Individual and service level factors that determine fitness measurement and outcomes in patients enrolled in a cardiac rehabilitation programme.

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May 2018

Abstract

Aim: Despite the recommendations by professional associations and clinical guidelines to measure physical fitness pre- and post-cardiac rehabilitation (CR) programmes, less than one third of CR patients have undertaken such an assessment. The Incremental Shuttle Walk Test (ISWT) is the most common fitness measurement tests in the UK. The minimum clinically important difference (MCID) for this test in CR patients is an improvement of 70 metres.

The main aims of this thesis were firstly, to examine the association between a patient undertaking a fitness test at baseline and completing their CR programme; secondly, to identify the predictors of the distance walked during the ISWT at baseline assessment; and thirdly, to identify the determinants of achieving the MCID for the ISWT.

Method: A critical review of the literature was conducted and an online survey was sent to 303 CR centres across the UK. Data from three observational studies using National Audit of Cardiac Rehabilitation (NACR) relating to CR patients was analysed. Stepwise linear regression and logistic regressions were used.

Result: Patients who undertook a fitness test were 1.48 times more likely to complete their CR programme. Age, gender and self-reported physical fitness were the predictors of the ISWT distance explaining 32% of the variance. Reference values for the ISWT baseline distance walked were produced. Fifteen determinants of achieving the MCID were identified.

Conclusion: Assessing fitness at baseline is not only a means of providing data to assist exercise prescription but also one of the most significant determinants of CR completion. The reference values produced will aid clinicians to set patient goals, improve patient risk assessment, and provide feedback relating to their fitness. Being aware of the determinants of achieving the MCID is important in helping clinicians to tailor the CR programme for the benefit of patients.

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Acknowledgements

There are many people I wish to thank. My sincere gratitude goes to my supervisor, Professor Patrick Doherty, for his patience and guidance – always answering my queries promptly. He generously offered his time and advice on avenues I could explore and I benefitted greatly from his wealth of experience. He has been very encouraging and supportive of me over the last four years.

I would also like to extend my sincere thanks to Professor Catherine Hewitt, my second supervisor, for her invaluable comments particularly in the area of statistics. Dr Paul Galdas also deserves thanks for his feedback and academic support. I am also immensely grateful to my statistics lecturer, Dr Mona Kanaan, for her advice and ongoing support.

Special thanks go to all the members of the NACR team Alexander Harrison, Corinna Petre, Jessica Hemingway, Karen Cardy and Nerina Onion, who were extremely helpful when I required NACR-related assistance. I would also like to extend my appreciation to the staff working at the Health Sciences Department at the University of York particularly Di Stockdale and Sally Evans. Very special thanks goes to my friend Abdulrahman Alquait for sharing the highs and lows of the research learning process. Thanks goes to my proofreader, Sally Jenkins, for her commitment and help.

The Medical Services Department at the Ministry of Defense / King Fahd Military Medical Complex in Dhahran is my sponsor and I would like to offer my thanks for giving me a scholarship and the opportunity to complete my PhD.

The Saudi Society in York provided support and a welcoming social outlet for my whole family and I would like to express my appreciation to all the members.

I would like to sincerely thank my family, which includes my parents and siblings back in Saudi Arabia for their prayers; my wife, Nadia, for her continuing support and encouragement and my children, Areeb, Hattan, Faisal and Youssef, for their understanding.

Declaration

I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References.

- **Published article from this thesis**

1- Alotaibi J and Doherty P. Evaluation of determinants of walking fitness in patients attending cardiac rehabilitation. BMJ Open Sport Exerc Med 2017; 2:e000203. doi:10.1136/bmjsem-2016- 000203 (Appendix 8.1)

- **Congress presentations and published abstracts**

1- Alotaibi J and Doherty P. Gender differences in achieving the minimum clinically important difference in the incremental shuttle walk test in coronary artery bypass graft patients, (2017) European Heart Journal 38(suppl_1) DOI10.1093/eurheartj/ehx493.P4909

2- Alotaibi J and Doherty P .An investigation of factors that best predict incremental shuttle walk test distance in cardiac rehabilitation patients (2016) European Heart Journal. Volume23 issue: 1_suppl, page(s): S33-S58

3- Alotaibi J and Doherty. Reference values for ISWT in CR patients: BACPR Exercise Professional Group Study Day 2017, (2017) Birmingham

Chapter 1. Introduction and initial review of literature

Cardiac rehabilitation (CR) programmes are designed to minimise the physiological and psychological impact of cardiac illness, lower the risk of sudden death or re-infarction, control cardiac symptoms, stabilise or even reverse the atherosclerotic process, and increase the psychosocial and vocational status of cardiac patients (Balady et al., 2007; Anderson et al., 2016; Price et al., 2016; BACPR, 2017). Assessing functional capacity (physical fitness) at baseline (start) and at the end of the CR programme is recommended by clinical guidelines and professional organisations (Price et al., 2016; BACPR, 2017). Ideally, exercise training, which underpins CR, should be based on the functional capacity test that precedes the CR programme. Assessing the patient's functional capacity at the beginning of the programme allows a safe and appropriate intensity of exercise to be prescribed; determines the level of supervision and monitoring required; classifies patients according to a risk stratification and informs physical activity guidance. After completion of the exercise sessions at the end of the CR programme, a functional capacity test assesses the effectiveness of the intervention and the response of the patient to the exercise during the CR programme. Furthermore, the functional test is also used as a prognostic prediction and informs a long-term maintenance plan for each patient (Arena et al., 2007; Mezzani et al., 2012; ACSM's, 2010; ACPICR, 2015; BACPR, 2017).

Despite the emphasis in the guidelines regarding the importance of assessment of functional capacity for CR patients, there is evidence from a small amount of studies, questioning the number of patients taking the baseline functional capacity assessment (Benzer et al., 2017; NACR, 2017). The National Audit of Cardiac Rehabilitation (NACR) annual report, on the quality and outcomes from CR showed that approximately 15% of patients who had started CR had undertaken a pre- and post-CR programme functional capacity assessment. This low percentage is supported by a study of 12 European countries where the findings reported only 28% of patients had undertaken a baseline functional capacity assessment. The percentage of patients who took the assessment at the end of the CR programme was lower still (16%) (Benzer et al., 2017). No study to date has highlighted the influence of this assessment on the adherence of the patients to their CR programme.

Offering an objective measure of fitness such as the Incremental Shuttle Walk Test (ISWT), the 6-minute walk test , the treadmill test, the Chester step test or the cycle ergometer requires a suitable location, trained staff and sufficient time to complete the test within the clinical setting (ACPICR, 2015; BACPR, 2017; Grove, Jones and Connolly, 2017). Some of these resources may not be available in some centres which might partly explain poor compliance with clinical recommendations for assessment of functional capacity. In order to address issues about the quality of CR delivery the BACPR-NACR National Certification Programme for Cardiovascular Rehabilitation (NCP_CR) established service delivery performance indicators to evaluate the performance of CR centres in the UK (Furze et al., 2016). Since that time, these indictors have been used to rate CR centres according to their performance in the NACR audit report (NACR, 2016). Whether there are differences between the centres which measure fitness and those which do not in terms of these service delivery performance indicators, has not been studied.

In the UK, the ISWT is the most common test used to measure functional capacity among the CR population (Grove, 2013). Despite this, there is only one study that has attempted to produce reference values and a prediction equation for the baseline distance walked during this test (Cardoso et al., 2016). However, this study is limited by the small number of patients, particularly of females. The need for robust reference values of physical fitness, which take account of patient characteristics, remains important as these values will help remove uncertainty around patient risk assessment prior to CR and future exercise prescription. They could also help clinical decision making around the need for a second ISWT, aid feedback to patients about their level of baseline fitness and help set rehabilitation goals. The minimum clinically important difference (MCID) is the smallest change that is important to patients (Copay et al., 2007). For the ISWT, the MCID is 70 metres (Houchen-

Wolloff, Boyce and Singh, 2014) and has been used as a measurement tool in the NACR audit since 2015 (NACR, 2015). The NACR report (2017) showed that 60% of the patients who undertook the ISWT as a functional capacity test achieved the MCID. However, no study to date has identified the determinants of achieving this MCID in the CR population.

1.1 Thesis aims, questions and structure

1.1.1 Aims

There are four main aims in this thesis. The first aim is to critically review the studies which identified the determinants of a change in fitness using an incremental test in patients enrolled in a CR outpatient programme. The second aim consists of two parts: the first is to examine the association between whether the patient's functional capacity is assessed at baseline and their completion of the CR programme.

The second part is to make a comparison between centres which measure fitness and those which do not according to the service delivery performance indicators established by the BACPR-NACR National Certification Programme for Cardiovascular Rehabilitation (NCP-CR).

Although the ISWT is the most commonly used tool for CR patients in the UK to test their functional capacity, expressed in the distance walked during the test, there are few studies which attempt to produce reference values for this test and identify the predictors of the baseline distance walked. Therefore, the third aim of this thesis is to produce a predictive equation and establish reference values for this test in CR patients.

Improving functional capacity is one of the main outcomes of CR. Using the minimum clinically important difference (MCID) is a key tool to show that an improvement has taken place. For the ISWT, achieving an improvement of 70 metres is considered the MCID. However, the characteristics which determine whether a patient achieves the MCID have not yet been identified. Consequently, the fourth aim of this thesis is to identify these determinants in the CR population.

This thesis aims to make a valuable contribution to the existing body of CR research by filling in the gaps around the lack of research in relation to the assessment of functional capacity, which will add to our understanding of the relationship between the assessment of functional capacity and the patients' completion of the CR programme, identifying the predictors of fitness at baseline, and identifying the determinants of achieving the MCID for the ISWT in this population.

1.1.2 Research questions

The main three research questions in this thesis which will be answered by the main three studies are:

1. a) Is completion of the CR programme associated with a patient undertaking a baseline fitness test?

   b) Is there any difference in terms of service delivery performance indicators between the centres which measure fitness and those which do not?
2. What are the baseline characteristics of patients that can predict the distance walked during the ISWT as the baseline functional capacity test?
3. What are the determinants of achieving the MCID for the ISWT in the CR population?

1.1.3 Structure

This thesis consists of eight chapters. The first chapter is an introduction and initial review of literature which briefly describes CR and its benefits. A definition of functional capacity is then given followed by an explanation of the importance of conducting a functional capacity assessment and the types of the test, ISWT is then described in detail as it is the main test reported in this thesis.

The second chapter is a critical review chapter for the determinants of the change in fitness among CR patients using incremental functional capacity tests while the third chapter relates to the methodology used in this thesis. The fourth chapter relates to the first study and is in two parts. The first part examines the association between whether the patient undertakes the baseline functional capacity test and the completion of the programme. The second part concerns a comparison between the centres which measure fitness and those which do not. The fifth chapter relates to the second study, which identified the predictors of the distance walked during the ISWT at the baseline assessment and produced reference values for this test, while the sixth chapter is related to the third study which identified the determinants of achieving the MCID for the ISWT in the CR population. Chapter seven is a synthesis of the main studies and the conclusion of the thesis.

1.2 Review of Cardiac Rehabilitation literature

1.2.1 The burden of cardiovascular disease

According to data from the World Health Organisation (WHO), cardiovascular disease (CVD), an overarching term used to describe a group of disorders which affect the heart and blood vessels, is globally the leading cause of death being responsible for 31% of the total number of deaths worldwide. It is estimated that 7.4 million and 6.7 million deaths were caused by coronary heart disease and stroke respectively (WHO, 2017) . It has been predicted that by 2030 the number of people worldwide who will die as a result of CVD will increase to approximately 23.7 million people annually (Stevens, 2009). In Europe, CVD is responsible for approximately 4 million of all-cause deaths (45%) with 2.1 million deaths for women (49%) and 1.8 million deaths (40%) for men. This has been estimated to cost the European economy around 210 billion euros each year (Wilkins et al., 2017). In the UK since 2016, CVD has been the second cause of premature death (26%) annually with cancer being the primary cause being responsible for 28% of premature deaths . Coronary heart disease (CHD), representing a blockage or interrupted blood supply to the heart in the coronary arteries, was the cause of 44% of the deaths resulting from CVD (BHF, 2017).

In the UK it is estimated that 4.3 million people are suffering from CHD. This high figure may be due to improved treatment and an ageing population. However, this high incidence of CVD and its associated problems places a heavy burden on healthcare budgets (BHF, 2017).

Experiencing a cardiac event is life-changing and so patients need the support and knowledge to live as normal a life as possible and to enable them to maintain their health and reduce the risk of a further occurrence (BACPR, 2017; ACPICR, 2015). Rehabilitation acts as a transition phase taking the patient from a state of acute illness into a relatively normal life (Haines et al., 1992).There is evidence that cardiac rehabilitation (CR) is one of the most vital, and clinically and cost-effective therapeutic interventions in the management of CVD in this population (Heran et al., 2011; Anderson et al., 2016; Shields et al., 2018)

1.2.2 Cardiac Rehabilitation

Cardiac rehabilitation has been defined as: ‘The coordinated sum of activities required to influence favorably the underlying cause of CVD, as well as to provide the best possible physical, mental and social conditions, so that individuals may, by their own efforts, preserve or resume optimal functioning in their community and through improved health behavior, slow or reverse progression of the disease” (BACPR 2017 p.1). This intervention has evolved from CR-exercise-based only to a comprehensive intervention which includes psychological support and education, management of risk factors and stress, risk assessments, smoking cessation, weight management, nutrition and physical activity counseling that is provided by a multidisciplinary team (BACPR, 2017) with a CR-exercise-based still considered to be the cornerstone of this intervention. CR intervention has been categorised as a class 1 recommendation by the European Society of Cardiology, the American Heart Association and the American College of Cardiology (Anderson et al., 2016). The concept of CR intervention in that the patient acquires the tools and the knowledge to enable him to live as normal a life as possible despite having heart disease (BACPR, 2017).

CR is also an effective intervention to limit the progression of the disease by beneficially influencing CVD risk factors (Gielen et al., 2014). These risk factors have been classified as modifiable and non-modifiable. Modifiable risk factors, such as diabetes, smoking, high blood pressure, cholesterol, obesity and physical inactivity, can be controlled through medical and lifestyle management. Non-modifiable risk factors, including age, gender, ethnicity of the patient and having a family history of heart disease, cannot be controlled. Although non-modifiable risk factors cannot be altered, the risk of developing cardiac disease can be significantly reduced through making changes to a patient's lifestyle. These changes include engaging in more physical activity, controlling for diabetes, adopting healthy eating habits, lowering blood pressure and cholesterol levels, controlling alcohol consumption and giving up smoking (Gielen et al., 2014; Dalal, Doherty and Taylor, 2015; ACPICR, 2015; BACPR, 2017).

Historically, patients with acute CHD were prescribed 6 weeks of bedrest. However, complications brought about by this restriction in mobility included a decline in functional capacity, long stays in hospital and even mortality(Mampuya, 2012). In 1951, Levine and Lown introduced chair therapy. The benefits of early mobilisation have gradually been recognised in terms of preventing many of the complications due to extended bedrest without any adverse effects (Kachur et al., 2017). In 1953 Morris and Heady found that double-decker bus drivers in London had a higher rate of CHD compared to double-decker bus conductors. This was attributed to the fact that bus drivers have a more sedentary job whereas bus conductors are more active in their work (Morris and Heady, 1953; Kachur et al., 2017).

Exercise as an aspect of therapy for CHD patients gained in popularity, after the efforts of Hellerstein and colleagues linked it to improvements in CHD outcomes, until it has become the cornerstone of a comprehensive secondary prevention programme, called CR, which includes lifestyle changes, psychological support, education and risk factor and stress management (Mampuya, 2012; Kachur et al., 2017)

1.2.2.1 Cardiac rehabilitation in the UK

In the UK, CR consists of four phases, however, in the USA and some other countries, phase 2 and 3 are combined giving a total of 3 phases (Bethell, Lewin and Dalal, 2009; Price et al., 2016). In the UK the first phase is the inpatient phase where the patient is still in hospital. It consists of progressive mobilisation including stair climbing which eventually reaches the level of activity required to complete simple tasks in the house. In addition, patients are given education regarding the event and its possible causes as well as guidance on lifestyle changes. Phase two starts when the patient is discharged from hospital with a heart manual which includes instructions regarding the recommended exercises to complete at home until his CR outpatient appointment. Phase three is the outpatient phase when the patient exercises in a clinical setting under supervision and attends education sessions related to the causes of the cardiac event, risk factors and how to mitigate against them, diet, misconceptions relating to cardiac disease and the role of exercise and drug treatment. Patients also receive guidance on stress management and methods of relaxation. The maintenance phase, which is the fourth phase, is when the patient finishes his outpatient CR programme and joins a community-based CR programme (Bethell, Lewin and Dalal, 2009; Price et al., 2016).

The National Service Framework (NSF) for Coronary Heart Disease (CHD) recommends that the NHS Trusts should establish agreed protocols where coronary heart disease patients, before being discharged, are invited to take part in a CR. The British Association for Cardiovascular Prevention and Rehabilitation (BACPR) represents all professionals involved in CR and to serve their interests. It aims to develop and improve core standards to provide safe and effective delivery of CR programmes in the UK. Its objectives are to produce national guidelines for CVD prevention and rehabilitation thereby improving the safety and standards of CR programmes nationally; developing education and training programmes; facilitating communication with other professional bodies and among BACPR members themselves. BACPR publish standards and core components for Cardiovascular

Disease Prevention and Rehabilitation. All CR programmes in the UK are run in accordance with these guidelines (http://www.bacpr.com/pages/default.asp). In 2005, the National Audit of Cardiac Rehabilitation (NACR) was established to ensure that all the BACPR guidelines are followed. Their first report was published in 2007. In 2013, with the support of the British Heart Foundation (BHF), the NACR increased the scope of the audit to include a service improvement and quality assurance system for the benefit of patients attending CR (NACR, 2013; Al Quait and Doherty, 2017). Currently, the UK is in the top 2% of countries in Europe regarding the uptake of CR programmes, reaching 50% of eligible patients (NACR, 2016).

The guidelines in the UK emphasise that the centres providing CR should have multi-disciplinary teams, including a physiotherapist, nurses, a dietician, an exercise specialist and a psychologist. There are various methods of delivery such as outpatient (either group-based or individual), home-based and Web-based and Telephone (BACPR, 2017; NACR, 2017).

1.2.2.2 Indications and Contraindications of Cardiac Rehabilitation

The health policies and politics of a country often dictate what kind of health provision prevails and this is also true for how CR is offered, therefore, there may be a difference between countries in the type of CR indications (Mampuya, 2012; Price et al., 2016). However, the patient types which are generally accepted onto a CR programme are myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), valve repair or replacement, heart failure and heart transplant patients (NICE, 2013; Price et al., 2016; BACPR, 2017; NACR, 2017). In the UK the National Institute for Health and Care Excellence (NICE), the Department of Health, the British Association for Cardiovascular Prevention and Rehabilitation (BACPR), and other European guidelines all concur that the patient groups shown in Table 1-1 would gain benefit from attending a CR programme (Dalal, Doherty and Taylor, 2015; Price et al., 2016).

Table 1-1Patient groups who benefit from CR*

Indication	Description
Acute coronary syndrome (ACS)	Including ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina also all patients undergoing reperfusion (such as CABG and PCI).
Heart Failure (HF)	Patients with newly diagnosed chronic HF and chronic HF with a step change in clinical presentation.
Heart surgery	Heart transplant, ventricular assist device, intra-cardiac defibrillator, valve replacement or repair and cardiac resynchronisation therapy.
Angina	Patients with a confirmed diagnosis of exertional angina.

*Modified from (Dalal et al. 2015) and (Al Quait and Doherty, 2017).

Contraindications to a CR programme are mainly associated with the exercise aspect. However, this form of exercise training is medically prescribed and supervised by a clinical specialist therefore the risk is minimal (ACPICR, 2015; BACPR, 2017). These contraindications include unstable angina, pulmonary embolism, decompensated HF, severe or symptomatic aortic stenosis, acute cardiac mural thrombus, acute deep venous thrombus, and severe obstructive cardiomyopathy (Mampuya, 2012; Kachur et al., 2017).

1.2.2.3 Risk associated with Cardiac Rehabilitation

A French prospective observational study, involving 25,420 patients from 65 CR centres, was conducted in order to determine the complication rate during CR exercise-based (Pavy et al., 2006). Participants undertook a total of 42 419 exercise stress tests and 743 471 patient-hours of exercise-based CR during a one-year period. It has been reported that one incidence of a cardiac event occurred per 8484 exercise stress tests performed. In addition, one cardiac event was recorded per 50,000 hours of exercise-based CR. The rate of cardiac arrest was equivalent to 1.3 per million patient-hours of exercise-based CR (Pavy et al., 2006).

In its 2007 scientific statement on exercise and acute CVD events, the American Heart Association (AHA) reported that the incidence of cardiac event in CHD patients during supervised exercised-based CR was estimated to be 1 major complication per 81 670 patient-hours,1 cardiac arrest per 116 906 patient-hours, 1 myocardial infarction per 219 970 patient-hours and 1 fatality per 752 365 patient-hours of participation (Thompson et al., 2007). This low death rate only refers to programmes with the equipment and expertise to deal with emergencies.

The result of a Japanese nationwide survey showed the lowest incidence of adverse events (Saito et al., 2014). This survey involved 136 CR programmes run in hospitals totalling 383,096 patient-hours of CR exercise-based to study the incidence of adverse events related to CR exercise-based. The findings revealed that during the CR exercise-based the incidence rate of life-threatening events (death, cardiac arrest, AMI and cardiac rupture) was only 1 per 383,096 patient-hours, which equates to 0.26 events per 100,000 patient-hours of CR exercise-based, while the incidence of adverse events was 12 per 383,096 patient-hours which equates to 3.13 events per 100,000 patient-hours.

Another study was conducted in 3 CR centres in Norway involving 4846 patients to evaluate the risk of a cardiac event occurrence during both high-intensity and moderate-intensity CR exercise(Rognmo et al., 2012). The incidence rate of a cardiac event was 1 in 23,182 hours of high-intensity and 1 per 129,456 hours of moderate-intensity exercise.

The benefits of CR outweigh the related risks: taking account of indications and contraindications, and the appropriate risk stratification are crucial in prescribing a safe exercise programme for patients. In general though, CR is safe and well-tolerated by patients and is associated with a low rate of complications in terms of cardiac arrest, myocardial infarction, serious injury or fatality (BACPR, 2017; Mampuya, 2012).

1.2.2.4 The benefit of Cardiac Rehabilitation

The merits of comprehensive CR are that it is robust is evidenced by a consistently favourable effect on cardiovascular mortality, hospital re-admission, an improved quality of life and psychological well-being, and an improvement in functional capacity. However, in terms of the effect of CR on all-cause mortality, some uncertainty remains (Anderson et al., 2016; Rauch et al., 2016; Powell et al., 2018). These benefits of CR will be discussed in detail in the next section.

1.2.2.4.1 *Impact of Cardiac Rehabilitation on all-cause and cardio-vascular mortality*

A meta-analysis of 25 randomised and non-randomised studies, known as a CROS study (Cardiac Rehabilitation Outcome study), from 1995 onwards was conducted to evaluate the prognosis of CR in terms of total mortality and other clinical endpoints (Rauch et al., 2016). The review consisted of one randomised control trial (RAMIT) and 24 cohort studies (7 prospective and 17 retrospective) which involved a total of 219,702 participants. The analysis showed that in the modern era of cardiology, CR is generally associated with a reduction in total mortality in ACS, CABG, and mixed coronary artery disease (CAD) patients. By evaluating large cohort studies, either prospective or retrospective, and not limiting the included studies to RCT, this review makes an important, independent contribution that replicates the situation in clinical practice in real-world CR. However, the only randomised control trial (The RAMIT) reported that there was no significant difference in the risk of mortality between the CR group and the control group after a two and a 7-9-year follow-up period (RR: 0.98, 95% CI: 0.74 to 1.30) and (RR: 0.99, 95% CI: 0.85 to 1.15) respectively (West, Jones and Henderson, 2012). The results of the RAMIT trial highlights the fact that some CR programmes may not be delivered in an effective way. However, these results are not representative of CR provision in the UK as shown by the data from routine clinical practice (Doherty and Lewin, 2012). The RAMIT study has limitations including the recruitment of a smaller sample (<23%) than should have been recruited, and the mean age of the participants was 11 years younger than the average age of the CR population in the UK.

The results of CROS that are related to total mortality are in contrast to the Cochrane systematic review conducted by Anderson and his colleagues (Anderson et al., 2016). Anderson et al. analysed the data of 14,486 CHD patients from 63 randomised control trials dated from 1970 to 2014, where the patients were randomly allocated to an exercise-based cardiac rehabilitation intervention or to usual care (the control group) with a follow-up programme of 12 months or more. They found a significant reduction in cardiovascular mortality (RR: 0.74; 95% CI: 0.64 to 0.86). This was obtained from 27 studies, which included 7469 patients, that only reported on cardiovascular mortality. However, a meta-analysis of 47 studies including 12455 patients, which only reported total mortality, showed that the reduction in total mortality was not statistically significant between the intervention groups and the control group (RR: 0.96; 95% CI: 0.88 to 1.04). These results of the two types of mortality were consistent in the meta-analysis of the 20 studies that reported both the cardiovascular and all-cause mortality in the same review, as the reduction was significant in cardiovascular mortality (RR: 0.78, 95% CI: 0.67 to 0.90) but insignificant in the all-cause mortality (RR: 0.91, 95% CI: 0.82 to 1.01). Furthermore, the same trend was shown in the subgroup of studies that were published after 1995.

Powell et al. (2018) systematically reviewed 22 RCTs which had been published since 2000 to examine the effectiveness of exercise-based CR programmes in relation to all-cause mortality, cardiovascular mortality and hospital admissions (Powell et al., 2018). The review included 4000 patients (78% males) with a mean age of 59.5 years. The findings showed that there was no difference between the intervention group (exercise-based CR) and the control group (no exercise) for all-cause mortality (risk difference 0.00, 95% CI −0.02 to 0.01, P=0.38). This result was based on 19 studies. In terms of cardiovascular mortality which was based on 9 studies, no difference was shown between the two groups (risk difference −0.01, 95% CI −0.02 to 0.01, P=0.25). However, a small reduction, which was of borderline statistical significance, was found in hospital admissions in 11 studies (risk difference −0.05, 95% CI −0.10 to −0.00, P=0.05). The mean age in this meta-analysis is lower and is not representative of the general CR population as seen in routine practice where the mean age is 67 years ((18 to 108) and almost no patients above 71 years participated in the RCTs. However, the NACR audit from 2017 reported that the number of patients above 75 years of age was 12,248, which demonstrates the difference between the RCT population and routine practice (NACR, 2017). In addition approximately 20% of the studies included in this systematic review were small trials with a sample size of less than 50. The quality of the Powell et al review has been questioned by leading authorities (Cowie et al., 2018; Grace, Ghisi and Chessex, 2018) .The review uses mortality as the main measure of the effectiveness of CR and claims that the contemporary CR approach is ineffective, however, the recent Cochrane review stressed that CR should focus on improving quality of life and reducing hospital admissions. The review claimed this it is contemporary despite including papers where the recruitment period was unspecified. Furthermore, the review focused on exercise even though 16 of 22 included trials used a comprehensive CR programme (Cowie et al., 2018; Grace, Ghisi and Chessex, 2018). Another criticism of the Powell et al study is that the follow-up periods were, in general, rather short. Taylor et al reported that taking part in a long CR programme (>36 months) with supervision may be associated with significantly improved chances of survival (Taylor et al., 2017). Although Powell et al. reported on the exercise doses of some of the studies in question, no mention was made of whether the patients had adhered to the exercise programme. Compliance with an exercise programme can be assessed by documenting a change in physical fitness. In addition, there was no mention of the change reported in the Powell et al. study, therefore assessing the effectiveness of a CR programme could be problematic (Buckley et al., 2018; Grace, Ghisi and Chessex, 2018).

A recent systematic review and meta-analysis conducted by Halewijn et al. (2017) included 18 RCT (7691 patients) trials from 2010 to 2015, which examined the effect of CR on mortality (Halewijn et al., 2017). The results supported the findings of Anderson et al. as the analysis showed a significant reduction of 58% in cardiovascular mortality (RR 0.42, 95% CI 0.21, 0.88). However, there was no significant reduction in all-cause mortality (RR 1.00, 95% CI 0.88 to 1.14). Nevertheless, in this review, the analysis of the subgroup where the CR comprehensive programmes were managing ≥ 6 risk factors, the reduction in the risk of all-cause mortality was significant (RR 0.63, 95% CI 0.43, 0.93) although it was not significant in those programmes managing fewer than 6 risk factors.

Sumner et al. (2017) conducted a systematic review of non-randomised control studies from the year 2000 onwards to evaluate the effect of multi-component CR on the mortality and other endpoints. A total of 8 studies (10 CR interventions) were included involving 9836 AMI patients. The analysis found that in 4 of the studies that reported all-cause mortality, CR reduced the risk with unadjusted OR 0.25 (95% CI 0.16, 0.40) and adjusted OR 0.47 (95% CI 0.38, 0.59) among this population, while the two studies that reported cardiovascular morality showed the reduction was also significant with OR 0.21 (95% CI 0.12, 0.37) and adjusted OR 0.43 (95% CI 0.23, 0.79) favouring CR.

1.2.2.4.2 ***Impact of Cardiac Rehabilitation on hospital readmission***

The systematic review that was conducted by Anderson et al. (2016) found that in the 15 studies involving 3030 patients which reported hospital admission, there was a reduction in admission of 18% [RR: 0.82 (95% CI 0.70, 0.96)] favouring CR compared to usual care. This finding supported the results from a previous systematic review (Heran et al. 2011). Heran et al. systematically reviewed 47 randomised control trials with a population size of 10,794 patients (with a 12, or more, month follow-up) to compare the effect of exercise-based cardiac rehabilitation and usual care. The findings revealed that in 10 studies involving 2379 patients which reported hospital admissions there was a significant reduction in total readmission of 31% (RR: 0.69, 95% CI 0.51, 0.93) in the studies where the follow-up period was up to 12 months. However, in the studies where the follow up period was longer than 12 months, there was no significant difference between the intervention and control groups. Whether hospital admission referred to the first admission or readmission was not specified in the studies included in these reviews (Kachur et al., 2017).

Furthermore, a review of 33 control randomised studies was restricted to heart failure patients who were classified as class II or III, according to the New York Heart Association classification, and with an ejection fraction < 40% conducted by Sagar et al. (2015) showed a reduction in all hospital admissions (15 trials) and heart failure specific readmission (12 trials) of 25% (RR: 0.75; 0.62 to 0.92) and 39% (RR: 0.61; 95% CI: 0.46 to 0.80) respectively in the studies which had a follow-up period of up to 12 months and which favoured comprehensive CR compared to usual care. This review was limited in that more than 78% of the included studies (26 out of 33) had a sample size of fewer than 100 participants and also included early studies with a short period of follow up. In contrast, a consistent connection between CR and a reduction in hospital readmissions could not be found in the results of the CROS study (Rauch et al., 2016).

This result is supported by Sumner et al. (2017), who conducted a systematic review of observational studies where a reduction in readmission of attenders of CR and the control group (non-attenders) was found not to be significant. However, in this review two studies reported the impact of CR on readmission and, due to methodological issues, only the result of one of these studies was reported (Sumner, Harrison and Doherty, 2017).

The results show that using CR produces a reduction in the number of hospital readmissions, which makes it a significant tool in tackling the challenges of the modern era of cardiology. Therefore, the outcomes can be said to exceed patient benefits to include improvements in cardiac care within the whole system (Al Quait and Doherty, 2017).

1.2.2.4.3 ***Impact of Cardiac Rehabilitation on Health-related quality of life and psychological wellbeing***

Cho et al. (2016) systematically reviewed 6 randomised control trials of 482 patients (261 CR and 221 control). The review aimed to evaluate the effect of CR on the Health-related

Quality of Life (HRQOL) in CVD patients (Cho et al., 2016). The HRQOL scores were expressed as mean differences. The findings showed that CR demonstrated improvements in the HRQOL. In the four studies (341 patients) that reported the Physical Component Summary (SF-PCS), there was a significant improvement in CR compared to the control group with standardised mean differences of 4.77 (95% CI 2.32 to 7.22). However, three studies (294 patients) reported the Mental Component Summary (SF-MCS) score and there was found to be no significant improvement observed in the mean difference (MD) of 2.65 (95%CI -3.96 to 9.27). Furthermore, a meta-analysis of three studies (192patients) reported the Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score and found the improvement was significant favouring CR with mean differences of -15.33 (95%CI -19.50 to -11.18). However, this review was limited by the small sample size of the included studies.

In the Cochrane systematic review performed by Anderson et al. (2016), 20 randomised control trials involving 5060 patients reported the assessment of the HRQOL using a range of generic and disease specific outcome measures. Due to the heterogeneity among these studies in the outcome measures and the methods used to report the findings, a meta-analysis to pool the mean differences was not performed. However, 14 out of these 20 studies reported the positive effect of CR in at least one or more of the subscales of the HRQOL. Furthermore, of the 14 studies, five reported that a higher level was observed in at least one-half or more of the domains (Anderson et al., 2016).

This result is in agreement with the result of the meta-analysis of 18 studies undertaken by Sagar et al. in their Cochrane systematic review (Sagar et al., 2015). The findings showed that, regardless of outcome measures, the pooling across the studies revealed there was a significant clinical improvement in HRQOL favouring CR-exercise compared to the control group (standardised mean difference -0.46, 95% CI −0.66 to −0.26). This positive effect of CR on the HRQOL was also found in the systematic review of observational studies (Sumner, Harrison and Doherty, 2017). In the two studies that reported the HRQOL there was significant improvement in at least one of the domains, however, the data could not be pooled due to the heterogeneity of the two studies. In addition, no adjustment for confounding was done in either of the studies.

With regard to psychological wellbeing, a large randomised control trial (HF-Action Randomized Trial) was conducted on 2322 heart failure patients at 82 centres in 3 different countries (USA, France and Canada) to assess the effect of exercise-based CR on depressive symptoms using the Beck Depression Inventory II (BDI-II) (Blumenthal et al., 2012). Participants in the CR group (1158 patients) took part in a 3-sessions-per-week CR-based exercise programme for 3 months while the control group (1164 patients) received the usual care. The analysis showed that exercise-based CR produced a significant improvement in symptoms of depression compared to the usual care.

Another study was conducted on 189 patients (65±11 years) with heart failure due to CHD to evaluate the impact of CR on depressive symptoms (Milani et al., 2011). There were 152 patients in the CR group who joined the exercise-based CR programme for 3 months within the period from January 2000 to December 2008 and compared them to 38 patients who dropped out of the CR exercise-based programme before undertaking any exercise. The Kellner Symptom Questionnaire was used to assess the level of depression in the patients. The findings showed that depressive symptoms were reduced by 40% in those who joined the CR programme. Furthermore, compared to the depressed dropout patients, those who completed the CR programme reduced their level of mortality by 59% (44% vs 18%, $p < 0.05$).

Milani and Lavie (2007) retrospectively studied 701 patients with CHD (mean age of 64±11 years), who enrolled on CR programmes between 2000 and 2005, to assess the effect of CR on depression and its mortality (Milani and Lavie, 2007). Of them, 522 patients completed their CR programmes while 179 did not participate in CR. The analysis showed that the prevalence of depression fell from 17% on entry to 6% following CR. In addition, in terms of mortality, depressed patients who completed CR showed a reduction of 73% in the risk of mortality compared to those who did not participate in CR (8% vs 30%). The mean follow-up period in this study was 1296 ± 551 days.

In order to assess the effectiveness of psychological intervention as a CR-component on psychological distress in patients with CHD compared to patients who received usual care (control group), Linden et al. conducted a meta-analysis of 23 RCT studies involving 3180 patients (Linden, Stossel and Maurice, 1996). A total of 2024 patients received psychosocial treatment (intervention group) in contrast to the 1156 patients in the control group who received no such treatment. The analysis showed a higher reduction in the level of psychological distress in the intervention group (with effect size differences of 0.34) compared to the control group.

1.2.2.4.4 ***Impact of Cardiac Rehabilitation on Risk factors profile***

The improvements in the CHD risk factors were likely to have been related to the medical management which constituted part of the CR programme. In the meta-analysis conducted by Halewijn et al. (2017), where six RCTs reported blood pressure, there was shown to be a significant reduction in systolic blood pressure in the CR programmes that prescribed and monitored BP medications with a mean difference of (−3.16 mm Hg 95% CI−5.55, −0.77) compared to those which did not. However, the reduction was not significant in the case of diastolic blood pressure in both types of programmes. Furthermore, the analysis of the five studies that reported the LDL cholesterol showed that in the CR programmes that prescribed and monitored medications there was a significant reduction in LDL cholesterol levels (random effect -0.31 mmol/l, 95% CI -0.58, -0.04) while there was no significant reduction in those programmes which did not prescribe and monitor the medications.

Lawler et al. (2011) conducted a systematic review and meta-analysis to assess the influence of CR on modifiable cardiovascular risk factors. The review included 34 RCTs, which were published before June 2010, and with a total population size of 6,111 (mean age 54.7 years). The analysis revealed a more favourable reduction in systolic and diastolic blood pressure, total cholesterol and prevalence of smoking in the intervention group compared to the control group, while in both groups the change in weight was minimal.

A systematic review of 48 studies (8940 patients) was conducted by Taylor et al. in order to assess the effect of exercise-based CR in patients with CHD (Taylor et al., 2004). The meta-analysis showed that, compared to the control group (usual care), there was a statistical reduction in systolic blood pressure (weighted mean difference, –3.2 mm Hg; 95% CI: –5.4 to –0.9 mm Hg), triglyceride level (weighted mean difference, –0.23 mmol/L, 95% CI: –0.39 to –0.07 mmol/L), total cholesterol level (weighted mean difference, –0.37 mmol/L, 95% CI: –0.63 to –0.11 mmol/L) and reduced rates of smoking (OR = 0.64; 95% CI: 0.50 to 0.83) in the intervention group (CR group). However, there were no significant differences in diastolic pressure, and HDL and LDL cholesterol levels.

1.2.2.4.5 *Impact of Cardiac Rehabilitation on functional capacity*

Improving functional capacity has become one of the main aspects of guidance relating to lifestyle and management advice for CHD patients. Exercise-based CR has been shown to produce a positive change in functional capacity (Uddin et al., 2015) with the improvement in functional capacity being closely related to the exercise component of the programme.

Sandercock et al (2013) conducted a retrospective study on 950 patients from four UK CR centres in order to assess the change in their fitness (Sandercock et al., 2013). These centres used different assessment tools. The first centre used the Bruce treadmill test, the ISWT and the 6-minute walk test while the second centre used both the ISWT and the incremental cycle ergometer test. The patients from the third and fourth centres were both assessed using the ISWT. They found a pooled fixed effect estimate of 0.52 METs (95% CI 0.51 to 0.53) for the mean change in fitness in all patients from the four centres, which is equal to a moderate effect size of d=0.59 (95% CI 0.58 to 0.60). The effect size of the change in fitness was large in patients who participated in the ISWT (d=0.85) and the Bruce treadmill test (d=0.85) whereas it was moderate (d=0.57) in those who were assessed on the cycle ergometry test and lower still (d=0.34) for those who were assessed using the 6-minute walk test. This improvement of 0.52 METs is one third of the improvement recorded in a meta-analysis of international studies (1.55 METs) into CR fitness. (Sandercock, Hurtado and Cardoso, 2013)

Sandercock et al. conducted a meta-analysis of trials and cohort studies and analysed 31 studies which included 3827 patients from an international CR population to evaluate the change in cardiorespiratory fitness pre and post exercise-based cardiac rehabilitation using different treadmill protocols. 48 separate groups of patients were identified from the 31 studies, who had a mean pre-versus post-test difference in fitness. The study reported a significant improvement in cardiorespiratory fitness (CRF) of an average of 1.5 MET, in other words, an improvement of an average 5.4 ml/kg/min in CRF. This result supports the evidence of the efficacy of cardiac rehabilitation to improve CRF (Sandercock, Hurtado and Cardoso, 2013).

Another meta-analysis involving studies conducted only in the UK was performed to determine the magnitude of the change in fitness in CR patients as expressed by the distance walked in the ISWT (Almodhy, Ingle and Sandercock, 2016). Eleven studies were analysed (1578 patients) and a significant improvement in the distance walked was found with a mean estimate of 84m. However, in this meta-analysis, five (45%) out of the 11 included studies had a small sample size (< 40 participants).

Benzer et al. in their European Register research, studied 2,054 patients in 12 European countries in order to assess the feasibility of a CR web-based registry in European countries (Benzer et al., 2017). This registry would provide a basis for a comparison of the quality of CR provision across Europe in terms of settings, interventions and outcomes. In terms of measuring fitness, they reported that only 28% (535 patients) of the total number of patients undertook the baseline assessment and this number fell to 16% (339 patients) by the end of the programme. The average exercise capacity in this group at baseline using bicycle ergometer was 104 ± 44watt and improved to 128 ± 50watt at the end of the programme. In this study, “CR success” was defined as an increase in exercise capacity of >25 watts after CR. The authors found that only 58% of the patients who took the fitness assessment succeeded in achieving this improvement. This achievement was greater in patients aged over 50 years of age and those who were employed compared to patients who were younger or retired.

Keteyian et al. (2016) retrospectively studied a large database relating to 8319 CR patients (5780 men with a mean age of 63±11 years and 2539 women with a mean age of 64 ±12 years) who participated in an outpatient CR programme at the Henry Ford Hospital, in Detroit, USA, and who completed ≥ 9 sessions (Keteyian et al., 2016). The study aimed to describe the amount of change in fitness at the end of CR programme. A treadmill exercise test was performed at entry and at the end of the programme and MET values were estimated based on the speed and grade of the treadmill. The analysis revealed that males improved their fitness by 45% (from 2.9 METs ± 0.8 to 4.1 ± 1.4 METs), which was higher than the improvement that the females achieved (from 2.4 ± 0.7 METs to 3.3.± 1 METs, 40%). However, whether this difference between the two groups is statistically significant or not was not reported.

A meta-analysis conducted by Uddin et al. (2015) aimed to assess the patient, intervention and trial-level factors that might predict the change in exercise capacity in coronary heart disease and heart-failure patients following exercise-based CR (Uddin et al., 2015). The authors included 7553 patients from 55 randomised controlled trials identified from three published systematic reviews. From these trials there were 61 comparisons, of them 26 were from coronary heart disease trials and 35 were from heart failure trials. The value of Vo_2 max and all its predictors were reported in 34 of the comparisons. The meta-analysis of the data from these 34 comparisons showed that the difference in the pooled exercise capacity between the exercise and control groups at the end of the CR programme was 3.1ml/kg/min. The only determinant of the change in exercise capacity identified in the multivariable meta-regression analysis was the intensity of the exercise.

Valkeinen et al (2010) conducted a systematic review and meta-analysis into the effect of exercise intervention on oxygen uptake (maximal or peak) in coronary heart disease patients (Valkeinen, Aaltonen and Kujala, 2010). The meta-analysis included 18 randomised controlled trials from 1995 to 2010 with 922 patients (485 participants in exercise intervention groups versus 437 in control groups). The pooled results showed the change in Vo_2max in the intervention group was 2.6±1.6 mL/kg/min and in the control group it was 0.3±1.4 mL/kg/min giving a net difference of 2.3mL/kg/min (0.66 MET). However, this systematic review was restricted to randomised trials that directly measured Vo_2max using either a bicycle ergometer or a treadmill. The authors reported that according to the assessment tool they used, the methodological quality of the studies which were included in this systematic review was classified as low. In addition, only 8% of patients were female and in 19% of the participants, gender was not reported.

Ades et al. aimed to establish the normative values for peak exercise capacity (peak Vo2) in 2896 CR patients who were enrolled in CR between 1996 and 2004 (Ades et al., 2006). They found that, in the 504 patients who had completed the exercise assessment at the end of the 36-session CR programme undertaken over three months, exercise capacity had improved by 17% compared to the baseline measurement. This improvement was significantly higher in men than in women.

A further retrospective study was conducted on data relating to 1909 patients (137 females), with a mean age of 54.7±9.18 years, who were enrolled in a CR programme at the University Hospital of Leuven between 1979 and 2000. The patients undertook a pre- and post-exercise test using a bicycle ergometer. An average improvement of 26% in fitness (from 22.7 ml/kg/min ± 5.9 to 28.2±7.1 ml/kg/min) was found (Vanhees et al., 2004).

1.2.3 Assessment of functional capacity

Assessing functional capacity at baseline and end of programme in patients attending cardiac rehabilitation (CR) is strongly recommended in the clinical guidelines and national and international standards published by organisations including the British Association for

Cardiovascular Prevention and Rehabilitation (BACPR), the European Association for Cardiovascular Prevention and Rehabilitation (EAPC), the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR), the Canadian Association of Cardiac Rehabilitation (CACR), the European Society of Cardiology and American Heart Association (AHA) and the Association of Chartered Physiotherapists in Cardiac Rehabilitation (ACPICR) (Arena et al., 2007; Piepoli et al., 2012; Mezzani et al., 2012; AACVRP, 2013; BACPR, 2017). BACR 2017, in its 3rd standard for the Cardiovascular Prevention and Rehabilitation, stated that an initial assessment should be carried out for each individual and include an exercise capacity assessment and a formal risk stratification for exercise utilising all relevant patient information (eg functional capacity). In addition, patients should undertake some type of on-going assessment during their CR programme. The assessments should use validated measures.

Ideally, based on the result of the functional capacity test that is undertaken prior to the CR programme, a safe and appropriate intensity of exercise can be prescribed; the level of supervision and monitoring required can be determined; patients can be classified according to a risk stratification and physical activity guidance can be described. The effectiveness of the intervention and the response of the patient to the exercise during the CR programme can be evaluated. In addition, the result of this functional test can also be used as a prognostic prediction and a long-term maintenance plan for each patient can be drawn up (Arena et al., 2007; Mezzani et al., 2012; ACSM's, 2010; ACPICR, 2015; BACPR, 2017). For example, if the CRF of the patient improves, then the patient can continue his tailored programme, but in the case of no improvement, the CR programme should be modified and the exercise should be revised to enable the patient to gain benefit from the programme (Shenoy and Patel, 2013). In the event that a pre-CR functional test is not conducted, the beneficial effects of exercise training during the CR programme might be limited and could negatively affect the patient's progress (Arena et al., 2007). However, despite the recommendations relating to assessing patients' level of functional capacity prior to the programme and following it, there are few studies which report on the frequency of patients taking the baseline assessment. Benzer et al (2017) reported that only 28% of the 2054 patients from 12 European countries who participated in their study had undertaken the baseline physical fitness assessment. However, this number decreased to 16% for those who took the end-of-programme assessment (Benzer et al., 2017). According to the NACR report (2017), the number of patients who undertook both pre-and post-programme functional capacity tests was only 15% of those who started the CR programme (NACR, 2017).

1.2.4 Functional capacity

Functional capacity, aerobic capacity, exercise capacity, cardiorespiratory fitness and fitness are generally used synonymously and indicates that the individual has exerted maximal effort (Nasim et al., 2013). However, in this thesis, the terms 'functional capacity' and 'fitness' will be used interchangeably. When reporting on other studies in this thesis, the terms utilised by the original authors will be used when the studies are being initially described.

"Functional capacity is the ability of an individual to perform aerobic work as defined by the maximal oxygen uptake (Vo_2 max)" (Arena et al., 2007,p 229). Vo_2 max is defined as the plateau of Vo_2 despite an increase in workload. Vo2 max is the product of maximal cardiac output and arterio-venous oxygen difference (a-Vo_2) at the stage of physical exhaustion. Maximal cardiac output is equal to heart rate (HR) multiplied by stroke volume (SV). Vo_2 max is represented by the following equation which is known as the Fick equation:

$$Vo_2 \text{ max} = (HR \text{ X } SV) \text{ X } a–Vo_2\text{diff}$$

Cardiorespiratory fitness (CRF) is defined as "The ability of the circulatory, respiratory, and muscular systems to supply oxygen during sustained physical activity" (Lee et al. 2010.p 27). CRF is the primary metric of functional capacity (Forman et al., 2017) and is expressed as maximal oxygen uptake (Vo_2 max), which is directly measured in litres of oxygen per minute (L/m) or millilitres of oxygen per kilogram of body weight per minute, which facilitates the comparison between individuals of different weights. Additionally, it can be expressed in metabolic equivalents (METs) when estimated from the work rate achieved, where one MET represents the energy expenditure at rest (3.5 mL O2.kg-1. min-1) (Arena et al., 2007; ACSM's, 2010). Vo_2 max is normally achieved through exercise which utilises around half of the total body musculature. Therefore, Vo_2 max is generally considered to be governed by maximal cardiac output and it is closely related to the functional capacity of the heart and not by peripheral factors (Arena et al., 2007; ACSM's, 2010).

Vo_2 max is the gold standard measure for CRF and can be measured either directly or indirectly. The direct measures of Vo_2 max are obtained at maximal exertion during graded treadmill exercise tests or on the cycle ergometer using the ventilatory expired gas analysis (Cardiopulmonary exercise testing (CPET)), which is the most precise measurement. Indirect measures estimate Vo_2 max using the heart rate response, peak workload or maximal exercise duration obtained during maximal or submaximal exercise tests. Vo_2 max can also be estimated using the time needed to walk or run a predetermined distance. However, when Vo_2 max is not achieved during the test, then the Vo_2 max obtained is termed Vo_2 peak (Noonan and Dean, 2000).

1.2.4.1 Prescribing exercise intensity

Assessing functional capacity allows the clinician to prescribe exercise intensity based on the percentage of maximal Vo_2 max, maximal HR or maximal HR reserved that is achieved during the exercise. This is important as prescribing an exercise intensity which is too high could put the patient at risk (ACSM's, 2010; ACPICR, 2015).

According to ACPICR, exercise intensity should be between 40% -70% HRR (Vo_2 max) or 11 –14 on the 6-20 Borg's Rating of Perceived Exertion (RPE) scale or 2 – 4 on the (C-R10) scale. However, low-risk patients or those who are more active are recommended to exercise towards the higher end of the targets related to exercise intensity 70% HRR or RPE 14 (6-20 scale) and 4 (CR-10), while those who are high risk, more sedentary should aim for the less strenuous end of the intensity targets 40% HRR, or RPE 11 (6-20 scale) and 2 (CR-10 scale) (ACPICR, 2015). The monitoring of a blood pressure response during the test in addition to an observation of any signs and symptoms, such as chest pain, breathlessness and fatigue is also recommended (ACPICR, 2015; Price et al., 2016).

1.2.4.2 Risk stratification

Risk stratification is a process of evaluating a patient based on their clinical and functional status in order to determine their level of risk using the patient's medical history and physical, laboratory and ancillary tests (Silva et al., 2014; AACVRP, 2013). Based on this stratification, the patient is classified as either low, moderate or high risk to enable the clinician to tailor the appropriate exercise intensity for the patient (Silva et al., 2014). The BACPR recommend using the risk stratification established by the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) (Appendix 8.1.1). In terms of functional capacity, if the patient achieves >7 METs at baseline, he/she is considered low risk whereas a patient achieving <5 METs during the test with the presence of angina or other significant symptoms such as dizziness or shortness of breath, s/he is considered to be high risk. A patient who falls between these two criteria is classed as at moderate risk.

Stratifying patients according to risk based on clinical features and the results of the exercise test at baseline will allow the clinician to determine the appropriate exercise prescribed, provide guidance for daily activities, choice of a suitable venue and staff levels and skills. In addition, providing and supporting resuscitation in accordance with the current Resuscitation Council UK / BACPR guidance can also be determined based on this stratification underpinned by a measure of functional capacity/fitness (BACPR, 2017) .

1.2.4.3 *The prognostic importance of the baseline fitness measurement and a change in fitness*

The baseline physical fitness level and the change in the fitness level is associated with survival in both healthy people and patients who suffer from coronary heart disease (Taylor et al., 2016; Barons et al., 2015; Franklin et al., 2013). Taylor et al. (2016) conducted a study using data from a community-based CR exercise programme in the UK to examine the association between both the baseline and the change in fitness and all-cause mortality in the CR population. They retrospectively analysed the data of 670 patients who joined the CR programme during the period between 1993 to 2006 and followed the patients to the end of 2013 (median 14 years). The patients' ages ranged from 22 to 82 years, 76% of them were male. The fitness was measured using a submaximal treadmill or cycle ergometer test and the outcome was estimated in METs. They found the baseline fitness level was a strong predictor of all-cause mortality. Patients with high (≥ 8 METs for males and ≥ 7 for females) and moderate levels of fitness (6 to <8 METs for males and 5 to < 7 for females) showed a 60% (HR 0.40; 95% CI 0.25 to 0.64), and 41% (HR 0.59; 95% CI 0.42 to 0.83) reduction in mortality risk respectively compared to the patients with a low level of baseline fitness (< 6METs for males and <5 for females). After multivariate adjustment, each increment of 1 MET in fitness at baseline resulted in an 11% reduction in mortality risk (HR 0.89; 95% CI 0.81 to 0.98).

In this study data relating to the 416 patients who undertook the post-programme fitness assessment following 14 weeks of CR, showed that an improvement of one MET was associated with a 27% (HR 0.73; 95% CI 0.57 to 0.94) reduction in mortality risk. However, there was no significant association between the change in fitness and the reduction in risk of mortality for those patients with a moderate or high level of baseline fitness. The authors reported that a higher relative risk of mortality was observed in patients with a low level of fitness at baseline and whose change in fitness was also low (HR 7.94; 95% CI 4.28 to 14.75).Barons et al. (2015) analysed the data of 1529 patients who undertook a fitness test at entry to CR in Hampshire, UK during the period 1993 to 2002 and followed the patients up to 2011 (a mean of 10.7 years) to examine the influence of the baseline measurement and the change in fitness in patients on all-cause and cardiovascular mortality (Barons et al., 2015). Fitness was expressed as predicted Vo_2 peak (in mL/kg/min) from either the cycle ergometer or treadmill test (Bruce and modified Bruce protocols). Patients were classified as having a high fitness level (Vo_2 peak >22 mL/kg/min), a low fitness level (Vo_2 peak <15 mL/kg/min) or a moderate level (from 15 to <22 mL/kg/min) for males while females were classified a having a high fitness level (Vo_2 peak >19 mL/kg/mi), a low fitness level (Vo_2 peak <13 mL/kg/mi) and a moderate fitness level (between 13 and 19mL/kg/min) for females. During the study 385 patients (25%) died. Of them, 192 deaths were due to cardiovascular reasons. The analysis showed that the baseline fitness level is a strong predictor of both all-cause and cardiovascular mortality with a lower fitness level associated with a higher risk of mortality. As the fitness level improved at the end of CR, the mortality risk becomes less except in the case of those who had a moderate level at baseline and who improved to a higher level where there was no significant difference compared to those who had a higher level of fitness at baseline (reference value). In addition to the baseline measurement and the improvement in fitness categories, age, gender, comorbidity score, statin, aspirin and diagnostic categories were shown to be other predictors for both types of mortality.

Martin et al (2013) aimed to measure the association between CRF at baseline; the change in CRF after 12 weeks; and again after one year following the end of the programme; and mortality using a treadmill graded exercise test (Martin et al., 2013). They conducted a retrospective analysis on the data relating to 5641 CR patients, of them 4282 were male (76%), who participated in a CR programme during the period between July 1996 and February 2009 in the Cardiac Wellness Institute of Calgary, Canada. Based on their baseline fitness assessments patients were classified into three categories: low level of fitness (< 5METs), moderate (5-8METs) and high (>8 MET). Both baseline fitness and the change in fitness were found to be inversely correlated with mortality. In terms of survival, after adjusting for age, gender, comorbidities and severity of disease and treatment, the CRF at baseline was strongly predictive of mortality. A CRF improvement after 12 weeks of the CR programme was associated with an overall reduction in mortality where each MET increase constituted a 13%-point reduction in mortality (hazard ratio [HR], 0.87; 95%CI, 0.79-0.96). In patients who started in the low fitness group this reduction was higher, with a 30% reduction in mortality for each MET increase. Assessment of the 3514 patients who undertook the exercise test after one year showed a 22% (HR, 0.78; 95% CI, 0.70-0.88) point reduction in mortality for each MET increase regardless of baseline categories.

Keteyian et al. (2008) conducted a study on 2812 patient (72% males) with a mean age of 61 years who entered CR in two centres in the U.S from 1996 and who were followed up until 2006 (a median of 59 months) in order to examine the ability of Vo_2 to predict the all-cause and cardiovascular mortality in this population in the era of statins and PCI interventions (Keteyian et al., 2008). At entry to the CR programme, fitness was assessed using a treadmill exercise test with an expired gas analysis and Vo_2 peak was expressed as mL/kg/min. Deaths of participants during this period numbered 280. A Cox regression analysis showed an increment in Vo_2 peak of 1 mL/kg/min resulted in a decrease in the mortality risk of 17% (HR, 0.83; 95% CI 0.80 to 0.83) and 16% (HR, 0.84; 95% CI 0.79 to 0.89) in all-cause and cardiovascular mortality respectively for males. The reduction in mortality risk was 14% for each1 mL/kg/min increment in Vo_2 peak among females for both types of mortality.

Further sub-analysis was conducted by the Keteyian et al. on patients who received what the authors termed ‘evidence-based care’ (statins and PCI interventions). The analysis showed that a peak Vo_2 was a predictor of both all-cause mortality (HR, 0.84, $p<0.001$) and cardiovascular mortality (HR, 0.87; $p=0.009$) in male patients while in females the analysis was conducted only for the all-cause mortality (HR, 0.78; $p=0.01$) and Vo_2 was also found to be a predictor. The authors were unable to conduct analysis on cardiovascular mortality due to the small number of deaths among female participants. The authors concluded that Vo_2 peak remains an independent predictor of the both types of mortality in both males and females regardless of the type of treatment (Keteyian et al., 2008). A Vo_2 value of ≤15 mL/kg/min for men and a value of ≤12 mL/kg/min for women were associated with a high risk of all-cause mortality. However, the patients in this study were comparatively young with an average age of 61 years. There was also a limited number of cardiac events among female patients.

A further study using data from 2,380 female patients with a mean age of 59.7 (±10years), who were referred to CR, investigated the association between a change in exercise capacity measured directly and mortality among women attending an outpatient CR programme at a single centre between 1973 and 1998 where the follow-up period was 6.1 ± 5 years (a median of 4.5 years with a range of 0.4 to 25 years) (Kavanagh et al., 2003). Before starting the CR programme, patients undertook an exercise test using a cycle ergometer with a respiratory gas analysis to directly measure the Vo_2 peak. During the follow up, 304 deaths were recorded, of them 95 were due to cardiac causes and the remaining were due to all-cause deaths. They found that when Vo_2 was treated as a continuous variable, each increment of 1 mL/kg/min in Vo_2 peak produced a 10% reduction in cardiac mortality (HR 0.90, 95% CI 0.85 to 0.96, p >0.001) while when Vo2 was treated as a binary variable, a 50% reduction in the cardiac mortality was shown in those whose Vo2 values ≥ 13 ml/kg/min compared to those who had Vo_2 values <13 ml/kg/min at the baseline fitness test. For the all-cause mortality the reduction was 29% in those whose Vo_2 values ≥ 13 ml/kg/min compared to those who had Vo_2 values of <13 ml/kg/min. The authors concluded that a Vo2 value of > 13 mL/kg/min showed a noticeable protective effect in relation to both all-cause and cardiovascular death in women who were referred to CR.

A year earlier, the same group (Kavanagh et al., 2002) conducted a study on 12169 male patients (a mean age of 55± 9.6 years) who were referred to CR in the U.S from 1968 to 1994 to examine the association between the VO2peak obtained from a cycle ergometer during the baseline fitness assessment and the all–cause and cardiovascular mortality in male patients. During the follow-up period, which ranged from 4 to 29 years (a median of 7.9 years), 2352 all-cause deaths and 1336 cardiac deaths were recorded.

Patients were categorised into three groups based on their baseline Vo_2 peak. The first group (Vo_2 peak of <15 mL/kg/min) were used as a reference group, the second group had a Vo_2 peak of 15 to 22 mL/kg/min and the third group had a Vo_2 peak of <22 mL/kg/min. The multivariate analysis showed that, compared to the reference group, there was a significant reduction of 38% and 61% in cardiac mortality in the second and third groups respectively. In terms of all-cause mortality, the reduction was 34% in the second group and 52% in the third group compared to the reference group. When the Vo_2 peak values were treated as a continuous variable the analysis showed that each increment of 1 mL/kg/min in the Vo_2 peak value resulted in an improvement of 9% in the prognosis. In addition, it was found that there was no difference in the prognostic power between measured or predicted Vo_2 value as shown by the area under the receiver operating characteristic curve.

Vanhees et al. (1995) studied 417 male patients (a mean age of 53±8 years) who joined a 3-month outpatient CR programme (3 sessions/week) in order to examine the relationship between the changes in fitness and cardiac and all-cause deaths between 1978 and 1988. The patients were followed up to December 1990. Participants undertook exercise test using a cycle ergometer with an expired gas analysis at entry and on completion of their programme to assess their fitness. There were 37 cases of death during the follow-up period of on average 6.2 years (a range of 0.07 to11.9 years). Of them, 21 died due to cardiovascular causes while the remaining 16 died from non-cardiovascular causes. In this study the baseline Vo_2 peak value, the post CR Vo_2 value and the absolute and relative differences in Vo_2 peak values were used. The analysis reported that after adjustments for covariates (age, referral diagnosis, diabetes, hypertension and smoking status), all Vo_2 values were shown to be predictors of cardiovascular mortality with an increment of 1 mL/kg/min produces a reduction in risk of 70%, 79% in the baseline Vo_2 value and the value of Vo_2 value on completion of the programme respectively. The same increment results in an 80% and 2%

reduction in the risk of cardiovascular mortality for the absolute and relative differences in Vo_2 peak respectively. However, for all-cause mortality the only significant predictor was the post CR Vo_2 peak value (HR, 0.41; 95% CI 0.19 to 0.90) (Vanhees et al., 1995).

The variation in the results of the above-mentioned studies in relation to the estimation of the risk of mortality may be due to the differences in the use of assessment tools, the medical regimens, whether the Vo_2 was directly measured or estimated and the sample population and sample size (Keteyian et al., 2008).

1.2.5 Fitness testing in Cardiac Rehabilitation

Cardiopulmonary exercise testing (CPET), either using a cycle or treadmill with ventilatory expired gas analysis, is considered the gold standard to assess CRF as Vo_2 max is directly measured during the test and indicates the achievement of maximum effort. These tests assist in ruling out the contra-indications to exercise, determining the maximal capacity with regards to Vo_2 peak, HR and maximum power, and optimising drug prescription. (Casillas et al., 2013; Gremeaux, 2015; Reeves, Gupta and Forman, 2016). When no ventilator expired gas analysis is use, this test is called a graded exercise test (GXT) in this case CRF is estimated in METs. However, these tests are costly and time-consuming and require trained staff and the presence of a physician. In some cases, patients with severe cardio-vascular impairment might not tolerate the tests well (Casillas et al., 2013; Gremeaux, 2015; Reeves, Gupta and Forman, 2016). It is recommended by the AHA and AACVPR, CACR and EAPC that this type of test is conducted while monitored on an Electrocardiogram (ECG). However, less technical submaximal exercise field tests, such as the ISWT and the six minute walk test (6MWT) are used in the UK and Australasia to assess functional capacity (Price et al., 2016). Nevertheless, the need to use an ECG-monitored exercise test is acknowledged in the case of high risk patients in these nations (Price et al., 2016).

These submaximal exercise field tests are usually carried out according to standardised protocols. Predetermined end points, for example 85% of age-predicted maximal HR, 70% of HR reserve, a score of <15 on the RPE Borg 6-20 scale and symptom-limited signs can be used (ACPICR, 2015; Grove, Jones and Connolly, 2017). The advantages of using such tests are that they are cost-effective, portable, do not require physicians during the test and replicate everyday activities. These tests can be used to evaluate the functional capacity, to prescribe exercise and to measure the change in fitness from the baseline.(Grove, Jones and Connolly, 2017)

Many CR programmes in the UK utilise field tests such as the ISWT, 6MWT and Chester step test (CST) in order to assess the functional capacity of their patients prior to and following the CR programme. In these tests, the functional capacity measurement is expressed as the distance walked in the ISWT and 6MWT, predicted VO2 max (ISWT and CST) and workload in the case of (CST). However, which exercise test is used depends on the availability of resources in the centre, such as space an d equipment, and patient factors including their physical activity status and comorbidities (ACPICR, 2015; Grove, Jones and Connolly, 2017).

A practice test has been shown to produce a more accurate recording of a change in fitness as it eliminates the learning effect. However, conducting a practice test prior to the actual test is often not possible in a clinical setting for reasons of cost and practicality(Grove, Jones and Connolly, 2017)

The 6MWT and the CST will be briefly described, however, as ISWT is the main test reported in this thesis, it will be described in more detail.

1.2.5.1 Six Minute Walk Test

This test was first described by Guyatt et al. (1985). In the test, the patient is asked to walk for six minutes back and forth along a 30-metre track at a self-paced speed. Patients can use their own walking devices if required. Due to the simplicity of the test, it is commonly used by patients with low functional capacity (HF patients) or those with co-morbidities which make it problematic to follow externally paced incremental tests. However, the 6MWT does not have a standardised method as the performance of the patient can be affected by their willingness to collaborate and the level of encouragement they receive. In addition, the test needs to be carried out in a long flat space (a minimum of 30 metres) (Pulz et al., 2008)

1.2.5.2 Chester Step Test

The patient performs this test by stepping onto a single 30 cm step and back down again following a metronome beat. At the first level of this test, the patient takes fifteen steps per minute for two minutes (level one). The metronome beat steadily increases in speed causing the patient to increase their performance by 5 steps per minute for each additional level. The maximum duration of the test is 10 minutes by which time 5 levels have been completed. However, this test is unsuitable for patients who have poor balance, a lack of mobility or knee pain as the patient is required to step backwards (Sykes, 1995; ACSM's, 2010; ACPICR, 2015).

1.2.5.3 Incremental shuttle walk test

The ISWT was primarily developed to assess functional capacity in patients with chronic obstructive pulmonary disease by Singh (Singh et al., 1992). This test was designed to enable patients to reach the maximal level of effort given their breathing symptoms. In the UK, it is the most commonly-used field test to measure functional capacity (Grove, 2013; Almodhy, Sandercock and Richards, 2012; NACR, 2015).The outcome of this fitness test is frequently in the form of absolute walking distances or the estimated METs. In this test, the patient walks continuously back and forth on a ten-metre course marked by two cones placed 0.5 metre inside to allow the patient to turn without any abrupt changes in direction (Figure 1.1). Each ten-metre walk is called a 'shuttle'. The test consists of 12 levels each having an incremental number of shuttles. An audio signal on a CD dictates the walking speed, which increases by 0.17m/s at each level and is indicated by a triple bleep from the CD. Heart rate (HR) and Rate Perceived Exertion (RPE) are measured during the test at each level. The test ends when the patient achieves 85% of the maximal heart rate (HR max = [210 - (0-65 x age)]), the RPE >15, or is no longer able to keep up with the audio signal (more than 0.5 metre from cone) or becomes too breathless (Singh et al., 1992; Grove, 2013). When the patient finishes the test, the number of shuttles the patient walked, and consequently the total of distance, is recorded (Woolf-May and Ferrett, 2008; Grove, 2013).

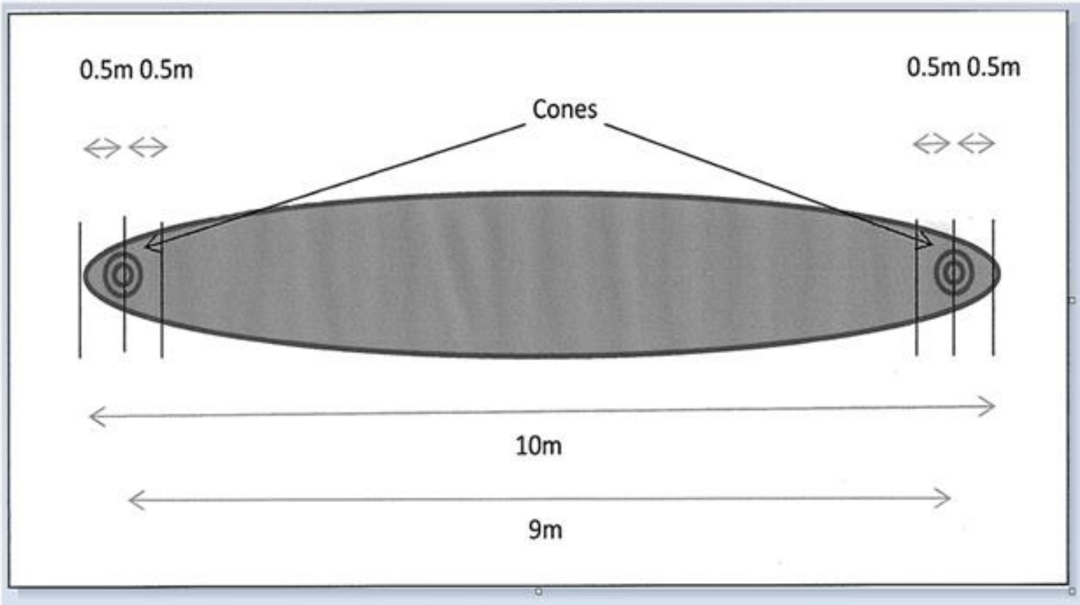

Figure 1.1 ISWT Diagram adapted from Woolf-May and Meadows 2013

However, to determine whether the ISWT is appropriate for a particular patient, their ability to do the test is assessed by asking them if they have any conditions (e.g. comorbidities) that could limit them from doing the test. Alternatively, the functional limitations domain of the 36-short form survey (SF-36) which consists of 10 questions and scored from 10 to 30 has been used. A patient who has serious limitations in performing everyday living activities would achieve a score of 10 whereas a patient with no limitations would score 30 (Grove, 2013). In terms of contraindications and precautions, the ISWT is the same as any other cardiopulmonary exercise testing (CPET) (Holland et al., 2014). The relative and absolute contraindications are listed in Appendix 8.1.2.

According to recommendations a practice test should be done before conducting the ISWT to mitigate against the effect of the patients becoming familiar with the test (Singh et al., 1992; Holland et al., 2014; Grove, 2013). Fowler et al found that there was a difference of approximately 40m (4 shuttles) between the first and second ISWT with no significant difference in the subjects' maximum heart rate. Authors reported that, due to this learning effect, the potential benefit of a CR exercise intervention may be overestimated. This difference between the practice and the second ISWT was also reported in a study conducted in 353 CR patients from the Birmingham Rehabilitation Uptake Study (BRUM) (Jolly et al., 2008). However, in this study there was a statistically significant difference between the practice ISWT and the second test while the HR was not significantly different. The authors speculate that this indicates that the increase in distance could be attributed to the familiarity to the test and not to motivation and stressed the importance of undertaking a practice test.

1.2.5.3.1 *Validity of ISWT in the cardiac rehabilitation population*

ISWT was proposed as a symptom-limited maximal performance test that aims to replicate the response produced by cardiopulmonary exercise testing (CEPT) (Gonçalves et al., 2015). This is supported by the strong relationship between the distance walked in the ISWT and the Vo_2 max or Vo_2 peak measurements obtained from the treadmill test, cycle ergometer or simultaneously during the ISWT in several studies from different populations. (r =0.75-0.88) (Parreira et al., 2014).

Parreira et al (2014) conducted a systematic review on the measurement properties of the ISWT and found that in 17 studies there was a strong correlation between Vo_2 and the distance walked in the ISWT test in different populations such as patients with COPD, cardiac disease, cardiac transplantation, operable lung cancer, idiopathic pulmonary fibrosis, general surgery and cystic fibrosis. One of these studies in a cardiac rehabilitation population, included 39 patients (34 males and 5 females) with a mean age of 61.2 ± 8.5 years, who had undergone coronary artery bypass graft surgery (CABG) (Fowler, Singh and Revill, 2005). In this study, patients undertook the ISWT three times, one on the first visit (Test 1) and the other two tests (Tests 2 and 3) on the second visit, which took place 6-8 weeks after surgery. During the second visit, the patient had a 45-minute rest between the two tests. It was found that there were strong correlations between the distances covered during the three shuttle walk tests and peak Vo_2 obtained from the treadmill test (r = 0.79, r

= 0.86 and r =0.87 respectively). This result was in accordance with the significant correlation between the distance walked during ISWT and the peak Vo_2 obtained from the treadmill test ($r=0.83$, $P<0.05$) and also between the peak Vo_2 obtained from ISWT and that obtained from the treadmill test ($r =0.73$, $P < 0.05$) as observed by Green et al in fourteen heart failure patients (13 males, 1 female) (Green et al., 2001). A similarly high correlation was obtained in a study by Lewis et al (2001). The correlation between the mean peak Vo2 obtained during the treadmill test and the ISWT distance was significant ($r = 0 .73$, $P < 0.05$) in 25 patients (21 males, 4 females) who were waiting for heart transplantation (Lewis et al., 2001). However, one of the limitations of the previous studies is that they were conducted on a small sample size and the population was predominantly male. In addition to that, in the Green et al (2001) and Lewis et al (2001) studies, the authors used correlation statistics which only measured the degree of association between the two measurements and not the degree of agreement between them.

This correlation was also shown to be strong in healthy subjects. Dourado et al (2013) evaluated 103 healthy participants (mean age 50±10 years) who took both a treadmill test and the ISWT and reported a strong correlation between the distance walked during ISWT and Vo_2 peak obtained during the treadmill test ($r = 0.86$, $p < 0.001$). A recent study undertaken by Neves et al (2015) recruited twelve participants for the first stage and 53 for the second. Twenty participants were used in the cross-validation group. Participants in the first stage did the ISWT and the treadmill test. It was found that the Vo2 peaks obtained from the treadmill test and the ISWT correlated strongly and significantly, and according to the Bland-Altman analysis, there was an agreement between the Vo_2 peak results derived from the two tests. Stage two participants completed two ISWTs. The results showed that there was a moderately significant correlation between the peak Vo2 obtained from the ISWT and the distance covered during the test (r=0.40, However, this study was restricted to male participants from a narrow age range who were eutrophic (<18.5 body mass index (BMI) <24.5).

1.2.5.3.2 ***Reliability of ISWT in CR population***

ISWT showed a good test-retest reliability in several populations of patients with intra-class correlation coefficients ranging from 0.76 to 0.99 (Parreira et al., 2014). In the cardiac rehabilitation population the reliability coefficients ranged from 0.8 to 0.99 between the first and second test (Jolly et al., 2008; Pepera, McAllister and Sandercock, 2010; Fowler, Singh and Revill, 2005; Green et al., 2001; Gargiulo et al., 2014; Obling et al., 2015; Hanson, Taylor and McBurney, 2015). ISWT also demonstrated a strong test retest reliability (ICC = 0.97-.997) between the second and third test (Fowler, Singh and Revill, 2005; Lewis et al., 2001; Hanson, Taylor and McBurney, 2015; Dourado et al., 2013).

Pepera et al (2010) conducted a study on 30 patients with cardiovascular disease. They reported no significant change in the distance walked between the first and second test with an ICC of 0.80. A study was carried out by Fowler et al in 2005 on patients who had undergone coronary bypass graft surgery to assess the reproducibility of the ISWT in this population. The test was repeated three times on two days over a period of a week. They found there was no significant change in the distance among the three tests. ICC for test one and two was 0.94 (95%, CI 0.89-0.97) and for the second and third test was 0.99 (95%, CI 0.99-0.99). These results were supported by a recent study by Hanson et al (2015), which studied 62 patients in order to assess the retest reliability of ISWT in a mixed cardiac rehabilitation population. Patients completed two ISWTs with a 30-minute break in between. A good retest reliability was found between the first and second test (ICC= 0.99, 95% CI: 0.928 to 0.997).

1.2.5.3.3 ***Minimum clinically important difference in ISWT in CR population***

The minimum clinically important difference (MCID) in the ISWT following cardiac rehabilitation is the smallest change that is important to patients (Copay et al., 2007). Houchen-Wolloff et al (2014) recruited 224 CR patients (170 males, 50 females) and asked them to rank their perceived change in exercise performance after completing their CR programme based on 5 Likert scale range from 1-better to 5-worse. They established that 70 metres (seven whole shuttles) or a 25% improvement from baseline was the threshold for a MCID for ISWT in this population. This is considered a benchmark for clinicians to judge patient success following a cardiac rehabilitation programme. It is also important as it informs the patient about the required change that is beneficial for his/her perceived health following cardiac rehabilitation (Houchen-Wolloff, Boyce and Singh, 2014). This MCID has been used as the main tool to evaluate the improvement in patients' functional capacity in the NACR annual audit report since 2015 (NACR, 2015). Using the MCID as a parameter of an improvement in fitness showed that only 60% of patients whose fitness was assessed using the ISWT improved their fitness (NACR, 2017).

1.2.5.3.4 ***Unit of measurement***

The main outcome in ISWT is the absolute distance walked in metres during the test. The distance walked measured during the ISWT is a product of increasing increments of speed during the test to assess fitness. This distance is calculated based on the total number of shuttles (each shuttle measures 10 metres) that patients completed during the test (distance = number of shuttles × 10).

Some studies have suggested distance values as important when predicting events or classifying patients into categories. For example, it has been reported that a distance of less than 450m during ISWT could be considered the threshold for predicting high risk for major cardiac events or referring patients with heart failure for heart transplantation (Morales, Montemayor and Martinez, 2000; Lewis et al., 2001; Grove, 2013). In terms of surgery, the ISWT was used to identify patients who are at increased peri-operative risk, Nutt & Russell (2012) found that patients who walk less than 250m prior to colorectal surgery were three times more likely to develop major complication after surgery. This distance is less than the 350m which is proposed for patients undergoing oesophageal surgery, while those who walked >400 m were considered at low risk for thoracic surgery (Murray et al., 2007; Lim et al., 2010).

Another outcome which can be used as a measurement for the test is the METs value. Each MET value corresponds to an ISWT level and is estimated using an equation recommended by the American College of Sports Medicine (ACSM), which is produced based on the linear regression between the Vo_2 peak obtained during the treadmill test and the walking speed derived from a small sample of healthy subjects (Buckley et al., 2016). MET values are used as one of the criteria for the risk stratification for cardiac patients. Achieving more than 7 METS indicates a low-risk patient while patients who achieve less than 5 METS are considered at moderate risk, or high risk based on whether other symptoms are present.(ACPICR, 2015; AACVRP, 2013)

However, cardiac patients have been reported to require more Vo_2 compared to healthy subjects (Woolf-May and Ferrett, 2008; Woolf-May and Meadows, 2013; Almodhy et al., 2014). In addition, Buckley et al (2016) found a positive curvilinear relationship between Vo_2 peak obtained during ISWT and walking speed(Buckley et al., 2016). They recruited 62 participants (32 cardiac rehabilitation patients and 30 non-cardiac participants) and found that the cardiac patients required up to 30% more oxygen compared to the healthy subjects while performing ISWT. The authors recommended using this equation: $4.4^{e\ 0.23\ \text{walking speed}}$ to estimate Vo_2 from ISWT for cardiac participants. They concluded that the ACSM equation underestimated Vo_2 and thus should not be used to estimate oxygen cost in cardiac population.

However, as the previous studies have used varying methodology to estimate METs, which has led to uncertainty about MET costs per level, this is one of the reasons this study will focus on distance walked as part of the ISWT. Distance walked is also what patients achieve and what clinicians actual record pre and post CR which is why this study has retained its focus on metres walked as the primary variable of interest.

Predicting the distance covered during the ISWT has been attempted in s only two studies using a CR population (Cardoso et al., 2016; Pepera et al., 2013). The Pepera et al study and the Cardoso et al study explained 20% and 25% of the variance in distance walked and the latter attempted to produce reference values for cardiac rehabilitation patients. Cardoso et al. found that age, height, BMI and presence of diabetes were significant predictors of the distance walked. The authors also attempted to produce a reference value for the baseline distance walked during the test. Height and BMI were the only significant predictors of the distance in the Pepera et al. study (these studies will be discussed in detail in chapter 5). However, the limited number of female participants and the small number of centres used limits the generalisability and clinical usefulness of these results. The need for robust reference values for the distance walked during the ISWT as a fitness measure, which take account of patient characteristics, remains important as they will help remove uncertainty around patient risk assessment prior to CR and future exercise prescription. These values could also help clinical decision making around the need for a second ISWT aid feedback to patients about their level of baseline fitness and help set rehabilitation goals

Chapter 2. Critical review of the studies identifying determinants of a change in fitness following a CR outpatient programme

2.1 Abstract

2.1.1 Aim

To critically review the studies which identified the determinants of a change in fitness in patients enrolled in CR outpatient programmes. Standardised appraisal tools were used to identify the limitations of the studies and thereby draw conclusions about the determinants of a change in fitness from the analysis.

2.1.2 Method

The literature search was performed using Medline, CINAHL plus (EBSCO), Cochrane Library (Wiley), EMBASE, AMED and web of science. Inclusion criteria for studies were (1) having adult patients (<18) who participated in a CR programme after a cardiac event (2) reporting determinants, predictors, factors or characteristics that influence the change in physical fitness expressed as Vo2 max or peak, METs, or distance walked (3) having measured physical fitness objectively using incremental tests before and at the end of CR using a treadmill, cycle ergometer, step test or incremental shuttle walk test as these tests are the ones commonly used in a CR population (4) having used multivariable analysis to clearly demonstrate the independent association between the potential determinant and the change in fitness and (5) having been written in English.

2.1.3 Results

Seventeen studies met the inclusion criteria. Thirteen were observational studies, two were randomised clinical trials and two were meta-analyses. The determinants were identified namely age, gender, BMI, waist circumference, baseline fitness levels, diabetes, depression, total of comorbidities, reason for referral, number of sessions, time from referral to start of

CR, self-reported physical function (36-sf), fasting glucose level, treadmill protocol, exercise intensity and handgrip strength.

2.1.4 Conclusion

There continues to be huge variation in the studies in terms of identifying the determinants of a change in fitness. In this review, there are some determinants which are highly likely to be determinants of a change in fitness namely diabetes, self-reported physical function (SF-36), handgrip strength and exercise intensity. Other variables such as baseline fitness levels, age, comorbidities, time from referral to start, and waist circumference were categorised as likely to be determinants**.** However, the ability to draw conclusions is hindered by significant inconsistencies in how studies were analysed with additional limitations in the studies with reference to sample size, population characteristics, potential confounders. Finally, the quality of study designs and reporting of study details in journal publications needs to improve so that critical and systematic reviews can be performed to the highest level.

2.2 Background

Exercise training is considered the cornerstone of cardiac rehabilitation (CR), which leads to an improvement in functional capacity (Valkeinen, Aaltonen and Kujala, 2010; Sandercock, Hurtado and Cardoso, 2013; Almodhy, Ingle and Sandercock, 2016). This is one of the main goals of CR. Therefore, assessing functional capacity is important at the pre- and post- CR programme stages as the change in fitness reflects the effectiveness of the exercise training intervention that the patient participated in (BACPR.2017), associated with an increase in independence and quality of life (Anderson et al., 2016). The extent of change in fitness is also considered a determinant of the cardio-vascular and all-cause mortality in healthy patients as well as those suffering with heart disease.(Taylor et al., 2016; Harber et al., 2017)

The gold-standard test for functional capacity is the graded cardiopulmonary exercise test (CPET) which allows for a direct measure of maximum oxygen consumption. However, this test requires the participant to achieve a high respiratory exchange ratio (> 1.1) which is ratio of carbon dioxide (CO_2) produced by metabolism and oxygen (O_2) used during the exercise test(ACSM's, 2010). This high level of exercise performance is best achieved through a maximal level of exertion, which brings a higher risk of adverse events in individuals with an intermediate to high risk of cardiovascular problems (ACSM's, 2010). Also such tests often are not available in a clinical setting due to time, cost restrictions and a lack of staff expertise (ACSM's, 2010). Therefore, submaximal exercise tests that can offer a valuable alternative are used (Sartor et al., 2013). These include treadmill, cycle ergometer, ISWT and the step test (Sartor et al., 2013; ACPICR, 2015). The outcome of these tests is expressed as Vo2 peak, estimated METs or the distance walked during the test.

Sandercock et al. (2013) conducted a meta-analysis across 31 international studies using a treadmill test and found that the change in fitness among CR patients was 1.5MET (e.g. this is equivalent to difference between walking briskly on level ground (3.3 METS) to dancing (4.8 METs) (Ainsworth et al., 2011)). This change was reported to be smaller (0.5MET) in UK studies (Sandercock, Cardoso and Almodhy, 2013). A meta-analysis conducted in the

UK using ISWT as the fitness assessment tool showed an improvement of 84m in the distance walk during the test. (Almodhy, Ingle and Sandercock, 2016). However 45% of the included studies had a small sample size less 50 participants.

Several studies have attempted to identify the determinants of this change in fitness in the CR population. Most studies measured the improvement in numerical values (post-CR programme minus pre-CR programme measurement) whereas a small number measured it as a percentage or classified the patients as improvers or non-improvers (Savage, Antkowiak and Ades, 2009). Although the change in fitness achieved in these studies has been measured and attempts have been made to identify the determinants of the change, to date there has been no comprehensive, critical review of the studies themselves.

2.2.1 Aim

The aim of this Chapter is to critically review these studies using standardised appraisal tools, identify the limitations of the studies and thereby draw a conclusion about the determinants of a change in fitness from the analysis.

2.3 Method

2.3.1 Critical review

The goal of a critical review is to show that the literature underpinning this thesis has been thoroughly researched and the quality of the literature has been critically examined and evaluated (Grant and Booth, 2009). A critical review does not follow a standard 'model' but it differs according to the subject and discipline (Jesson and Lacey, 2006). However, the focus of this type of review is a critical approach (Grant and Booth, 2009). There are different tools which can be used to assist in a critical appraisal.

2.3.2 Search strategy

The final literature search was performed for the period October week 3 2017 in Medline, CINAHL plus (EBSCO), Cochrane Library (Wiley), EMBASE (Ovid), AMED (Allied and Complementary Medicine) and web of science. Combinations of medical subject headings and keywords related to the following themes were used: cardiorespiratory fitness, exercise test, coronary artery disease, cardiac rehabilitation intervention, determinants or predictors of a change in fitness. The literature search was performed using the terms shown in the following table (Table 2.1) (Appendix 8.2.1).

Table 2-1 Search strategy

Searched term	**Description**
Search 1-fitness:	Fitness or Cardiorespiratory fitness or cardiopulmonary fitness or exercise capacity or functional capacity or aerobic capacity or aerobic fitness or functional fitness or Physical Endurance or cardiovascular fitness or Functional Training
Search 2-test outcomes:	Vo_2 or peak oxygen uptake or maximal oxygen uptake or oxygen consumption or Metabolic equivalent or MET* or Distance.
Search 3-types of test:	Treadmill or cycle ergometer or incremental shuttle walk test or step test.
Search 4- coronary artery disease:	Coronary artery disease or CAD or Coronary heart disease or CHD or coronary disease or heart disease or ischaemic heart disease or myocardial infarction or MI or myocardial ischemia or angina pectoris or coronary artery bypass graft or CABG or Percutaneous Coronary Intervention or PCI or percutaneous transluminal coronary angioplasty or PTCA or myocardial revascularization.

Search 5- rehabilitation:	Cardiac rehabilitation or cardiovascular rehabilitation or secondary prevention. Search 6-words: determin*or predict* or improve* or chang* or factor* or influence*
Search 6-words:	Determin*or predict* or improve* or chang* or factor* or influence*

2.3.3 Inclusion and exclusion criteria

To be included in the review, studies had to (1) include adult patients (<18 years) who participated in a CR programme after a cardiac event (2) report determinants, predictors, factors or characteristics that influence the change in physical fitness expressed as Vo2 max or peak, METs, or distance walked after a CR-exercise based programme to enable outcomes to be standardised across studies as these are the three most commonly used in clinical practice (3) have measured physical fitness objectively using incremental tests before and at the end of CR using a treadmill, cycle ergometer, step test or incremental shuttle walk test as these tests are the ones commonly used in a CR population (4) have used multivariable analysis to clearly demonstrate the independent association between the potential determinant and the change in fitness and (5) be written in English as no interpreting facilities were available. Studies related to heart failure patients were excluded as they tend to undergo non-incremental tests focusing on endurance such as the 6MWT which is routinely used in heart failure (NACR 2017).

2.3.4 Data extraction

From the seventeen studies which met the inclusion criteria of this review, data items including the study authors, the type of study, the sample size, the population, the mean age, the assessment tool used, the form of outcome reported, the change in fitness value, the independent variables used in the multivariable analysis and the significant determinants were extracted. Data extraction was undertaken by thesis author and checked for quality and accuracy by the second author (AA) where disagreement existed this was adjudicated by thesis supervisor (PD).

2.3.5 Quality assessment

Due to the designs of the included studies, three different types of quality assessment tool were used in this review. The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies developed by the National Heart and Lung Institute (NHLBI) and the Research Triangle Institute International was used for assessing the observational studies (National Heart and Lung Institute (NHLBI) and the Research Triangle Institute International). This tool is a standardised critical appraisal tool which was designed using existing quality assessment concepts and methods based on other tools which had been developed by researchers in the Cochrane Collaboration, the Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Centers, the National Health Service Centre for Reviews and Dissemination and the Scottish Intercollegiate Guidelines Network.

The aim of this tool is to assist the reviewer to focus on the important concepts which are necessary for a critical appraisal of a study's validity. The tools do not provide a numerical value for a list of factors. This is in accordance with the recommendations of the Cochrane Bias Methods Group and Statistical Methods Group, which state that quality tools or scales that utilise summary scores should be avoided (Higgins et al., 2011). The tools incorporate items which are designed to evaluate potential flaws in the method and implementation of the study. For each item, reviewers select 'Yes', 'No' or "Cannot determine/not reported/not applicable". Where 'No' or 'Cannot determine/not reported/not applicable' is selected, a potential flaw or risk of bias could be considered by the reviewer.

This tool consists of 14 questions that were applied to each study to assess factors such as study design, source of bias, confounding, study power and the strength of causality in the relation between interventions and outcomes. Each study was then rated Good, Fair or Poor where a 'good' study is considered to have the least risk of bias, 'fair' is susceptible to some bias and ‘poor’ indicates a risk of bias**.** For the randomised control studies, the Cochrane risk of bias tool was used to assess the quality(Higgins et al., 2011). The PRISMA tool was used to assess the meta-analysis studies.

2.4 Results

The database search identified 1783 articles from an initial search. After checking the titles, 176 were found to be potentially relevant. Eighteen duplicates were removed using the software reference manager (Mendeley). The abstracts of the remaining 158 articles were checked leaving 67 articles on which a full text screening was conducted. A manual search identified 11 potential relevant studies; however, none of these 11 studies met the inclusion criteria (see appendix 8.2.2 for excluded studies). The total number of eligible studies which met the inclusion criteria was 17 (Figure 2.1). Thirteen were observational studies, two were randomised clinical trials and two were meta-analyses. These studies were published between1995-2016 and were conducted in the USA (8 studies), the UK (4), France (2), Italy (1), Portugal (1) and South Korea (1).

The 17 studies comprised 42780 adult patients, who attended an outpatient CR programme. The sample size in these studies ranged from 46 to 32899 patients and the length of the CR programmes varied from four weeks to six months. The change in fitness measured in METs ranged from 0.41 to 2.9 METs (1MET=3.5 ml/kg.min-1), in Vo_2 peak from 1.2 to 6.4 ml/kg.min-1, and in the studies which used the distance walked in the ISWT, the range was 84m to 120 m. Table 2-2 below shows the studies characteristics.

One randomised study was conducted in female patients to compare the effect of a tailored female-only exercise programme compared to a more traditional mixed-gender group. Another randomised study was conducted in patients with type 2 diabetes and compared an insulin-intensive treatment programme to a control group which maintained their pre-enrolment anti-diabetic treatment.

Only ten out of the 17 studies aimed to investigate the determinants of the change in fitness in their population while the remaining studies focussed on the association between specific factors and the change in fitness. For example, Fell et al. (2016) assessed the effect of CR timing; Gee et al. (2014) and Lavie &Milani. (1995) examined the effect of gender on this change; Glazer et al. (2002) studied the effect of specific psychological factors; Verges et al. (2004) studied the effect of diabetes; Lim et al (2016) examined the effect of BMI; and Lavie et al. (2000) investigated age and baseline fitness.

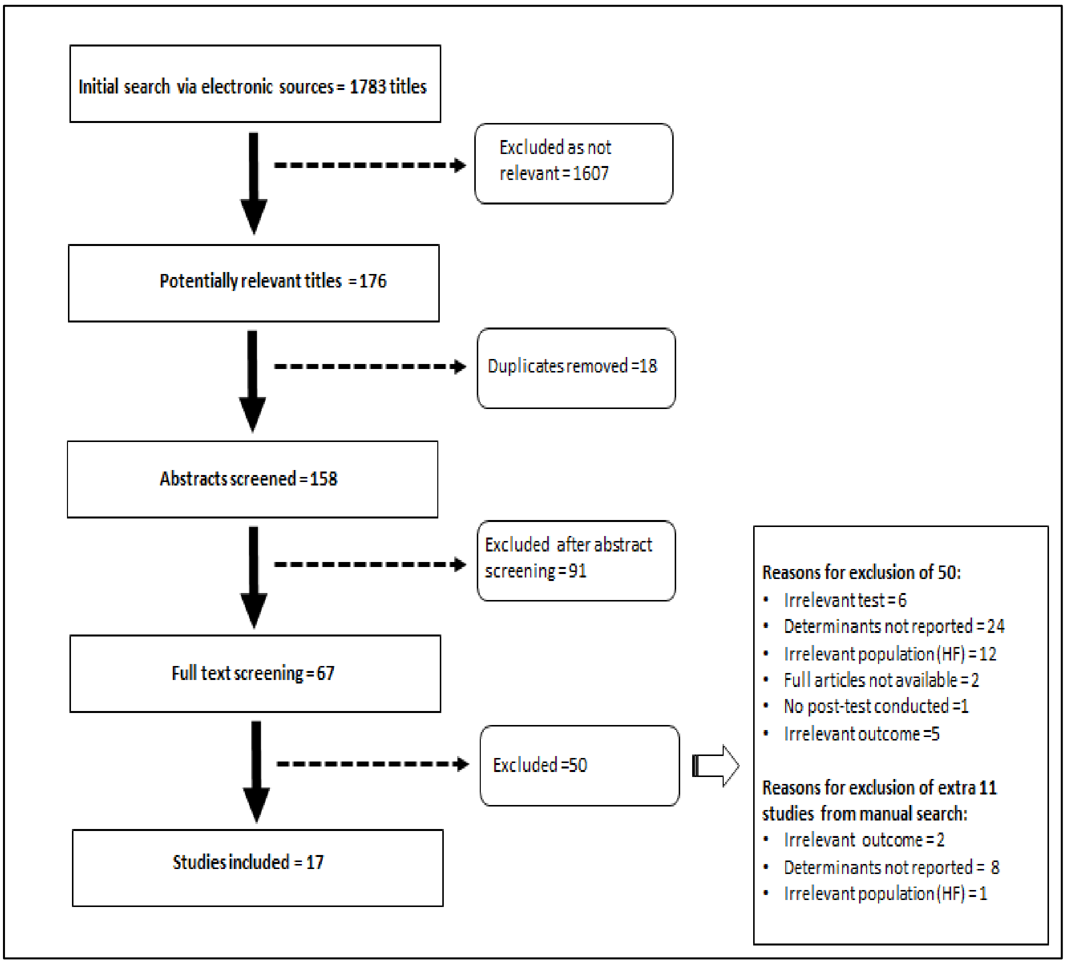

Figure 2.1 Search results and selection of studies included

Table 2-2 Studies characteristics

Author/study design/country	No. of patients	Population/ CR programme	Age (years)	Measure-ment tool	Outcome/ Change	Multivariable analyses result	
						Determinants	**Not significant/ Adjusted for but results not reported**
Fell et al. 2016, Retrospective, UK	n= 32,899 Male (77%) Early CR (n=12254) Late CR (n=20645)	Outpatients CR 8 weeks	Mean, 64.91±10.73 For early CR 63.86±10.76 For late CR 65.54±10.67	ISWT	Distance walk / Early CR Median (120m) For late CR, Median (90m)	CR-timing	**Adjusted for**: Age, gender, no. of comorbidities, Duration of CR (days), BMI, BP, smoking, ethnicity, treatmen type, physical activity level.
Baldasseroni et al. 2016, Prospective, Italy	n= 160 Male (n =113) Female (n= 47)	Outpatients CR ≥75 year. 5 times/week For 4 weeks	81±4	Cycle ergometer	Vo_2 peak/ 1.2 mL/kg/min (10.9%)	Baseline Vo_2	**Not significant**: Age, gender
Branco et al. 2015 Retrospective, Portugal	n=1399 (1125 complete) Male (n=886) Female (n=239)	Outpatients CR. 2 times/week lasting 8–12 weeks	61±11	Treadmill	Estimated METs/ 1.45±1.19 METs	Age Diabetes Reason for referral	**Not significant**: Gender, dyslipidemia, smoking, BMI, physical activity level.

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Author/study design/country	No. of patients	Population/ CR programme	Age (years)	Measure-ment tool	Outcome/ Change	Multivariable analyses result	
						Determinants	Not significant/ Adjusted for but results not reported
Lim et al. 2016 Retrospective, Korea	n=359 Koreans	Outpatients CR: AMI 6 weeks.	Obese 54.32±9.98 non-obese 59.12± 11.50	Treadmill	(METs) Obese (0.59METs) Non-obese (0.41METs)	None	**Adjusted for**: age Not significant: BMI (BMI ≥ 25 kg/m^2 Vs < $25kg/m^2$)
Beckie et al. 2013 RCT, USA	n=236 Tailored-programme (n=137) Traditional (n=99)	Female CR-outpatients 3 times/week for 12-weeks	63±12 Tailored-programme (64±11) Traditional (63±11)	Treadmill	Estimated METs/ traditional 1.5 METs Tailored 1.6 METs	Age Physical function score Baseline MET Waist Circumference	**Not significant**: Social-functioning, fasting glucose, Charlston Comorbidity Index (CMI), BMI, smoking, No. of sessions, LVEF
McKee. 2008 Prospective, UK	n= 119 Males (n=81) Females (n=38)	CR outpatients 6- or 8-week period	60.71± 8.94	Treadmill	Estimated METs/ 1.4 METs	Gender, Baseline fitness level	**Not significant:** Age, BMI.

Author/study design/country	No. of patients	Population/ CR programme	Age (years)	Measure-ment tool	Outcome/ Change	Multivariable analyses result	
						Determinants	**Not significant/ Adjusted for but results not reported**
Verges et al. 2015 RCT, France	n= 57 Control group (n= 31) Intensive group (n = 26)	Type 2 CR-diabetic patients	Control group 58±10 years Intensive treatment 60±10 years	Cycle ergometer	VO2 peak / Control group 3.1ml/kg/min Intensive-treatment 2.7ml/kg/min	Final fructosamine value	**Not significant**: Age, gender, baseline Fructosamine, diabetes duration, BMI, baseline fitness, type of ACS, treatment groups
Balady et al. 1996 Prospective, USA	n=778 (470 complete) Male (n=344) Female (n=126)	3 times/week For 10±2 weeks	Age group: <65, 65-75, <75years	-Treadmill -Cycle ergometer	Estimated METs (2.9 METs)	Baseline fitness level	**Not significant:** Age, gender, entry diagnosis
Pierson et al. 2014 Retrospective, USA	60 patients	3 times/week for 5-9 months	56.3±9.4	Treadmill	Estimated METs (2.1±1.7 METs)	Baseline fitness level	**Not significant:** Age, BMI, Anterior MI, recent MI, recent revascularisation, recent angina, Beta blocker medication, exercise-induced Ischemia

Author/study design/country	No. of patients	Population/ CR programme	Age (years)	Measure-ment tool	Outcome/ Change	Multivariable analyses result	
						Determinants	Not significant/ Adjusted for but results not reported
Svage et al. 2009 Retrospective USA	n=385 Male (n=308) Female (n=77)	Outpatient CR 3 times/week over 3 months (36 sessions)	Male (65±10) Female (67±77)	Treadmill	% peak $\dot{V}o_2$ 2.9 mL/kg/min Treadmill time	Exercise intensity (% peak VO2) Diabetes Baseline fitness Comorbidity score Physical function score Handgrip strength	**Not significant**: Age, gender, days between the index cardiac event and entry stress test, weight, change in weight, BMI[1], waist circumference, resistance training, (RER)[2], depression
Gee et al. 2014 Retrospective, USA	N= 781 Male (n= 554) Female (n= 227)	3times/week for 3 months (36 sessions)	Male 65.2 Female 66.4	Treadmill	Estimated METs/ Male (2.12) Female (1.66)	Gender	**Adjusted for:** Age, BMI, CR Indication

[1] Body mass index
[2] Respiratory exchange ratio
[3] Left ventricular ejection fraction

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Author/study design/country	No. of patients	Population/ CR programme	Age (years)	Measure-ment tool	Outcome/ Change	Multivariable analyses result	
						Determinants	**Not significant/ Adjusted for but results not reported**
Verges et al. 2004 Prospective, France	95 patients Diabetic: 59 Non-diabetic 36	CR 3 sessions/ week for 2 months	Diabetic 57.4 ± 8.8 Non-diabetic 56.7 ± 11.3	Cycle ergometer	peak Vo_2 (ml/kg/min) diabetic 2.40 (13%) Non-diabetic 6.4 (30%) Duration of the exercise test	In whole sample Diabetics In diabetic group Fasting blood glucose level BMI	***In whole sample*** Adjusted for BMI ***In diabetic group*** **Not significant:** -Age, duration of diabetes, BMI, presence or absence of microalbuminuria, LVEF[3], treatment with insulin
Glazeret et al. 2002, Prospective, USA	n=46 Male (n=34) Female (n=12)	Outpatient-CR 12 weeks 36 sessions	58±10	Treadmill	peak Vo_2 $ml/kg.m^{-1}$ 2 (10%)	Depression (Beck Depression inventory)	**Not significant:** Age, gender, optimism, neuroticism, no. of sessions, %LVEF

Author/study design/country	**No. of patients**	**Population/ CR programme**	**Age (years)**	**Measure-ment tool**	**Outcome/ Change**	**Multivariable analyses result**	
						Determinants	**Not significant/ Adjusted for but results not reported**
Lavie & Milani 2000, Retrospective, USA	182 patients Young group <55 (n=125) Elderly >70 (n=57)	3times/week for 12 weeks (36 sessions)	Young group <55 (mean 48±6) Elderly >70 (mean 78±)	Treadmill Cycle ergometer	peak Vo_2 ml/kg/m Elderly 1.9 (13%) Young 3.2(+18%)	Age	**Not significant:** -Weight, %fat. BMI, baseline Vo_2, quality of life (36_sf)
Lavie & Milani 1995 Retrospective, USA	n=458 Male (n=375) Female (n=83)	3times/week for 12 weeks (36 sessions)	Male 63±10 Female 61±10	Treadmill Cycle ergometer	METs Male 2.7METs (40%) Female 2METs (33%)	None	**Not significant**: Gender. Independent variables: Age, BMI, baseline METs, %fat, lipids
Almodhy et al. 2016 Meta-analysis, UK	n=1578	Outpatients CR	aged ≥18	ISWT	Distance walked/ 84 m	No. of sessions (≤12/>12)	**Not significant:** Age, Programme duration, programme type, primary diagnosis (MI Vs CABG and mix)

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Author/study design/country	No. of patients	Population/ CR programme	Age (years)	Measure-ment tool	Outcome/ Change	Multivariable analyses result	
						Determinants	**Not significant/ Adjusted for but results not reported**
Sandercock et al. 2013, Meta-analysis, UK	n=3827	Outpatients CR	aged ≥18	Treadmill	Estimated METs/ 1.55 METs	Age Gender Exercise modality Treadmill protocols	**Not significant**: CR type, study design, baseline fitness levels, no. of sessions, primary diagnosis (MI vs revascularisation and mix)

2.4.1 Quality Assessment

The quality assessment of the 13 observational studies included in this review are summarised in Table 2.3 according to the fourteen criteria in this tool. Overall, 6 studies were rated as 'fair',5 as poor (Low) and only two studies were rated as 'good'. In all studies the research objectives were clearly stated. Twelve studies defined the populations clearly while one did not explain the population in terms of gender (Pierson et al. 2004). In all studies, the participation rate was over 50%, and participants were recruited from the same population over the same period of time. Although the sample size was reported, none of the studies met the fifth criterion relating to justifying the sample size. Exposures of interest (independent variables) were reported to have been measured in all studies before the outcomes were assessed. The timeframe relating to these two measurements was reported to be sufficient. All studies reported the assessment of the exposures in multiple categories or as a continuum where appropriate. Nine studies clearly defined the exposures in a reliable and valid way and implemented the exposure measures across all participants. Of the four remaining studies, one study divided patients into three age groups: < 65, 65-75, and >75, however, the last group contained only 6 female patients (Balady et al., 1996); in the second study, the measurement of BMI was available in only 78 patients out of the total of 119 (McKee, 2008). The independent variables were not clearly reported in two studies (Lavie and Milani, 1995b, 2000). Two studies reported that the exposures were assessed more than once. However, this did not affect the quality of the studies that did not meet this criterion as the aim of these studies was to determine the change in fitness based on the baseline characteristics. Ten studies reported a clear, defined, valid way of outcome measurement which was implemented across all the participants while the other three studies did not. Balady et al. (1996) only used the same tool and test protocol for pre- and post-assessment in 49% (230) of the whole sample of participants (470) who completed the CR programme. This alteration in test protocol might have influenced the outcome results. In the study conducted by Pierson et al (2004), the determinants of change in fitness were mentioned without providing any statistical results. The outcome measurement protocol in the Branco et al study (2015) was also not reported clearly and the details given were not sufficient to replicate the test. None of these observational studies reported whether the outcome assessors were blinded to the exposure status of the participants. Only the Balady et al. study (1996) reported a loss of 20% or more of participants (40%) before the completion of the study. In terms of confounders, those used across the studies differed both in number and type. Using a more comprehensive list of confounders was one of the main characteristics of studies which were rated as “good”. Ten studies met the final criterion regarding measuring the impact of key potential confounders. However, although these studies reported some of the key confounders, the number of confounders was varied. This might have had an influence on the result.

Figure 2.2 shows the assessment of the randomised control trials using the Cochrane risk of bias tool. Based on this tool the Beckie et al 2013 and Vegres et al 2015 were rated as fair and lower quality respectively. The two meta-analyses (Sandercock, Hurtado, et al. 2013; Almodhy et al. 2016) using the PRISMA tool (Appendix.8.2.3). These studies were ranked as fair studies as number of groups which were used during the meta-regression analysis was considered small (less than 10 in each group) which limited their result.

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Table 2-3 Quality assessment for observational studies

	Fell et al.2016	Baldasseroni et al . 2016	Lim et al. 2016	Branco et al. 2015	Gee et al. 2014	McKee, 2008	Savage et al. 2009	Pierson et al. 2004)	Verges et al. 2004	Glazeret al. 2002	Lavie et al. 2000	Balady et al. 1996	Lavie et al. 1995
1. Was the research question or objective in this paper clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Was the study population clearly specified and defined?	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
3. Was the participation rate of eligible persons at least 50%?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5. Was a sample size justification, power description, or variance and effect estimates provided?	N	N	N	N	N	N	N	N	N	N	N	N	N
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7.Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8. For exposures that can vary in amount or level, did the study	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

	Fell et al.2016	Baldasseroni et al . 2016	Lim et al. 2016	Branco et al. 2015	Gee et al. 2014	McKee, 2008	Savage et al. 2009	Pierson et al. 2004)	Verges et al. 2004	Glazeret al. 2002	Lavie et al. 2000	Balady et al. 1996	Lavie et al. 1995
examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?													
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	N
10. Was the exposure(s) assessed more than once over time?	N	N	N	N	N	N	Y	N	N	Y	N	N	Y
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	N	Y
12. Were the outcome assessors blinded to the exposure status of participants?	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
113. Was loss to follow-up after baseline 20% or less	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y

+	Low risk of bias		
−	Risk of bias		
?	Unclear		
Domain	Sub-domain	Beckie et al (2013)	Verges et al (2015)
Selection bias	Random sequence generation	+	?
	Allocation concealment	+	?
Reporting bias	Selective reporting	+	+
Other bias	Other sources of bias	−	+
Performance bias	Blinding (participants & personnel)	−	?
Detection bias	Blinding (outcome assessment)	+	?
Attrition bias	Incomplete outcome data	+	?

Figure 2.2 Cochrane risk of bias table for the two RCT studies.

2.4.2 Outcome:

The change in fitness in the included studies was expressed in three different forms using three different assessment tools. Three studies used both a treadmill and cycle ergometer while nine of the studies utilised only a treadmill tool, three used only a cycle ergometer and two used an ISWT as the physical fitness assessment. In terms of outcomes, seven studies reported in METs, six reported in Vo2 peak (ml/kg/min) of them the three studies that using the cycle ergometer only. The third measure of a change in fitness reported in this critical review was the distance walked during the ISWT reported in two studies (Table 2.1). The studies which used a treadmill estimated METs from the final speed and grade. Some studies used more than one treadmill protocol (Lavie and Milani, 1995b; Balady et al., 1996; Lavie and Milani, 2000; Savage, Antkowiak and Ades, 2009; Sandercock, Hurtado and

Cardoso, 2013; Gee et al., 2014) while others used only one specific protocol (Glazer et al., 2002; Pierson, Miller and Herbert, 2004; McKee, 2008; Beckie et al., 2013; Lim, Han and Choe, 2016). However, in the Branco et al. (2015) study, the protocol was not specified.

Three studies categorised their patients as improvers or non-improvers according to their outcome measurement. Baldasseroni et al. (2016) predefined a 15% increase in fitness as a clinically meaningful improvement and used this as a basis to classify their patients as having improved or not. Savage et al. (2009) classified his patients based on the mathematical difference between their pre- and post-programme peak Vo_2 where a difference >0 was considered an improvement, while in a third study, Fell et al. (2016) categorised the outcome based on the participants achieving the minimum clinically important difference (MCID) of 70m during the ISWT.

2.4.3 Determinants

There were 39 independent variables which were used in the analyses of the 17 included studies. About 70% (26) of these variables were reported in only ≤ 2 of the studies (Figure 2.3) of these 39 variables 17 were reported to be significant determinants of the change in fitness in CR population. However, none of them were reported to be a significant determinant in all studies (Figure 2.4).

Age was reported in all studies in this review. Of the 17 studies, age was shown to be a significant determinant in four (24%). However, the results were varied with three studies reporting that the younger groups improved more while in the remaining study, the association between age and the change in fitness level was positive, as the age increased the change in fitness increased. Seven studies out of the 17 found that age was not a significant determinant. Furthermore, six studies adjusted for age in the analysis but did not report their results.

Twelve studies reported gender as a potential confounder. Of these, three studies found that gender was a significant determinant of the change in fitness with males tending to show a larger improvement in fitness than females. However, gender was shown not to be a significant predictor in six of the studies. The other three studies, despite using gender in the analysis, did not report its results.

Baseline fitness level was reported in 10 studies out of the 17 studies included in this review. Regardless of the way the value of the change in fitness was expressed, the results of the multi-variable adjustment analyses used in the included studies showed the baseline fitness level was the most common significant determinant as it was reported in 6 studies. In these studies, patients with a low baseline fitness level generally showing more improvement in their fitness, with the exception of the Beckie et al. study where the association between the baseline fitness level, reported as a continuous value, and the association with change in fitness was positive. The further three studies showed that baseline fitness level was not a significant determinant. The remaining study was adjusted for fitness level without the results being reported.

Out of the 17 included studies, diabetes was reported in three. All three studies reported diabetes as a significant determinant of a change in fitness with diabetic patients showing a lower level of improvement compared to non-diabetics. Another potential factor which was reported was self-reported physical function using a short form 36-survey questionnaire (36-SF). The association between this and the change in fitness was investigated in three studies. Two of these studies reported that self-reported physical function was a significant determinant of the change in fitness while the other study showed no such association.

Only one study in a diabetic CR population found that BMI was a significant determinant of a change in fitness whereas seven of the studies did not. Five studies adjusted for BMI as a potential confounder but did not report its result.

The reason for patients being referred to CR was reported in 9 studies out of the 17 included studies. Only one study showed that the reason for referral was a significant determinant in the change in fitness with patients who were referred post-CABG showing more improvement compared to other referral groups. Six studies reported that the reason for referral was not a determinant while two studies adjusted for it in the analysis without reporting the result.

Depression, waist circumference, CR-timing (time from referral to start of CR) and fasting glucose level were reported in two studies as independent variables. In each case, the variable was shown to be a significant determinant in only one of the two studies. Total of comorbidities was reported in three studies with two of them using Comorbidity scores. In one study this score was a significant determinant in the change of fitness but not in the other. In the third study, the total number of comorbidities was adjusted without reporting its results. The total number of sessions which patients attended was found to be significant determinant in one meta-analysis study and not significant in three other studies.

Other variables namely handgrip strength, exercise intensity as well as exercise modality were found to be significant determinants in only one study. Treadmill protocol was found to be a significant determinant in a meta-analysis study. The final fructosamine value (which estimates the mean glycaemic level over the 2–3 previous weeks and reflects glycaemic control) was reported to be the only determinant of this change in a study conducted in only diabetic CR population.

Some potential confounders such as dyslipidemia, smoking, physical activity level, left ventricular ejection fraction (%) and Beta blocker medication and zip code prosperity were taken into account while conducting the multivariate analyses in some of the included studies, however, they were found not to be significant. Further variables were reported in only one study and were found not to be significant determinants. These were systolic and diastolic blood pressure, exercise-induced ischemia, respiratory exchange ratio, presence of Anterior MI, 0.1mV.ST depression, zip code prosperity, exercise resistance, optimism and neuroticism.

Programme duration, programme type (comprehensive vs exercise only) and study design (trial vs observational) were reported only in meta-analysis studies, however, they were not significant determinants of the change in fitness.

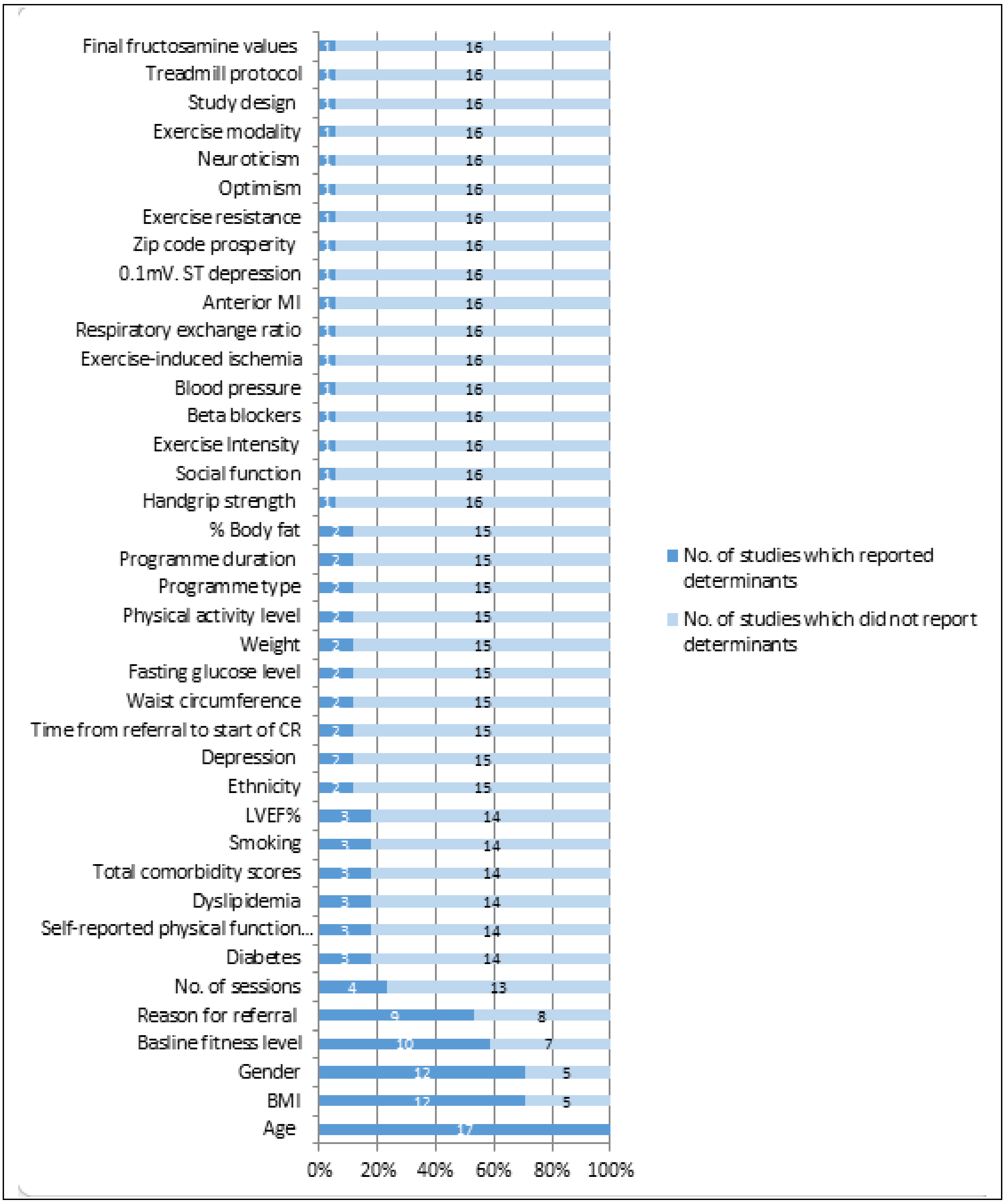

Figure 2.3The number of studies which reported individual determinants

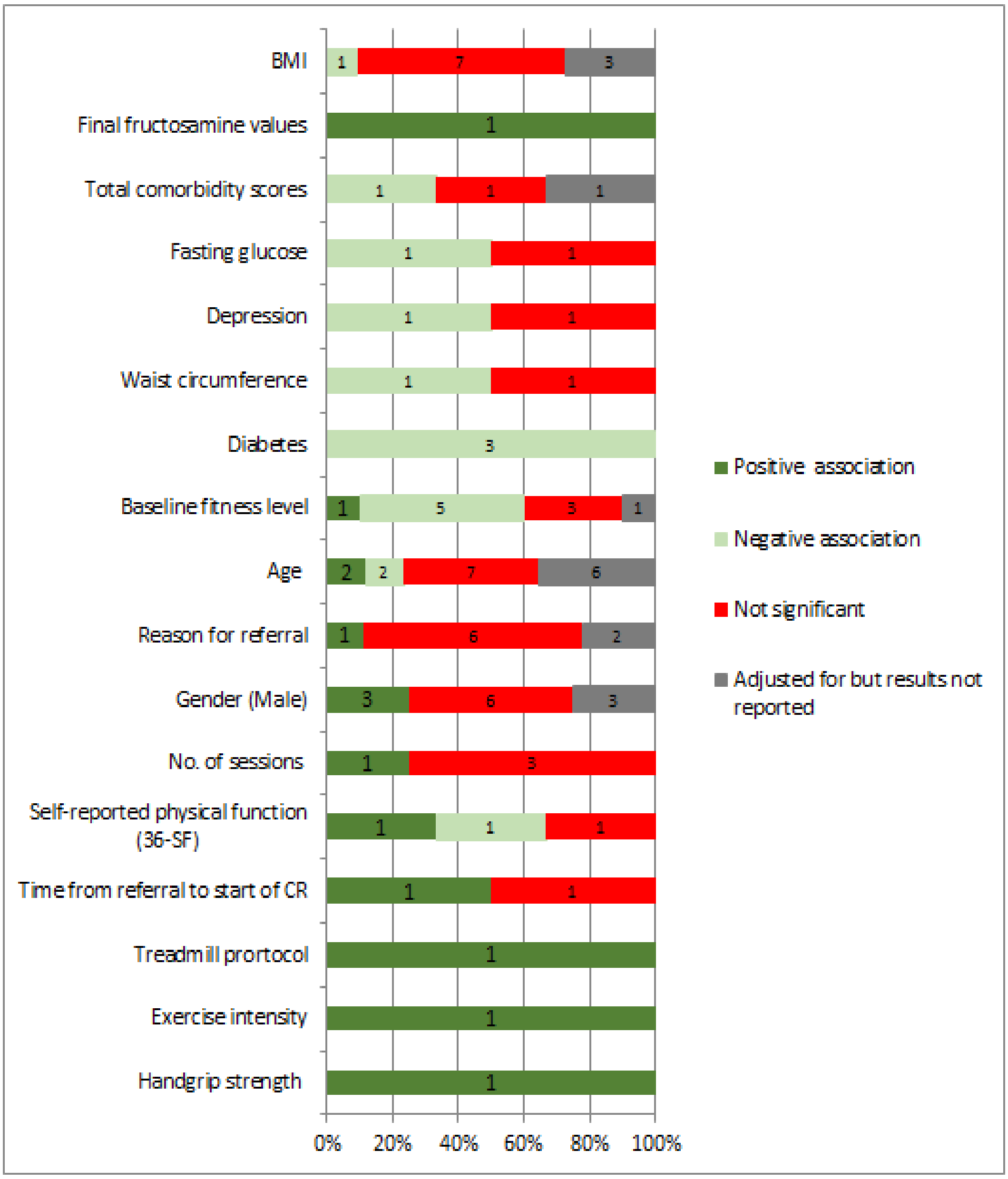

Figure 2.4 Direction and percentage of association across significant determinants

2.5 Discussion

The aim of this study was to critically review the studies which set out to investigate the determinants of the change in fitness in the CR population, after completing their CR programmes, using incremental fitness tests. This review showed that there was a lack of consistency in reporting the determinants across the included studies. The results of some studies showed the variable as a significant determinant while the others reported that it was not. Even among those studies which reported the variable as a significant determinant, the direction of the association was not consistent. Explanations for this inconsistency may be due to a variation in sample size, which may influence the statistical significance of the result. A further explanation could be the sample characteristics where some studies were restricted to a specific population, for example Beckie et al. (2015) studied only female patients, Verges et al. (2015) used diabetic patients and Baldasseroni et al. (2016) conducted the study in the elderly. The statistical analysis used could be another reason for inconsistency as the studies employed a different number of potential confounders (Miles and Shevlin, 2003; Palmer and Connell, 2009).

In this review, with regard to quality assessment, the majority of studies (9) were rated as 'fair'(Lavie and Milani, 2000; Vergès et al., 2004; McKee, 2008; Beckie et al., 2013; Sandercock, Hurtado and Cardoso, 2013; Gee et al., 2014; Branco et al., 2015; Almodhy, Ingle and Sandercock, 2016; Baldasseroni et al., 2016), and 5 as 'low' (Lavie and Milani, 1995b; Balady et al., 1996; Glazer et al., 2002; Vergès et al., 2015; Lim, Han and Choe, 2016), while only two studies were rated as 'good'(Savage, Antkowiak and Ades, 2009; Fell, Dale and Doherty, 2016). Savage et al. (2009) conducted a study on 385 consecutive CR patients (20% female) to identify the characteristics of patients who showed no improvement in their fitness after their CR programme and to describe the determinants of the change in fitness. This change was expressed as Vo_2 max (ml/kg/min), which was directly measured during the treadmill test. Participants performed the treadmill test using one of the following protocols: modified Balke, Naughton or Bruce. At the post-CR assessment, patients undertook the test using the same protocol that was used at the initial assessment. A difference of ≤ 0 in the change of the Vo_2 value between pre- and post-assessment was defined as a non-improvement. The result showed an overall improvement in fitness of 16% (2.9ml/kg/min). Despite this, 21% of patients were classified as non-improvers. A stepwise multivariable analysis using age, gender, weight, BMI, the baseline value of Vo_2, total comorbidity score, self-reported physical function (36-SF), depression, handgrip strength, exercise intensity (% peak Vo_2 and HR) and the time from the cardiac event to the baseline assessment as independent variables and the percentage of the change in Vo_2 as an independent variable was conducted. The analysis showed that baseline values of Vo_2, the presence of diabetes, the total comorbidity score, the self-reported physical function and exercise intensity (% peak Vo2) were significant determinants of the change in the percentage of fitness (Vo_2). Baseline fitness, total comorbidity score, self-reported physical function scores and presence of diabetes were negatively associated with the change in the percentage of Vo_2 peak while exercise intensity (% peak Vo2) and handgrip strength were positively correlated. Although Savage et al. (2009) included a sufficient number of confounders, the study used a comorbidity score which is not commonly used therefore its reliability and validity has not been proved. Classifying the participants as improved or non-improved was based on the mathematical calculation of post peakVO2 – pre peakVO2. This might result in an underestimate of the proportion of patients who were non-improvers.

Fell et al. (2016) retrospectively analysed data relating to 32,899 (77% male) CR patients using NACR data from 2012 to 2015. The aim was to investigate the association between CR timing and patient outcomes in terms of physical fitness expressed as the change in the distance walked during the ISWT. CR timing was classified as early (0-28 days for MI and PCI patients or 0-42 days for CABG patients) or late (≥ 29 days for MI and PCI patients or ≥ 43 days for CABG patients). the median improvement in distance walked during ISWT was 120 m for those patients in the early CR group and 90m for patients in the late CR group. Logistic regression was performed using CR timing as the main independent variable and adjusted for age, gender, BMI, smoking status, number of comorbidities, systolic and diastolic blood pressure (mm Hg), ethnicity, type of treatment and baseline physical activity level. The 70m MCID in the ISWT was the outcome. The authors concluded that CR timing was a significant determinant of the change in fitness (Fell, Dale and Doherty, 2016). Although this study had a large sample size and the method used was conducted well using a robust approach to take account of the nature of the nested data and including a sufficient number of potential confounders, the study has some limitations. One of the inclusion criteria was that patients had completed their CR. However, completing CR was defined as a programme duration of in excess of seven days. The authors did not take into account potential variables such as psychological factors.

2.5.1 Quality of assessment:

As one of the aims of the included studies was to identify the determinants and demonstrate the independent association between them and the outcome, multivariable models were used in the included studies. However, from a statistical point of view, it is recommended that there should be at least ten participants for each independent variable used in this type of analysis (Miles and Shevlin, 2003; Palmer and Connell, 2009). This recommendation was not adhered to in five studies (29%) (Balady et al., 1996; Glazer et al., 2002; Pierson, Miller and Herbert, 2004; Vergès et al., 2004, 2015), which means the results of these studies should be interpreted cautiously.

The number of independent variables that should be used is considered a key indication of the quality of the method of a study. Taking account of the potential confounders is important in regression analysis, making the study results more valid, and therefore the number of independent variables has been highlighted to indicate the quality of the included studies. Of the 17 significant variables that were reported in the included studies, 16 variables were chosen to be used as references and represented 100% of the total number of potential confounders in this review (age, gender, BMI, waist circumference, baseline fitness levels, diabetes, depression, total of comorbidities, reason for referral, number of sessions, time from referral to start of CR, self-reported physical function (36-sf), Fasting glucose, treadmill protocol, Exercise intensity and handgrip strength). The remaining significant variable, which was the final fructosamine value, was excluded as it is a specific measurement used for diabetic patients only**.** Therefore, based on how many of these variables were reported in each study, the quality of the studies in terms of reporting the potential confounders, was categorised as ‘low’ if they reported less than 32% of the determinants (≤5 variables), 'fair' if they reported from 33-66%, and 'high' if they reported more than 67% of the determinants(≥11variables).

It appears that in several of the included studies, there might be the potential for selection bias as the patients in these studies were referred to, participated in and completed a CR programme.

2.5.2 Determinants

2.5.2.1 Baseline fitness level

The most common significant determinant was the baseline level of patient fitness as reported in six studies regardless of whether it was reported as a continuous value (Pierson, Miller and Herbert, 2004; McKee, 2008; Savage, Antkowiak and Ades, 2009; Beckie et al., 2013; Baldasseroni et al., 2016), or categorised into two groups (< 5 METs and >5 METs) as in the Balady et al (1996) study. In five of these six studies, the baseline fitness level was inversely correlated with the change in fitness (figure 2.4), with patients who had a low level of fitness at baseline assessment showed more gain in fitness at the end of their CR programme. In other words, the least fit improved the most. Balady et al. (1996) assessed the baseline fitness and the change in fitness in a cohort of CR patients using the Massachusetts Association of Cardiovascular and Pulmonary Rehabilitation Multicenter Database. One of the aims of the study was to assess the patient factors that correlate with a change in fitness. The 778 patients in the study were enrolled in the CR programme and, of them, 470 (126 females) completed the programme of 10+2 weeks. Exercise capacity was assessed using a cycle ergometer or treadmill. Different protocols were used for the treadmill test. Patients were stratified according to their age and gender and were grouped into <65 years, 65-75 years, and >75 years. The exercise capacity of those patients who completed the programme improved significantly by an average of 2.4 METs (7.9+3 to 10+3 METs). The multivariable analysis, using age, gender, baseline fitness level (<5METs vs ≥5METs) and entry diagnosis (MI, CABG, Angina, PTCA, and others) as independent variables and change in fitness as a dependent variable, showed that baseline fitness level is a significant determinant, with patients with a low level of baseline fitness (<5 METs) having the greatest improvement, while age, gender and entry diagnostic were not significant determinants. However, only 243 patients out of the 470 who completed the CR programme had used the same tool and test protocol for pre- and post-assessment. This alteration in test protocol might have influenced the study results. In addition, a further limitation was the sample of patients in the elderly group (<75) which was small as there were only 6 female participants, and in terms of entry diagnostics, there were only 4 PTCA patients, 5 CABG patients and 4 patients who had other diagnoses. This small number of participants in the higher age group might make the results of the multiple regression analysis questionable as the recommendation for independent variables in a multiple regression is that there should be at least 10 patients for each variable (Miles and Shevlin, 2003). Baldasseroni et al (2016) conducted a study in 160 elderly CR patients (≥75 years), of whom 70% were male, in order to investigate the predictors of a clinically meaningful improvement (pre-defined by the authors as an improvement of 15%) in their functional capacity using a cycle ergometer. They found that the baseline Vo_2 peak was the only predictor of change in Vo_2. However, age and gender were not significant determinants among this group of patients (Baldasseroni et al., 2016). Pierson et al (2004) studied 60 CR outpatients to identify the predictors of the change in fitness using a treadmill test. The participants attended 3 sessions per week for 5 to 9 months. They found that the mean change in fitness was 2.1 ± 1.7 METs which represents a 26% improvement. Multivariable analysis, using age, BMI, Anterior MI, reason for referral (MI, revascularisation, angina), baseline peak METs, Beta blocker medication, and 0.1MV ST depression during the test as independent variables, showed that the baseline fitness level was the only predictor of the change in fitness. McKee (2008) similarly attempted to identify the predictors of the change in 119 patients (81 males, 38 females) with a mean age of 60 ± 9. The participants used a treadmill and the mean change in fitness was 1.39 ± 2.11 METs (16%). Age, gender, BMI and the baseline fitness level were used as independent variables in a multiple linear regression and the change in fitness was the outcome. Patients with an initial low baseline fitness level showed significantly better improvements compared to those with a higher fitness level. Gender was also a significant predictor in this study while neither age nor BMI were significant. The three studies mentioned above (Pierson, Miller and Herbert, 2004; McKee, 2008; Baldasseroni et al., 2016) have limitations which could limit the generalisability of their results. For example, in the Pierson et al (2004) study, a small number of participants (60) was used in the multiple linear regression analysis despite the recommendation that 10 participants should be used for each independent variable. Further limitations of this study are that the statistical results of the multivariable analysis were not clearly reported and the gender of the participants was also not given. McKee et al (2008), on the other hand, used a limited number of confounders (age, BMI, gender and initial fitness level) in their study. Furthermore, BMI data was missing for 41 patients and the authors did not explain how this problem would be dealt with. The small range of ages used in the Baldasseroni (2016) study might be a drawback to the study.

In contrast to the previous studies, Beckie et al. (2013) found that the patients with a higher level of baseline fitness improved more than those with a lower level of fitness at baseline. In other words, there was a positive correlation between baseline fitness level and a change in fitness. Restricting the inclusion criteria to female participants who were literate in English and were covered by health insurance for at least 36 electrocardiogram (ECG)-monitored exercise sessions made the results of the Beckie et al. (2015) study less generalisable.

However, the results which show that baseline fitness is a significant determinant are in contrast to Sandercock et al (2013), Verges et al (2015) and Lavie & Milani (2000). Sandercock et al. conducted a meta-analysis of 31 international studies, including 48 subgroup comparisons, to determine the change in fitness in the CR population using a treadmill. They found that the improvement in fitness was 1.5METs. Regarding the baseline fitness, the groups were divided into a low baseline fitness level group if their fitness level was less than 6.6METs, or a high fitness level group if the baseline fitness level was ≥

6.6METs. They found that in a meta-regression analysis, baseline fitness was not a significant determinant of the change in fitness, however, the categorisation was arbitrary based on the median. This cut-off point of 6.6 METs is higher than the 5 METs which is recommended by the American College of Sports Medicine (the ACSM) as a cut-off point for a low fitness level (ACSM's, 2010).

2.5.2.2 Age

Age was a determinant of a change in fitness in four studies (Lavie and Milani, 2000; Beckie et al., 2013; Sandercock, Hurtado and Cardoso, 2013; Branco et al., 2015). In three of these studies, advanced age was inversely correlated to an improvement in the change of fitness. Sandercock et al (2013) divided the 48 groups in their study into three age groups: young (<50), old (50-65) and oldest (> 65) and the meta-regression analysis showed that the youngest group showed a significant positive change in their fitness compared to the other groups. However, patient-level data that is used in meta-regression is known to be prone to regression bias (Rao et al., 2017). These results support the study conducted by Lavie & Milani (2000) on 182 CR outpatients. They compared the improvement in fitness in two age groups: the first group consisted of 125 younger patients (<55 years with a mean age of 48 + 6 years, of them 15% were females) and the second group included 57 older patients (>70 years with a mean age of 78 + 3 years, of them 26% were females). They found that although both groups improved (13% for elderly and 18% for the younger group), the multivariable analysis showed that the younger group had improved more. The baseline fitness level was found not to be a significant determinant. However, there was insufficient reporting of analytical methods as the authors did not clearly state which independent variables from the baseline characteristics were used in the multivariable analysis. The statistical result of this analysis was also not clearly reported. In addition, the way of grouping patients into age groups did not seem to be justified.

This correlation between advanced age and the change in fitness was not the case in the Branco et al. (2015) study, where the two older groups (45-64 and 65 and over) showed more improvement than the younger group (<45). In the Branco et al. retrospective study, data relating to 1125 patients from 2008 to 2013 were analysed to determine which cardiovascular risk factors could influence physical fitness in CR patients expressed in METs using a treadmill stress test. Multiple linear regression was conducted using age, gender, BMI, diabetes, smoking, dyslipidemia, reason for referral and physical activity level (using the International Physical Activity Questionnaire (IPAQ) as independent variables and the change in fitness expressed in METs as the dependent variable. They grouped patients according to age and found that patients aged below 45 gained less improvement than those aged 45-64 and over 65. Diabetic patients in this study also showed less significant statistical improvement compared to non-diabetics. The reason for referral was also a significant determinant (Branco et al., 2015). However, the authors did not clearly explain the type and protocol of the exercise test that was used. In addition, the way of grouping the participants into such age groups was not justified in studies

In contrast, seven studies did not find age to be significant (Balady et al., 1996; Pierson, Miller and Herbert, 2004; McKee, 2008; Savage, Antkowiak and Ades, 2009; Vergès et al., 2015; Almodhy, Ingle and Sandercock, 2016; Baldasseroni et al., 2016). However, the limitations in some of these studies as mentioned above should be considered. Almodhy et al. (2016) conducted a meta-analysis involving 11 studies containing 16 groups of patients to measure the change in fitness in the CR population as expressed in the distance walked during ISWT. The meta-regression analysis revealed that age (>63 and ≤63) was not a significant determinant of this change. However, in this meta-analysis, five (45%) out of the 11 included studies had a small sample size (< 40 participants).

Age was adjusted for as a potential confounder in the analysis of six further studies as these studies aimed to identify the ability of a specific variable to determine the change in fitness. For example, Fell et al. (2016) was examining CR timing; Gee et al. (2016) and Lavie & Milani (1995) was examining gender while Verges et al. (2004) was investigating diabetes.

2.5.2.3 Gender

Gender was a further significant determinant of a change in fitness reported in three studies included in this review (McKee, 2008; Sandercock, Hurtado and Cardoso, 2013; Gee et al., 2014). The female gender was found in all three studies to be independently associated with a decreased improvement in the change in fitness, while the male gender was positively associated with greater improvement. Gee et al. (2014) conducted a retrospective study on data relating to 781 patients (men 554 and women 227), with a mean age of 65.2 for males and 66.4 for females, between 2002 and 2011 to investigate the difference in improvement in fitness between males and females participating in a CR programme. The patients attended a programme consisting of three sessions a week for a period of three months. The change in fitness was 2.12 METs and 1.66 METs for males and females respectively. In their analysis, the authors took account of covariates such as baseline total cholesterol, resting blood pressure and zip code prosperity, however, these variables did not show any significant correlation with a change in fitness, therefore, they were not included in the regression analysis. The multivariable analysis, adjusted for age, BMI and reason for referral, showed that gender is a significant determinant of a change in fitness with males achieving more improvement than the females (Gee et al., 2014). However, the small number of Asian (4) and Hispanic (5) women might limit the result of this study. Sandercock et al. (2013) reported that males who were in the male-only group showed a significant improvement compared to those males who participated in the mixed group, and compared to the female-only group. However, the number of female groups was very small (3groups) which limits the meta-regression analysis results (Rao et al., 2017).

In contrast, gender was found to be a non-significant determinant in six studies (Lavie and Milani, 1995b; Balady et al., 1996; Savage, Antkowiak and Ades, 2009; Branco et al., 2015; Vergès et al., 2015; Baldasseroni et al., 2016). Lavie & Milani (1995) retrospectively analysed data relating to 458 patients, 83 females with a mean age of 61 + 10 years and 375 males with a mean age of 63 + 10 years. The patients attended 36 sessions over twelve weeks of an outpatient CR programme and showed an average improvement in their fitness of 2 METs in women participants and 2.7 METs in men. The multivariable analysis showed that gender was not a significant determinant of the change of fitness. However, the independent variables that were used in the regression analysis were not clearly reported and the results were not adequately reported. Two studies adjusted for but did not report any results at all for gender (Glazer et al., 2002; Fell, Dale and Doherty, 2016). However, Beckie et al (2013) studied only a female population and another study conducted on 60 patients reported results without specifying the participants' gender (Pierson et al. 2004).

2.5.2.4 Diabetes

The presence of diabetes was found to be a predictor of the change in fitness in three studies (Vergès et al., 2004; Savage, Antkowiak and Ades, 2009; Branco et al., 2015), with diabetic patients showing less improvement compared to non-diabetics. Verges et al. (2004) compared 59 diabetic CR outpatients, with a mean age of 57.4 + 8.8 years, to 36 non-diabetic CR outpatients with a mean age of 56.7 + 11.3 years, in order to investigate the effect of the presence of diabetes on the change in fitness on completion of the CR programme. The patients attended three sessions per week for two months. The change in fitness (peak Vo2), measured using a cycle ergometer, was 13% in the diabetic patients and 30% in the non-diabetics. In the study, after adjusting for BMI, the difference in the change in fitness between the diabetics and non-diabetics was significant. The authors conducted further analysis to identify the determinants of the change in fitness among the diabetic group only. They used a stepwise multiple linear regression analysis with age, BMI, fasting blood glucose, duration of diabetes, presence or absence of microalbuminuria, homeostasis model assessment (HOMA), presence or absence of treatment with insulin and left ventricular ejection fraction (%) as independent variables and a change in fitness expressed in peak Vo_2 as a dependent variable. The analysis showed that fasting blood glucose level and BMI were significant determinants of a change in fitness in the diabetic group. A further study conducted by Verges et al (2015) had a secondary aim to identify the determinants of the change in fitness in diabetic CR patients. The authors ran randomised control trials which aimed to determine whether good glycemic control could bring about an improvement in peak Vo2 by the end of the CR programme. They divided their patients into two groups, an intensive treatment group with 26 patients with a mean age of 60 and a control group with 31 patients with a mean age of 58. The intensive treatment group received basal-bolus insulin therapy and the control group continued on the antidiabetic treatment they were receiving at the beginning of the study. The patients were enrolled on a 20-session CR programme taking place over a period of approximately 8 weeks. The whole population showed an average improvement of 2.7±2.5 ml/kg/min. They reported the only determinant was the final fructosamine value (negative association). Neither age, gender, baseline fitness level, BMI nor the duration of diabetes were significant determinants in this study. However, this study was limited to a small sample of diabetic patients.

2.5.2.5 BMI

BMI was reported to be a significant determinant in only one of the included studies, which was conducted on a CR group of diabetic patients (Vergès et al., 2004). An inverse association between BMI and the change in fitness was shown. However, in seven other studies BMI (Pierson, Miller and Herbert, 2004; McKee, 2008; Savage, Antkowiak and Ades, 2009; Beckie et al., 2013; Branco et al., 2015; Vergès et al., 2015; Lim, Han and Choe, 2016) was found not to be a significant determinant regardless of whether it was measured as a continuous variable (Pierson, Miller and Herbert, 2004; McKee, 2008; Beckie et al., 2013; Vergès et al., 2015) or categorised into groups (Branco et al., 2015; Lim, Han and Choe, 2016) including one study by Verges et al. (2015) which also used only diabetic patients who attended a CR programme. Lim et al. (2016) compared the change in fitness between 359 obese (BMI ≥ 25) and non-obese (BMI <25) patients who had suffered acute MI and were attending a 6-week CR programme. 170 obese patients with a mean age of 54.32+10 years and 189 non obese patients with a mean age of 59.12+11.5 years undertook a functional capacity exercise test using the modified Bruce treadmill protocol. The change in fitness was 1.6 METs in the obese patients and 1.9 METs in the non-obese. The analysis showed, after adjusting for age, there was no significant difference in the change in fitness between the two groups. However, the authors found that there was a statistically significant difference between the two groups in the baseline characteristics regarding the smoking status and consumption of alcohol. Despite this, these variables were not taken into account during the analysis. Furthermore, the authors reported that the BMI classification, where patients with a BMI of > 25 were classified as obese and <25 were considered normal, was based on the Korean National Health and Nutrition Examination Survey (NHANES. A further five studies controlled for BMI in their analysis but did not report the results relating to BMI.

2.5.2.6 Reason for referral

Another significant determinant which was reported, was the reason that patients were referred to a CR programme. Branco et al (2013) found patients who were referred post-CABG achieved a significant improvement in their fitness compared to those who were referred due to acute coronary syndrome (ACS) who in turn showed a significantly greater gain in fitness than those with elective PCI. The authors reported that CABG patient had lower baseline fitness than the other group. However, six studies reported that the reason for referral was not a significant determinant of the change in fitness (Balady et al., 1996; Pierson, Miller and Herbert, 2004; Vergès et al., 2004; Sandercock, Hurtado and Cardoso, 2013; Vergès et al., 2015; Almodhy, Ingle and Sandercock, 2016). However, the two meta-analysis studies (Sandercock, Hurtado and Cardoso, 2013; Almodhy, Ingle and Sandercock, 2016) were limited by the number of groups of both CABG and MI patients. In the Almodhy study, there were only 2 groups of each while in the Sandercock study, there were 4 groups of MI patients and 5 groups of CABG patients. These small numbers of groups might limit the generalisability of the results.

2.5.2.7 Depression

Only a relatively small number of psychological variables were assessed as potential confounders in the included studies. Two studies reported depression as an independent variable. One of these, conducted by Glazer et al. (2002), studied the effects of optimism, depression and neuroticism on the CR physical fitness outcomes and the drop-out rates of 46 participants (34 men) with a mean age of 58±10 years over a 12-week CR programme. The participants showed an improvement of 10% in their VO_2 (ml/kg/min). The Beck Depression inventory (BDI) was used to measure depression and the State-Trait Anxiety inventory and the Life Orientation Test to measure neuroticism and optimism respectively. After controlling for age and gender, it was found that the baseline depression score was a significant predictor of the change in physical fitness whereas optimism, neuroticism and the number of CR sessions attended were not (Glazer et al., 2002) . However, the sample size used in this study is considered small in terms of the number of predictors. Savage et al. (2009) reported that depression was not a significant determinant, however, a different tool was used to assess depression namely the Geriatric Depression score.

2.5.2.8 Self-reported physical function (36-SF) and Waist circumference

Two studies found that self-reported physical function, measured using a short form 36-survey questionnaire, was one of the significant determinants(Savage, Antkowiak and Ades, 2009; Beckie et al., 2013). Savage et al. (2009) found that patients who had a high baseline score experienced less relative improvement in their fitness in contrast to the Beckie et al. (2013) results which showed that patients who reported a high baseline score in self-reported physical function gained more improvement in their fitness. However, this could be due to the different independent variables used in the multivariate analysis in the two studies. Furthermore, Beckie et al. reported their results based on the change in fitness in female patients only while in the Savage et al. study (2009) the females represented only 20% of the total number of patients. In addition, the participants in the Beckie et al trial received at least 8 sessions of education.

Waist circumference was reported to be a determinant in the Beckie et al. (2013) study, with a small waist circumference at baseline being positively associated with a change in fitness whereas this was found not to be significant in the Savage study (2009). This could be due to the different between studies that mentioned above.

2.5.2.9 Total score of Comorbidities

The total score of comorbidities was found to be a significant determinant in the Savage et al study. They assigned each patient a score ranging from 1-12 depending on the severity of the limitation caused by certain comorbidities (Savage, Antkowiak and Ades, 2009). In contrast, Beckie et al (2015) used the Charlston comorbidity index, however, it was reported that this index was not a significant predictor of a change of fitness. Fell et al (2016) adjusted for the total number of comorbidities in their analysis without specifically reporting how this altered the results.

2.5.2.10 Number of sessions

The meta-regression analysis performed in the Almodhy et al. (2016) study showed that the number of sessions that patients attended was the only significant determinant of the change in fitness as expressed in the distance walked during ISWT, with attending >12 session being associated with a gain in fitness in CR patients. This result is limited by the small number of programmes which consisted of **>1**2 sessions. However, the number of sessions attended was found not to be significant in a further three studies which reported it (Glazer et al., 2002; Sandercock, Hurtado and Cardoso, 2013; Beckie et al., 2013). In the meta-analysis conducted by Sandercock et al. (2013), the CR programmes were divided into three groups according to the number of sessions (<36, 36 and > 36). Although the programmes that consisted of more than 36 sessions reported a higher gain in fitness than others, this gain was not statistically significant. However, only five programmes consisted of more than 36 sessions, which made the results of the meta-regression analysis questionable. The other two studies used the number of sessions as a continuous variable. The limitation of these studies has been discussed above.

2.5.2.11 Time from referral to the start of CR

Fell et al. (2016) found that the waiting time from referral to the start of the CR programme (CR timing) was a significant determinant of a change in fitness expressed by a change in the distance covered during the ISWT regardless of whether it was a continuous or categorical variable with late CR timing showing less improvement (OR= 0.79, 95% CI.669 to 0.941). In contrast to this, Savage et al reported that CR timing was not a determinant of a change of fitness. These differences may be explained by varying definitions of timing of CR in that Savage et al used referral to baseline assessment whereas Fell et al used referral to start of CR. In addition, the large sample size in fell et al study (32,899 patients) compared to the sample size in savage et al study (385 patients) and the difference in numbers of the confounders used in these studies hinders direct comparisons.

2.5.2.12 Other determinants

Greater hand grip strength and higher exercise intensity (Vo_2%) at baseline were reported in one of the 17 included studies (Savage et al. 2009) to be significant determinants with a positive association with a change in fitness. This is less surprising in respect of exercise intensity which is deemed as a core component of prescription (ACSM’s, 2010) whereas grip strength is perhaps more surprising. That said there is some evidence that grip strength is a reasonable surrogate of overall fitness ((Harrison et al., 2013)

Exercise modality and treadmill protocols were reported in one meta-analysis study (Sandercock et al. 2009) where the groups were divided into three based on the types of exercise modality: aerobic (19 groups), resistance (2 groups) and mixed (26 groups). In a meta-regression analysis, the exercise modality was found to be a significant determinant with programmes that used aerobic and mixed modality exercises. The patients in these programmes showed larger gains in fitness than those in programmes which prescribed resistance exercise only. However, the number of programmes (2 programmes) using resistance exercise was small, which limits the results of the meta-regression analysis.

In terms of treadmill protocols, programmes which used the Naughton protocol in exercise tests showed a significantly larger gain in the change in fitness compared to other programmes using different protocols. However, the number of programmes which used the Naughton protocol was also small (5 programmes).

2.5.2.13 Non-Significant Determinants

Smoking was found not to be a determinant of the change in fitness in two studies (Beckie et al., 2013; Branco et al., 2015). However, these studies have limitations as described above in section (2.4.2.1 Baseline fitness level , 2.4.2.2 Age, respectively). In the Gee et al. study (2002), there appeared to be an association between race and a change in patient fitness. Although, this was not statistically significant, which might be due to the small number of Asian and Hispanic participants. Race was adjusted for in the Fell et al. study (2016) but the results were not reported.

The Left ventricle ejection fraction (LVEF%), which had until recently been seen as a determinant of a cardiac patients ability to exercise, was reported to be a non-significant determinant in three studies (Glazer et al., 2002; Vergès et al., 2004; Beckie et al., 2013). Programme duration was reported as a non-significant determinant in the two meta-analyses. Sandercock et al. (2013) classified the programmes that were included in their study into two groups, those which lasted <12 weeks and those which lasted >12weeks, while Almodhy et al (2016) classified the programmes they analysed into those which lasted >7weeks and those which lasted < 7weeks. However, neither of them showed any significance. Sandercock et al. (2013) also found the study design (trial vs observational) and programme type (comprehensive vs exercise only) not to be significant determinants of the change in fitness.

Some determinants were reported in only one study and were found not to be significant: dyslipidaemia (Branco et al., 2015), weight (Savage, Antkowiak and Ades, 2009), physical activity (Branco et al., 2015), Beta-blocker medication, the location of the infarction, the presence of ST segment depression of at least 0.1 MV, and the exercise-induced ischemia (Pierson, Miller and Herbert, 2004), respiratory rate change (RPR) (Savage, Antkowiak and Ades, 2009), zip code prosperity (Gee et al., 2014), optimism and neuroticism (Glazer et al.,

2002) and social function (Beckie et al., 2013). However, due to the limitations of the studies, mentioned above, that reported these variables as non-significant, the interpretation of their results should be treated with caution.

2.5.3 Synthesis of determinants

In this review, the consistency of any determinant variable was classified into three categories: (no association) if reported by 33% or fewer of the studies; (indeterminate / possible) if supported by between 34 and 59% of the studies; and association (determinant) if found as significant in 60-100% of the studies (Table 2-4). This type of classification has been widely used in previous reviews (Sallis, Prochaska and Taylor, 2000; Trost et al., 2002; Hinkley et al., 2008; Hesketh et al., 2017).

Table 2-4 Categories for classifying the consistency of reporting of determinants

% of studies reporting a determinant	Summary code	Meaning of code
0-33	0	No association
34-59	?	Indeterminate / inconsistent
60-100	+ –	Positive association Negative association
Adapted from Sallis et al. 2000		

Based on this classification, in this review baseline fitness, diabetes, self-reported physical function (SF-36), handgrip strength and exercise intensity were classified as determinants as they were supported by more than 60% of the included studies which reported these determinants. Depression, time from referral to start of programme, waist circumference, comorbidities and fasting glucose level were classified as indeterminate / possible as they were supported by 34-59% of the studies while gender, reason for referral and BMI were classified as having no association where they were supported by less than 34% of the studies which reported them (Table 2-5).

The quality assessment and this proportion classification were synthesised to establish the likelihood of the potential confounders being determinants (Table 2.6). This likelihood was classified into three: 'highly likely' if the quality of the study is good and the proportion of the studies that reported the determinant as significant is high (≥60%); 'likely' if the quality of the study is good and the percentage of the studies that reported the determinant as significant ranged between 34-59%, or if the quality is fair and the percentage is 60% and above. 'Less likely' refers to studies where the quality is fair with the percentage is less than 60% or if the quality of study is low. Based on this synthesis, Table 2-6 shows that diabetes, self-reported physical function (SF-36), handgrip strength and exercise intensity are highly likely to be determinants of a change in fitness. Baseline fitness levels, waist circumference, comorbidities, time from referral to start and age were likely to be determinants while depression, gender, BMI, reason for referral and fasting glucose level were less likely to be significant determinants.

Table 2-5 Summary of determinants showing the type and direction of association with a change in fitness by study.

	Association with a change in fitness Orientation of Papers (studies)					**Summary Code**	
Determinant Variable	Positive association	Negative association	No sig association	**Total of studies**	**No. of sig associations /total studies**	% of studies reporting a determinant	Code
Baseline fitness level	[9]	[2] [5] [7] [8] [15]	[3] [10] [13]	9	6/9	(67%)	±
Diabetes		[6] [8] [12]		3	3/3	(100%)	-
Self-reported physical function (SF-36)	[9]	[3]	[3]	3	2/3	(67%)	±
Handgrip strength	[8]			1	1/1	(100%)	+
Exercise intensity	[8]			1	1/1	(100%)	+
Waist circumference		[9]	[8]	2	1/2	(50%)	?
Comorbidities		[8]	[9]	2	1/2	(50%)	?
Depression		[4]	[8]	2	1/2	(50%)	?
Time referral to start		[16]	[8]	2	1/2	(50%)	?
Fasting glucose level		[6]	[9]	2	1/2	(50%)	?
Gender (male)	[7] [10] [11]		[1] [2] [7] [12] [13] [15]	9	3/9	(33%)	0
BMI		[6]	[5] [7] [8] [9] [12] [13][17]	7	1/8	(13%)	0
Reason for referral	[12]		[2][5] [6] [10][13] [14]	7	1/7	(14%)	0
Age	[12] [10]	[3] [9]	[2] [5] [7] [8] [13] [14] [15]	11	4/11	(36%)	0
Number of sessions	[14]		[4][9][10]	4	1/4	(25%)	0

[1] Lavie and Milani 1995; [2]Balady et al. 1996;[3] Lavie and Milani 2000; [4] Glazer 2002; [5] Pierson et al. 2004; [6] Verges 2004 ; [7] McKee 2008; [8] Savage et al. 2009; [9] BecKie et al. 2013; [10] Sandercock et al. 2013; [11] Gee et al. 2014; [12] Branco et al.2015;[13] Verges 2015; [14] Almodhy 2016; [15] Baldasseroni et al. 2016; [16] Fell et al 2016; [17] Kim et al. 2016.

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Table 2-6: The likelihood of variables being determinants based on a synthesis of the quality of the study and the proportion of the studies reporting them.

Variable	Assessment		Symbol	Likelihood
Diabetes	Quality of studies	2(F)1(G)		Highly likely
	Proportion of studies reporting it	100%		
Self-reported physical function (SF-36)	Quality of studies	1(F)1(G)		Highly likely
	Proportion of studies reporting it	67%		
Handgrip strength	Quality of studies	1(G)		Highly likely
	Proportion of studies reporting it	100%		
Comorbidities	Quality of studies	1(G)		Highly likely
	Proportion of studies reporting it	50%		
Time from referral to start	Quality of studies	1(G)		Highly likely
	Proportion of studies reporting it	50%		
Exercise intensity	Quality of studies	1(G)		Highly likely
	Proportion of studies reporting it	100%		
Baseline fitness level	Quality of studies	2(L)3(F)1(G)		likely
	Proportion of studies reporting it	67%		
Age	Quality of studies	4(F)		likely
	Proportion of studies reporting it	36%		
Waist circumference	Quality of studies	1(F)		Likely

	Proportion of studies reporting it	50%		
Fasting glucose level	Quality of studies	1(F)		Likely
	Proportion of studies reporting it	50%		
Gender (Male)	Quality of studies	3(F)		Likely
	Proportion of studies reporting it	33%		
Depression	Quality of studies	1(L)		Less Likely
	Proportion of studies reporting it	50%		
BMI	Quality of studies	1(F)		Less Likely
	Proportion of studies reporting it	18%		
Reason for referral	Quality of studies	1(F)		Less Likely
	Proportion of studies reporting it	14%		
Number of sessions	Quality of studies	1(F)		
	Proportion of studies reporting it	25%		

: represents the quality of studies that reported the determinants in percentage terms where red represents low quality, brown represents fair quality and green represents good quality.

: represents the proportion of studies that reported the determinant where red represents <34%, quality, brown represents 34-59% and green represents ≥60%.

2.5.4 Limitations of included studies

A common limitation identified in the studies included in this critical review was the small sample size in terms of the number of potential confounders. This means the validity of the findings of the statistical multivariable analyses that were used by the authors should be interpreted with caution. A further limitation was that some of the studies did not provide a sufficient number of confounders, for example, Lim et al adjusted only for BMI as a confounder and in McKee et al. (2008) only four confounders were used which represent (28%) of the potential confounders that were reported in the included studies in this review. A further limitation is that some potential confounders, such as psychological variables, were taken into account in only a few studies. Furthermore, some studies chose the independent variables that they used in the multivariate analysis based on the univariate association between the variable and the outcome. However, the confounder tended to have a correlation with both the outcome and other variables. Some studies reported insufficient demographic data and referred to them as the variables that were used in a univariable and multivariable analysis without reporting the results. The reporting of the methods and results in some studies was not sufficient or clear enough to evaluate the studies.

Although the ISWT is known to be the common field test used in the UK, there is a lack of studies which have attempted to identify the determinant of a change in fitness in patients using this test. Only the study conducted by Fell et al. (2016) examined the effect of CR timing on the change in fitness as expressed in the distance walked during the ISWT. However, as mentioned above, this study reported the result for the main independent variable (CR timing) only, while the other independent variables were adjusted for without reporting the results. Almodhy et al. also attempted to identify these determinants in their meta-analysis. Another study conducted by McKee et al. (2013) attempted to identify the determinants of the change of fitness as expressed in the distance walked during the ISWT. They found that age and baseline fitness levels were the determinants, however, this study was excluded from this review as the authors included heart failure patients.

2.5.5 Strengths and limitations of this review

One of the strengths of this critical review is that the included studies were restricted to those that used multivariable analysis which demonstrates the independent association between the independent variables and the outcomes. This limits the inherent bias which results from unadjusted outcomes. The comprehensive search of the literature using several search engines is a further strength of this review. However, this review is not without limitations as the search was restricted to published sources written in English. In the method where a determinant was classified according to its proportionality, this could be affected by the number of studies that reported a particular determinant. For example, in the case of handgrip strength, only one study was reported which resulted in a proportion of 100%, therefore this result should be interpreted carefully. Two of the studies (Balady et al., 1996; Lavie and Milani, 1995b) that were included in this review were also included in the meta-analysis conducted by Sandercock et al. (2013). However, as these two studies were included in a group of 31 studies in the meta-analysis, this is unlikely to affect the results.

2.6 Conclusion

This study critically reviewed the studies that attempted to identify the determinants of a change in fitness using incremental tests in CR patients. There continues to be huge variation in the studies in terms of identifying the determinants of a change in fitness. Diabetes, self-reported physical function (SF-36), handgrip strength and exercise intensity are highly likely to be determinants of a change in fitness. Baseline fitness levels, waist circumference, comorbidities, time from referral to start and age were likely to be determinants while depression, gender, BMI, reason for referral and fasting glucose level were less likely to be significant determinants. The ability to draw conclusions is hindered by significant inconsistencies in how studies were analysed with additional limitations in the studies with reference to sample size, population characteristics and potential confounders. Finally, the quality of study designs and reporting of study details in journal publications needs to improve so that critical and systematic reviews can be performed to the highest level. However, the results of the variables that were classified as ‘indeterminate’ or ‘no association’ should be interpreted cautiously as the studies which generated these results had some limitations as mentioned above.

Future studies should be conducted with larger samples, include more potential confounders and utilise robust statistical methods. Due to the lack of studies attempting to identify the determinants of the change in fitness using the ISWT, therefore further research is also required in this area (see chapter 6).

Due to a lack of consistency in the reporting of determinants, the potential independent variables which have been identified in this review will be taken into account in the study in chapter six as potential confounders with an emphasis on the significant determinants, if data relating to them is available in NACR database.

Chapter 3. Methodology

The philosophy behind the choice of study design, the collection of data and the approaches utilised in the analysis in research is called the methodology (Kumar, 2014).. The method, on the other hand, is the strategy or plan that will be used to collect and analyse the data to enable the researchers to conduct their study

To answer the questions in this thesis (see section 1.1.2), retrospective observational studies using NACR secondary data have been used. In this chapter the study design, data collection and statistical analysis approaches that have been used in this thesis will be justified and explained.

3.1 The study design

The study design is defined by Parahoo (2006, p142) as "*a plan that describes how, when and where data are to be collected and analysed*" (Parahoo, 2006). This design is considered the backbone of research and is crucial in terms of the quality, execution and interpretation of any research (Knight, 2010; Thiese, 2014). Based on this design, the best analysis approach for the data generated is decided. For any study, identifying the correct design is more important than the analysis process as a study with an inappropriate design cannot be recovered while a study with inappropriate analysis can be analysed again to arrive at a meaningful conclusion (Bhalerao and Parab, 2010). Therefore the validity and consequently generalisability of the research results are dependent on the design of the study (Kendall, 2003).

Experimental and observational designs are the two main broad categories of research design. The main difference between these two designs is that in an experimental design the investigator administers an intervention to one group and controls for the other groups (they do not receive an intervention) in order to compare the effect of the intervention while an observational design is non-interventional. An experimental design includes randomised control trials (RCT) or non-randomised control trial studies whereas the observational design can include cohort (prospective and retrospective), cross-sectional or case-series studies (Thiese, 2014).

In the current era of evidence-based medicine, the study designs have been classified in an evidence hierarchy according to their strength of evidence. RCT studies are the most common type of experimental designs used for clinical research. They are considered the gold standard, which places these studies at the top of the evidence hierarchy (Kendall, 2003; Ligthelm et al., 2007). However, this type of study cannot be used in some situations, for example, for ethical reasons or when the research question does not focus on the outcome. Therefore using observational studies overcomes this shortcoming (Ligthelm et al., 2007; Yang et al., 2010; Thiese, 2014; Faraoni and Schaefer, 2016). The comparison of RCTs and observational studies will be discussed in the next section where the strengths and limitations of each type will be reported.

3.1.1 Observational vs Randomised Control Trial

In an RCT study the subjects are assigned randomly to either the intervention group where the intervention (treatment, procedure or service) is being tested or to the control group, where there is no intervention. Then both groups are followed up to establish if there is a difference between the two groups due to the effectiveness of the intervention (Kendall, 2003). This randomisation, which is considered one of the strengths of its design, reduces the incidence of bias by ensuring the groups are as similar as possible in terms of baseline characteristics and both known and unknown factors that might affect the outcome. Therefore, the intervention and any variations in the outcome is the only difference between the groups (Hannan, 2008; Frieden, 2017). A good allocation concealment and blinding are the two other strong features which ensure that the randomisation process is done completely in blinded way to participants and personnel. The randomisation process limits selection bias and confounding. Furthermore, allocation concealment and the blinding process reduce the effect of performance and detection biases (Clancy, 2002; Higgins JPT, 2011).

Despite this, RCTs are not without limitations. They are expensive, time consuming and may have difficulty recruiting the required and representative number of participants.. For example, in the cardiac rehabilitation field the RAMIT trial Recruited less than 25% of the required sample (Doherty and Lewin, 2012). The study population, in RCTs might be considered highly selected and less representative of the typical population, due to the strict inclusion and exclusion criteria which might limit it external validity. Compared to the general population, they tend to be younger, for instance the mean age in recent Cochrane Review by Anderson et al (2016) where the mean age is 11 younger than recruited through routine practice as shown in NACR report (56 years vs 67, respectively) (NACR 2017). RCTs also tend to have fewer comorbidities, and their disease may be less severe (Yang et al., 2010; Chavez-MacGregor and Giordano, 2016). Furthermore, RCTs generally compare new treatments (intervention) not with the best treatments currently used but with placebos thereby making it problematic for clinicians to decide which treatment is more effective.

In addition, RCTs are limited to a short follow-up period, which could lead to the adverse effects of the treatment being missed as some negative effects develop over a longer period. Furthermore, RCTs have a more restricted number of patients and this limited number may result in otherwise common adverse events not being identified. However, there are some situations where a RCT is an inappropriate approach, for example, for ethical reasons, when randomisation is not practical, or when clinical trials may be irrelevant to the study population (Chavez-MacGregor and Giordano, 2016).

A well-design observational study is considered an alternative approach when an RCT is not appropriate and can also be viewed as a natural next step when investigating the extent to which clinical trials have been implemented in routine clinical practice. With over 63 clinical trials and many clinical guidelines observational studies using routine data are ideally placed to evaluate the effectiveness of CR and to ensure that the type of CR delivered aligns with minimum clinical standards. Furthermore, when the intervention (for example, a medicine) has received approval from the regulatory bodies, findings from observational studies are important as they provide information concerning the safety, efficacy and tolerability of the intervention in a clinical setting so in this case the observational study acts as a supplement to the RCT (Ligthelm et al., 2007; Yang et al., 2010)

In observational studies there is no intervention demonstrated but the effects of the intervention are observed between those who received or were exposed to the intervention previously and those who were not. There is no randomisation required and the allocation of participants is based on usual clinical practice not by the researcher. Observational studies assist in the identification of the effects of intervention that cannot be detected by RCTs, the understanding of prognoses, the monitoring of the safety of intervention in a real-world setting, the development and validation of risk scores in order to target appropriate treatment, and the improvement in the reliability of diagnoses. Observational studies often precede RCTs as the relationships identified in these studies assist in formulating hypotheses that will be tested in RCTs at a later stage. Furthermore, as RCTs often take time to conduct, observational studies could help to predict cause and effect relationships before the RCTs are complete. (Mann, 2003; Ligthelm et al., 2007; Yang et al., 2010)

Observational studies reflect the real-world clinical settings and have the following advantages compared to RCTs. They are more affordable, use a larger number of participants, have a longer follow-up time, are an efficient use of data, include a more representative sample of population which makes the results of the studies more generalisable. Furthermore, several outcomes can be examined in a single study (Mann, 2003; Yang et al., 2010).

This type of study has some inherent limitations such as selection bias due to the absence of randomisation and consequentely confouding bias. However, these limitations can, to a large amount, be overcome by using data from a large sample size that includes variables related to the study, and applying advanced methods of analysis such as multivariable regression models, which are often used to adjust for confounders (Concato, 2012).

The research design selected to address the research questions in this thesis was a retrospective observational design. This is the preferred design as it will enable a large enough sample of patients and their respective comorbidities to be investigated, which was the main limitation of the previous studies. The research questions focus on determinants and not outcomes which means RCT designs are not appropriate. As evidenced from the papers informing this review prospective cohort studies have struggled to recruit sufficient patients and in most cases the analyses were unable to or failed to take account to known and potential confounders. Although there are inherent weaknesses with retrospective studies, this thesis intends to take account of these in the design process.

3.2 Source of data

As mentioned above the source of the data that was used in this thesis was the NACR database.

3.2.1 The National Audit of Cardiac Rehabilitation

NACR is a national quality-assurance project funded by BHF established since 2005 which is designed to ensure that the optimum CR outcomes are achieved with patients with cardiovascular disease and that the CR programmes follow good practice as defined by the clinical minimum standards (Doherty et al., 2015). This is achieved by the centres entering the routine clinical data into the NHS Digital online system. This data relates to patients who joined CR, in terms of quality of care, type of service offered and patients' clinical outcomes. The patient identifiers are then removed and a link-n anonymised version is made available to the NACR. These collected data firstly help local CR teams to produce their own reports about the progress of their patients and secondly enables the NACR to monitor and facilitate the improvement in quality of CR services nationwide. The general aims of NACR as stated on the NACR website (http://www.cardiacrehabilitation.org.uk/about-us.htm) are shown in Figure 3.1.

The NACR aims to:

1. Monitor and support cardiovascular rehabilitation (CR) teams and commissioners in delivering high-quality and effective services, to evidence-based standards, for the benefit of all eligible patients.
2. Map the extent of provision and highlight inequalities and insufficiencies in delivery against key service indicators at Strategic Clinical Network, Clinical Commissioning Group, Health Board and Cardiac Network levels for over 320 programmes in the UK.
3. Design and implement research to determine the effectiveness of routinely delivered CR services on patient agreed outcomes, cardiovascular disease risk profiles and health and social care utilisation.
4. Use audit and research data generated through the NACR to inform:
    - NICE clinical guidance and service specification development
    - Clinical practice standards from national associations
    - NHS healthcare commissioning processes and decision making
    - The public and cardiac patient groups about how their local services are performing.

Figure 3.1 NACR aims.

These data come from a collaboration between NACR and NHS Digital where patient and service-level data is directly entered into a secure online system. Only users who are clinically approved, verified by a Caldicott Guardian, are able to input the data. This database includes information concerning the patients' demographic and anthropometric details, initial event, risk factors, treatment, medications, physical fitness status, physical activity status and clinical outcomes of programmes following CR (NACR, 2015). In addition to this, other details such as uptake and dropout rates, and duration of the programmes are included. Furthermore, data related to the type of staff in each centre and hours of work which were collected from the annual NACR survey report were added to NACR database.

3.2.1.1 Ethical Approval

Under Section 251 of the NHS Act 2006, the NACR through NHS Digital has approval (from the Health Research Authority's Confidentiality Advisory Group (CAG)) to collect identifiable data without gaining explicit consent from patients. Section 251 approval relates to the roles of the NHS Digital, the BHF and the NACR personnel who handle the data ensuring that procedures for the gathering, sharing and use of the data is performed to the highest standards. It also requires that only the data relating to a patient's CR experience is used. The approval and the role that NACR plays is reviewed by the CAG annually (NACR, 2017).

Obtaining patient consent during the management of a cardiac event would be problematic and place a huge burden on the staff and services. Therefore, in order to use this data for national audit purposes, the NHS has implemented an 'exemption from consent' process whereby data is inputted into the NHS systems without individual consent. Patients are informed of the reason for the collection of the data, how it will be utilised, who will have access to it, and their right to refuse consent without it affecting their treatment. This information is given through face-to-face communication and through the information on the front of the assessment questionnaires which they complete during their assessment (NACR, 2017) (Appendix 8.3.1)

The NACR data is secondary data that is used for different purposes including annual reports, Best Practice Tariff reporting, bespoke reports for third party organisations, informing commissioners/funding bodies and as content for undergraduate, postgraduate and PhD theses (NACR Information Sheet 2017). Due to the strict Data Sharing Agreement between NACR and NHS Digital, any researcher who uses this data must adhere to the regulations concerning the use of NACR data that is stated in the NACR Information Sheet 2017 (Appendix 8.3.2). Furthermore, completing and passing the information Security Training Online Course, which is arranged by the University of York, is mandatory.

3.3 Primary vs Secondary data analysis:

According to the National Institute of Health (NIH), the term 'primary data analysis' means that the data has been analysed by the research team who collected it in order to answer their research questions while 'secondary data analysis' refers to the analysis of data collected for another purpose regardless of whether the analysis is conducted by the same team or not (Cheng and Phillips, 2014). The collection of large quantities of secondary data is becoming more prevalent, therefore using existing data for research purposes is becoming more commonplace (Andrews et al., 2012; Johnston, 2014)

The analysis that is conducted on secondary data is known as retrospective analysis. There are some advantages to analysing and using the secondary data compared to primary data (prospective analysis). It is relatively inexpensive, saves time in terms of collecting data, uses a large sample size from a real-world population is of higher quality than the researcher could reasonably expect to collect himself, it is generally easier to access, it makes international comparative studies and longitudinal studies feasible. For example, in government censuses, official registers or audits when data is collected regularly, monitoring change over time is easier. There is less risk of personal prejudice in secondary data compared to primary data (Andrews et al., 2012; Cheng and Phillips, 2014).

However, secondary data is not without its limitations. As the data was collected for a different purpose, it may not be suitable for certain research questions and some required information may be unavailable. Furthermore secondary data usually suffers from missing data and outliers (Andrews et al., 2012; Cheng and Phillips, 2014). These are frequently encountered when dealing with secondary data.

As there is no access to the original data, dealing with secondary data requires the researcher to have a good knowledge of statistics in order to manipulate the data to enable him/her to obtain as much information as possible to analyse so as to answer the research questions. In addition, statistical knowledge will enable the researcher to deal with outliers and missing values appropriately. In order to do that, the author of this thesis, attended and completed basic and advanced statistics modules that used SPSS and Stata software packages provided by the Department of Health Sciences at the University of York. Senior statistical support was available through the Department of Health Sciences and the NACR provides researchers with statistical support.

3.3.1 Missing data:

Missing data simply means the information is missing for some cases on some variables in the dataset. According to Little et al (2010, p1356) missing values refers to '*values that are not available and that would be meaningful for analysis if they were observed"*(Little et al., 2010). This issue is common in clinical and epidemiological research. There are a number of reasons for data being missing, for example, the refusal of an individual to participate in the study or to provide answers to questions, equipment malfunctions, participants not completing the study, or data which could not be read by the person inputting the data into the database or omitting to enter it (Hayati Rezvan, Lee and Simpson, 2015; Garson, 2015). In clinical research, missing data could threaten the validity of the study and consequently its conclusion. However, it is difficult to avoid (Penny and Atkinson, 2012). There are problems which arise from missing data which include a reduced statistical power, possible bias in the estimation of parameters, a reduction in the representativeness of the sample, and the analysis of the study may become problematic. Each of these may threaten the validity of the studies, which consequently may affect its generalisability (Kang, 2013). This could be considerably worse if the amount of missing data was large or when the missing data relates to multiple variables. Therefore, researchers should utilise all available data to conduct the most efficient study.

According to Rubin (1987), the missing data is classified into three categories depending on the reasons for the data being missing (Bland, 2015). These are: missing at random (MAR), missing not at random (MNAR) and missing completely at random (MCAR). MAR refers to a situation when the missing values depend on the observed values but not on the unobserved values of the dataset. In other words, the missingness is related to the person and can be predicted from the available data related to this person. For instance, only elderly people have missing values for the intelligence quotient (IQ). However, if the missing values do depend on the unobserved values in the dataset, this is referred to as MNAR. For instance, the patient did not attend the drug test because he took drugs the previous night. MCAR is when missingness does not depend on either the observed or unobserved values of the data set, for example if a blood sample is damaged while being processed in the laboratory (Schafer and Graham, 2002; Altman, Bland and Bland, 2007). In the case of MCAR, the estimated parameters remain unbiased although the power may be lost in the study design (Kang, 2013).

Several methods have been developed to deal with analysing the missing data including complete case analysis, which is also known as casewise deletion or listwise deletion. This approach uses only cases that are complete in all variables. This can result in a small sample if there are missing data from different variables which may lead to a reduction in the statistical power for any statistical test conducted. However, if the data is MCAR, this complete-case analysis approach is less likely to be biased (Kang, 2013).

The second method is available-case analysis, also known as pairwise deletion. The analysis used in this method is conducted on the observed values of the cases in the variables that have been selected and the cases with a missing value are excluded. Although this method is considered more efficient than the complete-case analysis, it has disadvantages as there is a variation in the number of cases in the analysis thereby reducing the precision of estimates which might differ depending on the variables which are being compared (Haukoos and Newgard, 2007; Penny and Atkinson, 2012; Kang, 2013).

A weighting method is another technique where more weight is given to the cases that are similar to those which were excluded from the data set, in order to reduce the bias that results from the missing data. However, estimating the variance (and errors) is increased when using such a technique, which consequently reduces the precision of the estimate (Haukoos and Newgard, 2007; Penny and Atkinson, 2012; Kang, 2013).

Single imputation methods are a further way to deal with missing data. The notion behind this technique is to replace the missing values with an imputed value from the observed data. Mean imputation is one single method imputation where the missing values are replaced with the mean. Another form of single imputation method uses the last observation carried forward where the missing values are replaced with the last measured value from the same case. The disadvantage of this technique is that it causes the standard errors to be too small as it does not take the uncertainty about the missing values into account (Newgard and Haukoos, 2007; Penny and Atkinson, 2012; Kang, 2013). Expectation maximisation is another approach which is used to deal with missing values. However, this approach is limited as it does not provide an estimate of the standard errors and the confidence intervals of estimated parameters (Dong and Peng, 2013).

Multiple imputation is considered one of the most sophisticated methods that is becoming widely used in clinical research to deal with missing data as it is shown to generate less biased estimates with more statistical efficiency (Kang, 2013). This approach is now standard in the majority of statistical software packages. This approach replaces missing data set of with plausible imputed values that are predicted using the existing data from other variables which are associated with missing data. After the replacing of missing data, new imputed data is created. This process is repeated to create several imputed data sets known as multiple imputation (Kang, 2013). This phase is called the imputed phase and is considered the first phase of the imputation process. In the second phase, which is the analysis phase, the statistical analysis is conducted in each set of these imputed completed data. In the third phase, the results of these sets are pooled (the pooling phase) to produce a single combined analysis result. The estimate of each parameter is the average of total of the imputed data. However, the variances are calculated by pooling the combining of the within and the between imputation variance.

As mentioned above, the variables with missing data are entered into the imputation to replace their missing values. There are auxiliary variables which are the other variables in the data that could be entered into the imputation process in order to help in predicting the imputed values. These variables are in addition to a dependent variable recommended to be used and entered during the imputation phase thereby increasing precision and reducing bias (Johnson and Young, 2011; Manly and Wells, 2014). In general, the number of imputed datasets is 5, 10 or 20. A higher number of imputed datasets can be used, however, obtaining more datasets involves more computing time, which can become burdensome. In this thesis, 20 imputed datasets will be used as is commonly recommended (Graham, Olchowski and Gilreath, 2007; Royston, White and Wood, 2011; Manly and Wells, 2014).

The multiple imputation technique is considered to be robust to the violation assumptions of normality. Furthermore, in the case when the data size is small or when the data has a large number of missing values, this technique produces an appropriate result (Kang, 2013).

However, a clear limitation of using multiple imputation is the inability of utilising another sophisticated statistical technique such as multilevel modelling or bootstrapping. The decision of what technique to choose and what to scarify should be made by the researcher based on the nature of his data and the research questions. This advance technique was used in this thesis to replace the missing data.

3.3.2 Outliers

An outlier, as defined by Barnett and Lewis (1994), is one that seems to differ considerably from the other values in the sample in which it appears. It is usually extremely large or small compared with the other values in the data set (Barnett & Lewis. 1994). It is important to detect the outliers as they could have a detrimental effect on the data analysis by reducing normality, influencing the assumptions in a statistical test, decreasing the power of statistical tests and increasing the error variance. However, useful information could be obtained when examining an unusual response given in an outlier. Outliers can arise due to errors in recording, entering or collecting data or at the measurement stage (Barnett & Lewis. 1994).

There are several methods for detecting outliers during the descriptive process of the data including the Standard Deviation (SD) method, Tukey's method (boxplot). The commonly used ones are SD and the boxplot. In this study, we used the 3SD method as this is considered the common way used in clinical research to detect outliers.(Field, 2013)

3.4 Statistical analysis of data for all studies in the thesis

Regression was the main statistical analysis approach that was used in this thesis. Regression is a technique for modelling the relationship between the dependent variable (outcome) and one or more independent variables in a simplified mathematical form (Schneider, Hommel and Blettner, 2010). There are several types of regression including linear regression, logistic regression, Cox regression and Poisson regression. There are two general applications for multiple regression (MR): prediction and explanation. In terms of prediction, the aim is to use the available data to create an optimal regression equation in order to predict a particular outcome. When multiple regression is used for explanatory reasons, the relationships between variables is examined with the purpose of investigating a phenomenon. The aim is then to be able to generalise this association to the wider population.(Palmer and Connell, 2009)

As the thesis questions focus on identifying (1) the predictors of the baseline ISWT distance as a measurement of fitness in CR (first study) and (2) the determinants of the MCID for ISWT in the same population, this type of statistical method was chosen as the best method to use. Multiple linear regression was utilised to answer the question in the first study as the outcome (distance walked) was a continuous variable and more than one independent variable was used in the regression. Multiple logistic regression was used to answer the question in the second study as the outcome was binary (MCID achieved versus not achieved). These two types of regression will be discussed in the next section. Logistic regression was also used in the third study to explain the relationship between whether the centres measure fitness or not and the patient-related outcome.

3.4.1 Linear regression

Multiple linear regression is used only if there is a linear relationship between the independent variables and the dependent variable (outcome). The outcome can then be predicted from the independent variables. The predicted values are produced using a linear equation

Figure 3.2.).

$Y = a + b_1 X_1 + b_2 X_2 + b_n \times X_n$ Where: Y = dependent variable Xi = independent variables a = constant (y-intersect) b = regression coefficient of the variable X n=the number of independent variables

Figure 3.2 Regression equation for multiple linear regression

There are certain assumptions that should be met when performing a multiple linear regression. The first assumption is that the dependent variable should be continuous, and the independent variables should be two or more either continuous or categorical variables. These assumptions relate to the study design. However, other assumptions are known to be related to the nature of the data. Linearity is where the relationship between the dependent variable and each independent variable should be linear. Normality is concerned with the residuals or errors (observed values – predicted value) which should be normally distributed. This can be examined by using a quantile-quantile plot (QQ-plot) or histogram. A further assumption is the Independence of residuals, where there should be no correlation between the residuals for any two cases. Furthermore, homoscedasticity (variability) refers to the variance of residuals which should be equally distributed along the line of best fit. Heteroscedasticity is the statistical term which is used when this assumption is violated. Finally, avoidance multicollinearity refers to the correlation between the independent variables which should not be high (higher than 0.9.). This can be examined using the tolerance test value and the VIF (Variation Inflation Factor) test value, which is the reciprocal of tolerance test (1/tolerance) (Tabachink and Fidell, 2007).

3.4.2 Binary Logistic regression

Binary logistic regression, which is also known as logistic regression, is different from linear regression as the outcome (the dependent variable) is a dichotomous (binary) variable which takes only two available values that are coded as either 0 or 1 where 0 represents the absence of the outcome of interest and 1 indicates the presence of this outcome (LaValley, 2008). Therefore, using a straight-line equation, as in a linear regression, will not be applicable because the outcome in a logistic regression is either 0 or 1 and the predicted values could be larger than 1 or smaller than 0. In addition, the assumption is that all variance of residuals, which should be equally distributed along the line of best fit, will be violated as this assumption does not match the behaviour of the binary outcome (LaValley, 2008). Given that in logistic regression the dependent variable is dichotomous, and the aim is to predict the probability of the case being classified into one of the two outcomes of interest, using the probability means that the values will be restricted between 0 and 1. This is considered a problem as the predicted value could be greater than 1 or less than 0 as mentioned above (LaValley, 2008; Menard, 2008). In order to overcome this problem, the probability (P) is replaced by the odds as shown in the following formula:

$\text{Odds}\ (Y=1) = P\ (Y = 1) / [1 - P\ (Y = 1)]$.

Although the odds have a value of positive infinity, they are still restricted to a minimum value which is 0 so there are no odds having a value of less than 0. The final step in solving this problem is to use a log transformation of odds which is called logit (y) and is also known as logistic regression as shown in the following formula:

$\ln\{P(Y = 1) / [1 - P\ (Y = 1)]\}$,

This transformation produces a value that varies from negative infinity to positive infinity. The equation that describes the relationship between a dichotomous dependent variable and independents variables is as follows (

Figure 3.3).

$$Logit(p)=a + b_0+b_1X_1+\_b_2X_2 +b_nX_n$$

Where:
Xi = independent variables
a = constant (y-intersect)
b = regression coefficient of the variable X
n=the number of independent variables

Figure 3.3 Regression equation for multiple logistic regression

Therefore, in logistic regression the independent variables are used to predict the probability of logit transformation of the presence of the outcome of interest. This logit transformation can be converted to odds by exponentiation which could then be converted to probability using a specific formula (LaValley, 2008; Menard, 2008).

As in linear regression there are certain assumptions that should be met when performing logistic regression. First the outcome should be a dichotomous variable; there are two or more independent variables; the independence of observation; and avoidance multicollinearity. Linearity is a further assumption, however, in logistic regression the linear relationship should be between the logit transformation of the outcome and any continuous independent variable, while in linear regression this relationship should be between the outcome and the independent variables (LaValley, 2008; Menard, 2008)..

3.4.3 Selection of variables

In health research variables which decided to enter in the regression analysis are generally selected based on previous literature or a plausible clinical or biological reason (Clancy, 2002). In multiple regression, there are several methods of entering the variables in the regression: forward selection, where the model starts from nothing then each variable is added in turn; backward elimination, where the model starts with all potential variables then insignificant variables are removed until the final model is obtained; stepwise method, which is the most commonly used, is a combination of the two previous methods.

3.4.4 Goodness-of-fit measurements

A good model fits the data and predicts the values which are closer to the observed values. In multiple linear regression, this is obtained by using an Ordinary Least Square (OLS) method that minimises the difference between the observed values and the predicted values (residual sum of squares) from the model. Generally, to evaluate the model, the Coefficient of Determination (R^2) is used as a goodness-of-fit measure. R^2 is produced as the regression output during the analysis. It represents the percentage of variance in the dependent variable that can be explained by the independent variables. This R^2 is calculated as the regression sum of square divided by the total sum of square and its value is restricted to between 0 and 1, with a value closer to 0 showing a poor fit of the model whereas a value closer to 1 shows a good fit (Sweet and Grace-Martin, 2012).

According to Cohen (1998), R^2 is equal to the effect size in multiple linear regression where $R^2 = 0.02$ is considered a small effect, $R^2 = 0.13$ medium, and a large effect when $R^2 = 0.26$ (Miles and Shevlin, 2003). However, a pitfall of R^2 is that each independent variable added to the model would lead to an increase in the R^2 value irrespective of the significance of the variable. Therefore, adjusted-R^2 is used to compensate for this by increasing it only if a new added independent variable has a correlation with the outcome and will improve the model more than would be expected by chance. The adjusted-R^2 value will be decreased if the added variable has no correlation with the outcome and improves the model by less than would be expected by chance. Adjusted-R^2 value can be considered an indicator of whether the predicted models are valid and provides a better estimate of the population (Miles and Shevlin, 2003; Sweet and Grace-Martin, 2012).

In logistic regression, Pseudo-R^2 corresponds to R^2 which is used in multiple linear regression. However, it is calculated differently using a maximum likelihood method.

Pseudo-R^2 = 1- log likelihood ratio

A log likelihood ratio represents the log likelihood of the full model (only constant) over the log likelihood of the null model. As in the case of R^2 in linear regression, the values of pseudo- R^2 range between 0 and 1 where the value closer to 1 shows that the predicted model has a good predictive power.

Regardless of whether the regression is linear or logistic, the best model is one with a smaller number of predictors and a higher R^2 or pseudo- R^2 values (Palmer and Connell, 2009). However, when the aim of the regression analysis is prediction, the value of R^2 is important while if the aim is to understand the relationship between the outcome and the independent variables, then the value of R^2 is less important (Sweet and Grace-Martin, 2012).

Another measure is the receiving operating characteristics curve (ROC curve) which is an effective method to evaluate the performance of the classifier and the accuracy of model prediction. This technique is a graphical representation of plot test sensitivity, which is the ability of the model to predict the occurrence of outcome of interest correctly (true positive) as the Y coordinate against its 1-specificity (false positive) rate as the X coordinate (Park, Goo and Jo, 2004; Hajian-Tilaki, 2013).

The greater the area under the curve, the more accurate the test. However, this area ranges between the value of 0.5 and 1, with a value above 0.8 showing that the model has a good power of prediction (Lakshmi Prasad, 2016). These approaches, R^2, pseudo- R^2 and ROC are referred to as predictive power evaluation approaches (Paul D. Allison, 2014).

Using the Hosmer and Lemeshow test is another measure of goodness-of-fit. In this test the predicted values are arranged from lowest to the highest values. Then the cases are grouped (the recommendation is 10 groups) according to their percentile of predicted values. After that a Chi-square test is run to compare observed and predicted values for each group with $p > 0.05$ indicating goodness-of-fit(Hosmer and Lemeshow, 2013).

These approaches mentioned above are used to evaluate how the predicted model fits the whole sample of observations. However, to evaluate whether an individual observation might influence the model, regardless of the regression type, the outliers or influential observations should be checked. This can be done by plotting the predicted values against the residuals (LaValley, 2008).

3.4.5 Validation of the model

The model is termed valid if it can be used on different samples in the same population without losing its power of prediction. There are three methods that can be employed to cross-validate the model. The first method is external validation, where an independent sample is used to validate the model. This method is costly and so rarely used. The second is to divide the sample into two groups, one of them is used as the exploratory group to create the model and the second group is used as a validation group. The third method uses adjusted-R^2 as an indicator of whether the predicted models are valid and provides a better estimate of the population.(Palmer and Connell, 2009)

Chapter 4. The association between fitness measurement, service delivery type and CR completion

4.1 Abstract

Aims: This chapter consists of two parts. For the first part, the primary aim was to examine the association between whether the patient's fitness is measured and the completion of their CR programme. The secondary aim was to establish whether an association existed between whether the patient's fitness is measured and meeting the physical activity recommendations and also the patients' self-reporting of their physical fitness, according to the Dartmouth COOP scale.

In the second part the study compared the centres which measure fitness and those which do not according to the service delivery indicators and staff profile.

Method: A retrospective observational study using NACR data from January 2015 to April 2016 was conducted to address these aims. A sub-analysis was conducted on data relating patients who attend centres which measured fitness. An online survey was sent to 303 CR centres to enquire about their practice of objectively measuring functional capacity. Logistic regression was constructed and multiple imputation was used to replace missing values.

Results: Data relating to 31,433 patients (mean age of 65.20±11.80 years, 73% of whom were male) from the 102 CR centres which returned the survey was analysed. Out of the total number of patients, 9,785 (31%) undertook a fitness assessment at baseline. Patients whose fitness was measured were 48% more likely to complete their CR programme compared to those whose fitness was not measured. There was no association between measuring fitness at baseline and meeting physical activity recommendations or self-reporting of physical fitness. The same results were obtained from the sub-analysis which was conducted on the patients from centres which measured fitness.

Compared to centres which did not measure fitness (9 centres), those which did (93 centres) appeared to meet the service delivery indicators and there was a higher proportion of these centres which were classified as 'high performers'.

Conclusion: Patients are more likely to complete CR if their fitness is measured at baseline which represents one the largest modifiable service-level characteristics reported in CR. A higher percentage of centres that measure fitness met the service delivery performance standard, particularly in terms of waiting time, which would also help them achieve key elements of the NCP-CR certification requirements.

4.2 Introduction

Assessing functional capacity for patients entering a CR programme is strongly recommended by various organisations. Based on the result of this assessment, the intensity of exercise is prescribed, the risk is stratified and by the end of the programme, the effectiveness of the exercise intervention is evaluated (Arena et al., 2007; Piepoli et al., 2012; Mezzani et al., 2012; AACVRP, 2013; BACPR, 2017). However, despite the recommendations relating to assessing patients' level of functional capacity prior to the programme and following it, less than one -third of CR patients undertook this test (Benzer et al., 2017; NACR, 2017). The NACR report (2017) showed 83% of patients who start a CR programme had a pre-programme assessment (which may or may not have included a fitness test) and 66% had a post-programme assessment. However, only approximately 14% of the patients who start a CR programme undertook a fitness test before and after the CR programme. This low percentage is in line with the result from a study by Benzer et al. which was conducted across 12 European countries and reported on data relating to 2095 patients (Benzer et al., 2017). Their aim was to compare the quality of CR provision across Europe in terms of settings, interventions and outcomes by assessing the feasibility of drawing up a web-based registry. Only 28% of these patients (535) were reported to have undertaken a baseline physical fitness assessment and this number dropped to only 16% (339) at the end of the CR programme (Benzer et al., 2017).

In general for the UK, the percentage of patients who did not complete CR remains high and ranges from 20% to 30% of those who enrolled in a CR programme (NACR, 2017). This high drop-out rate is despite CR being classified as a class I recommendation by different international CR organisations and the evidence of the positive effect of CR in promoting a healthy lifestyle, decreasing the risk factors, improving health-related quality of life, and reducing cardiovascular mortality (Heran et al., 2011; Anderson et al., 2016; Rauch et al., 2016; Cho et al., 2016; Sumner, Harrison and Doherty, 2017).

Several studies have reported factors which could be determinants of adherence of the CR programme. These factors could be described as patient-related factors or service-related factors (Ruano-Ravina et al., 2016). Patient-related factors include age, gender, ethnicity, employment, comorbidities, BMI, anxiety, depression and smoking, while service-related factors include the number of sessions and duration of the programme (Yohannes et al., 2007; Casey et al., 2008; Turk-Adawi et al., 2013; Doll et al., 2015; Ruano-Ravina et al., 2016). However, whether measuring the patients' functional capacity at baseline is associated with the likelihood of patients completing the CR programme has yet to be examined.

Meeting the physical activity recommendations of 150 minutes per week is recommended by the Chief Medical Officers across the UK and is a requirement of clinical standards and reported annually by the NACR (BACPR, 2017; NACR, 2017). In addition, the self-perception of physical fitness (Dartmouth COOP) is one of the health-related quality of life (HRQOL) subsets that is also used by NACR as a self-assessment tool to measure the extent of improvement in the patients' quality of life. These two measurements capture the patient-reported perspective of physical activity status and routinely show positive yet variable improvements in patients after CR (NACR, 2017; Dibben et al., 2018). Although some studies have investigated the relationship between fitness and physical activity status (Dyrstad et al., 2015) whether measuring the patients' functional capacity at baseline is associated with the likelihood of patients meeting the physical activity recommendation or whether it is associated with the patients' perceived level of physical fitness has yet to be examined in patients attending CR.

Using an objective test such as the Incremental Shuttle Walk Test (ISWT), the 6-minute walk test, the treadmill test, the Chester step test or the cycle ergometer to measure a patient's fitness, requires specific resources such as a suitable location, trained staff and sufficient time to complete the test within the clinical setting (ACPICR, 2015; Grove, Jones and Connolly, 2017). Some centres may not have access to such resources therefore, these centres are not able to offer a baseline fitness test to their patients. CR programmes carried out in centres in the UK and Europe are in accordance with the published clinical standards (Piepoli et al., 2012; Price et al., 2016; BACPR, 2017). Despite these guidelines, there is a wide variation in the practice and performance of CR programmes (Dalal, Doherty and Taylor, 2015; Doherty et al., 2017; NACR, 2017). Therefore, BACPR-NACR National Certification Programme for Cardiovascular Rehabilitation (NCP_CR) drew up service delivery performance indicators and the NACR use these indicators in order to evaluate the performance of CR centres in the UK (Furze et al., 2016). The NACR examined the extent to which CR programmes meet the national minimum standards for CR provision in the UK (Doherty et al., 2017). The study included data from the NACR database relating to 170 centres during the period 2013/2014. Each centre was giving a rating from 1 to 6 based on whether they met each of the 6 NCP-CR measures used to assess the quality of service delivery. The programmes were classified into three groups: high (achieving a score of 5-6 measures), middle (achieving a score of 3-4 measures) and low (achieving a score of 1-2). Programmes not achieving any of the criteria were deemed to have failed. The study found that only 30% of these CR programmes were classified as high performers; 45.9% were considered mid-level performing programmes; 18.2% of the programmes were categorised as low-level performers; while 5% of the programmes failed to meet any of the criteria and therefore failed. Whether there are differences between the centres which measure fitness and those which do not according to these service delivery indictors has yet to be studied. Given that a physical exercise test requires motivation on the part of the patient, this study will test the hypothesis that such commitment would be positively associated with CR completion.

4.2.1 The aim of this study

This study consists of two parts. In the first part, the primary aim of this study was to evaluate the association between the patients whose fitness was measured and those whose fitness was not measured and the extent by which this influences completion of the CR programme. The main hypothesis is that there is an association between measuring patient's fitness at baseline and the likelihood of completion of CR programme

The secondary aim was to evaluate this association between these two types of patients (assessed and not assessed) and the likelihood of them meeting the physical activity recommendations and the self-reporting physical fitness (Dartmouth COOP scale) at the end of their CR programme. Meeting physical activity recommendations and the self-perception of physical fitness are used as a standard tool in the NACR report to evaluate the improvement in patients' physical status. Therefore, they were used in this study to examine the association between them and whether fitness was measured at baseline. The secondary hypothesis is that there is an association between measuring patient's fitness at baseline and the likelihood of a positive self-reported response to these variables,

In the second part, this study aimed to examine the difference between centres which measure fitness and those which do not according to the national averages for service delivery performance indicators, and also in terms of the existence of multi-disciplinary teams (MDT) within the centres. The aim of these performance indicators is to set a minimum level of service delivery across the UK. The hypothesis is that a higher proportion of the centres which measure fitness will meet the service delivery indicators compared to those centres which do not measure fitness.

4.3 Method

4.3.1 Study Design

The primary design used in this study is an observational retrospective approach using routinely-collected data derived from the NACR database from January 2015 to April 2016 (see section 3.2.1). This data was merged with additional data obtained from a prospective survey which was carried out as part of the study in order to verify which centres measure fitness and which do not, as some centres which measure fitness may not enter their results into the NACR dataset.

An observational design using NACR data was chosen in this study as it allows the recording of data from clinical practice and reflects how the service is delivered as it occurs in real life. The participants in this type of study are thought to be more representative of the CR population than those recruited for RCTs especially in terms of mean age and the ratio of female participants (see Section 3.1.1).

4.3.1.1 Survey approach

A survey was conducted prior to main statistical analysis and the main questions asked were related to whether an objective fitness test was used to assess patients' fitness levels before starting CR (Appendix 8.4.1). This survey was developed using the survey monkey programme licenced to the University of York. The NACR system was chosen as it has a registry of all the primary contacts for all CR programmes. The survey was sent through the NACR system to 303 cardiac rehabilitation centres in order to establish which centres measure fitness and which do not as there are some centres which measure fitness but might not enter the results into the NACR dataset.

4.3.2 Data collection

The survey data for the centres registered in the NACR database were merged with the NACR data relating to the year January 2015 to January 2016, with information relating to the specialism of the staff working in the CR centres obtained from the NACR annual staff survey, as this data has the latest information regarding the centres' performance indicators. The merged data was used in the analyses for the two main parts of this study. The inclusion criteria and outcomes relating to the two parts of the study will be discussed below.

4.3.2.1 Part one: outcomes related to patients' fitness measurement status

In the first part, the association between whether the patients undertook a fitness test as part of their baseline assessment or not, and the following three outcomes at the end of the CR programme were investigated: completion of the programme, meeting the physical activity recommendations and the patient's perception physical fitness status according to the Dartmouth COOP tool.

In order to minimise the effect of the possible differences in infrastructure in the centres which measure fitness and those which do not, a further sub-analysis was conducted only in the centres which measure fitness. In these centres, there are two types of patients: those whose fitness was measured and those whose fitness was not. A sub-analysis was conducted between the two groups of patients to investigate the same three outcomes mentioned above (figure 4.1)

4.3.2.1.1 ***Inclusion Criteria***

The inclusion criteria for this part of the study included patients who were aged 18 and over; had started CR; had undertaken a general assessment conducted at baseline (which may or may not have included a fitness test); had completed a post-CR assessment regarding their physical activity level, their self-perception of their physical fitness status and whether they had completed their CR programme.

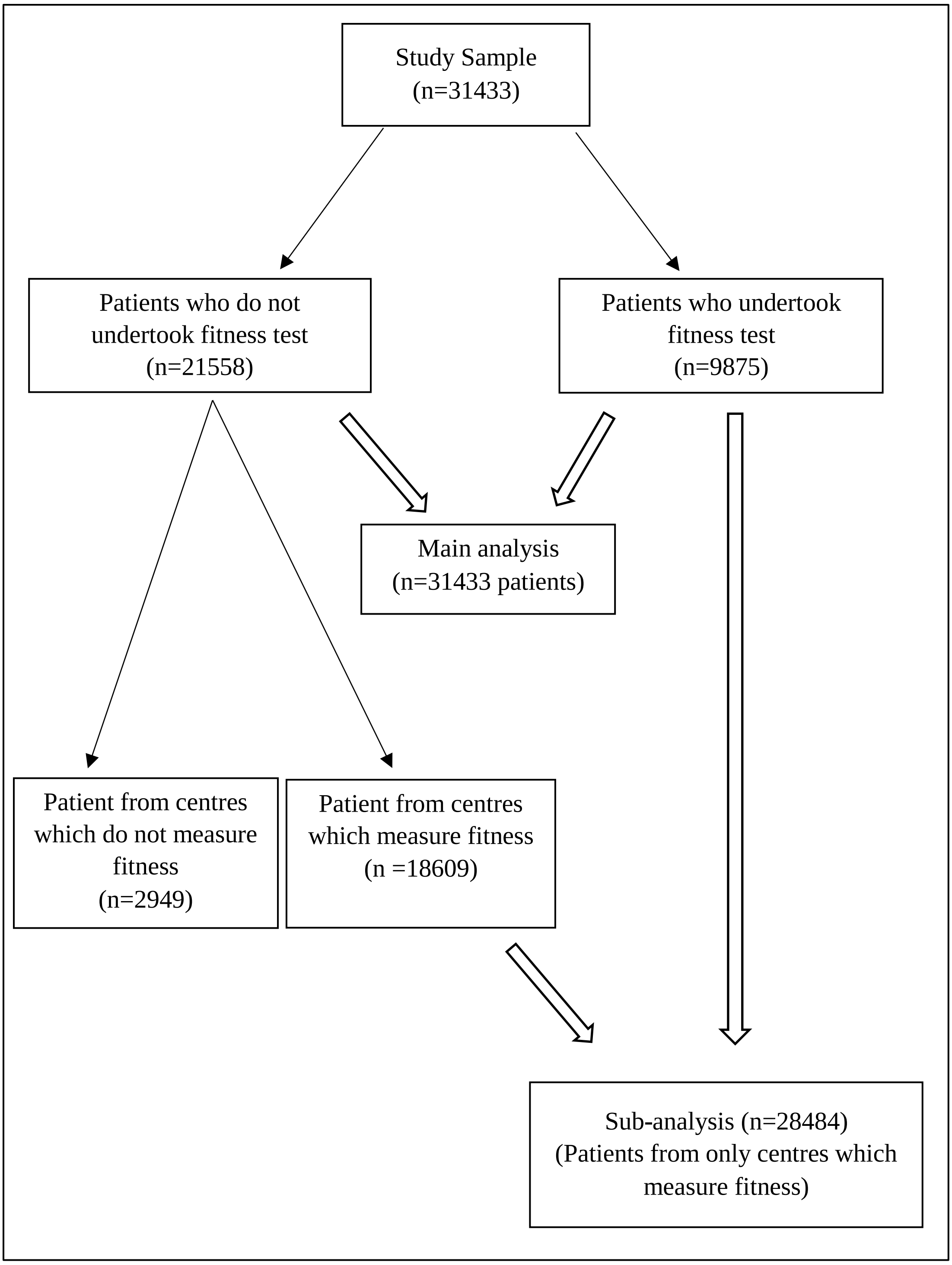

Figure 4.1. Flow diagram of main and sub-analysis in the study

4.3.2.1.2 ***Outcomes***

For this part of the study, the outcomes reported were whether the patient had completed their CR programme (Yes = 1, No = 0), met the physical activity recommendations (Yes = 1, No = 0) and recorded their self-perception of physical fitness (high intensity = 1, low intensity = 0).

Patients were considered to have completed the CR programme if their post assessment measurement and the completion date were recorded, and were classified according to whether they had met the recommended physical activity level at the end of the CR programme (150 minutes per week). The patients were also categorised according to how they perceived their own physical fitness status using the physical fitness scale taken from the Dartmouth COOP tool, which measures health-related quality of life and is used as part of a patient's routine assessment before starting a CR programme in the UK (NACR, 2015). In this scale, patients are asked to identify the hardest physical activity that they had done during the previous week. Patients were given a numerical value of 1 if their definition of the hardest physical activity they were able to do for a period of two minutes in the previous week was self-assessed as 'moderate' to 'very heavy' activity on the physical fitness scale- for example, walking at a medium pace or carrying a heavy load on level ground (25 lbs / 10 kgs). Patients were given a numerical value of 0 if they described the 'light' activities on the fitness scale as the most physically demanding.

4.3.2.2 Part two: comparison between centres which measure fitness and those which do not

The second part of this study was a comparison between the two types of centres: centres which used an objective fitness measurement such as the Incremental Shuttle Walk Test (ISWT), the 6-minute walk test, the step test, the bicycle ergometer or the treadmill to assess patient fitness at baseline, and those which did not measure patient fitness. The comparison was conducted according to the service delivery performance indicators that are used in the NACR audit. In this specific sub study the analytical comparison was mostly descriptive with minimal interferential statistics due to the small number of centres which did not measure fitness (9 centres).

4.3.2.2.1 ***Inclusion criteria***

In this part of the study, centres were included if they replied to the survey and entered their patients' data onto the NACR database during the period January 2015 to January 2016.

4.3.2.2.2 ***Outcome***

The comparison between the two types of centres was conducted according to the service delivery performance indicators, the presence of staffing, and the existence of a multi-disciplinary team (MDT). The aim of these performance indicators is to set a minimum level of service delivery across the UK.

4.3.3 Analyses

Beyond descriptive statistics an independent t-test was performed to compare the difference in the means of the continuous variables of baseline characteristics between the two groups of patients and chi-square tests were performed for categorical variables.

Logistic regression was used to investigate the association between the two types of patients (those whose fitness was measured and those whose fitness was not) and the outcomes. Factors taken into account were those previously identified in the literature as known confounders including age, gender, Body Mass Index (BMI), employment status (employed, unemployed or retired), marital status (single, in a current relationship, previously in a relationship), total number of comorbidities (<3 or ≥ 3), ethnic background (white-British or other), smoking status (smoker, stopped since the CR event or non-smoker), meeting the physical activity recommendations (Yes, No), diagnosis/reason for referral (MI, PCI, CABG, HF, valve surgery and others), hypertension (Yes, No), family history of heart disease (Yes, No), hypercholesteremia (Yes, No), diabetes (Yes, No) , anxiety (Yes, No), depression (Yes, No) or musculoskeletal comorbidities (Yes, No), experience of a previous event (Yes, No), the time from event to start of the CR, duration of the CR (in weeks) , the total number of sessions. Other variables which were also taken into account were self-reported physical fitness (Dartmouth COOP scale), social support (Dartmouth COOP scale), whether the programme was supervised or self-delivered, and if the programme was conducted in a group or individually (Appendix 8.4.2).

The level of performance of the centres (high, mid or low), the existence of an MDT (Yes, No) and the volume of patients in the centres were also taken into account as confounders to minimise any differences between the centres. Significance in this study was set at the $p < 0.05$ level. A robust Standard Errors (SE) method was used, namely the cluster-robust sandwich estimator, to take account of the nested nature of the data, that is, patients treated within centres. If this is accounted for, the assumption of the independency of observations will be met (Rogers, 1993; Williams, 2000) (Section 3.41).

4.3.3.1 Multiple imputations

Due to the nature of a retrospective study, it is not uncommon to have missing values in some variables. The missing values ranged from 5% to 20 % with the highest percentage being for social support domains as measured on the Dartmouth COOP scale. The variable which included missing variables were employment, marital, smoking and physical activity statuses, the number of sessions, the duration of the programme and the time from event to start of the CR programme, whether the programme was supervised or self-delivered and whether the programme was conducted in a group or individualy. Under the assumption that missing values were missing at random, a multiple imputation with chained equations (Royston, White and Wood, 2011) was conducted using 20 imputed data sets to replace the missing values (see section 3.3.1). Furthermore, age and gender were entered in the multiple imputation procedure as passive variables in addition to the main outcomes, since adding such variables to the process is recommended. The results of the pooled estimates were combined using Rubin’s rule. Descriptive analyses and the multiple imputation process were performed using SPSS software version 24 and the logistic regression analysis was performed using STATA SE software version 15.

4.4 Result

Prior to the study analysis, the fitness status of patients in the NACR data from 2013 to 2017 was described to gain a general impression of fitness measurements in this population. The analysis showed that only 27% of patients who started CR had undertaken an objective fitness test. Of them, 49% had undertaken a fitness test at the end of their CR programme.

In the NACR data the results of fitness tests are reported in terms of the distance walked during the ISWT or the 6MWT, or as METs estimated from the treadmill, bicycle ergometer or step test. The ISWT was the most common test as it was used to assess 47% of patients who had a baseline fitness test, the 6MWT was used by 32% and 21% used either the treadmill, bicycle ergometer or step test (Figure 4.2).

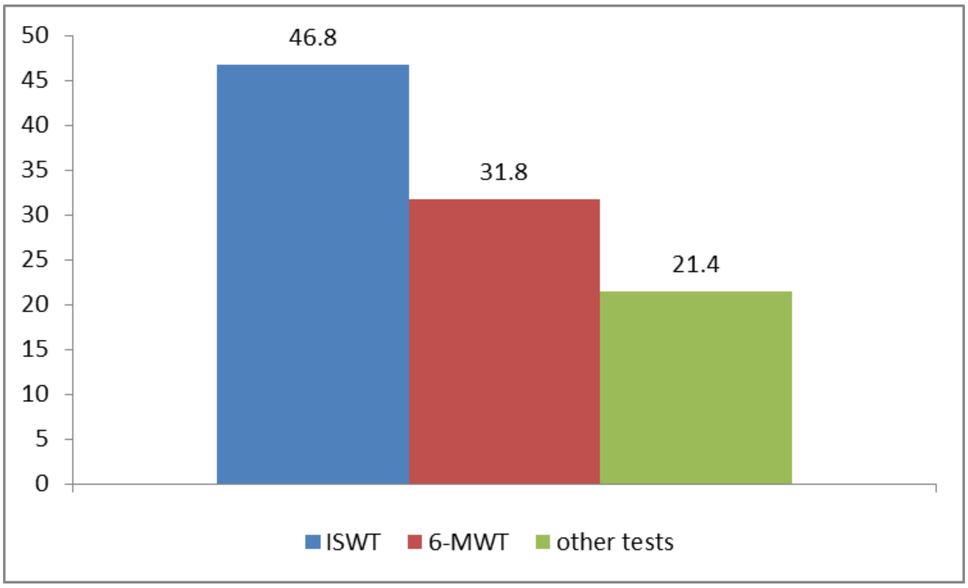

Figure 4.2 Percentage of fitness tests that were reported in the NACR.

4.4.1 Part one: outcomes related to patients' fitness measurement status

Data relating to a total of 31433 patients were included in the study, 73% of whom were male, with a mean age of 65.20±11.80 years. The patients were divided into two groups according to whether their fitness had been measured at baseline using an objective fitness test or not. The baseline characteristics and demographics are summarised in Table 4-1.

In our sample 9875 patients had their fitness measured while 21558 did not. There was no difference in age between the patients who took part in the fitness test and those who did not. In terms of gender, the percentage of females in the two groups was similar (25%) and (27%) respectively. However, the presence of some comorbidities was higher in patients who undertook the fitness test such as hypertension (37.9%), a family history of heart disease (23.3%), hypercholesterolaemia (28.8%), diabetes (16.6%), depression (5.6%), anxiety (5.2%) and Musculoskeletal comorbidities (21.5 %). For those patients who did not undertake a fitness test, the percentages for the same comorbidities were (30.8%, 15.6%, 20.8%, 13.5%, 4.0%, 3.2% and 15.6% respectively.

Table 4-1 Baseline characteristics of patients with and without a fitness test

Baseline Characteristics	Overall (n = 31433)	Patients without a fitness test (n=21558)	Patients with a fitness test (n=9875)	P-value
Mean age, years (SD)	65.2 (±11.8)	65.7 (±12.0)	64.2 (±11.5)	< 0.001
Gender, males (%)	73.4	72.6	74.9	< 0.001
Ethnicity, British (%)	81.7	80.9	83.3	< 0.001
Mean BMI >30 (%)	31.9	31.8	32.0	0.71
Diabetes	14.5	13.5	16.6	< 0.001
Hypertension	33.0	30.8	37.9	< 0.001
Dislipidaemia	23.3	20.8	28.8	< 0.001
COPD	2.4	2.2	2.8	0.001
Anxiety	4.1	3.2	5.1	< 0.001
Depression	4.9	4.0	6.6	< 0.001
Family history	18.0	15.6	23.2	< 0.001
Musculoskeletal comorbidities	17.4	15.6	21.5	< 0.001
Physical activity status (150 min/week) (%/yes)	39.9	40.7	38.2	<0.01
QoL Physical fitness status (%)	41.7	41.3	42.1	0.29
3 < comorbidities (%)	30	26.9	36.7	< 0.001
Smokers %	6.9	7.3	6.4	< 0.001
MI	12.6	14.2	9.1	< 0.001
MI/PCI	32.3	31.2	32.5	0.55
PCI	17.3	17.0	17.8	0.08
CABG	16.0	15.1	17.7	< 0.001
Heart failure	4.9	4.8	5.1	0.10
Angina	3.5	2.8	3.8	< 0.001
Valve surgery	6.3	5.8	7.3	< 0.001
Other	7.2	7.1	7.5	0.14
Previous event	5.0	4.9	5.1	0.43
Employment status				
Employed	29.4	29.8	28.9	0.20
Unemployed	17.0	14.9	19.8	< 0.001
Retired	53.6	55.3	51.3	< 0.001
Marital status;				
In a relationship	77.6	77.0	78.7	0.006
Previous relationship	14.1	14.2	13.7	0.33
Single	8.3	8.8	7.6	0.004

In terms of completing CR, 83% of the patients whose fitness was measured completed their CR compared to 76% of those who did not undertake a fitness test. By the end of the CR programme using data relating to meeting physical activity recommendation, the percentage of patients who did not undertake a fitness test rose to 68% while the percentage of those who undertook a fitness test was 70%. The same trend could be seen in the data relating to self-reported physical fitness (Dartmouth COOP tool) with 73% and 76% respectively.

The analysis showed that after taking account of other confounders, patients whose fitness was measured at entry to the programme were 1.38 times (CI 95% 1.04-1.83) more likely to complete it. However, there was no significant difference in the likelihood of meeting the physical activity recommendations or patients' perception of their own physical fitness (according to the Dartmouth Coop Scale) between the two groups (Table 4-2), this analysis was conducted on 12704 patients who had a recorded regarding this physical activity and self–reported physical fitness physical subset (Dartmouth COOP) at the end of their CR programme.

Table 4-2 Regression findings for association between whether the patients' fitness had been measured and the outcomes*.

Outcome	Odds Ratio	[95% CI]		P value
Completion of programme	1.38	1.04	1.83	0.02
Meeting physical activity recommendations	1.10	0.80	1.52	0.57
Physical fitness (Dartmouth QoL tool)	1.10	0.89	1.34	0.38

*Patients whose fitness was not measured used as a reference group

4.4.1.1 *Sub-analysis in patients who attended centres which measured fitness*

A sub-analysis was conducted in patients who attended centres which routinely measured fitness to establish if the likelihood of CR completion of the programme was consistent between the patients whose fitness was measured (9875) and those whose fitness was not (18609). In this sub-analysis, there was a total of 28484 patients with a mean age of 65.1(± 11.8) years. 27% of them were female. Table 4-3 summarises the baseline and demographic characteristics of these patients.

The results showed that patients whose fitness was measured were 48 % more likely to complete the CR programme than those whose fitness was not. However, in terms of meeting the physical activity recommendation or the patients' perception of their own fitness, there was no difference and this analysis was conducted on 11793 patients who had a recorded regarding the physical activity and self–reported physical fitness physical subset (Dartmouth COOP) in this group (Table 4-4)

Table 4-3 The baseline characteristics of patients, used in the sub-analysis, who undertook a fitness test and those who did not (from the centres which measured fitness)

Baseline characteristics	Total	Patients without a fitness test (n=18609)	Patients with a fitness test (n=9875)	P-value
Mean age, years (SD)	65.1 (±11.8)	65.6 (± 12.0)	64.2 (±11.5)	< 0.001
Gender, males (%)	73.3	72.4	74.9	< 0.001
Ethnicity, British (%)	81.2	80.9	83.3	< 0.001
BMI >30 (%)	32.3	32.5	32.0	0.49
Diabetes	14.6	13.6	16.6	< 0.001
Hypertension	32.9	30.3	37.9	< 0.001
Dislipidaemia	23.4	20.5	28.8	< 0.001
COPD	2.4	2.2	2.8	0.001
Anxiety	4.3	3.4	6.1	< 0.001
Depression	5.0	4.1	6.6	< 0.001
Family history	18.0	15.3	23.2	< 0.001
Musculoskeletal comorbidities	17.8	15.8	21.5	< 0.001
Meeting physical activity recommendation (150 min/week) (%/yes)	39.9	40.9	38.8	< 0.006
Physical fitness status on QOL (%)	41.3	40.5	42.1	0.04
3 < comorbidities (%)		27.1	36.7	< 0.001
Smokers %	7.1	7.7	6.4	< 0.001
MI	12.6	14.5	9.1	< 0.001
MI/PCI	31.3	30.7	32.5	0.02
PCI	16.7	16.2	17.8	< 0.001
CABG	16.0	15.0	17.7	< 0.001
Heart failure	5.4	5.5	5.1	0.16
Angina	3.7	4.2	2.8	< 0.001
Valve surgery	6.5	6.1	7.3	< 0.001
Other	7.7	7.7	7.5	.053
Previous event	4.9	4.8	5.1	0.18
Employment status:				
Employed	29.1	29.8	28.9	0.69
Unemployed	18.0	16.3	19.8	< 0.001
Retired	52.9	54.5	51.3	< 0.001
Marital status:				
In relationship	77.5	76.7	78.7	.002
Previous relationship	14.0	14.1	13.7	0.45
Single	8.5	9.1	7.6	< 0.001

Table 4-4 Regression result for association between whether the patients' fitness had been measured and the outcomes in this study (in centres which measured fitness)

Outcome	Odds Ratio	[95% CI]		P value
Completion of programme	1.48	1.12	1.94	0.01
Meeting physical activity recommendations	1.10	0.84	1.45	0.49
Physical fitness (Dartmouth QLF tool)	1.11	0.88	1.40	0.36

4.4.2 Part two: A- The Survey

According to the NACR 2017 report, 303 CR programmes delivered core CR in the UK. Of them, 224 entered their data electronically in the NACR portal. The survey was sent to the 303 centres. After 12 weeks the responses from 152 centres were returned. Of these, 118 centres were registered with NACR dataset. Of the 152 centres, 139 (91%) stated that they conduct a fitness test at the beginning of the rehabilitation programme while the remaining 13 do not use any objective fitness test.

The main reason given by 12 centres for not conducting a fitness test with their patients was a lack of time (92%). Other reasons cited by the centres were a lack of staff reported by 6 centres (46%), a lack of space given by 5 centres (38%) and 3 centres (30%) stated a lack of equipment prevented them from conducting the fitness test (Figure 4.3) The ISWT and the 6-minute walk test are the most commonly used tests in centres. The step test, the bicycle ergometer test and the treadmill test were also used. Sixty-nine per cent of the centres that measure fitness reported that the test is conducted by a physiotherapist, 43% of the centres stated that an exercise specialist runs the test while in 55% of the centres a nurse manages it.

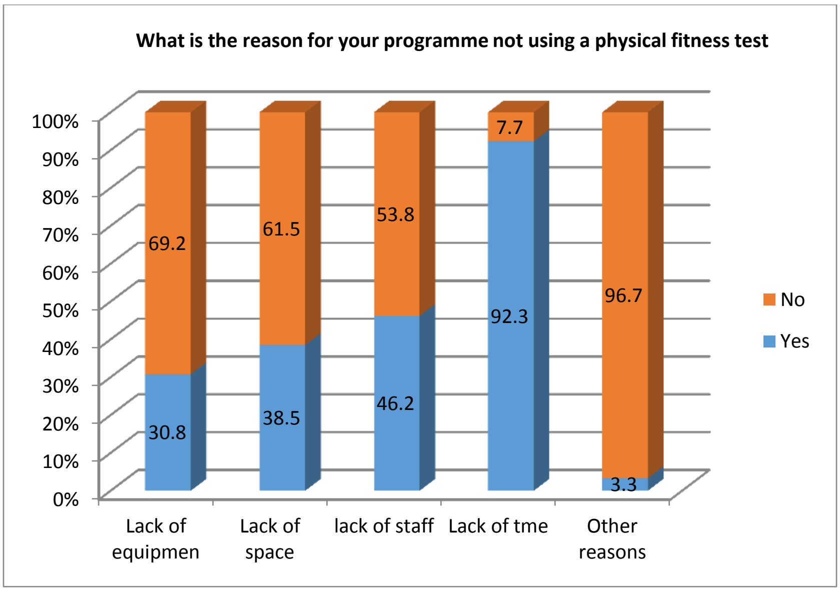

Figure 4.3 The reasons for programmes not using a physical fitness test

4.4.3 Part two: B- Comparison between centres which measure fitness and those which do not

Of the 118 centres which returned the survey and were registered with NACR, 102 (93 centres measure fitness, while 9 do not) had data relating to their patients' fitness status while the remaining 16 centres had only recently joined the NACR. These 102 centres will be used in the study comparing centres which measure fitness and those which do not. This comparison will be conducted according to service delivery performance indicators (Figure 4.4) and whether there is an MDT in the centres.

The first standard was "Did the centre have all five priority groups?" Centres will be considered as having met the standard if the services are provided to the following types of patients namely: MI, PCI, CABG, HF. All centres but one of those which do not measure fitness (89%) and 93% of the centres that measure fitness met this standard.

The second standard was "Did the programme have a median duration of 56 days or longer?" Centres measuring fitness were shown to have met this standard (70%). In contrast, only 44% of the centres which did not measure fitness reached this standard.

The third standard was “Did the patients who started CR have assessment 1?” Both types of centre showed approximately the same percentage (77%) in terms of meeting this standard while in terms of the fourth standard, which was “Did the patients who started CR have assessment 2?”, 78 % of the centres which do not measure fitness met the standard compared to the 67% of centres which measure fitness. The fifth standard was “Did the MI/PCI patients have a short wait time?” 43 % of the centres which measure fitness met this standard compared to only 33% of the centres which do not measure fitness. This trend also applied to the sixth standard which was “Did the CABG patients have a short wait time?” as centres which measured fitness and those which did not accounted for 47 % and 44% respectively.

Thirty-nine percent of the centres measuring fitness were classified as high-performing centres while 54% and 18% of the centres measuring fitness were classified as middle and low performers respectively according to the service delivery performance indicators. However, only two centres (22%) which do not measure fitness were rated as high performers, while 66% and 11% were classified as middle and low performers respectively.

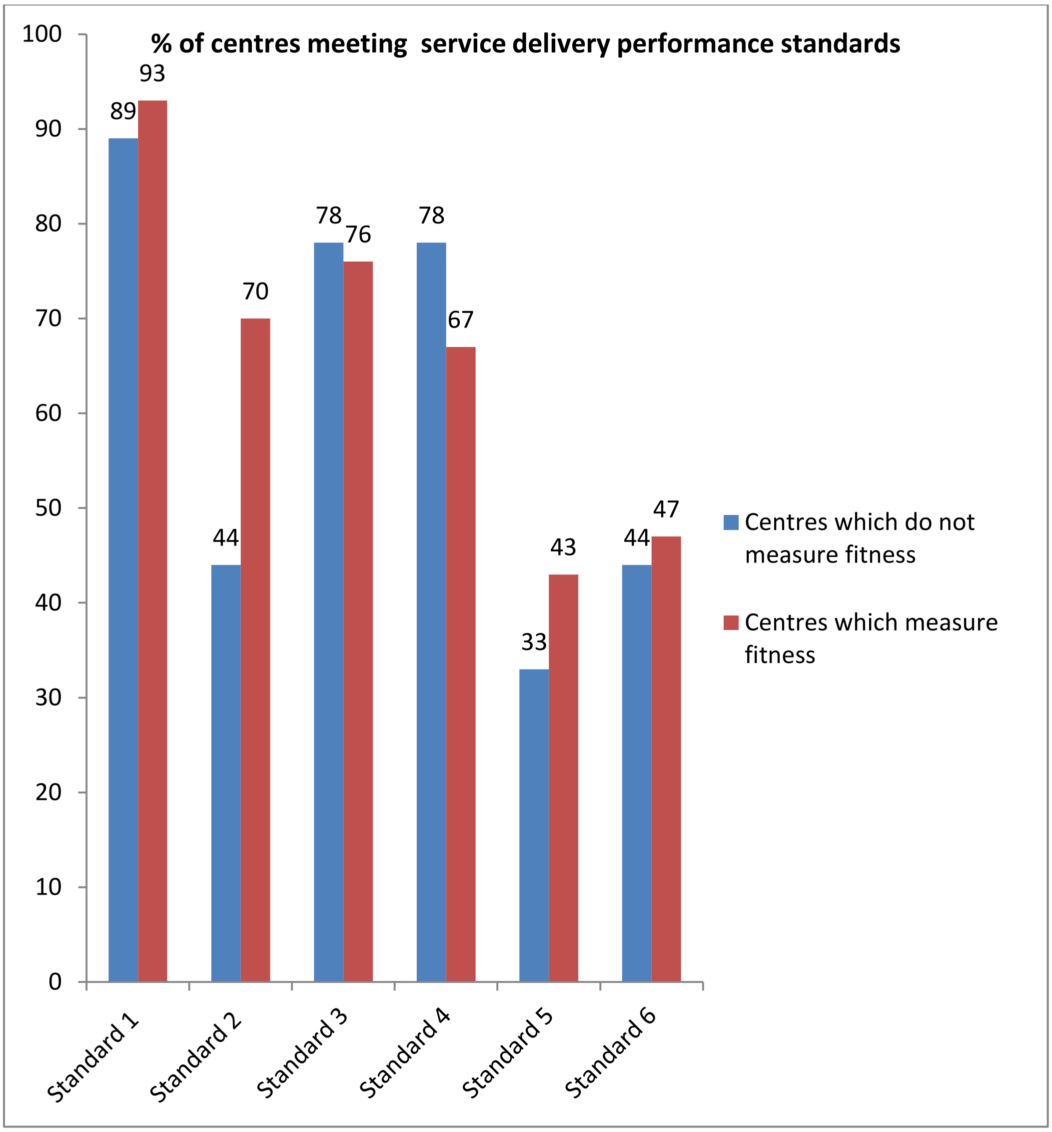

Figure 4.4 Percentage of CR programmes meeting each service delivery standard

4.4.3.1 Staff and MDT

In this section, a descriptive analysis of the staff who work in these two types of centre will be given (Figure 4.5). There was little difference in the number of nurses in the centres which measured fitness and those which did not at 98% and 100% respectively. In terms of physiotherapists, physio assistants and doctors, the picture was slightly different with the centres measuring fitness having a higher percentage at 82%, 44% and 11% respectively. In contrast, centres which do not measure fitness had 67%, 22% and 0% respectively for the same health professionals.

The centres which do not measure fitness had higher percentages for the following health professionals: exercise specialists (89%), dieticians (89%), psychiatrists (33%) and administrative support (89%) compared to centres which do measure fitness with (53%), (67%), (24%) and 77%) for the same health professionals.

In terms of MDT, the BACPR recommends that each CR centre should have at least three health care professionals. All the centres which did not measure fitness met this recommendation while of those centres which measured fitness, all except six centres did not meet the MDT recommendation (94%).

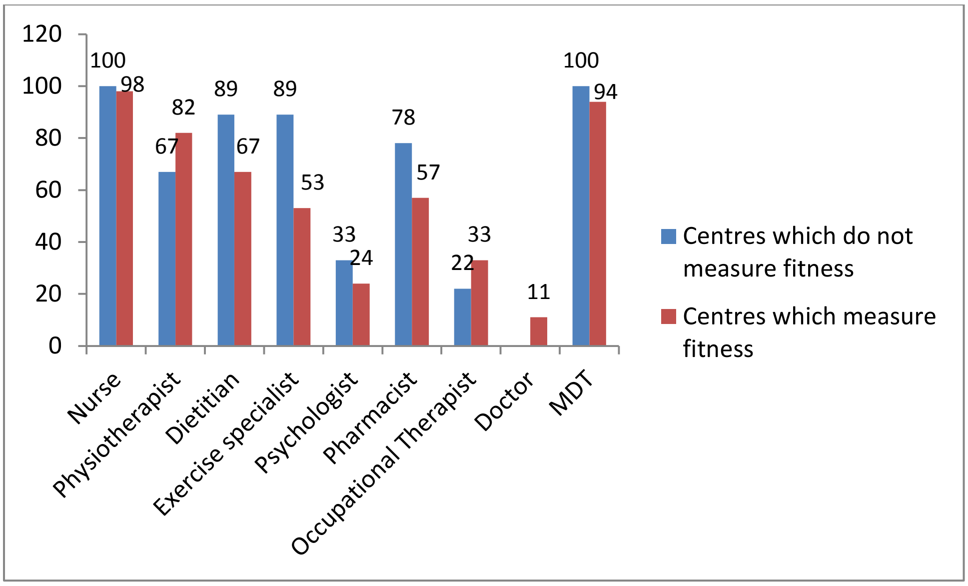

Figure 4.5 Percentage of each type of professional in both groups of centres

4.5 Discussion

Despite the recommendations to conduct an objective fitness test prior the start of a CR programme, the data from the UK audit showed that less than one third (27%) of the CR patients who joined a CR programme had undertaken this assessment. According to the survey conducted in this study, 90% of the UK centres stated that they generally conducted fitness assessment prior to the start of the CR programme. However, NACR data relating to patients from these centres showed that only 31% of patients had had their fitness assessed.

Although some CR programmes do not enter data to the NACR these findings remain important for providers, commissioners and professional associations involved with CR.

4.5.1 Part one: Comparison between patients whose fitness was measured and those whose fitness was not

The primary goal of this study was to investigate whether there is an association between measuring fitness at baseline and the likelihood of programme completion. In addition, a further goal was to examine whether this measurement has an effect on meeting the physical activity recommendations and patients' perception related to their physical fitness according to the Dartmouth Coop scale at the end of the CR programme. Measuring patients' fitness at baseline has been strongly recommended by various CR bodies in order to prescribe a safe level of exercise intensity, to stratify patients' risk, and to determine the amount of supervision and monitoring required (Arena et al., 2007; Mezzani et al., 2012; ACSM's, 2010; ACPICR, 2015; BACPR, 2017).

The result of this multi-variable analysis showed that measuring fitness at baseline might play a role in motivating patients to complete their programme by increasing their awareness of their fitness capability, which may result in an increase in patients' confidence in their ability to do physical activity. The findings showed that patients whose fitness was measured were 36% more likely to complete their CR programme compared to those whose fitness was not measured.

In terms of the physical activity recommendations (150 minutes per week) and the self-perception of fitness (Dartmouth COOP tool), the findings showed there was no such association between the two groups of patients (those whose fitness was measured and those whose fitness was not) and these measurements. Physical activity, which is defined as "*any bodily movement, produced by skeletal muscles, that results in energy expenditure"* (Caspersen, Powell and Christenson, 1985) *(p128)*,is measured in this study using a self-reported questionnaire which is given to the patient pre- and post-CR programme as a part of the assessment. The patient confirms whether they have met the physical activity recommendation (150 minutes over 7 days) or not by giving the response Yes or No. This self-reported measure has been found to be less valid and reliable compared to direct measurements (Alharbi et al., 2017). However, Alharbi et al conducted a narrative literature review on physical activity measurements and they concluded that there is no definitive physical activity measure recommended due to a lack of strong evidence. Due to variations in the CR population, such as age, severity of disease and diagnoses, measuring physical activity in the CR setting is problematic(Le Grande et al., 2008).

The patients in this study came from two types of centre: centres which measured fitness and those which did not. Although the multi-variable analysis controlled for centre volume, the presence of an MDT, and the classification of centres according to their performance indictors, there might be some possible differences in infrastructure between the two types of centres. Therefore, to minimise this effect, a sub-analysis was conducted only in patients who attended centres which measured fitness. However, even in these centres, the majority of patients were shown not to have had their fitness measured. The sub-analysis showed a consistency with the previous results in that patients whose fitness was measured at baseline were 1.48 times more likely to complete their CR programme. The results of this study, which have not been shown before, shows that patients are 48% more likely to complete CR if fitness is assessed. This is one of the largest modifiable service-level characteristics reported in CR. Nevertheless, no association was found in terms of meeting the physical activity recommendations or the patients' self-perception of their own fitness according to the Dartmouth COOP scale between the two groups in this sub-analysis.

4.5.2 Part two: comparison between centres which measure fitness and those which do not

A larger percentage (70%) of centres which measure fitness at baseline met the standard for the median duration of the CR programme (56 days or more). This is in line with previous results from Doherty et al (2017) that showed 66.5% of centres met this criterion. However, the percentage of centres which do not measure fitness (44%) is smaller than in the Doherty et al. study. In the Doherty et al. study, however, no differentiation was made between centres which measure fitness and those which do not.

This trend is also apparent with the third and fourth standards regarding wait time where a higher percentage of MI/PCI (57%) and CABG (52%) patients were seen within the recommended wait time in centres which conduct a fitness assessment at baseline. The percentage for meeting the standard for the MI/PCI wait time was higher than those reported previously e.g 49% for MI/PCI while the percentage for CABG patients was similar (54%). However, the percentages of centres which do not measure fitness that met the wait time standard for MI/PCI and CABG patients were smaller (33% and 44% respectively) than those reported by Doherty et al. It is generally held among practitioners that measuring fitness might delay the patients' start of the CR programme (Reeves, Gupta and Forman, 2016), however, the findings showed that a higher percentage of centres which measure fitness met these standards regarding wait time for MI/PCI and CABG patients compared to centres which do not measure fitness.

The percentage of centres which measured fitness which met the second standard relating to the baseline assessment was similar to that reported in the Doherty et al. study (70% vs 72%), while the percentage of centres which did not measure fitness but met the second standard was smaller (40%). In terms of the third standard regarding the assessment on completion of the programme, the percentages for both types of centres was higher than those reported in the Doherty et al. study (56%).

In terms of high-performing centres, compared to the requirements for NCP-CR (Furze et al., 2016) and the NACR based study (Doherty et al., 2017), the centres which measured fitness in this study showed a higher percentage (30% versus 39% respectively) while the centres which did not measure fitness in this study had a lower percentage of 18% (2 centres). However, these two centres, despite being classified as high performers, conducted a baseline assessment but failed to include a fitness assessment. This might highlight the need for future BACPR standards to specify more exactly what the baseline assessment should include, as a fitness assessment is the basis for prescribing exercise intensity for individual patients. Future NACR reporting should make this a priority as the present standards and reporting of assessment nationally is potentially misleading.

4.5.2.1 Staff and MDT

It is recommended by the BACPR that CR should be delivered by a MDT of skilled and experienced staff (ACPICR, 2015; BACPR, 2017). The existence of MDT staff was reported by all the centres which do not measure fitness and a high percentage of those centres which do (94%), which is similar to the national average (NACR, 2017).

All the centres which do not measure fitness reported that they had nurses on their team and 98% of centres which measured fitness recorded the same. This is in line with the NACR report (97%). In terms of physiotherapists, the centres which measure fitness had a higher percentage than the national average (82% and 71% respectively) while 67% of the centres which do not measure fitness reported having a physiotherapist on their staff while exercise specialists were more commonly found in centres which did not measure fitness.

Despite the existence of MDT staff and a professional who usually conducts the fitness test in the majority of centres, only a small percentage of patients in these centres undertook a functional capacity baseline assessment, which is considered a basic tool to assist in the tailoring of programmes for patients. Therefore, it might be more appropriate, at a programme level, to align CR staff with the clinical CR tasks that reflect their training. This should also be considered as part of the next set of BACPR standards so it is clear who is responsible for conducting this functional capacity assessment. This clarify in role of existing core NHS staff in CR programmes may positively influence patients' perception of the need to do a fitness assessment.

These results in line with a previous study (Brodie, Bethell and Breen, 2006). Brodie et al. conducted a study to establish programme details, staffing levels, data collection and funding in England. Questionnaires were sent to 28 centres, one in each Strategic Health

Authority and key staff in each centre were also interviewed. In terms of staffing, all centres reported having an MDT. Each centre had a nurse and the majority of centres also had a physiotherapist and dietician. In terms of exercise testing, it was found that 71% of the included centres reported using a range of methods, including treadmill tests (in 10 centres), ISWTs (in 5 centres), step tests (in 3 centres) while two centres used the 6MWTs which fits with BACPR and ACPICR recommendations for a range of approaches. .

The strength of this study is the large amount of clinical data referring to routine clinical practice in the centres and the use of a robust analysis that took account of the nested nature of the data where patients were treated within centres. In addition, a multiple imputation technique was used to replace missing values and maximise the sample size in the study. A multivariable analysis was also used to adjust for bias and potential confounders. A sub-analysis which was conducted minimised any potential effect of differences in infrastructure between the two types of centre. However, this study is limited as only 159 centres responded to the survey out of a possible 303 centres contacted. In addition, the number of centres which do not measure fitness is small in this study (only 9 centres).

4.6 Conclusion

Measuring patients' fitness at baseline is strongly associated with completing CR programme which has never been shown before. Patients were 1.48 times more likely to complete CR if fitness is assessed which represents one the largest modifiable service-level characteristics reported in CR. Therefore, in light of this, clinicians should consider conducting an actual physical fitness test on all patients. Centres that measure fitness also appear to have higher percentage in meeting the service delivery performance standard than those which do not, particularly in term of waiting time which would also help them achieve key elements of the NCP-CR certification requirements.

However, whether fitness was measured or not was poorly associated with meeting the physical activity recommendations (150 mins per week) and patients' self-perception of physical fitness according to the Dartmouth COOP scale.

4.6.1 Recommendations:

1. Clinicians should seek to include physical fitness assessment into their practice for all relevant patients.

2. BACPR should put a stronger emphasis on training CR practitioners in the use of physical fitness tests. The next version of the BACPR standards should also stress the importance of physical assessment not only as a means of providing data to assist exercise prescription but also because it is one of the biggest determinants of CR completion.

3. The next set of BACPR standards should make it clear whose responsibility it is the conduct the functional capacity assessment, thereby aligning the appropriate CR staff with the clinical tasks that reflect their training.

4. NACR should, as part of its annual report, give a clearer breakdown on the types of assessment carried out by programmes, especially physical fitness, which is known to improve the likelihood of completing CR. The BACPR and NACR could use these findings to help shape their future CR certification approach.

Chapter 5. Evaluation of determinants of walking fitness in patients attending cardiac rehabilitation

5.1 Abstract

Aim: To investigate the ability of patients' baseline characteristics to predict the distance walked during the Incremental Shuttle Walk Test (ISWT) in the Cardiac rehabilitation (CR) population and to produce reference values to guide practice.

Methods: Secondary analysis was conducted on National Audit Cardiac Rehabilitation (NACR) data collected between January 2010 and August 2015. Patients (n=8863) were included if they were ≥18years and had a recorded ISWT score assessed before starting CR. Stepwise regression was used to identify factors predicting the ISWT distance. Age, gender, BMI, height, weight; presence of hypertension, dyslipidaemia or diabetes; smoking, self-reported physical fitness (Dartmouth COOP tool) and physical activity were independent variables. ISWT distance was the dependent variable. The 25th, 50th and 75th percentiles of the ISWT distance were used as reference values.

Results: Age and gender explained 27% of the variance of the distance covered in the ISWT (R^2 = 0.27, adjusted R^2= 0.27, $P < 0.001$). This percentage increased to 32% when the self–reported physical fitness Dartmouth COOP subset was added to the equation. Reference values using age and gender categories were developed.

Conclusions: Significant factors for predicting the walking fitness in the CR population were age, gender and self-reported physical fitness (Dartmouth COOP scale), with age being the best predictor. The age and gender reference values produced represent a potentially valuable tool to be used in the clinical setting. These results could help practitioners in their initial expectations of patients' performance in the ISWT, aid them in establishing the level of risk in terms of functional capacity, enable them to interpret the test results in order to patients of their fitness level in relation to their peers, and could help in the setting of realistic CR goals.

5.2 Introduction

Assessing functional capacity at baseline and end of program in patients attending cardiac rehabilitation (CR) is strongly recommended in the clinical guidelines and national standards (Arena et al., 2007; Piepoli et al., 2015; BACPR, 2017). Assessing the patient's fitness level at the beginning of the program allows the appropriate intensity of exercise to be prescribed, determines the level of supervision and monitoring required, and allows for the assessment of the effectiveness of the intervention at the end of CR program. (Mezzani et al., 2012; BACPR, 2017)

Using laboratory maximal exercise tests on treadmills or cycle ergometers to assess functional capacity by directly measuring the maximal oxygen uptake (Vo_2 max or Vo_2 peak) is regarded as the gold standard (ACSM's, 2010). However, these tests are not widely available as they are costly and require sophisticated technical resources and skilled staff to administer them (Arena et al., 2007; Houchen-Wolloff, Boyce and Singh, 2014). Furthermore, these tests might not be suitable for elderly patients or those with severe comorbidities (Casillas et al., 2013). Less technical types of testing to assess functional capacity are used as standard in Australasia and the UK and some Europe countries (Price et al., 2016). These tests are in the form of the Incremental Shuttle Walk Test (ISWT) and 6-minute walk test. Compared to the gold standard methods, these functional fitness walk tests are simple and safe to use and are a reasonable surrogate measure of functional capacity. (Singh et al., 1992) In the UK, the most commonly used field test, in CR and COPD patients, is the ISWT which is an objective test widely used in clinical settings to assess the extent of physical fitness (Pepera, McAllister and Sandercock, 2010; Houchen-Wolloff, Boyce and Singh, 2014). This type of test is shown to be strongly correlated with the cardiopulmonary exercise test (CPET) (Parreira et al. 2014). It is a submaximal, incremental, externally-paced test that to evaluate functional capacity based on the distance covered during the assessment (Singh et al., 1992; Neto and Farinatti, 2003). The recommended protocol is a 20-minute test followed by a 30-minute rest period and then the test is repeated.

The best outcome of the two tests is recorded (Singh et al., 1992; Grove, 2013; Holland et al., 2014). However, in routine clinical practice the ISWT is generally performed just once (Pepera et al., 2013) despite emerging research suggesting that the learning effect may influence the distance achieved as evidenced through a second baseline test (Jolly et al., 2008) in clinical stetting programmes struggle to carry out even a single baseline fitness test (Grove, Jones and Connolly, 2017), which makes undertaking a second test unrealistic (Pepera, McAllister and Sandercock, 2010). To date very few studies have tried to establish reference values as a comparison with the first ISWT attempt and where it has been attempted the sample size has been insufficient within the proposed categories (Cardoso et al., 2016; Pepera et al., 2013).

Healthy individuals have been shown to walk double the distance of cardiac patients during the ISWT (600-800m vs 300-400m respectively) (Cardoso et al., 2016). Predicting the distance covered during the ISWT has been attempted in several studies in healthy populations (Jürgensen et al., 2011; Dourado, Vidotto and Guerra, 2011; Probst et al., 2012; Dourado et al., 2013; Harrison et al., 2013) However, to date, only two studies have been published using a CR population (Cardoso et al., 2016; Pepera et al., 2013). The Pepera et al study and the Cardoso et al study explained 20% and 25% of the variance in distance walked and the latter attempted to produce reference values for cardiac rehabilitation patients. Age, height, BMI and presence of diabetes were found to be significant predictors in the Cardoso study while Pepera found only height and BMI were significant. However, the limited number of female participants and the small number of centres used limits the generalisability and clinical usefulness of these results. The need for robust reference values for the distance walked during the ISWT which use the patients' baseline characteristics remains important. These values could assist in decision making in a clinical setting as they help remove uncertainty around patient risk assessment before the CR programme begins and aid in future exercise prescription. These values could help the clinician decide whether a second ISWT is necessary and inform patients in relation to their level of fitness at baseline and enable the setting of goals for rehabilitation (Harrison et al., 2013).

5.3 Literature review

5.3.1 Predicting ISWT distance:

Several studies have been carried out to determine the predictors of the ISWT distance. Seven of these studies were conducted on healthy adult populations from Brazil, the UK, Japan, Spain and India. One studied healthy children and adolescents from Brazil and two studies investigated the cardiac rehabilitation population in the UK (Table 5.1). These studies will be discussed in turn below.

5.3.1.1 Predicting ISWT distance in healthy subjects

The first study aimed to establish reference equations for predicting the distance covered during the ISWT in healthy people (Jürgensen et al., 2011). Jürgensen et al. recruited 131 Brazilian participants (70 females and 61 males) aged 40 to 84 years (mean age 58±11 years). A model was created based on demographic (age and gender) and anthropometric (height and weight) attributes as independent variables. Participants were classified according to their BMI into four groups: obese group (40>BMI>30 kg/m2), overweight group (BMI, 25-29.9 kg/m2), normal weight group (BMI, 18.5–24.9 kg/m2) and underweight group (BMI< 18.5 kg/m2), 30). The average distance walked during the test was 606 ±167. The regression analysis revealed that age, gender, height and weight jointly explained 50.3% of the total variance in the distance covered during the ISWT. To verify this model, they measured the ISWT distance of an additional 20 participants with the same inclusion criteria. They found that the there was no difference between the measured walking distance of the second group and the distance predicted by the model (Jürgensen et al., 2011). However, the small size of the study sample might limit the generalisability of its results. In addition to that the authors also did not state the coefficient of determination (R^2) for each of these independent variables which is established practice in reporting regression findings. R^2, preferably ‘adjust R^2’ is important as it explains how each variable accounted for the variance in the distance covered during the ISWT or which variable was the best predictor of variance. Furthermore, they excluded smokers and the obese (BMI>40 kg/m2) who are prevalent in Western societies and should therefore be taken into consideration.

Table 5-1 Studies which predicted ISWT distance

Study	Sample and population	Inclusion criteria	Predictors	R^2	Mean distance walked
Jürgensen et al (2011)	131 Brazilian 70 females 61 males	Healthy Aged 40 - 84	Age, height, weight and gender	.50	Females 443 ± 117 m Males 606 ± 167
Dourado et al (2011)	98 Brazilian 40 males	Healthy Aged 60 ± 9 years BMI of < 30Kg	Age, height, gender and weight	.64	Females 417 ± 103 m males 600 ± 91 m
Probst et al (2012)	243 Brazilian 103 males 140 females	Aged 18-83	Age, gender and BMI	.71	Females 720 [480-910] Males 1010[755-1200] m
Harrison et al (2013)	140 British	Healthy age groups (40-49, 50-59, 60-69 and >70)	Age, BMI, FEV_1, QMVC and DASI.	.50	737 m (183 m)
Dourado et al (2013)	103 Brazilian 54 women 49 men	Healthy Aged ≥ 40	Age, gender, height, BMI, Age, gender, height, BMI, and Hand grip strength Age, gender, height, BMI,LBM and TBF	.65 .73 .68	510 ± 148 m

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Study	Sample and population	Inclusion criteria	Predictors	R^2	Mean distance walked
Itaki et al (2014)	399 Japanese 134 males 265 females	Healthy Aged 20 - 80	Age, gender and height	.53	580m

Study	Sample and population	Inclusion criteria	Predictors	R^2	Mean distance walked
Gimeno Santos **et al (2015)**	568 Spanish Male 48%	Healthy Aged 62 +11	Females Age and weight Males Height and resting heart rate	.53	Females 497 (154)m Males 632 (191)m
Lanza et al (2015)	108 Brazilian children and adolescents	Healthy Aged 6 - 19	Age, sex and BMI	.48	Girls 889 + 159m Boys 1060 + 254m
Pepera et al (2013)	1st cohort: 16 participants 9 males 7 females	CR patients referred to an outpatient CR	1st cohort: Step length Leg length Height	 .68 .58 .58	479 139 m
	2nd cohort: 113 participants 82 males, 31 females	CR patients referred to an outpatient CR	2nd cohort: Height and BMI	 .20	 360 (90) m

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Study	Sample and population	Inclusion criteria	Predictors	R^2	Mean distance walked
Cardoso et al (2016)	547 population 415 males 132 females	CR outpatients Aged 63 +11	Age and gender	.25	Females 269m (+118)
			Females age, height and the presence of diabetes	.24	Males 395m (+165)
			Males BMI was added to these factors	.25	

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In a study with quite similar results, Dourado et al (2011) aimed to predict the distance covered in the 6-minute walk test and the Incremental Shuttle Walk Test using demographic and anthropometric variables namely age, gender, weight and height in addition to grip strength (GS) (Dourado, Vidotto and Guerra, 2011). The mean distance walked during the ISWT was 474 ±131 m. They found that age, height, gender and weight accounted for 65% of the variance in the distance covered during the ISWT in 90 healthy subjects over 40 years with a mean age 60 ± 9 years (40% males). Eight additional subjects (5 of them females; 59 ± 10 years) were used as a validation sample. Adding grip strength (GS) as an independent variable to their model had no significant effect. However, this study excluded people with a BMI of >30Kg/m2 and the size of the validation sample was very small. The methods of recruitment in both studies (Jürgensen et al., 2011; Dourado, Vidotto and Guerra, 2011) might have caused selection bias. In addition neither study evaluated the agreement between the actual ISWT and the predicted distance using appropriate approach such as Bland Altman plot (Osborne, 2014; Giavarina, 2015).

In 2012, Probst et al conducted a study which included 243 participants (103 males and 140 females) from a wider age range (18-83) to establish a reference equation to ISWT distance in apparently healthy participants. The participants walked an average of 810 metres [572 - 1030] based on the best test measurement from the two ISWTs. They used demographics and anthropometric variables that are routinely measured in clinical assessment. Age, gender and BMI as independent variables explained 71% of the variance in ISWD. When the model was applied to the validation sample that consisted of 23 subjects with the same inclusion criteria, there was no difference between the actual and predicted distance (839 ±269 m vs. 838± 271 m respectively)(Probst et al., 2012). The validated sample was small and the coefficients of determination (R^2) values were not reported for each predictor neither did the authors state which variable was the best predictor of the distance covered during the ISWT. The independent variables used in regression analysis were not reported. Probst et al (2012) reported that 99% of the participants reached their maximum predicted heart rate. However, 45% of the participants used drugs which are known to alter heart rate and/or blood pressure, which might have influenced the accuracy of the formula that is used to predict the maximum HR: (220-age in years) (ACSM's, 2010).

A study by Harrison et al (2013) investigated age-specific normal values for the ISWT in a healthy British population. The 140 participants (60% females) aged between 40 and 90 were divided into four age groups (40-49, 50-59, 60-69 and >70). The mean distance walked during the test by participants was 737 (±183) m. There was no difference between males and females in the distance walked in the ISWT whereas, there was a difference between the oldest and youngest age bands. The authors developed a reference equation that explained 50% of the variance of the distance walked during ISWT. They used more variables than in previous studies: in addition to age and BMI they used forced expiratory volume (FEV1), quadriceps maximum voluntary contraction (QMVC) and Duke Activity Status Index (DASI). The authors reported that the reference equation developed by Probst et al (2012) only explained 15% of the variance in the ISWT distance in their population (Harrison et al., 2013). However, 19 participants who completed the ISWT and another 7 participants who achieved the maximal on (QMVC) were excluded because the authors could not ensure that those participants had exerted maximum effort. In addition, the measurement of some variables used in this study, such as lung function, (QMVC) and DASI, may not always be possible in routine clinical practice which might limit the generalizability of the study result.

In the same year, Dourado et al (2013) conducted a study on 103 healthy participants in order to determine reference values for the ISWT. Of them, 54 were women and 49 were men, aged over 40 years. They used three models to predict the ISWT distance. In the first model, age, gender, height and BMI were the independent variables and explained 65% of the variance in the ISWT distance. In the second model, hand grip strength (HGS) was added explaining 73%. In the third model, lean body mass (LBM) and total body fat (TBF) were added to the variables used in the first model. This explained 68% of the variance. However, there were several limitations to the study. Firstly, the sample size was small in relation to the number of independent variables used (Miles and Shevlin, 2003; Nathans, Oswald and Nimon, 2012). In addition, the participants were all aged over 40 and the models were not validated. Some of the variables which were used are not routinely measured in clinical practice.

Another study consisting of 399 healthy participants aged between 20 and 80 years (134 males and 265 females) from Japan was conducted by Itaki et al (2014). The mean distance walked by the participants was 580m. The results showed that age, gender and height were significant predictors and explained 53% of the variance in the ISWT distance (Itaki et al., 2014). The same researchers conducted another study to investigate whether there was any difference in the distance walked during ISWT between 207 males and 322 females across different age groups (20–29, 30–39, 40–49, 50–59, 60–69, and 70–80 years) (Nishinakagawa et al., 2014). The researchers found that apart from those in the > 70 year old group, males walked further than females, and the difference in the distance was statistically significant. In addition, they reported that there was a direct correlation between age and distance walked with the younger groups walking further than the older groups.

This result was similar to one from a Spanish population obtained by Gimeno-Santos et al, who carried out a study on 568 healthy participants from 17 different centres across Spain. The mean age of the participants was 62 (±11) years. The mean distance walked by the males was 632 (±191)m and for females 497 (±154)m. It was found that age and weight were the only predictors in females and explained 53% of the variability in distance walked during ISWT whereas in the males height and resting heart rate, in addition to age and weight, explained this variance (Gimeno-Santos et al., 2015).

A more recent study was conducted by Agarwal et al (2016) involving 862 healthy Indian participants, 50% of them males, to produce reference values for ISWT. The authors divided the participants into three groups based on age: Group 1: 17-40 years (males = 288, females = 289), group 2: 41-65 years (males = 98, females = 97), and group 3: >65 years (males =

45, females = 45) this classification of age groips was based on groups as per Erickson's classification as the authors state. It was established that age and gender explained 68% of the variance in the distance walked during the ISWT. Males walked 10-30% further than females, the distance walked declined with the increase in age across the three groups. The model created in this study was also not validated and the agreement between both the estimated and actual distance walked during the ISWT was not measured. In this study, smokers were excluded and the reference values which were produced for the over 65 age groups were based on a small group of only 45 participants for both genders.

Producing a reference equation for the ISWT distance has not only been restricted to adults. A study involving children and adolescents was conducted by Lanza et al (2015). The researchers studied 108 healthy participants (52% female) with ages ranging between 6 and 19 years. In this population 48% of the variance in distance walked was explained by age, sex and BMI. The authors report that the adolescents (>13 years) walked further than the children (<12) and the girls walked a shorter distance than the boys (889 + 159m vs 1060 + 254m respectively).

5.3.1.2 Predicting ISWT distance in CR population

Pepera et al 2013 conducted a study to determine whether demographic, anthropometric and selected biomechanical measures can predict shuttle walking test distance in patients with cardiovascular disease. This was the first study conducted on a population of patients undertaking CR. Participants were from two cohorts. The first cohort was composed of 16 patients (nine males and seven females), who were participating in community-based cardiac rehabilitation. These patients had completed the outpatient cardiac rehabilitation programme successfully before being referred to a community-based CR programme and had achieved at least 5 METs in the exercise test during the outpatient phase of CR. This is one of the risk assessment criteria used to refer the patients to community-based CR. One hundred and thirteen patients (82 males, 31 females) who were referred to an outpatient CR programme at a local hospital comprised the second cohort. In the first cohort Pepera et al used step length, leg length and height separately as independent variables. Stepwise regression analysis showed that step length was the most predictive variable of ISWT distance at 66% of the maximum walking speed explaining 68% of the variance in the distance covered during the ISWT while leg length and height explained 58% and 57% respectively. However, step length and leg length were excluded as these measures are clinically impractical and not routinely used as assessments. Height was the only predictor variable used in the model. For the second cohort, Pepera et al used baseline characteristics commonly used in clinical practice (gender, height, weight, age, and BMI) to create a second model. The stepwise regression analysis indicated that 20% of the variance in the distance covered during the ISWT was explained by height and BMI. Height alone was the best predictor for ISWT distance (R2 = 0.17, SEE = 133 m) in this group. However, there were several limitations. The models developed in this study were based on a relatively small sample of participants who came from a narrow age range (69 years ± 9) and who were predominantly men. The result was based on an analysis using univariate predictors in the first cohort which did not account for the potential influence of other factors. In addition, the authors did not validate their final model or measure the agreement between the actual and predicted distance value.

The latest study, conducted by Cardoso and his group (2016), analysed the clinical records of 547 (415 males and 132 females) participants who were cardiac rehabilitation outpatients at four different UK hospitals in order to predict the distance walked during ISWT and to produce reference values for this type of patient. The participants' mean age was 63 (+11) years. There was a significant difference in the distance walked between males and females with a mean distance of 395m (+165) for males while females walked 269m (+118).

It was found that age was the best predictor and accounted for 16% and 20% of the variance in the distance walked in males and females respectively. The analysis showed that gender explained 11% of the variance in the whole group. As a result, the group was divided according to gender. Regression analysis revealed that age, height and the presence of diabetes were significant predictors which explained 24% of the variance in the distance walked in females. Adding BMI to these factors explained a total of 25% of the variance in males. The authors constructed reference data by dividing the patients according to gender and assigning each patient to one of 13 age bands from 25 to 90 (at 5-year intervals). Across all age bands, the values for males were higher than for females. However, in this study, the reference values produced were based on a very small sample size, particularly of females where there were only 10 on average in each age band, therefore these values could be considered non-representative. In addition, the significance of the presence of diabetes as a predictor should be cautiously interpreted as it was based on a small group of only 35 female participants. The authors did not state clearly in their method which variables were used in the regression models as independent variables and also did not report that they took any confounding variables into account. In addition to this, regarding the coefficients of determination (R2), the authors reported the value of R2 not the value of the adjusted-R2. However, it is known that the value of R2 does not reflect the true value of the explanation as it inflates as the number of independent variables increases. Also the models in this study have not been validated and the agreement between the predicted and actual distance walked ISWT was not assessed. These limitations could make the results less generalisable. The authors did not state the period of time which the patients' data relates to. It would also appear that the data from five female patients were not included in the analysis. Although this is a small number, the critical appraisal tools emphasise the importance of reporting any missing data.

5.3.2 The gap in the literature

The previous studies mentioned above in healthy subjects have identified age, gender, height, weight and BMI as the commonly determined key factors of the ISWT distance, which are frequently used as predictors of the distance walked during ISWT, there have only been two studies in the CR population to date attempting to determine the predictors and each study identified different factors.

The determination of reference values for ISWT distance as a measure of fitness is crucial particularly for CR patients. These values allow a comparison of the distance walked by an individual patient with other patients of the same gender and age, and with the established norms allowing the measurement of their distance to be benchmarked. This facilitates realistic clinical goals to be formulated, and could increase patients' motivation to undertake a CR exercise programme (Harrison et al., 2013). These values help clinicians make a decision concerning whether a second ISWT is necessary and also help in removing uncertainty around patient risk assessment before the CR begins. It is also valuable in giving patients feedback on their level of baseline fitness compared to their peers and aids in the setting of rehabilitation goals.

5.3.3 Rationale of the Study

Given the importance of the ISWT distance as a tool for assessing functional capacity, particularly in the CR population, and crucially to have reference values to establish what constitutes a normal value for this test, there is a lack of studies that determine the potential predictors of the distance walked and that establish reference values for the ISWT in the CR population. Therefore the aims of this study are to:

- determine the potential predictors of the distance walked during ISWT in the CR population

- establish what constitutes normal reference values across different age-bands and to propose an approach for benchmarking performance following the test.

5.3.4 The research questions being tested in this study

To what extent do patients' characteristics predict the baseline distance walked during the ISWT as a measure of fitness? The hypothesis will test if age, gender, height, weight, BMI and other NACR related variables are associated with ISWT distance.

5.4 Methods

5.4.1 Study design

The research design selected to address these research questions was an observational cross-sectional one. Secondary analysis was conducted on data extracted from the National Audit Cardiac Rehabilitation (NACR) from January 2010 to August 2015. This is the preferred design as it will enable large enough sample of patients to be investigated, using robust methods accounting for the number of variables included, which was one of the main limitation of the previous studies (see section 3.11).

5.4.2 Data Collection

This observational study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (Elm et al., 2007). Secondary analysis was conducted using anonymised individual patient data from the NACR database from 2010 to 2015. NACR is a national quality-assurance project which is designed to ensure that the optimum CR outcomes are achieved with patients with cardiovascular disease and that the CR programmes follow good practice as defined by the clinical minimum standards(NACR, 2015). The NACR data is collected under 251 approval by NHS Digital. The data is entered by the centres themselves into the NHS Digital online system who then remove patient identifiers and make an anonymised version available to the NACR. This database includes information concerning the patients' demographic and anthropometric details, initial event, risk factors, treatment, medications, fitness, physical activity status and clinical outcomes following CR (NACR, 2015) (see section 3.2.1) .

5.4.3 Inclusion criteria

Patients were included in the analysis, if the following conditions were fulfilled: they were adults (≥ 18years); were post myocardial infarction (MI), coronary artery bypass grafting (GABG), percutaneous coronary intervention (PCI) or valve surgery patients who had already been assessed at baseline before starting CR; they had undertaken the ISWT and hence their functional capacity had been assessed; and their information regarding age, gender, height, weight, BMI, comorbidities, depression and anxiety levels, and self-reported physical activity and fitness status had been recorded.

5.4.4 Sample size

There are different guidelines regarding the sample size requirement for multiple regressions. Tabachink and Fidell 2007 devised the following formula:

N> 50+8m (where N= total sample and m =the number of independent variables)

According to this formula, for example, a sample of 98 subjects is needed when 6 independent variables are used. Steven (1996), recommended 15 subjects for each independent variable. It has also been suggested that if stepwise regression is used, a ratio of 40 subjects for every predictor is needed. However, if the dependent variable is skewed, more subjects are required (Tabachink and Fidell, 2007).

5.4.5 Statistics

5.4.5.1 Statistical models used in this analysis

Data was presented as mean and standard deviations for the continuous variables (Age, BMI. Weight, Height, and ISWT distance walked) while the categorical variables were presented as a percentage. Independent t-tests and Chi-squares were used to determine the differences between males and females at baseline as appropriate. Pearson's correlation was used to study the relationship between the outcome and the potential predicted variables. The difference in the distance walked between males and females in general and across age bands was assessed using two-way ANOVA with post hoc Bonferroni test.

In order to validate the prediction model, it was cross-validated in an independent sample using the same inclusion criteria and population. The agreement between the actual ISWT distance and the predicted value was evaluated using the Bland-Altman analysis which plots the difference between the actual and the predicted values versus the mean values. Multiple imputation technique was used to replace the missing data, 20 iterations data set were created and the pooled results were reported. A P-value of <0.05 is considered to be significant.

5.4.5.2 Variables used in regression analyses

One of the aims of this study was to identify which factors can determine and predict the distance covered during the ISWT as a level of fitness at baseline in a CR population. Stepwise regression analysis, which is used to predict an equation and to investigate to what extent each independent variable could explain the variance of the dependent variable in the equation, was conducted.

Age, gender, BMI, height and weight were identified as independent variables prior to being entered into the regression analysis. These variables were chosen based on the findings in the literature. Interaction between age and gender was also assessed. The analyses also took into account known confounders of fitness, namely presence of diabetes, hypertension, or dyslipidaemia, smoking (Yes, No), ethnicity (British, non-British) and self-reported physical activity or self-reported physical fitness (Fell, Dale and Doherty, 2016). In this study, the self-reported physical activity level at baseline was based on meeting the 150-minute recommendation (Yes, No). The scale used in the self-reporting of physical fitness was taken from the Dartmouth COOP tool which measures health-related quality of life and is used as part of a patient's routine assessment before starting a CR programme in the UK. According to the literature, adding self-reported physical activity or fitness measurements as independent variables might make a valuable contribution to the prediction of functional capacity and might explain more of the variance (Jackson et al., 2009).

5.4.5.3 Outcome

The outcome (dependent variable) in this study was the distance covered during the ISWT in metres. This measurement was chosen as it is an absolute measure, easily interpreted by clinicians and meaningful for patients.

5.4.5.4 Cross-validation sample

Adjusted- R^2 value can be considered an indicator of whether the predicted models are valid and provide a better estimate of the population. However, using a cross-validation sample is the ideal method to check the validity of the models (Miles and Shevlin, 2003). In this study, the cross-validation sample was used from the 2016 data.

5.4.5.5 The assumptions of the regression

The assumptions of the regression model were checked and there were no violations. Certain statistical assumptions should be met before carrying out the multiple regression analysis namely linearity, independence of residuals, normality and avoidance of multicollinearity. The independence of residuals was met. There was no violation of the assumption of multicollinearity as the bivariate correlations between the independent variables were not higher than 0.9.The tolerance test value was greater than 0.1 and the VIF (Variation Inflation Factor) test value, which is the reciprocal of tolerance (1/tolerance), was below 10 (Tabachink and Fidell, 2007). The histogram and the Normal Probability Plot showed that the Regression Standardised Residual of ISWT was normally distributed and the assumption of normality was met (Appendix 9.5.1)

The value of the multiple correlation coefficient R, coefficient of determination R^2 and adjusted-R^2 was reported according to the recommendations from the literature (Neto & Farinatti 2003). However, in stepwise regression the variables which are entered are chosen based on statistical criteria. This means that certain variables could be excluded even if they are likely to be useful to the study. To overcome this issue, the 'Backaward' and 'Forward' approaches were also used also to verify the robustness of the model in this study.

5.4.5.6 3.4.6 Reference values

Reference values based on the age-gender model were produced using the 25th, 50th and 75th percentiles of the distance walked. Patients were classified into 9 age bands intervals starting from: group 1: $\leq$ 44 years (males = 357, females = 88), thereafter at 5-year categories group 2: 45-49 years (males = 473, females = 115), group 3: 50-54 years (males = 798, females = 141), group 4: 55-59 years (males = 985, females = 236), group 5: 60-64 years (males = 1085, females = 254), group 6: 65-69 years (males = 1209, females = 379), group 7: 70-74 years (males = 926, females = 337), group 8: 75-79 years (males = 701, females = 271) and group 9: ≥80 years (males = 359, females = 149).

5.4.5.7 Statistical Package

Data were analysed using IBM Statistical Package for Social Science version 24 (SPSS, Chicago, Illinois, USA).

5.5 Results

The study population comprised patients from 48 centres in the UK who had undertaken the ISWT as a baseline fitness assessment. Of the 8863 patients, 6893 (77.78%) were male and 1970 (23.22%) were female from the post myocardial infarction (MI), coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) and valve surgery population.

The patient demographics and the baseline characteristics are summarised in table 5.2 The mean age of the group was 63.26 ± 11.09 years, with ages ranging from 20 to 99 years, and the mean BMI was 27.86 ± 4.56 kg/m2. There was a significant difference between the mean age of males and females (62.7 ± 11 vs. 65.11 ± 11.24, $p < 0.001$) respectively. Males were also significantly taller (174.27 ± 7.00) than females (160.16 ± 6.64). The mean distance covered in the ISWT by the overall sample was 358.11 m ± 174.40. After taking account of age in the analysis, the males walked significantly further than the females (384.24 m ± 175.41 and 266.58 ± 135.94, $p < 0.001$ respectively (Figure.5.1)

The most prevalent comorbidities among the participants were hypertension, dyslipidaemia and diabetes. Seven per cent of the participants were smokers. Based on their self-reports, males were shown to be more active than females (43% vs 33%, p≤ 0.001 respectively) and perceived themselves to be fitter.

Table 5-2 Patient demographics and baseline characteristics

Factor	**Total sample**	**Male**	**Female**	**p-value**
Sample size	n=(8863)	n= 6983(77.8%)	n=1970 (23.2%)	
Age (years)	63.26 ± 11.09	62.73 ± 11	65.10 ± 11.25	≤ 0.001
Height (cms)	171.14 ± 9.11	174.27 ± 7	160.16 ± 6.64	≤ 0.001
Weight (kgs)	81.80 ± 15.51	84.78 ± 14.4	71.4 ± 14.8	≤ 0.001
BMI (kg/m^2)	27.86 ± 4.56	27.89 ± 4.29	27.81 ± 5.42	0.55
ISWT (m)[a]	358.11 ± 174.40	384.24 m ± 175.41	266.58 ± 135.94	≤ 0.001
Hypertension (%)	40.1	39.0	43.0	0.03
Dyslipidaemia (%)	31.3	31.2	31.8	0.62
Diabetes (%)	16.0	16.2	15.5	0.43
Physical activity*(%)	40.5	43.0	33.0	≤ 0.001
Physical fitness(%)**	45.4	48.0	35.0	≤ 0.001
Smokers (%)	7.3	7.2	7.7	0.46
MI[b] (%)	8.6	7.3	13.0	≤ 0.001
PCI[c] (%)	60.1	60.8	57.3	≤ 0.001
CABG[d] (%)	22.1	24.4	14.2	≤ 0.001
Valve surgery (%)	9.2	7.4	15.6	≤ 0.001

*Physical activity: based on meeting the 150-minute /week recommendation

**Physical fitness: taken from the Dartmouth COOP questionnaire

[a] Incremental shuttle walk test

[b] Myocardial infarction myocardial infarction

[c] Percutaneous coronary intervention

[d] Coronary artery bypass surgery

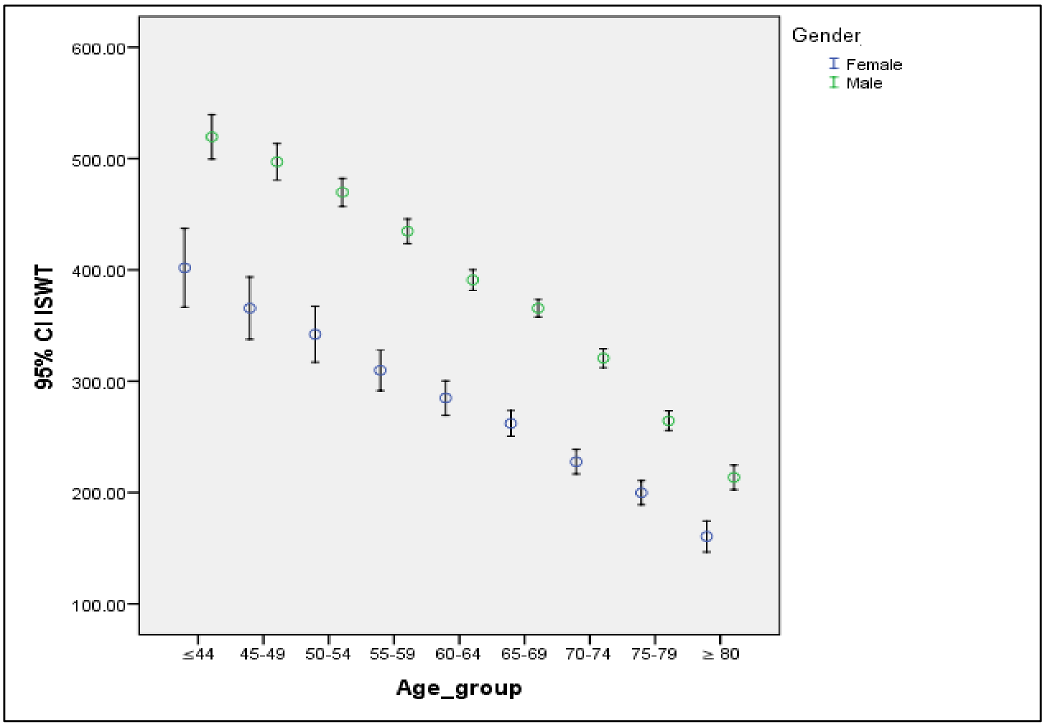

Figure.5.1 Difference in distance walked between males and females in each age band

The analysis showed that ISWT distance correlated significantly with age ($r = -0.46$, $P \leq 0.001$) and that age, gender and self-reported physical fitness scale variables were significant predictors of the distance walked during the ISWT. Stepwise regression analysis using age and gender as independent variables explained 27% of the variance in the distance covered during the ISWT (Table 5-3). The interaction between age and gender was statistically significant (Model 1) (Table 5-4) and is referred to as ordinal interaction as the predicted values cross over outside the range of observed values(Figure 5.2). Age was the best predictor explaining 21% of this variance ($r= 0.455$, $R^2 = 0.21$, adjusted $R^2=0.21$, $P< 0.001$). The strength of prediction increased to 32% when the self-reported physical fitness scale variable was added ($R^2 = 0.32$, adjusted $R^2= 0.32$, $P < 0.001$) (Model 2) (Table 5-5).

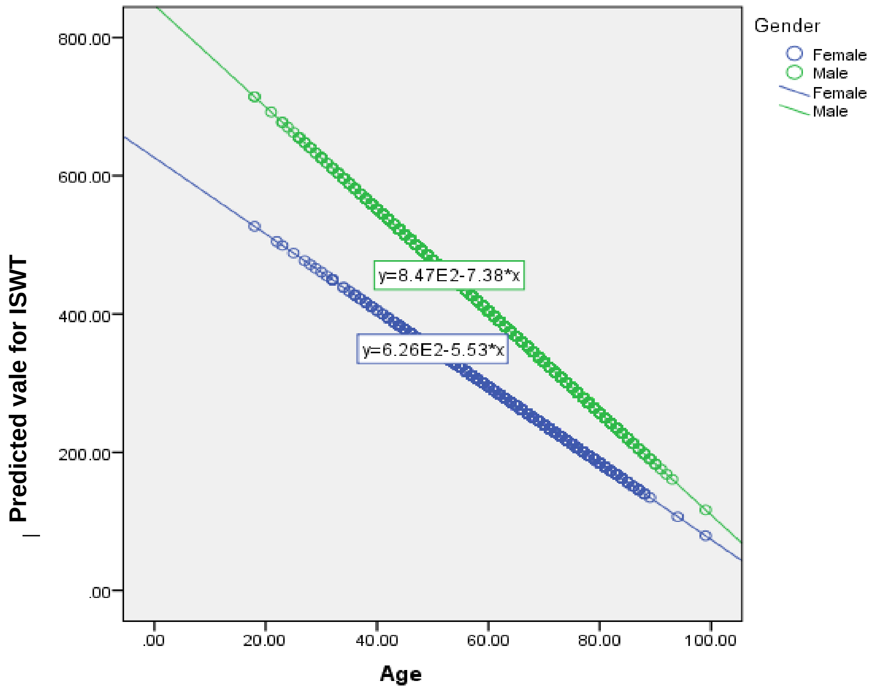

Figure 5.2. The interaction between age and gender

In this study, two models were constructed with the first using age and gender and the interaction between these factors (Model 1) (Table 5-4). These variables are easily measured in a clinical setting. However, as the self-report physical fitness scale variable was a significant predictor, a second model was devised adding this variable to the first model. The second model was considered as the main model in this study (Table 5-5) and was validated in the cross-validation sample.

Table 5-3 Age and gender as predictor variables

Variable	Unstandardised coefficient (b)	95% CI	P value
Age	-6.95	-7.23.to – 6.67	P> 0.001
Gender	101.18	93.7 to 108.66	P> 0.001
Constant	719.2	699.80 to 738.60	P> 0.001

Table 5-4 Predictor variables in model 1 for distance walked in the ISWT

Variable	Unstandardised coefficient (b)	95% CI	P value
Age	-5.53	-6.11 to – 4.94	P> 0.001
Gender	220.72	177.15 to 262.28	P> 0.001
Gender x age	-1.85	-2.52 to -1.19	P> 0.001
Constant	626.42	587.88 to 664.95	P> 0.001

Table 5-5. Predictor variables in model 2 for distance walked in the ISWT

Variable	Unstandardised coefficient (b)	95% CI	P value
Age	-5.01	-5.58 to – 4.44	P> 0.001
Gender	214.63	172.29to 265.98	P> 0.001
Gender x age	-1.90	-2.54 to -1.25	P> 0.001
Physical fitness scale*	81.53	74.80 to 88.26	P> 0.001
Constant	564.34	526.6 to 602	P> 0.001

*Physical fitness: taken from the Dartmouth COOP questionnaire

The equations which were developed in this study in order to predict the ISWT distance are:

626.42 - (5.53 x Age) + (220.72 x Gender) - (1.85 (Gender x Age))

(Where male = 1 and female = 0) (Model 1)

564.34 - (5 x Age) + (214.63 x Gender) + (81.53 x physical fitness scale) – (1.90(Gender x Age)) (Where male = 1 and female = 0) (Model 2)

To simplify the equation in model 1:

For males (where males = 1) the equation will be:

847.1- (7.38x Age)

For females (where females = 0) the equation will be:

626.42 - (5.53 x Age)

To simplify the equation in model 2: For males (where males = 1) the equation will be:

779 - (6.9 x Age) + (81.53x physical fitness scale)

For females (where females = 0) the equation will be:

564.34 - (5 x Age) + (81.53x physical fitness scale)

Table 5-6 Regression results for model 2

Predictor	**R**	**R^2**	**Adjusted-R**	**SE**	**R^2-change**
Age	.464[a]	0.215	0.215	154.56954	0.215
Physical fitness scale	.526[b]	0.276	0.276	148.40573	0.061
Gender	.570[c]	0.325	0.324	143.38881	0.048
Age X Gender	.572[d]	0.327	0.327	143.10679	0.003

There was no significant difference between the predicted distance and the actual ISWT distance in the two models: (358.10 ± 91.5 vs 358 ± 179) for the first model and (358.05 ± 99.8 vs 358.10 ± 174.5) for the second model.

The correlation between the predicted and the actual values was significant in both models ($r=0.53$, $p<0.0001$, $r=0.57$, $p<0.0001$, respectively). The Bland-Altman plots show an agreement between the predicted and actual ISWT distance as the majority of values fall within the range established by ± 2SDs, which indicates a good agreement between the actual and the predicted ISWT values (Figure 5.3 and Figure 5.4)

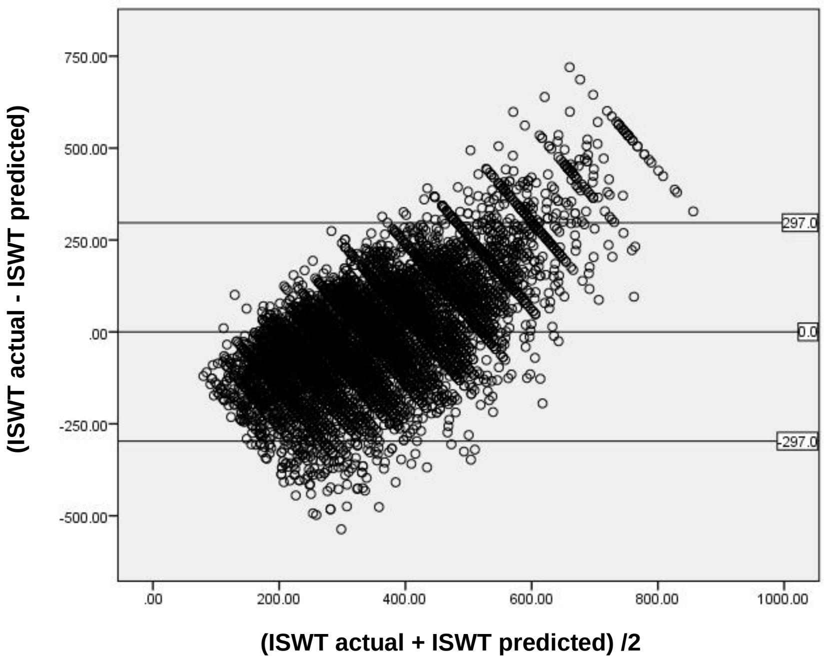

Figure 5.3 Bland Altman plot of the difference between the actual and predicted ISWT distance value derived from model1 plotted against the mean of the actual and the predicted value of the ISWT. The central solid line represents the central mean bias

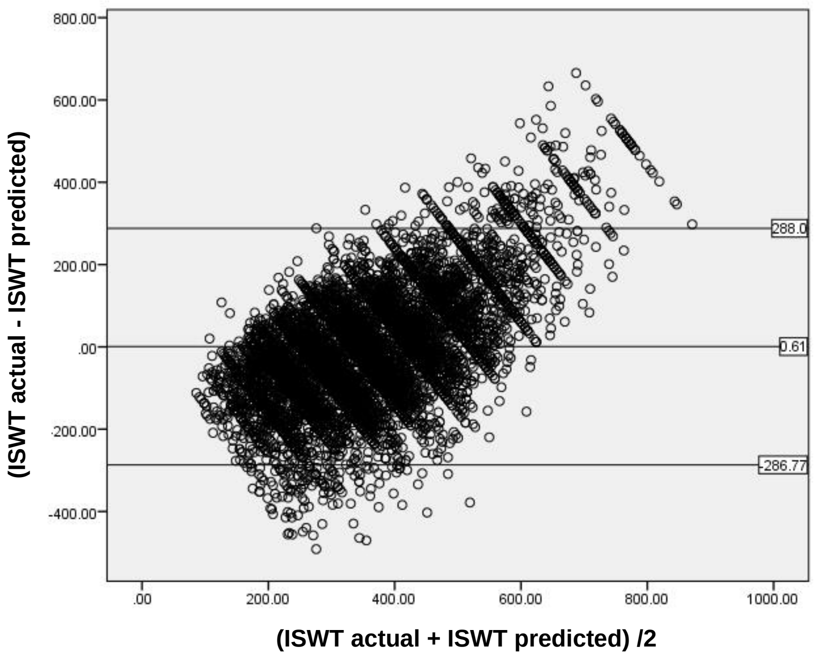

Figure 5.4 Bland Altman plot of the difference between the actual and predicted ISWT distance value derived from model 2 plotted against the mean of the actual and the predicted value of the ISWT. The central solid line represents the central mean bias

Although the following variables: BMI, height, weight, presence of hypertension, dyslipidaemia, diabetes, smoking, physical activity level and ethnicity, were statistically significant, when they were collectively taken into account in the analysis, none of them made a considerable contribution as predictors to the models and could not improve the power of models as the values of the variance which they explained were very small (<1%).

5.5.1 Missing data

The descriptive analysis of the data relating to the independent variables shows that there were only three variables with missing data. These were the self-reported physical fitness scale and the self-reported physical activity level variable both at 17% and the smoking variable which was 5%. To determine whether the missing data was missing completely at random or not, the Little's test was used, which resulted in chi-square = 13.022 (p=0.023). This indicates that a multiple imputation technique is recommended. Therefore, it was used to replace the missing values. The imputed variables were the self-reported physical fitness scale, the self-reported physical activity level variable and the smoking variable. The age, gender and reasons for referral variables were added as auxiliary variables to the imputation process, which could help in predicting the values of the imputed variables.

5.5.2 Cross-validation sample

Both predicted models in the present study were cross-validated. The cross-validation sample consisted of 889 participants whose data were extracted from the NACR database. Of them, 696 (78%) were male. The patient demographics and the baseline characteristics are summarised in Table 5-7. The average age of this group was 62.77 years (SD = 11.19). Males were younger (62.28±11.34 vs 64.56±10.48, P=0.012), taller (174.84±6.92 vs 161.15±716, P>0.000) and walked further during the ISWT (390.91±175.73 vs.281.00 ±130.45, P<0.000) compared to the females in this sample, which was a similar profile to the main sample. There was no significant difference between the actual ISWT distance and the predicted value of this distance (367.16 ±172.87 vs 366.39 ± 99.3, P=0.87). A statistically significant correlation was found between the actual and the predicted distance (r = 0.55, P < 0.000).

Model 1 explained 26% of the variance in the ISWT distance walked in the cross validation sample (r= 0.51, R2=26, F (311.74), p<0.001 whereas model 2 explained 30% of this variance (r= 0.55, R2=30, F (384.15), p<0.001). This resulted in a 1% and 2% shrinkage for model 1 and 2 respectively, indicating a good outcome (Osborne, 2014) which was similar to the prediction in the main sample. Figure 5.5 and Figure 5.6 show a good agreement between the predicted and actual ISWT distance values with only a few values falling outside the boundary of ± 2SDs.

Table 5-7. Patient demographics and baseline characteristics for validation sample

Factor	Total sample	Male	Female	p-value
Sample size	n=(889)	n= 696 (78%)	n=193 (22%)	
Age (years)	62.77 ± 11.19	62.28 ± 11.34	64.56 ± 10.48	0.012
Height (cms)	171.88 ± 8.97	174.84±6.92	161.15±716	≤ 0.001
Weight (kgs)	84.10 ± 15.951	86.42 ± 15	75.66± 16.5	≤ 0.001
BMI (kg/m^2)	28.47 ± 4.95	28.27 ± 4.57	29.13 ± 6.11	0.08
ISWT (m)[a]	367.16 ±172.87	390.91m ± 175.73	281.00 ± 130.45	≤ 0.001
Hypertension (%)	40.1	40.7	43.0	0.56
Dyslipidaemia	31.3	33.3	37.3	0.30
Diabetes	16.0	15.5	15.5	0.99
Physical activity*	40.5	44.0	33.0	≤ 0.001
Physical fitness**	45.4	47.0	36.3	≤ 0.001
Smokers	7.3	7.5	6.8	0.73
MI[b]	11.0	11.2	10.4	
PCI[c]	67.6	67.2	68.9	
CABG[d]	14.6	15.8	10.4	
Valve surgery	6.7	5.7	10.4	

*Physical activity: based on meeting the 150-minute /week recommendation
**Physical fitness: taken from the Dartmouth COOP tool
[a] Incremental shuttle walk test
[b] Myocardial infarction myocardial infarction
[c] Percutaneous coronary intervention
[d] Coronary artery bypass surgery

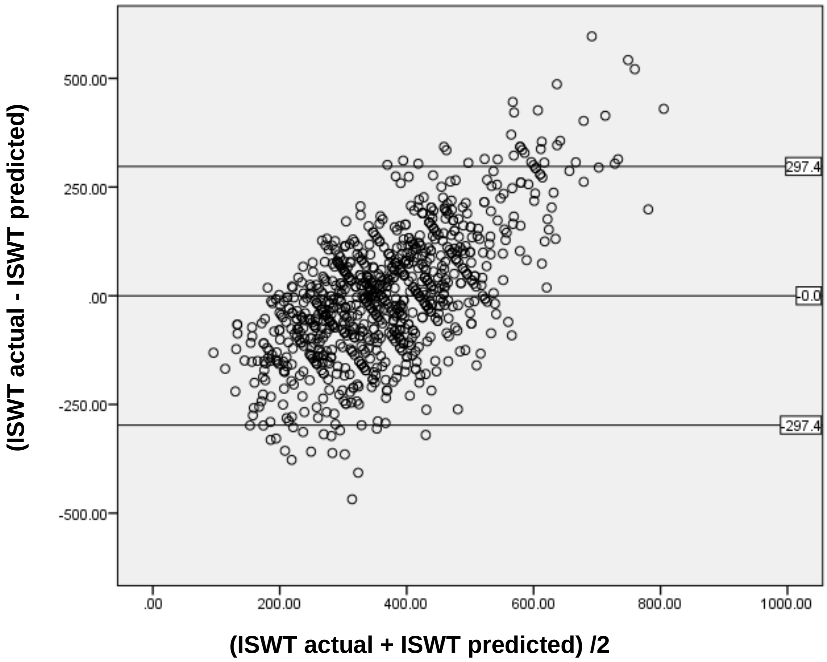

Figure 5.5 Bland Altman plot of the difference between the actual and predicted ISWT distance value in cross validation sample derived from model 1 plotted against the mean of the actual and the predicted value of the ISWT. The central solid line represents the central mean bias

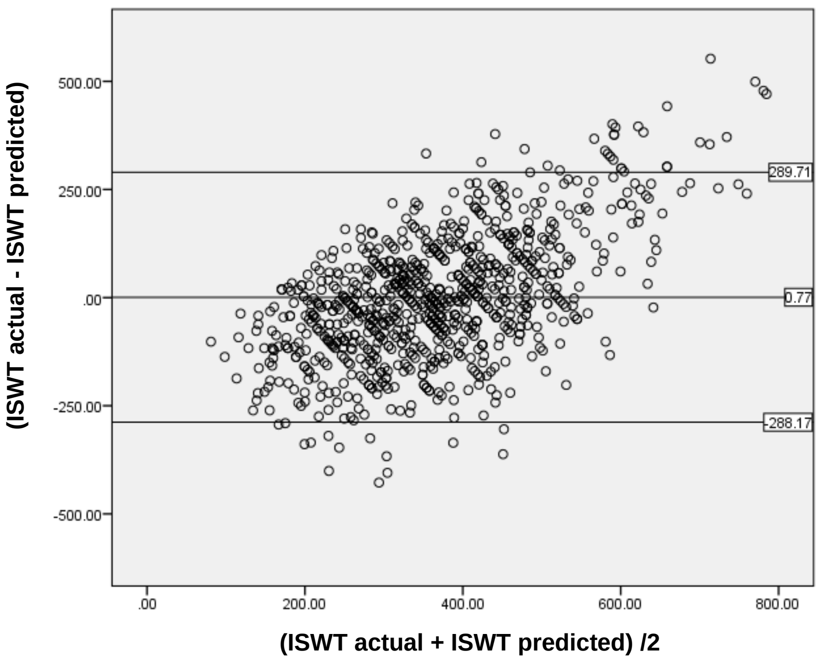

Figure 5.6 Bland Altman plot of the difference between the actual and predicted ISWT distance value in cross validation sample derived from model 2 plotted against the mean of the actual and the predicted value of the ISWT. The central solid line represents

5.5.2.1 *Comparison between study sample and those who did not meet inclusion criteria*

There was little difference between the study sample and the excluded group in terms of age and gender, however, there was no difference in BMI. The percentage of patients who met the physical recommendation and the percentage with hypertension was more apparent in the study sample. The percentage of PCI patients was higher in the group studied. There was no difference in the percentage of diabetic patients between the two groups.

Table 5-8 Comparison of baseline characteristics for study sample and non-valid group

Factor	Study sample	Excluded group
Sample size	n=(8863)	n=168292
Age (years)	62.7 ± 11.19	64.6 ± 11.85
Gender (male %)	78	74
BMI (kg/m^2)	28.47 ± 4.95	28.20 ± 5.24
Hypertension (%)	40.1	30.0
Diabetes	16.0	14.205
Physical activity*	40.5	28.00
Physical fitness**	45.4	40.6
Smokers	7.3	18.4
MI[b]	11.0	14.2
MI/PCI	36.0	31.5
PCI[c]	37.6	16.7
CABG[d]	14.6	17.2
Valve surgery	6.7	6.4

*Physical activity: based on meeting the 150-minute /week recommendation
**Physical fitness: taken from the Dartmouth COOP tool
[a] Incremental shuttle walk test
[b] Myocardial infarction myocardial infarction
[c] Percutaneous coronary intervention
[d] Coronary artery bypass surgery

5.5.3 Reference values

Tables 5.9 and 5.10 show the age-related reference values according to patient gender. In each age band the distances walked by the females were significantly shorter than the males. There was an inverse relationship between the values of mean distance walked and age bands for both males and females. The youngest age group (≤ 44 years) for both genders walked the furthest and the oldest age group (≥ 80) walked the shortest distance and this remained true for each centile value. Males walk significantly further than females across all age-bands.

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Table 5-9 Centile values for total distance walked during the ISWT by female patients assessed at entry to outpatient cardiac rehabilitation

Females

Age-band	*Sample*	*C 25*	*C 50*	*C 75*	*Mean*	*SD*
≤44	88	300	375	500	402	167
45-49	115	270	350	440	366	151
50-54	141	250	330	440	342	151
55-59	236	220	290	390	310	142
60-64	254	200	270	360	285	125
65-69	379	180	250	340	262	116
70-74	337	150	220	290	228	103
75-79	271	130	190	260	200	91
≥ 80	149	100	160	200	160	86

Age bands (years) in 5-year increments. C: centile value for distance walked in metres:

Table 5-10 Centile values for total distance walked during the ISWT by female patients assessed at entry to outpatient cardiac rehabilitation

Males

Age-band	*Sample*	*C 25*	*C 50*	*C 75*	*Mean*	*SD*
≤44	357	420	520	630	519	193
45-49	473	370	510	620	497	182
50-54	798	340	460	570	470	182
55-59	985	330	420	540	435	176
60-64	1085	280	380	490	391	156
65-69	1209	270	360	450	366	141
70-74	926	220	330	420	321	134
75-79	701	180	250	330	264	118
≥80	359	140	200	280	214	107

Age bands (years): in 5-year increments; C: centile value for distance walked in metres

Tables 5.11 and 5.12 below shows that the Metabolic Equivalent (MET) values corresponded to the distance walked based on the Buckley equation (Buckley et al., 2016). This table will help in risk stratification in terms of functional capacity. It shows that female participants up to the age of 70 years are at moderate risk (<7 METs and >5 METs) and those above this age are classified as high-risk patients. However, in males, patients below 60 years of age are classified as low risk and those between 60 and 80 are at moderate risk while those over 80 are high-risk patients.

Table 5-11 METs values based on the reference values for females

Females age-band	Mean distance	ISWT stage	Speed	METs
≤44	402	7	3.4	6.3
45-49	366	7	3.4	6.3
50-54	342	7	3.4	6.3
55-59	310	6	3.02	5.6
60-64	285	6	3.02	5.6
65-69	262	6	3.02	5.6
70-74	228	5	2.64	4.9
75-79	200	5	2.64	4.9
≥ 80	160	4	2.26	4.2

Table 5-12 METs values based on the reference values for males

Males age-band	Mean distance	ISWT stage	Speed	METs
≤44	519	8	3.78	7
45-49	497	8	3.78	7
50-54	470	8	3.78	7
55-59	435	8	3.78	7
60-64	391	7	3.4	6.3
65-69	366	7	3.4	6.3
70-74	321	6	3.02	5.6
75-79	264	6	3.02	5.6
≥80	214	5	2.64	4.9

5.6 Discussion

The current research represents the largest-scale UK study to date in a cardiac rehabilitation population. It aimed to determine the factors which best predict the distance covered in the ISWT at baseline CR assessment and to produce the reference values using national level data from routine clinical practice.

The main findings of this study were that age and gender were significant predictors of the variance in the distance walked during the ISWT with age being the best predictor explaining 21% of the variance and showing an inverse correlation with the walking fitness. The direction of this correlation might be due to changes which occur in parallel with ageing such as cardiovascular responses related to a decrease in the maximal heart rate, arteriovenous oxygen difference, ejection fraction, and a reduction in maximal cardiac output (Stratton et al., 1994; K. F. Hossack, 1982; Lakoski et al., 2011) or the decrease in maximal oxygen uptake, and a reduction in both muscle mass and muscle strength (Jürgensen et al., 2011). This 21% value is in agreement with the result reported in the female participants in the Cardoso et al study but it is higher than in the males (16%) in the same study, and also exceeds the 4% reported in a previous study by Dourado et al (2011). In terms of gender, this present study is in agreement with the Dourado et al study, where it explained 6% of the variance. However, gender was reported to account for more of the variance (11%) in the Cardoso et al study.

, The results in this study explained more of the variance in the distance walked in both model 1 and 2 (27% and 32% respectively) than that found in previous studies in a similar CR population (Pepera et al., 2013; Cardoso et al., 2016). The study conducted by Cardoso et al reported that age, height and the presence of diabetes explained 24% and 25% of the variance in the distance walked by female and male participants respectively, while in males an additional significant predictor was BMI. However, the results for the female participants were based on a very small sample of diabetic patients (n=35) and in the current study the presence of diabetes did not contribute significantly to the explanation of the variance in either males or females. In the Pepera et al study (2013), height and BMI collectively explained 20% of this variance, however, unlike in the current study, neither age nor gender were significant predictors. This might be due to the lower age range of the participants (69 years, SD=9.0) and the small sample of females.

In this study, a second model was created by adding the physical fitness scale to the original predictors to improve the explanation of variance and this resulted in a stronger prediction of the variance at 32%. The Dartmouth COOP physical fitness scale used in the present study is a self-reported measure in which the patients rate their activity level as 'moderate to high' or 'low', based on the level of physical activity that they can sustain for at least two minutes. The ability of the variable to explain the variance in the distance covered in ISWT was 5%. This self-reported physical fitness scale has not been used in previous studies. Patients who rated their level as 'moderate to high' walked 83m further than those who rated their level as 'low'. Harrison (2013) used the Duke Activity Status Index (DASI), however, the authors reported the value of R^2 for the whole model but omitted to report the contribution that DASI made to the model. However, the DASI is a self-administered questionnaire which is used to obtain an approximate estimate of a patient's peak oxygen uptake. It was found that using self-reported physical activity scales that describe the intensity of the activity produced a more accurate prediction of fitness compared to the participants simply reporting whether they consider themselves to be fit or not (Neto and Farinatti, 2003)). However, measurements from scales such as these were not available in the NACR patient data.

Although the R^2 values in this study were the highest compared to studies conducted in a CR population, they were lower than those reported in previous studies where reference equations were developed to predict the distance covered during ISWT in a healthy population (Jürgensen et al. 2011; Dourado et al. 2011; Dourado et al. 2013; Probst et al. 2012; Harrison et al. 2013; Agarwal et al. 2016). In these studies, as the subjects were healthy, the protocol of the ISWT was extended from 12 to 15 levels to avoid the ceiling effect (Jürgensen et al. 2011; Dourado et al. 2011; Probst et al. 2012) whereas in a typical CR patient, achieving a distance over and above the standard ISWT (12 levels) is unlikely (Grove, 2013).

The two models developed in the present study explained a moderate variance and the predicted walking distance derived from the models and the actual distance obtained from the ISWT were similar in the main and cross-validated samples for both models. In addition, the Bland-Altman analysis supported the good agreement between the two measurements, thus demonstrating the feasibility of applying these models to a CR population. The adjusted R^2 values were also the same as the R^2 values for the models in the main and cross-validated samples. This model stability may indicate that these models could be generalisable across similar populations.

In the current study, the unexplained value of the variance in the walking distance covered highlights the complexity of attempting to predict the ISWT distance and hence CRF. Pepera et al (2013) reported that step length at 66% of maximum speed during ISWT explained 68% of this variance and leg length explained 58%. However, the difficulty of obtaining precise measurements, due to, for example, obesity or discomfort in the patient, makes this impractical in real clinical practice. In order to measure leg length, the distance between the anterior superior iliac to the medial malleolus needs to be assessed. This measurement may be more problematic to take in those with limited range of motion in the lower body, the obese or patients with ankle swelling.

Moreover, previous studies reported that heritable factors explained from 30% to 50% of the variance in CRF. Genetic variation results from factors such as maximum exertional oxygen uptake, heart size, muscle strength, lean mass, skeletal muscle growth and bone mineral density (Montgomery & Safari 2007; Williams 2010; Lakoski et al. 2011; Harrison et al. 2013). Such factors may potentially contribute to the remaining unexplained value of the variance.

The model produced by the Pepera et al study was based on the UK CR population where height and BMI were the predictors explained 10% of the variance of the ISWT distance in our study sample. This explanation used the equation without any adjustment for other variables. However, when adjusted for age and gender, height and BMI explained only 1%, which could be explained by the large effect of age and gender. Validating Cardoso et al models was not possible as the value of the constants in the models were not stated.

5.6.1 Reference Values

Given the importance of the ISWT distance as a tool for assessing functional capacity, it is crucial to have reference values to establish what constitutes a normal value. Therefore, the distance walked by the patients can be compared to these values which represent the distance that their peers of the same gender and in the same age-band would be expected to walk.

In this study, reference values for the ISWT distance were produced according to age and gender. Age was the stronger predictor and gender, in addition to its modest predictive function, is routinely used in literature to differentiate fitness values (Arena et al., 2007; Cardoso et al., 2016; Fletcher et al., 2001; Wang et al., 2010). The practical implications of these reference values are to guide practitioners' expectations about how well patients might perform in an ISWT in order to assist in the initial interpretation of the ISWT results to assess the need for a second test; to help patients understand their fitness level in relation to their peers; and to facilitate the setting of realistic goals to enable them to improve their physical condition.

As mentioned previously, there is only one study which has attempted to produce ISWT reference values for the CR population (Cardoso et al., 2016). Cardoso et al produced reference values for patients who joined the outpatient CR programme based on 547 patients: 132 females and 415 males. The patients were divided into age bands at 5-year intervals from 25 to 90 (13 bands) according to gender. However, the use of these reference values might be considered poorly representative due to the small number of participants, most notably females, which resulted in an average number of approximately 10 participants in each band. In addition, the data was obtained from only four UK hospitals, compared to 48 programmes in the present study, which might be considered unrepresentative of the general cardiac population.

In the current study, we divided the group into 9 bands, 7 of them at 5-year intervals. The two remaining bands, namely the first and last band, were larger as we found that there was no significant difference in the mean of the ISWT distance walked between the patients within each of these marginal bands regardless of age. The median distance walked by males and females in the youngest age band (≤44 years) was 520m and 375m respectively, which was more than twice the distance walked in the oldest age band (≥ 80 years) at 200m for males and 160m for females. These results are in line with previous studies that report that the distance walked decreased steadily with age, this decline was less steep in females than males (Agarwal et al., 2016; Cardoso et al., 2016). However, the mean values for each age-band in current study, irrespective of gender, are lower than those produced by Cardoso et al, which could be explained by the small, potentially biased, sample size in Cardoso's study.

The 25th and 75th percentiles were used as they are a useful guide for CR practitioners to evaluate baseline scores and help with goal-setting as part of core CR delivery. For example, if a patient's ISWT distance is below the 25th percentile, they are performing below that expected for their age and gender. This could indicate that the patient has poor walking fitness or was not performing the test to their full ability. In this case, a second test might be needed to confirm poor fitness or establish if the low performance is due to the learning effect. If the patient falls in the 50th percentile (the median), this shows the patient has performed well in the test according to his age and gender, which might rule out the need for a second test.

The MET values, which corresponded to the distance walked for each age group, were important for aiding in the stratification of patients in terms of functional capacity. These values showed that male patients below the age of 60 were categorised as low risk while those above 80 years of age were classified as high risk. Female patients, on the other hand, under the age of 70 were at moderate risk whereas women above the age of 70 were at high risk. Therefore clinicians should be aware of this when tailoring the CR programme for individual patients and when supervising and monitoring levels.

5.6.2 Strengths and limitations

The major strength of this study was the use the NACR database, which is the largest database in the UK for the CR population. This is the preferred design as it will enable large enough sample of patients to be investigated which was the main limitation of the previous studies. The research question focuses on determinants and not outcomes which means RCT designs are not appropriate. As evidenced from the papers informing this review prospective cohort studies have struggled to recruit sufficient patients. Although there are inherent weaknesses with retrospective studies this thesis intends to account for these as part of the design.

However, the study was not without limitations. Due to the retrospective nature of the study, some significant predictors that were reported in previous studies were not recorded in the NACR database such as resting heart rate, Rate of Perceived Exertion and hand strength grip, leg length and step length and so these predictors were precluded.

The normative values proposed in this paper assume that the ISWT was carried out in a rigorous way but we are unable to substantiate this. The test is however is supported by a clinician and the patient follows the verbal and bleep commands from the ISWT audio recording, which gives some confidence that it was delivered in a consistent manner.

5.7 Conclusion

The commonly determined key factors in predicting the ISWT distance in the CR population were age and gender, with age being the best predictor. The ability of patients to rate their own level of physical activity was shown to be a modest determinant of their walking fitness. The reference values produced in this study represent a valuable tool to be used in a clinical setting for CR or other multi-morbid populations. These findings may assist practitioners in their initial expectations of patients' performance in the ISWT, aid them in establishing the level of risk in terms of functional capacity, enable them to interpret the test results in order to better inform patients of their fitness level, and potentially aid patients in the setting of realistic CR goals around physical activity.

Chapter 6. Determinants of achieving the minimum clinically important difference for the Incremental Shuttle Walk Test in a cardiac rehabilitation population

6.1 Abstract

Aim: The primary aim in this chapter was to identify the determinants of achieving the minimum clinically important difference (MCID) for the Incremental Shuttle Walk Test (ISWT) in the CR population. The secondary aim was to examine whether achieving MCID in ISWT at the end of the CR programme is associated with the likelihood of patients meeting the physical activity recommendation or whether it is associated with the patients' self-reported physical fitness (Dartmouth COOP tool) at the end of the CR programmme.

Method: Routine clinical data related to patients who undertook ISWT as a pre- and post-CR functional capacity assessment were taken from National Audit of Cardiac Rehabilitation (NACR) during the 2013 to 2016 and retrospectively analysed. A sub-analysis was conducted to address the secondary aim. Logistic regression approaches, taking account of potential confounders were constructed. Due to the nature of the nested data, the Huber-White-sandwich estimator robust method was used. Multiple imputation technique was applied to replace the missing values.

Results: For the main study, data from 9,786 patients (mean age of 63.9±10.7), 77.5% of whom were male, were analysed. Sixteen determinants for achieving the MCID for ISWT in CR patients were identified. A sub-analysis was also conducted on 7,950 to address the secondary aim. Patients who achieved the MCID were 30% more likely to meet the physical activity recommendation and 60% more likely to rate themselves positively on the self-reported physical fitness Dartmouth COOP scale.

Conclusion: The magnitude of the change in fitness expressed as the distance walked during the ISWT in the CR population was 97m. Results such as these, derived from this study, reflect routine clinical practice, giving clinicians a picture about how the patient and service level factors that they see every day can be altered to help optimise fitness levels post CR. Knowing these factors may help clinicians to tailor individual therapeutic plans to guarantee that patients exert optimal effort in order to gain the recommended improvement in their functional capacity. The achievement of the MCID during the ISWT at the end of the CR programme was associated with an improvement in physical activity status (meeting 150 minutes per week) and a patient's self-reported physical fitness (Dartmouth COOP tool).

6.2 Introduction

Improving functional capacity is one of the main goals of a CR programme as this improvement reflects the effectiveness of the exercise training programme (BACPR, 2017) and is a significant determinant of long-term survival after a cardiac event (Kavanagh et al., 2003; Martin et al., 2013; Barons et al., 2015; Taylor et al., 2016, 2017).

In the UK, the most commonly used field test to measure a change in functional capacity is the Incremental Shuttle Walk Test (ISWT). The distance walked measured during the ISWT is a product of increasing increments of speed during the test to assess fitness. This distance is the main outcome obtained from this test and is used routinely in clinical practice with the change in fitness being expressed as the change in the ISWT distance walked prior to and after the CR programme (Singh et al., 1992; Almodhy, Ingle and Sandercock, 2016). This test is used as the main tool to evaluate the improvement in patients' functional capacity in the NACR annual audit report (NACR, 2017). An improvement of 70 metres or a 25% improvement in the patients' baseline measurement in this test is considered to be the minimum clinically important difference (MCID) (Houchen-Wolloff, Boyce and Singh, 2014), which is the benchmark that clinicians use to judge patients' achievement and reaching it reflects the patients' successful performance.

The NACR annual audit report (2016) states that only 62% of the CR patients who undertook the ISWT achieved the MCID in terms of their functional capacity, which means that approximately one third of these patients were unable to achieve this desired improvement in their functional capacity. Investigating the characteristics of CR patients who are unable to achieve the MCID as well as those who are, is crucial as being aware of these characteristics would assist clinicians in tailoring their practice to patients' needs.

Few studies have attempted to identify the factors that influence the change in functional capacity expressed as a change in the distance walked during ISWT (McKee et al., 2013; Almodhy, Ingle and Sandercock, 2016). McKee et al. (2013) found that age and baseline functional capacity were the significant predictors of the changes in functional capacity as defined by ISWT distance in CR patients. Almodhy et al. (2016) conducted a meta-analysis into the change in functional capacity resulting from using the ISWT in the CR population. They concluded that the number of sessions prescribed was the only significant determinant of an improvement in fitness during the ISWT. It was found that patients who were prescribed more than twelve sessions showed a significantly greater change in their physical fitness compared to those who received fewer sessions.

However, the change in fitness was reported as a numerical value and neither of these studies demonstrated whether this change was clinically important. Using a numerical value could overestimate the proportion of patients who improved as even slight improvements in fitness, although statistically significant, may be perceived as meaningful. Therefore, the concept of the minimum clinically important difference (MCID) is recommended (Houchen-Wolloff, Boyce and Singh, 2014). To date, there is no study which has attempted to identify the patient or programme characteristics which might be associated with achieving the MCID in the ISWT.

There are two tools used to measure the patient-reported perspective of physical activity status which are used in the NACR annual report (BACPR, 2017; NACR, 2017). The first is meeting the physical activity recommendations (150 minutes per week), which is a requirement of clinical standards and the second is the self-perception of fitness (Dartmouth COOP tool) is one of the health-related quality of life (QOL) subsets. These measurements are taken pre- and post-CR programme and assess the amount of improvement in the patients' physical activity status and their health-related quality of life. Whether achieving the MCID is associated with the likelihood of patients meeting the physical activity recommendation or whether it is associated with the patients' perceived level of fitness has not been examined in patients attending CR.

6.2.1 Previous studies

In this section, further studies that attempt to identify the determinants of the change in fitness in a CR population who participated in an outpatient CR programme will be discussed. These studies were not included in the previous critical review chapter as they did not meet the focus or stated inclusion criteria for that particular study .

Only one observational study aimed to identify the determinants of the change in distance walked during ISWT in a CR population (McKee et al., 2013). McKee et al. (2013) conducted a retrospective study on 154 patients with a mean age of the 64±10 years (75% were male) attending outpatient CR programmes to determine the influencing factors on the change in functional capacity, BMI, and anxiety and depression. Participants were classified based on their age into three groups; <45years, 45-65years and > 65 years. The ISWT was used to assess the change in functional capacity by comparing the pre- and post-programme measurements. By completion of the programme, there was a significant improvement in the distance walked during the test from 479.3 ± 231.2m to 584.4 ± 248.2m (22%). Multivariable analysis showed that age, gender, reason for referral, BMI and baseline functional capacity as a model, explained 20% of the change in ISWT. However, only age and baseline functional capacity were significant predictors in this model. The authors concluded that the greatest gain in fitness was observed in those patients who were younger and less fit (McKee et al., 2013). However, the patients in this study were drawn from a single centre. In addition, there were only 5 patients in the younger group (<45 years) and only 6 patients in the clinically depressed group. This small number of participants in these groups limited the generalisability of the results of this study.

Furthermore, other studies using a treadmill or bicycle ergometer aimed to identify determinants of the change in fitness in the CR population have been conducted. Uddin et al. (2015) found that the only determinant of the change in exercise capacity identified in their multivariable meta-regression analysis was the intensity of the exercise. Another study conducted by Johnson et al. (2014) recruited 1,096 patients (169 African Americans and 927

Whites) who were participating in a CR programme consisting of 36 sessions which included lifestyle modification, exercise and pharmacotherapy. They aimed to study the differences in outcomes after CR between the two groups of participants. functional capacity was one of these outcomes expressed in METs, which were recorded automatically from exercise devices or estimated from a standardised formula. Multiple linear regression analysis showed that race, gender, BMI, smoking, diabetes, unemployment and left ventricular ejection fraction were predictors of a change in exercise capacity expressed in METs. Race (being African American), increased age, gender (being female), increased BMI, unemployment, smoking, diabetes and having a reduced left ventricular ejection were inversely correlated with an improvement in functional capacity while completing post-high school education was positively associated with this improvement. However, the data relating to 19 patients were missing from the analysis and no clear explanation was given for this.

Another study aimed to compare the differences in the CR outcomes, including exercise capacity and cardiac risk factors, in diabetic and non-diabetic participants (St. Clair et al., 2014). St Clair et al. retrospectively studied 1312 patients who had enrolled on a 36-session outpatient CR programme at Wake Forest Baptist Medical Centre during the period of 2004 to 2008. One of the aims of this study was to compare the change in fitness between diabetic (370) and non-diabetic (942) patients. At entry to the programme, the diabetic patients had a higher prevalence of risk factors and showed significantly lower METs values compared to the non-diabetics (2.4 vs 2.7 respectively). The baseline METs values were obtained during the first session and METs values were also recorded in each subsequent session from exercise devices. The change in METs was calculated by subtracting the initial METs values from the highest METs values which were recorded during the programme. The multivariable linear regression analysis using change in METs as a dependent variable showed that advanced age, female gender, increased BMI, diabetes, a left ventricular ejection fraction <35% and lung disease were found to be significant determinants of a decrease in the improvement in fitness level. Three-way interaction between diabetes, gender and BMI was also found to be a predictor of a change in fitness. However, this study has some limitations. It was not reported whether patients used the same assessment tool to measure their fitness levels prior to and following the CR programme as the authors merely reported that the MET values were recorded from the exercise device without specifying which device had been used. Furthermore, there was insufficient reporting of analytical methods as the independent variables that were used in the regression analysis were not reported clearly. There was a significant difference in the baseline characteristics between the two groups which was not adjusted for during the analysis such as the baseline METs values.

Vanhees et al. (2004) attempted to determine the factors which could predict both the absolute and relative change in fitness expressed as peak Vo2 in participants who had enrolled in supervised outpatient CR programmes which consisted of 3 sessions per week for a period of 3-6 months and who had undertaken a bicycle ergometer exercise test prior to and following the end of the programme. The analysis revealed an improvement of 26% and that eleven factors namely: age, gender, BMI, baseline exercise duration, intensity of exercise (%), frequency of exercise (no. of sessions per week), smoking, complaints of dyspnoea, presence of intermittent claudication, heart transplantation and other cardiac surgery were determinants of a change in absolute values. In addition to these determinants, treatment with diuretics and treatment with digitalis were also found to be determinants of a relative change in fitness. However, neither diabetes, sitting blood pressure nor the presence of ST depression (≥1mm) were found to be determinants of this change (Vanhees et al., 2004).

6.2.2 The Gap in the Literature

No studies to date have attempted to identify the determinants of the achieving MCID for the ISWT as a measurement of fitness used in the outpatient CR population. Although some studies have investigated the relationship between fitness and physical activity status

(Dyrstad et al., 2015), whether achieving the MCID in the ISWT at the end of the CR programme is associated with the likelihood of patients meeting the physical activity recommendation or whether it is associated with the patients' perceived level of fitness has yet to be examined in patients attending CR.

6.2.3 Rationale for the study

The ISWT is the most common field test in the UK and the primary fitness measurement in the NACR data. The MCID in the distance walked during the ISWT is considered a benchmark of an improvement in fitness. Identifying the determinants of achieving this MCID for the ISWT in the CR population was the rationale of this chapter. The related determinants that were reported in the critical review chapter (Chapter 2), in the studies mentioned in the previous section (above section 6.2.1) and those which appear in the NACR data will be used as independent variables in the analysis in this study. Meeting the physical activity recommendations and the self-report of physical fitness (Dartmouth COOP tool) are two measurements which routinely show positive yet variable improvement, at programme and patient level, in patients after CR (NACR, 2017; Dibben et al., 2018).

6.2.4 Aim of this chapter

The primary aim of this chapter is to identify the determinants which might be associated with achieving the MCID in the ISWT and to use these findings to help clinicians to tailor the CR programme to suit individual patient's needs in order to help patients to achieve an improvement in their fitness. The secondary aim is to examine whether achieving MCID in ISWT at the end of the CR programme is associated with the likelihood of patients meeting the physical activity recommendation or whether it is associated with the patients' perceived level of fitness has yet to be examined in patients attending CR.

6.3 Method

6.3.1 Study design

This is a retrospective observational cohort study analysing data extracted from the NACR database from 2013 to 2016 (for justification using this design section 5.41)

6.3.2 Subjects

The main study sample consisted of 9786 cardiac rehabilitation patients aged from 20-99 years old. The inclusion criteria for this study were: adult patients aged over 18 who had taken the ISWT before and after their cardiac rehabilitation programme to assess their CRF and who were referred to CR as post myocardial infarction (MI), coronary artery bypass grafting (GABG), percutaneous coronary intervention (PCI) or valve surgery patients, with complete records of their age, gender and diagnosis. Heart failure patients were excluded.

In relation to the secondary aim, a sub-analysis was conducted on those patients who had a complete record regarding their physical activity status and their self-perception of physical function (Dartmouth COOP scale).

6.3.3 Statistical Analysis

6.3.3.1 Main study

The descriptive data relating to the patients were reported as the mean and standard deviation for the continuous variables and as a frequency and percentage for the categorical variables. The differences between the two groups of patients were assessed using Chi-square and t-tests as appropriate. Logistic regression was used to establish which factors were determinants of whether patients were able to achieve the MCID for ISWT or not on completion of the CR programme. A backwards selection approach of regression was used, where all the selected variables were simultaneously entered into the regression. Any non-significant variables which had a p-value >0.05 were removed. The process was repeated until the remaining variables were statistically significant (p-value <0.05). Due to the nature of the nested data, the Huber-White-sandwich estimator robust method was used to assume the independence of the observations in each centre (Rogers, 1993; Williams, 2000).

6.3.3.1.1 ***Independent variables used in regression analysis***

The independent variables which were used in this study were age, gender, BMI; diagnosis/treatment; presence of diabetes, dyslipidaemia, anxiety and/or depression (Yes/No); smoking status, employment and marital status; ethnicity; the duration of the CR programme; the number of sessions which patients had attended; whether the patients had attended CR phase I; the time from the cardiac event to starting CR; and patients' self-reported physical activity (150 mins/week). These variables were selected based on the literature or were significant in the preliminary analysis.

Age, baseline distance walked and time from the event to the start of CR were used as continuous variables in this study. However, patients were categorised into two groups based on their BMI (<30kg/m^2 and >30kg/m^2). In terms of diagnosis and treatment, patients were classified into four groups: MI (used as the reference group), PCI, surgery (CABG and valve surgery) and others. |In terms of comorbidities, patients were dichotomised (Yes/No) according to whether they had diabetes, dyslipidaemia, anxiety or depression.

Patients' smoking status was described as non-smoker (used as the reference group), current smoker and non-smoker since the cardiac event. Employment status was given as employed (used as the reference group), unemployed and retired. Patients' marital status was one of three possibilities: single (used as the reference group), currently in a permanent relationship (married or co-habiting) and previously in a relationship (separated, divorced or widowed). Patients' ethnicity was dichotomised as White British (used as the reference group) or not. The number of sessions which the patient attended was classified into two groups (<12 (used as the reference group) and ≥12) and whether the patient had received a phase I in-patient CR (used as the reference group) or not was also recorded. The physical activity status described whether the patient self-reported that they met (Yes / No) the recommended 150 minutes of physical activity per week.

6.3.3.1.2 ***The outcome main analysis***

The main outcome of this study was to establish if the patients had achieved an improvement in the ISWT based on the MCID so the patients were coded 0 if s/he did not achieve the improvement and coded 1 if the improvement was achieved. This improvement was based on achieving 70m or achieving a 25% improvement.

6.3.3.2 Sub-analysis

A binary logistic regression was used to examine the association between achieving the MCID in relation to meeting the physical activity recommendations and patients' perception of their own physical fitness according to the Dartmouth COOP scale. Whether the patient achieved the MCID or not was the main independent variable (if the patient did not achieve the MCID s/he was coded 0, if s/he achieved the MCID, s/he was coded 1) while the determinant variables identified in the main study were taken into account as confounders.

6.3.3.2.1 ***The outcome of the sub-analysis***

1. Meeting the physical activity recommendations: patients were assigned the number '0' if he/she did not meet the recommendations while the number '1' was assigned to those who did.
2. In terms of self-report physical fitness (Dartmouth COOP scale): patients who were able to sustain moderate to very heavy physical activity for a minimum of two minutes were assigned the number '1', whereas those who were only able to maintain light or very light physical activity for two minutes were assigned the number '0'.

6.3.3.3 Minimum clinically important difference in ISWT in CR population

The MCID in the ISWT following cardiac rehabilitation is the smallest change that is important to patients. Houchen-Wolloff et al (2014) recruited 224 CR patients (170 males, 50 females) and asked them to rank their perceived change in exercise performance after completing their CR programme based on a 5 Likert scale range from 1-better to 5-worse. They established that 70 metres (seven whole shuttles) or a 25% improvement from baseline was the threshold for a MCID for ISWT in this population. This is considered a benchmark for clinicians to judge patient success following a cardiac rehabilitation programme. It is also important as it informs the patient about the required change that is beneficial for his/her perceived health following cardiac rehabilitation (Houchen-Wolloff, Boyce and Singh, 2014).

6.3.3.4 Multiple imputation

The percentage of missing values in this study ranged from 4% to 20%. The following variables had missing values and were imputed: meeting of physical activity recommendation (150 min/week), self-reported physical function (Dartmouth COOP scale), marital status, employment status, the time of the event to the start of CR, the number of sessions, BMI, ethnicity, smoking status and programme duration. Little's test was used to explore the missing data mechanism and this indicated that data were missing at random. Multiple imputation with chained equations (Royston, White and Wood, 2011) was used to impute the data with 20 imputed data sets and estimates were combined using Rubins rules. Imputation was conducted for these missing variables. Age, gender, number of comorbidities, height, weight and baseline ISWT distance were entered in the multiple imputation procedure as passive variables in addition to the main outcome, which is whether MCID was achieved or not as adding such a variable to the process is recommended.

6.4 Results

6.4.1 Main study

The patients in this study numbered 9786, of them 77.5% were male. Ages ranged from 18-99 with a mean age of 64 years. These patients took the ISWT pre- and post-cardiac rehabilitation programme and showed a mean difference in distance of 97.7m (± 93.9). The percentage who achieved the recommended MCID was 64%. The main reason for referral to CR was MI 10%, PCI intervention 56%, post cardiac surgery 29% and other 5%. The median time from event to start of CR was 43 days for the sample in this study and 54% of them took part in an in-patients CR programme.

The patient demographics and the baseline characteristics are summarised in Table 6.1 based on achieving MCID or not. In our sample, 6275 patients achieved MCID (64%) while 3511 were unable to achieve it. Patients who achieved MCID tended to be slightly younger (63.4±10.7vs 64.9±10.6, $p<0.001$), male and non-diabetic whereas those who did not achieve MCID were obese (>30 BMI) (31.4%). The mean values of the ISWT pre- and post CR programme for those who were unable to achieve the recommended MCID were (393.5 ± 167.45 and 402.3 ± 167.7 respectively) while for those who achieved the MCID, the mean values were 353.3 ± 171.8 and 507.0 ± 196.8 respectively. The distance covered during the baseline ISWT was significantly further in those who did not achieve MCID compared to the other group (393.51 ± 167 vs 353.3 ± 171.8).

Table 6-1 Patient demographics and baseline characteristics of the two groups (main study)

Baseline characteristics	Whole sample	MCID not achieved (n=3511)	MCID achieved (n=6275)	P value
Age in years (Mean± SD)	63.9±10.7	64.9 ± 10.57	63.4 ± 10.68	<0.001
Male (%)	77.6	75	79	<0.001
BMI ≥ 30kg/m^2 (%)	28.4	31.4	26.8	<0.001
Reason for referral (%)				
MI	10.1	10.2	10.0	0.75
PCI	55.9	58.8	54.3	<0.001
Surgery (CABG or valve)	28.8	25.6	30.6	<0.001
Other	5.2	5.4	5.1	0.57
smoking status (%)				
(Non-smoker)	84.8	84.5	84.9	0.29
Smoker	4.8	5.2	4.5	0.12
Stopped smoking since event	10.4	10.2	10.6	0.55
Diabetic (%)	17.1	18.5	16.3	0.01
Hypertension (%)	39.0	39.5	38.6	0.39
Dislipidaemia (%)	33.5	33.0	33.7	0.48
Anxiety (%)	4.6	3.7	5.2	0.001
Depression (%)	4.6	4.2	4.8	0.18
Meeting physical activity recommendations (150min/week) (%)	40.9	39.7	41.6	0.10
Marital status (%)				
Single	7.2	7.4%	7.1%	0.62
In relationship	76.0	74.6%	76.8%	0.03
Previously in a relationship	16.7	18.0%	16.1%	0.03
Ethnicity (%)				
White-British	85.9	85.0%	86.5	.053
Employment status (%)				
Employed	29.7	28.3	30.4	0.04
Unemployed	52.6	22.1	23.4	0.17
Retired	47.4	49.7	46.2	0.002
Pre-ISWT (Mean±SD)	367.7	393.5± 167.5	353.3 ± 171.8	<0.001
Post-ISWT (Mean±SD)	465.4	402.3 ± 167.8	500.7 ± 196.8	<0.001
Time from event to start of CR in days (Mean±SD)	47.3	49.42± 26.77	46.14 ± 25.6	<0.001
No. of sessions (≥ 12) (%)	26.9	23%	29%	<0.001
Duration of programme in weeks (mean)	10.8	10.7	10.8	0.44

The initial regression analysis of all potential variables that were used in this study showed that depression, hypertension, self-reported physical function, the total number of comorbidities, and the programme duration were non-significant and were therefore removed (Table 6.2).

Table 6-2 Pooled results of logistic regression analysis of all the investigated potential determinants

Factor (reference group)	Odds ratio	p-value	95% CI for OR	
			Lower	Upper
Age in years	0.96	<0.001	0.949	0.962
Gender (Female)	1.70	<0.001	1.47	1.97
BMI (>30)	1.59	<0.001	1.43	1.76
Reason for referral (MI)				
PCI	0.95	0.58	0.79	1.14
Surgery	1.25	0.01	1.05	1.48
Other	0.98	0.85	0.73	1.30
Ethnicity (Other)				
White-British	1.30	0.001	1.11	1.51
Marital status (Single)				
In a relationship	1.27	0.01	1.06	1.52
Previous relationship	1.15	0.17	0.94	1.41
Employment status (Employed)				
Unemployed	0.82	0.07	0.68	1.00
Retired	0.98	0.78	0.83	1.14
Diabetes (No)	0.79	<0.001	0.70	0.89
Dyslipidaemia (No)	1.16	0.04	1.01	1.33
Anxiety (No)	1.41	0.007	1.10	1.81
Smoking status (non-smoker)				
Current smoker	0.67	0.003	0.52	0.87
Stopped since event	0.85	0.04	0.73	0.99
Baseline ISWT distance (metres)	0.996	<0.001	0.995	0.997
Attending phase I CR (No)	1.30	0.01	1.06	1.60
No. of sessions (<12 sessions)	1.37	0.001	1.13	1.65
Time from event to start of CR in days	0.994	<0.001	0.991	0.996
Meet physical activity recommendation (No)	1.13	0.03	1.02	1.26
Depression (No)	0.93	0.45	0.76	1.13
Hypertension (No)	0.98	0.74	0.85	1.12
Self-reported physical function (No)	1.11	0.071	0.99	1.23
Total of comorbidities	0.99	0.64	0.93	1.05

The regression was then run again and all the remaining variables namely age, gender, BMI (<30), reason for referral to CR, being diabetic, having hyperlipidaemia, suffering anxiety, the number of sessions which patients had attended, whether the patients had attended CR phase I, and time from the cardiac event to the start of CR, were found to be statistically significant (Table 6-3).

Table 6-3 Pooled results of logistic regression analysis for the final determinants

Pooled results of logistic regression analysis for the final determinants				
Factor (reference)	Odds ratio	p-value	95% CI for OR	
			Lower	Upper
Age in years	0.96	<0.001	0.94	0.96
Gender (Female)	1.71	<0.001	1.48	1.99
BMI (>30)	1.59	<0.001	1.43	1.76
Reason for referral (MI)				
PCI	0.95	0.57	0.79	1.14
Surgery	1.22	0.02	1.03	1.45
Other	0.98	0.85	0.73	1.30
Ethnicity (Other)				
White-British	1.31	<0.001	1.12	1.52
Marital status (Single)				
In a relationship	1.27	0.01	1.06	1.51
Previous relationship	1.14	0.19	0.94	1.40
Employment status (Employed)				
Unemployed	0.82	0.049	0.68	0.99
Retired	0.98	0.78	0.83	1.14
Diabetes (No)	0.78	<0.001	0.68	0.88
Dyslipidaemia (No)	1.12	0.02	1.02	1.24
Anxiety (No)	1.31	0.02	1.05	1.63
Smoking status (non-smoker)				
Current smoker	0.67	0.003	0.52	0.87
Stopped since event	0.85	0.04	0.73	0.99
Baseline ISWT distance (metres)	0.997	<0.001	0.996	0.997
Attending phase I CR (No)	1.29	0.02	1.05	1.58
No. of sessions (<12 sessions)	1.34	0.001	1.12	1.61
Time from event to start of CR in days	0.994	<0.001	0.991	0.997
Meeting physical activity recommendation (No)	1.16	0.01	1.04	1.29

In terms of achieving the MCID, while accounting for other multi-variables used in this logistic regression analysis (Table 6.3), the odds reduced by 4% for each additional year of age. Males were 71% more likely than females to be successful and patients whose BMI was <30 were 1.6 times more likely to achieve the MCID. Patients suffering from anxiety tended to be 31% more likely to achieve this improvement. However, diabetic patients were 22% less likely to achieve it. With reference to the reason the patient was referred to CR, those who had had cardiac surgery (CABG and valve surgery) were significantly more likely to achieve the MCID compared to the reference categories (MI) by 22% while the other groups were not statistically significant. Patients who had attended twelve or more sessions were 1.3 times more likely to achieve a desirable improvement during the test compared to those who attended fewer sessions. Patients who were in a current relationship, and those whose ethnicity was White British were 1.3 times more likely, compared to their reference categories, to reach the MCID, while unemployed patients were shown to be 18% less likely to achieve it compared to the employed. However, there was no significant difference between retired patients and the reference category. The probability of achieving the MCID was small and was inversely related to both the period from the event to the start of CR, and the patients' baseline distance walked. These variables are nevertheless important and should be taken into account during the analysis.

6.4.2 Sub analysis study

A total of 7950 patients, with a mean age of 64 ±10.54 years who had completed their physical activity recommendation and elf-report Physical fitness (Dartmouth COOP scale) assessment at the end of their programme, were included in this study. There were 5087 patients who had achieved the ISWT MCID with a mean age of 63.5 +10.6, and 2863 who had not, with a mean age of 64.9 ± 10.4.

The patients' demographic and baseline characteristics are summarised in

Table 6-4. In terms of those patients who did not achieve the MCID, they tended to be more obese, diabetic and retired, while those who achieved the MCID tended to be male, had achieved a lower baseline distance during the ISWT and had had CABG or valve surgery.

Table 6-4 Patient demographics and baseline characteristics of the two groups (sub-analysis study)

Baseline characteristics	**MCID not achieved (n=2863)**	**MCID achieved (n=5087)**	**P value**
Age in years (Mean±SD)	64.9 ±10.4	63.5± 10.6	<0.001
% Male	75.4	79.5	<0.001
% BMI > 30	30.9	26.3	<0.001
% Reason for referral			
MI	10.1	9.8	0.84
PCI	58.8	53.8	<0.001
Surgery (CABG or valve)	25.6	31.2	<0.001
Other	5.4	5.1	0.57
Smoking status (Non-smoker)	81.8	82.5	0.42
Smoker	4.3	3.5	0.06
Stopped smoking since event	10.0	10.5	0.55
% Diabetic	18.4	16.8	0.03
% Hypertension	39.9	40.0	0.97
% Dislipidaemia	33.0	33.7	0.48
% Anxiety	3.7	5.3	0.002
% Depression	3.9	4.8	0.0.7
% Meet physical activity recommendations (150min/week)	40.2	41.9	0.16
Physical fitness (Dartmouth COOP)	48.3	47.1	0.12
% Marital status			
Single	7.3	7.2	0.62
In relationship	74.5	76.6	0.05
Previously in a relationship	18.2	16.2	0.04
% Ethnicity			
White-British	85.4	86.5	.053
% Employment status			
Employed	28.9	30.4	0.20
Unemployed	21.7	23.6	0.06
Retired	49.4	46.0	0.01
Pre-ISWT (Mean±SD)	401.8±167.1	361.7±171.8	<0.001
Post-ISWT (Mean±SD)	410.4± 167.8	510.2 ± 197.2	<0.001
Time from event to start of CR in days (Mean±SD)	50.0±26.7	46.14±25.6	<0.001
% No. of sessions ≥ 12	23.7	29.9	<0.001
Duration of programme in weeks (mean±SD)	10.7	10.8	0.25

The patients who achieved the MCID were found to be 1.29 times more likely to meet the physical activity recommendations at the end of their CR programme and 1.55 % times more likely to perceive themselves as fit according to the Dartmouth COOP physical fitness scale (Table 6-5).

Table 6-5 Regression result for the sub-analysis in this study (with groups not achieving the MCID used as the reference group)

Outcome	**Odds Ratio**	**[95% CI]**		**P value**
Meeting physical activity recommendations	1.29	1.07	1.56	0.57
Physical fitness (Dartmouth QoL tool)	1.55	1.34	1.80	<0.001

6.4.3 Comparison between the study population and the non-valid population

The sample used in the present study is considered representative of the CR population in the UK as the table (6.6) below shows there is no great difference between our sample and the non-valid population (those which did not meet the inclusion criteria for this study) in terms of age; gender; BMI; presence of diabetes, anxiety or depression; the time from cardiac event to start of CR; and the number of sessions. However, there are some small differences in percentage in areas such as smoking, treatment procedures and meeting the physical activity recommendation.

Table 6-6 Comparison between the present study and the non-valid population

	Study sample	Non-valid population
Age (years)	63.9±11	65.0±12
Gender (%male)	77.6	72.7
BMI (kg/m)	27.9±4.7	28.3±5.3
Ethnicity (%White British)	79	81
Diabetes (%)	15.6	14.3
Hypertension (%)	39	32
Anxiety (%)	4.6	3.4
Depression (%)	4.6	3.9
Meeting physical activity recommendation (%)	40.9	36.9
Smoking (%)	5	9
Duration of programme in weeks (median) (%)	10±5.3	10±7.0
Number of sessions(mean±SD)	9.7±3.7	8.1±53
Time from cardiac event to start of CR in days (median)	44	43
MI (%)	7.6	13.7
MI/PCI (%)	34	31
PCI (%)	21	17
CABG (%)	20	15
Valve (%)	8.2	6.8

6.5 Discussion

The mean change in the distance walked in the current study was 97m, which was similar to that reported in previous studies where a change of approximately 100m in the distance walked in the ISWT in the CR population was achieved (Sandercock et al., 2013; Almodhy, Ingle and Sandercock, 2016). The main finding of this study showed that 64% of patients who undertook the ISWT as a baseline functional capacity test were able to achieve MCID in their fitness, which means that about one in three of these CR patients could not achieve one of the main desirable goals of their CR programme, as they did not gain a clinically important improvement in their fitness.

These result were comparable with the results reported by the European registry which showed that only 58% of patients achieved an improvement in their exercise capacity (< 25 watts) (Benzer et al., 2017). This was a lower percentage than the 79% reported by Savage et al (2009). However, Savage et al. classified their participants according to a mathematical calculation where participants who achieved ≤ 0 METs (post-test measurement – pre-test measurement) were classified as non-improvers. The result of savage et al study might therefore underestimate the number of participants who were physiological non-improvers.

The multivariable analysis in this study reveals that age, gender, BMI, reason for referral to CR, ethnicity, marital status, employment status, smoking status, presence of diabetes, anxiety status, baseline fitness level expressed as distance walked in ISWT, the number of sessions attended and whether the patient had received phase 1 CR (as an in-patient), meeting the physical activity recommendations (150min/week) and the period from event to start of CR, influenced the likelihood of patients achieving the MCID in the ISWT

6.5.1 Significant Determinant

6.5.1.1 Age

The current study found that a one-year increase in age, in the study population, resulted in a 4% drop in the likelihood of patients achieving the MCID. This inverse association between age and change in fitness is in accordance with a previous study (McKee et al., 2013) which showed that age was an inversely significant predictor of the change in distance walked during ISWT where the younger group improved more compared to old group. This finding is also supported by results from previous that found that younger CR patients (≤ 65years) improved their walking fitness more than older patients (>65) using the ISWT (Al Quait and Doherty, 2016). However, the statistical analysis could have been stronger as the association found in their results was based on a univariate association and did not take into account the effect of other potential confounders such as gender where the percentage of males was significantly higher in the younger group compared to the elderly group. Furthermore, the nested nature of the data from NACR where the patients were treated within different centres was also not accounted for. This negative association between age and a change in fitness was reported also in studies using other fitness assessment tools (Lavie and Milani, 2000; Sandercock, Hurtado and Cardoso, 2013; Beckie et al., 2013; Johnson et al., 2014; St. Clair et al., 2014; Johnson et al., 2015).These studies have been explained and criticised in the previous chapter (Critical Review chapter).

Izawa et al. (2010) conducted a longitudinal observational study on 442 patients who were enrolled on a CR-outpatient programme in Japan. The authors aimed to investigate the differences in physiological and psychosocial outcomes between a middle-aged group of patients (< 65years) and an older group (≥65 years). The studies included 242 patients aged < 65years and 200 patients aged ≥65 years. All patients had undertaken a treadmill exercise test prior to and following the CR programme to measure the fitness level expressed as Vo_2 peak. At baseline, the older group had a statistically significant lower baseline Vo_2 than the middle-aged group (21.9±4.5 vs 24.4± 5 respectively). At the end of the CR programme, patients in both groups had demonstrated significant improvements in peak Vo_2, however, the middle-aged group of patients showed greater percentage improvements compared to the older age group (13.1% vs 8.7% , respectively) (Izawa et al., 2010). Although there is a statistical difference at the baseline of Vo_2 peak value, handgrip strength and knee extensor muscle strength, a univariate analysis was the only method used in this study without adjusting for these variables. This might limit the generalisability of its results (Miles and Shevlin, 2003; Palmer and Connell, 2009).

The ageing process is known to have a negative impact on oxygen uptake, muscle mass deterioration and muscle strength (Fleg and Lakatta, 1988; Ogawa et al., 1992). Despite this, Branco et al (2015) found that both middle-aged (45- 65) and elderly (>65) patients gained more improvement in exercise capacity than younger patients (<45). This is in agreement with the results of a study conducted on 458 patients who attended 36-sessions of a CR outpatients programme (Lavie and Milani, 1995a). The patients were classified into two groups: an elderly group of 199 patients (≥65years) and a younger group of 259 patients (<65years). The elderly group showed an improvement in their fitness of 43% (from 5.4±1. 8 METs to 7.7±2.5 METs). This improvement was significantly higher than that shown by the younger group (32% from7.5±3 METs to 9.9±3.5METs). However, the percentage of obese and diabetic patients was significantly higher in the younger group at baseline while the elderly group had a significantly lower fitness level. Despite this, no statistical adjustment was made for this during the analysis which could limit the results of this study. The improvement in the elderly group, which was greater than that in the younger group, could be due to the lower baseline fitness measurement of the older patients (Lavie and Milani, 1994; Sandercock, Hurtado and Cardoso, 2013).

However, several studies reported that age was not a significant determinant of the change in fitness in a CR population (Balady et al., 1996; Pierson, Miller and Herbert, 2004; McKee, 2008; Savage, Antkowiak and Ades, 2009; Vergès et al., 2015; Almodhy, Ingle and Sandercock, 2016; Baldasseroni et al., 2016). These studies have some limitations. The main common limitation was the small sample size. In the Balady et al (1996) study, only 50% of patients completed their CR programme and used the same pre- and post-assessment tool and protocol. McKee (2008) used a limited number of confounders while Savage (2009) classified their participants as improved or non-improved according to a mathematical calculation (post peak VO2-pre-peak VO2). Verges' sample included only diabetic patients while Baldasseroni used a small sample with a restricted range of ages. In the meta-analysis conducted by Almodhy et al (2016) the number of groups used in the meta-regression was small.

6.5.1.2 Gender

In terms of gender, male patients were 1.7 times more likely to achieve the MCID compared to females. This association between female gender being less likely to exhibit a comparable change in fitness to males following exercise training has been evaluated previously based on treadmill and bicycle ergometer test data (Vanhees et al., 2004; Sandercock, Hurtado and Cardoso, 2013; Gee et al., 2014; Johnson et al., 2014; St. Clair et al., 2014; Johnson et al., 2015). Two further studies reported that males had gained more of an improvement in their fitness after their CR programme compared to female patients (Gulanick et al., 2002; Ades et al., 2006). However, the results of these studies were limited by the use of univariate analysis without any adjustment for other potential confounders (Miles and Shevlin, 2003; Palmer and Connell, 2009).

The results of these studies are in contrast to several studies (Lavie and Milani, 1995b; Balady et al., 1996; Savage, Antkowiak and Ades, 2009; McKee et al., 2013; Branco et al., 2015; Vergès et al., 2015; Baldasseroni et al., 2016) which showed that gender has no significant impact on the change in fitness among CR patients. McKee et al. (2013) explained that their result might be due to the multivariate analysis they used. However, the current study also used multivariate analysis although more factors were taken into account compared to the McKee study. Ades et al. (1992) studied 226 patients aged ≥62 years who attended a 12-week CR outpatient programme. At baseline assessment, female patients had a significantly lower Vo_2 peak level than males (16 ± 5 vs 20 ±5 ml/kg/min respectively). However, both males and females showed a similar improvement at the end of the programme (17% in women and 19% in men) (Ades et al., 1992). Cannistra et al. (1992) examined whether there was a difference in clinical profile and outcome between males and females who enrolled on an exercise-based CR programme. They conducted a study on 174 male participants with a mean age of age 54 ± 10 and 51 females with a mean age of 56 ± 10. At the baseline assessment, more female patients were diabetic, hypertensive and had higher cholesterol. They were also more likely to be non-white, unemployed and unmarried compared to the male patients in this study (Cannistra et al., 1992). Although females were less fit than males at entry to the programme, both groups revealed the same percentage of improvement. However, the results of these two studies (Ades et al., 1992; Cannistra et al., 1992) were limited by the systematic bias where there was a significant difference in baseline characteristics which was not taken into account and adjusted for during the analysis.

Keteyian et al. (2016) retrospectively studied data relating to 8319 CR patients (5780 men with a mean age of 63±11 years and 2539 women with a mean age of 64 ±12years) who participated in an outpatient CR programme at the Henry Ford Hospital, Detroit, USA. The aim was to describe the amount of change in fitness in both male and female patients at the end of the CR programme. The analysis revealed that males improved by 45% (from 2.9 METs ± 0.8 to 4.1 ± 1.4 METs) which was higher than the 37% improvement achieved by females (from 2.4 ± 0.7 METs to 3.3.± 1 METs) (Keteyian et al., 2016). However, whether this difference in improvement between males and females was statistically significant or not, was not reported.

6.5.1.3 BMI

BMI was a significant determinant of MCID with patients whose BMI was less than 30 kg/m^2 (non-obese) were 60% more likely to achieve this improvement compared to obese patients (BMI >30 kg/m^2). This result, in conjunction with the previous studies, demonstrates that obesity has a negative impact on the improvement in exercise capacity (Lavie and Milani, 1997; Gunstad et al., 2007; Martin et al., 2012; Gomadam et al., 2016). The recent study by Gomadam and colleagues was conducted on 1320 participants who were enrolled on a 12-week CR programme during the period from 2004 to 2013 to explore the impact of the degree and direction of change in weight on risk factors and exercise capacity in this population. The participants were categorised into five groups according to their BMI: 318 normal weight patients (BMI 18.5 to 24.9), 487 overweight patients (BMI 25 to 29.9) while there were 318 class I obese patients (BMI 30 to 34.9), 128 class II obese patients (BMI 35 to 39.9) and 69 class III obese (BMI ≥ 40) patients**.** Participants attended a 3-session per week exercise-based programme (36 sessions in total). Exercise capacity was recorded from exercise devices prior to and at the end of the programme. On entry to the programme, significant trends were identified for all BMI groups for age, female gender, diabetes, hypertension, hyperlipidemia with the class III obese group consisting of more females, being younger and showing a higher prevalence of diabetes. Fitness levels were also reported to be similar across all the groups. On completion of the programme, improvement in fitness was evident in all groups, however, as BMI increased, the amount of this improvement decreased with the Class III obese group showing significantly less improvement compared to the other groups. Further analysis relating to the percentage of weight loss showed that participants who lost >10% of their body weight showed a more significant improvement than other groups. It should be noted that there were significant differences between the groups in terms of baseline variables for example, age, gender, presence of diabetes and hypertension. However, these differences were not taken into account during the statistical analysis. In addition, the authors reported that the METs values were obtained from exercise devices although it was not clearly stated whether they used the same devices to obtain the METs values prior to and at the end of the programme.

Martin et al. (2012) studied 3997 patients who joined a 12-week CR outpatient programme during the period from 1996 to 2010 to investigate the influence of BMI on a change in fitness in this population. The population consisted of 3288 males and 709 females who were classified based on their BMI into three groups: 993 obese patients (≥30 kg/m^2) (79% male), 1929 overweight patients (25.0–29.9 kg/m^2) (81% male), and 1075 normal weight patients (18.5–24.9 kg/m^2) (73% male). At baseline and completion of the 12-week CR programme treadmill test were undertaken by all participants and an estimated METs value was calculated, based on the grade and the treadmill speed, in order to evaluate the change in fitness. Obese patients had a significantly lower baseline METs level compared to normal and overweight groups (7.4±1.9 vs 8.3±2 and 8.2±1.9 respectively) while on completion of the 12-week programme, the normal weight group showed a larger improvement (1±0.9METs) in their fitness compared to the overweight and obese groups (0.92±9 and 0.87±0.9 respectively). Furthermore, the authors reported that the fitness gain after one year was higher in normal weight participants, in both males and females, than in the other groups. However, there were significant differences between groups at baseline as the obese group was younger, more likely to be smokers and had a higher prevalence of diabetes, hypertension and hyperlipidemia than other groups. These variables were not adjusted for during the statistical analysis, which could limit generalisability of the results of this study.

This result supports the findings of a study by Gunstad et al. (Gunstad et al., 2007). They recruited 388 patients who attended a 12-week CR outpatient programme during the period from 2001 to 2005 at Summa Health System's Akron City Hospital, USA. The aim was to examine whether the gain in fitness in normal-weight patients differed from the gain in overweight and obese patients. Patients were classified into four groups according to their BMI with 71 patients in the normal weight group (BMI, 18.5–24.9), 173 patients in the overweight group (BMI, 25– 29.9), 85 patients in the class I obese group (BMI, 30–34.9, and 64 patients in the class II/III obese groups (BMI, ≥35; n=64). The treadmill exercise test was used to measure fitness which was expressed in estimated METs. At the beginning of the CR programme, patients who were in the class II/III were less fit than other groups. By the end of the programme, a significant improvement in fitness was reported in all groups. However, the multivariate analysis showed a significant difference in the change in fitness between the groups, with patients who were classified in class II/III gaining the smallest improvement, and the normal weight group gaining a larger improvement (Gunstad et al., 2007).

This is in agreement with a study by Lavie et al. (1997) which aimed to examine the impact of CR and weight reduction on exercise capacity and risk factors in obese and non-obese patients. They categorised 588 CR patients who attended a 3-month CR outpatient programme at two institutions into two groups according to their BMI; obese (BMI ≤ 27.8 kg/m^2 in men and ≤ 2 7.3 kg/m^2 in women) and non-obese (BMI < 27.8 kg/m^2 in men and <2 7.3 kg/m^2 in women). In the obese group there were 235 patients, which represents 40% of the study population, with a mean age of 59 ±10years, while in the non-obese group there were 353 patients with a mean age of 63 ±11years. The patients took part in a CR programme that consisted of 36 sessions. Before starting the programme, fitness levels were assessed using a treadmill exercise test and estimated METs were recorded. The majority of patients used the standard Bruce protocol while one third used another protocol or a bicycle ergometer test. However, a similar protocol was used in the assessment at the end of the CR programme. At baseline the non-obese group had a higher fitness level approaching a statistically significant level ($p<0.07$). Both obese and non-obese groups showed a significant improvement in their fitness. The change in fitness was considerably higher in the non-obese group compared to the obese group (39% vs 27% respectively). Further analysis was conducted comparing the change in fitness between obese patients who achieved >5% loss weight reduction compared to those who did not achieve any reduction. This showed that those who lost weight gained a significant improvement compared to the other groups (Lavie and Milani, 1997). Although the obese group were younger, had a higher percentage of body fat, were more likely to be diabetic and hypertensive, they had a lower level of HDL cholesterol and exercise capacity compared to the other groups. However, no adjustment was made for these variables during the analysis.

Nevertheless, the result of the present study is in contrast to a previous study which showed BMI was not a significant determinant of physical fitness as defined by the change in the distance walked in the ISWT (McKee et al., 2013) or by treadmill or bicycle(Pierson, Miller and Herbert, 2004; McKee, 2008; Savage, Antkowiak and Ades, 2009; Sadeghi, Esteki Ghashghaei and Rouhafza, 2012; Branco et al., 2015; Vergès et al., 2015; Lim, Han and Choe, 2016). Sadeghi et al. (2012) studied 205 female patients who were enrolled in an outpatient CR programme between 2000 and 2011 in Iran in order to investigate the difference in the change in functional capacity between obese (BMI ≥ 30) and non-obese (BMI<30) women as a result of their CR programme. Eighty-four obese and 212 non-obese patients, with a mean age of 57.6 ± 7.94 years and 58.09 ± 8.95 years respectively, undertook a treadmill exercise test. The participants joined an 8-week CR outpatients' exercise-based programme which was held 3 times per week (a total of 24 sessions). At baseline assessment non-obese patients had significantly higher fitness levels compared to obese patients (6.96 ± 2.44METs vs 5.94 ± 1.68). After completing the programme, a significant improvement in fitness was reported in both groups (8.70 ± 2.53 METs vs 7.87 ± 2.08METs respectively). However, no significant difference was found between the two groups. The description of the method in this study was inadequate as the authors did not clearly report the baseline characteristics of the sample. As mentioned previously, only a univariate analysis was used without adjustment for any potential confounders.

6.5.1.4 Diabetes

Diabetic patients in the present study were less likely to achieve MCID compared to non-diabetic (OR 0.83, CI, 0.70 to 0.99). This result is in line with previous studies (Vergès et al., 2004; Savage, Antkowiak and Ades, 2009; St. Clair et al., 2014; Branco et al., 2015). St. Claire et al. (2014) found that despite the adjustment for age, gender, BMI, and LVEF, diabetes was a significant determinant of a change in fitness. The study reported that both diabetic and non-diabetic patients showed significant improvement in their fitness level after completion of the CR, however, the diabetic patients were reported to show a significantly less improvement compared to non-diabetics (1.7 METs vs 2.5 METs respectively).

The smaller improvement that is shown in diabetic patients could be explained by the higher myocardial oxygen demands and musculoskeletal dysfunction associated with the disease leading to a reduction in patients' exercise capacity (Scheuermann-Freestone et al., 2003; Branco et al., 2015; Foo et al., 2004). However, good glycaemic control has been reported to facilitate the improvement in exercise capacity in diabetic patients (Verges et al. 2015).

In contrast to the result of the present study, several studies reported that diabetic and nondiabetic patients showed a similar improvement in their fitness after their CR programme (Banzer et al., 2004; Vanhees et al., 2004; Hindman et al., 2005; Mourot et al., 2010; Armstrong et al., 2014). Armstrong et al. (2014) retrospectively studied 7036 non-diabetic and 1546 diabetic patients who enrolled on a 12-week CR outpatient programme at the Cardiac Wellness Institute of Calgary, Canada, during the period from 1996 to 2010 in order to examine whether the change in fitness differed between the two groups. Of those who began the programme, 5973 non-diabetics and 1230 diabetics completed it. On entry to the programme, the patients undertook a treadmill exercise test and their METs were recorded.

The patients repeated the same test at the end of the programme. The non-diabetic group had a higher baseline METs value than the diabetic group. By the end of the 12-week CR programme, the change in fitness had significantly increased in both the diabetic and non-diabetic groups. This improvement was similar for both groups (11% vs 12% respectively). The multivariate analysis showed that diabetes was a significant determinant of a change in fitness with adjustments made for age, gender, treatment types and the presence of COPD and peripheral artery disease (PAD). However, the diabetic patients had a significantly higher prevalence of congestive heart failure and hypertension. These variables were not adjusted for during the analysis. Further analyses in the same study were conducted after a one-year follow-up on 3773 non-diabetics and 660 diabetics who were re-assessed. The change in fitness was 11% and 13% in non-diabetic men and women respectively and was 8% in diabetic men and 7% in diabetic women. The author concluded that diabetic patients were less likely to maintain the improvement in fitness after a one-year follow-up compared to CR nondiabetic patients (Armstrong et al., 2014).

This is in agreement with Mourot et al. who recruited 1027 patients, 614 non-diabetics with a mean age of 56.8+10.3 years, and 413 diabetic patients with a mean age of 56.9+7.9 years. The patients participated in an exercise-based CR outpatient programme at the Sainte Clotilde Cardiovascular Rehabilitation Center in France to assess functional capacity and risk factors of diabetic and non-diabetic patients before and after completion of the programme. In this programme patients attended educational and exercise-based sessions 5 times per week for 6 weeks. At the baseline assessment patients undertook a treadmill exercise with a direct measurement of gas exchange and Vo_2max values were recorded. Furthermore, patients took part in a 6-minute walk test. Compared to non-diabetics, diabetic patients had lower Vo2max values, walked shorter distances, were less likely to smoke. In addition, the percentage of CABG patients was also significantly higher in the diabetic group compared to the non-diabetic group (55% vs 37% respectively). After completion of the programme, both groups showed significant improvements in the Vo2max (28%

ml/kg/min vs 31% ml/kg/min) for diabetics and non-diabetics respectively and improvement in the distance walked during the 6-minute walk test (21%-both groups) for diabetics and non-diabetics respectively. However, the percentage of these improvements were shown to be similar in both groups. One explanation for this could be that the diabetic group had a higher percentage of CABG patients who tend to have a lower initial fitness level but achieve a higher improvement. In addition, diabetic patients were more obese and were less likely to smoke. The authors did not consider these variables in their analysis.

These findings supported a result from a previous study (Banzer et al., 2004). Banzer et al. (2004) conducted a prospective study on 702 non-diabetic patients with a mean age of 61±11 and 250 diabetic patients with a mean age 62±10 years to evaluate the influence of exercise-based CR on functional capacity and risk factors, and compliance in these two types of patients. The participants attended a 10-week CR programme (3 sessions per week) at Boston University Medical Center, USA, during the period 1993 to 2001. At entry to the programme, the fitness level of the patients was measured using a treadmill test and expressed as peak METs. The same protocol was used at the end of the programme by all patients. The diabetic group included more females who were obese, black and had a higher prevalence of peripheral vascular disease and lower METs values (5.7+2.3) than the non-diabetic group (7+2 METs). By completion of the programme, the METs values had increased significantly in both groups and there was no significant difference in the percentage of the change in fitness between the two groups (26% for the diabetics vs 27% for the non-diabetics) (Banzer et al., 2004). These improvement percentages were similar to the findings of Hindman et al. (2005) where the diabetic group showed an improvement in their fitness after a 10-week CR programme of around 26% and the non-diabetic group of 25% (Hindman et al., 2005). The authors conducted a retrospective study on data relating to 1505 patients, who enrolled on a CR programme aimed at comparing the improvement in CR outcomes profile between the diabetic and non-diabetic patients. Regarding exercise capacity, the non-diabetic patients had a higher baseline fitness level. However, both groups showed a similar improvement at the end of their programme. In this study, diabetic patients were significantly more obese, there were more CABG patients, and they had higher triglycerides. Despite this, adjustment for these variables during the analysis was not taken into account, which might limit the generalisability of the study results.

6.5.1.5 Baseline fitness level

The ability to meet the MCID is not determined by the baseline level of fitness, as defined by the walked distance during the ISWT at entry to the programme, even though statistically the initial fitness level is shown to be significant, as the effect is less than 1% (OR 0.996, 95% CI 0.994 to 0.997). This statistical significance could be due to the large sample size. This result builds on previous findings from three particular studies_(Lavie and Milani, 2000; Sandercock, Hurtado and Cardoso, 2013; Vergès et al., 2015) which were described in the (Critical Review Chapter. section X)

However, this contradicts the results from the McKee et al. study (2013), which reported that baseline fitness level influences the change in fitness expressed as distance walked during the ISWT, and other studies, which used the treadmill test and bicycle ergometer (Pierson, Miller and Herbert, 2004; McKee, 2008; Savage, Antkowiak and Ades, 2009; Beckie et al., 2013; Baldasseroni et al., 2016) (Vanhees et al., 2004). One of the limitations of these studies is that either a univariate or a multivariate analysis was used, where the adjusted variables were few in number, as has been discussed previously, These findings could arguably be explained by the law of initial values where the individual with a low baseline fitness level may show the largest improvement, which was seen in a CR population (Lavie and Milani, 1994). This phenomenon is known statistically as regression to the mean (Miles and Shevlin, 2003). An early study by Lavie and Milani (1994) reported that following CR, less improvement in fitness was seen in patients with a high baseline fitness level compared to those who started with a lower level (Lavie and Milani, 1994). They studied 288 patients who were categorised based on their initial fitness level into two groups, 163 patients who were classified as having a high baseline fitness level (≥ 6 METs) and 125 who had a low fitness level (<6METs).

6.5.1.6 Marital status

Regarding patients' marital status, those in a stable relationship were more likely to be able to achieve the MCID by 26% compared to those who were single. However, those who were previously in a relationship did not differ from the single participants. The scarcity of research examining the influence of marital status on the change in fitness in CR patients does not allow a direct comparison with our results.

A study conducted by Ortega et al (2011) examined the association between marital status transitions and changes in fitness in 8,871 healthy participants, 6,900 of whom were men, for a median follow-up period of 3.4 years using a maximal treadmill test. They analysed the participants in three groups of pairs a participant who remained single compared to a single participant who married; a married participant who remained married compared to a married one who divorced; and a divorced participant compared to divorce one who remarried. They found, after adjustment for age, BMI, baseline fitness, physical activity status and the period of time between assessments, that participants who were married showed a reduction in their change of fitness compared to participants who remained single. However, the difference was not statistically significant. The change in fitness increased significantly in divorced male participants compared to those who remained married while there was no statistically significant difference in the change of fitness in women who divorced compared to those who remained married. The authors also found that divorced male participants exhibited a decrease in the change in their fitness compared with divorced males who remarried showing a significantly greater reduction. The authors conclude that the change in fitness was lower in participants who transitioned to being married whereas being divorced is associated with a small rise in the change in fitness in men. The results for women were inconclusive.

This is in contrast to the results of the current study, however, the participants in the Ortega et al study were healthy whereas the participants in our study were taking part in a CR programme after a cardiac event and therefore being in a stable relationship provides partner support and is associated with better health and lower risk factors (Manfredini et al., 2017).

6.5.1.7 Employment status

Employment status was a significant determinant in the current study as the analysis showed that compared to the employed, unemployed patients were statistically less likely to achieve the MCID. Johnson and his group found the same result in two separate studies using data from Wake Forest Baptist Medical Center (Johnson et al., 2014, 2015). This result also supports the findings obtained from the European Cardiac Rehabilitation Registry and Database (EuroCaReD) study (Benzer et al., 2017). Benzer et al. classified their patients in terms of whether they achieved success in their exercise capacity, with success being defined as achieving an improvement of >25 watts during their bicycle ergometer test. They found that the percentage of employed patients who were successful was higher whereas the opposite was true for the unemployed and retired patients. Being unemployed has been reported to be associated with poor outcomes after CR (Harrison et al., 2016)

6.5.1.8 Ethnicity

MCID for the ISWT is also determined by the ethnicity of patients in this study. The likelihood of white British participants achieving this MCID increased by 30% compared to the non-white British group**.** This is in agreement with a previous study conducted in a CR population (Johnson et al., 2015). Johnson et al. 2015 reported that race was a determinant of the change in fitness expressed in METs, with the African American race being a predictor of decreased improvement in fitness. They found white patients had a significantly higher baseline fitness level compared to African Americans (2.7± 0.9 METs vs 2.4±0.7 METs respectively). Regardless of race, CR was beneficial in improving the fitness level of the patients, however, the improvement was significantly higher in white patients than in African American patients (2.4 METs vs 1.6 METs respectively).

However, Gee et al. (2014) reported in their analysis that although white patients showed a larger increase in their METs from the baseline to the end of the programme compared to black patients, this was not statistically significant. This is in agreement with a study by Cannistra et al. (1995) who compared the difference in CR outcomes between 35 black and 47 white women. At entry to the CR programme and again at the end, exercise capacity was measured using a treadmill exercise test or cycle ergometer and estimated METs values were recorded. There was no significant difference in the baseline fitness level between the two groups. Only 18 black women and 20 white women completed the12-week programme with both groups showing a similar improvement (Cannistra, O'Malley and Balady, 1995). However, this study was limited by its small sample size.

6.5.1.9 Anxiety

Patients exhibiting anxiety were 1.3 times more likely to achieve this recommended clinical improvement, which is in line with a study conducted by Egger et al. (2008) in CR patients. The authors studied 114 patients in order to investigate the effect of depression and anxiety on the change in exercise capacity in CR patients expressed in watts using a bicycle ergometer. They found that after controlling for age, gender, programme duration, HAD score for depression pre-programme, and baseline exercise capacity, the patients with higher anxiety levels gained more improvement in their exercise capacity. It seems that anxiety may act as a motivator as these patients showed a higher commitment to exercise (Egger et al., 2008).

A recent study conducted on 233 CR patients (70% men) who attended a 21-day CR programme at the Clinic of the Behavioral Medicine Institute at the Lithuanian. The study examined the relationship between mental distress factors (anxiety and depression) and the change in exercise capacity by the end of the CR programme. They found that there is an inverse association between HADS scores for anxiety and depression, and the patients' fitness level at the end of the programme (Kazukauskiene et al., 2017).

6.5.1.10 Hyperlipidaemia

Patients who had hyperlipidaemia as a comorbidity in the present study were 1.2 times more likely to achieve the MCID compared to those who did not. This result was in contrast to the results of the study by Branco et al. (2015) and Gee et al. (2014). However, these two studies used total cholesterol as a continuum in their analysis. In general there is a lack of studies which investigate the correlation between dyslipidaemia and the change in fitness in the CR population.

6.5.1.11 Smoking

Compared to non-smokers, patients who stopped smoking after their event were 15% less likely to achieve the ISWT MCID. This percentage doubled (30%) in the patients who continued to smoke. This is in agreement with previous studies by Johnson et al. (2014, 2015) which found that, after adjustments made in the multivariable analysis, the smoking status variable was a significant predictor of a change in fitness with being a smoker at entry to the programme associated with reduced improvement in fitness (2014, 2015).

Other studies reported that smoking was not a determinant of a change in fitness in (Branco et al 2015, Beckie et al 2015). Beckie's study (2015) used a population which was restricted to female participants who completed 36 CR sessions, which limited the generalisability of the results. However, Branco et al. (2015) classified the smoking status of the patients as either smoker or non-smoker while in the present study, patients were grouped according to whether they smoked, did not smoke or had stopped since the cardiac event. Furthermore, Branco et al. only used around 70% of the variables used in the current study while Beckie used even fewer.

6.5.1.12 Number of sessions

The total number of sessions that patients attended has been reported to be a determinant of a change in fitness. Almodhy et al. (2016) found that attending at least 12 CR sessions is a significant determinant in achieving an improvement in fitness during the ISWT (Almodhy, Ingle and Sandercock, 2016). These findings were confirmed in the present study where the patients who attended at least 12 sessions were 1.3 times more likely to achieve the MCID than those who attended fewer sessions. This cut-off point was reported previously in a meta-analysis which included 11 UK studies (Almodhy, Ingle and Sandercock, 2016). Furthermore, it also represents the median value split of the number of sessions in this study.

These findings were supported by Keteyian et al. (2016), who stratified the patients in their study into three categories according to the number of sessions that patients attended: patients who attended 9-15 sessions (group 1); patients who attended 16-30 sessions (group 2); and patients who attended 31 or more sessions (group 3). The authors reported that among the male patients, the improvement was higher in the third group (56%) followed by the second group (47%) and then the first group (40%). This trend of improvement was also present in female patients (51%, 41% and 34% respectively).

In contrast to this result, some studies reported that the number of sessions that patients attended was not a significant determinant of the change in fitness (Glazer et al., 2002; Beckie et al., 2013; Sandercock, Hurtado and Cardoso, 2013) as reported in Critical Review chapter. However, both Beckie et al. (2013) and Glazer at al. (2002) used this variable as a continuum in their analyses. Glazer reported that they considered any patient who attended fewer than two thirds of the total of 36 sessions (<23 sessions) as a dropout and the patient was excluded from their analysis. However, this number of sessions in some other countries might be considered large and comparable to a complete programme. (Sandercock, Hurtado and Cardoso, 2013; Almodhy, Ingle and Sandercock, 2016; NACR, 2017)

6.5.1.13 Reason for referral

The reason for referral variable was a statistically significant determinant. Compared to MI as a reference category, patients who were post-CABG or -valve surgery in the current study were 23% more likely to achieve a clinically important improvement in their exercise capacity. This is in line with studies which show that CABG patients achieve a larger improvement in their fitness compared to MI patients (Branco et al., 2015). However, there is no significant difference between the patients who were referred as MI patients and the other referral categories**.**

Jelinek et al. (2013) conducted a study comparing 22 patients with PCI and 16 with CABG who attended a 6-week CR programme to study the difference in the Vo_2 peak and the change in the distance walked measured during the 6-MWT. The patients preformed the 6-MWT with gas analysis at entry and at the end of the programme. Patients with PCI improved their Vo_2 peak from 12.6 ± 1.0 to 13.3 ±1.3. This improvement was higher in CABG patients who improved from 11.9 ±1.6 to 12.9 ±1.6. The change in the mean distance walked for CABG patients was 61m, which exceeded the MCID for the 6-MWT for the CR population (54 m), while the mean difference in the distance walked for the PCI patients was 41m, which is less than the MCID.

Another study compared the change in peak Vo_2 in CABG and PCI patients (Lan et al., 2002). Lan et al (2002) recruited 44 (24 PCI and 20 CABG) patients for a 12-week CR programme delivered 3 times per week. All patients performed an exercise test using a cycle ergometer with a gas analysis at entry and at the end of the programme. At baseline, CABG patients had a significantly lower VO_2 peak compared to PCI patients (19.8±2.2 vs ml/kg/min vs 23.3±3.5 ml/kg/min respectively). However, on completion of the programme, although both groups achieved a significant improvement, the CABG patients achieved a greater improvement than the PCI patients (30% vs 14%).

This greater improvement seen in CABG patients compared to PCI patients is usually due to their initial lower level of fitness (Lavie and Milani, 1994, 2011), which means they are likely to show a bigger improvement. This initial lower level of fitness might be attributed to CABG patients generally staying in hospital longer and requiring a longer period to convalesce (Ades et al., 2006). However, Vanhees et al. (1995) reported that there was no significant difference in the improvement in exercise capacity between the MI, CABG and MI+CABG groups after the outpatient CR programme (Vanhees et al., 1995).

6.5.1.14 Time from cardiac event to start

Starting rehabilitation as early as possible is recommended in the current CR guidelines (Piepoli et al., 2012). In the present study, the time from the cardiac event to the start of CR expressed as a continuous variable was shown to be a statistically significant determinant, however, this effect was very small at less than 1% (OR 0.994, 95% CI 0.991 to 0.997), which means the significance might be due to the large sample size and might be considered not of clinical significance. This result showing that this variable was statistically significant but perhaps not clinically significant this was in agreement with Savage et al. (2009) but in contrast to a study conducted by Fell et al. (2016) on a CR population, which concluded that a delay in starting a CR programme reduces the extent of the improvement in a patient's fitness (Fell, Dale and Doherty, 2016). Marzolini et al. (2015) reported that a long waiting time is associated with less improvement in cardiorespiratory fitness in post-CABG patients (Marzolini et al., 2015). They studied 6497 post-CABG patients, 4747 of whom completed a CR programme. The wait time was classified into referral wait time (the time from cardiac surgery to receiving a referral), cardiac rehab wait time (the time from receiving the referral to starting CR), and the total wait time (the time from cardiac surgery to starting CR). The same exercise test was conducted both prior to and following the CR programme and patients used either a treadmill or cycle ergometer for both tests. The median of the total wait time was 101.1 + 47 days. A multivariable analysis was conducted for each stage. However, this result was restricted to CABG patients and the mean and median total wait time for the present study was shorter.

These results are supported by results from Johnson et al. (2014) who studied 1241 CR patients to investigate the effect of early enrolment onto a CR programme on CR outcomes. They divided their patients into those who enrolled within 30 days (further divided into patients who enrolled from 0 to 15days and from 16 to 30 days) and those who enrolled later than 30 days (Johnson et al., 2014). Both groups showed an improvement in exercise capacity, however, this improvement was significantly higher for the group who enrolled between 0 to 15 days (3METs) and between 16 to 30 days (3METs) compared with those who enrolled later than >30 days (1.8 Mets). After multivariate adjustment, they concluded that, compared with 0 to 15 days, a delay time of >30 days was a significant predictor of a decrease in improvement in exercise capacity.

However, the time which elapsed between the cardiac event and the initial assessment was reported to be inversely associated with a lower initial fitness level. Females, CABG patients and those being medically treated for angina and older patients were reported to delay entry to the programme (Ades et al., 2006; Marzolini et al., 2015).

6.5.1.15 Attending inpatient CR (phase I)

Attending inpatient CR sessions (phase I) was also found to be a significant determinant in this study. Patients who attended this phase were 1.3 times more likely to achieve the MCID. Salzwedel et al. (2014) studied 1253 CR patients attending inpatient CR programmes. At discharge, it was found that nearly two-thirds of the patients had improved their physical fitness in both their exercise capacity, measured during the bicycle exercise stress test, and the distance walked during the 6-MWT (Salzwedel et al., 2014). However, there is a lack of follow-up studies to investigate the influence of this phase on change in physical fitness after discharge in CR population.

6.5.1.16 Self-reported physical activity (meeting the recommended 150 min/week)

In this study patients who self-reported that they met the recommended 150 minutes of physical activity per week were 16% more likely to achieve the MCID compared to those who did not meet the physical activity recommendations, thus adding to the literature by confirming a positive relationship between physical activity status and a clinically important difference in fitness.

The result of the present study is in contrast to a previous study (Branco et al., 2015) where the physical activity level at entry to the CR programme did not determine the change in fitness. However, in the Branco et al. study (2015), the level of physical activity was measured using the International Physical Activity Questionnaire (IPAQ) which classified the individuals in one of three categories; vigorous activity (>3000 METs/min/week) moderate activity (600–3000 METs/min/week); and sedentary (<600 METs/min/week), while in this study the patients answered ‘yes’ or ‘no’ based on whether they spent 150 mins per week on physical activity (Department of Health Physical Activity Health Improvement and Protection, 2011).

6.5.1.17 Non-significant Determinants

Neither depression, duration of the programme, the number of total comorbidities nor the IMD index were significant determinants of MCID in this study. Depression was not a significant determinant in the present study which concurs with McKee et al. (2013). In contrast to the present study, Egger et al. (2008) reported that higher levels of depression at baseline were associated with less improvement in fitness following an outpatient CR programme (Egger et al., 2008). This is supported by the result of a recently-published study (Kazukauskiene et al., 2017). However, these studies categorised their patients into three groups based on the HAD scale and the change in fitness was recorded as a numerical value while in the present study patients were classified as having depression (as a comorbidity) or not and the patient outcome was based on the patient achieving the MCID or not. Furthermore, in the previous studies the number of confounders was less than in the present study and the sample size was smaller and derived from a single centre.

The duration of the CR programme has been reported to be insignificant in the literature (Sandercock, Hurtado and Cardoso, 2013; Almodhy, Ingle and Sandercock, 2016). However, the duration of the programme which was used in these studies was represented as an aggregate of each study and was categorised into groups while in the present study, the duration of the programme was expressed as a continuous variable and represented the actual time that patients spent on the programme.

6.5.2 Sub analysis.

This study found that patients who achieved the MCID in the ISWT at the end of their CR programme were 29% more likely to meet the physical activity recommendations (150 min/per week). This improvement was also reflected in the self-reporting of their physical fitness (Dartmouth COOP scale) as they were shown to be 55% more likely to describe the activity they could sustain for two minutes as moderate to very heavy in terms of intensity according to the Dartmouth COOP scale compared to those who did not achieve the MCID. This means that the improvement in fitness as expressed by achieving the MCID for the ISWT reflected positively in the patient physical activity status and increased the likelihood of an improvement in the physical fitness subset in patients' health-related quality of life for those patients who participant in CR. This might be explained by the patients feeling that they are more confident in their physical ability. A recent systematic review was conducted in 40 RCTs involving 6480 patients to examine the impact of a CR intervention on physical activity. The findings showed that there was a statistically significant improvement in the CR group compared to the control group. This result was consistent irrespective of the type of physical activity measurement or CR intervention (Dibben et al., 2018). However, the authors highlighted that the quality of reporting and the physical activity assessment was comparatively poor and the included studies were at high risk of bias.

The improvement in these two variables is considered important as it has been reported that individuals' perceptions of their physical activity is a strong predictor of mortality. Zahrt and Crum (2017), in healthy participants, found that compared to those individuals who described themselves as active, those who were less active were 71% more likely to die in the follow-up period (Zahrt and Crum, 2017).

6.5.3 Implications

Knowing the characteristics of patients who do not achieve the MCID during their end-of-programme ISWT, which reflects their change in fitness, gives clinicians opportunity to more closely tailor their practice to the needs of their future patients. Factors such as being female, older, diabetic, obese, a smoker, non-white, unemployed, attending less than twelve sessions and being inactive are associated with being unable to achieve the MCID. Clinicians should pay particular attention to these types of patients by modifying the standard CR programme to take into account these patients' specific needs, which would assist in improving their fitness by, for example, In diabetic patients, for instance, optimising glycaemic control was demonstrated to significantly enhance the improvement in the fitness gain (Vergès et al., 2015). or maximising the number of sessions (Almodhy, Ingle and Sandercock, 2016; Keteyian et al., 2014).

This study shows that patients with anxiety (as comorbidity) tend to achieve better results than those less anxious. Therefore, paying attention to less anxious patients is important to encourage them to improve their fitness. In addition, patients who do not meet the physical activity recommendations at baseline need to be motivated to improve their performance in this area.

Tailoring a CR programme to an individual based on these determinants leads to the achievement of the MCID, which is consequently reflected in the patients' self-perception of physical fitness and physical activity status.

6.5.4 Study strength and limitations

One of the strengths of this study was that it captured routine clinical practice among multi-centre CR programmes in the UK using a large database (NACR) in preference to a standardised clinical trial, which is known to be poorly representative of patients attending routine practice. For example, in the Cochrane review, the mean age is 56 years, 10% of the participants were females with minor comorbidities whereas routine CR practice attracts patients with a mean age of 67 years and 33% of the population is female with two or more comorbidities (NACR, 2017). As a common limitation of the majority of the previous studies mentioned above was the use of univariate analysis. A further strength of this study was the use of the robust method which utilised multivariable analysis to adjust for bias and potential confounders, took into: account the nested nature of the data where the patients were treated in different centres, and applied an imputation technique to replace the missing data in order to maximise the sample size of the study. In addition, this study used the concept of MCID, which produced a more clinically meaningful measurement than a mathematical value derived from the post-programme minus the pre-programme value.

However, this study is not without limitations. Due to the nature of retrospective studies, the data relating to some factors which have been reported to influence the change in functional capacity , such as exercise intensity, were not available (Uddin et al., 2015). In addition, the patients' waist circumference variable in this data had more than 60% missing values, which precluded a multiple imputation for this variable. As there is no clear agreement on how to categorise variables such as baseline fitness level and time from cardiac event to start of CR, they have been reported on a continuum in the present study while the majority of the previous studies reported them in a variety of categories without a clear justification, which may explain the difference in results.

6.6 Conclusion

The magnitude of the change in fitness expressed as the distance walked during the ISWT in the CR population was 97m. Results demonstrate that the following factors namely: older age, female gender, obesity, presence of diabetes, being a smoker, not being in a stable relationship, unemployment, non-attendance of a phase 1 in-patient programme, having a higher baseline fitness, not being physically active, attending fewer than 12 sessions, and not being white British were likely to be determinants of being unable to achieve the MCID for the ISWT as a fitness measurement in CR patients.

Results such as these, derived from this type of study, reflect routine clinical practice, giving clinicians a picture about how the factors that they see every day can be altered to help optimise the fitness levels patients can achieve following CR. Therefore, clinicians and service providers should target these types of patients, creating individual therapeutic plans to guarantee that patients exert optimal effort to enable them to achieve the recommended gains in their exercise capacity.

The achievement of the MCID during the ISWT at the end of the CR programme was associated with an improvement in physical activity status (meeting 150 minutes per week) and a patient's self-perception of physical fitness.

Chapter 7. Synthesis and conclusion

7.1 Synthesis

The findings from chapter four showed that although assessing functional capacity at baseline is recommended by various organisations, the percentage of patients who take this test was low with less than one-third reported to have undertaken this assessment (Benzer et al., 2017; NACR, 2017). However, the findings of this chapter showed the importance of conducting this assessment was not only as a means of providing data to assist exercise prescription but also because it is one of the biggest determinants of CR completion as patients who undertook a baseline functional capacity test were 1.48 times more likely to complete their CR programme. No study has reported this result before. It has also been shown in this chapter that, in terms of the service delivery performance indicators, the percentage of programmes which measure fitness was higher than the percentage of those centres which did not. The result of this chapter also showed that ISWT was the most common test used in the CR population in the UK. The fifth chapter showed that there was a lack of studies that attempt to produce reference values and identify the predictors of the baseline distance walked for this test. Variables such age, gender, height, weight and BMI were reported by previous studies (Pepera et al., 2013; Cardoso et al., 2016), however, there was no consistency between these studies. The study in chapter five confirmed that age, gender and self-reported physical function subset from the Dartmouth COOP tools) were predictors of the distance walked, as a measurement of their fitness level, during the ISWT at the baseline assessment. These predictors explained 32% of the variance in the distance walked. This percentage is higher compared to previous studies (Pepera et al., 2013; Cardoso et al., 2016). In this chapter, the reference values that were produced will assist clinicians in their initial expectations of patients' performance in the ISWT, to inform patients of their level of fitness compared to their peers, and to set realistic CR goals for their patients

These variables age and gender were also determinants of achieving the MCID of the ISWT. Therefore, they should be considered when assessing a patient's level of fitness. The NACR report (2017) showed that only 60% of the patients who undertook the ISWT at baseline achieved the MCID by the end of their programmes, which means that although the improvement in patient fitness is one of the major CR goals, 40% of these patients had not achieved it. This is the only study (chapter six) that has identified the determinants of achieving the MCID in the CR population, which will be of use to clinicians when tailoring a programme for individual patients. Seventy per cent of the determinants of achieving the MCID that were identified in the sixth chapter in this thesis had previously been identified in the critical review study (chapter two) as being determinants of the change in fitness in the CR population.

This improvement in fitness as expressed in achieving the MCID for ISWT is reflected in an improvement in patients' self-perception of their physical capability as those who achieved the MCID were approximately 1.5 times more likely to perceive themselves as able to complete activities classified as moderate to high intensity and 1.3 times more likely to meet the physical activity recommendations (at least 150 minutes of moderate exercise per week) as is shown in the sub-analysis in chapter six. However, there was no association between these two variables and whether the patients' fitness had been measured or not as shown in the fourth chapter.

In the critical review chapter, the previous studies varied in their attempts to identify the determinants of a change in fitness. Drawing conclusions relating to this identification was made more difficult due to inconsistencies in the analysis relating to limitations in sample size, potential confounder and population characteristics.

7.2 Conclusion

Although measuring functional capacity is recommended by various organisations, the studies show that there is a small percentage of patients who have undertaken this assessment in routine practice and there are few studies which have highlighted this issue. However, patients whose fitness was measured at baseline were more likely to complete their CR programme. The centres which do not measure fitness appear to have lower performance in terms of service delivery according to the service delivery performance indicators (Furze et al., 2016; BACPR, 2017) compared to those which do.

The ISWT is the commonly used assessment as a functional capacity assessment in the UK. In this thesis, reference values were produced based on age-gender categories, which will help remove uncertainty around patient risk assessment prior to CR and future exercise prescription. They could also help clinical decision making around the need for a second ISWT, aid feedback to patients about their level of baseline fitness and help set rehabilitation goals.

When the studies that attempted to identify the determinants of a change in fitness in CR patients were critically reviewed, there continues to be a large variation in the studies in terms of identifying the determinants of a change in fitness. The ability to draw conclusions is hindered by significant inconsistencies in how studies were analysed with additional limitations in the studies with reference to sample size, population characteristics and potential confounders.

In this thesis, the determinants of achieving the MCID for the ISWT in the CR population was identified. Achieving the MCID is an indication that improvement has taken place. Therefore, being aware of these determinants is important as it helps clinicians to tailor the CR programme to suit individual patient's needs in order to help patients to achieve an improvement in fitness. This is shown to be reflected in a patient's self-perception of their physical fitness and activity level.

7.2.1 Key findings

1 The critical review chapter highlights the huge variation in the studies in terms of identifying the determinants of a change in fitness. The quality of study designs and the reporting of study details in journal publications needs to improve so that critical and systematic reviews can be performed to the highest level.

2 The analysis of the first study was the first ever to confirm an association between the measurement of fitness at baseline and the completion of the CR programme.

Reference values that were produced in the second study (chapter four) will help clinicians in their initial expectations of patients' performance, aid in patient risk assessment before CR, support future exercise prescription, inform patients of their fitness level compared to their peers, establish whether a second ISWT is required and enable clinicians to set realistic CR goals.

3 The findings from the third study identified key determinants of the MCID for the ISWT which will aid clinicians in tailoring programmes for individual patients to improve their functional capacity, which in turn reflects on the self-reported physical activity status and quality of life as shown in the sub-analysis.

7.2.2 Key Strengths and Limitations

7.2.2.1 Strengths

One of the strengths of this thesis was the use of large amount of data from routine clinical practice carried out in CR programmes in the UK. This clinical data was taken from the NACR database, which is the largest database in the UK for the CR population. A further strength was the multivariable analysis conducted on the large number of variables. In addition, a robust analysis was used to take account of the nested nature of the data where patients were treated within centres. A multiple imputation technique was also used to overcome the issue of missing data which is usually observed in secondary data analysis.

7.2.2.2 Limitations

Despite using a large high-quality database (NACR) which consists of all the variables which relate to patients' characteristics and service programmes, a considerable amount of data was missing. Although a multiple imputation approach was used, the means of replacing the missing data is a computational approximation. As the data is entered manually by the programme centres to the NACR database, human error also impacts the quality of the data and consequently the outcome results.

There might be selection bias due to the nature of observational studies despite applying a rigorous approach to take account of the potential confounders. Furthermore, although the data had a large number of variables, there might be some variables that were identified in the studies as determinants but were not available in these data.

7.2.3 Recommendations

1- Assessing fitness is strongly recommended for CR patients pre- and post-CR programme to assess risk and make an accurate exercise prescription. Despite this, the evidence of this research showed that only a small percentage of CR patients (28%) are assessed. Therefore, action should be taken to ensure that this assessment is conducted and the reason for not conducting the test should be included in the audit data. In addition, centres should be encouraged to assemble the resources to enable them to conduct the assessment.

2- Knowledge of the characteristics of patients who do not achieve the MCID should inform the clinician in their design of an individual programme for this type of patient.

3- Future NACR reporting should make it a priority to specify more precisely what the baseline assessment should include as the present standards and reporting of assessment nationally is potentially misleading.

4- Based on the evidence from the critical review, the quality of study designs and the reporting of study details in journal publications needs to improve so that critical and systematic reviews can be performed to the highest level.

5- BACPR should clarify whose responsibility it is to conduct the functional capacity assessment, thereby aligning the appropriate CR staff with the clinical tasks that reflect their training and more strongly emphasise the need for training CR practitioners in the use of physical fitness tests.

7.2.4 Further research

This thesis has highlighted several areas that require further investigation regarding the assessment of functional capacity at the pre- and post-CR programme stage.

1- As the ISWT is one of the most common tests in the UK, examining the association between change in actual fitness levels and MCID in terms of patient and the survival rates is now possible and should be pursued.

2- The association between whether the patient achieves the MCID and the other CR outcomes would be a valuable area to research.

3- A qualitative evaluation of the barriers and facilitators to measuring fitness in routine practice would be valuable.

Chapter 8. Appendices

Appendix 8.1 Publication paper

Open Access

Original article

BMJ Open Sport & Exercise Medicine

Evaluation of determinants of walking fitness in patients attending cardiac rehabilitation

Jassas FM Alotaibi, Patrick Doherty

To cite: Alotaibi JFM, Doherty P. Evaluation of determinants of walking fitness in patients attending cardiac rehabilitation. *BMJ Open Sport Exerc Med* 2017;2:e000203. doi:10.1136/bmjsem-2016-000203

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjsem-2016-000203).

Accepted 9 January 2017

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ABSTRACT

Aim: This study aims to investigate the ability of patients' baseline characteristics to predict the distance walked during the incremental shuttle walk test (ISWT) in the cardiac rehabilitation (CR) population and to produce reference values to guide practice.

Methods: Secondary analysis was conducted on National Audit Cardiac Rehabilitation data collected between 2010 and 2015. Patients (n=8863) were included if they were aged ≥18 years and had a recorded ISWT score assessed before starting CR. Stepwise regression was used to identify factors predicting the ISWT distance. Age, gender, body mass index, height, weight; presence of hypertension, dyslipidemia or diabetes; smoking and physical activity were independent variables. ISWT distance was the dependent variable. The 25th, 50th and 75th percentiles of the ISWT distance were used as reference values.

Results: Age and gender explained 27% of the variance of the distance covered in the ISWT (R^2=0.27, adjusted R^2=0.27, Standard Error of the Estimate (SEE) = 148.7, $p<0.001$). Reference values using age and gender categories were developed.

Conclusion: Age and gender were the significant factors for predicting the walking fitness in the CR population, with age being the best predictor. The age and gender reference values produced represent a potentially valuable tool to be used in the clinical setting.

INTRODUCTION

Assessing physical fitness at baseline and end of programme in patients attending cardiac rehabilitation (CR) is strongly recommended in clinical guidelines and national standards.[1–3] Assessing a patient's fitness level at the beginning of the programme enables the appropriate intensity of exercise to be prescribed, determines the level of supervision and monitoring required and allows for the assessment of the effectiveness of the intervention.[3 4]

Using laboratory maximal tests on treadmills or cycle ergometers to assess cardiorespiratory fitness by directly measuring the maximal oxygen uptake (Vo_2 max or Vo_2 peak) is regarded as the gold standard. However, these tests are not widely available.[1 5] Compared with the gold standard methods, functional fitness walk tests are simple and safe to use and are a reasonable surrogate measure of fitness.[6] In the UK, the most commonly used field test in CR and chronic obstructive pulmonary disease patients is the incremental shuttle walk test (ISWT), which is an objective test widely used in clinical settings to assess the extent of physical fitness.[5 6] This type of test is shown to be *reliable* and strongly correlated with the cardiopulmonary exercise test (CPET).[7 8] The ISWT is a submaximal, incremental, externally paced test that evaluates physical fitness based on the distance covered during the assessment.[6 8] The recommended protocol is a 20 min test followed by a 30 min rest period before the test is repeated. The best outcome of the two tests is then recorded. However, in routine clinical practice, the ISWT is generally performed just once despite emerging research suggesting that the learning effect may influence the distance achieved as evidenced through a second baseline test.[9] Most CR programmes struggle to carry out even a single baseline fitness test,[10] which makes undertaking a second test unrealistic. To date, very few studies have tried to establish reference values as a comparison with the first ISWT attempt, and where it has been attempted, the sample size has been insufficient within the proposed categories.[11 12]

Healthy individuals have been shown to walk double the distance of patients with cardiac disease during the ISWT (600–800 m vs 300–400 m, respectively).[11] Predicting the distance covered during the ISWT has been attempted in several studies in healthy populations[13–17]; however, to date, only two studies have been published using a CR population.[11 12] These two studies conducted by Pepera et al (2013) and

Appendix 8.1.1 AACVPR risk stratification

From: AACVRP. (2013). Guidelines for cardiac rehabilitation and secondary prevention programs. Fifth edit. Champaign, IL : Human Kinetics

AACVPR criteria for risk stratification in patients with low, moderate and high risk of events during the year.

Low Risk

- Absence of complex ventricular dysrhythmia during exercise testing and recovery
- Absence of angina or other significant symptoms (e.g., unusual shortness of breath, light-headedness, or dizziness heart rate and systolic blood pressure with increasing workloads and recovery)
- Presence of normal hemodynamics during exercise testing and recovery (i.e., appropriate increases and decreases in heart rate and systolic blood pressure with increasing workloads and recovery)
- Functional capacity ≥ 7 METs

Non exercise testing findings

- EF ≥ 50% at rest
- Uncomplicated MI or revascularization procedure
- Absence of complicated ventricular arrhythmias at rest
- Absence of CHF
- Absence of signs or symptoms of post-event or post-procedure ischemia
- Absence of clinical depression

Nonexercise testing findings

- EF ≥ 50% at rest
- Uncomplicated MI or revascularization procedure
- Absence of complicated ventricular arrhythmias at rest
- Absence of CHF

- Absence of signs or symptoms of post-event or post-procedure ischemia
- Absence of clinical depression

Moderate Risk

- Presence of angina or other significant symptoms (e.g., unusual shortness of breath, light headedness, or dizziness occurring only at high levels of exertion [<7METs])
- Mild to moderate level of silent ischemia during exercise testing or recovery (ST-segment depression < 2 mm from baseline)
- Function capacity < 5 METs

Non exercise testing findings:

- EF = 40% to 49% at rest

High Risk

- Presence of complex ventricular arrhythmias during exercise testing or recovery
- Presence of angina or other significant symptoms (e.g., unusual shortness of breath, light-headedness, or dizziness at low levels of exertion [≥ 5 METs] or during recovery)
- High level of silent ischemia (ST-segment depression ≥ 2 mm from baseline) during exercise testing or recovery
- Presence of abnormal hemodynamics with exercise testing (i.e., chronotropic incompetence or flat or decreasing systolic BP with increasing workloads) or recovery (i.e., severe postexercise hypotension)

Nonexercise testing findings:

- EF < 40% at rest History of cardiac arrest or sudden death Complex dysrhythmias at rest
- Complicated MI or revascularization procedure
- Presence of CHF
- Presence of signs or symptoms of postevent or postprocedure ischemia
- Presence of clinical depression

METs : Metabolic Equivalent; EF: Ejection Fraction; MI: Myocardial Infarction; CHF: Congestive Heart Failure; BP: Blood Pressure

Appendix 8.1.2 Absolute and relative contra-indications

Absolute Contraindications	**Relative Contraindications**
1-Acute myocardial infarction (MI), within 2 days 2-Ongoing unstable angina 3-Uncontrolled cardiac arrhythmia with hemodynamic compromise 4-Active endocarditis 5-Symptomatic severe aortic stenosis 6-Decompensated heart failure 7-Acute pulmonary embolism, pulmonary infarction, or deep vein thrombosis 8-Acute myocarditis or pericarditis 9-Acute aortic dissection 10-Physical disability that precludes safe and adequate testing	1-Known obstructive left main coronary artery stenosis 2-Moderate to severe aortic stenosis with uncertain relation to symptoms 3-Tachyarrhythmias with uncontrolled ventricular rates 4-Acquired advanced or complete heart block 5-Hypertrophic obstructive cardiomyopathy with severe rest- ing gradient 6-Recent stroke or transient ischemic attack 7-Mental impairment with limited ability to cooperate 8-Resting hypertension with systolic or diastolic blood pressures >200/110 mm Hg 9-Uncorrected medical conditions, such as significant anemia, important electrolyte imbalance, and hyperthyroidism
SpO_2: arterial oxygen saturation measured by pulse oximetry. #: exercise patient with supplemental oxygen. (Adapted from ACSM 9th edition p 238).	

Appendix 8.2.1 Example of search strategy

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update

Search Strategy:

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1 Cardiorespiratory fitness.mp. or exp Physical Fitness/ or exp Oxygen Consumption/ or exp Cardiorespiratory Fitness/ or exp Physical Exertion/ or exp Exercise Test/ (220073)

2 exp exercise test/ or exp walk test/ (61659)

3 cardiopulmonary fitness.mp. (220)

4 exercise/ or exp high-intensity interval training/ or exp walking/ (134694)

5 functional capacity.mp. (10274)

6 aerobic capacity.mp. (4142)

7 aerobic fitness.mp. (2361)

8 functional fitness.mp. (260)

9 exp physical endurance/ or exp anaerobic threshold/ or exp exercise tolerance/ (31449)

10 cardiovascular fitness.mp. (1066)

11 Functional Training.mp. (296)

12 exp oxygen consumption/ or exp metabolic equivalent/ (106264)

13 Vo2.mp. (12715)

14 oxygen uptake.mp. (17734)

15 fitness.mp. (66717)

16 (determin* or predict*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3785363)

17 (improve* or chang*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3852097)

18 influence.mp. (799341)

19 exp coronary disease/ or exp coronary artery disease/ (212239)

20 Coronary heart disease.mp. (44494)

21 exp heart diseases/ or exp myocardial ischemia/ (1068330)

22 exp Myocardial Infarction/ (169875)

23 cardiac surgery.mp. or Thoracic Surgery/ (43175)

24 exp myocardial revascularization/ or exp coronary artery bypass/ (89484)

25 Percutaneous Coronary Intervention.mp. or exp Percutaneous Coronary Intervention/ (52475)

26 myocardial revascularization.mp. or exp Myocardial Revascularization/ (90318)

27 cardiac rehabilitation.mp. or Cardiac Rehabilitation/ (5288)

28 exp Cardiac Rehabilitation/ (1461)

29 CARDIOVASCULAR REHABILITATION.mp. or Cardiac Rehabilitation/ (1578)

30 DISTANCE.mp. (162535)

31 2 and 30 (3606)

32 2 or 31 (61659)

33 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 32 (383572)

34 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (1129554)

35 33 and 34 (56006)

36 16 or 17 or 18 (7203998)

37 35 and 36 (28194)

38 SECONDARY PREVENTION.mp. or Secondary Prevention/ (30410)

39 28 or 29 or 38 (31830)

40 37 and 39 (346)

Appendix 8.2.2.A List of excluded studies in critical review

Study	Reason for exclusion
Ades et al 1999 **Determinants of physical functioning in coronary patients: Response to cardiac rehabilitation**	Irrelevant
Ades et al 2002 **Determinants of disability in older coronary patients**	Irrelevant outcome
Ades 2006 **Aerobic capacity in patients entering cardiac rehabilitation**	No determinants reported (Univariate analysis)
AlQuait et al 2016 **Does cardiac rehabilitation favour the young over the old?**	No determinants reported
Armstrong et al 2013 **Patients with Diabetes in Cardiac Rehabilitation: Attendance and Exercise Capacity**	Irrelevant population (HF)
Balsam et al 2013 **The effect of cycle ergometer exercise training on improvement of exercise capacity in patients after myocardial infarction**	No determinants reported

Study	Reason for exclusion
Banzer et al 2004 **Results of cardiac rehabilitation in patients with diabetes mellitus. Am J Cardiol. 2004;93:81–84.**	Univariate analysis
Bargehr et al 27 **Predictors of suboptimal gain in exercise**	Irrelevant test
Brody et al 2002 **Estimation of oxygen consumption for cardiac rehabilitation patients during three modes of exercise.**	No determinants reported
Cannistra et al 1992 **Comparison of the clinical profile and outcome of women and men in cardiacrehabilitation**	No determinants reported
Digenio et al 1997 **Predictors of exercise capacity and adaptability to training in patients with coronary artery disease**	Irrelevant population (HF)
Digenio et al 1997 **Predictors of exercise capacity and adaptability to training in patients with coronary artery disease.**	Irrelevant population (HF) .
Gomadam et al 2016 **Degree and Direction of Change of Body Weight in Cardiac Rehabilitation and Impact on Exercise Capacity and Cardiac Risk Factors.**	No determinants reported
Gunstad et al 2007 **Effects of Obesity on Functional Work Capacity and Quality of Life in Phase II Cardiac Rehabilitation**	Irrelevant population (HF)
Hammond eat al al 1985 **Use of Clinical Data in Predicting Improvement in Exercise Capacity After Cardiac Rehabilitation**	Irrelevant outcome
Hansen et al 3007 **The Importance of an Exercise Testing Protocol for Detecting Changes of Peak Oxygen Uptake in Cardiac Rehabilitation**	No determinants reported

Study	Reason for exclusion
Hevey et al 2003 **Four-week Multidisciplinary Cardiac Rehabilitation Produces Similar Improvements in Exercise Capacity and Quality of Life to a 10-week Program**	No determinants reported
Hindman et al 2005 **Clinical profile and outcomes of diabetic and nondiabetic patients in cardiac rehabilitation.**	No determinants reported
Isse et al 2002 **O2 extraction during exercise determines training effect after cardiac rehabilitation in myocardial infarction**	No determinants reported
Izawa ET AL 2010. **Age-Related Differences in Physiologic and Psychosocial Outcomes After Cardiac Rehabilitation**	No determinants reported
Johnson et al 2015 **Effect of Early Enrolment on Outcomes in Cardiac Rehabilitation**	Irrelevant population (HF)
Johnson et al 2015 **Cardiac Rehabilitation in African Americans Evidence for poorer outcomes compared with whites, especially in women and diabetic participants**	Irrelevant population (HF)
Keteyian et al 2017 **Exercise Training Workloads Upon Exit from Cardiac Rehabilitation in Men and Women: The Henry Ford HOSPITAL EXPERIENCE**	Irrelevant population (HF)
Lan 2002 **Improvement of cardiorespiratory function after percutaneous transluminal coronary angioplasty or coronary artery bypass grafting**	No determinants reported
Lavie &Milani et al 1999 **Effects of Cardiac Rehabilitation and Exercise Training on Peak Aerobic Capacity and Work Efficiency in Obese Patients With Coronary Artery Disease**	No determinants reported

Study	Reason for exclusion
Lee et al 2000 **Factors influencing the long-term effects of supervised cardiac rehabilitation on the exercise capacity of patients with acute myocardial infarction**	irrelevant test
Maniar,et al 2009 **Comparison of Baseline Characteristics and Outcomes in Younger and Older Patients Completing Cardiac Rehabilitation**	irrelevant outcome
Marchionni et al 2000 **Determinants of exercise tolerance after acute myocardial infarction in older persons**	No post-test conducted
Martin et al 2012 **Obesity Negatively Impacts Aerobic Capacity Improvements Both Acutely and 1-Year Following Cardiac Rehabilitation**	Irrelevant population (HF)
Marzolini et al 2008 **Sex differences in completion of a 12-month cardiac rehabilitation programme: An analysis of 5922 women and men**	Irrelevant outcome
McKee 2013 **Factors that influence obesity, functional capacity, anxiety and depression outcomes following a Phase III cardiac rehabilitation programme.**	Irrelevant population (HF)
McPhee	Full articles not available
Milani et al 1991 **Factors predicting improvement in exercise capacity following cardiac rehabilitation and exercise program**	No determinants reported
Milani et al 1996, **Behavioral Differences and Effects of Cardiac Rehabilitation in Diabetic Patients following Cardiac Rehabilitation**	No determinants reported

Study	Reason for exclusion
Mourot et al 2010 **Cardiovascular rehabilitation in patients with diabetes.**	No determinants reported
O'Farrell et al 2000 **Sex differences in cardiac rehabilitation.**	No determinants reported
Pasquali et al 2003 **Effect of cardiac rehabilitation on functional outcomes after coronary revascularization**	Irrelevant test
Peixoto et al 2015 **Exercise-Based Rehabilitation Improves Health-Related Quality of Life and Functional Capacity After Acute Myocardial Infarction: A Randomized Controlled Trialrly Exe**	Irrelevant test
Salzwedel et al 2015 **Impact of clinical and sociodemographic patient characteristics on the outcome of cardiac rehabilitation in older patients**	irrelevant outcome
Shiran et al. 1997 **Determinants of improvement in exercise capacity in patients undergoing CR.**	Irrelevant test
Shubair et al 2004 **Metabolic profile and exercise capacity outcomes: their relationship to overweight and obesity in a Canadian cardiac rehabilitation setting.to check**	No determinants reported
St. Clair et al 2014 **Effects of cardiac rehabilitation in diabetic patients: Both cardiac and noncardiac factors determine improvement in exercise capacity**	Irrelevant population (HF)
Svacinova et al 2008 **Effects of cardiac rehabilitation on exercise capacity in Type 2 diabetic patients with coronary artery disease**	No determinants reported

Study	Reason for exclusion
Temfemo et al 2011 **Is there a beneficial effect difference between age, gender, and different cardiac pathology groups of exercise training at ventilatory threshold in cardiac patients?**	Irrelevant population (HF)
Thomaes 2012 **Muscular strength and diameter as determinants of aerobic power and aerobic power response to exercise training in CAD patiensts**	Full articles not available
Turner et al 2002 **Patient characteristics and outcomes of cardiac rehabilitation**	No determinants reported
Uddin et al 2015 **Predictors of exercise capacity following exercise-based rehabilitation in patients with coronary heart disease and heart failure: A meta-regression analysis.**	Irrelevant population (HF)
Vanhees et al 2004 **Determinants of the effects of physical training and of the complications requiring resuscitation during exercise in patients with cardiovascular disease**	Irrelevant population (HF)
Wojciech Szot **The effects of cardiac rehabilitation on overall physical capacity and myocardial perfusion in women with microvascular angina**	No determinants reported
Yu et al 2003 **Long-term changes in exercise capacity, quality of life, body anthropometry, and lipid profiles after a cardiac rehabilitation program in obese patients with coronary heart disease**	No determinants reported

Appendix 8.2.2B Excluded studies which identified from Hand search

Study	Reason for exclusion
1. **Ades and Grunvald** **Cardiopulmonary exercise testing before and after conditioning in older coronary patients.**	No determinants reported
2. **Ades et al 1992** **Referral patterns and exercise response in the rehabilitation of female coronary patients aged ≥ 62**	No determinants reported
3. **Carroll et al 2011** **Differential Improvements in Lipid Profiles and Framingham Recurrent Risk Score in Patients With and Without Diabetes Mellitus Undergoing Long-Term Cardiac Rehabilitation**	No determinants reported
4. **Gulanick 2002** **Outcomes in Cardiac Rehabilitation Programs Across Illinois**	No determinants reported.
5. **Helda let al** **Simple clinical data are useful in predicting effect of exercise training after myocardial infarction**	irrelevant outcome
6. **Lavie &Milani et al 1995** **Effects of cardiac rehabilitation programson exercise capacity, coronary risk factors, behavioral characteristics, and qualify oflife in a large elderly cohort**	No determinants reported
7. **Lavie &Milani et al 1996** **Effects of cardiac rehabilitation programs on exercise capacity, coronary risk factors, behavioral characteristics, and qualify of life in a Obese Coronary Patients**	No determinants reported
8. **Lavie &Milani et al 1996** **Effects of Cardiac Rehabilitation and Exercise Training in Obese Patients Coronary Artery Disease**	No determinants reported
9. **Lavie CJ,et al 1993;** **Benefits of cardiac rehabilitation and exercise training in secondary coronaryprevention in the elderly**	Irrelevant population (HF)
10. **Sadeghi 2012** **The effect of the cardiac rehabilitation program on obese and non-obese females with coronary heart disease**	No determinants reported
11. **Suresh V et al 2001** **Standard cardiac rehabilitation is less effective for diabetics.**	irrelevant outcome

Appendix 8.2.3 PRISM check list

Section/topic	#	Checklist item	Reported on page #
TITLE : Effects of exercise-based cardiac rehabilitation on cardiorespiratory fitness: A meta- analysis of UK studies (Almodhy et al 2016)			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Y 644
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Y 644
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Y 645
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Y 645
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Y645
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Y645
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Y645
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Y645
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Y645
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Y645
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Y645

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Y645
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Y 645 publica tion bias
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Y 645
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Y 646
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Y 647
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Y 647
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Y 648
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N any assess ment of risk of bias
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Y 645-46
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Y 646 No the strengt h of eviden ce
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Y 650
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Y 650
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Section/topic	#	Checklist item	Reported on page #
TITLE Changes in cardiorespiratory fi tness in cardiac rehabilitation patients Sandercock et al 2013			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Y 894
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Y 894
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Y 894
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Y 894
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Y 895
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Y 895
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Y895
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Y895
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Y895
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Y895
Risk of bias in individual	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how	N

studies		this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Y895
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Y895-6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Y897 publication bias
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	YY896
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Y 895 No flow diagram
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Y 897
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Y 896
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Y 896
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N any assessment of risk of bias
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Y 895-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Y 898 No the strength of evidence
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	N
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Y898-9
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit: **www.prisma-statement.org**.

Appendix 8.3.1 Regulations concerning the using of NACR data

The regulations concerning the using of NACR data.

Permitted Uses:

- The researcher is permitted, based on pre-arranged meetings with data controller/supervisor, to report aggregated versions of the data in thesis', publications and conferences abstracts. Note all versions of the data/iterations prior to submission must be signed off by the NACR Lead/ NACR team/supervisor/.
- Outputs from the original data may be stored on a private network for processing and writing of dissemination material, this does not include any data.
- Data can be archived on the Department of Health Sciences network for retrospective review and analysis. Access may be given for review post the timescale or research project has terminated depending on approval from the NACR Lead.

Non-permitted Uses:

- The data must not be copied or removed from the Department of Health Sciences secure network ("I Drive") in original or altered forms unless using an approved password protected external storage device.
- The data must not be transferred onto online storage platforms such as Google Drive or Dropbox and should never be shared through email with internal (NACR) or external staff and researchers.
- The data must only be processed in approved manners, with research plans set out in meetings with the NACR Lead, supervisors or the NACR Team. Additionally, the data must not be merged with any secondary data unless agreed to do so by the NACR Lead, supervisors or the NACR Team
- No dissemination of original or processed material is permitted without the approval from the NACR Lead/ NACR team/ supervisor.
    - This includes primary or secondary research articles, update papers, conference abstracts and presentations, talks, interviews, personal use and any other non agreed uses.
- Once the research or enrolment period ends access to the Department of Health Sciences shared network will be removed, at which point all data must be provided to the NACR team for archiving.
- The data must never be presented as non-aggregated data, and although every effort will be made to anonymise the names and locations of Cardiac Rehabilitation organisations within the data, no organisation should ever be presented as identifiable without approval from the NACR Lead/ NACR team /supervisor.

Appendix 8.3.2 Questionnaire Master Assessment 1 - National Audit of Cardiac (from NACR website http://www.cardiacrehabilitation.org.uk/nacr/dataset/Questionnaire%201.pdf)

CR National Audit

The National Database for Cardiac Rehabilitation

QUESTIONNAIRE MASTERS
Assessment 1

CONTENTS

THE QUESTIONNAIRES AND THE NATIONAL AUDIT OF CARDIAC REHABILITATION

Cardiac rehabilitation starts with an assessment to see how we can help you and we would be grateful if you would fill in the attached questionnaire. This information is also used for the National Audit of Cardiac Rehabilitation.

We will ask you to fill the questionnaire in again at the end of the rehab programme and then again 12 months later. The reason for collecting the data is to measure what you achieve on this programme, and through combining everyone's information in the National Audit Programme to find ways to improve cardiac rehabilitation. It is also very helpful for us to compare how we are doing here so that, if necessary, we can improve our programme.

WHAT HAPPENS TO THE INFORMATION?

We enter the information into a computer programme in the hospital and this is treated in the same way as all information you provide to your healthcare team.

The data is collected by the Health and Social Care Information Centre (HSCIC) who hold NHS data for administrative purposes. They anonymise it and send it to the BHF Care and Education Research Group at the University of York, who combine the data into an annual report. You can download the previous reports here:
http://www.cardiacrehabilitation.org.uk/nacr/downloads.htm

WHO SEES MY INFORMATION?

The staff who treat you here and staff in the HSCIC. Staff of the National Audit in York see the same information but with the names removed so they don't know who it is from.

DO I HAVE TO TAKE PART

No you don't, this is completely voluntary. If you don't want to take part it will not effect your treatment in any way. If you start but want to stop later that is fine too.

QUESTIONS?

If you have further questions please ask any of the staff.

THANK YOU FOR YOUR HELP

ABOUT YOU

NAME .... **DOB**.......................

Date: ....

Gender (please tick)			
Male	☐1	Female	☐2

Marital Status (please tick)			
Single	☐1	Married	☐2
Permanent partnership	☐3	Divorced	☐4
Widowed	☐5	Separated	☐6

Other heart problems you have had: (please tick all that apply)			
Myocardial Infarction (Heart Attack)	☐	Acute Coronary Syndrome	☐
Bypass Surgery	☐	Angioplasty (Balloon in artery)	☐
Cardiac Arrest	☐	Angina	☐
Other Surgery	☐	Heart failure	☐
Pacemaker	☐	Implanted defibrillator (ICD)	☐
Heart transplant	☐	Congenital heart problem	☐
LV Assist Device	☐	Other	☐

ETHNIC CLASSIFICATION

We are collecting this information to check that everyone has fair access to the help that they need. Please tick the one that describes you best, or, if none of them do, tick number 6 (any other).

What is your ethnic group?

1	**White**	
	British	☐1
	Irish	☐2
	Any other White background	☐3
	....	
2	**Mixed**	
	White and Black Caribbean	☐4
	White and Black African	☐5
	White and Asian	☐6
	Any other Mixed background	☐7
	....	
3	**Asian or Asian British**	
	Indian	☐8
	Pakistani	☐9
	Bangladeshi	☐10
	Any other Asian background	☐11
	....	
4	**Black or Black British**	
	Caribbean	☐12
	African	☐13
	Any other Black background	☐14
	....	
5	**Chinese or other ethnic group**	
	Chinese	☐15
6	Any other	☐16

3

OTHER ILLNESSES YOU HAVE BEEN TOLD YOU HAVE

Have you ever been told by a doctor that you have definitely had any of the following illnesses? Please answer every question even if they are all NO.

Angina	NO	☐	YES	☐
Arthritis (osteoarthritis)	NO	☐	YES	☐
Cancer	NO	☐	YES	☐
Diabetes	NO	☐	YES	☐
Rheumatism	NO	☐	YES	☐
A stroke	NO	☐	YES	☐
Osteoporosis	NO	☐	YES	☐
Hypertension	NO	☐	YES	☐
Chronic bronchitis	NO	☐	YES	☐
Emphysema	NO	☐	YES	☐
Asthma	NO	☐	YES	☐
Hypercholesterolaemia	NO	☐	YES	☐
Leg pain when walking due to poor blood supply - Claudication	NO	☐	YES	☐
Back problems or chronic pain	NO	☐	YES	☐
Other illnesses	NO	☐	YES	☐

Describe Other Complaint ....

PILLS, SMOKING AND WEIGHT/HEIGHT

4

Are you currently taking these 5 medicines for your heart (please tick a Yes or a No for each one)

1. Aspirin or other anticoagulant No ☐ Yes ☐

if allergic to aspirin you may be taking: Clopidogrel or Dipyridamole

2. ACE inhibitor and angiotensin II receptor blockers (A2RBs) No ☐ Yes ☐

Examples include:

- captopril (*Capoten, Capozide*)
- enalapril (*Innovace*)
- imidapril (*Tanatril*)
- moexipril (*Perdix*)
- quinapril (*Accupro*)
- trandolapril (*Gopten, Odrik*)
- candesartan cilexietil (*Amias*)
- irbesartan (*Aprovel*)
- olmesartan (*Olmetec*)
- cilazapril (*Vascase*)
- fosinopril (*Staril*)
- lisinopril (*Carace, Zestril*)
- perindopril (*Coversyl Plus*)
- ramipril (*Tritace*)
- valsartan (*Diovan*)
- eprosartan (*Teveten*)
- losartan (*Cozaar*)
- telmisartan (*Amias*)

3. Beta Blocker No ☐ Yes ☐

Examples include:

- acebutolol (*Sectral*)
- betaxolol (*Betoptic*)
- carvedilol (*Eucardic*)
- esmolol (*Brevibloc*)
- metoprolol (*Betaloc, Lopresor*)
- nebivolol (*Nebilet*)
- pindolol (*Visken*)
- atenolol (*Atenix, Tenormin*)
- bisoprolol (*Cardicor, Emcor*)
- celiprolol (*Celectol*)
- labetalol (*Trandate*)
- nadolol (*Corgard*)
- oxyprenol (*Trasicor*)
- sotalol (*Beta-Cardone, Sotacor*)

4. Cholesterol pills (Statins) No ☐ Yes ☐

Examples include:

- simvastatin (*Zocor*)
- atorvastatin (*Lipitor*)
- *fluvastatin (Lescol)*
- pravastatin (*Lipostat*)
- rosuvastatin (*Crestor*)

5. Omega 3 No ☐ Yes ☐

Examples include:

- omacor

SMOKING

Have you smoked in the last 4 weeks? No ☐ Yes ☐

Weight (kg) and Height (m):

Weight ☐ kg or ☐ st ☐ lbs

Height ☐ m or ☐ ft ☐ inches

Waist Circumference ☐ cm or ☐ inches

5

HAD Scale

Name: Date:

Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he will be able to help you more.
This questionnaire is designed to help your doctor to know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week.
Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

Tick only one box in each section

I feel tense or 'wound up':
- Most of the time ....
- A lot of the time ....
- Time to time, Occasionally ....
- Not at all ....

I still enjoy the things I used to enjoy:
- Definitely as much ....
- Not quite so much ....
- Only a little ....
- Hardly at all ....

I get a sort of frightened feeling as if something awful is about to happen:
- Very definitely and quite badly ....
- Yes, but not too badly ....
- A little, but it doesn't worry me ......
- Not at all ....

I can laugh and see the funny side of things:
- As much as I always could ....
- Not quite so much now ....
- Definitely not so much now ....
- Not at all ....

Worrying thoughts go through my mind:
- A great deal of the time ....
- A lot of the time ....
- From time to time but not too often .
- Only occasionally ....

I feel cheerful:
- Not at all ....
- Not often ....
- Sometimes ....
- Most of the time ....

I can sit at ease and feel relaxed:
- Definitely ....
- Usually ....
- Not often ....
- Not at all ....

I feel as if I am slowed down:
- Nearly all the time ....
- Very often ....
- Sometimes ....
- Not at all ....

I get a sort of frightened feeling like 'butterflies' in the stomach:
- Not at all ....
- Occasionally ....
- Quite often ....
- Very often ....

I have lost interest in my appearance:
- Definitely ....
- I don't take so much care as I should
- I may not take quite as much care ..
- I take just as much care as ever ......

I feel restless as if I have to be on the move:
- Very much indeed ....
- Quite a lot ... .
- Not very much ....
- Not at all ....

I look forward with enjoyment to things:
- As much as ever I did ....
- Rather less than I used to ....
- Definitely less than I used to ....
- Hardly at all ....

I get sudden feelings of panic:
- Very often indeed ....
- Quite often ... .
- Not very often ....
- Not at all ....

I can enjoy a good book or radio or TV programme:
- Often ....
- Sometimes ....
- Not often ....
- Very seldom ....

Do not write below this line

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6

PHYSICAL ACTIVITY

1 Considering a 7-day period (a week), how many times on average do you do the following kinds of exercise for **more than 15 minutes**? (write the appropriate number in the boxes)

Number of times

a. Strenuous Activity (heart beats rapidly/tiring)
(e.g. running, jogging, vigorous long distance cycling, circuit training, aerobic dance, skipping, football, squash, basketball, roller skating, vigorous swimming) ☐

b. Moderate Activity (not exhausting)
(e.g. fast walking, mowing the lawn, tennis, easy cycling, badminton, easy swimming, ballroom dancing, fast or high step-ups) ☐

c. Mild Activity (minimal effort)
(e.g. easy walking, slow dancing, standing active fishing, bowling, golf, low step-ups) ☐

2 Considering a **7-day period** (a week), how often do you engage in any regular activity long enough to work up a sweat? (heart beats rapidly)

Please tick only one box

A Often ☐

B Sometimes ☐

C Never/Rarely ☐

3 Do you take regular physical activity of at least 30 minutes duration on average 5 times a week?

Please tick only one box

YES ☐ NO ☐

7

QUALITY OF LIFE

PHYSICAL FITNESS. During the past week what was the hardest physical activity you could do for at least 2 minutes? (Place a tick in the box next to the one you feel best describes your fitness)

Very heavy, for example: run at a fast pace or carry a heavy load upstairs or uphill (25 lbs / 10 kgs)		1
Heavy: for example: jog, slow pace or climb stairs or a hill at moderate pace		2
Moderate: for example: walk at medium pace or carry a heavy load on level ground (25 lbs / 10 kgs)		3
Light: for example: walk, medium pace or carry a light load on level ground (10 lbs / 5 kgs)		4
Very light: for example: walk at a slow pace, wash dishes		5

FEELINGS. During the past week how much have you been bothered by emotional problems such as feeling anxious, depressed, irritable or downhearted and blue? (Place a tick in the box next to the one you feel best describes your feelings)

Not at all		1
Slightly		2
Moderately		3
Quite a bit		4
Extremely		5

DAILY ACTIVITIES. During the past week how much difficulty have you had doing your usual activities or task, both inside and outside the house because of your physical and emotional health?

No difficulty at all		1
A little bit of difficulty		2
Some difficulty		3
Much difficulty		4
Could not do		5

8

SOCIAL ACTIVITIES. During the past week has your physical and emotional health limited your social activities with family, friends, neighbours or groups?

Not at all		1
Slightly		2
Moderately		3
Quite a bit		4
Extremely		5

PAIN. During the past week how much bodily pain have you generally had?

No pain		1
Very mild pain		2
Mild pain		3
Moderate pain		4
Severe pain		5

CHANGE IN HEALTH. How would you rate your overall health now compared to a week ago?

Much better		1
A little better		2
About the same		3
A little worse		4
Much worse		5

OVERALL HEALTH. During the past week how would you rate your health in general?

Excellent		1
Very good		2
Good		3
Fair		4
Poor		5

9

SOCIAL SUPPORT. During the past week was someone available to help you if you needed and wanted help? For example:

- if you felt nervous, lonely, or blue,
- got sick and had to stay in bed,
- needed someone to talk to,
- needed help with daily chores,
- needed help with taking care of yourself

Yes, as much as I wanted		1
Yes, quite a bit		2
Yes, some		3
Yes, a little		4
No, not at all		5

QUALITY OF LIFE. How have things been going for you during the past week?

Very well: could hardly be better		1
Pretty good		2
Good & bad parts about equal		3
Pretty bad		4
Very bad: could hardly be worse		5

Please check that you have ticked or circled one answer for every question on all 3 pages

10

WORK AND EMPLOYMENT

Please complete your employment status as it is at the time of completing

IF YOU ARE IN PAID WORK, OR CURRENTLY LOOKING FOR WORK AND COULD START IN THE NEXT 2 WEEKS, OR ARE RETRAINING FOR WORK, CHOOSE ONE BOX FROM THE GREY BOX

IF YOU ARE NOT PAID, OR ARE ON TEMPORARY OR LONGTERM SICKNESS BENEFITS, PLEASE CHOOSE ONE BOX FROM THE WHITE BOX.

please choose one only		please choose one only	
Employed full time	☐ 1	**Looking after family/home**	☐ 7
Employed part time	☐ 2	**Retired**	☐ 8
Self-employed full time	☐ 3	**Permanently sick / disabled**	☐ 9
Self-employed part time	☐ 4	**Temporarily sick or injured**	☐ 10
Unemployed looking work	☐ 5	**Student**	☐ 11
Gov. training course	☐ 6	**Other reasons**	☐ 12

THANK YOU FOR YOUR HELP
THE INFORMATION WILL BE USED TO IMPROVE OUR SERVICES TO YOU

Appendix 8.4.1 Online survey

CR National Audit — Physical Fitness Measures

* 1. Please give your contact/programme details here:

Primary Contact Name

Primary Contact Email

Programme Name

Programme Address

Postcode

* 2. Does your programme measure Cardiac Rehab patients' physical fitness before the start of their Core/Phase 3 Rehab programme?

- Yes, for all patients
- Yes, for some patients
- No

3. If you answered 'Yes for some patients' for Q2, please say why some patients may not be measured (you can select more than one)

- High Risk
- Clinically Unstable
- Physically unable to do the test (eg. disability)
- Location issues (eg. home based)
- Insufficient time

Other (please specify)

4. How do you measure Physical Fitness?

- Objectively (eg. ISWT, 6-min Walk, Step Test etc)
- Subjectively (eg. questionnaire or self-assessment)
- Both Objectively and Subjectively

5. Which of these physical fitness tests do you use (you can choose more than one)

- ☐ Treadmill
- ☐ Bicycle
- ☐ Incremental Shuttle Walk (ISWT)
- ☐ 6-minute Walk Test
- ☐ Step Test
- ☐ Other (please specify)

6. If you use the ISWT, do your patients practice the test before the main test?

- ◯ Yes
- ◯ Sometimes
- ◯ No
- ◯ Do not use ISWT

7. Please specify who usually adminsters the physical fitness test (you can select more than one)

- ☐ Physiotherapist
- ☐ Exercise specialist
- ☐ Nurse
- ☐ Other (please specify)

8. What is the reason for your programme not using a physical fitness test (you can choose more than one)

- ☐ Lack of equipment
- ☐ Lack of space
- ☐ Lack of time
- ☐ No staff available with experience to do the test
- ☐ The test is not considered necessary
- ☐ Other (please specify)

Appendix 8.4.2 Description of the variables used in analysis

Variable	Description
Age	Patient's age on admission (in years)
Sex	Male coded as 1, female as 0
BMI	Body Mass Index coded as 0 if >30kg/m^2 and coded as 1 if <30kg/m^2
Ethnicity	Patient's ethnic group (White British coded as 1, other coded as 0)
Employment status	(unemployed coded as 0, employed coded as 1, or retired coded as 2)
Marital status	Patient's marital status during event (single coded as 0, in a partnership coded as 1 or in a previous relationship coded as 2)
Diabetes, Hypertension, Hyperlipidaemia , Depression, Anxiety, Family history, Musculoskeletal comorbidity	If patient was documented with each of these comorbidities during hospital admission ('yes' coded as 1), otherwise 'no' is coded as 0
Self-reported physical activity	Meeting physical activity recommendations of 150 mins per week coded as 1, coded as 0 if s/he did not meet the recommendation
Self-reported physical fitness (Dartmouth COOP)	A patient was coded as 1 if the hardest physical activity s/he was able to do for a period of two minutes in the previous week was self-assessed as 'moderate' to 'very heavy' and coded as 0 if s/he described the 'light' activities as the most physically demanding.
Smoking status	A non-smoker was coded as 0, stopped smoking since event were coded as 1 and a smoker was coded as 2
Total number of comorbidities	As reported in NACR dataset. Patient was coded 0 if s/he had no comorbidities, coded 1 if s/he had less than 3 and coded 2 if s/he had 3 and more
Previous cardiac event	Patient was coded 0 if s/he had not experienced a previous cardiac event, s/he was coded 1 if they had.

supervised or self-delivered	Supervised rehabilitation is all group-based, ward-based, home visit-based, clinical and face to face versions of rehabilitation. Self-delivered is all home-based, web-based or telephone rehabilitation that is delivered with facilitation from the CR team.
level of performance of the	level of performance of the centres (high, mid or low
Reason for referral	(MI, PCI, CABG, valve surgery and other)

Appendix 8.4.3.A STAT regression findings for association between whether the patients' fitness had been measured and the outcomes

```
. mi estimate,or: logistic Completerehab_2 i.patients_MF_vs_NMF Age_new i.Gender_2_01 i.Ethnicity_2_01 i.Employment1_Staus3Cat i.Marital_status_2n
> d_3cage i.BMI_0_1 i.Physical_fitne_Dartm_1 i.Smoking1_3CAT_SND i.comorbidity_3categ_2nd i.Supervied_vs_Self i.Group_alone_Deliver i.Performance_
> 3categ i.Muscoskel_comorbi_01 i.Social_support_Dar_01 i.Physical_activity_150min i.Dignosis_Group i.MDT_LL_j_no_missing i.Alcohol_J1 i.Previous_
> event_01 i.AcDiabetes4 i.AcHypertension8  i.AcFamily16 i.AcAnxiety14 i.AcDepression15 i.AcHyper18 Duration_Weeks NumberOfSessions_Completed even
> t_Core i.Cenres_volume ,cluster (Location_Core)

Multiple-imputation estimates                   Imputations       =         20
Logistic regression                             Number of obs     =     31,433
                                                Average RVI       =     0.5991
                                                Largest FMI       =     0.7933
DF adjustment:   Large sample                   DF:     min       =      31.19
                                                        avg       =  15,425.61
                                                        max       = 171,798.42
Model F test:       Equal FMI                   F(  45, 5973.8)   =      18.30
Within VCE type:       Robust                   Prob > F          =     0.0000

                             (Within VCE adjusted for 102 clusters in Location_Core)
```

Completerehab_2	Odds Ratio	Std. Err.	t	P>|t|	[95% Conf.	Interval]
1.patients_MF_vs_NMF	1.384082	.1985274	2.27	0.024	1.044795	1.83355
Age_new	1.015036	.0035552	4.26	0.000	1.008048	1.022073
Gender_2_01						
Male	1.026495	.0428932	0.63	0.532	.9456124	1.114296
Ethnicity_2_01						
White	1.138082	.1060107	1.39	0.165	.94802	1.366247
Employment1_Staus3Cat						
UnEmployed	.8846286	.0758387	-1.43	0.158	.7453639	1.049914
Retierd	.9543186	.0742346	-0.60	0.551	.8161872	1.115827
Marital_status_2nd_3cage						
in relationship	1.251632	.1108387	2.53	0.012	1.051784	1.489453
Not in relationship	.996372	.0862306	-0.04	0.967	.8402432	1.181512
BMI_0_1						
<30	1.117841	.0501875	2.48	0.015	1.022397	1.222196
Physical_fitne_Dartm_1						
Yes	1.255764	.0802714	3.56	0.001	1.104019	1.428366
Smoking1_3CAT_SND						
Yes	.5707814	.0420841	-7.61	0.000	.4932299	.6605265
Stooped Smoking since event	.7147906	.0541041	-4.44	0.000	.6156939	.829837
comorbidity_3categ_2nd						
less than 3 "<3"	.8954674	.1455177	-0.68	0.497	.6512135	1.231335
3 or more "=>3"	.8576454	.1617291	-0.81	0.415	.5926353	1.241161
Supervied_vs_Self						
Supervised	1.023956	.4654525	0.05	0.959	.4052764	2.587087
Group_alone_Deliver						
GroipDelivered	.5455519	.1765148	-1.87	0.067	.2844415	1.046355
Performance_3categ						
2	.5986112	.1371888	-2.24	0.025	.3819968	.9380586
3	.748231	.2013496	-1.08	0.281	.4415331	1.267968
1.Muscoskel_comorbi_01	1.070865	.0717637	1.02	0.307	.9390456	1.221189
1.Social_support_Dar_01	.9925572	.067357	-0.11	0.913	.8667084	1.13668
Physical_activity_150min						
meet	1.304812	.0909126	3.82	0.000	1.135937	1.498793
Dignosis_Group						
MI/PCI	1.064861	.104506	0.64	0.522	.8783688	1.290949
PCI	.9538617	.1043222	-0.43	0.666	.7696902	1.182102
CABG	1.032914	.1037108	0.32	0.747	.8480797	1.258032
Heart Failure	.6497903	.1172372	-2.39	0.017	.4561013	.9257317
Angina	.6174425	.0843626	-3.53	0.000	.4723362	.8071269
Valve Surgery	1.041826	.114433	0.37	0.709	.8399197	1.292268
Other	.6439726	.0787748	-3.60	0.000	.506615	.8185717
1.MDT_LL_j_no_missing	.8085456	.2650184	-0.65	0.517	.42526	1.537285
Alcohol_J1						
yes	1.056925	.0631332	0.93	0.356	.9387467	1.189981
1.Previous_event_01	.8718913	.1621634	-0.74	0.461	.6055245	1.255431
AcDiabetes4						
Yes	.8317738	.0501187	-3.06	0.002	.7391096	.9360557
AcHypertension8						
Yes	1.047168	.0596351	0.81	0.418	.9365599	1.170838
AcFamily16						
Yes	1.01574	.0866547	0.18	0.855	.8593029	1.200656
AcAnxiety14						
Yes	1.154294	.1029983	1.61	0.108	.9690625	1.374931
AcDepression15						
Yes	.8466513	.0729441	-1.93	0.053	.7150816	1.002429
1.AcHyper18	1.111314	.0939115	1.25	0.212	.9416444	1.311555
Duration_Weeks	.9546709	.0103784	-4.27	0.000	.9344586	.9753203
NumberOfSessions_Completed	1.342318	.0356335	11.09	0.000	1.274223	1.414052
event_Core	1.000383	.0001774	2.16	0.031	1.000035	1.000731
Cenres_volume						
1	1.270411	.5780837	0.53	0.599	.5207249	3.099415
2	1.334687	.6304658	0.61	0.541	.5288041	3.368714
3	1.102893	.5381604	0.20	0.841	.4238101	2.870088
4	1.848916	.8541291	1.33	0.183	.747638	4.572388
5	1.309372	.6695277	0.53	0.598	.48061	3.567246
_cons	.3489686	.238144	-1.54	0.124	.0910793	1.337066

Note: _cons estimates baseline odds.

```
. mi estimate,or: logistic Physical_ftiness2_no_imput i.patients_MF_vs_NMF Age_new i.Gender_2_01 i.Ethnicity_2_01 i.Employment1_Staus3Cat i.Marita
> l_status_2nd_3cage i.BMI_0_1 i.Physical_fitne_Dartm_1 i.Smoking1_3CAT_SND i.comorbidity_3categ_2nd i.Supervied_vs_Self i.Group_alone_Deliver i.P
> erformance_3categ i.Muscoskel_comorbi_01 i.Social_support_Dar_01 i.PA_150min i.Dignosis_Group i.MDT_LL_j_no_missing i.Alcohol_J1 i.Previous_even
> t_01 i.AcDiabetes4 i.AcHypertension8  i.AcFamily16 i.AcAnxiety14 i.AcDepression15 i.AcHyper18 Duration_Weeks NumberOfSessions_Completed event_Co
> re i.Cenres_volume ,cluster (Location_Core)

Multiple-imputation estimates                Imputations      =         20
Logistic regression                          Number of obs    =     12,704
                                             Average RVI      =     0.1570
                                             Largest FMI      =     0.3702
DF adjustment:   Large sample                DF:     min      =     145.28
                                                     avg      =  25,638.14
                                                     max      = 171,165.61
Model F test:       Equal FMI                F(  45,47050.6)  =      54.83
Within VCE type:       Robust                Prob > F         =     0.0000

                                 (Within VCE adjusted for 91 clusters in Location_Core)
```

Physical_ftiness2_no_imput	Odds Ratio	Std. Err.	t	P>|t|	[95% Conf.	Interval]
1.patients_MF_vs_NMF	1.095556	.1144867	0.87	0.382	.8926464	1.34459
Age_new	.9587681	.0042393	-9.52	0.000	.9504936	.9671146
Gender_2_01						
Male	1.387018	.0932482	4.87	0.000	1.215737	1.582431
Ethnicity_2_01						
White	1.46403	.1268953	4.40	0.000	1.235076	1.735427
Employment1_Staus3Cat						
UnEmployed	.6374382	.0847332	-3.39	0.001	.4911179	.8273522
Retierd	.7751198	.065337	-3.02	0.003	.6568976	.9146184
Marital_status_2nd_3cage						
in relationship	1.47604	.1765644	3.25	0.001	1.165258	1.869711
Not in relationship	1.212729	.1704729	1.37	0.172	.9185722	1.601084
BMI_0_1						
<30	1.315551	.0732597	4.92	0.000	1.179459	1.467345
Physical_fitne_Dartm_1						
Yes	5.809094	.9670348	10.57	0.000	4.191745	8.050483
Smoking1_3CAT_SND						
Yes	.5615597	.0657184	-4.93	0.000	.4464106	.7064109
Stooped Smoking since event	.9214424	.0979276	-0.77	0.442	.7480577	1.135014
comorbidity_3categ_2nd						
less than 3 "<3"	1.164157	.0848927	2.08	0.037	1.009111	1.343026
3 or more "=>3"	.9260487	.1005895	-0.71	0.479	.7484657	1.145765
Supervied_vs_Self						
Supervised	1.443838	.2118626	2.50	0.013	1.081821	1.927001
Group_alone_Deliver						
GroipDelivered	.8785808	.0944866	-1.20	0.229	.7115812	1.084773
Performance_3categ						
2	.8290031	.1672076	-0.93	0.352	.5582956	1.230972
3	1.182814	.2258546	0.88	0.379	.8135402	1.719703
1.Muscoskel_comorbi_01	.8845521	.0555006	-1.96	0.051	.7821932	1.000306
1.Social_support_Dar_01	1.295549	.1072904	3.13	0.002	1.101191	1.52421
PA_150min_2						
meet	2.723188	.1541053	17.70	0.000	2.437213	3.042718
Dignosis_Group						
MI/PCI	1.12082	.1216431	1.05	0.293	.9060351	1.386522
PCI	1.031993	.1072068	0.30	0.762	.8418622	1.265065
CABG	1.121393	.1157604	1.11	0.267	.915971	1.372885
Heart Failure	.4957381	.0847744	-4.10	0.000	.3545598	.6931307
Angina	.7771291	.1274434	-1.54	0.124	.5634758	1.071793
Valve Surgery	1.083529	.1328936	0.65	0.513	.8519968	1.37798
Other	.8218377	.1154283	-1.40	0.162	.624056	1.082302
1.MDT_LL_j_no_missing	.8613215	.186673	-0.69	0.491	.563216	1.317212
Alcohol_J1						
yes	.6684783	.0701837	-3.84	0.000	.5434178	.8223199
1.Previous_event_01	.830244	.1029803	-1.50	0.134	.6510648	1.058735
AcDiabetes4						
Yes	.686667	.0489434	-5.27	0.000	.597136	.7896218
AcHypertension8						
Yes	.9933434	.0566895	-0.12	0.907	.888222	1.110906
AcFamily16						
Yes	1.230312	.1166891	2.19	0.029	1.021589	1.481681
AcAnxiety14						
Yes	.9915883	.1267702	-0.07	0.947	.771801	1.273965
AcDepression15						
Yes	.8758975	.1102952	-1.05	0.293	.6843253	1.121099
1.AcHyper18	1.038556	.0705048	0.56	0.577	.9091644	1.186363
Duration_Weeks	.9903355	.0065655	-1.46	0.143	.9775483	1.00329
NumberOfSessions_Completed	1.022542	.0068137	3.35	0.001	1.009249	1.036011
event_Core	1.000139	.0002514	0.55	0.581	.9996461	1.000632
Cenres_volume						
1	1.287881	.5587955	0.58	0.560	.5502177	3.014512
2	1.26995	.5661117	0.54	0.592	.5300664	3.042586
3	1.428653	.6377524	0.80	0.424	.5955797	3.426997
4	1.743546	.7659918	1.27	0.206	.7369914	4.124816
5	1.273541	.586663	0.52	0.600	.5162929	3.141446
_cons	4.631563	2.387479	2.97	0.003	1.686229	12.72151

Note: _cons estimates baseline odds.

.

Appendix 8.4.3.B STAT Regression result for the sub-analysis in this study (with groups not achieving the MCID used as the reference group)

```
. mi estimate,or: logistic Completerehab_2 i.Centres_measured_fitness_only Age_new i.Gender_2_01 i.Ethnicity_2_01 i.Emp
> loyment1_Staus3Cat i.Marital_status_2nd_3cage i.BMI_0_1 i.Physical_fitne_Dartm_1 i.Smoking1_3CAT_SND i.comorbidity_3c
> ateg_2nd i.Supervied_vs_Self i.Group_alone_Deliver i.Performance_3categ i.Muscoskel_comorbi_01 i.Social_support_Dar_0
> 1 i.Physical_activity_150min i.Dignosis_Group i.MDT_LL_j_no_missing i.Alcohol_J1 i.Previous_event_01 i.AcDiabetes4 i.
> AcHypertension8  i.AcFamily16 i.AcAnxiety14 i.AcDepression15 i.AcHyper18 Duration_Weeks NumberOfSessions_Completed ev
> ent_Core i.Cenres_volume ,cluster (Location_Core)

Multiple-imputation estimates                   Imputations       =         20
Logistic regression                             Number of obs     =     28,484
                                                Average RVI       =     0.5964
                                                Largest FMI       =     0.7432
DF adjustment:   Large sample                   DF:     min       =      35.73
                                                        avg       =  23,341.46
                                                        max       = 282,805.21
Model F test:       Equal FMI                   F(  45, 6034.4)   =      20.03
Within VCE type:       Robust                   Prob > F          =     0.0000

                                          (Within VCE adjusted for 93 clusters in Location_Core)
------------------------------------------------------------------------------------------------
                Completerehab_2 | Odds Ratio   Std. Err.      t    P>|t|     [95% Conf. Interval]
--------------------------------+---------------------------------------------------------------
1.Centres_measured_fitness_only |   1.477309   .2072331     2.78   0.005     1.122098    1.944965
                        Age_new |   1.014082   .0036152     3.92   0.000      1.00698    1.021233
                                |
                    Gender_2_01 |
                          Male  |   1.024179   .0463515     0.53   0.598     .9370788    1.119375
                                |
                 Ethnicity_2_01 |
                         White  |   1.091597   .1070974     0.89   0.372      .900539    1.323191
                                |
          Employment1_Staus3Cat |
                    UnEmployed  |   .8877118   .0799501    -1.32   0.191     .7414757    1.062789
                       Retierd  |   .9599195   .0783213    -0.50   0.618     .8145676    1.131208
                                |
       Marital_status_2nd_3cage |
              in relationship   |   1.265779   .1153379     2.59   0.010     1.058391    1.513805
          Not in relationship   |   .9957331   .0912318    -0.05   0.963     .8312087    1.192823
                                |
                        BMI_0_1 |
                           <30  |   1.115146   .0537874     2.26   0.027     1.013062    1.227517
                                |
          Physical_fitne_Dartm_1 |
                           Yes  |   1.242813    .078558     3.44   0.001     1.094679    1.410992
                                |
               Smoking1_3CAT_SND |
                           Yes  |   .5819745   .0453627    -6.94   0.000     .4987243    .6791213
   Stooped Smoking since event  |   .7026387   .0559155    -4.43   0.000     .6005324    .8221059
                                |
         comorbidity_3categ_2nd |
              less than 3 "<3"  |   .9003421   .1603096    -0.59   0.555     .6351052    1.276349
               3 or more "=>3"  |    .850161    .172294    -0.80   0.423     .5714674    1.264768
                                |
              Supervied_vs_Self |
                    Supervised  |   1.038152   .4347664     0.09   0.929     .4439134    2.427862
                                |
            Group_alone_Deliver |
                GroipDelivered  |   .5338331   .1575769    -2.13   0.038     .2958571    .9632278
                                |
             Performance_3categ |
                             2  |   .5357964   .1380287    -2.42   0.015     .3233802    .8877408
                             3  |   .7073794   .2118347    -1.16   0.248     .3933172    1.272219
                                |
          1.Muscoskel_comorbi_01 |   1.098362    .071853     1.43   0.152     .9661738    1.248637
         1.Social_support_Dar_01 |   .9884467   .0689328    -0.17   0.868     .8600232    1.136047
                                |
       Physical_activity_150min |
                          meet  |   1.339155   .0940879     4.16   0.000     1.164271    1.540307
                                |
                 Dignosis_Group |
                        MI/PCI  |   1.072757   .1106271     0.68   0.496     .8763228    1.313224
                           PCI  |   .9939476   .1134875    -0.05   0.958     .7945596     1.24337
                          CABG  |   1.079042   .1124027     0.73   0.465     .8795465    1.323787
                 Heart Failure  |    .703935   .1268816    -1.95   0.052      .494314    1.002449
                        Angina  |   .6492753   .0905576    -3.10   0.002     .4939285    .8534805
                 Valve Surgery  |    1.10571   .1263736     0.88   0.379     .8837121    1.383477
                         Other  |   .6689534   .0844802    -3.18   0.001     .5222143    .8569253
                                |
           1.MDT_LL_j_no_missing |   .7646782   .2600254    -0.79   0.430     .3926484    1.489202
                                |
                     Alcohol_J1 |
                           yes  |   1.038034   .0641236     0.60   0.547     .9182473    1.173446
             1.Previous_event_01 |   .8465083   .1763219    -0.80   0.424     .5627493    1.273349
                                |
                    AcDiabetes4 |
                           Yes  |   .8538604   .0532808    -2.53   0.011     .7555521    .9649599
                                |
                 AcHypertension8 |
                           Yes  |   1.032308    .061077     0.54   0.591     .9192712    1.159244
                                |
                     AcFamily16 |
                           Yes  |    1.01344   .0924851     0.15   0.884       .84742    1.211986
                                |
                    AcAnxiety14 |
                           Yes  |   1.181023   .1080692     1.82   0.069     .9871013    1.413041
                                |
                  AcDepression15 |
                           Yes  |   .8395441   .0752261    -1.95   0.051     .7043061     1.00075
                     1.AcHyper18 |   1.149025   .0992478     1.61   0.108     .9700571     1.36101
                  Duration_Weeks |   .9580419   .0103789    -3.96   0.000     .9378269    .9786926
     NumberOfSessions_Completed |   1.329765   .0361493    10.48   0.000     1.260734    1.402577
                      event_Core |    1.00039   .0001842     2.12   0.034     1.000029    1.000751
                                |
                   Cenres_volume |
                             1  |   1.352622   .6102909     0.67   0.503     .5586218    3.275177
                             2  |   1.250846   .5837383     0.48   0.632     .5011502     3.12205
                             3  |    1.03858   .5398956     0.07   0.942     .3749248    2.876973
                             4  |   1.898452   .8637224     1.41   0.159     .7782751    4.630906
                             5  |   1.302522   .6705377     0.51   0.608     .4748662     3.57272
                                |
                          _cons |   .4061806    .278099    -1.32   0.189      .105628    1.561922
------------------------------------------------------------------------------------------------
Note: _cons estimates baseline odds.
```

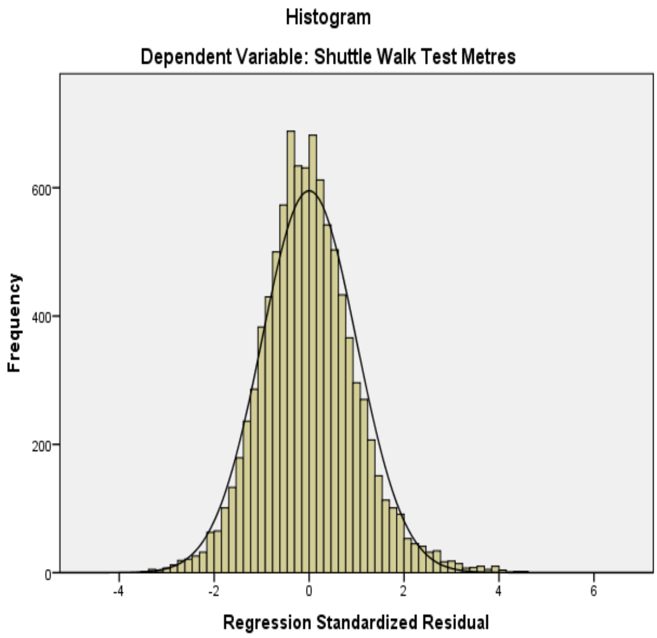
```
. mi estimate,or: logistic Exercise_50_A2 i.Centres_measured_fitness_only Age_new i.Gender_2_01 i.Ethnicity_2_01 i.Empl
> oyment1_Staus3Cat i.Marital_status_2nd_3cage i.BMI_0_1 i.Physical_fitne_Dartm_1 i.Smoking1_3CAT_SND i.comorbidity_3ca
> teg_2nd i.Supervied_vs_Self i.Group_alone_Deliver i.Performance_3categ i.Muscoskel_comorbi_01 i.Social_support_Dar_01
>  Physical_activity_150min i.Dignosis_Group i.MDT_LL_j_no_missing i.Alcohol_J1 i.Previous_event_01 i.AcDiabetes4 i.AcH
> ypertension8  i.AcFamily16 i.AcAnxiety14 i.AcDepression15 i.AcHyper18 Duration_Weeks NumberOfSessions_Completed event
> _Core i.Cenres_volume ,cluster (Location_Core)

Multiple-imputation estimates                Imputations       =         20
Logistic regression                          Number of obs     =     11,793
                                             Average RVI       =     0.2057
                                             Largest FMI       =     0.3260
DF adjustment:   Large sample                DF:     min       =     186.87
                                                     avg       =  43,497.18
                                                     max       = 401,552.30
Model F test:       Equal FMI                F(  45,30360.6)   =      42.19
Within VCE type:       Robust                Prob > F          =     0.0000

                                (Within VCE adjusted for 83 clusters in Location_Core)
```

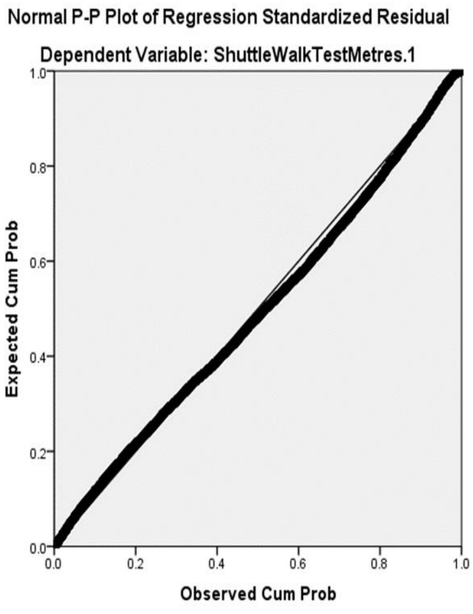
Exercise_50_A2	Odds Ratio	Std. Err.	t	P>|t|	[95% Conf.	Interval]
1.Centres_measured_fitness_only	1.102161	.1551179	0.69	0.489	.8364633	1.452257
Age_new	.975973	.0035204	-6.74	0.000	.9690954	.9828994
Gender_2_01						
Male	1.152076	.055495	2.94	0.003	1.048226	1.266215
Ethnicity_2_01						
White	1.031432	.1078415	0.30	0.767	.8402736	1.266079
Employment1_Staus3Cat						
UnEmployed	1.059799	.0985288	0.62	0.532	.883165	1.27176
Retierd	1.334387	.1002137	3.84	0.000	1.151425	1.546421
Marital_status_2nd_3cage						
in relationship	1.259263	.1302468	2.23	0.027	1.027099	1.543905
Not in relationship	1.116289	.1295872	0.95	0.345	.8878398	1.40352
BMI_0_1						
<30	1.305434	.0699372	4.98	0.000	1.175277	1.450004
Physical_fitne_Dartm_1						
Yes	1.410601	.0965771	5.02	0.000	1.233181	1.613547
Smoking1_3CAT_SND						
Yes	.7033321	.0762181	-3.25	0.001	.5687126	.8698174
Stooped Smoking since event	.8714194	.0763418	-1.57	0.116	.7338636	1.034759
comorbidity_3categ_2nd						
less than 3 "<3"	1.075059	.0856784	0.91	0.364	.9195851	1.256819
3 or more "=>3"	.9037043	.0937062	-0.98	0.329	.7374996	1.107365
Supervied_vs_Self						
Supervised	1.306092	.2858239	1.22	0.224	.8481711	2.011241
Group_alone_Deliver						
GroipDelivered	.7516282	.1184362	-1.81	0.070	.551705	1.023998
Performance_3categ						
2	1.048737	.2200643	0.23	0.821	.6951072	1.582274
3	1.428589	.3256897	1.56	0.118	.9137967	2.233393
1.Muscoskel_comorbi_01	.8570026	.0525948	-2.51	0.012	.7598756	.9665442
1.Social_support_Dar_01	1.244536	.0907329	3.00	0.003	1.077957	1.436857
Physical_activity_150min	5.742809	.9921929	10.12	0.000	4.093112	8.057406
Dignosis_Group						
MI/PCI	1.117522	.1050679	1.18	0.237	.929448	1.343652
PCI	1.025568	.098457	0.26	0.793	.8496569	1.237898
CABG	1.248105	.129844	2.13	0.033	1.017879	1.530404
Heart Failure	.9277475	.1268759	-0.55	0.583	.7096004	1.212958
Angina	.8015537	.1074689	-1.65	0.099	.6163022	1.042489
Valve Surgery	1.072114	.1229323	0.61	0.544	.8563239	1.342283
Other	.94009	.1091899	-0.53	0.595	.748689	1.180422
1.MDT_LL_j_no_missing	.8128072	.1806805	-0.93	0.351	.5257119	1.256687
Alcohol_J1						
yes	.9033951	.069075	-1.33	0.185	.7772007	1.05008
1.Previous_event_01	1.079347	.1310156	0.63	0.529	.8508186	1.369257
AcDiabetes4						
Yes	.7928843	.0526542	-3.49	0.000	.6961162	.9031042
AcHypertension8						
Yes	1.108875	.0562972	2.04	0.042	1.003841	1.224899
AcFamily16						
Yes	1.127792	.1005282	1.35	0.177	.9470097	1.343085
AcAnxiety14						
Yes	1.165301	.1413934	1.26	0.207	.9186583	1.478162
AcDepression15						
Yes	.838712	.0876907	-1.68	0.093	.6833027	1.029467
1.AcHyper18	1.068864	.0818013	0.87	0.384	.9199799	1.241842
Duration_Weeks	.9920117	.0074704	-1.07	0.287	.9774758	1.006764
NumberOfSessions_Completed	1.015789	.0087726	1.81	0.070	.9987357	1.033134
event_Core	.9999504	.0002605	-0.19	0.849	.9994399	1.000461
Cenres_volume						
1	.9881401	.3834848	-0.03	0.975	.4617881	2.114435
2	1.013506	.3988567	0.03	0.973	.4686137	2.191986
3	.8643958	.3656692	-0.34	0.730	.3772281	1.980712
4	.7600365	.2933627	-0.71	0.477	.356652	1.619661
5	.7883421	.3199769	-0.59	0.558	.3558015	1.746713
_cons	2.361197	1.079701	1.88	0.060	.9632639	5.787873

Note: _cons estimates baseline odds.

.

Appendix 8.5.1 Regression assumption





Appendix 8.6.1 STATA results of logistic regression analysis for the final determinants

```
Multiple-imputation estimates                 Imputations       =         20
Logistic regression                           Number of obs     =      9,786
                                              Average RVI       =     0.1608
                                              Largest FMI       =     0.3505
DF adjustment:   Large sample                 DF:     min       =     161.93
                                                      avg       = 3971564.34
                                                      max       =   4.08e+07
Model F test:       Equal FMI                 F(  21,20565.3)   =      27.21
Within VCE type:       Robust                 Prob > F          =     0.0000
```

(Within VCE adjusted for 35 clusters in LOCATION_COPY)

Achieved_MCID__01	Odds Ratio	Std. Err.	t	P>|t|	[95% Conf.	Interval]
Age	.9550034	.0034465	-12.76	0.000	.9482711	.9617835
Gender_0_1						
Male	1.714969	.1288968	7.18	0.000	1.480063	1.987159
BMI_30						
less than <30	1.588577	.083448	8.81	0.000	1.43309	1.760935
Dignostic_4group						
PCI_intervention	.9487208	.0885738	-0.56	0.573	.7900765	1.13922
SURGERY	1.224076	.1071673	2.31	0.021	1.031065	1.453219
other	.9812874	.1423124	-0.13	0.896	.7384986	1.303895
1.Ethinicty_01	1.305603	.0998347	3.49	0.000	1.123862	1.516733
Marital_status_3group						
In Relation	1.266186	.1131227	2.64	0.009	1.061396	1.510489
not inRelation	1.144282	.1169029	1.32	0.189	.9353675	1.399857
Employment_Status_3group						
unemployed	.8232506	.0811615	-1.97	0.049	.678518	.9988557
Retaired	.9770756	.0789783	-0.29	0.774	.8338436	1.144911
1.Diabetic_01	.7762717	.0502637	-3.91	0.000	.6837515	.881311
AcAnxiety14						
Yes	1.305471	.1462519	2.38	0.017	1.04811	1.626025
Smoking_3Categ						
Current smoking	.6707376	.0901953	-2.97	0.003	.5153141	.8730384
Stopped somking since event	.8509145	.0671312	-2.05	0.041	.7289866	.9932357
Basline_ISWT_1_adj	.9965697	.0004674	-7.33	0.000	.995654	.9974863
StartPh1EarlyYN						
Yes	1.28874	.1344377	2.43	0.015	1.050438	1.581103
1.Number_sessions_12_or_more	1.343569	.1232523	3.22	0.001	1.122457	1.608237
Time_from_event_to_start1	.9941514	.0014581	-4.00	0.000	.9912974	.9970137
Exercise_50_A1						
Yes	1.160744	.0613714	2.82	0.005	1.046297	1.287709
1.Hypercholesterolaemia	1.120319	.0560124	2.27	0.023	1.015744	1.23566
_cons	41.04893	12.80942	11.90	0.000	22.26751	75.67148

Note: _cons estimates baseline odds.

.

```
. mi estimate,or: logistic fit_2_ab i.Achieved_MCID__01  Age i.Gender_0_1 i.BMI_30 i.Dignostic_4group i.Ethinicty_01 i.Marital_status_3group i.Employment_Status_3group i.Diabetic_01 i.AcAnxiety14 i.Smoking_3Categ   Basline_ISWT_1_adj
> i.StartPh1EarlyYN  i.Number_sessions_12_or_more Time_from_event_to_start1 i.Exercise_50_A1 i.Hypercholesterolaemia i.Physical_function ,cluster(LOCATION_COPY )

Multiple-imputation estimates               Imputations     =         20
Logistic regression                         Number of obs   =      7,950
                                            Average RVI     =     0.2468
                                            Largest FMI     =     0.3546
DF adjustment:   Large sample               DF:     min     =     158.25
                                                    avg     = 520,878.99
                                                    max     = 8373085.18
Model F test:       Equal FMI               F(  23,11208.7) =      73.39
Within VCE type:       Robust               Prob > F        =     0.0000

                             (Within VCE adjusted for 34 clusters in LOCATION_COPY)
```

fit_2_ab	Odds Ratio	Std. Err.	t	P>|t|	[95% Conf.	Interval]
1.Achieved_MCID__01	1.554855	.1181008	5.81	0.000	1.339787	1.804446
Age	.9876078	.0052499	-2.35	0.019	.9773691	.9979537
Gender_0_1						
Male	1.04688	.0924356	0.52	0.604	.8805193	1.244672
BMI_30						
less than <30	1.034004	.0482242	0.72	0.473	.9436128	1.133054
Dignostic_4group						
PCI_intervention	1.071408	.1156524	0.64	0.523	.867106	1.323846
SURGERY	1.21773	.1616307	1.48	0.138	.9387926	1.579547
other	.9163405	.103204	-0.78	0.438	.7348321	1.142683
1.Ethinicty_01	1.81204	.2261688	4.76	0.000	1.418804	2.314264
Marital_status_3group						
In Relation	1.127181	.1480252	0.91	0.362	.8710141	1.458688
not inRelation	.9328069	.1409763	-0.46	0.645	.6933828	1.254904
Employment_Status_3group						
unemployed	.8049862	.1276053	-1.37	0.171	.5898268	1.098632
Retaired	.7663368	.0813225	-2.51	0.013	.6214345	.9450266
1.Diabetic_01	.7536505	.0665321	-3.20	0.001	.6339075	.8960125
AcAnxiety14						
Yes	.7754521	.1008915	-1.95	0.051	.6009076	1.000696
Smoking_3Categ						
Current smoking	.7018576	.0996976	-2.49	0.013	.5312306	.9272886
Stopped somking since event	.7618161	.0850899	-2.44	0.015	.612024	.9482697
Basline_ISWT_1_adj	1.004551	.0004001	11.40	0.000	1.003767	1.005336
StartPh1EarlyYN						
Yes	.9276547	.1011211	-0.69	0.491	.7492025	1.148612
1.Number_sessions_12_or_more	1.015601	.0917435	0.17	0.864	.850774	1.212362
Time_from_event_to_start1	.9970785	.0013446	-2.17	0.030	.9944431	.9997209
Exercise_50_A1						
Yes	1.376677	.1107103	3.98	0.000	1.175524	1.612251
1.Hypercholesterolaemia	1.042724	.0954622	0.46	0.648	.8714471	1.247664
Physical_function						
Yes	3.009446	.2466528	13.44	0.000	2.562412	3.534468
_cons	.7902647	.2798485	-0.66	0.506	.3947178	1.582189

Note: _cons estimates baseline odds.

Exercise_50_A2	Odds Ratio	Std. Err.	t	P>|t|	[95% Conf.	Interval]
1.Achieved_MCID__01	1.291443	.1244925	2.65	0.008	1.069107	1.560018
Age	.9914474	.0053044	-1.61	0.108	.9811046	1.001899
Gender_0_1						
Male	.9513098	.0707166	-0.67	0.502	.8223313	1.100518
BMI_30						
less than <30	1.17198	.0832659	2.23	0.026	1.019621	1.347104
Dignostic_4group						
PCI_intervention	1.245259	.1466677	1.86	0.063	.9885625	1.56861
SURGERY	1.461808	.2011824	2.76	0.006	1.116202	1.914423
other	.9580185	.1417397	-0.29	0.772	.7168655	1.280295
1.Ethinicty_01	.9940414	.1833897	-0.03	0.974	.6924126	1.427066
Marital_status_3group						
In Relation	1.098168	.1161245	0.89	0.376	.8923426	1.351468
not inRelation	1.033687	.12501	0.27	0.784	.81499	1.31107
Employment_Status_3group						
unemployed	1.021358	.1259365	0.17	0.864	.8020502	1.300631
Retaired	1.249084	.1198799	2.32	0.021	1.034753	1.50781
1.Diabetic_01	.8350713	.0833311	-1.81	0.071	.6867247	1.015464
AcAnxiety14						
Yes	1.033263	.154933	0.22	0.827	.7701535	1.38626
Smoking_3Categ						
Current smoking	.7771008	.1122027	-1.75	0.081	.5855447	1.031323
Stopped somking since event	.8891132	.0800052	-1.31	0.192	.7453406	1.060619
Basline_ISWT_1_adj	1.000994	.000431	2.31	0.021	1.00015	1.001839
StartPh1EarlyYN						
Yes	1.218713	.1832388	1.32	0.188	.9076522	1.636377
1.Number_sessions_12_or_more	.8426415	.1134339	-1.27	0.203	.6472258	1.097059
Time_from_event_to_start1	.9967947	.0018057	-1.77	0.076	.9932614	1.000341
Exercise_50_A1						
Yes	3.211093	.3669408	10.21	0.000	2.566659	4.01733
1.Hypercholesterolaemia	.9631695	.0987015	-0.37	0.714	.7879074	1.177417
_cons	1.565952	.6819653	1.03	0.303	.6669317	3.676845

Abbreviations

Acronyms	**Full Name**
6MWT	Six minute walk test
AACVPR	American Association of Cardiovascular and Pulmonary Rehabilitation
ACPICR	Association of Chartered Physiotherapists in Cardiac Rehabilitation
ACS	Acute Coronary Syndrome
ACSM	The American College of Sports Medicine
AHA	American Heart Association
a-Vo$_2$	Arterio-venous oxygen difference
BACPR	British Association for Cardiovascular Prevention and Rehabilitation
BHF	British Heart Foundation
BMI	Body Mass Index
CABG	Coronary artery bypass graft
CACR	Canadian Association of Cardiac Rehabilitation
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CI	Confidence Interval
CPET	Cardiopulmonary Exercise Test
CR	Cardiac Rehabilitation
CRF	Cardiorespiratory fitness
CST	Chester Step Test
CVD	Cardiovascular Diseases
EAPC	European Association for Cardiovascular Prevention and Rehabilitation
ECG	Electrocardiogram
ESC	European Society of Cardiology
GXT	Graded Exercise Test
HF	Heart Failure
HR	heart rate
HRQOL	health-related quality of life
ISWT	Incremental shuttle walk test

LVEF	left ventricular ejection fraction
METs	Metabolic Equivalent
MI	Myocardial Infarction
NACR	National Audit of Cardiac Rehabilitation
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
PCI	Percutaneous Coronary Intervention
RCT	Randomised Control Trial
RPE	Borg's Rating of Perceived Exertion
STEMI	ST Elevation Myocardial Infarction
SV	stroke volume
Vo_2 max/peak	Maximal/peak oxygen uptake
WHO	World Health Organisation

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