimer et al. 2001 | Sweden<br>Single centre RCT | HF<br>Intervention: LVEF 0.35±0.12,<br>NYHA class 2.1±0.7. Control: LVEF 0.38±0.10, NYHA class 2.4±0.7<br>N= 54 (intervention 17, control 20) | Exercise only<br>Centre-based<br>Duration: 16 weeks, 2 sessions/week increasing to 3 after week 7. 15 mins/session increasing to 45. | Asked not to change their degree of physical activity during the active study period |

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| | | Age: Intervention: 64±5, Control:64±8 years<br>Sex: intervention 29%, control 30% female<br>Ethnicity: not reported | Intensity: 80% peak VO2 ±5bpm. Or RPE 15 (Borg scale, for those with AF)<br>Modality: cycle ergometer, interval training. No resistance training included. Supervised by physiotherapist. | |
| Witham et al. 2007 | UK<br>Single centre RCT | HF<br>NYHA class II/III – 56%/44%<br>LV systolic dysfunction: Mild 35%, Moderate 30%, Severe 34%<br>N= 82 (intervention 41, control 41)<br>Age: Intervention: 80±6, Control:81±4 years<br>Sex: intervention 37%, control 54% female<br>Ethnicity: not reported | Exercise only<br>Centre-based, then home-based<br>Duration: 6 months, 2-3 sessions/week, 20 minutes/session<br>Intensity: Borg scale RPE 11-13<br>Modality: Chair based aerobic exercise. No resistance training included. Supervised by physiotherapist during centre-based phase. | Usual care with no special instructions regarding exercise |
| Witham et al. 2012 | UK<br>Single centre RCT | HF<br>LVEF not reported<br>Intervention group: NYHA class II/III – 70/30%. Control | Comprehensive rehabilitation - Exercise, education and psychosocial support | Usual care – given a booklet with general advice on diet, exercise, and |

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| | | group: NYHA class II/III – 89/11%<br>N=107 (intervention 53, control 54)<br>Age: Intervention: 80.4±5.8, Control: 79.5±4.9 years<br>Sex: intervention 34%, control 31% female<br>Ethnicity: not reported | Centre-based progressing to home-based<br>Duration: 24 weeks, 2 sessions/week, up to 60 mins/session.<br>Intensity: Not reported other than intensity increased incrementally by raising the number of repetitions and resistance level of elasticated bands.<br>Modality: Shuttle walking and resistance exercises. Centre-based supervised by physiotherapist. | lifestyle. Participants not discouraged from exercise if already in the habit of doing so. |
| Zwisler et al. 2008 | Denmark<br>Single centre RCT | CHF (12%), IHD (58%), HR (30%)<br>N= 770 (intervention 380, control 390)<br>Age: Intervention: median 66 (range 33-91), Control: median 66 (range 29-94) years | Comprehensive rehabilitation – exercise, education, dietary counselling, smoking cessation, psychosocial support, risk factor management and clinical assessment<br>Centre-based | Usual care |

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| | Sex: Intervention 36%, control 37% female<br>Ethnicity: not reported | Duration: 6 weeks (12 weeks for HF patients), 2 sessions/week, 90 mins/session.<br>Intensity: 60-85% HRR based on initial bike test and perceived exertion. HF patients exercised at about 50% of the theoretical maximum heart rate.<br>Modality: Mixture of endurance and strengthening training using various upper and lower body modalities. Supervised exercise. |

*Unless otherwise stated, numbers refer to mean ± standard deviation. RCT=Randomised controlled trial, CHD=coronary heart disease, MI=myocardial infarction, HR=heart rate, AMI=acute myocardial infarction, HF=heart failure, NYHA=New York Heart Association, LVEF=left ventricular ejection fraction, PA=physical activity, RPE=rating of perceived exertion, LV=left ventricular, CABG=coronary artery bypass graft, PCI=percutaneous coronary intervention, ACS=acute coronary syndrome, CR=cardiac rehabilitation, HRR=heart rate reserve, UAP=unstable angina pectoris, IHD=ischaemic heart disease.

**Appendix 2.5: Description of methods of physical activity assessment and summary**

| Author | Physical Activity Measure | |
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| | Objective | Subjective |
| **Astengo et al. 2010** | N/A | Name: Not stated<br>Type: Not stated<br>Validated? Not reported<br>Evidence of outcome validated for use in population? Uncertain<br>Derived measure: Training days/week, minutes/session<br>Time frame: Not described<br>Units of PA: Days/week |
| **Bengtsson 1983** | N/A | Name: not stated<br>Type: Not described<br>Validated? Not reported<br>Evidence of outcome validated for use in population? Uncertain<br>Derived measure: (1) habits to exercise, (2) leisure time exertion<br>Time frame: not reported |

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| | | Units of PA: (1) N patients habits to exercise (1. Never, 2. 1-2 times per month, 3. 1-3 times per week, 4. Daily)<br>(2) N patients undertaking (1. Much less, 2. Rather less, 3. Unchanged, 4. Rather more, 5. Much more) leisure time exertion compared to before infarction |
| **Bertie et al. 1992** | Device name: Not stated<br>Type: Pedometer<br>Placement site: Not described<br>Epoch length*: Not described<br>Number of days of observation: 7 days<br>Criteria for a valid day defined? Not described<br>Minimum data requirement for inclusion in analysis defined? Not described<br>Data reduction techniques† defined? Not described<br>Units of PA: Mean daily mileage walked | N/A |
| **Borland et al. 2014** | Device name: KeepWalking LS2000<br>Type: Pedometer<br>Placement site: Waist (or ankles for overweight patients)<br>Epoch length*: Not reported<br>Number of days of observation: 7 days | Name: IPAQ<br>Type: Questionnaire<br>Validated? Yes, but reference provided shows use of IPAQ as indicator for PA is weak |

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| | Criteria for a valid day defined? Not fully described – Patients instructed to wear pedometer throughout the day and register the total number of steps on a log sheet at bedtime and reset device to zero each morning.<br>Minimum data requirement for inclusion in analysis defined? Not described<br>Data reduction techniques† defined? Not fully described – pedometer data was divided into 3 categories: 0-4396, 4397-5999 and ≥6000 steps/day.<br>Units of PA: steps/day | Evidence of outcome validated for use in population? Validated internationally in healthy population, not in CHD<br>Derived measure: Category (low/moderate/high) and time sitting<br>Time frame: 7 days<br>Units of PA: IPAQ category, minutes sitting |
| **Carlsson et al. 1997** | N/A | Name: Not reported<br>Type: Questionnaire<br>Validated? Not reported<br>Evidence of outcome validated for use in population? Uncertain<br>Derived measure: Habitual PA level (1. Sedentary, 2. Walking or bicycling daily with minimum 30 minutes, 3. Sport activities in average once weekly, 4. Sport activities in average twice or more weekly, 5. Vigorous physical training)<br>Time frame: Not reported |

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| | | Units of PA: Number of patients considered physically active |
| **Cowie et al. 2011** | Device name: ActivPAL™<br>Type: Accelerometer<br>Placement site: Front of thigh<br>Epoch length*: Not reported<br>Number of days of observation: 7 days<br>Criteria for a valid day defined? Not described<br>Minimum data requirement for inclusion in analysis defined? Not described<br>Data reduction techniques† defined? Not fully described – monitor produces signal related to inclination and movement of the thigh which is interpreted by algorithms using the proprietary software.<br>Units of PA: Mean time spent sitting and standing, mean number of steps, over an average 24-hr period. Walking pattern also recorded – mean steps/day and mean cadence during 'extra long', 'long', 'moderate', and 'short' walks over an average 24-hr period | N/A |
| **DeBusk et al. 1979** | N/A | Name: not reported<br>Type: Questionnaire |

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| | | Validated? Not reported<br>Evidence of outcome validated for use in population? Uncertain<br>Derived measure: walking distance<br>Time frame: not reported<br>Units of PA: miles/day |
| **Devi et al. 2014** | Device name: Sensewear Pro 3<br>Type: Accelerometer<br>Placement site: Right upper arm<br>Epoch length*: Not reported.<br>Number of days of observation: 2 weekdays (12 hours per day)<br>Criteria for a valid day defined? Not described<br>Minimum data requirement for inclusion in analysis defined? Not described<br>Data reduction techniques† defined? Not fully described – monitor uses physiological signals, bodily movement and in-built algorithms to estimate physical activity.<br>Units of PA: Daily average step count. Secondary – energy expenditure, duration of sedentary activity, duration of moderate activity. | N/A |

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| **Engblom et al. 1992** | N/A | Name: not reported<br>Type: questionnaire<br>Validated? Not reported<br>Evidence of outcome validated for use in population? Uncertain<br>Derived measure: exercise habits<br>Time frame: not reported<br>Units of PA: 3 categories: no exercise, exercise in conjunction with other hobbies, and regular exercise. |
| **Erdman et al. 1986** | N/A | Name: N/A<br>Type: structured interview<br>Validated? Not reported<br>Evidence of outcome validated for use in population? Uncertain<br>Derived measure: habitual exercise (measured in a binary fashion, yes or no)<br>Time frame: not reported<br>Units of PA: % patients with specific answer pattern at the three time points. |
| **Gottlieb et al. 1999** | (1) Name: N/A<br>Type: Doubly labelled water<br>Placement site: N/A | N/A |

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| | Epoch length*: N/A<br>Number of days of observation: 10 days<br>Criteria for a valid day defined? Not described<br>Minimum data requirement for inclusion in analysis defined? Not described<br>Data reduction techniques† defined? Equations for calculating energy expenditure reported.<br>Units of PA: total energy expenditure, kcal/day<br>(2) Name: Caltrac<br>Type: Accelerometer<br>Placement site: Hip<br>Epoch length*: not reported<br>Number of days of observation described? Not described<br>Criteria for a valid day defined? Not described<br>Minimum data requirement for inclusion in analysis defined? Not described<br>Data reduction techniques† defined? Not described<br>Units of PA: total energy expenditure, kcal/day | |
| **Gulanick 1991** | N/A | Name: not reported<br>Type: questionnaire<br>Validated? Yes, by author |

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| | | Evidence of outcome validated for use in population? Yes, validated by author in pilot study with recovering cardiac patients.<br>Derived measure: Performance of physical activity score, broken down into each activity and total.<br>Time frame: not described<br>Units of PA: performance of physical activity score |
| **Hämäläinen et al. 1989** | N/A | Method of obtaining PA data not described<br>Units of PA: % patients taking moderate to heavy exercise regularly |
| **Hambrecht et al. 1993** | N/A | Name: modified Minnesota leisure time physical activity questionnaire<br>Type: questionnaire<br>Validated? Not reported, reference to validation provided, but validated against physical capacity not energy expenditure.<br>Evidence of outcome validated for use in population? No evidence of validation in CHD population<br>Derived measure: energy expenditure in leisure time PA<br>Time frame: previous weekend and on the previous 2 days |

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| | | Units of PA measure: Kcal/week |
| **Heath et al. 1987** | N/A | Name: Harvard Alumni Activity Survey<br>Type: questionnaire<br>Validated? Not reported but reference provided<br>Evidence of outcome validated for use in population?<br>Validated in healthy population, not CHD<br>Derived measure: leisure time physical activity<br>Time frame: not described<br>Units of PA: kcal/week |
| **Higgins et al. 2001** | N/A | Name: N/A<br>Type: interview<br>Validated? Not reported<br>Evidence of outcome validated for use in population?<br>Uncertain<br>Derived measure: exercise habits<br>Time frame: previous 3 months<br>Units of PA: exercise participation classification: very active (exercising more than 3 times per week for at least 20 mins per time), moderately active (exercising less than 3 times per week for at least |

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| | | 20 mins per time), or sedentary (exercising less than 20 min, once per week) |
| **Houle et al. 2011** | Name: Yamax Digiwalker NL-2000<br>Type: pedometer<br>Placement site: waist<br>Epoch length*: not described<br>Number of days of observation: 7 consecutive days<br>Criteria for a valid day defined? Not fully described – morning to bedtime.<br>Minimum data requirement for inclusion in analysis defined? Not described<br>Data reduction techniques† defined? Not described<br>Units of PA: average daily steps | N/A |
| **Lidell & Fridlund. 1996** | N/A | Name: WHO questionnaire<br>Type: questionnaire<br>Validated? Uncertain, reference provided but unable to locate full publication<br>Evidence of outcome validated for use in population? uncertain<br>Derived measure: PA habits (dichotomised – started to exercise after MI, did not start to exercise after MI)<br>Time frame: not described |

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| | | Units of PA: % patients physically exercising |
| **Maddison et al. 2015** | N/A | Name: IPAQ<br>Type: questionnaire<br>Validated? Yes, reference provided for validation study<br>Evidence of outcome validated for use in population? Validated internationally in healthy population, not in CHD<br>Derived measure: Total physical activity, leisure time physical activity and walking time<br>Time frame: 7 days<br>Units of PA: minutes per week |
| **Mueller et al. 2007** | N/A | Name: not described (interview using questionnaire modelled after Harvard Alumni studies of Paffenberger and colleagues (1986))<br>Type: questionnaire<br>Validated? Not reported (3 different references provided in description of PA measure)<br>Evidence of outcome validated for use in population? Uncertain<br>Derived measure: energy expenditure<br>Time frame: the previous year<br>Units of PA: kcal/week |

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| **Naser et al. 2008** | N/A | Name: not reported<br>Type: questionnaire<br>Validated? Not reported<br>Evidence of outcome validated for use in population? uncertain<br>Derived measure: physical activity level – exercising vigorously 20min 3 times per week<br>Time frame: 3 days<br>Units of PA: % patients exercising |
| **Oldenberg et al. 1995** | N/A | Name: Self-report inventory (adapted from National Heart Foundation's 1986 Risk Factor Prevalence Survey.<br>Type: questionnaire<br>Validated? Not reported<br>Evidence of outcome validated for use in population? Uncertain<br>Derived measure: exercise classification<br>Time frame: not described<br>Units of PA: Classification ("regular exerciser" – 3+ times per week, "moderately regular exerciser" – 2 times per week, "non-exercisers" – 1 or less times per week. |

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| **Oliveira et al. 2014** | Name: Actigraph GT1M<br>Type: accelerometer<br>Placement site: right hip<br>Epoch length*: not reported<br>Number of days of observation: 7 consecutive days<br>Criteria for a valid day defined? Not fully described – during the day except while sleeping, bathing and during aquatic activities<br>Minimum data requirement for inclusion in analysis defined? Not described<br>Data reduction techniques† defined? Not described<br>Units of PA: Average minutes per day spent at sedentary, light, moderate-vigorous intensity PA | N/A |
| **Ornish et al. 1998** | N/A | Name: not reported<br>Type: questionnaire<br>Validated? Not reported<br>Evidence of outcome validated for use in population? Uncertain<br>Derived measure: frequency and duration of exercise.<br>Time frame: not reported<br>Units of PA: Exercise times per week, exercise hours per week |

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| **Otterstad et al. 2003** | N/A | Name: food frequency questionnaire<br>Type: questionnaire (patients in intervention group also kept diaries)<br>Validated? Not reported<br>Evidence of outcome validated for use in population? Uncertain<br>Derived measure: exercise habits<br>Time frame: not reported<br>Units of PA: amount of exercise per week |
| **Reid et al. 2011** | Name: Yamax DIGI-WALKER<br>Type: pedometer<br>Placement site: hip<br>Epoch length*: not described<br>Number of days of observation: 9 days, first and last day discarded<br>Criteria for a valid day defined? Not described<br>Minimum data requirement for inclusion in analysis defined? Not described<br>Data reduction techniques† defined? Not described<br>Units of PA: steps per day | Name: Modified version of the Godin Leisure-Time Exercise Questionnaire<br>Type: questionnaire<br>Validated? Yes<br>Evidence of outcome validated for use in population? Previously validated in population by authors.<br>Derived measure: Frequency and duration of moderate and vigorous exercise<br>Time frame: ‘a typical week’<br>Units of PA: Total minutes of moderate and vigorous exercise per week. |
| **Ribeiro et al. 2012** | Name: ActiGraph<br>Type: accelerometer | N/A |

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| | Placement site: waist<br>Epoch length*: not described<br>Number of days of observation: 7 consecutive days<br>Criteria for a valid day defined? Not described – asked to wear during all waking hours<br>Minimum data requirement for inclusion in analysis defined? Not described<br>Data reduction techniques† defined? Analysed with a computer programme (ActiLife Software, ActiGraph), computing the average min/day spent at different PA intensities according to cut points relating to cound/min to PA intensity (Freedson, Melanson, Sirard 1998).<br>Units of PA: Minutes per day performing light, moderate, vigorous and very vigorous PA | |
| **Senden et al. 2005** | N/A | Name: Modified Baecke questionnaire for physical activity in elderly people.<br>Type: questionnaire<br>Validated? Yes<br>Evidence of outcome validated for use in population? Validated for Dutch elderly population, not in HF.<br>Derived measure: DPA score |

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| | | Time frame: over the past year<br>Units of PA measure: DPA score |
| **Sivarajan et al. 1982** | N/A | Name: Activity summary questionnaire<br>Type: questionnaire<br>Validated? Reference for validation study reported.<br>Evidence of outcome validated for use in population? Validated for use in cardiac rehabilitation.<br>Derived measure: activity level<br>Time frame: not described<br>Units of PA: METS, and maximum distance walked (miles) in a day at least 3 times per week |
| **Ståhle et al. 1999** | N/A | Name: N/A<br>Type: Self-reported estimation of physical activity level<br>Validated? Not reported, reference of previous use provided.<br>Evidence of outcome validated for use in population? Literature search shows use of tool in elderly, but not CHD<br>Derived measure: Score 1-6 where 1 corresponds to sedentary and 6 to strenuous exercise comprising at least 3h a week on activities such as |

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| | | jogging, skiing, tennis, swimming and aerobic training.<br>Time frame: A typical week<br>Units of PA: classification scale, 1-6 |
| **Todd & Ballantyne 1992** | N/A | Name: N/A<br>Type: activity diary<br>Validated? Not reported<br>Evidence of outcome validated for use in population? Uncertain<br>Derived measure: level of PA<br>Time frame: not reported<br>Units of PA: not described |
| **Toobert et al. 1998** | N/A | Name: (1) Stanford 7 day recall<br>(2) Summary of Self-Care Activities Questionnaire<br>Type: questionnaire<br>Validated? Not described in paper, but literature search showed both measures validated.<br>Evidence of outcome validated for use in population? Neither measure validated in CHD population.<br>Derived measure: (1) Average kcal per day<br>(2) number of days and amount of time engaged in physical activity in last 7 days |

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| | | Time frame: 7 days<br>Units of PA: (1) Average daily kcal, (2) Number of days and amount of time |
| **Van den Berg-Emons et al. 2004** | Name: Activity monitor AM<br>Type: accelerometer<br>Placement site: Four uniaxial accelerometers attached to trunk and thighs, connected to the AM worn around the waist.<br>Epoch length*: not described<br>Number of days of observation: 2 randomly selected consecutive weekdays (48 hours)<br>Criteria for a valid day defined? Not described<br>Minimum data requirement for inclusion in analysis defined? Not described<br>Data reduction techniques† defined? Not fully described – data calculated per day and averaged over 2 days.<br>Units of PA: (1) % of 24 hours engaged in dynamic activity, (2) G, (3) Number of transitions, (4) Number of walking periods >10s, (5) Number of walking periods >5s | N/A |
| **Wall et al. 2009** | N/A | Name: Yale Physical Activity Survey (YPAS)<br>Type: questionnaire |

| | | |
|---|---|---|
| | | Validated? Yes<br>Evidence of outcome validated for use in population? Validated in healthy older populations, not HF patients<br>Derived measure: Vigorous activity, leisurely walking, moving, standing, sitting and total index scores.<br>Time frame: typical week<br>Units of PA: index score. |
| **Wang et al. 2016** | N/A | Name: Myocardial infarction dimensional assessment scale (MIDAS) – physical activity one of the subscales<br>Type: questionnaire<br>Validated? Yes<br>Evidence of outcome validated for use in population? Validated in MI patients<br>Derived measure: Physical activity score<br>Time frame: not described<br>Units of PA: Likert scale 1-5 |
| **West et al. 2012** | N/A | Name: N/A<br>Type: structured interview<br>Validated? Not reported |

| | | |
|---|---|---|
| | | Evidence of outcome validated for use in population? Uncertain<br>Derived measure: Undertaking physical exercise (>100kcal/day)<br>Time frame: not reported<br>Units of PA: Number (%) patients undertaking physical exercise |
| **Willenheimer et al. 2001** | N/A | Name: N/A<br>Type: interview<br>Validated? Not reported<br>Evidence of outcome validated for use in population? Uncertain<br>Derived measure: degree of habitual physical activity (score calculated by average time (min/week) x intensity (1 to 3)$^2$ / 100)<br>Time frame: 1 week<br>Units of PA: Total activity score |
| **Witham et al. 2007** | Name: Stayhealthy RT3<br>Type: accelerometer<br>Placement site: waist<br>Epoch length*: 1 minute<br>Number of days of observation: 7 days | N/A |

| | | |
|---|---|---|
| | Criteria for a valid day defined? Not fully described, first and last days discarded to reduce influence of incomplete days and transport artefact. Participants asked to wear device from when they first dressed in the morning to when they retired at night.<br>Minimum data requirement for inclusion in analysis defined? Not described<br>Data reduction techniques† defined? Not described.<br>Units of PA: Counts/24 hours | |
| **Witham et al. 2012** | Name: Stayhealthy RT3<br>Type: accelerometer<br>Placement site: waist<br>Epoch length*: not reported<br>Number of days of observation: 7 days<br>Criteria for a valid day defined? Not described<br>Minimum data requirement for inclusion in analysis defined? Not described<br>Data reduction techniques† defined? Not described<br>Units of PA: Counts/24 hours | N/A |
| **Zwisler et al. 2008** | N/A | Name: N/A<br>Type: adapted interview questionnaire<br>Validated? Not reported |

| | |
|---|---|
| | Evidence of outcome validated for use in population? Uncertain<br>Derived measure: physical activity level<br>Time frame: not reported<br>Units of PA: % patients undertaking <4hours per week |

PA=physical activity, IPAQ=international physical activity questionnaire, kcal=kilocalories, CHD=coronary heart disease, WHO=world health organisation, MI=myocardial infarction, METS=metabolic equivalents. *Epoch length: the defined time interval over which data is recorded. †Data reduction techniques: the criteria used to define valid data for use in analysis.

**Summary:**

Subjective methods: The most commonly used subjective approach was questionnaires (20 studies). [17,18,20,22,25,27,28,31-36,38,39,41,42,45,47,48] Fourteen different questionnaires were used across the studies, and six did not provide a name for the questionnaire that was used. Eleven of the questionnaires were validated, [XII-XVIII] however only four were clearly validated in the appropriate cardiac populations. [XIX-XXII] Other subjective methods included structured interview in five studies, [23,29,49,50,53] an activity diary, [44] self-reported estimation, [43] and no description provided in three studies. [14,15,26]

Objective methods: Eight studies used accelerometers, [19,21,24,36,40,46,51,52] four used pedometers [16,17,30,39] and one used doubly labelled water. [24] The number of days observation was most commonly seven days [16,17,19,30,36,39,40,51,52], two studies used two day observation, [21,46] and one study did not describe the observation days.[24] Placement of the pedometers and accelerometers also varied across studies; most frequently used was waist placement [17,30,40,51,52] followed by hip placement, [24,36,39] and thigh, [19] upper arm, [21] and trunk [46] in one study

each. Epoch length was described in one study only. [51] Similarly, data reduction techniques were described adequately in one study only. [40] The criteria for a valid day was not defined sufficiently in any study, nor the minimum data requirement for inclusion in analysis.

**Appendix 2.6: Descriptive summary of PA results between intervention and control**

| Author (year) | Class of PA outcome | PA outcome | Intervention vs control result<br>% or mean (SD), P-value, unless otherwise stated<br>[a] p-value between groups<br>[b] p-value between group change<br>[c] p-value interaction effect time x group | Categorisation of effect | Comments |
|---|---|---|---|---|---|
| Bertie et al. 1992 | Objective | Mean daily mileage (km) | 8.2 (0.6) vs 6.6 (0.5), <0.05[a] | I>C | |
| Cowie et al. 2011 | Objective | Steps/day | 4849 (2866)* vs 5458 (2678)* vs 4052 (1910), 0.1[a] | I=C | *Both intervention groups<br><br>No significant differences across the three groups for any within group change |
| | Objective | Upright duration (hours/day) | 4.32 (1.45)* vs 4.9 (1.78)* vs 3.85 (1.85), 0.29[a] | I=C | |
| | Objective | Steps/day during extra-long walks | 672 (751)* vs 1264 (1640)* vs 417 (713), 0.05[a] | I>C | |
| | Objective | Steps/day during long walks | 1312 (1224)* vs 1557 (1039)* vs 825 (641), 0.11[a] | I=C | |
| | Objective | Steps/day during moderate walks | 2294 (1078)* vs 2291 (867)* vs 1658 (1052), 0.14[a] | I=C | |
| | Objective | | 956 (311)* vs 1129 (474)* vs 955 (474), 0.39[a] | I=C | |
| | Objective | | 95 (65)* vs 98 (57)* vs 70 (57), 0.36[a] | I=C | |
| | Objective | | 80 (12)* vs 84 (18)* vs 77 (23), 0.95[a] | I=C | |

| | | | | |
|---|---|---|---|---|
| | Objective | Steps/day during short walks | 62 (6)* vs 61 (5)* vs 59 (5), 0.39[a] | I=C |
| | Objective | Cadence during extra-long walks<br>Cadence during long walks<br>Cadence during moderate walks<br>Cadence during short walks | 49 (9)* vs 49 (4)* vs 51 (9), 0.81[a] | I=C |
| Devi et al. 2014 | Objective | Steps/day | Difference at 6 weeks: 497 (2171) vs -861 (2534), 0.02[b]<br>6 months: NR vs NR, 0.15[b] | I>C<br>I=C |
| | Objective | Daily EE (kcal) | Difference at 6 weeks: 43.94 (271.9) vs -133.01 (302.01), 0.01[b] | I>C<br>I=C |
| | Objective | Duration of sedentary activity (min) | 6 months: NR vs NR, 0.14[b]<br>Difference at 6 weeks: -7.79 (40.14) vs 23.23 (62.78), 0.01[b] | I>C<br>I=C |
| | Objective | | 6 months: NR vs NR, 0.2[b] | I>C |

| | | | | | |
|---|---|---|---|---|---|
| | | Duration of moderate activity (min) | Difference at 6 weeks: 6.31 (34.37) vs -22.29 (61.34), 0.01[b]<br>6 months: NR vs NR, 0.24[b] | I=C | |
| Gottlieb et al. 1999 | Objective | Daily EE (kcal) doubly labelled water | 273 (133) vs NR, NR | ? | No significant difference in EE with exercise training Between group not reported |
| | Objective | Daily EE (kcal) accelerometer | 361 (224) vs NR, NR | ? | |
| Houle et al. 2011 | Objective | Steps/day | 3 months: 9234 (3502) vs 7972 (3828), <0.001[c] | I>C | |
| | | % patients active (>7500 average daily steps) | 12 months: 9850 (3282) vs 7970 (3433), 0.003[c] | I>C | |
| | Objective | | 3 months: NR vs NR, 0.098[c] | I=C | |
| | | | 6 months: 75% vs 41%, 0.01[c] | I>C | |
| | | | 9 months: 68% vs 36%, 0.03[c] | I>C | |
| | | | 12 months: 83% vs 55%, 0.042[c] | I>C | |
| Oliveira et al. 2014 | Objective | Total PA (counts/min) | 479.3 (262.9) vs 402.9 (162.8), 0.056[c] | I=C | |
| | Objective | Sedentary (min/day) | 372 (66.2) vs 382.5 (85.6), 0.04[c] | I>C | |
| | Objective | Light (min/day) | 278.2 (93.2) vs 297.2 (104.9), 0.106[c] | I=C | |
| | Objective | | 43 (32.3) vs 35.7 (24.7), 0.301[c] | I=C | |

| | | | | |
|---|---|---|---|---|
| | | MVPA (min/day) | | |
| Ribeiro et al. 2012 | Objective | Daily light PA change (min/day) | 53.3 (94.3) vs -11.1 (120.3), >0.05[b] | I=C |
| | Objective | | 12.9 (21.3) vs -0.7 (13.4), <0.05[b] | I>C |
| | | Daily moderate PA change (min/day) | | |
| Van den Berg-Emons et al. 2004 | Objective | %24hr engaged in dynamic activity | 9.9 (4.2) vs 7.4 (2.9), >0.05[b] | I=C |
| | Objective | | 0.026 (0.009) vs 0.02 (0.007), >0.05[b] | I=C |
| | Objective | | 0.18 (0.06) vs 0.18 (0.07), >0.05[b] | I=C |
| | | Body motility (g) | | |
| | Objective | | 132 (55) vs 129 (57), >0.05[b] | I=C |
| | Objective | Motility during walking (g) | 318 (109) vs 165 (62), >0.05[b] | I=C |
| | | Transitions (n) | | |
| | Objective | Walking periods >10s (n) | 318 (109) vs 255 (88), >0.05[b] | I=C |
| | | Walking periods >5s (n) | | |

| | | | | |
|---|---|---|---|---|
| Witham et al. 2007 | Objective | Change in accelerometry counts from baseline | 3 months (median % (IQR): 18.7 (-27.5 to 51.8) vs 7 (-29.1 to 36.8), 0.51[b] | I=C |
| | | | 6 months (median % (IQR): 2.3 (-11.1 to 46.6) vs -14 (-37.7 to 25.4), 0.036[b] | I>C |
| | | | 19 months (mean (95% CI)): -5139 (-26859 to 16580) vs -28184 (-56865 to 497), 0.18[b] | I=C |
| Witham et al. 2012 | Objective | Change in accelerometry counts exercise vs control | 8 weeks: 270, 0.97[b] | I=C |
| | | | 24 weeks: 7992, 0.42[b] | I=C |
| Borland et al. 2014 | Objective | Steps/day | 4963 (2950) vs 3063 (2226), 0.351[b] | I=C |
| | Subjective | IPAQ category | 2 (1-3) vs 1 (1-3), 0.008[b] | I>C |
| | Subjective | IPAQ sitting time (mins) | 330 (170) vs 423 (173), 0.551[b] | I=C |
| Reid et al. 2011 | Objective | Steps/day | 7392 (3365) vs 6750 (3366), 0.656[c] | I=C |
| | Subjective | MVPA (min/week) | 201.4 (179.8) vs 169.6 (152.6), 0.782[c] | I=C |
| Astengo et al. 2010 | Subjective | Training (days/week) | 4.5 (1.8) vs 0.1 (0.8), <0.001[b] | I>C |
| | Subjective | Training (min/session) | 31 (20) vs 6 (23), <0.001[b] | I>C |

| | | | | | |
|---|---|---|---|---|---|
| Bengtsson 1983 | Subjective | Habits to exercise: | 10% vs 15%, >0.05[a] | I=C | |
| | | Never exercise | 7% vs 5%, >0.05[a] | I=C | |
| | | 1-2 times/month | 37% vs 38%, >0.05[a] | I=C | |
| | | | 48% vs 43%, >0.05[a] | I=C | |
| | Subjective | 1-3 times/month | | | |
| | | Daily exercise | 44% vs 34%, >0.05[a] | I=C | |
| | | Leisure time exertion: | 24% vs 34%, >0.05[a] | I=C | |
| | | | 29% vs 31%, >0.05[a] | I=C | |
| | | Much less | 2% vs 0%, >0.05[a] | I=C | |
| | | Rather less | 0% vs 0%, >0.05[a] | I=C | |
| | | Unchanged | | | |
| | | Rather more | | | |
| | | Much more | | | |
| Carlsson et al. 1997 | Subjective | Regularly training | 13% vs 17%, >0.05[a] | I=C | |
| | Subjective | Sedentary | 77% vs 70%, >0.05[a] | I=C | |
| DeBusk et al. 1979 | Subjective | Miles/day (mean (SE)) | 2 (0.6)* vs 2.1 (1.6)* vs 2.9 (1.4), <0.05[a] | I<C | *Both intervention groups |
| Engblom et al. 1992 | Subjective | Exercise 1-2x per week (%) | 6 month: 13% vs 9%, >0.05[a] | I=C | |
| | | | 12 month: 11% vs 10%, >0.05[a] | I=C | |

| | | | | | |
|---|---|---|---|---|---|
| | Subjective | Exercise ≥3x per week (%) | 6 month: 29% vs 29%, >0.05[a]<br>12 month: 31% vs 25%, >0.05[a] | I=C<br>I=C | |
| | Subjective | Exercise 15-29 min (%) | 6 month: 10% vs 6%, >0.05[a]<br>12 month: 8% vs 6%, >0.05[a] | I=C<br>I=C | |
| | Subjective | Exercise 30-59 min (%) | 6 month: 22% vs 22%, >0.05[a]<br>12 month: 19% vs 14%, >0.05[a] | I=C<br>I=C | |
| | Subjective | Exercise ≥60 min (%) | 6 month: 10% vs 10%, >0.05[a]<br>12 month: 15% vs 15%, >0.05[a] | I=C<br>I=C | |
| | Subjective | No regular exercise (%) | 6 month: 58% vs 62%, >0.05[a]<br>12 month: 58% vs 65%, >0.05[a] | I=C<br>I=C | |
| Erdman et al. 1986 | Subjective | Patients undertaking habitual exercise (%) | 6 months: 86% vs 33%, 0.01 <P< 0.001[a]<br>5 years: 52% vs 33%, 0.01 <P< 0.001[a] | I>C<br>I>C | |
| Gulanick 1991 | Subjective | Walk (score) | 4 week: 13.5 (4.9)* vs 11 (3.5)* vs 10.3 (3.4), >0.05[a]<br>9 week: 17.2 (4.4)* vs 14.6 (3.9)* vs 15.8 (5.3), >0.05[a] | I=C<br>I=C | *Both intervention groups All groups sig. decreased (p<0.001) from before hospital to 4 weeks recovery |
| | Subjective | Climb (score) | 4 week: 11.4 (5.3)* vs 10.4 (2.4)* vs 9.2 (3.7), >0.05[a]<br>9 week: 14.3 (5)* vs 13.2 (2.5)* vs 12.3 (4.9), >0.05[a] | I=C<br>I=C | |
| | Subjective | Lift (score) | 4 week: 9.9 (5.4)* vs 9.1 (5.2)* vs 7.5 (3.3), >0.05[a]<br>9 week: 15.5 (4.3)* vs 15.5 (6.8)* vs 12.7 (5.6), >0.05[a] | I=C<br>I=C | |
| | Subjective | Chores (score) | 4 week: 13.6 (3.8)* vs 14.1 (2.9)* vs 13.2 (3), >0.05[a]<br>9 week: 16.9 (3.1)* vs 17.7 (2.7)* vs 15.9 (2,9), >0.05[a] | I=C<br>I=C | |
| | Subjective | Social (score) | 4 week: 13 (4.5)* vs 13.8 (2.8)* vs 10.9 (1.6), >0.05[a] | I=C | |

| | | | | | |
|---|---|---|---|---|---|
| | | | 9 week: 18.8 (3.8)* vs 17.2 (2.8)* vs 17.3 (4.2), >0.05[a] | I=C | (except for |
| | Subjective | Drive (score) | 4 week: 12.8 (5.1)* vs 11.5 (2.7)* vs 10.4 (2.8), >0.05[a] | I=C | walking). |
| | | | 9 week: 19.4 (3.9)* vs 16.3 (3.8)* vs 15.7 (4.3), >0.05[a] | I=C | All groups sig. |
| | Subjective | Sex (score) | 4 week: 9.6 (5.2)* vs 7.8 (4.4)* vs 7.3 (2.8), >0.05[a] | I=C | increased |
| | | | 9 week: 14.6 (6.8)* vs 12.5 (6.2)* vs 10 (4.8), >0.05[a] | I=C | (p<0.001) from |
| | Subjective | Total (score) | 4 week: 83.8 (28)* vs 77.5 (13.9)* vs 68.4 (13), >0.05[a] | I=C | 4 weeks to 9 |
| | | | 9 week: 116.4 (24.3)* vs 106 (17.7)* vs 97 (20.9), | I=C | weeks |
| | | | >0.05[a] | | recovery. |
| | | | | | All groups sig. |
| | | | | | increased |
| | | | | | walking |
| | | | | | (p<0.001) from |
| | | | | | before hospital |
| | | | | | to 9 weeks |
| | | | | | recovery. |
| Hämäläinen et al. 1989 | Subjective | % patients taking moderate to vigorous exercise | NR vs NR, >0.05[a] | I=C | |
| Hambrecht et al. 1993 | Subjective | EE in leisure time PA (kcal/week) | 1876 (163) vs 1187 (97), <0.001[a] | I>C | |

| | | | | | |
|---|---|---|---|---|---|
| Heath et al. 1987 | Subjective | Kcal/week | 2549 (970)* vs 2058 (800)* vs 1089 (795), <0.01[a] | I>C | *Both intervention groups |
| Higgins et al. 2001 | Subjective | % patients currently exercising | 10 weeks: 88% vs 59%, <0.01[a]<br>51 weeks: 72% vs 61%, >0.05[a] | I>C<br>I=C | |
| Lidell & Fridlund. 1996 | Subjective | % patients physically exercising | 1 year: 66.7% vs 27.6%, <0.001[a]<br>5 years: 40.9% vs 27.5%, 0.112[a] | I>C<br>I=C | |
| Maddison et al. 2015 | Subjective | Total PA (min/week) | 1555 (NR) vs 1321.1 (NR), 0.22[a] | I=C | |
| | Subjective | Leisure time PA (min/week) | 383.2 (NR) vs 273 (NR), 0.04[a] | I>C | |
| | Subjective | Walking (min/week) | 512.3 (NR) vs 360.9 (NR), 0.02[a] | I>C | |
| | Subjective | Sitting time (min/week) | NR vs NR, >0.05[a] | I=C | |
| Mueller et al. 2007 | Subjective | Current recreational activity (kcal/week) | 2704 (1970) vs 2085 (1522), 0.4[a] | I=C | |

| | | | | | |
|---|---|---|---|---|---|
| Naser et al. 2008 | Subjective | % exercising vigorously 20min 3x per week | 88% vs 20%, <0.05[a] | I>C | |
| Oldenberg et al. 1995 | Subjective | Exercise classification | Both groups' level of activity generally changed over time (Z=3.52, p<0.001) | ? | Between group not reported |
| Ornish et al. 1998 | Subjective | Exercise (times/week) | 1 year: 4.97 (0.35) vs 2.87 (0.7), 0.06[b]<br>5 years: 4.34 (0.49) vs 3.57 (0.56), 0.64[b] | I=C<br>I=C | |
| | Subjective | Exercise (hours/week) | 1 year: 5.02 (0.61) vs 2.52 (0.7), 0.12[b]<br>5 years: 3.56 (0.56) vs 2.9 (0.65), 0.5[b] | I=C<br>I=C | |
| Otterstad et al. 2003 | Subjective | % exercising >1hr/week | 6 months: 93% vs 72%, <0.001[a]<br>2 years: 67% vs 46%, <0.01[a] | I>C<br>I>C | |
| | Subjective | % no exercise | 2 years: 7% vs 22%, <0.01[a] | I>C | |
| Senden et al. 2005 | Subjective | DPA score | 13.2 (7.5) vs 12.8 (7.3), >0.05[a] | I=C | |
| Sivarajan et al. 1982 | Subjective | MET level | 3 months: 5 (NR)* vs 4.6 (NR)* vs 4.3 (NR), NR<br>6 months: 5.2 (NR)* vs 5 (NR)* vs 4.7 (NR), NR | ?<br>? | *Both intervention groups |
| | Subjective | Max walking distance (miles) | 3 months: 2.4 (NR)* vs 2.2 (NR)* vs 1.5 (NR), <0.001**[a], <0.01***[a]<br>6 months: NR* vs NR* vs NR, <0.04**[a], >0.05***[a] | I>C<br>I>C (exercise only) | ** Exercise only vs control<br>*** exercise/teaching vs control |

| | | | | |
|---|---|---|---|---|
| Ståhle et al. 1999 | Subjective | Self-estimated PA | 3 months (difference): 1.4 (1.2) vs 0.7 (1.0), <0.01[b]<br>12 months (difference): 0.7 (1.0) vs 0.4 (1.1), >0.05[b]<br>3-6 years (median (range)): 4 (3-6) vs 4 (1-6), 0.06[a] | I>C<br>I=C<br>I=C |
| Todd & Ballantyne 1992 | Subjective | Self-reported PA | NR vs NR, >0.05[a] | I=C |
| Toobert et al. 1998 | Subjective | Stanford 7 day recall (kcal/day) | 4 months: 164 (101) vs 128 (87), 0.497[a]<br>12 months: 198 (99) vs 138 (76), 0.307[a] | I=C<br>I=C |
| | Subjective | Summary of self-care activities (days exercise/week) | 4 months: 4.8 (1) vs 2.4 (1.1), 0.00[a]<br>12 months: 4.5 (1.6) vs 2.5 (1.8), 0.03[a]<br>24 months: 3.7 (2) vs 2.7 (1.6), 0.005[a] | I>C<br>I>C<br>I>C |
| Wall et al. 2009 | Subjective | Vigorous activity index score change (mean (SE)) | 6 months: 1.88 (7.25) vs 2.14 (3.06), >0.05[a]<br>12 months: 6.88 (8.34) vs 2.86 (2.86), >0.05[a] | I=C<br>I=C |
| | Subjective | Leisurely walking index score change | 6 months: 1,78 (2.32) vs 1.71 (2.45), >0.05[a]<br>12 months: 4.89 (3.25) vs 1.71 (2.74), >0.05[a] | I=C<br>I=C |
| | Subjective | Moving index score change | 6 months: 0.33 (1.17) vs 0.3 (1.22), >0.05[a]<br>12 months: 1 (0.71) vs 0.9 (0.46), >0.05[a] | I=C<br>I=C |

| | | | | | |
|---|---|---|---|---|---|
| | Subjective | Standing index score change | 6 months: -0.02 (0.4) vs 0.25 (0.25), >0.05[a]<br>12 months: -0.89 (0.35) vs 0 (0), <0.05[a] | I=C<br>I>C | |
| | Subjective | Sitting index score change | 6 months: 0.33 (0.44) vs -0.1 (0.28), >0.05[a]<br>12 months: 0.11 (0.39) vs 0.1 (0.41), >0.05[a] | I=C<br>I=C | |
| | Subjective | Total index score change | 6 months: 3.89 (7.52) vs 2.8 (5.13), >0.05[a]<br>12 months: 11.22 (7.86) vs 2.4 (4.2), >0.05[a] | I=C<br>I=C | |
| Wang et al. 2016 | Subjective | MIDAS PA score | 9.27 (9.71) vs 14.63 (11.09), 0.02[c] | I>C | Low score favourable |
| West et al. 2012 | Subjective | % exercising >100kcal/day | 9% vs 12%, <0.05[a] | I<C | |
| Willenheimer et al. 2001 | Subjective | PA score | 4 months: 60 (85) vs 42 (55), 0.507[b]<br>10 months: 48 (41) vs 32 (41), 0.481[b] | I=C<br>I=C | |
| Zwisler et al. 2008 | Subjective | % PA <4 hours per week | 34% vs 43%, 0.01[a] | I>C | |

PA=physical activity, EE=energy expenditure, NR=not reported, MVPA=moderate-vigorous physical activity, IPAQ=international physical activity questionnaire, IQR=interquartile range, CI=confidence interval, SE=standard error, MET=metabolic equivalent.

**Effect categorisations**:

I=C: no statistical difference in PA between intervention and control

I>C: PA statistically superior in intervention compared to control

I<C: PA statistically superior in intervention compared to control

?: between group not reported, difference between intervention and control uncertain

**Appendix 2.7: Vote counting – subjective vs objective PA measures**

| Direction of result | Number of results | | |
|---|---|---|---|
| | **All studies** | **Objective PA method used** | **Subjective PA methods used** |
| PA in CR same as control (P>0.05) | 100 (69%) | 30 (65%) | 70 (71%) |
| PA in CR higher than control (P≤0.05) | 38 (26%) | 14 (31%) | 24 (24%) |
| PA in control higher than CR (P≤0.05) | 2 (1%) | 0 | 2 (2%) |
| PA difference between CR and control not clear (no P-value reported) | 5 (3%) | 2 (4%) | 3 (3%) |
| Total | 145 | 46 | 99 |

**Appendix 2.8: Vote counting – comparing statistical methods**

| Direction of result | Number of results | | | |
|---|---|---|---|---|
| | **All studies** | **P-value between group difference** | **P-value between group change in PA** | **P-value interaction time x group** |
| PA in CR same as control (P>0.05) | 100 (69%) | 70 (75%) | 24 (71%) | 6 (46%) |
| PA in CR higher than control (P≤0.05) | 38 (26%) | 21 (23%) | 10 (29%) | 7 (54%) |
| PA in control higher than CR (P≤0.05) | 2 (1%) | 2 (2%) | 0 | 0 |
| PA difference between CR and control not clear (no P-value reported) | 5 (3%) | NA | NA | NA |
| Total | 145 | 93 | 34 | 13 |

**Appendix 2.9: Vote counting – comparing diagnoses**

| | Number of results | | | |
|---|---|---|---|---|
| **Direction of result** | **All studies** | **CHD** | **Heart failure** | **Both** |
| PA in CR same as control (P>0.05) | 100 (69%) | 62 (63%) | 36 (86%) | 2 (40%) |
| PA in CR higher than control (P≤0.05) | 38 (26%) | 31 (32%) | 4 (10%) | 3 (60%) |
| PA in control higher than CR (P≤0.05) | 2 (1%) | 2 (2%) | 0 | 0 |
| PA difference between CR and control not clear (no P-value reported) | 5 (3%) | 3 (3%) | 2 (4%) | 0 |
| Total | 145 | 98 | 42 | 5 |

**Appendix 2.10: Vote counting – comparing dose of exercise (dose units = weeks of exercise training x average sessions/week x average duration of session (minutes)**

| | Number of results | |
|---|---|---|
| **Direction of result** | **Dose ≥2000 units** | **Dose <2000 units** |
| PA in CR same as control (P>0.05) | 24 (56%) | 55 (85%) |
| PA in CR higher than control (P≤0.05) | 16 (37%) | 8 (12%) |
| PA in control higher than CR (P≤0.05) | 1 (2%) | 1 (1.5%) |
| PA difference between CR and control not clear (no P-value reported) | 2 (5%) | 1 (1.5%) |
| Total | 43 | 65 |

**Appendix 2.11: Vote counting – sensitivity analysis, removing frequency of exercise outcomes, and removing studies pre-1990**

| Direction of result | Number of results | | |
|---|---|---|---|
| | **All studies** | **PA outcome results based on frequency of exercise removed** | **Pre-1990 studies removed** |
| PA in CR same as control (P>0.05) | 100 (69%) | 70 (67%) | 90 (71%) |
| PA in CR higher than control (P≤0.05) | 38 (26%) | 29 (28%) | 33 (26%) |
| PA in control higher than CR (P≤0.05) | 2 (1%) | 1 (1%) | 1 (1%) |
| PA difference between CR and control not clear (no P-value reported) | 5 (3%) | 4 (4%) | 3 (2%) |
| Total | 145 | 104 | 127 |

**Appendix 2.12: Vote counting – comparing CR intervention type**

| Direction of result | Number of results | | |
|---|---|---|---|
| | **All studies** | **Exercise only intervention** | **Comprehensive CR intervention** |
| PA in CR same as control (P>0.05) | 100 (69%) | 25 (61%) | 75 (72%) |
| PA in CR higher than control (P≤0.05) | 38 (26%) | 13 (32%) | 25 (24%) |
| PA in control higher than CR (P≤0.05) | 2 (1%) | 1 (2%) | 1 (1%) |
| PA difference between CR and control not clear (no P-value reported) | 5 (3%) | 2 (5%) | 3 (3%) |
| Total | 145 | 41 | 104 |

## Appendix 3.1: Study protocol

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# Identifying physical activity through accelerometry in heart failure

**Study Protocol**

| | |
|---|---|
| Protocol Number | 1.2 |
| Version Date | 04/05/2018 |
| Sponsor | University of Exeter Medical School |
| Principal Investigator | Grace Dibben |
| IRAS project ID | 225596 |

# Table of Contents

## 1. Summary

| | |
|---|---|
| Study Title | Identifying physical activity through accelerometry in heart failure |
| Study Design | Cohort study |
| Study Participants | Heart failure patients |
| Planned Size of Sample (if applicable) | 18-30 |
| Follow up duration (if applicable) | NA |
| Planned Study Period | February 2018 - December 2018 |
| Research Question/Aim(s) | The primary objective of this study is to identify and evaluate the range of values provided by accelerometers during a variety of typical daily lifestyle activities, and to relate these to the intensity of performing each activity in the heart failure population. |

## 2. Key Roles

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## 3. Introduction

### 3.1 Background information

Physical activity is defined as bodily movement produced by skeletal muscles that results in energy expenditure beyond resting expenditure (Caspersen, Powell & Christenson, 1985). The current national recommendation for physical activity in adults and older adults is at least 150 minutes of moderate intensity activity in bouts of 10 minutes or more (Department of Health, Physical Activity, Health Improvement and Protection, 2011). Physical inactivity is common in patients with chronic diseases such as heart failure, where dyspnoea and fatigue cause restrictions to the performance of daily physical activity such as walking and household chores (Dontje et al., 2014). The ability to accurately measure physical activity is important in order to properly evaluate interventions aimed at improving levels of physical activity (Van Remoortel et al., 2012).

Daily physical activity levels are closely linked to exercise capacity and to clinical prognosis in patients with heart failure (Walsh, Charlesworth, Andrews, Hawkins & Cowley, 1997; Jehn et al., 2009). One of the key aims of cardiac rehabilitation is to improve total daily energy expenditure alongside physical fitness (BACPR, 2017). However, previous research has demonstrated that a large proportion of patients with heart disease are failing to meet recommended daily levels of physical activity (Dontje et al., 2014; Yates, Pozehl, Kupzyk, Epstein, & Deka, 2015).

Daily physical activity can be estimated via numerous methods; questionnaires are commonly utilised, however these rely on the subject's recollection and may lack the accuracy to detect changes in daily physical activity. There are a range of devices available to objectively measure physical activity, such as accelerometers, which provide information on the amount, frequency, duration and intensity of activity and are able to overcome the limitations of self-report measures. In a review of the validity of activity monitors in health and chronic disease by Van Remoortel at al., (2012), the majority of validation studies had been performed in healthy adults and not in older or chronically ill, where movements tend to be slower and exercise capacity is reduced. They also found that activity monitors are less accurate at slower walking speeds and therefore concluded that proper validation studies in chronic disease populations are required prior to their inclusion in clinical trials. Hall, Howe, Rana, Martin and Morey (2013) also confirmed that those with chronic conditions demonstrated significantly greater work rates in terms of metabolic equivalents (METS) compared to healthy counterparts, and identified the need for regression equations and cut points specific to older adults, suggesting that the same is required specific to the heart failure population.

### 3.2 Rationale

Advances in physical activity monitoring technology allow for raw signal data to be equated to energy expenditure. This can then be classified into light, moderate or vigorous intensity activity. Activity monitors such as accelerometers have been mostly calibrated in the young and healthy, and not in those with chronic diseases such as

heart failure, where daily activity habits are different and movements tend to be slower. In order to accurately estimate physical activity levels in heart failure patients, a calibration study is necessary to identify the range of acceleration values provided by accelerometry for behaviours of varying intensities.

## 4. Aims/objectives

The primary objective of this study is to identify and evaluate the range of values provided by accelerometers during a variety of typical daily lifestyle activities for heart failure patients, and to relate these to the measured intensity of performing each activity in the heart failure population.

## 5. Participants, interventions, and outcomes

### 5.1 Study design

This study will be a single centre, observational study of a cohort of heart failure patients. This design is based on the experiences of three studies previously completed by Phillips, Parfitt and Rowlands (2013), Hildebrand et al., (2014) and Hildebrand et al., (2017).

### 5.2 Study setting

This is a single centre study, that will be run from the Sport and Health Sciences department at St Luke's campus, University of Exeter. The Royal Devon & Exeter NHS Foundation Trust will be a Patient Identification Centre (PIC), only.

At St Luke's Campus, recruitment and consent of patients will take place, along with data collection. The Sport and Health sciences department is set up with all the necessary equipment and appropriately trained staff in order to run the study.

### 5.3 Study participants

Participating patients will be adults aged 18 years or older, with confirmed diagnosis of heart failure within the past 5 years. Patients with contraindications to exercise testing or physical activity will be excluded from the study. Complete inclusion and exclusion criteria are detailed below.

Participants are free to withdraw from the study at any time, and do not have to give a reason for their withdrawal. Data collected on participants prior to withdrawal will be retained for analysis.

#### 5.3.1 Inclusion Criteria

- Patient willing and able to give written informed consent to participate in study
- Adult (aged ≥18 years)
- Patients with confirmed diagnosis of heart failure (HFrEF or HFpEF) within the past 5 years.
- NYHA class ≤III
- Stable symptoms of heart failure

#### 5.3.2 Exclusion criteria

- Patients with contraindications to exercise testing or physical activity
- Patients who are in a long term care establishment or who are unwilling or unable to travel to research site
- Patients who are unable to understand the study information.

- Patients judged to be unable to participate in the study for any other reason (e.g. diagnosis of dementia, psychiatric disorder, life-threatening comorbidity).

5.4 Device specifications

GENEActiv accelerometer:
The GENEActiv accelerometer is manufactured and distributed by Activinsights Ltd., UK. It is a small, body worn, tri-axial accelerometer which continuously records raw data up to 100Hz.

5.5 Outcomes

The primary outcome of the study is the acceleration (mg) values obtained via GENEActiv accelerometer (Activinsights, Kimbolton, UK) at multiple wear locations (both wrists, left hip), during typical daily physical activities of different intensity.

Secondary outcomes will include the oxygen consumption ($VO_2$), carbon dioxide production ($VCO_2$), and RER obtained via breath-by-breath analysis using indirect calorimetry (OxyCon Pro, CareFusion, Basingstoke, UK). Rating of perceived exertion (RPE) will be recorded during the last 30 seconds of each activity using the Borg 6-20 scale.

5.6 Participant timeline

Study visit appointments will all take place in the morning. Participants will be asked to take all their medication with water as normal prior to the study visit. Participants will be required to attend the visit having fasted overnight, however, they will be provided breakfast and refreshments throughout the visit.
If patients attend the visit and have not fasted overnight, and would still like to participate in the study, they will be invited to attend a second visit where the resting metabolic rate will be measured.

Upon arrival, participants will be given the opportunity to ask investigators any final questions they may have, before the informed consent form is countersigned by the investigator. Participants will be given a copy of this along with the PIS for their records.

Anthropometric measures:
Prior to starting the protocol, the following anthropometric measures will be taken and recorded:

- Height (cm, using freestanding stadiometer)
- Weight (kg, electronic scales)
- Body mass index (BMI) calculated using the standard formula
- Blood pressure (mmHg, using automated sphygmomanometer).

Following these measurements, participants will be fitted with three GENEActiv accelerometers (Activinsights, Kimbolton, UK); at the right and left wrists, and over the left hip (via an elasticated waist band). Participants will also be fitted with the Oxycon Pro (OxyCon Pro, CareFusion, Basingstoke, UK) to measure energy expenditure. Participants will then be asked to lie down on a bed for 30 minutes in order to estimate their resting metabolic rate. After 30 minutes, participants will be asked to sit comfortably for 5 minutes. The metabolic rate measured here will be used as a reference point for resting periods later during the visit.

At this point, participants will be provided with breakfast, followed by a short period of rest.

Incremental shuttle walk test:

Participants will complete the incremental shuttle walk test established by Singh, Morgan, Scott, Walters and Hardman (1992) in order to estimate their maximum exercise capacity. Participants are required to walk between two cones placed 10m apart at a speed dictated by signals from a CD player. The walking speed starts at 0.5 $ms^{-1}$ and increases in small increments (0.17 $ms^{-1}$), at 1 minute intervals. The test may be terminated by investigators when the participant is unable to complete a shuttle in the time allowed, or by the participant if they feel too breathless or fatigued to continue the test. During the test, Heart rate (bpm) and rating of perceived exertion (RPE) using Borg 6-20 scale will be recorded at the end of each minute stage. Upon completion the number of shuttles completed, peak heart rate, peak RPE, and reason for termination will be recorded on the data collection form.

Lifestyle activities:

After a period of rest, participants will be asked to perform a variety of lifestyle based activities of varying intensity whilst wearing the accelerometers and Oxycon Pro (further detail of these activities is provided in table 1). RPE will be measured in the last 30 seconds of each activity using the Borg 6-20 scale. There will be a one minute transition period between each activity to allow for set up, and a five minute rest period between all ambulatory activities to allow metabolism to return to a value close to rest.

Table 1: Activities

| Duration | Activity | Notes |
|---|---|---|
| 30 minutes | Laying down on a bed | Resting metabolic rate measured |
| 5 minutes | Sitting | Metabolic rate measured here used as reference point for rest periods. |
| Breakfast provided | | |
| 20 minutes (approx.) | Incremental Shuttle Walk Test | |
| Rest period* | | |
| 5 minutes | Sitting watching television | |
| 5 minutes | Standing washing dishes | |
| 5 minutes | Sitting | |
| Rest period* | | |
| 5 minutes | Light intensity walk | Pace derived from ISWT (RPE 11) |
| 5 minutes | Rest, sitting | |
| 5 minutes | Moderate intensity walk | Pace derived from ISWT (RPE 13) |
| 10 minutes | Rest, sitting | |
| 5 minutes | Light intensity walk carrying shopping bag | Pace derived from ISWT (RPE 11) |
| Equipment returned and patients provided with refreshments | | |

* Where there are resting periods, patients will be asked to sit until their metabolic rate reaches that measured during the first sitting session, and has remained there for 15 minutes.

Once all activities have been completed, the equipment will be removed, and participants provided with refreshments and allowed to rest under supervision for as long as desired before leaving.

5.7 Sample size

Assuming a conservative expectation of a ROC AUC of 0.85 (based on lowest AUC reported in the papers by Hildebrand et al., 2017; Hildebrand et al., 2014; and Phillips et al., 2013), and assumed null AUC of 0.5 (no association) at 90% power and 5% alpha, a minimum sample size of 18 patients is required. Therefore a sample size of at least

18, and no more than 30 patients will be recruited.

5.8 Recruitment

Potential participants will be identified by the local cardiologist, Dr Manish Gandhi in the Royal Devon & Exeter NHS Foundation Trust heart failure clinic. At their routine clinic appointments, patients will be given a one page information leaflet with brief details about the study and an invitation to contact the investigator via telephone, email or post if they are interested in participating in the study or wish to find out more information. The leaflet contains a page for patients to write down their contact number and sign to say they are happy to be contacted by the chief investigator, which will be collected by the clinic staff and posted to the chief investigator.

Once the patient has made contact with the chief investigator, and they have indicated an interest in participating, more detailed information sheets will be sent via email or post, along with a copy of the consent form to ensure they are fully informed of the requirements. Patients will be given at least 24 hours to consider whether they would like to participate and for appointments made for the study visit. Upon making the appointment, patients will be asked to sign the consent form and bring it with them to their appointment to be countersigned by the investigator, and reminded that they will need to fast overnight prior to attending their appointment.

On occasion, the chief investigator will attend the heart failure clinics, where patients who are identified as potential participants will be directed by the HF nurses to meet with the chief investigator in a nearby room to discuss the study and be provided the information leaflet and full patient information sheets. These patients will not be consented at this initial meeting, and will follow the same recruitment process as the patients that are first approached by the HF nurses.

If participants attend the visit and have not fasted, but would still like to participate in the study; they will be invited to attend a second visit, ensuring they are fasted in order to measure resting metabolic rate.

Participating patients will be reimbursed for transport to and from the university campus.

## 6. Data collection, management and analysis

6.1 Data collection methods

GENEActiv accelerometers will be placed on both wrists and the left hip and worn continuously throughout the testing period. Manufacturer's software will be used to initialise and extract data from both devices. Further data processing will be undertaken using custom programmes written in the statistics package R.

Oxygen consumption ($VO_2$), carbon dioxide production ($VCO_2$), and RER obtained via breath-by-breath analysis using indirect calorimetry (OxyCon Pro, CareFusion, Basingstoke, UK). Expired air passes through a facemask connected via a bidirectional flowmeter to oxygen and carbon dioxide analysers allowing the determination of $FEO_2$ and $FECO_2$. Oxygen consumption and $CO_2$ production will be averaged over a 30-second period at rest and the last 30-seconds of each exercise stage.

RPE will be collected using the Borg 6-20 RPE scale during the last minute of each activity by the chief investigator asking patients to describe which number on the scale represents their perceived level of exertion and the number recorded on a paper data collection form.

If data is missed due to technical issues with the equipment, participants may be asked to return for a second visit in order to complete data collection.

6.2 Data management

Electronic data will be stored on a password protected computer, and only immediate members of the research team will have access to the data. Signed informed consent forms and paper data collection forms will be stored in a locked cabinet in the lead researcher's secure office.

Participants will be assigned a unique ID number on a password protected database and only these labels will be used for data analysis.

6.3 Statistical methods

Descriptive statistics will be used to determine the range of mg values for each behaviour.

Receiver operator characteristic (ROC) curve analysis will be used to determine the mg value with the highest sensitivity, specificity and area under the curve for classifying accelerometer intensity thresholds (Hildebrand et al., 2017; Hildebrand et al., 2014; Phillips et al., 2013). Manufacturer's software will be used to initialise and extract data from both devices. Further data processing will be undertaken using custom programmes written in the statistics package R.

## 7. Monitoring

7.1 Data Monitoring

A data monitoring committee (DMC) is not required for this study as the study will be running for a short period only, and the protocol is unlikely to be modified regardless of the interim data. In addition the likely risks are minimal in this study due to the nature of the activities.

7.2 Adverse Events

A full risk assessment can be found in the appendices.

The incremental shuttle walk test is a predictive fitness test that has been tested and validated for use in the heart failure population. Participants will be monitored closely at all times by investigators during their test and participants will be advised to report any discomfort or desire to stop the exercise test immediately.

As the proposed protocol requires the completion of typical daily activities in the heart failure population the risks associated with all other aspects of the study are minimal.

Any adverse events that occur during the participant's visit will be documented on the data collection form.

Serious adverse events (SAEs) are defined as any untoward occurrence that (a) results in death, (b) is life-threatening, (c) requires inpatient hospitalisation or prolongation of

existing hospitalisation, (d) results in persistent or significant disability or incapacity or (e) consists of a congenital anomaly or birth defect. SAEs will be reported by investigators to the Research Ethics Committee within 15 days of becoming aware of the event.
Patients will be asked on the ICF whether they give permission for their GP to be informed of their participation in the study. A space is provided for them to enter their GP's name and the name of the surgery in order for the chief investigator to post the GP letter.

7.3 Auditing

Internal audit of data collection, data entry, and documentation will be completed after the first participant has completed the study, and then after every 5th participant until recruitment has ended. This will be conducted by the chief investigator in order to ensure the quality of research is maintained.

## 8. Ethics and dissemination

8.1 Research ethics approval

Before the start of the study a favourable ethical opinion will be sought for the study protocol, informed consent form, patient information sheet, patient leaflet and GP letter from an NHS Research Ethics Committee (REC).

All correspondence with the REC will be retained in the ISF. The REC will be notified of the end of the study by the chief investigator. An annual progress report will be submitted to the REC within 30 days of the anniversary date on which favourable opinion was given, and annually until the study is declared ended. If the study is ended prematurely, the chief investigator will notify the REC, and include the reasons for premature termination. Within one year after the end of the study, the chief investigator will submit a final report with the results, including any publications/abstracts to the REC.

8.2 Protocol amendments

Substantial amendments that require review by REC will not be implemented until favourable opinion is granted.

8.3 Patient and public involvement

During the study design phase, the proposed data collection protocol was presented to a local heart failure PPI group for feedback. The group was made up of heart failure patients and their caregivers. The patients provided feedback on the protocol, and as a result of this, the protocol was shortened and some activities amended to suit the daily lives of the patient group.

8.4 Consent or assent

Informed consent will be obtained from participants by the lead researcher prior to any study related activity being undertaken on the morning of the visit. Participants will be asked to sign and date the informed consent form and will be given a copy of this to keep for their own records.

8.5 Confidentiality

All investigators and study site staff will comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Participants will be assigned a unique ID number in order to ensure anonymity. Electronic data will be stored on an encrypted password protected computer, and only immediate members of the research team will have access to the data. Paper based information such as signed informed consent forms and data collection forms will be stored in a locked cabinet in the lead researcher's secure office.

Personal data will be stored for 6-12 months after the study has ended in order for the research team to post study newsletters with results of the study to participants if they requested this at study entry. Anonymised data will be securely stored electronically for at least 5 years in the University of Exeter open research repository, according to the University of Exeter data management policy.

8.6 Declaration of interests

There are no financial or other competing interests for investigators for the overall trial.

8.7 Access to data

All members of the research team involved in the study will have a duty of confidentiality, and nothing that could reveal the patient's identity will be disclosed outside the research team. Information will be collected and stored in accordance with the Data Protection Act 1998.

The participants' names and other identifying information will be removed from any study data, and will be linked to an anonymous ID number on a password protected database so that they cannot be identified from the data.

8.8 Ancillary and post-trial care

Arrangements have been made through University of Exeter for insurance and/or indemnity to meet the potential legal liability of the sponsor for harm to participants arising from the management/conduct/design of the research.

8.9 Dissemination policy

Results will be written up and submitted to a peer review journal and presented at conferences. The study will also form part of a PhD thesis.

Participants will be given a newsletter at the end of the study to inform them of the results.

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**Appendix 3.2: Participant information sheet**



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# Participant Information Sheet

## Study title

Identifying physical activity through accelerometry in heart failure

## Invitation and brief summary

We would like to invite you to take part in a research study to help better understand physical activity in patients with your heart condition. Participation is entirely voluntary, and before you decide whether or not you would like to take part, we would like you to understand why the research is being done, and what would be involved. After reading this information sheet, please do not hesitate to ask the research team any questions you may have, to help you decide whether or not you would like to take part.

Thank you for taking the time to read this information.

## What is the purpose of the study?

The proposed research study is being undertaken as part of a PhD.

Advances in physical activity monitoring means that we are now able to estimate the intensity of specific behaviours with wearable devices. These devices (similar to a watch) need to be tested within a laboratory before they can be applied to research. Previous laboratory tests have been performed with young and healthy people but not in people with heart conditions. We know that in patients with heart conditions, their fitness levels may not be as high as a healthy adult, therefore we need to perform the laboratory test in patients with your heart condition to make sure we are accurately measuring physical activity.

The aim of this study is to identify the range of values provided by activity monitors during a variety of typical daily activities (e.g. lying, sitting, standing, walking), and to relate these to the energy cost (or intensity) of performing each activity.

Participants will be required to have their fitness measured via an incremental shuttle walk test, and will also be asked to complete numerous activities that represent everyday life, such as lying, sitting, walking and household tasks. These will be completed whilst wearing activity monitors (on the wrists and hip) and a facemask to measure expired air.

## What would taking part involve?

We have invited you to take part in the study because we are looking for patients with your heart condition aged 18 years and above, who meet a range of eligibility criteria for the study. We will be recruiting 18-30 heart failure patients in total.

If you agree to take part you will be asked to attend the Sports Science laboratory, in the Richard's Building, at the University of Exeter's St. Luke's campus on Heavitree Road for a single visit that should last approximately 3 hours. You will be reimbursed for your travel to and from the campus.

Please wear comfortable, loose clothing and appropriate footwear for physical activity.

**Fasting**

**You will need to attend fasted for us to measure your resting metabolism, however breakfast will be provided once these measures are complete (within the first hour of the visit), and refreshments at the end of the visit.**

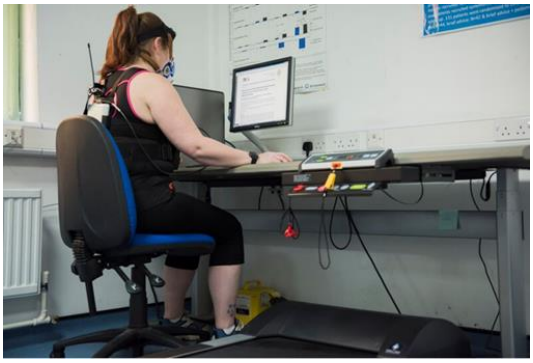
**Please ensure that you have nothing to eat or drink (other than water) for 8-12 hours (overnight) prior to attending your appointment. All appointments will be in the morning. Ensure that you drink plenty of water to stay well hydrated and take your medications as normal in the morning.**

If you attend the appointment but have not fasted overnight, and still wish to participate, we will complete the physical activities and then we will ask you to come back and complete the resting metabolism at another time.

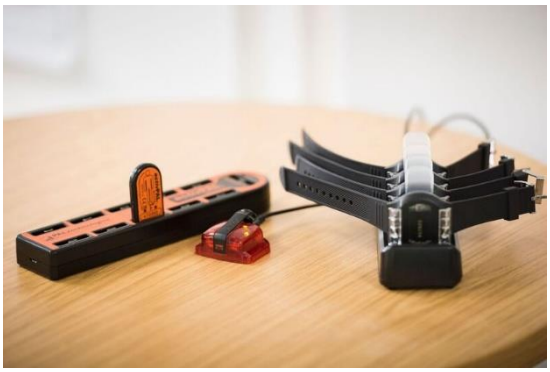
Overview of the day:

Before starting you will have the opportunity to discuss any final questions you may have about the study with the research team. You will then be asked to sign a written informed consent form stating that you are happy to take part.

We will collect some preliminary measurements including height, weight, and blood pressure. You will then be fitted with a portable gas analyser which consists of a rubber face mask, attached to two small boxes which you will wear in a harness on your chest (see picture 1); and accelerometers (one on each wrist, and one on the hip (see picture 2)).



*Picture 1*



*Picture 2*

The activities that you will be asked to complete are detailed in Table 1 below. There will be a one minute transition between each activity. The metabolic rate that is measured during the first sitting period will be used to determine your resting time. During your rest periods you will be seated until you return to this resting rate, and remain at this for 15 minutes. Then you will move on to the next block of activities.

*Table 4: Description of activities*

| Duration | Activity |
|---|---|
| 30 minutes | Laying down on a bed |
| 5 minutes | Sitting |
| Breakfast | |
| 20 minutes (approx.) | Incremental Shuttle Walk Test |
| Rest period | |
| 5 minutes | Sitting watching television |
| 5 minutes | Standing washing dishes |
| 5 minutes | Sitting |
| Rest period | |
| 5 minutes | Light intensity walk |
| 5 minutes | Rest, sitting |
| 5 minutes | Moderate intensity walk |
| 10 minutes | Rest, sitting |
| 5 minutes | Light intensity walk carrying shopping bag |
| Equipment returned and refreshments provided | |

The incremental shuttle walk test is an exercise test used to estimate your fitness. During the test you will be asked to walk between two cones spaced 10 metres apart in time with beeps on a pre-recorded CD. The pace will start off very slow, and increase gradually every minute, getting faster until you are unable to keep up with the set pace, or feel too breathless or tired to continue. During the last 30 seconds of each stage we will ask you to rate how difficult you are finding the activity using the rating of perceived exertion scale.

During the final minute of each activity we will be asking you to rate how difficult you are finding the activity using the rating of perceived exertion scale.

Once all the activities are complete we will provide you with some refreshments and allow you to rest under supervision for as long as desired before returning to your day.

## What are the possible benefits of taking part?

The main benefits of the study will be informative and there will be limited personal benefit to you. The results will help to increase our understanding of physical activity in the heart failure population.

## What are the possible disadvantages and risks of taking part?

We don't expect you to be harmed in any way by taking part in this study. The incremental shuttle walk test is a predictive fitness test that has been tested and validated in the heart failure population, it is commonly used in cardiac rehabilitation. The physical activities that you will be asked to undertake should replicate activities you usually undertake on a day to day basis, therefore have little risk involved. You may experience some side effects from fasting, such as light-headedness. However, while fasted you will only be laying down and sitting to have your metabolic rate measured before you can eat.

You will be monitored closely at all times during the visit and you will be advised to report any discomfort or desire to stop the activities immediately.

Your attendance at the university campus may incur an expense to you in the first instance. However, please be assured that any travel expenses for taking part in the study, including those incurred through use of your own vehicle will be reimbursed at public transport rates. The research team member will let you know how to claim travel expenses at the research visit.

## Do I have to take part?

Participation in this study is entirely voluntary. It is your choice whether you would like to take part or not and if you decide to take part, you are free to withdraw from the study at any time without giving a reason as to why you wish to do so. If you do decide to participate in this study you will be asked to sign a consent form before you start. You will be given a copy of the consent form and this information sheet for your own records.

Your participation will not affect your routine patient care now, or in the future.

## Are my results confidential?

If you consent to take part in this study, all information that is collected about you will be kept strictly confidential. Your medical records will be reviewed by your clinical care team at the RD&E clinic to confirm eligibility to take part**.** The chief investigator may review your medical records to collect clinical data about the type and degree of heart failure, or this information will be passed onto the research team via secure NHS email. The research team at University of Exeter will prepare the trial data collected about you for analysis. Your name and other identifying information will be removed from any study data, and will be linked to

an anonymous ID number on an encrypted password protected database so that you cannot be identified from the data.

Paper based information will be stored in locked cupboards in locked offices and information stored on computers will be stored securely on a system maintained by the University of Exeter. Your name, address and GP details will be stored securely on computers, accessible only by members of the study team for the purposes of contacting you, mailing information and results about the study if requested, and in order to contact your GP about participation in the study. Your personal information will be stored separately from the research information collected in the study. Any communication between your clinical care team and the investigator will be done via secure NHS email.

All members of the research team involved in the study will have a duty of confidentiality to you as a research participant, and nothing that could reveal your identity will be disclosed outside the research team. Information will be collected and stored in accordance with the Data Protection Act 2018.

## What will happen to the results of this study?

The results will increase our understanding of the lifestyle physical activities of heart failure patients. We will aim to publish the findings in research journals and to present them at conferences in the UK or abroad. If you are interested we will send you a newsletter at the end of the study to inform you of the results. Your data will always remain anonymous and your name will not appear on any results.

## How have patients and the public been involved in this study?

A heart failure patient and public involvement group, consisting of heart failure patients and their caregivers were involved in designing this study; we have taken into account patient opinions of the frequency and length of participant visits and the physical activities included in the protocol.

## Involvement of your General Practitioner/Family Doctor (GP)

With your permission, we will write to your GP to inform them of your participation in this study. They may also be contacted should the research team have any concerns about your health during your involvement with the study.

## Who has reviewed this study?

All research activity in the NHS is reviewed by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by East of England - Cambridge South Research ethics committee Research Ethics Committee.

## Contacts for further information

If you would like more information or if you have any further questions about the study please contact the investigators using the details below:

| | |
|---|---|
| Grace Dibben | Associate Professor Melvyn Hillsdon |
| European Centre for Environment and Human Health | School of Sport and Health Sciences |
| University of Exeter Medical School | Richards Building |
| Knowledge Spa | St. Lukes Campus |
| Royal Cornwall Hospital | Exeter University |
| Truro, TR1 3HD | EX12LU |
| Tel: 01872 255179 | Tel: 01392 722868 |
| Email: gd318@exeter.ac.uk | Email: m.hillsdon@exeter.ac.uk |

If you would like to make a complaint please contact:
Professor Rod Taylor, Tel: 01392 726053, Email: r.taylor@exeter.ac.uk

## Appendix 3.3: Informed consent form

**Sport and Health Sciences**
**College of Life and Environmental Sciences**
St Luke's Campus,
Heavitree Road, Exeter,
EX1 2LU
Telephone: +44 (0)1392 26
Email: sshs-school-office@ex.ac.uk
Web: www.ex.a.uk

**Study:** Identifying physical activity through accelerometry in heart failure
**Researcher:** Grace Dibben
**Organisation:** The University of Exeter
**Version**: #1.2 04/05/2018: reviewed by East of England - Cambridge South Research ethics committee
**IRAS project ID**: 225596

Participant Identification Number:

### Informed Consent form for participants

**Please initial box**

I confirm that I have read and understand the information sheet version #1.2 dated 04.05.18 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

I understand that my personal details will be kept securely and confidentially, and any information that is entered onto a computer will be password protected. My personal details will be stored separately from the data I provide (which will be stored anonymously) and none of my identifiable details will appear in any reports, articles or presentations by the research team. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason or affect on my care now or in the future. ☐

I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University of Exeter, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

optional

I give permission for my GP to be informed of my participation in the study. ☐

GP name and surgery:

I understand that if the researcher becomes aware of any factors relating to my health that they consider pose a serious threat to my well-being they will act in my best interest and inform my GP as a matter of urgency, without my express permission if considered necessary. In the very unlikely event that this will occur I understand that the researcher will always inform me that they have contacted my GP and tell me what information they have passed. ☐

I understand that in order for resting metabolism to be measured I will be required to fast overnight, prior to attending my appointment the following morning. I understand that I will be provided breakfast once these measures are complete. ☐

I agree to take part in the above study. ☐

| Name of Participant | Date | Signature |
|---|---|---|
| | | |

| Name of Researcher | Date | Signature |
|---|---|---|
| | | |

## Appendix 3.4: Health research authority favourable ethical opinion letter

NHS
Health Research Authority

Miss Grace Dibben
PhD Student
F037B, European Centre for Environment and Human
Health, University of Exeter Medical School
Royal Cornwall Hospital
Truro
TR1 3HD

Email: hra.approval@nhs.net

19 February 2018

Dear Miss Dibben,

**Letter of HRA Approval**

| | |
|---|---|
| **Study title:** | **Identifying physical activity through accelerometry in heart failure** |
| **IRAS project ID:** | **225596** |
| **Protocol number:** | **1617/036** |
| **REC reference:** | **18/EE/0019** |
| **Sponsor** | **University of Exeter** |

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

**Participation of NHS Organisations in England**

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

*Appendix B* provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from the HRA website.

**Appendices**

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

**After HRA Approval**

The document *"After Ethical Review – guidance for sponsors and investigators",* issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

**Scope**

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found through IRAS.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

**User Feedback**

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

procedure. If you wish to make your views known please use the feedback form available on the HRA website.

**HRA Training**

We are pleased to welcome researchers and research management staff at our training days – see details on the HRA website.

Your IRAS project ID is **225596**. Please quote this on all correspondence.

Yours sincerely

Aliki Sifostratoudaki
Assessor

Email: hra.approval@nhs.net

*Copy to:* *Mrs G M Seymour, University of Exeter, Sponsor Contact*
*Ms Claire Heaver, Royal Devon & Exeter NHS Foundation Trust, R&D Contact*

**Appendix A - List of Documents**

The final document set assessed and approved by HRA Approval is listed below.

| *Document* | *Version* | *Date* |
|---|---|---|
| Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [EL PL letter] | | 31 October 2017 |
| GP/consultant information sheets or letters [GP letter] | 1.1 | 05 February 2018 |
| HRA Schedule of Events [225596_SOE_PICs_Assessed by the HRA] | 1 | 15 February 2018 |
| HRA Statement of Activities [225596_SOA_PICs_Assessed by the HRA.xls] | 1 | 15 February 2018 |
| Instructions for use of medical device [geneactiv_instruction_manual_v1.2] | 1.2 | 29 March 2012 |
| IRAS Application Form [IRAS_Form_15122017] | | 15 December 2017 |
| Letter from sponsor [Sponsorship confirmation] | | 29 August 2017 |
| Letter from statistician [Statistical review letter] | 1.0 | 14 December 2017 |
| Letters of invitation to participant [Patient recruitment leaflet] | 1.1 | 01 February 2018 |
| Other [Provisional Opinion response letter] | 1.0 | 08 February 2018 |
| Other [Supporting Cardiologist CV] | | |
| Other [Supervisor CV - Dalal] | | |
| Other [Supervisor CV - Melvyn Hillsdon] | | |
| Other [Borg RPE scale] | 1.0 | |
| Other [Evidence of Sponsor insurance or indemnity (non-NHS Sponsors only)] | | 21 November 2017 |
| Other [Cardiologist letter of support] | 1.0 | 06 November 2017 |
| Other [CI GCP certificate] | 1.0 | 28 June 2017 |
| Other [Risk Assessment] | 1.0 | 20 October 2017 |
| Participant consent form [ICF] | 1.1 | 01 February 2018 |
| Participant information sheet (PIS) [PIS] | 1.1 | 05 February 2018 |
| Referee's report or other scientific critique report [Scientific review letter] | 1.0 | 14 December 2017 |
| Research protocol or project proposal [Protocol] | 1.1 | 01 February 2018 |
| Summary CV for Chief Investigator (CI) [CI Summary CV] | 1.0 | 25 August 2017 |
| Summary CV for student [CI Summary CV] | 1.0 | 25 August 2017 |
| Summary CV for supervisor (student research) [Supporting Cardiologist CV] | | |
| Summary CV for supervisor (student research) [Supervisor CV - Rod Taylor] | | |

| IRAS project ID | 225596 |
|---|---|

**Appendix B - Summary of HRA Assessment**

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

**For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations, capacity and capability* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.**

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Name: Mrs G M Seymour

Tel: 01392726621

Email: g.m.seymour@exeter.ac.uk

### HRA assessment criteria

| Section | HRA Assessment Criteria | Compliant with Standards | Comments |
|---|---|---|---|
| 1.1 | IRAS application completed correctly | Yes | The Applicant clarified that there is only one site type involved in this study, Participant Identification Centres (PICs).<br><br>The Applicant confirmed that the devices used for this study are CE marked. |
| | | | |
| 2.1 | Participant information/consent documents and consent process | Yes | For the purpose of HRA assessment revisions were to the participant information sheet and consent form in order to bring them in line with HRA standards. |
| | | | |
| 3.1 | Protocol assessment | Yes | No comments |
| | | | |
| 4.1 | Allocation of responsibilities and rights are agreed and documented | Yes | The Sponsor contact has confirmed that the Statement of Activities and the Schedule of Events will form the agreement between the Sponsor and |

| Section | HRA Assessment Criteria | Compliant with Standards | Comments |
|---|---|---|---|
| | | | the research sites.<br><br>Revisions were made to the Statement of Activities and Schedule of Events. |
| 4.2 | Insurance/indemnity arrangements assessed | Yes | The Applicant clarified that the University of Exeter indemnity will apply for the conduct of the study.<br><br>Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this research study |
| 4.3 | Financial arrangements assessed | Yes | This study is not funded. |
| | | | |
| 5.1 | Compliance with the Data Protection Act and data security issues assessed | Yes | No comments |
| 5.2 | CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed | Not Applicable | No comments |
| 5.3 | Compliance with any applicable laws or regulations | Yes | No comments |
| | | | |
| 6.1 | NHS Research Ethics Committee favourable opinion received for applicable studies | Yes | The REC Favourable Opinion letter has been issued. |
| 6.2 | CTIMPS – Clinical Trials Authorisation (CTA) letter received | Not Applicable | No comments |
| 6.3 | Devices – MHRA notice of no objection received | Not Applicable | No comments |
| 6.4 | Other regulatory approvals and authorisations received | Not Applicable | No comments |

## Participating NHS Organisations in England

| *This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.* |
|---|
| There is one site type involved in this study – PIC sites. PIC sites will be responsible for identifying, initially approaching participants about the study and providing the research team with patient details (such as clinical information i.e. degree of left ventricular dysfunction, NYHA class).<br><br>The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website.<br><br>If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision. |

## Confirmation of Capacity and Capability

| *This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.* |
|---|
| Participating NHS organisations in England **will be expected to formally confirm their capacity and capability to host this research**.<br>• Following issue of this letter, participating NHS organisations in England may now confirm to the sponsor their capacity and capability to host this research, when ready to do so. How capacity and capacity will be confirmed is detailed in the *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* section of this appendix.<br>• The Assessing, Arranging, and Confirming document on the HRA website provides further information for the sponsor and NHS organisations on assessing, arranging and confirming capacity and capability. |

## Principal Investigator Suitability

| *This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).* |
|---|
| A key contact would be expected to identify and initially approach participants about the study.<br><br>Neither a Principal Investigator nor a Local Collaborator will be expected at this site type.<br><br>GCP training is not a generic training expectation, in line with the HRA/MHRA statement on training expectations. |

| IRAS project ID | 225596 |
|---|---|

## HR Good Practice Resource Pack Expectations

| *This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken* |
|---|
| No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. |

## Other Information to Aid Study Set-up

| *This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.* |
|---|
| The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio. |

## Appendix 3.5: Health research authority favourable ethical opinion letter for substantial amendment

NHS
Health Research Authority

**East of England - Cambridge South Research Ethics Committee**

The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

**Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.**

19 June 2018

Miss Grace Dibben
F037B, European Centre for Environment and Human Health
University of Exeter Medical School
Knowledge Spa, Royal Cornwall Hospital
Truro, Cornwall
TR1 3HD

Dear Miss Dibben,

| | |
|---|---|
| **Study title:** | **Identifying physical activity through accelerometry in heart failure** |
| **REC reference:** | **18/EE/0019** |
| **Protocol number:** | **1617/036** |
| **Amendment number:** | **Substantial Amendment 1** |
| **Amendment date:** | **25 May 2018** |
| **IRAS project ID:** | **225596** |

The above amendment was reviewed on 15 June 2018 by the Sub-Committee in correspondence.

**Ethical opinion**

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The Sub-Committee were in agreement that the Substantial Amendment did not raise any material ethical issues.

**Approved documents**

The documents reviewed and approved at the meeting were:

| *Document* | *Version* | *Date* |
|---|---|---|
| Copies of advertisement materials for research participants [Clean] | 1.2 | 25 May 2018 |
| Copies of advertisement materials for research participants [Tracked Changes] | 1.2 | 25 May 2018 |
| GP/consultant information sheets or letters [Clean] | 1.2 | 04 May 2018 |
| GP/consultant information sheets or letters [Tracked Changes] | 1.2 | 04 May 2018 |
| Notice of Substantial Amendment (non-CTIMP) | Substantial Amendment 1 | 25 May 2018 |
| Participant consent form [Tracked Changes] | 1.2 | 04 May 2018 |
| Participant consent form [Clean] | 1.2 | 04 May 2018 |
| Participant information sheet (PIS) [Clean] | 1.2 | 04 May 2018 |
| Participant information sheet (PIS) [Tracked Changes] | 1.2 | 04 May 2018 |
| Research protocol or project proposal [Clean] | 1.2 | 04 May 2018 |
| Research protocol or project proposal [Tracked Changes] | 1.2 | 04 May 2018 |

**Membership of the Committee**

The members of the Committee who took part in the review are listed on the attached sheet.

**Working with NHS Care Organisations**

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

**Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

| **18/EE/0019:** | **Please quote this number on all correspondence** |
|---|---|

Yours sincerely,

P. P.

**Dr Leslie Gelling**
**Chair**

E-mail: nrescommittee.eastofengland-cambridgesouth@nhs.net

*Enclosures:* *List of names and professions of members who took part in the review*

*Copy to:* *Ms Claire Heaver, Royal Devon & Exeter NHS Foundation Trust*
*Miss Grace Dibben*

**East of England - Cambridge South Research Ethics Committee**

**Attendance at Sub-Committee of the REC meeting on 15 June 2018**

**Committee Members:**

| *Name* | *Profession* | *Present* | *Notes* |
|---|---|---|---|
| Dr Leslie Gelling | (Chair) Reader in Research Ethics | Yes | |
| Mrs Alison Hall | Programme Lead - Humanities | Yes | |

**Also in attendance:**

| *Name* | *Position (or reason for attending)* |
|---|---|
| Kate Loven | REC Assistant |

**Appendix 3.6: Sensitivity, specificity, area under the curve and resulting intensity thresholds for each accelerometer, and each data reduction method**

| | Inactivity (<1.5 METS) | | | | MVPA (≥3.0 METS) | | | |
|---|---|---|---|---|---|---|---|---|
| | **Sensitivity (%)** | **Specificity (%)** | **AUC (95% CI)** | **Threshold (mg)** | **Sensitivity (%)** | **Specificity (%)** | **AUC (95% CI)** | **Threshold (mg)** |
| ***SVM Right Wrist*** | | | | | | | | |
| All patients (n=21, obs =168) | 94.5 | 96.1 | 0.96 (0.93-0.99) | 15.2 | 89.2 | 85.5 | 0.90 (0.85-0.95) | 35.7 |
| Excluded aided walking activity data* (n=21, obs=159) | 91.5 | 98.7 | 0.96 (0.92 to 0.99) | 20.5 | 100.0 | 81.6 | 0.91 (0.85 to 0.95) | 30.0 |
| Excluded aided walking and washing up activity data† data (n=21, obs=138) | 91.9 | 97.4 | 0.96 (0.92-1.00) | 15.2 | 100.0 | 97.7 | 1.00 (0.98-1.00) | 30.0 |
| ***SVM Left wrist*** | | | | | | | | |
| All patients (n=20, obs =160) | 92.0 | 91.8 | 0.96 (0.92-0.99) | 16.9 | 84.1 | 85.6 | 0.91 (0.87-0.96) | 39.5 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Excluded aided walking activity data* (n=21, obs=151) | 92.3 | 94.5 | 0.96 (0.92-0.99) | 19.8 | 96.3 | 83.5 | 0.93 (0.89-0.97) | 36.4 |
| Excluded aided walking and washing up activity data† (n=21, obs=131) | 88.1 | 98.6 | 0.95 (0.91-1.00) | 29.9 | 98.0 | 97.5 | 0.99 (0.98-1.00) | 36.4 |
| ***SVM Waist*** | | | | | | | | |
| All patients (n=21, obs =168) | 90.1 | 90.9 | 0.95 (0.92-0.98) | 5.6 | 95.4 | 98.1 | 0.99 (0.98-1.00) | 16.2 |
| Excluded aided walking activity data* (n=21, obs=159) | 86.6 | 97.4 | 0.94 (0.91-0.98) | 6.1 | 94.6 | 98.1 | 0.99 (0.98-1.00) | 16.2 |
| Excluded aided walking and washing up activity data† (n=21, obs=138) | 87.1 | 100.0 | 0.93 (0.89-0.98) | 26.0 | 100.0 | 97.7 | 1.00 (0.99-1.00) | 26.0 |
| ***MAD Right wrist*** | | | | | | | | |
| All patients (n=21, obs =168) | 75.8 | 63.6 | 0.76 (0.69-0.84) | 6.7 | 58.5 | 68.9 | 0.67 (0.59-0.75) | 22.4 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Excluded aided walking activity data* (n=21, obs=159) | 82.9 | 63.6 | 0.79 (0.72-0.86) | 6.7 | 67.9 | 68.9 | 0.71 (0.63-0.79) | 22.4 |
| Excluded aided walking and washing up activity data† (n=21, obs=138) | 77.4 | 64.5 | 0.76 (0.68-0.84) | 6.7 | 65.4 | 81.4 | 0.78 (0.70-0.85) | 22.4 |
| ***MAD Left wrist*** | | | | | | | | |
| All patients (n=21, obs =168) | 77.0 | 63.0 | 0.73 (0.65-0.81) | 7.7 | 74.6 | 51.6 | 0.61 (0.52-0.69) | 7.7 |
| Excluded aided walking activity data* (n=21, obs=159) | 80.8 | 63.0 | 0.75 (0.67-0.83) | 7.7 | 79.6 | 51.6 | 0.63 (0.54-0.72) | 7.7 |
| Excluded aided walking and washing up activity data† (n=21, obs=138) | 74.6 | 63.9 | 0.72 (0.63-0.80) | 7.7 | 78.0 | 61.7 | 0.71 (0.62-0.80) | 7.7 |
| ***MAD Waist*** | | | | | | | | |
| All patients (n=21, obs =168) | 83.5 | 87.0 | 0.90 (0.85-0.95) | 1.0 | 90.8 | 86.4 | 0.94 (0.90-0.97) | 1.5 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Excluded aided walking activity data* (n=21, obs=159) | 84.2 | 87.0 | 0.90 (0.85-0.95) | 1.0 | 92.9 | 86.4 | 0.95 (0.92-0.98) | 1.6 |
| Excluded aided walking and washing up activity data† (n=21, obs=138) | 87.1 | 90.8 | 0.91 (0.85-0.97) | 1.2 | 94.2 | 91.9 | 0.97 (0.94-1.00) | 1.6 |

METS, metabolic equivalents; MVPA, moderate-vigorous physical activity; AUC, area under the curve; SVM, sum of vector magnitude; MAD, mean amplitude deviation.* Excluded walking activity data for n=3 patients using walking aids. † Excluded walking activity data for n=3 patients using walking aids and all washing up activity data.

## Appendix 3.7: Leave-one-out cross validation

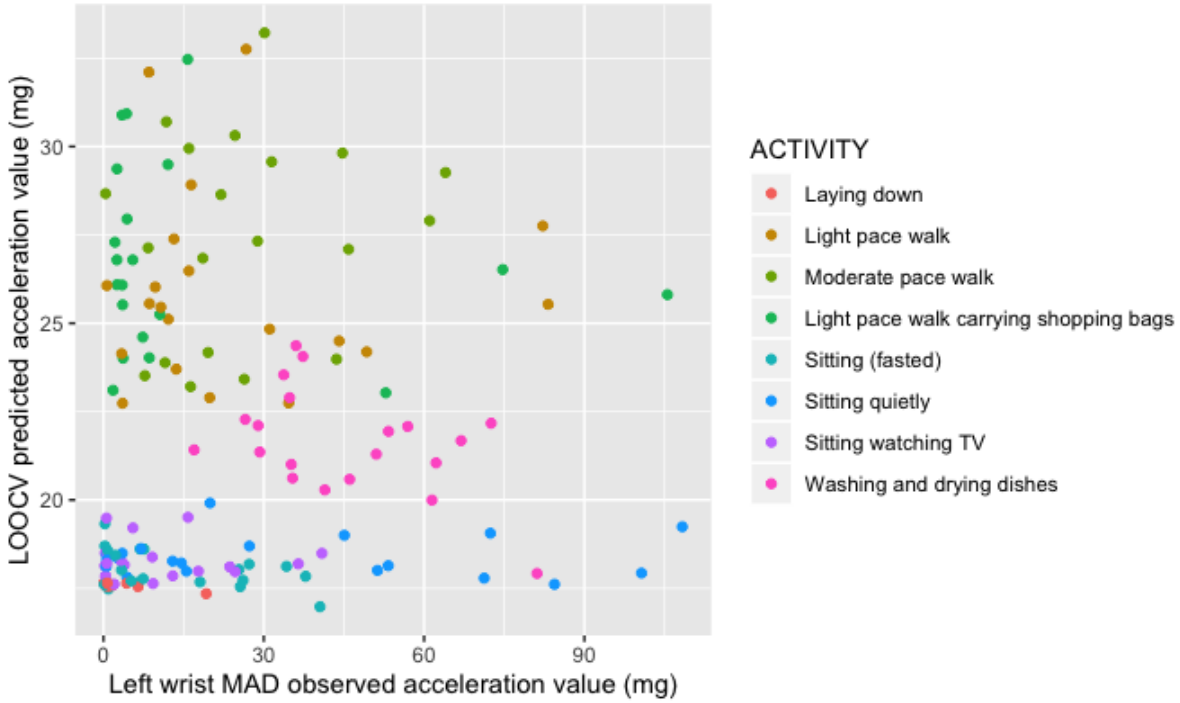



Figure B1 – Scatter plot where each point represents the prediction from a multilevel mixed effects regression linear regression model leaving out one observation against the observed left wrist MAD acceleration value, shaded by activity.

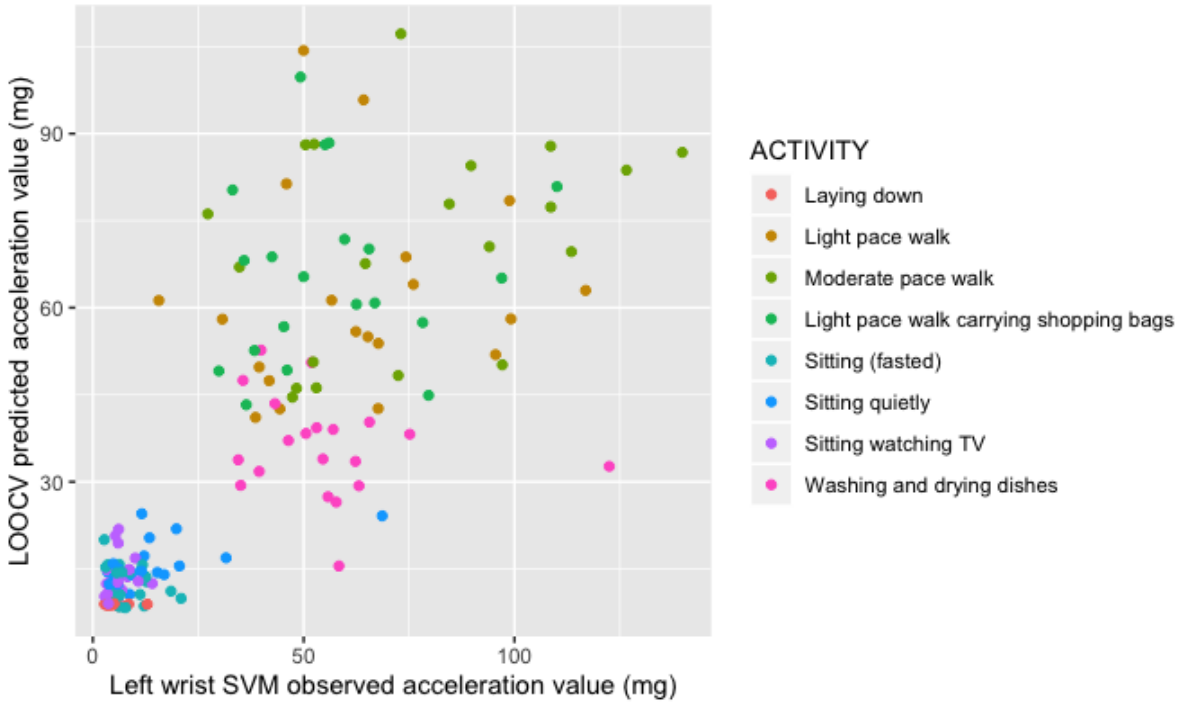



Figure B2 - Scatter plot where each point represents the prediction from a multilevel mixed effects regression linear regression model leaving out one observation against the observed left wrist SVM acceleration value, shaded by activity.

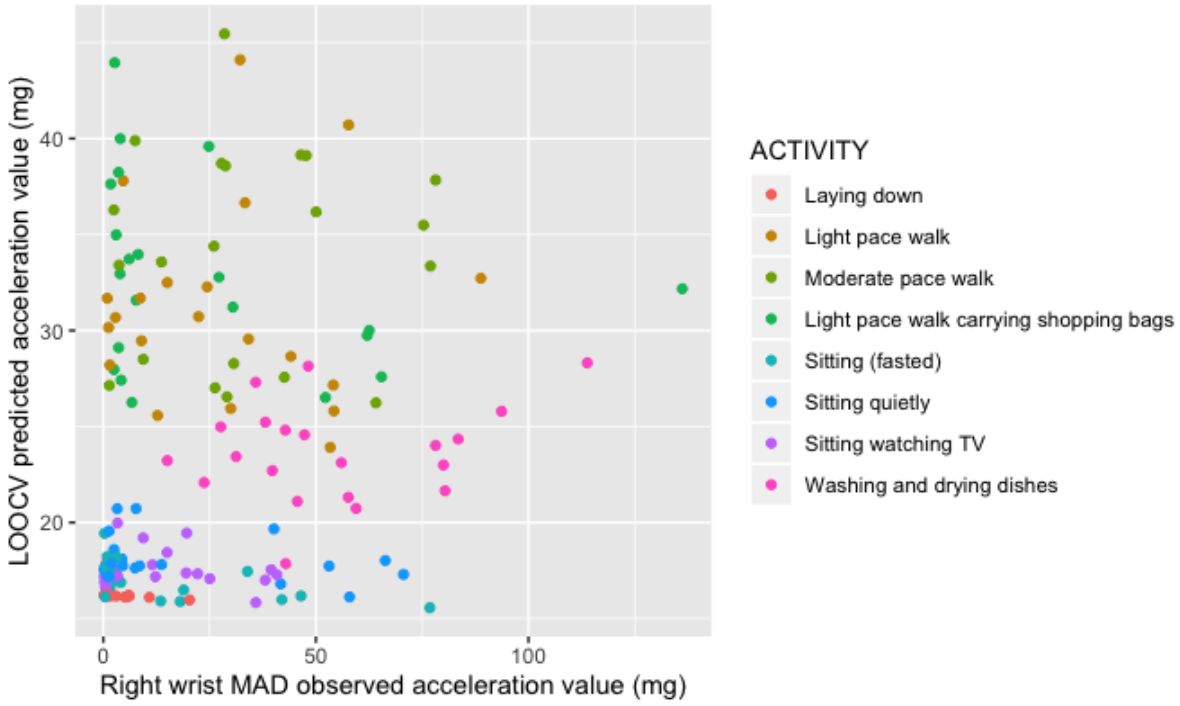



Figure B3 - Scatter plot where each point represents the prediction from a multilevel mixed effects regression linear regression model leaving out one observation against the observed right wrist MAD acceleration value, shaded by activity.

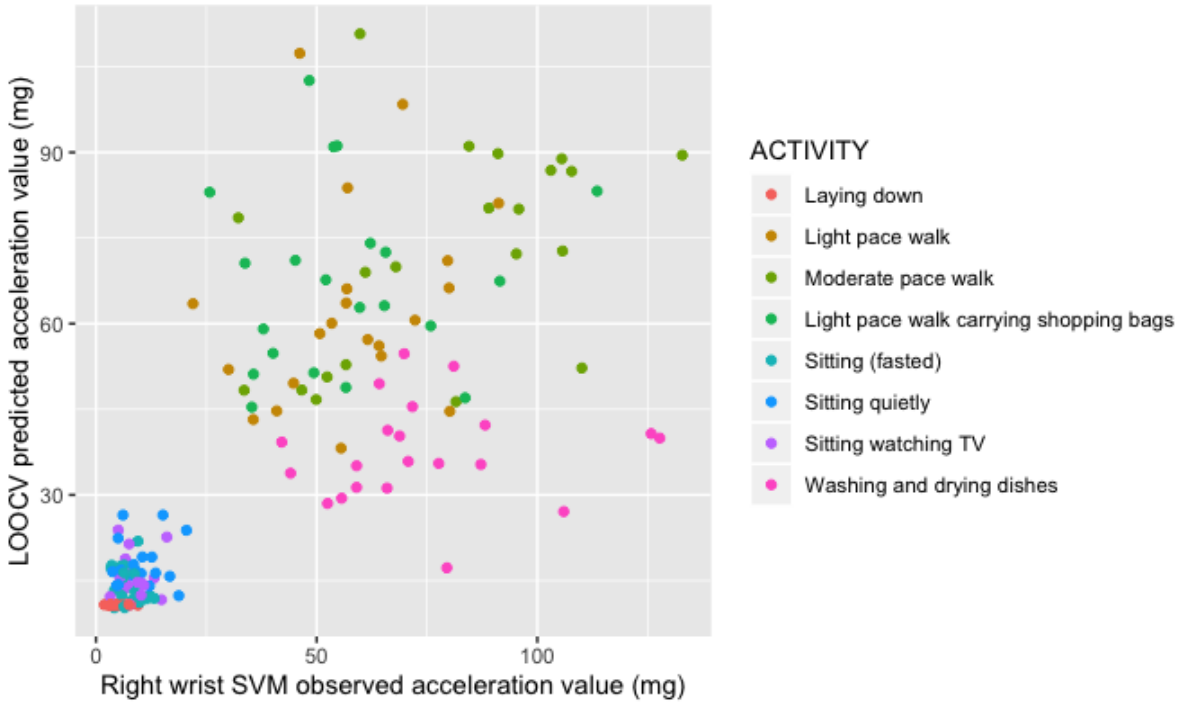



Figure B4 - Scatter plot where each point represents the prediction from a multilevel mixed effects regression linear regression model leaving out one observation against the observed right wrist SVM acceleration value, shaded by activity.

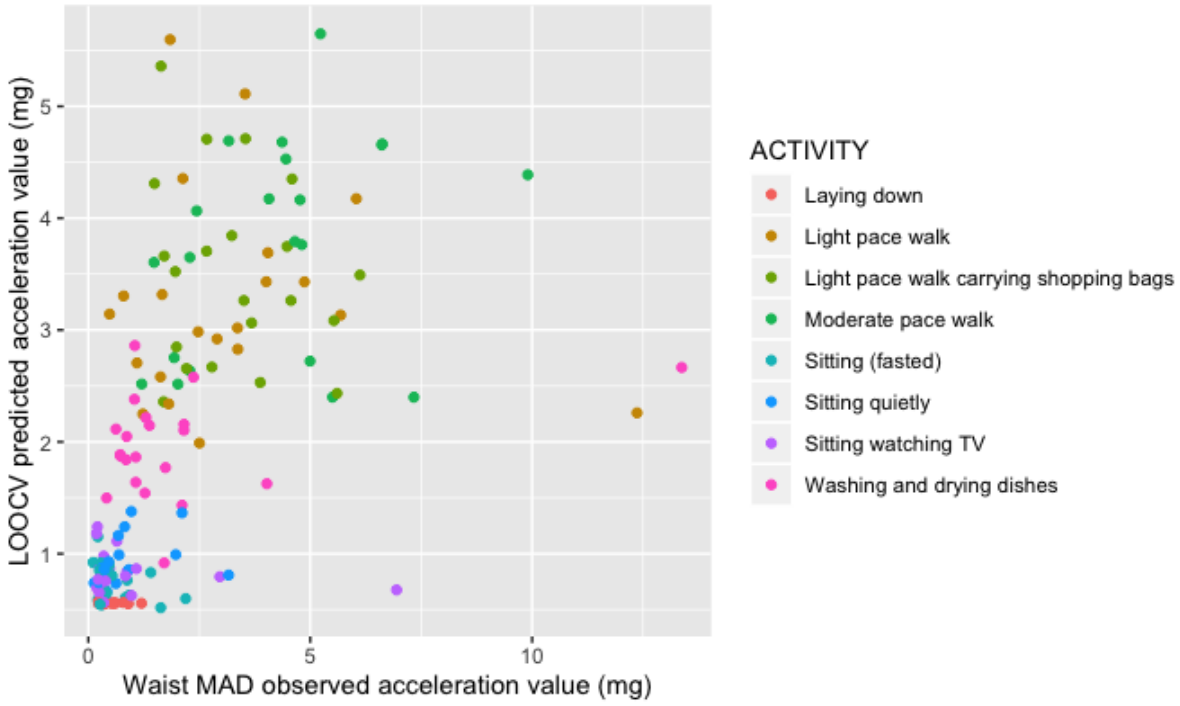



Figure B5 - Scatter plot where each point represents the prediction from a multilevel mixed effects regression linear regression model leaving out one observation against the observed waist MAD acceleration value, shaded by activity.

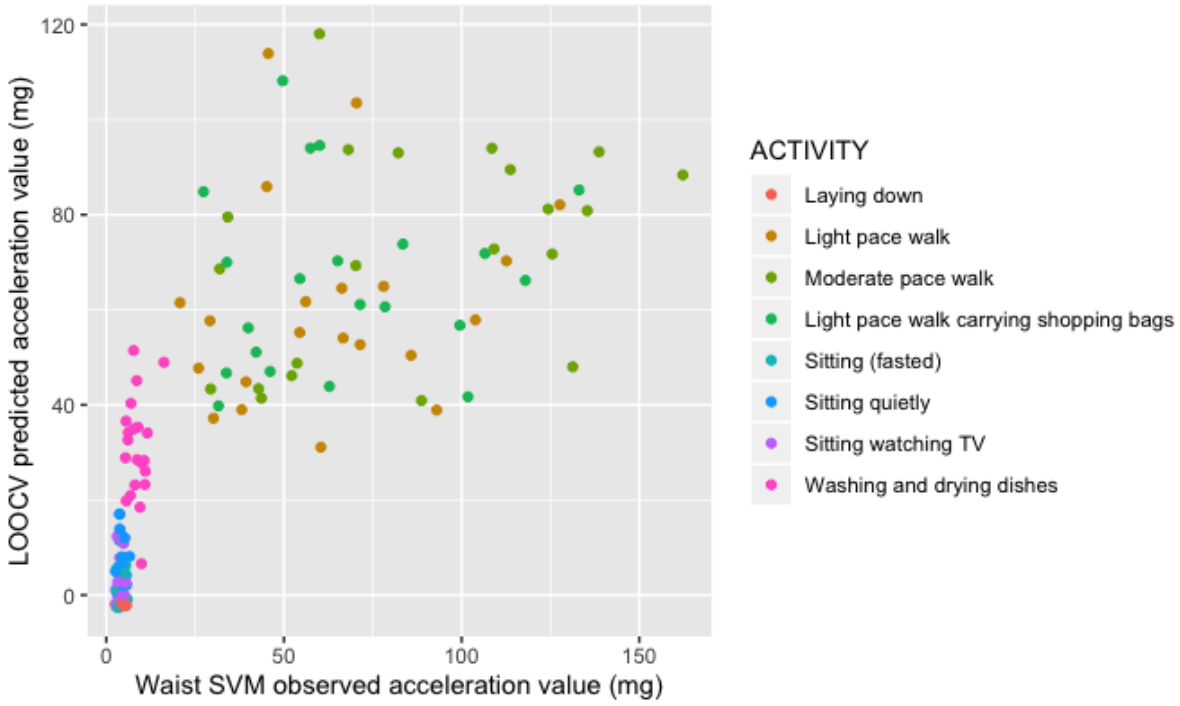



Figure B6 - Scatter plot where each point represents the prediction from a multilevel mixed effects regression linear regression model leaving out one observation against the observed waist SVM acceleration value, shaded by activity.

**Appendix 3.8: Letter to the editor associated with Chapter 3 of this thesis**

One size does not fit all – application of accelerometer thresholds in chronic disease

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Comment on: Physical activity of UK adults with chronic disease: cross-sectional analysis of accelerometer-measured physical activity in 96706 UK Biobank participants.

We would like to congratulate the recent publication from Barker et al., comparing physical activity (PA) of those with and without chronic disease from the UK Biobank participants.(1) The authors conclude that those with chronic disease have lower PA levels than their healthy peers. However, we would like to draw attention to what believe a key limitation of this study.

The accelerometer thresholds used by the authors to classify PA into moderate (100m*g*) or vigorous (400m*g*) intensity have been applied to all study participants, both with and without chronic disease. These thresholds are derived from a study of 30 healthy adults (2), and have been used in a number of studies including those of older adults and patients with heart failure.(3-4) Applying the same intensity thresholds to all individuals, make the strong (and we believe inappropriate) assumption that energy expenditure is the same for all i.e. an activity that generates a vector magnitude between 100-400mg requires 3-6 METS for everyone, and does not take into account an individual's exercise capacity.

We have recently conducted an accelerometer calibration study in 21 heart failure patients (paper currently in preparation), and have derived acceleration values that relate to moderate intensity activity in this population. The value of 100m*g* used in the paper by Barker et al.(1) is more than double the values that we observed (i.e. 43.2 to 45.5m*g*).

We do not dispute that PA levels of those with chronic disease are lower than those of their healthy counterparts. However, the magnitude of the difference between these two groups may be exaggerated with the application of the same intensity threshold of 100m*g*. As a result, the amount of MVPA in those with chronic disease, such as heart failure, has been underestimated in the study of Barker et al.

It is vital that accelerometer data is interpreted correctly. If a PA threshold is applied that is too high it will result in activity recommendations that are inappropriate and likely to be too difficult for patients perform. As a result, patients may become demoralised, demotivated and less likely to make the behaviour change that is so important for their health.(5)

References

1. Barker J, Smith Byrne K, Doherty A, et al. Physical activity of UK adults with chronic disease: cross-sectional analysis of accelerometer-measured physical activity in 96706 UK Biobank participants. International Journal of Epidemiology 2019; 1-8.

2. Hildebrand M, van Hees VT, Hansen BH, Ekelund U. Age group comparability of raw accelerometer output from wrist- and hip-worn monitors. Med Sci Sports Exerc 2014;46(9):1816-1824.

3. Dalal HM, Taylor RS, Jolly K, et al. The effects and costs of home-based rehabilitation for heart failure with reduced ejection fraction: The REACH-HF multicentre randomized controlled trial. Eur J Prev Cardiol [Internet]. 2018 Oct 10 [cited 2019 Mar 6];26(3). Available from: https://journals.sagepub.com/doi/10.1177/2047487318806358. doi.org/10.1177/2047487318806358.

4. Menai M, van Hees VT, Elbaz A, Kivimaki M, Singh-Manouz, Sabia S. Accelerometer assessed moderate-to-vigorous physical activity and successful ageing: results from the Whitehall II study. Scientific Reports [Internet] 2017 [cited 2019 Apr 05]; 7. Available from: https://www.nature.com/articles/srep45772.

5. American College of Sports Medicine: ACSM's Guidelines for Exercise Testing and Prescription. Philadelphia, PA: Lippincott, Williams and Wilkins, 2010

## Appendix 4.1: REACH-HF trials full inclusion and exclusion criteria

### HFrEF trial

*Inclusion criteria*

- Provision of informed consent to participate
- Adults (aged ≥18 years)
- Confirmed diagnosis of systolic heart failure on echocardiography (i.e. left ventricular ejection fraction <45% within the past 5 years)
- Patients who have experienced no deterioration of heart failure symptoms in the past 2 weeks resulting in hospitalisation or alteration of heart failure medication.

*Exclusion criteria*

- Patients who have undertaken cardiac rehabilitation in the last 12 months
- Patients who have received an intracardiac defibrillator (ICD), cardiac resynchronisation therapy (CRT) or combined CRT/ICD device implanted in the last 6 months
- Patients who have any of the following contraindications to exercise testing or exercise training:
    - Early phase after acute coronary syndrome (up to 2 days)
    - Untreated life-threatening cardiac arrhythmias
    - Acute heart failure (during the initial period of haemodynamic instability)
    - Uncontrolled hypertension (systolic blood pressure >200 and/or diastolic blood pressure >100)
    - Advanced atrioventricular block
    - Acute myocarditis and pericarditis
    - Symptomatic aortic stenosis
    - Severe hypertrophic obstructive cardiomyopathy
    - Acute systemic illness
    - Intracardiac thrombus
    - Progressive worsening of exercise tolerance or dyspnoea at rest over previous 3–5 days

    - Significant ischaemia during low-intensity exercise (<2 Metabolic equivalents, <50 Watts)
    - Uncontrolled diabetes (blood glucose >16 mmol/L or glycated hemoglobin >9% or equivalent unit)
    - Recent embolism
    - Thrombophlebitis
    - New-onset atrial fibrillation/atrial flutter
- Patients who are in a long term care establishment or are unwilling or unable to travel to research assessments or accommodate home visits
- Patients who are unable to understand the study information or unable to complete the outcome questionnaires
- Patients judged to be unable to participate in the study for any other reason (eg, psychiatric disorder, diagnosis of dementia, life threatening co-morbidity)
- Patients participating in concurrent interventional research which may over-burden the patient or confound data collection.

**HFpEF trial**

*Inclusion criteria*

- Adult aged ≥18 years
- Patients with heart failure defined by the presence of at least one of the following symptoms at the time of screening:
    - Paroxysmal nocturnal dyspnoea
    - Orthopnoea
    - Dyspnoea on mild or moderate exertion

  AND at least one of the following signs prior to study entry:

    - Basal crepitations
    - Elevated jugular venous pressure
    - Lower extremity oedema
    - Chest radiograph demonstrating pleural effusion, pulmonary congestion or cardiomegaly.
- Patients with left ventricular ejection fraction ≥45% obtained within 6 months prior to randomisation and after any myocardial infarction or

other event that would affect ejection fraction (ideally obtained by echocardiography, although radionuclide ventriculography and angiography are acceptable)

- Provision of informed consent to participate

*Exclusion criteria*

- Patients who have undertaken cardiac rehabilitation in the last 6 months
- Patients with severe chronic pulmonary disease defined as requiring home oxygen or hospitalisation for exacerbation within 12 months or significant chronic pulmonary disease in the opinion of the investigator
- Patients who have any of the following contraindications to exercise testing or exercise training:
    - Early phase after acute coronary syndrome (up to 2 days)
    - Untreated life-threatening cardiac arrhythmias
    - Acute heart failure (during the initial period of haemodynamic instability)
    - Uncontrolled hypertension (systolic blood pressure >200 and/or diastolic blood pressure >100)
    - Advanced atrioventricular block
    - Acute myocarditis and pericarditis
    - Symptomatic aortic stenosis
    - Severe hypertrophic obstructive cardiomyopathy
    - Acute systemic illness
    - Intracardiac thrombus
    - Progressive worsening of exercise tolerance or dyspnoea at rest over previous 3–5 days
    - Significant ischaemia during low-intensity exercise (<2 metabolic equivalents, <50 W)
    - Uncontrolled diabetes (blood glucose >16 mmol/L or HbA1C >9% or equivalent unit)
    - Recent embolism
    - Thrombophlebitis
    - Recent-onset atrial fibrillation/atrial flutter (in the last 4 weeks)

- Patients who are unable to understand the study information or unable to complete study procedures
- Patients who are in a long-term care establishment or who are unwilling or unable to travel to research assessments or accommodate home visits
- Patients judged to be unable to participate in the study for any other reason, for example, psychiatric disorder, diagnosis of dementia, life-threatening comorbidity
- Patients participating in concurrent interventional research which may overburden the patient or confound data collection.

**Appendix 4.2: Univariate linear regressions between MVPA and sociodemographics, exercise capacity and health status variables**

| Sociodemographic, exercise capacity and health status variables<br>N=247 unless otherwise stated | Unstandardized beta coefficient (95% CI) | p-value | $R^2$ |
|---|---|---|---|
| Age | -11.44 (-16.13 to -6.75) | <0.001 | 0.09 |
| Gender | 3.92 (-108.68 to 116.52) | 0.95 | <0.001 |
| BMI (N=246) | -13.96 (-21.94 to -5.99) | 0.001 | 0.05 |
| Employment status | | <0.001 | 0.14 |
| In employment/Self-employed | Comparison group | | |
| Retired | -435.64 (-579.59 to -291.69) | | |
| Housework | -621.03 (-1378.5 to 136.41) | | |
| Unemployed | -285.04 (-556.16 to -13.92) | | |
| Other | -160.2 (-492.73 to 172.28) | | |
| Ethnicity (white vs other) | -70.4 (-316.24 to 175.44) | 0.57 | 0.001 |
| NYHA class | | <0.001 | 0.14 |
| NYHA I | Comparison group | | |
| NYHA II | -303.94 (-436.43 to -171.45) | | |
| NYHA III-IV | -475.74 (-627.39 to -324.08) | | |
| Time since HF diagnosis | | 0.30 | 0.01 |
| 0 years | Comparison group | | |
| 1 year | 14.61 (-113.73 to 162.94) | | |
| 2 years | -73.21 (-189.68 to 43.26) | | |
| Cause of HF | | 0.03 | 0.03 |
| Ischaemic | Comparison group | | |
| Non-ischaemic | 131.87 (28.28 to 235.45) | | |
| Not known/classified | 179.40 (-30.63 to 389.44) | | |
| LVEF (%) (N=188) | 1.37 (-2.25 to 4.99) | 0.46 | 0.003 |

| | | | |
|---|---|---|---|
| NT-proBNP (pg/ml) | -0.03 (-0.06 to -0.001) | 0.04 | 0.02 |
| Living alone | -148.13 (-261.28 to -34.98) | 0.01 | 0.03 |
| Living with partner | 52.28 (-53.21 to 157.77) | 0.33 | 0.004 |
| Living with child >18 | 213.72 (15.08 to 412.35) | 0.04 | 0.02 |
| Living with child <18 | 258.26 (-100.59 to 617.11) | 0.16 | 0.008 |
| Living with parent | 320.25 (-37.81 to 678.31) | 0.08 | 0.01 |
| Smoking history | | 0.008 | 0.04 |
| Current smoker | Comparison group | | |
| Ex-smoker | 76.28 (-143.42 to 295.97) | | |
| Never smoked | 228.90 (4.44 to 453.35) | | |
| Trial site | | 0.43 | 0.02 |
| Truro | Comparison group | | |
| Gwent | -8.29 (-31.21 to 14.62) | | |
| Birmingham | -13.64 (-36.02 to 8.73) | | |
| York | 7.07 (-15.06 to 29.20) | | |
| Dundee | -7.60 (-29.85 to 14.65) | | |
| Comorbidities | | | |
| Angina | -108.32 (-222.75 to 6.11) | 0.06 | 0.01 |
| Diabetes | -128.01 (-245.92 to -10.09) | 0.03 | 0.02 |
| MI | -69.89 (-182.15 to 42.37) | 0.22 | 0.006 |
| Hypertension | -74.64(-176.07 to 26.78) | 0.15 | 0.009 |
| Osteoporosis | -153.66 (-353.17 to 45.85) | 0.13 | 0.009 |
| Stroke | -41.25 (-198.80 to 116.30) | 0.61 | 0.001 |
| Asthma | -105.58 (-265.09 to 53.93) | 0.19 | 0.007 |
| Chronic back pain | -29.67 (-139.55 to 80.21) | 0.60 | 0.001 |
| Chronic renal impairment | -0.23 (-0.57 to -1.03) | 0.57 | 0.001 |
| Arthritis | -4.16 (-106.56 to 98.25) | 0.94 | <0.001 |
| Atrial fibrillation | -46.77 (-148.18 to 54.65) | 0.37 | 0.003 |
| COPD | -108.45 (-270.51 to 53.60) | 0.19 | 0.007 |
| Depression | -47.36 (-164.88 to 70.16) | 0.43 | 0.003 |
| Total number of comorbidities | -38.76 (-60.58 to -16.93) | 0.001 | 0.05 |
| Total number of cardiorespiratory and metabolic comorbidities* | -63.95 (-99.70 to -28.20) | 0.001 | 0.05 |

| | | | |
|---|---|---|---|
| Total number of physical and musculoskeletal comorbidities† | -18.03 (-73.89 to 37.84) | 0.53 | 0.002 |
| Medication | | | |
| Angiotensin II receptor | 24.96 (-90.23 to 140.16) | 0.67 | 0.0007 |
| antagonist | 25.53 (-79.38 to 130.44) | 0.63 | 0.001 |
| ACE inhibitor | -8.99 (-110.57 to 92.59) | 0.86 | <0.001 |
| Aldosterone antagonist | -57.26 (-158.80 to 44.27) | 0.27 | 0.005 |
| Anticoagulant | 67.02 (-56.30 to 190.34) | 0.29 | 0.005 |
| Beta blocker | 11.47 (-127.69 to 150.62) | 0.87 | <0.001 |
| Digoxin | -104.91 (-331.78 to | 0.36 | 0.003 |
| Ivabradine | 121.96) | 0.02 | 0.02 |
| Loop diuretic | -133.41 (-241.67 to -25.16) | 0.14 | 0.009 |
| Nitrate | -106.34 (-246.34 to 33.67) | 0.27 | 0.005 |
| Thiazide diuretic | -224.02 (-625.05 to 177.01) | | |
| Type of HF (HFrEF vs HFpEF) | -29.64 (-156.83 to 97.55) | 0.65 | 0.001 |
| ISWT (peak distance) (N=229) | 1.19 (0.88 to 1.51) | <0.001 | 0.20 |
| MLHFQ | | | |
| Overall | -3.40 (-05.49 to -1.30) | 0.002 | 0.04 |
| Physical | -7.96 (--12.20 to --3.73) | <0.001 | 0.05 |
| Emotional | -8.22 (-15.06 to -1.39) | 0.02 | 0.02 |
| HADS | | | |
| Anxiety | -0.09 (-11.57 to 11.39) | 0.99 | <0.001 |
| Depression | -26.18 (-40.37 to -11.98) | <0.001 | 0.05 |
| HeartQoL | | | |
| Global | 94.20 (29.66 to 158.74) | 0.004 | 0.03 |
| Physical | 96.48 (37.30 to 155.65) | 0.001 | 0.04 |
| Emotional | 35.42 (-22.51 to 93.35) | 0.23 | 0.005 |
| EQ-5D-3L (N=244) | 282.61 (86.81 to 478.41) | 0.005 | 0.03 |
| SCHFI | | | |
| Maintenance | 0.73 (-2.49 to 3.96) | 0.66 | 0.001 |
| Management (N=139) | 0.21 (-2.38 to 2.80) | 0.87 | 0.0002 |

| | | | |
|---|---|---|---|
| Confidence | 1.08 (-1.01 to 3.17) | 0.31 | 0.004 |

BMI, body mass index; NYHA, New York heart association; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, NT-pro-brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; ISWT, incremental shuttle walk test; MLHFQ, Minnesota living with heart failure questionnaire; HADS, hospital anxiety and depression scale; SCHFI, self-care of heart failure index.

* cardiorespiratory and metabolic comorbidities = angina, asthma, AF, CVD, hypertension, stroke, valvular heart disease, COPD, diabetes, PVD

† physical and musculoskeletal comorbidities = arthritis, chronic back pain, osteoporosis, connective tissue disorder

**Appendix 4.3: Univariate logistic regressions between meeting PA guidelines and sociodemographics, exercise capacity and health status variables**

| Sociodemographic, exercise capacity and health status variables N=247 unless otherwise stated | OR (95% CI) | p-value | Pseudo $R^2$ |
|---|---|---|---|
| Age | 0.95 (0.93 to 0.97) | <0.001 | 0.04 |
| Gender | 1.13 (0.65 to 1.97) | 0.66 | <0.001 |
| BMI (N=246) | 0.95 (0.91 to 0.99) | 0.02 | 0.02 |
| Employment status | | | |
| In employment/Self-employed | Comparison group | 0.001 | 0.06 |
| Retired | 0.18 (0.08 to 0.45) | | |
| Housework | omitted | | |
| Unemployed | 0.44 (0.10 to 2.00) | | |
| Other | 0.58 (0.09 to 3.88) | | |
| Ethnicity (white vs other) | 0.44 (0.12 to 1.72) | 0.24 | 0.005 |
| NYHA class | | | |
| NYHA I | Comparison group | <0.001 | 0.07 |
| NYHA II | 0.38 (0.18 to 0.80) | | |
| NYHA III-IV | 0.13 (0.05 to 0.32) | | |
| Time since HF diagnosis | | | |
| 0 years | Comparison group | 0.64 | 0.003 |
| 1 year | 1.37 (0.66 to 2.85) | | |
| 2 years | 1.02 (0.57 to 1.81) | | |
| Cause of HF | | | |
| Ischaemic | Comparison group | 0.15 | 0.01 |
| Non-ischaemic | 1.67 (0.99 to 2.82) | | |
| Not known/classified | 1.61 (0.56 to 4.61) | | |
| LVEF (%) (N=188) | 1.00 (0.98 to 1.02) | 0.99 | <0.001 |
| NT-proBNP (pg/ml) | 1.00 (1.00 to 1.00) | <0.001 | 0.05 |
| Living alone | 0.52 (0.29 to 0.93) | 0.03 | 0.01 |
| Living with partner | 1.65 (0.97 to 2.81) | 0.06 | 0.01 |
| Living with child >18 | 1.10 (0.41 to 2.94) | 0.86 | <0.001 |

| | | | |
|---|---|---|---|
| Living with child <18 | 1.86 (0.31 to 11.34) | 0.5 | 0.001 |
| Living with parent | 1.86 (0.31 to 11.34) | 0.5 | 0.001 |
| Smoking history | | | |
| Current smoker | Comparison group | 0.41 | 0.006 |
| Ex-smoker | 2.01 (0.60 to 6.73) | | |
| Never smoked | 2.30 (0.67 to 7.84) | | |
| Trial site | | 0.12 | 0.02 |
| Truro | Comparison group | | |
| Gwent | 0.76 (0.34 to 1.68) | | |
| Birmingham | 0.5 (0.23 to 1.11) | | |
| York | 1.38 (0.64 to 2.98) | | |
| Dundee | 0.63 (0.29 to 1.38) | | |
| Comorbidities | | | |
| Angina | 0.70 (0.39 to 1.24) | 0.22 | 0.004 |
| Diabetes | 0.55 (0.30 to 1.01) | 0.05 | 0.01 |
| MI | 0.76 (0.43 to 1.32) | 0.33 | 0.002 |
| Hypertension | 0.83 (0.50 to 1.38) | 0.48 | 0.002 |
| Osteoporosis | 0.49 (0.17 to 1.43) | 0.19 | 0.005 |
| Stroke | 0.85 (0.39 to 1.86) | 0.68 | <0.001 |
| Asthma | 0.77 (0.34 to 1.72) | 0.52 | 0.001 |
| Chronic back pain | 0.99 (0.57 to 1.70) | 0.97 | <0.001 |
| Chronic renal impairment | 1.01 (0.98 to 1.03) | 0.68 | 0.005 |
| Arthritis | 1.06 (0.64 to 1.76) | 0.81 | <0.001 |
| Atrial fibrillation | 0.72 (0.43 to 1.19) | 0.20 | 0.005 |
| COPD | 0.58 (0.25 to 1.34) | 0.20 | 0.005 |
| Depression | 1.05 (0.59 to 1.88) | 0.86 | <0.001 |
| Total number of comorbidities | 0.87 (0.77 to 0.97) | 0.01 | 0.02 |
| Total number of cardiorespiratory and metabolic comorbidities* | 0.79 (0.65 to 0.95) | 0.01 | 0.02 |
| Total number of physical and musculoskeletal comorbidities† | 0.95 (0.72 to 1.26) | 0.74 | <0.001 |
| Medication | | | |
| Angiotensin II receptor antagonist | 0.90 (0.51 to 1.60) | 0.73 | <0.001 |
| ACE inhibitor | 1.46 (0.86 to 2.46) | 0.16 | 0.006 |
| | 1.30 (0.79 to 2.15) | 0.31 | 0.003 |

| | | | |
|---|---|---|---|
| Aldosterone antagonist | 0.58 (0.35 to 0.96) | 0.04 | 0.01 |
| Anticoagulant | 1.19 (0.65 to 2.21) | 0.57 | <0.001 |
| Beta blocker | 0.83 (0.41 to 1.66) | 0.59 | <0.001 |
| Digoxin | 1.05 (0.34 to 3.23) | 0.93 | <0.001 |
| Ivabradine | 0.45 (0.26 to 0.78) | 0.004 | 0.02 |
| Loop diuretic | 0.99 (0.49 to 1.98) | 0.98 | <0.001 |
| Nitrate | 0.40 (0.04 to 3.93) | 0.43 | 0.002 |
| Thiazide diuretic | | | |
| Type of HF (HFrEF vs HFpEF) | 0.73 (0.39 to 1.38) | 0.33 | 0.003 |
| ISWT (peak distance) (N=232) | 1.01 (1.00 to 1.01) | <0.001 | 0.11 |
| MLHFQ | | | |
| Overall | 0.99 (0.98 to 1.00) | 0.04 | 0.01 |
| Physical | 0.98 (0.95 to 1.00) | 0.03 | 0.01 |
| Emotional | 0.96 (0.93 to 1.00) | 0.05 | 0.01 |
| HADS | | | |
| Anxiety | 1.02 (0.96 to 1.08) | 0.49 | 0.001 |
| Depression | 0.90 (0.84 to 0.98) | 0.01 | 0.02 |
| HeartQoL | | | |
| Global | 1.17 (0.84 to 1.62) | 0.35 | 0.003 |
| Physical | 1.23 (0.91 to 1.66) | 0.19 | 0.005 |
| Emotional | 0.97 (0.73 to 1.29) | 0.81 | <0.001 |
| EQ-5D-3L (N=244) | 3.04 (1.08 to 8.51) | 0.04 | 0.01 |
| SCHFI | | | |
| Maintenance | 1.00 (0.98 to 1.02) | 0.98 | <0.001 |
| Management (N=139) | 1.00 (0.98 to 1.02) | 0.99 | <0.001 |
| Confidence | 1.00 (0.99 to 1.01) | 0.56 | 0.001 |

BMI, body mass index; NYHA, New York heart association; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, NT-pro-brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; ISWT, incremental shuttle walk test; MLHFQ, Minnesota living with heart failure questionnaire; HADS, hospital anxiety and depression scale; SCHFI, self-care of heart failure index.

* cardiorespiratory and metabolic comorbidities = angina, asthma, AF, CVD,

hypertension, stroke, valvular heart disease, COPD, diabetes, PVD

† physical and musculoskeletal comorbidities = arthritis, chronic back pain, osteoporosis, connective tissue disorder

**Appendix 5.1: Intervention effects at final follow-up, unbouted PA data**

| | Baseline | | Final follow-up | | Δ to final follow-up | | Between group difference (mean, 95% CI) p-value |
|---|---|---|---|---|---|---|---|
| | REACH-HF mean (sd, N) | Control mean (sd, N) | REACH-HF mean (sd, N) | Control mean (sd, N) | REACH-HF mean (sd, N) | Control mean (sd, N) | |
| *All days unbouted* | | | | | | | |
| MVPA (min/day) | 185.98 (86.30, 80) | 190.47 (96.18, 93) | 186.76 (97.24, 80) | 180.30 (97.22, 93) | 0.78 (55.62, 80) | -10.17 (43.89, 93) | 9.86 (-4.96 to 24.69) p=0.19 |
| Light (min/day) | 195.39 (48.24, 80) | 194.29 (46.69, 93) | 193.36 (52.48, 80) | 189.97 (46.66, 93) | -2.03 (33.65, 80) | -4.32 (34.66, 93) | 2.35 (-7.65 to 12.35) p=0.64 |
| Inactive (min/day) | 1058.63 (108.27, 80) | 1055.24 (118.54, 93) | 1059.88 (121.89, 80) | 1069.73 (122.72, 93) | 1.25 (73.95, 80) | 14.49 (68.52, 93) | -11.97 (-33.12 to 9.18) p=0.27 |
| *Weekend days unbouted* | | | | | | | |
| MVPA (min/day) | 183.15 (91.01, 80) | 175.14 (91.13, 93) | 173.76 (94.23, 80) | 169.86 (91.67, 93) | -9.39 (62.73, 80) | -5.28 (54.92, 93) | -2.87 (-19.97 to 14.23) p=0.74 |
| Light (min/day) | 193.14 (54.28, 80) | 188.28 (49.54, 93) | 185.07 (55.34, 80) | 189.01 (50.88, 93) | -8.07 (47.07, 80) | 0.73 (45.62, 93) | -6.97 (-19.89 to 5.94) p=0.29 |
| Inactive (min/day) | 1063.71 (177.88, 80) | 1076.58 (120.30, 98) | 1081.17 (125.01, 80) | 1081.13 (118.25, 93) | 17.46 (92.05, 80) | 4.55 (83.95, 93) | 10.07 (-15.22 to 35.35) p=0.43 |
| *Week days unbouted* | | | | | | | |
| MVPA (min/day) | 187.11 (86.72, 80) | 196.60 (101.66, 93) | 191.96 (100.34, 80) | 184.47 (102.63, 93) | 4.85 (58.35, 80) | -12.13 (45.46, 93)* | 15.18 (-0.32 to 30.67) p=0.06 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Light (min/day) | 196.29 (48.94, 80) | 196.70 (49.06, 93) | 196.68 (53.23, 80) | 190.36 (48.31, 93) | 0.39 (33.02, 80) | -6.34 (37.88, 93) | 6.30 (-4.05 to 16.65) p=0.23 |
| Inactive (min/day) | 1056.60 (109.35, 80) | 1046.70 (123.47, 93) | 1051.36 (124.37, 80) | 1065.17 (129.8, 93) | -5.24 (76.14, 80) | 18.47 (72.05, 93)* | -21.25 (-43.24 to 0.75) p=0.06 |

REACH-HF: Rehabilitation enablement in chronic heart failure; SD: standard deviation; MVPA: moderate-to-vigorous physical activity; PA: physical activity

* $p<0.05$ REACH-HF group vs control

**Appendix 5.2: Intervention effects on PA outcomes at post-intervention follow-up, bouted PA data**

| | Baseline | | Post-intervention | | Δ to post-intervention | | Between group difference (mean, 95% CI) p-value |
|---|---|---|---|---|---|---|---|
| | REACH-HF mean (sd, N) | Control mean (sd, N) | REACH-HF mean (sd, N) | Control mean (sd, N) | REACH-HF mean (sd, N) | Control mean (sd, N) | |
| *All days bouted* | | | | | | | |
| MVPA (min/day) | 37.90 (47.51, 98) | 44.96 (65.58, 100) | 39.64 (51.15, 98) | 46.96 (72.11, 100) | 1.74 (26.42, 98) | 2.00 (33.08, 100) | -0.76 (-9.26 to 7.74) p=0.86 |
| Light (min/day) | 197.91 (103.22, 98) | 219.30 (108.05, 100) | 198.23 (105.26, 98) | 213.05 (114.25, 100) | 0.31 (70.48, 98) | -6.25 (76.81, 100) | 0.98 (-19.09 to 21.06) p=0.92 |
| Inactive (min/day) | 1204.19 (133.00, 98) | 1175.74 (151.00, 100) | 1202.14 (140.26, 98) | 1179.99 (164.00, 100) | -2.05 (76.55, 98) | 4.25 (92.03, 100) | -2.40 (-26.20 to 21.40) p=0.84 |
| *Weekend days bouted* | | | | | | | |
| MVPA (min/day) | 39.01 (53.54, 98) | 37.03 (56.49, 100) | 36.62 (53.77, 98) | 43.99 (66.40, 100) | -2.39 (33.09, 98) | 6.96 (50.56, 100) | -9.12 (-20.82 to 2.57) p=0.13 |
| Light (min/day) | 194.02 (116.16, 98) | 198.50 (111.91, 100) | 182.82 (109.02, 98) | 192.50 (113.65, 100) | -11.21 (88.87, 98) | -6.00 (102.58, 100) | -7.63 (-31.90 to 16.64) p=0.54 |
| Inactive (min/day) | 1206.97 (148.83, 98) | 1204.48 (145.62, 100) | 1220.56 (144.51, 98) | 1203.51 (155.21, 100) | 13.59 (96.46, 98) | -0.97 (126.04, 100) | 15.84 (-13.92 to 45.59) p=0.30 |
| *Week days bouted* | | | | | | | |
| MVPA (min/day) | 37.46 (47.03, 98) | 48.13 (72.86, 100) | 40.85 (53.13, 98) | 48.15 (77.36, 100) | 3.39 (30.04, 98) | 0.01 (36.18, 100) | 2.26 (-7.16 to 11.67) p=0.64 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Light (min/day) | 199.47 (104.88, 98) | 227.63 (114.60, 100) | 204.39 (108.06, 98) | 221.27 (120.74, 100) | 4.92 (75.09, 98) | -6.35 (81.07, 100) | 3.39 (-17.91 to 24.70) p=0.75 |
| Inactive (min/day) | 1203.07 (133.15, 98) | 1164.24 (161.83, 100) | 1194.76 (143.28, 98) | 1170.58 (174.37, 100) | -8.31 (85.00, 98) | 6.34 (96.79, 100) | -13.53 (-39.31 to 12.25) p=0.30) |

REACH-HF: Rehabilitation enablement in chronic heart failure; SD: standard deviation; MVPA: moderate-to-vigorous physical activity; PA: physical activity

**Appendix 5.3: Intervention effects at post-intervention follow-up, unbouted PA data**

| | Baseline | | Post intervention | | Δ to post-intervention | | Between group difference (mean, 95% CI) p-value |
|---|---|---|---|---|---|---|---|
| | REACH-HF mean (sd, N) | Control mean (sd, N) | REACH-HF mean (sd, N) | Control mean (sd, N) | REACH-HF mean (sd, N) | Control mean (sd, N) | |
| *All days Unbouted* | | | | | | | |
| MVPA (min/day) | 171.51 (79.28, 98) | 185.77 (88.79, 100) | 170.34 (83.87, 98) | 182.84 (95.19, 100) | -1.17 (37.95, 98) | -2.93 (44.70, 100) | 0.58 (-11.17 to 12.34) p=0.92 |
| Light (min/day) | 191.83 (47.69, 98) | 194.95 (46.02, 100) | 189.74 (46.55, 98) | 190.66 (41.19, 100) | -2.09 (32.45, 98) | -4.28 (32.49, 100) | 1.14 (-7.18 to 9.46) p=0.79 |
| Inactive (min/day) | 1076.66 (102.53, 98) | 1059.28 (110.43, 100) | 1079.92 (106.13, 98) | 1066.50 (114.70, 100) | 3.27 (60.16, 98) | 7.22 (68.83, 100) | -0.65 (-18.56 to 17.26) p=0.94 |
| *Weekend days Unbouted* | | | | | | | |
| MVPA (min/day) | 169.77 (84.81, 98) | 170.92 (82.42, 100) | 160.49 (86.13, 98) | 171.80 (92.20, 100) | -9.28 (45.26, 98) | 0.88 (63.94, 100) | -10.48 (-25.78 to 4.81) p=0.18 |
| Light (min/day) | 189.50 (53.00, 98) | 187.11 (49.14, 100) | 181.25 (52.40, 98) | 181.35 (42.84, 100) | -8.25 (46.60, 98) | -5.76 (42.95, 100) | -1.75 (-12.71 to 9.20) p=0.75 |
| Inactive (min/day) | 1080.73 (113.23, 98) | 1081.98 (111.68, 100) | 1098.26 (115.25, 98) | 1086.85 (114.35, 100) | 17.53 (79.97, 98) | 4.88 (93.05, 100) | 13.10 (-9.90 to 36.11) p=0.26 |
| *Week days Unbouted* | | | | | | | |
| MVPA (min/day) | 172.20 (79.63, 98) | 191.72 (94.89, 100) | 174.28 (85.32, 98) | 187.26 (99.35, 100) | 2.07 (42.27, 98) | -4.46 (46.60, 100) | 4.29 (-8.27 to 16.86) p=0.50 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Light (min/day) | 192.77 (48.69, 98) | 198.08 (48.26, 100) | 193.14 (46.97, 98) | 194.39 (43.64, 100) | 0.37 (33.14, 98) | -3.69 (34.36, 100) | 2.34 (-6.30 to 10.98) p=0.59 |
| Inactive (min/day) | 1075.03 (103.46, 98) | 1050.20 (115.91, 100) | 1072.59 (106.80, 98) | 1058.36 (119.56, 100) | -2.44 (64.34, 98) | 8.15 (71.34, 100) | -5.43 (-24.22 to 13.36) p=0.57 |

REACH-HF: Rehabilitation enablement in chronic heart failure; SD: standard deviation; MVPA: moderate-to-vigorous physical activity; PA: physical activity

**Appendix 5.4: Intervention effects on proportion of patients meeting PA guidelines at post-intervention follow-up**

| | Baseline | | Post-intervention | | OR (95% CI) p-value |
|---|---|---|---|---|---|
| | REACH-HF (n, N, %) | Control (n, N, %) | REACH-HF (n, N, %) | Control (n, N, %) | |
| Bouted Proportion meeting guidelines | 47, 98, 48% | 47, 100, 47% | 49, 98, 50% | 47, 100, 47% | 0.79 (0.34 to 1.84) p=0.59 |
| Unbouted Proportion meeting guidelines | 98, 98, 100% | 100, 100, 100% | 96, 98, 98% | 100, 100, 100% | - |

REACH-HF: Rehabilitation enablement in chronic heart failure; OR: odds ratio

**Appendix 5.5: Univariate association with change in MVPA at final follow-up, controlling for trial stratifiers, group and baseline MVPA**

| Sociodemographic, exercise capacity and health status variables<br>N=173 unless otherwise stated | Unstandardized beta coefficient (95% CI) | p-value |
|---|---|---|
| Age | -0.77 (-1.49 to -0.05) | 0.04 |
| Gender | 1.19 (-13.50 to 15.89) | 0.87 |
| BMI | -0.46 (-1.68 to 0.75) | 0.45 |
| Employment status | | |
| In employment/Self-employed | Comparison group | 0.26 |
| Retired | -17.13 (-38.46 to 4.19) | |
| Housework | -18.44 (-105.09 to 68.21) | |
| Unemployed | -39.19 (-82.28 to 4.41) | |
| Other | -38.71 (-84.28 to 6.86) | |
| Ethnicity (white vs other) | -20.33 (-56.51 to 15.86) | 0.27 |
| NYHA class | | |
| NYHA I | Comparison group | 0.10 |
| NYHA II | -17.20 (-34.54 to 0.14) | |
| NYHA III-IV | -21.84 (-43.34 to -0.34) | |
| Time since HF diagnosis | | |
| 0 years | Comparison group | 0.27 |
| 1 year | -11.12 (-30.01 to 7.76) | |
| 2 years | -11.72 (-26.48 to 3.03) | |
| Cause of HF | | |
| Ischaemic | Comparison group | 0.44 |
| Non-ischaemic | 8.53 (-4.84 to 21.90) | |
| Not known/classified | 0.91 (-30.46 to 32.29) | |
| LVEF (%) (N=137) | -0.52 (-1.57 to 0.52) | 0.33 |
| NT-proBNP (pg/ml) | -0.003 (-0.009 to 0.004) | 0.42 |
| Living alone | -3.06 (-18.40 to 12.28) | 0.69 |
| Living with partner | -3.06 (-18.40 to 12.28) | 0.69 |
| Living with child >18 | 25.98 (1.80 to 50.16) | 0.04 |
| Living with child <18 | -1.16 (-50.64 to 48.33) | 0.96 |

| | | |
|---|---|---|
| Living with parent | -45.62 (-94.86 to 3.62) | 0.07 |
| Smoking history | | |
| Current smoker | Comparison group | 0.61 |
| Ex-smoker | 16.14 (-16.57 to 48.84) | |
| Never smoked | 16.28 (-17.23 to 49.80) | |
| Trial site | | |
| Truro | Comparison group | 0.17 |
| Gwent | -9.09 (-27.90 to 9.72) | |
| Birmingham | 15.20 (-5.94 to 36.35) | |
| York | -2.93 (-21.72 to 15.87) | |
| Dundee | -10.67 (-29.41 to 8.07) | |
| Comorbidities | | |
| Angina | 0.16 (-15.50 to 15.82) | 0.98 |
| Diabetes | -12.85 (-27.80 to 2.09) | 0.09 |
| MI | -5.75 (-20.12 to 8.62) | 0.43 |
| Hypertension | -1.92 (-15.17 to 11.33) | 0.78 |
| Osteoporosis | 6.64 (-19.25 to 32.52) | 0.61 |
| Stroke | -7.21 (-27.07 to 12.64) | 0.47 |
| Asthma | 4.16 (-18.08 to 26.41) | 0.71 |
| Chronic back pain | 1.60 (-11.91 to 15.11) | 0.82 |
| Chronic renal impairment | -3.58 (-21.05 to 13.89) | 0.69 |
| Arthritis | 9.77 (-3.38 to 22.91) | 0.14 |
| Atrial fibrillation | -10.54 (-23.55 to 2.47) | 0.11 |
| COPD | -15.62 (-35.03 to 3.79) | 0.11 |
| Depression | -2.0 (-17.05 to 13.06) | 0.79 |
| Total number of comorbidities | -1.29 (-4.45 to 1.87) | 0.42 |
| Total number of cardiorespiratory and metabolic comorbidities* | -4.56 (-9.47 to 0.35) | 0.07 |
| Total number of physical and musculoskeletal comorbidities† | 3.85 (-3.25 to 10.95) | 0.29 |
| Medication | | |
| Angiotensin II receptor antagonist | 4.66 (-9.91 to 19.23) | 0.53 |
| ACE inhibitor | -0.59 (-14.16 to 12.98) | 0.93 |
| | 4.13 (-9.52 to 17.78) | 0.55 |
| | -7.62 (-20.70 to 5.47) | 0.25 |

| | | |
|---|---|---|
| Aldosterone antagonist | -7.79 (-24.33 to 8.75) | 0.35 |
| Anticoagulant | -0.52 (-18.20 to 17.16) | 0.95 |
| Beta blocker | 5.48 (-25.45 to 36.42) | 0.73 |
| Digoxin | -12.65 (-26.68 to 1.39) | 0.08 |
| Ivabradine | -1.50 (-21.28 to 18.27) | 0.88 |
| Loop diuretic | -15.84 (-65.32 to 33.65) | 0.53 |
| Nitrate | | |
| Thiazide diuretic | | |
| Type of HF (HFrEF vs HFpEF) | collinearity | |
| ISWT (peak distance) (N=165) | 0.06 (0.01 to 0.12) | 0.02 |
| baseline | | |
| Overall ENMO | 1.44 (-0.52 to 3.39) | 0.15 |
| MLHFQ | 0.04 (-0.26 to 0.33) | 0.81 |
| Overall | | |
| Physical | -0.14 (-0.74 to 0.47) | 0.66 |
| Emotional | 0.47 (-0.43 to 1.36) | 0.31 |
| HADS | | |
| Anxiety | 1.83 (0.40 to 3.25) | 0.01 |
| Depression | -0.13 (-2.27 to 2.01) | 0.91 |
| HeartQoL | | |
| Global | -2.09 (-11.01 to 6.82) | 0.64 |
| Physical | -0.66 (-9.02 to 7.69) | 0.88 |
| Emotional | -3.82 (-11.27 to 3.64) | 0.31 |
| EQ-5D-5L (N=172) | 4.58 (-22.35 to 31.52) | 0.74 |
| SCHFI | | |
| Maintenance | 0.19 (-0.25 to 0.64) | 0.39 |
| Management (N=94) | -0.01 (-0.28 to 0.25) | 0.92 |
| Confidence | 0.01 (-0.26 to 0.27) | 0.96 |

BMI: body mass index; NYHA: New York Heart Association; HF: heart failure; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal proB-type natriuretic peptide; MI: myocardial infection; COPD: chronic obstructive pulmonary disease; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; ISWT: incremental shuttle walk test; ENMO: Euclidean norm minus one; MLHFQ: Minnesota living with heart

failure questionnaire; HADS: hospital anxiety and depression scale; SCHFI: self-care in heart failure index.

**Appendix 5.6: Univariate association with change in MVPA at post-intervention follow-up, controlling for trial stratifiers, group and baseline MVPA**

| Sociodemographic, exercise capacity and health status variables<br>N=198 unless otherwise stated | Unstandardized beta coefficient (95% CI) | p-value |
|---|---|---|
| Age | -0.39 (-0.85 to 0.08) | 0.11 |
| Gender | -5.74 (-15.85 to 4.37) | 0.26 |
| BMI | -0.19 (-1.00 to 0.63) | 0.65 |
| Employment status | | |
| In employment/Self-employed | Comparison group | 0.30 |
| Retired | -10.83 (-25.08 to 3.41) | |
| Housework | -10.65 (-72.68 to 51.38) | |
| Unemployed | -29.16 (-56.92 to -1.40) | |
| Other | -3.58 (-32.96 to 25.81) | |
| Ethnicity (white vs other) | -1.91 (-27.60 to 23.77) | 0.88 |
| NYHA class | | |
| NYHA I | Comparison group | 0.17 |
| NYHA II | -5.67 (-17.94 to 6.59) | |
| NYHA III-IV | -13.58 (-28.25 to 1.08) | |
| Time since HF diagnosis | | |
| 0 years | Comparison group | 0.80 |
| 1 year | -3.15 (-16.06 to 9.76) | |
| 2 years | -3.30 (-13.30 to 6.70) | |
| Cause of HF | | |
| Ischaemic | Comparison group | 0.78 |
| Non-ischaemic | -2.90 (-11.93 to 6.12) | |
| Not known/classified | 1.62 (-18.58 to 21.82) | |
| LVEF (%) (N=151) | -0.08 (-0.67 to 0.51) | 0.79 |
| NT-proBNP (pg/ml) | -0.0003 (-0.004 to 0.003) | 0.87 |
| Living alone | -5.25 (-15.76 to 5.25) | 0.33 |
| Living with partner | 2.94 (-6.55 to 12.42) | 0.61 |
| Living with child >18 | 2.94 (-14.88 to 20.76) | 0.33 |

| | | |
|---|---|---|
| Living with child <18 | 5.81 (-29.66 to 41.29) | 0.32 |
| Living with parent | 25.68 (-1.81 to 53.16) | 0.07 |
| Smoking history | | |
| Current smoker | Comparison group | 0.21 |
| Ex-smoker | 6.47 (-14.09 to 27.04) | |
| Never smoked | -1.55 (-22.93 to 19.83) | |
| Trial site | | |
| Truro | Comparison group | 0.76 |
| Gwent | 4.19 (-8.66 to 17.03) | |
| Birmingham | 5.20 (-8.71 to 19.12) | |
| York | -1.81 (-14.46 to 10.84) | |
| Dundee | -2.57 (-15.59 to 10.46) | |
| Comorbidities | | |
| Angina | -1.72 (-11.93 to 8.48) | 0.74 |
| Diabetes | -12.67 (-22.52 to 2.81) | 0.01 |
| MI | 3.43 (-6.40 to 12.26) | 0.49 |
| Hypertension | -2.67 (-11.57 to 6.23) | 0.55 |
| Osteoporosis | -10.64 (-29.90 to 8.61) | 0.28 |
| Stroke | -1.65 (-15.44 to 12.14) | 0.81 |
| Asthma | 8.83 (-5.38 to 23.04) | 0.22 |
| Chronic back pain | -8.46 (-17.87 to 0.94) | 0.08 |
| Chronic renal impairment | 0.01 (-0.05 to 0.07) | 0.68 |
| Arthritis | -2.62 (-11.67 to 6.43) | 0.57 |
| Atrial fibrillation | -2.47 (-11.36 to 6.42) | 0.58 |
| COPD | -4.18 (-18.58 to 10.21) | 0.57 |
| Depression | -3.33 (-13.99 to 7.32) | 0.54 |
| Total number of comorbidities | -1.05 (-3.13 to 1.04) | 0.32 |
| Total number of cardiorespiratory and metabolic comorbidities* | -1.77 (-5.04 to 1.51) | 0.29 |
| Total number of physical and musculoskeletal comorbidities† | -3.33 (-8.37 to 1.71) | 0.19 |
| Medication | | |
| Angiotensin II receptor antagonist | -0.99 (-10.74 to 8.76) | 0.84 |
| ACE inhibitor | 5.54 (-3.47 to 14.56) | 0.23 |
| | 3.87 (-5.29 to 13. 03) | 0.83 |

| | | |
|---|---|---|
| Aldosterone antagonist | -8.31 (-17.13 to 0.51) | 0.07 |
| Anticoagulant | -3.34 (-14.57 to 7.89) | 0.56 |
| Beta blocker | -2.71 (-14.63 to 9.21) | 0.65 |
| Digoxin | 12.82 (-5.30 to 30.94) | 0.16 |
| Ivabradine | 1.37 (-8.41 to 11.15) | 0.78 |
| Loop diuretic | -9.24 (-24.63 to 3.15) | 0.14 |
| Nitrate | -13.77 (-49.04 to 21.50) | 0.44 |
| Thiazide diuretic | | |
| Type of HF (HFrEF vs HFpEF) | -2.57 (-15.59 to 10.46) | 0.70 |
| ISWT (peak distance) (N=188) | 0.06 (0.02 to 0.09) | 0.001 |
| baseline | | |
| Overall ENMO | 1.12 (-0.23 to 2.47) | 0.10 |
| MLHFQ | -0.12 (-0.32 to 0.07) | 0.21 |
| Overall | | |
| Physical | -0.26 (-0.65 to 0.13) | 0.20 |
| Emotional | -.025 (-0.86 to 0.36) | 0.42 |
| HADS | | |
| Anxiety | 0.30 (-0.71 to 1.32) | 0.56 |
| Depression | -0.01 (-1.39 to 1.37) | 0.99 |
| HeartQoL | | |
| Global | 4.36 (-1.58 to 10.30) | 0.15 |
| Physical | 4.52 (-0.97 to 10.00) | 0.11 |
| Emotional | 1.56 (-3.62 to 6.75) | 0.55 |
| EQ-5D-5L (N=196) | 7.54 (-10.96 to 26.03) | 0.42 |
| SCHFI | | |
| Maintenance | -0.32 (-0.60 to -0.04) | 0.03 |
| Management (N=106) | 0.06 (-0.22 to 0.34) | 0.69 |
| Confidence | -0.07 (-0.25 to 0.11) | 0.43 |

BMI: body mass index; NYHA: New York Heart Association; HF: heart failure; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal proB-type natriuretic peptide; MI: myocardial infection; COPD: chronic obstructive pulmonary disease; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; ISWT: incremental shuttle walk test; ENMO: Euclidean norm minus one; MLHFQ: Minnesota living with heart

failure questionnaire; HADS: hospital anxiety and depression scale; SCHFI: self-care in heart failure index.

**Appendix 5.7: Comparison of multivariable models to predict change in minutes/day MVPA at post-intervention follow-up.**

| Multivariable model | Variables included in model (p<0.05) | Unstandardized beta coefficient (95% CI) | t-statistic | Variable P-value | Model Adjusted $R^2$ (p-value) |
|---|---|---|---|---|---|
| 1. Socio-demographic | Group | 0.48 (-6.24 to 7.22) | 0.14 | 0.89 | 0.10 (<0.001) |
| | Baseline MVPA | -0.12 (-0.18 to -0.06) | -3.81 | <0.001 | |
| | Centre | 0.18 (-2.12 to 2.54) | 0.15 | 0.88 | |
| | BNP <>2000 | -3.93 (-12.96 to 5.11) | -0.86 | 0.39 | |
| | Live with parent | 34.98 (13.41 to 56.55) | 3.20 | 0.002 | |
| | Diabetes | -12.17 (-20.08 to -4.27) | -3.04 | 0.003 | |
| | constant | 7.13 (-2.08 to 16.34) | 1.53 | 0.13 | |
| 2. Exercise capacity and health status | Group | 0.18 (-6.0 to 6.34) | 0.06 | 0.95 | 0.10 (<0.001) |
| | Baseline MVPA | -0.15 (-0.21 to -0.09) | -4.73 | <0.001 | |
| | Centre | 0.54 (-1.61 to 2.68) | 0.49 | 0.62 | |
| | BNP 2000 | -2.03 (-10.29 to 6.23) | -0.49 | 0.63 | |
| | ISWT peak | 0.04 (0.02 to 0.07) | 3.52 | 0.001 | |
| | constant | -6.39 (-16.77 to 3.99) | -1.21 | 0.23 | |
| 3. Socio-demographic, exercise capacity and health status* | Group | 2.02 (-4.8 to 8.83) | 0.58 | 0.56 | 0.14 (<0.001) |
| | Baseline MVPA | -0.16 (-0.23 to -0.09) | -4.55 | <0.001 | |
| | Centre | 0.80 (-1.59 to 3.20) | 0.66 | 0.51 | |
| | BNP 2000 | -3.67 (-12.83 to 5.48) | -0.79 | 0.43 | |

| | | | | |
|---|---|---|---|---|
| | Live with parent | 37.47 (13.69 to 61.24) | 3.11 | 0.002 |
| | Diabetes | -11.99 (-19.98 to -4.01) | -2.96 | 0.003 |
| | ISWT peak | 0.04 (0.01 to 0.06) | 2.82 | 0.005 |
| | constant | -2.75 (-14.31 to 8.82) | -0.47 | 0.64 |

MVPA: moderate-to-vigorous physical activity; BNP 2000: NT-proBNP above or below 2000 pg/ml; ISWT: incremental shuttle walk test; HADS: hospital anxiety and depression score

* all variables $p<0.05$ from multivariate models 1 and 2